UNIVERSITÉ DE STRASBOURG

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EDSC
Ecole Doctorale des Sciences Chimiques

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES

UMR 7509

THÈSE

présentée par

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soutenue le : **14 décembre 2012**

pour obtenir le grade de

Docteur de l'université de Strasbourg

Discipline / Spécialité : Chimie Organique

Novel Access to Heteroaromatic Building Blocks bearing Diversely Fluorinated Substituents

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"Success is not final, failure is not fatal: it is the courage to continue that counts."
Winston Churchill

A mes parents,
A mes sœurs,

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Acknowledgements

Le travail de recherche présenté dans ce manuscrit a été effectué au sein du laboratoire de Stéréochimie, à l'Ecole Européenne de Chimie, Polymères et Matériaux (ECPM), université de Strasbourg. Tout d'abord, je remercie le Professeur Françoise Colobert de m'avoir accueillie dans son laboratoire.

Je tiens tout particulièrement à remercier le Docteur Frédéric Leroux pour son encadrement tout au long de ma thèse. Merci de m'avoir accueillie dans ton équipe, pour les précieux conseils, les discussions et ta disponibilité sans limite, même depuis que tu as pris de hautes responsabilités au niveau national. Merci également d'avoir été à l'écoute, car l'encadrement scientifique ne fait pas tout d'un chef, le côté humain est aussi très important. La confiance que tu m'as donnée au niveau de la recherche, ainsi que le fait d'avoir su me recadrer lorsque je me dispersais m'ont beaucoup appris et ont fait de moi la chimiste que je suis aujourd'hui. Finalement, merci de m'avoir supportée lorsque je mettais la musique trop fort dans le labo et quand je pestais bruyamment sur ma chimie !

Je voudrais également remercier le Professeur Philippe Compain, ainsi que les Docteurs Emmanuel Magnier et Thierry Billard d'avoir accepté de juger ce travail.

Je voudrais adresser toute ma reconnaissance aux Docteurs Sergiy Pazenok et Jean-Pierre Vors pour la collaboration. Merci pour vos précieux conseils, en chimie des hétérocycles et en chimie du fluor. Je tiens également à remercier l'entreprise Bayer CropScience pour le financement de ces travaux de recherche.

Je remercie chaleureusement toutes les personnes qui m'ont permis de faire les analyses : Estelle Motsch (Estelle « de la masse ») pour les ESI, les GCMS, et son sourire permanent, Michel Schmitt pour les RMN en catastrophe et tout le reste, Matthieu et Marie-Céline pour les GC, ainsi que les services de RMN, masse, cristallographie et d'analyse élémentaire de l'esplanade.

Le laboratoire n'est pas seulement un lieu de travail, c'est aussi un lieu où on rencontre des collègues, qui parfois deviennent des amis. Ma thèse ne se serait pas passée de la même manière sans vous, je tiens à tous vous remercier. Grâce à votre accueil je me suis sentie chez moi en Alsace, moi la sudiste. Que de souvenirs, des moments de rigolade, des moments où il faut se remonter le moral, les sorties labo, les repas de Noël, j'en passe et des meilleurs. Plus particulièrement : Marie ou Dr MB, merci pour l'écoute, et SURTOUT le soutien mutuel permanent, à tous nos fous-rires sur le balcon du R2. Un grand merci à Nico, Nigga, pour les bons moments sans oublier l'organisation de la SECO 49 dont je garde un souvenir mémorable !!! Anaïs, ma petite saucisse, merci pour les parties de rigolade au labo, et ton mariage : encore une fois félicitations et beaucoup de bonheur. Stéphanie, un grand merci pour tout, tes conseils dans la rédaction du manuscrit et surtout pour les relectures intensives ! N'oublie pas que tu me dois une danse. Dr Camille Decroocq, merci de m'avoir aiguillée dans toutes les démarches administratives, les soucis de mise en page, c'est plutôt cool d'avoir une copine qui soutient sa thèse un mois avant… Que dire de plus, à part : tu te gaves ! Armen, pour ta bonne humeur, Sabine, pour les conseils en chimie et le sourire, ainsi que les restes de chocolats de tes filles ! Je

tiens également à remercier : Agnès, le Docteur Gilles Hanquet, Bruno, Boubacar, Maggie, Arlette, Didier, Bouchra, Merco, Rafeta, Leti, Irene, Baptiste, Vincent, Manon, Noelline, Sandra et Thomas « de chez Ziessel », Meera, Thibault, Laure, Karene, ainsi que tous ceux que j'ai oubliés ici…

J'ai une grande reconnaissance envers des amies que j'ai rencontrées ici, et que j'espère bien garder encore longtemps : Caro et Aude. Votre amitié infaillible m'a été d'une grande aide au long de ces trois années. Merci pour votre écoute, les repas filles, les soirées talons et j'en passe… Vous m'avez permis de me sentir à Strasbourg comme chez moi, et je ne saurai jamais vous remercier assez.

Merci aussi à Gé, tu es une précieuse amie. Merci pour ton soutien, et de m'avoir changé les idées quand j'en avais besoin. Une spéciale dédicace pour la soirée Joe Dassin au Zénith de Strasbourg qui restera gravée dans ma mémoire pour longtemps…

Il y a aussi les amis que j'avais rencontrés bien avant mon arrivée à Strasbourg, et pour qui j'ai une pensée, Nico, Fabrice, Janguy, Hugues, Chloé, JB, Coco, Raph, Bru, LP, Tom, Laure, Beurt, Cam : les potos de l'école que je ne risque pas d'oublier !!! Et au bébé Beurton-Dujoncquoy à naître, qui est prévu pour le 14 décembre… J'ai aussi une pensée pour toi Grati, qui nous as quittés trop vite mais qui est toujours présent dans nos cœurs.

Je voudrais exprimer toute ma gratitude à ma famille, notamment à mes parents sans qui rien n'aurait été possible. Merci de m'avoir soutenue dans mes choix, même si vous ne les avez pas toujours compris. Je pense également à mes sœurs, qui m'ont rendu visite régulièrement et qui m'ont soutenue dans les moments les plus difficiles.

Enfin, je tiens à te remercier Thomas. Pour ton aide sur le projet 3,5-bis(fluoroalkyl) pyrazoles, ta disponibilité et la relecture de nombreux chapitres. Mais surtout, pour ton infinie patience et ton inestimable soutien.

Abbreviations

ABCN: 1,1'-Azobis(cyclohexanecarbonitrile)
Ac: acetyl
AIBN: azobis-*iso*-butyronitrile
Ar : aryl
Boc: *t*-butyloxycabonyl
Bu : *n*-butyl
COX-2: cyclooxygenase-2
DAST: Diethylaminosulfur trifluoride
DBH: *N,N*-dibromohydantoin
DCM: Dichloromethane
DMAc: dimethylacetamide
DMAP: *N,N*-dimethylaminopyridine
DMF: dimethylformamide
DMSO: dimethylsulfoxyde
DP: desired product
ESI: Electron Spray Ionization
Et: ethyl
eq. : equivalent
FAR: fluoroalkyl amino reagents
F-TEDA: Selectfluor®
GC: Gas Chromatography
GCMS: Gas Chromatography – Mass Spectrometer
*i*Pr : *iso*-propyl
LAH: lithium aluminum hydride
LDA : lithium diisopropylamide
LiTMP: lithium tetramethylpiperidide
Me : methyl
MeCN: acetonitrile
MS : Mass Spectrometry
MSDS: Material Safety Data Sheet
MTBE: methyl *tert*-butyl ether
MW: micro-wave
nAChRs: nicotinic acetylcholine receptors
NBS: *N*-bromosuccinimide
NCS: *N*-chlorosuccinimide
NIS: *N*-iodosuccinimide
NMP: 1-methyl-2-pyrrolidinone
NMR : Nuclear Magnetic Resonance
ORTEP : Oak Ridge Thermal Ellipse Program
Ph : phenyl
ppm: parts per million
*p*Ts: *para*-toluene sulfonyl
Py: pyridine
Rf: fluoroalkyl
rt : room temperature
SDHI: succinate-dehydrogenase inhibitors
SM: starting material
TAS: tris(dimethylamino)sulfonium
TBAF : tetra-*n*-butylammonium fluoride
TBAT: Tetra-*n*-butylammonium difluorotriphenylsilicate
*t*Bu : *tert*-butyl
TFA : trifluoroacetic acid
TFE: tetrafluoroethylene
TFEDMA: 1,1,2,2-tetrafluoroethyl dimethylamine
TFMT: Trifluoromethyl trifluoromethane sulphonate
THF : tetrahydrofurane
THP: tetrahydropyrane
TMS : trimethylsilyl
TREAT-HF: triethylamine trishydrofluoride
Ts : tosyl
UV: ultra violet

Résumé en Français

Le fluor F_2 a été isolé pour la première fois par Henri Moissan en 1886, et ceci a marqué le début de l'ère moderne de la chimie du fluor. Cependant, il a été utilisé essentiellement pour la métallurgie jusque dans les années 1950. Avec la découverte de la formidable augmentation de l'activité biologique du fluorouracile grâce à l'introduction d'un atome de fluor, il a fait son entrée en chimie médicinale.[1]

Depuis, son utilisation en chimie pharmaceutique ainsi qu'en agrochimie s'est démocratisée. De nombreux produits pharmaceutiques et phytosanitaires contiennent du fluor. Il est ainsi reconnu qu'aujourd'hui environ 20% des produits pharmaceutiques[2] et 30% des molécules agrochimiques contiennent au moins un atome de fluor. Par exemple, l'agent anti-inflammatoire Celecoxib (Pfizer), l'antidépresseur Fluoxetine (Prozac®, Eli Lilly), le fongicide Bixafen (Bayer CropScience) et l'herbicide Fludioxonil (Syngenta) comportent du fluor sous forme de substituants trifluoromethyl, difluoromethyl et *gem*-difluoro.

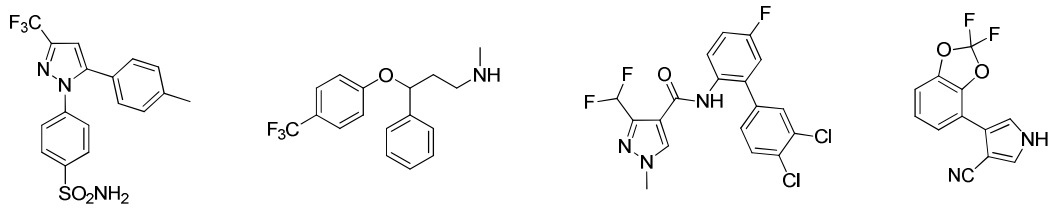


Figure 1: Molécules pharmaceutiques et agrochimiques contenant du fluor

Très peu présent dans les produits naturels[3] (seulement une quinzaine de produits naturels contenant du fluor ont été recensés à ce jour), l'introduction de fluor dans des molécules biologiquement actives est essentiellement faite par la main de l'homme. Ainsi, il a été et il est toujours très important de développer des méthodes permettant l'introduction d'atomes de fluor afin d'étendre les voies d'accès à de nouveaux composés fluorés d'intérêt thérapeutique ou phytosanitaire.

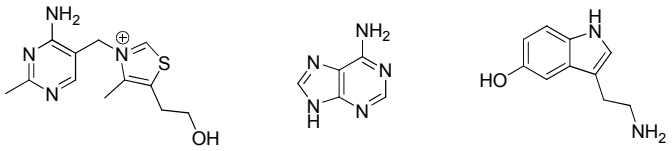
Les propriétés de l'atome de fluor permettent d'altérer le comportement des molécules dans un milieu biologique. Il est l'élément le plus électronégatif du tableau périodique (électronégativité de 4.0 sur l'échelle de Pauling), il est donc compréhensible qu'il influe sur la distribution électronique des molécules.[4]

De plus, le fluor possède un faible rayon de van der Waals (1.47Å), ce qui fait de lui le deuxième plus petit élément après l'atome d'hydrogène. Il est situé entre l'hydrogène (1.20 Å) et l'oxygène (1.52 Å). Ainsi, il peut substituer un atome d'hydrogène ou une fonction hydroxy tout en conservant un volume comparable dans le site actif, mais en changeant les propriétés de la molécule.

Grâce à ces particularités, les substituants fluorés influent sur les activités biologiques des molécules. Tout d'abord, sa grande électronégativité entraîne une diminution des p*K*a des fonctions voisines.[5] De plus, sa présence sur des noyaux aromatiques augmente la lipophilie des

molécules.[5] Substituer un atome d'hydrogène par un atome de fluor peut également permettre d'augmenter la stabilité métabolique d'un composé. En effet, la liaison C-F est haute en énergie (116 kcal·mol^{-1}), et n'est pas sujette à l'oxydation métabolique *in vivo*.[6] Ainsi, il découle de ces nombreux facteurs que la fluoration de molécules bioactives augmente leur biodisponibilité.

En ce qui concerne les hétérocycles, on peut aisément affirmer que ceux-ci sont très importants en sciences de la vie. En effet, un grand nombre de molécules hétérocycliques sont impliquées dans des processus biologiques. Par exemple, on retrouve des hétérocycles dans les vitamines, les bases nucléiques, ainsi que les neurotransmetteurs (Figure 2).



Vitamine B_1 (Thiamine) Adénine Sérotonine

Figure 2: Produits naturels hétérocycliques impliqués dans des processus biologiques

En conséquence, les chimistes médicinaux s'inspirant de la nature, de nombreux principes actifs de molécules pharmaceutiques et agrochimiques comportent des hétérocycles. En 2007, 71 molécules du top 100 des médicaments les plus vendus aux Etats-Unis comprenaient un building block hétérocyclique.[7]

Il est certain que les composés hétérocycliques sont essentiels pour la recherche pharmaceutique et phytosanitaire et que les substituants fluorés ont des effets bénéfiques sur l'activité biologique de certains composés. Ainsi, on peut imaginer que la combinaison composés hétérocycliques/substituants fluorés pourra mener à des molécules présentant une activité encore supérieure.

Il existe de nombreuses méthodes pour la préparation de composés hétérocycliques portant un seul atome de fluor ou un groupement trifluorométhyl.[8] Par contre, les voies d'accès à d'autres groupements plus « exotiques » tel que le trifluorométhoxy ou le difluorométhyl sont beaucoup moins courantes.[9] Il est donc nécessaire d'effectuer une recherche constante pour développer des méthodologies efficaces et adaptables à une échelle industrielles pour la synthèse de composés hétérocycliques portant des substituants fluorés originaux.

Dans cette optique, nous nous sommes intéressés à deux types d'hétérocycles : les pyridines et les pyrazoles, qui sont parmi les hétérocycles aromatiques les plus représentés en chimie du vivant.[10] Notre but était de développer des voies synthétiques vers des building blocks hétérocycliques fluorés en peu d'étapes, et idéalement transposables à grande échelle.

Le travail de recherche a été divisé en trois projets. Le premier a porté sur l'extension d'une méthodologie déjà décrite par notre groupe. Lors d'une étude précédente, une voie d'accès à des trifluorométhoxy pyridines a été développée, et leur fonctionnalisation a mené à une librairie de building blocks portant des acides carboxyliques, des amines et des halogènes. Afin de valoriser ce travail, nous avons préparé un analogue trifluorométhoxylé d'une molécule biologiquement active connue afin de comparer les activités biologiques, et nous avons préparé

un building block hautement fonctionnalisable. Enfin, nous avons voulu étendre la méthodologie à d'autres hétérocycles : les pyrazoles.

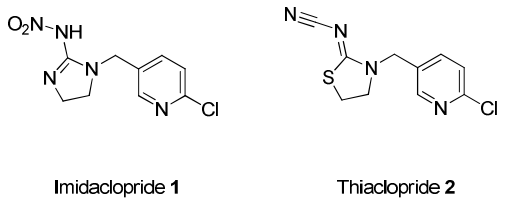
Le second projet a consisté en le développement d'une voie d'accès à des pyridines portant des groupements fluorés mixtes : chlorodifluorométhoxy (OCF_2Cl) et dichlorofluorométhoxy ($OCFCl_2$).

Lors d'un troisième projet, nous avons mis au point la synthèse de pyrazoles comprenant deux substituants fluorés différents en position 3 et 5 du cycle. Nous avons pu libérer la position 4 ainsi que l'atome d'azote afin de pouvoir préparer des building blocks qui peuvent être fonctionnalisés sur ces positions avec n'importe quel substituant sur demande.

1. Hétérocycles trifluorométhoxylés

1.1. Analogue trifluorométhoxylé de l'Imidaclopride

L'Imidaclopride **1** et la Thiaclopride **2** (Figure 3) sont des insecticides phares de la société Bayer CropScience. Ces molécules de la famille des néonicotinoïdes ont une forte affinité pour les récepteurs cholinergiques (nAChRs) situés dans le système nerveux central des insectes. Ils bloquent ces récepteurs, entraînant la paralysie et la mort des insectes.



Imidaclopride **1** Thiaclopride **2**

Figure 3: Structures de l'Imidaclopride et de la Thiaclopride

Contrairement à la nicotine, ces composés ont très peu d'affinité pour les récepteurs cholinergiques des mammifères, et cette sélectivité les rend très attractifs pour l'agrochimie. Ces deux molécules présentent le même motif chloro-pyridine, et diffèrent de par la nature du second hétérocycle et de la fonction azotée terminale.

Le groupement trifluorométhoxy a été surnommé « pseudo-halogène »,[11] ceci étant dû à ses propriétés lipophiles et électroattractrices qui sont comparables à celles d'un atome de chlore ou de fluor. Ainsi, nous avons voulu préparer un analogue trifluorométhoxylé de ces molécules afin d'étudier l'influence de la substitution de l'atome de chlore par un groupement trifluorométhoxy sur l'activité biologique des molécules.

Notre travail s'est limité à la préparation du précurseur de ces molécules, la pyridine **6** qui, par couplage avec l'hétérocycle correspondant, permet la préparation de l'Imidaclopride **1** et de la Thiaclopride **2** (Figure 4). Le composé chloré **6** peut être obtenu par chloration de l'alcool terminal de **5**, qui lui-même est préparé par réduction de l'acide nicotinique **4**. Enfin, l'acide nicotinique **4** peut être synthétisé à partir de la 2-chloro-6-trifluorométhoxy pyridine **3** en utilisant la méthode précédemment développée par notre groupe.

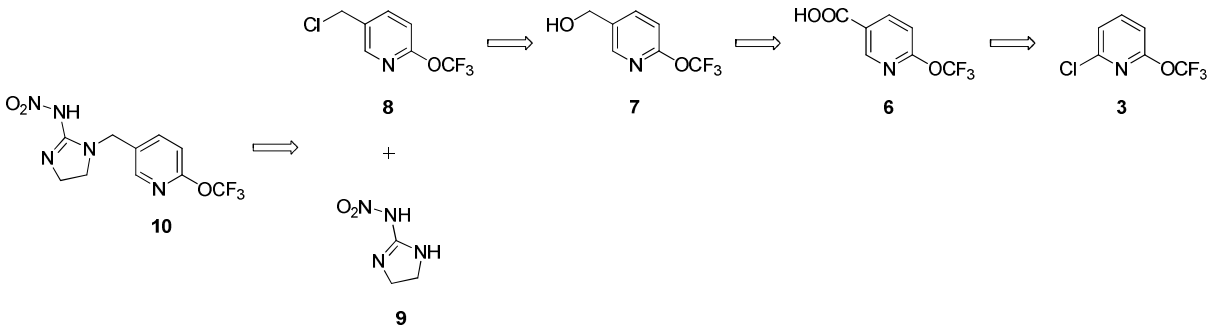


Figure 4: Schéma rétrosynthétique de la synthèse de l'OCF_3-Imidaclopride 1

Cette molécule a été synthétisée en partant de la 6-chloro-2-trifluorométhoxy pyridine **3** dont on protège la position 3 avec un groupement triméthylsilyle (Schéma 1). On procède ensuite à une lithiation suivie d'un piégeage avec CO_2 solide afin d'obtenir l'acide **5** correspondant avec un rendement de 50%. On effectue par la suite une déchloration catalysée par le palladium sur charbon en présence d'ammonium formiate, puis une réduction de l'acide avec BH_3 dans le THF pour obtenir l'alcool primaire **7**. Enfin, une chloration de cet alcool en présence de chlorure de mésyle et de triéthylamine dans le dichlorométhane conduit au produit désiré **8**.

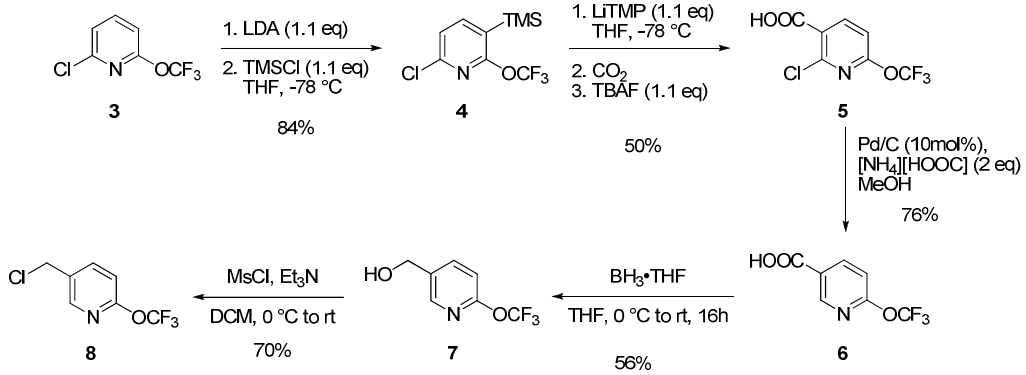


*Schéma 1: Synthèse de la pyridine **8***

Après une optimisation des étapes de réduction et de chloration de l'alcool primaire nous avons pu obtenir le précurseur de l'Imidaclopride et de la Thiaclopride avec un rendement global de 12.5% sur 5 étapes. Ce précurseur a été envoyé sur le site de Bayer CropScience à Monheim afin d'effectuer la dernière étape de couplage pour obtenir les analogues trifluorométhoxylés **10** et **11** des deux insecticides (Figure 5).

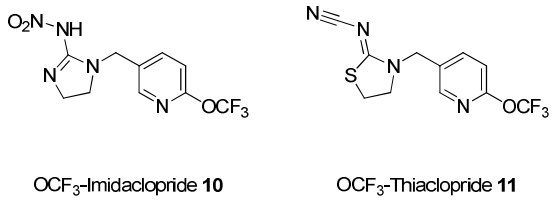


Figure 5: OCF_3-Imidaclopride et Thiaclopride

Enfin, des tests biologiques *in vitro* sur des récepteurs cholinergiques et *in vivo* sur *Myzus Persicae*, le puceron vert du pêcher, ont été effectués. Malheureusement, il se trouve que les analogues trifluorométhoxylés ont présenté une activité biologique beaucoup moins importante

que les insecticides chlorés. Dans ce cas-là, l'activité biologique a été diminuée, mais il ne faut pas conclure que l'utilisation d'un groupement trifluorométhoxy aura cette influence à chaque fois. Ici, il se peut qu'il ait diminué l'affinité de la molécule pour les récepteurs biologiques, mais dans un autre cas son introduction aura un effet positif.

1.2. Trifluorométhoxy "Magic Pyridine"

La "Magic Pyridine" ou 2,3-dichloro-5-trifluorométhyl pyridine **12** est un building block très important car elle est hautement fonctionnalisable. En effet, ses positions 4 et 6 peuvent être atteintes *via* une métallation en présence d'un organolithien, et la position 2 étant chlorée, elle peut être fonctionnalisée par S_NAr. Enfin, les deux atomes de chlore peuvent être soit utilisés pour la fonctionnalisation, soit éliminés *via* une déchloration pallado-catalysée.

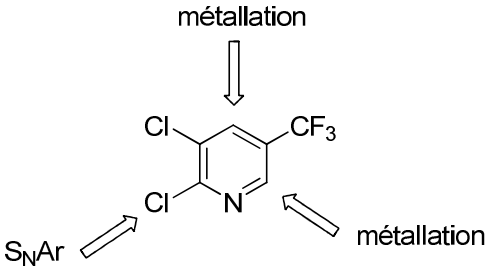


*Figure 6: "Magic Pyridine" **12***

Nous nous sommes donc intéressés à la préparation d'une version trifluorométhoxy de ce building block, qui, offrant de nombreuses options pour la fonctionnalisation, pourrait être utilisé pour synthétiser des principes actifs contenant un motif trifluorométhoxy pyridine.

Ainsi, nous avons pensé que le building block **19** (Figure 7) pourrait être synthétisé en utilisant la méthode développée au laboratoire pour la préparation de trifluorométhoxy pyridines à partir du composé hydroxylé **16**. Celui-ci n'étant pas commercial, il peut être préparé à partir de la pyridine iodée **15** selon une séquence de borylation/oxydation. La pyridine **15** peut être obtenue en soumettant l'amino pyridine **14** à des conditions de Sandmeyer, et enfin, l'amino pyridine **14** serait préparée par réduction de la fonction nitro de **13**.

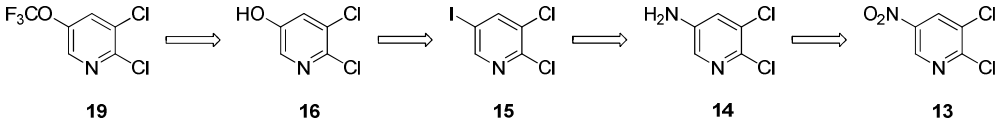


Figure 7: Schéma rétrosynthétique de la préparation de la OCF_3-« Magic Pyridine »

Nous avons donc soumis la pyridine **13** à la voie de synthèse que nous avions imaginée (Schéma 2). La réduction du groupement nitro a été effectuée en présence de Fe et HCl avec 85% de rendement. Une diazotation en présence de nitrite de sodium suivie par un piégeage avec de l'iodure de potassium a conduit à la 2,3-dichloro-5-iodo pyridine **14** avec un rendement élevé de 82%. Enfin, une séquence de borylation/oxydation en conditions basiques a permis d'isoler l'hydroxy pyridine **16** avec 90% de rendement.

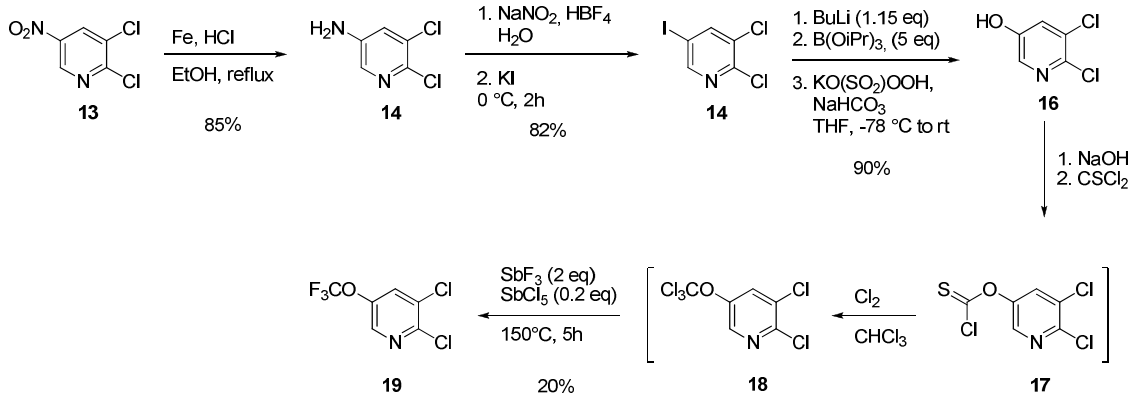


*Schéma 2: Synthèse de la trifluorométhoxy "Magic Pyridine" **19***

Finalement, nous avons soumis **16** à une séquence d'alkylation/chlorodésulfuration/ fluoration afin d'obtenir la pyridine **19** en 20% de rendement sur deux étapes. Cette séquence consiste en une *O*-alkylation en présence de thiophosgène pour conduire au chlorothionoformiate **17** qui n'est pas isolé. Celui-ci est directement soumis à une chloration pour donner le composé **18**, puis une fluoration en présence de trifluorure d'antimoine et de pentachlorure d'antimoine en quantité catalytique conduit au produit final **19**.

Ainsi, nous avons pu développer une voie d'accès rapide et efficace à ce composé hautement fonctionnalisable, tout en utilisant la séquence d'alkylation/chlorodésulfuration/ fluoration développée par notre groupe.

1.3. 5-OCF_3 Pyrazoles

Dans cette troisième partie, les travaux portent sur la synthèse de 5-OCF_3 pyrazoles. Le but étant de construire des building blocks fonctionnalisables par la suite, nous avons décidé de nous intéresser à la synthèse de pyrazoles comportant des groupements fonctionnels variés et modifiables. A ce jour, aucune synthèse de trifluorométhoxy pyrazoles n'a été décrite.

Il avait précédemment été décrit par notre groupe[12] qu'il était possible, en utilisant la méthode développée par T. Hiyama[13] sur des composés aliphatiques et aromatiques, de construire un groupement –OCF_3 en position 4 d'un pyrazole (Schéma 3). Le 4-hydroxy pyrazole **20** a été transformé par construction d'un groupement dithiocarbamate en présence de thiophosgène de et de thiométhanolate de sodium pour obtenir **21**. Ensuite, ce pyrazole a été soumis à des conditions de fluoration oxydante en présence de HF/pyridine 70% et de *N,N*-dibromohydantoïne afin d'obtenir le 4-trifluorométhoxy pyrazole **23** en 44% de rendement après une débromation réductrice en présence de zinc.

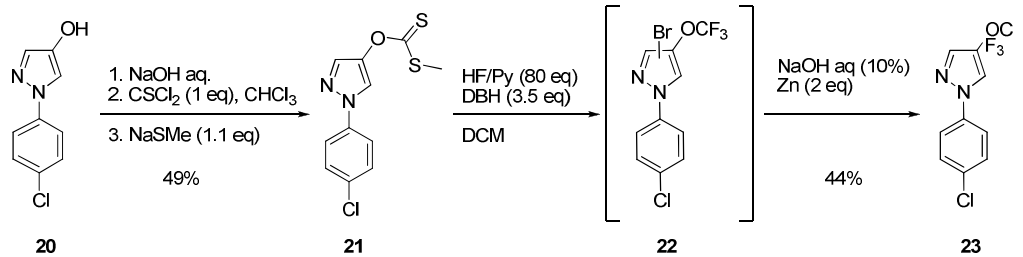


Schéma 3: Préparation d'une 4-OCF_3 pyrazole

Etant donné les rendements modérés de ces deux étapes, nous avons décidé de nous intéresser à la synthèse de 3- et 5- trifluorométhoxy pyrazoles. Notre but étant de préparer des building blocks non fonctionnalisés, nous avons commencé notre étude avec des 5-hydroxy pyrazoles non fonctionnalisés. Or, nous avons réalisé que la *N*-alkylation était préférée à l'*O*-alkylation dans le cas de ces composés. Nous avons donc décidé d'introduire un substituant sur le cycle, et nous avons opté pour les halogènes. Nous pensions ainsi pouvoir construire un thiocarbamate et procéder à sa fluoration, puisque cette méthode avait fait ses preuves pour la préparation de 4-OCF_3 pyrazoles.

Les pyrazoles de départ sont synthétisés en faisant réagir la *N*-méthylhydrazine **24** sur le diéthyl (éthoxyméthylène)malonate[14] **25** en présence de carbonate de potassium dans l'eau avec 83% de rendement (Schéma 4). L'hétérocycle est ensuite bromé en présence de *N*-bromosuccinimide sans solvant[15] avec un rendement de 92%. Enfin, le but était de convertir le groupement hydroxy en -OCF_3.

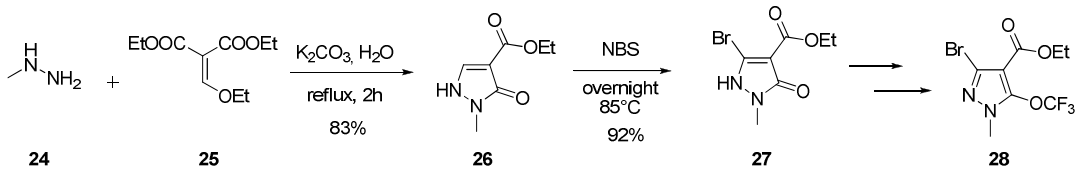


Schéma 4: Synthèse de 5-trifluorométhoxy pyrazoles fonctionnalisés

La voie de synthèse décrite ici représentait l'intérêt de donner accès à des pyrazoles fonctionnalisés portant des groupements *N*-protecteurs variés grâce à la première étape de synthèse. L'étape de fluoration n'a donné aucun résultat, malgré tous nos efforts (Schéma 5). Nous avons essayé plusieurs réactions de fluoration sans jamais toucher au but.

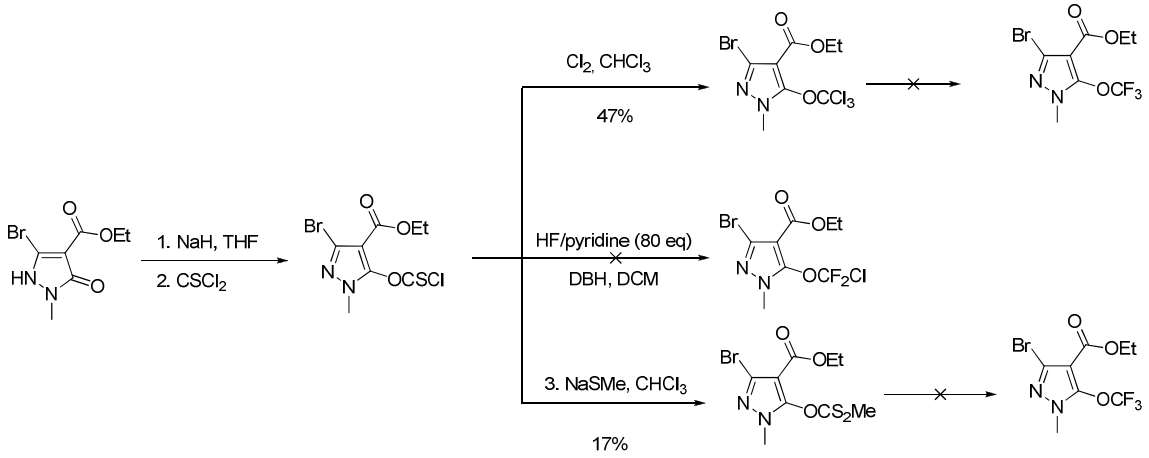


Schéma 5: Essais de fluoration de pyrazoles

Nous avons donc décidé d'abandonner ce projet au profit d'un autre plus prometteur en termes de résultats. Il serait surement plus judicieux de préparer ces building blocks *via* des produits de départ comprenant déjà le groupement trifluorométhoxy.

2. Pyridines α-Fluoro Ethers

Il existe très peu de méthodes décrites dans la littérature permettant la préparation d'aromatiques comprenant un groupement $-OCFCl_2$ ou $-OCF_2Cl$. C'est pourquoi nous nous sommes intéressés à la préparation de tels groupements sur des pyridines, ce qui n'a jamais été décrit.

2.1. $-OCF_2Cl$ Pyridines

En 1992, Hiyama[13] a décrit une réaction de synthèse de groupements trifluorométhoxy sur des alkyles (Schéma 6) : désulfuration/fluoration oxydante. Cette réaction a été décrite pour la première fois sur des pyridines par notre groupe.[16]

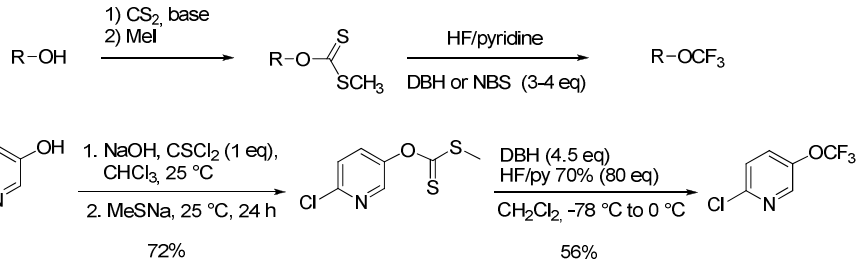


Schéma 6: Réaction d'Hiyama

Nous avons directement soumis les chlorothionoformiates à ces conditions afin de voir si on pouvait s'arrêter au groupement chlorodifluorométhoxy (Schéma 7). Après plusieurs essais, nous avons pu obtenir les molécules voulues avec des rendements satisfaisants, avec la synthèse d'un groupement $-OCF_2Cl$ inédite sur de telles molécules, puisque l'insertion sélective de deux atomes de fluor est très délicate.

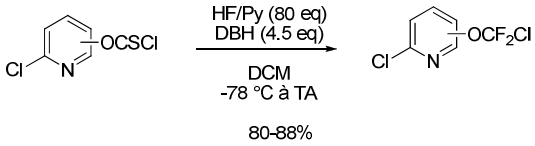


Schéma 7: Synthèse de $-OCF_2Cl$ pyridines

Afin de diminuer les quantités de réactifs utilisés, nous avons optimisé les conditions réactionnelles, et nous avons finalement pu préparer les chlorodifluorométhoxy pyridines en présence de 20 équivalents de HF/pyridine et de 3 équivalents de DBH.

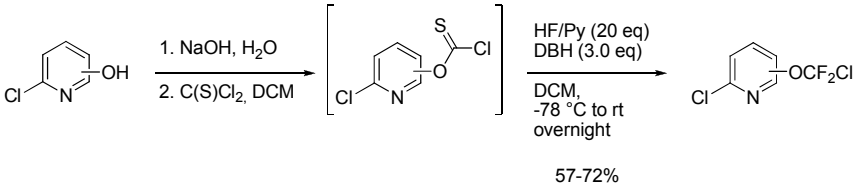
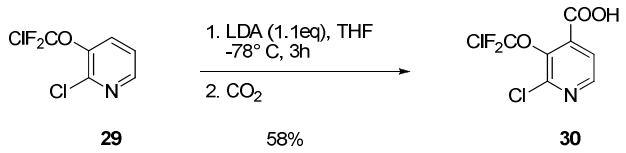


Schéma 8: Préparation de chlorodifluorométhoxy pyridines

Afin d'étudier la réactivité de ces molécules, nous avons procédé à une métallation de la 2-chloro-3-chlorodifluorométhoxy pyridine **25** en présence de Lithium diisopropyl amine (LDA)

suivie d'une carboxylation avec CO_2 afin d'obtenir l'acide carboxylique **26** correspondant (Schéma 9).



29 58% **30**

Schéma 9: Carboxylation d'une –OCF_2Cl Pyridine

2.2. –OCF_2Cl Pyridines

Nous avons également étudié la synthèse sélective d'un groupement dichlorofluoro--méthoxy. L'idée ici était de substituer sélectivement un atome de chlore par un atome de fluor sur un groupement trichlorométhyl éther, ce qui avait été décrit sur des trichlorométhoxy benzènes.[17]

Après optimisation de la réaction, cette insertion d'un seul atome de fluor a été observée avec un très bon rendement (Schéma 10) en présence de $(HF)_3/Et_3N$, alors qu'aucune réaction n'a eu lieu avec HF/pyridine.

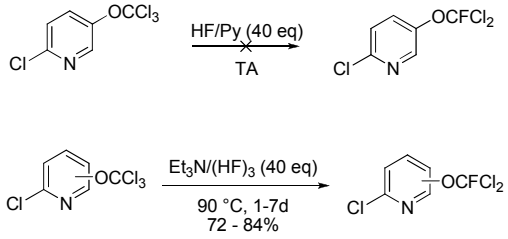


Schéma 10: Synthèse de dichlorofluorométhoxy pyridines

Encore une fois, il est important de souligner la nouveauté de cette réaction, puisqu'elle n'avait jamais été réalisée sur un hétérocycle auparavant, et qu'aucune réaction connue ne permet l'insertion sélective d'un atome de fluor.

3. 3,5-Bis(fluoroalkyl) Pyrazoles

Dans le cadre de ce projet, nous avions pour but de développer un accès à des pyrazoles comprenant deux groupements fluorés différents, ce qui est très peu décrit dans la littérature. Il existe quelques exemples de pyrazoles comprenant deux groupements fluorés en position 3 et 5 de l'hétérocycle, et ces deux groupements sont toujours identiques sauf dans le cas d'un brevet.[18] Celui-ci décrit la synthèse de 5-trifluorométhyl pyrazoles dont la position 3 est un groupement méthyle ou un groupement aldéhyde qui est fluoré en présence de trifluorure de diethylamino sulfure (DAST) pour donner respectivement un groupement $–CFH_2$ ou $–CF_2H$.[19]

Deux stratégies ont été pensées : la première était de partir d'un building-block qui serait fluoré lors d'une étape de la synthèse, et la dont dernière étape serait la cyclisation (Schéma 11). Cela permettrait d'avoir une grande diversité de produits finaux, puisque l'introduction du nombre d'atomes de fluor se ferait à volonté à partir de produits chlorés ou bromés.

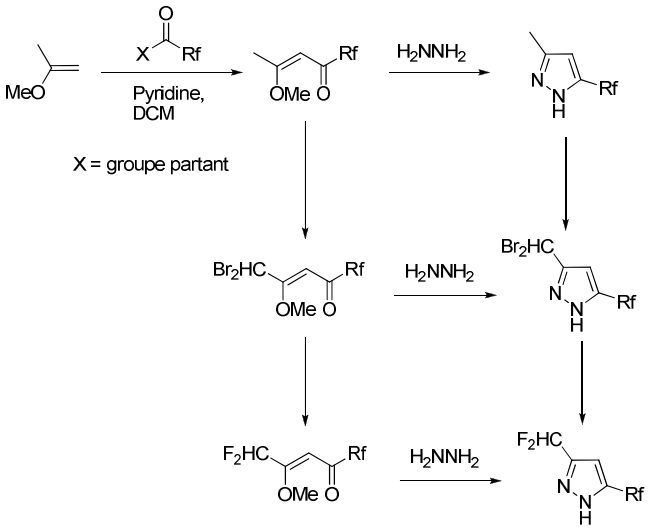


Schéma 11: Première stratégie pour la synthèse de 3,5-bis(fluoroalkyl) pyrazoles

Dès les premiers essais, nous avons rencontré de nombreux problèmes lors de la bromation ou de la chloration des produits en vue de faire une fluoration. Dans le cas de la bromation de l'énone non cyclisée, nous obtenions dans différentes conditions un mélange inséparable des produits monobromé et dibromé. Dans celui du pyrazole protégé, il ne nous a jamais été possible d'observer une quelconque bromation, aussi bien en présence de NBS/AIBN que de dibrome (Schéma 12).

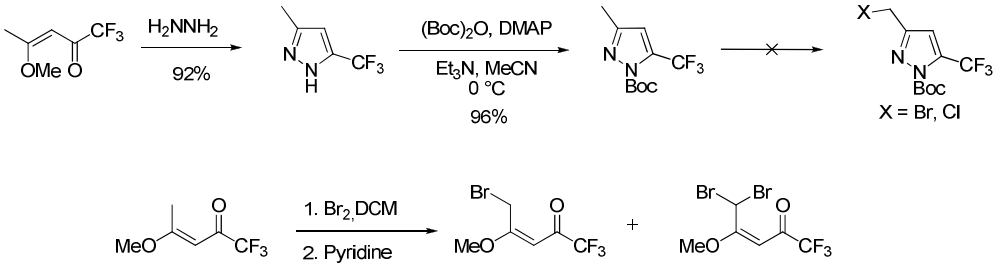


Schéma 12 : Tentatives de bromation de précurseurs et de pyrazoles protégés

Nous avons finalement décidé d'abandonner cette première voie et de se tourner vers la seconde stratégie de synthèse. Les essais ont été menés en parallèle, et celle-ci s'est révélée plus prometteuse. Elle consiste en l'utilisation d' α,α-Fluoroalkyl Amino Reagents (FAR). Ce sont des amines perfluorées couramment utilisées dans la fluoration d'alcools et de groupements carbonylés (Schéma 13).[20]

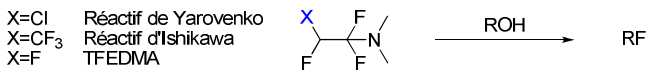


Schéma 13 : Réactifs FAR

Mais il a récemment été découvert que ces réactifs, notamment la 1,1,2,2-tetrafluoroethyl-*N,N*-dimethylamine (TFEDMA), peuvent également servir à l'introduction d'un groupement difluorométhyl (Schéma 14).[21]

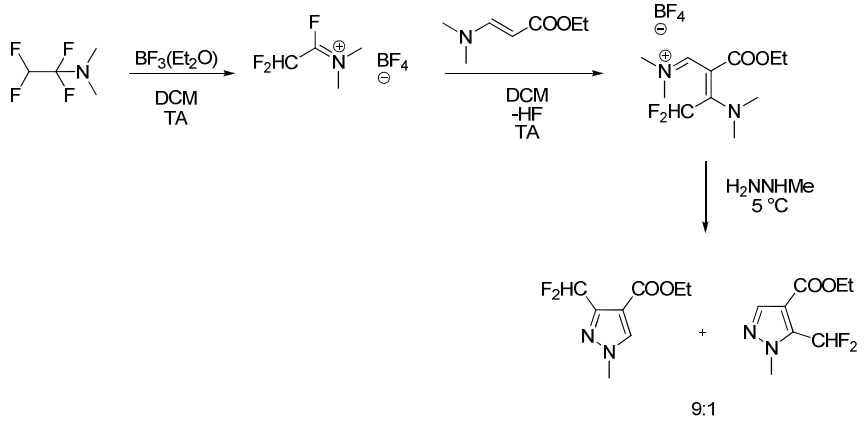


Schéma 14 : Utilisation de TFEDMA pour l'introduction d'un groupement fluoré

Ici, on peut voir que la TFEDMA activée par le trifluorure de bore peut être attaquée par l'énaminone afin de former une énaminone fluorée après élimination d'une molécule d'acide fluorhydrique. Celle-ci sera elle-même attaquée par l'hydrazine afin de former la pyrazole fluorée désirée en un mélange inséparable de deux isomères.

Dans ce projet, notre but était d'utiliser un acétoacétate comprenant déjà un groupement fluoré à la base afin de pouvoir synthétiser des pyrazoles portant deux groupements différents aux positions 3 et 5 du cycle (Schéma 15).

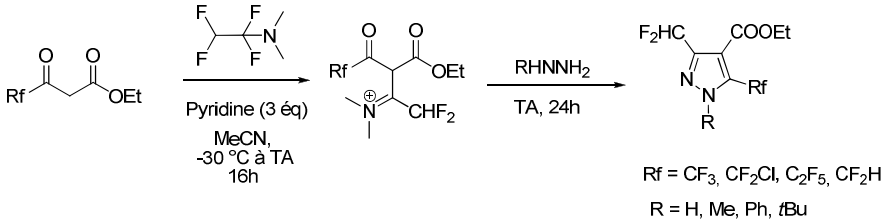


Schéma 15 : Synthèse de 3,5-bis(fluoroalky)l pyrazoles

Après optimisation des conditions réactionnelles, nous avons pu obtenir des rendements de 29 à 85% pour l'étape de cyclisation en fonction de l'hydrazine et de l'acétoacétate fluoré utilisés. De plus, celle-ci se fait de manière totalement régiosélective, et l'unique régioisomère formé est le 3-CHF_2-5-Rf pyrazole.

Dans les étapes suivantes, nous souhaitions trouver un moyen de saponifier et décarboxyler l'ester présent en position 4. Nous avons donc effectué la saponification de l'ester, et les acides carboxyliques ont été obtenus avec de très bons rendements allant de 90 à 99%. Par contre, l'étape de décarboxylation des pyrazoles nous a posé beaucoup plus de problèmes. En effet, nous avons commencé par des conditions classiques (HCl, EtOH), et n'avons observé que la dégradation des produits. Nous avons donc essayé plusieurs conditions décrites dans la littérature[22] : Catalyses Ag_2CO_3/AcOH, AgOAc/K_2CO_3, Cu/quinoléine, CuI/NMP, Cyclohénone / Cyclohexanol, et une réaction tandem décarboxylation / bromation en présence de NBS et de $NaHCO_3$. Toutes ces procédures ont conduit soit à la dégradation soit à une récupération totale du produit de départ.

Finalement, une décarboxylation décrite par Goossen *et al.*[22d] sur des composés aromatiques en présence d'une quantité catalytique de Cu_2O (5 mol%) et de 1,10-phénanthroline (10 mol%) dans un mélange de NMP-quinoléine (3 :1) nous a permis d'obtenir les produits décarboxylés avec des rendements allant de 50 à 88% (Schéma 16).

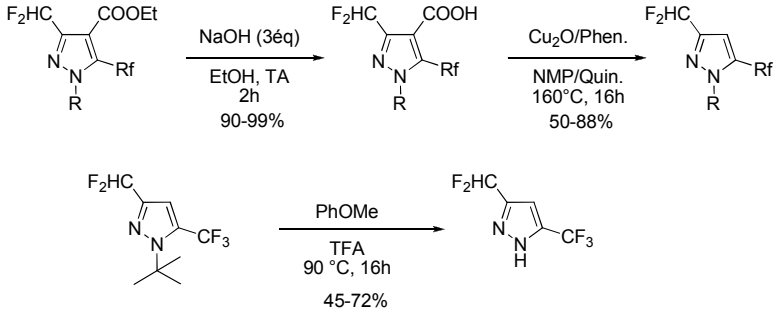


Schéma 16 : Décarboxylation et N-déprotection des pyrazoles fluorés

Malgré ce succès, nous avons observé la dégradation des pyrazoles comprenant un substituant $-CF_2Cl$, et la saponification n'a pas fonctionné sur les *N*-H pyrazoles. C'est pourquoi nous avons travaillé sur les *N*-*t*Bu pyrazoles afin de les déprotéger après l'étape de décarboxylation. Cette déprotection a été effectuée avec succès sur deux produits (Schéma 16) avec des rendements de 46 et 72%.

En conclusion, nous avons travaillé sur deux types d'hétérocycles : les pyrazoles et les pyridines. Ces travaux nous ont permis de développer des vois d'accès faciles, rapides et adaptables à grande échelles à des pyridines et des pyrazoles comportant plusieurs groupements fluorés.

Tout d'abord, nous avons pu valoriser la méthode qui avait précédemment été développée au laboratoire pour la synthèse de trifluorométhoxy pyridines. Pour ce faire, nous avons préparé des analogues trifluorométhoxylés de l'Imidaclopride et de la Thiaclopride. Ceci nous a permis d'évaluer l'influence de la substitution de l'atome de chlore par un groupement trifluorométhoxy sur l'activité biologique de la molécule. Dans ce cas, l'activité a été diminuée par la présence du trifluorométhoxy, mais il est certain que dans d'autres cas il pourra avoir une influence positive. Nous avons également mis au point une voie de synthèse de la trifluorométhoxy « Magic Pyridine », ce qui permettra son utilisation pour la préparation de produits biologiquement actifs.

Dans un second projet, nous avons développé une méthode pour la construction de groupements chlorodifluorométhoxy et dichlorofluorométhoxy sur des pyridines. Ceci a été fait en une ou deux étapes à partir des hydroxy pyridines commerciales avec de bons rendements.

Enfin, nous avons mis au point une voie d'accès à des pyrazoles portant deux groupements fluorés différents aux positions 3 et 5 du cycle. La régiochimie de la cyclisation est contrôlée, avec l'obtention d'un seul régioisomère. De plus, le développement d'une séquence de saponification/décarboxylation nous a permis d'accéder aux pyrazoles non substitués en position 4, ce qui ouvre de nombreuses possibilités en vue d'une fonctionnalisation ultérieure.

Ainsi, nous avons pu donner de nouveaux outils de synthèse pour la préparation de composés biologiquement actifs comportant des pyrazoles ou des pyridines fluorés.

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Chapter 1. General Introduction

1.1. General information

1.1.1. Discovery of fluorine

"The whole world admired the exceptional experimental skills with which you have isolated and studied fluorine, this ferocious animal among the elements." Pr. P. Klason, president of the Royal Swedish Academy told Henri Moissan when he received his Nobel Prize in November 1906.

On the 28th of June, 1886, Henri Moissan had performed the first isolation of fluorine (F_2).[1] In a U-tube platinum apparatus at low temperature (-50 °C), a solution of hydrogen fluoride and potassium bifluoride (KHF_2) was electrolysed. A colourless gas was observed at the anode of the electrolyser, which was identified as fluorine.[2]

This represented the first step towards modern fluorine chemistry. After that discovery, fluorine was mostly used for metallurgy purposes, and mostly metallic fluorides have been studied.

Organofluorine chemistry emerged in the mid 1950's, with the discovery of antitumoral properties of fluoro-uracil and the drastic improvement of the biological activity of corticoids by introduction of a fluorine atom.[3] These were the first proofs that the presence of a single fluorine atom could have a profound influence onto the behaviour of molecules in a biological environment.

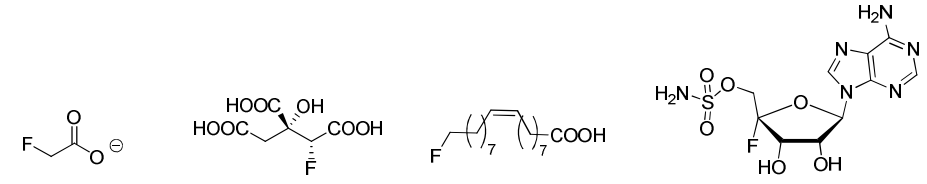
Despite this remarkable discovery, organofluorine chemistry was not developed until the 1970's. This might be due to the fact that medicinal chemists are often inspired by nature, and that one of the few natural fluorinated compounds was fluoroacetic acid. Given that it is a powerful poison, one can understand that it was not inspiring.[4]

1.1.2. Fluorine in nature

Natural organic compounds bearing fluorine are rare, compared to the chlorinated, brominated and iodinated ones which can be found in nature.[5] To give an order of comparison, ca. 3000 natural products have been reported to contain halogens, and only ca. 13 have been reported to contain fluorine.

Even if fluorine is the 13th most abundant element in the Earth's crust (much more than chlorine and bromine), it is mostly found as minerals which are insoluble in water. This induces that fluorine is not available to living organisms, hence it cannot be found in numerous natural products.[6]

Among fluoroorganic compounds, the most famous is certainly fluoroacetate **1**, which has been identified in 1943 (Figure 1.1). It is present at low concentrations in a wide variety of plants, and can be found at high concentrations in 35 species of plants, mostly in the south hemisphere, which are known as fluoroacetate-accumulating plants.[5]

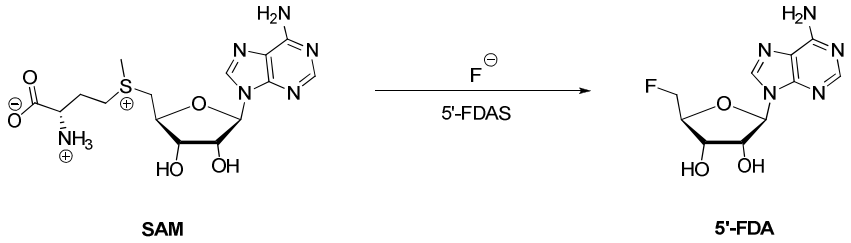


Fluoroacetate **1** (2*R*, 3*R*)-Fluorocitrate **2** *ω*–fluorooleic acid **3** Nucleocidin **4**

Figure 1.1: Fluorinated natural products

Fluoroacetate is converted *in vivo* in (2*R*, 3*R*)-fluorocitrate **2**, therefore many plants which contain fluoroacetate also contain **2**, which also presents acute toxicity. The seeds of a shrub found in western Africa, *Dichapetalum toxicarum*, are frequently the origin of livestock losses. The responsible poison in these seeds has been found to be ω-fluorooleic acid **3**.

Nucleocidin **4** has been isolated from a bacterium, *Streptomyces calvus*, found in an Indian soil sample. D. O'Hagan and coworkers studied the bacterium *Streptomyces cattleya* which secretes fluoroacetate when grown in presence of fluoride anions. Its ability to synthesise fluorinated compounds was demonstrated, and the enzyme 5'-fluoro-5'-deoxyadenosine synthase (5'-FDAS) was isolated (Scheme 1.1).[7]



Scheme 1.1: Fluorination of S*-adenosyl*-L*-methionine (SAM)*

5'-FDAS is responsible for the catalysis of the formation of C-F bonds: *S*-adenosyl-*L*-methionine (**SAM**) has been fluorinated in presence of 5'-FDAS and fluoride anions, releasing *L*-methionine and 5'-fluoro-5'-deoxyadenosine (**5'-FDA**).

Given the very little occurrence of fluorinated compounds in nature, methods for producing fluorinated molecules have been and are currently developed by man. Research for the construction of various types of fluorinated substituents is very important, especially when one realises that introduction of fluorine into agrochemical and pharmaceutical candidates has become common.

1.2. Fluorine in agrochemistry and pharmaceutical chemistry

Indeed, numerous agrochemical and pharmaceutical ingredients contain one or more fluorine atoms. It can be found as a single fluorine atom, a trifluoromethyl group and more scarcely as a trifluoromethoxy or a difluoromethyl substituent for instance.

Because of its properties, fluorine is often used in agrochemical research (Figure 1.2). Several insecticides present fluorinated substituents: the pro-insecticide Chlorfenapyr (BASF) contains a pyrrole core bearing a trifluoromethyl substituent. Fipronil (BASF) contains a trifluoromethyl sulfinyl pattern, and Tefluthrin (Syngenta) also presents a trifluoromethyl and a perfluorobenzyl substituent. The fungicide Bixafen (Bayer CropScience) contains a pyrazole pattern bearing a difluoromethyl group, and the herbicide Fludioxonil (Syngenta) a benzodioxole moiety bearing a *gem*-difluoride.

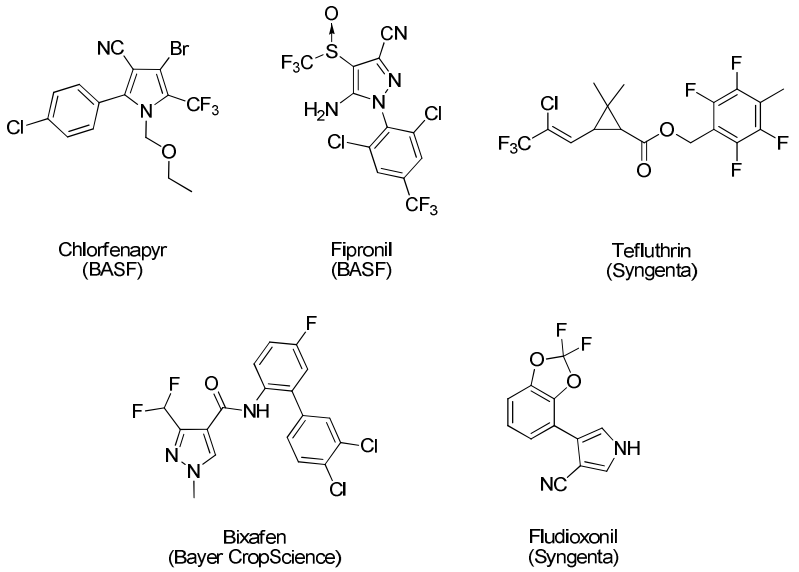


Figure 1.2: Pesticides bearing fluorinated substituents

In addition, the introduction of a fluorinated substituent is commonplace in pharmaceutical research, during structure-activity relationship studies (Figure 1.3). This has been the case of the anti-inflammatory agent Celecoxib (Pfizer) and the "block buster" Fluoxetine (Eli Lilly, Prozac®) used for the treatment of obsessive-compulsive disorder and bulimia. Similarly, Efavirenz (Bristol-Myers Squibb, Sustiva®), a non-nucleoside reverse transcriptase inhibitor used in the treatment of patients with HIV, contains a trifluoromethyl group attached to a stereogenic centre.[8]

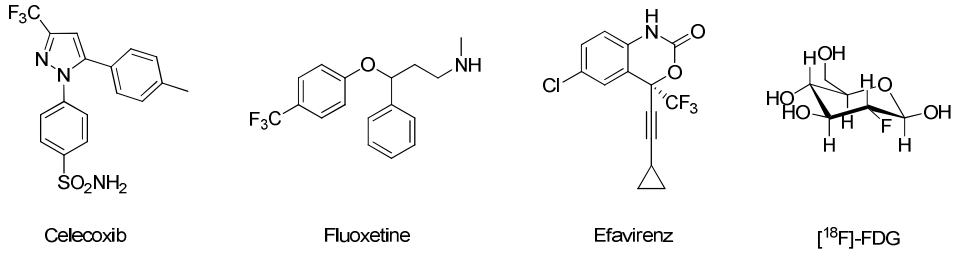


Figure 1.3: Pharmaceuticals bearing fluorinated substituents

The few examples showed here are far to be exhaustive. Indeed, fluorinated molecules find applications in the treatment of cardiovascular diseases, in antipsychotic drugs, as well as in the treatment of diabetes and hypercholesteremia.[9]

Fluorine is also found in the field of medical imaging. Its radioactive isotope is used in positron emission tomography (PET imaging). Radiolabelling of molecules with ^{18}F allows, among other applications, medical diagnosis as a non-invasive imaging technique. For example, PET imaging using [^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]-FDG, Figure 1.3) allows the detection of several types of human tumours.[10]

To conclude, fluorinated molecules are a very important class of compounds, as they represent ca. 20% of all marketed pharmaceuticals. This is even more important in the agrochemical area, as around 30% of all marketed active ingredients contain at least one fluorine atom.[11]

1.3. Properties of fluorine

"Fluorine leaves nobody indifferent; it inflames emotion, be that affections or aversions. As a substituent it is rarely boring, always good for a surprise, but often completely unpredictable."[12]

What is so exciting about fluorine? What causes its influence onto the biological properties of a molecule?

First of all, fluorine is the most electronegative of all the elements (4.0, Pauling scale). This has a great influence on the electron distribution in a molecule. Hence, its electronic effects are numerous: it stabilises α-carbocations and destabilises β-carbocations, it can have +M and +I effects in aromatic rings.[13] But the high electronegativity of fluorine is more importantly demonstrated by its effect on the acidity of vicinal functional groups.[14]

In addition, fluorine has a small van der Waals radius (1.47 Å), situated between that of hydrogen (1.20 Å) and oxygen (1.52 Å): it is the second smallest element after hydrogen. Hence, it can replace a hydrogen atom or a hydroxy group, as its volume is not much different.

These two physical properties of the fluorine atom involve several consequences onto the physicochemical properties of molecules that are useful in the design of bioactive molecules.

1.4. Influence of fluorine on bioactive molecules

1.4.1. Influence on the p*K*a

As fluorine is the most electronegative element, its effects on the acidity of vicinal functional groups can be profound. The p*K*a of a neighbouring basic or acidic function can decrease of several *log* units.[15] For instance, the p*K*a's of acetic acid and its fluorinated analogues decrease with the introduction of fluorine atoms (Table 1-1). The same kind of influence has been shown onto basic groups, which present lower basicities with the presence of fluorine.

Entry	Acid	pKa
1	CH_3COOH	4,76
2	CH_2FCOOH	2,59
3	CHF_2COOH	1,24
4	CF_3COOH	0,23

Table 1-1: Acidities of fluorinated acetic acids

This can be very useful for the design of drugs and agrochemicals, as the change of a p*K*a can have influence onto the binding affinity of a molecule and its pharmacokinetic properties. Indeed, a basic function can be crucial for the binding of a molecule to an enzyme, but it can also limit its bioavailability due to its non-ability to go through cells membranes. Hence, the presence of a fluorine atom can help in decreasing the basicity of a functional group while keeping its affinity for the active site of the enzyme.

1.4.2. Effects on molecular lipophilicity

It is popular that fluorine increases the lipophilicity of molecules. However, this is only true when the fluorinated group is incorporated onto aromatic rings and/or next to atoms capable of π-bonding, as it decreases lipophilicity when introduced into saturated alkyl groups.[16]

A study of the influence of the replacement of a hydrogen atom by a fluorine atom on ca. 300 compounds revealed that the lipophilicities of the fluorinated molecules are roughly increased by 0.25 *log* units.[15]

Lipophilicity is a key parameter in medicinal chemistry. Low lipophilic substrates cannot go through cell membranes, thus cannot reach the active site of the enzyme. But highly lipophilic molecules can stay trapped into the lipid core or present reduced solubility limiting their bioavailability.[8] Hence, the introduction of fluorine must be submitted to a "fine-tuning" in order to find a good compromise.

1.4.3. Metabolic stability

Metabolic stability represents a challenge in a lot of drug discovery projects.[15] Bioactive molecules are submitted to changes *in vivo*, and they are metabolised prior to elimination by the living organism. Enzymes contained in Cytochrome P450 are responsible for most of the oxidative metabolism of bioactive molecules. Oxidation at strategic positions reduces their lipophilicity what facilitates their clearance.[8]

The C-F bond presents a high energy (116 kcal·mol^{-1}), and this can be exploited in order to enhance the metabolic stability of a molecule.[13] Therefore, substitution of a metabolically labile position with a fluorine atom can increase bioavailability.

However, this might cause problems in case the molecule is too stable. For instance, during the development of Celecoxib (Figure 1.3), the lead compound presented a very long half-life. Replacement of the fluorine atom of the phenyl ring (Figure 1.4) by a less metabolically stable methyl group reduced the half-life to an acceptable level.[14]

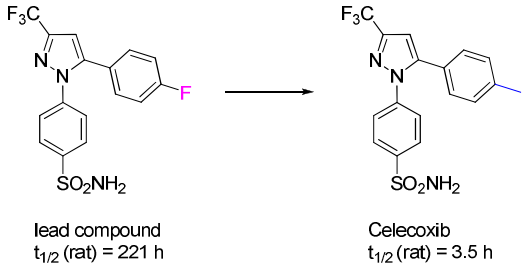
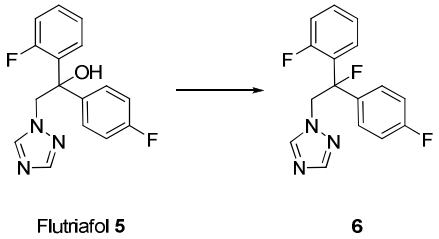


Figure 1.4: Reduction of the metabolic stability of Celecoxib

1.4.4. Steric effects and molecular conformation

Due to its van der Waals volume between that of hydrogen and oxygen, fluorine can mimic a hydrogen atom or a hydroxy substituent. Indeed, it will occupy the same volume at receptor sites, hence the binding of the molecule to the enzyme will not be dramatically changed.

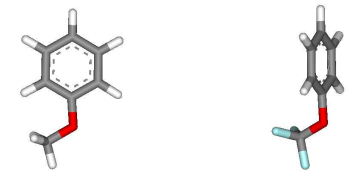
As an example, the hydroxy function in the fungicide Flutriafol **5** (Syngenta) was replaced by a fluorine atom.[13] Some bioactivity was retained, even if it was reduced (Figure 1.5).



Flutriafol **5** **6**

Figure 1.5: Replacement of a hydroxy group with fluorine

In addition, the trifluoromethyl group is believed to present quite the same van der Waals volume as an isopropyl group,[13,17] or twice that of a methyl group. Finally, the effect of fluorine substitution can be difficult to predict. For instance, methoxy benzene adopts a planar conformation when there is no *ortho* substituent. In the case of trifluoromethoxy benzene, most of the time a twisted conformation is preferred, and the dihedral C-C-O-C angle is ca. 90° (Figure 1.6).

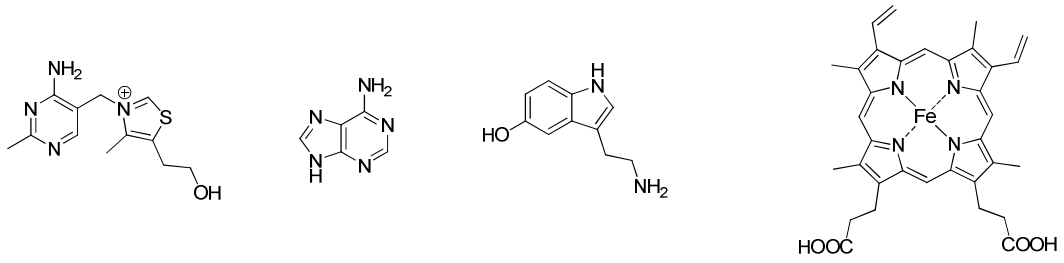


Methoxy benzene Trifluoromethoxy benzene

Figure 1.6: Preferred conformation of methoxy and trifluoromethoxy benzenes

1.5. Importance of heterocycles

Heterocycles are an exceedingly important class of compounds: they represent more than half of all known organic compounds.[18] Their importance is not only due to their abundance, but also to their significance in the chemical and the biological fields. Many natural products and most of the molecules involved in natural processes contain heterocyclic structures: vitamins, enzymes, nucleic bases, neurotransmitters, etc (Figure 1.7).



Vitamin B_1 (Thiamin) Adenine Serotonin Haem B

Figure 1.7: Natural heterocyclic-products involved in biological processes

Heterocyclic natural products have been used as drugs for centuries. For instance, South American natives already used cinchona bark before arrival of the Spanish colonists. It was brought to Europe by Jesuits around 1640, and has been widely used as an anti-malarial agent. But it was only in 1820 that quinine was isolated as the active ingredient.[19]

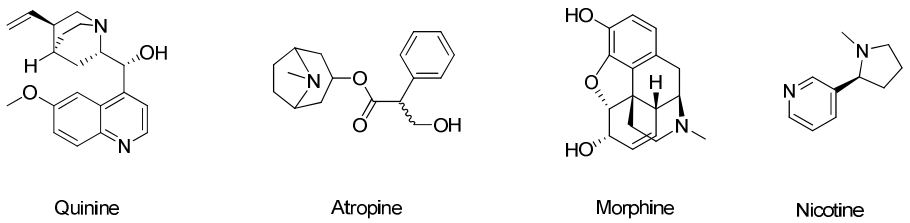


Figure 1.8: Natural alkaloids used as drugs and pesticides

Quinine is an isolated example, but numerous natural products have been used as drugs for centuries, mainly alkaloids isolated from plants: morphine, codeine, atropine, etc. (Figure 1.8). Similarly, natural products have also been used in agriculture: nicotine has been used as an insecticide.

These heterocycles are widely spread across natural products because they are able to be involved in a wide range of reaction types.[18] Due to the presence of the heteroatom, they can behave as acids or bases, depending on the medium. In addition, some of them can be the target of electrophilic reagents, whereas others are able to undergo nucleophilic attack. Some heterocycles will be readily oxidised and able to resist reduction, and it will be the contrary with others. Finally, all of these properties, depending on the electronic distribution into the heterocycle, will influence the biological activity of heterocyclic molecules.

As the aim of chemists is to produce compounds which are active *in vivo*, the easiest way to do this is to mimic nature. Hence, heterocycles are widely represented among synthetic bioactive compounds. As an example, in 2007, among the top 100 best selling drugs in the US, 71 contained a heterocycle.[19] In addition, the same kind of trend can be observed in agrochemistry.

As an edifying example, some of the biggest commercial products contain heterocyclic structures.[20] The cholesterol reducer Atorvastatin (Lipitor®, Pfizer), used to prevent cardiovascular diseases is the best-selling drug in the US and is a heterocyclic compound (Figure 1.9). Similarly, the broad-spectrum fungicide Azoxystrobin (Amistar®, Syngenta) contains a heteroaromatic ring.

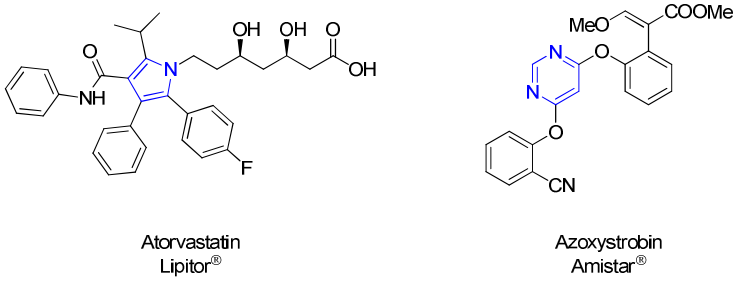


Figure 1.9: Pharmaceuticals and agrochemicals containing heteroaromatics

Finally, we can claim that heterocycles are widespread among biologically active molecules and that agrochemical and pharmaceutical research could not do without this class of compounds. More precisely, heteroaromatic structures such as pyridines, pyrazoles and pyrimidines are numerous and present interesting properties.[13]

1.6. Objectives

Having realised the importance of heterocyclic compounds in agrochemical and pharmaceutical research, it appears clearly that providing synthetic methods for such compounds bearing novel substituents is very important.

In addition, we have detailed the several properties that the presence of a fluorine atom can confer to a molecule. Indeed, fluorine can increase lipophilicity of the molecule, it can block metabolically labile positions, it influences the p*K*a of vicinal functional groups, and it can change the conformation of a molecule, and thus influence its binding onto the active sites of enzymes.

As heterocycles have proven to have biological activity, the introduction of fluorine can enhance this activity. In order to be able to join the advantages of heterocyclic structures and of fluorine, developing methods for the preparation of heterocyclic compounds bearing diversely fluorinated substituents is essential.

Approaches allowing the preparation of heterocyclic molecules bearing a single fluorine atom or a trifluoromethyl group have been widely studied.[21] There is a critical need of novel accesses to less common fluorinated substituents in order to provide a wider panel of fluorinated heterocycles for the preparation of active ingredients. As an example, the trifluoromethoxy and difluoromethyl substituents are scarcely described on heterocycles.[21, 22]

The two possible approaches towards heteroaromatic fluorinated building blocks consist in (1) the construction of the fluorinated substituent on the heterocycle and (2) cyclisation leading to the heterocycle using fluorinated precursors. When the fluorinated group is constructed onto the heterocycle, issues are often brought by the fluorinating reagent, which is either expensive and scarcely available, or not suitable for a scale-up. When fluorinated precursors are used the usual issue is regioselectivity, as cyclisations can often occur through several pathways and one has to find a way to control it.

Hence, our objective has been to investigate several approaches for the preparation of heteroaromatic building blocks bearing fluorinated substituents. Our aim was to develop efficient and straightforward methods providing the building block in a few steps from the commercially available substrate. Ideally, the methods would be scalable, and readily transposable to an industrial scale. The research work has been divided in three different projects, consisting in the study of two kinds of compounds of agrochemical and pharmaceutical interest: pyrazoles and pyridines.

The obtention of trifluoromethoxy pyridines and a study of their reactivity have led to a library of trifluoromethoxy pyridines bearing carboxylic acids, amines and halogens.[23] In a first chapter, we will detail the research work that has been done is the continuation of this method. The aim was to valorise this method preparing trifluoromethoxy analogues of known important compounds bearing a pyridine core. The second aim of this part has been to develop an efficient access to 3- and/or 5-trifluoromethoxy pyrazoles.

In a second chapter, we will detail a study of the preparation of pyridines bearing mixed chloro/fluoro methyl ethers. We will present the several approaches we have studied and the chosen method for the preparation of $-OCF_2Cl$ and $-OCFCl_2$ pyridines.

The last chapter is dedicated to the development of an efficient approach towards pyrazoles bearing two different fluorinated substituents at the 3- and 5-positions. We will discuss the several approaches we have studied, and explain the choice of the most efficient method. Finally, we will detail how we investigated the obtention of the unsubstituted pyrazoles at the 4-position and at the nitrogen atom in order to provide an access to nude 3,5-bis(fluoroalkyl) pyrazoles with potential for further functionalisation.

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Chapter 2. Synthesis of Trifluoromethoxy-substituted Heteroaromatic Building Blocks

Among the heteroaromatic building blocks which can be found in agrochemical and pharmaceutical ingredients, pyridines and pyrazoles are widely represented. The access to their fluorinated derivatives has been extensively investigated during the last decades, as the properties of fluorine can dramatically influence the bioactivity of a molecule.[1]

In order to explore the full potential of fluorine, a lot of substitution patterns are still to explore. Indeed, the most common fluorinated substituents on these heteroaromatic building blocks are a single fluorine atom or a trifluoromethyl group, and less common fluorinated substituents are still complicated to access. Among them, the trifluoromethoxy group is becoming more and more important in agrochemical and pharmaceutical research.[2] According to the 14th edition of the Pesticide Manual,[3] only five registered agrochemicals contain a trifluoromethoxy group (Figure 2.1). Among them, the fungicide Thifluzamide (Dow), the insecticide Triflumuron (Bayer CropScience), and the herbicide Flucarbazone-sodium (Syngenta) include a -OCF_3 substituent, but on the aromatic part of the molecule, and never on the heteroaromatic moiety.

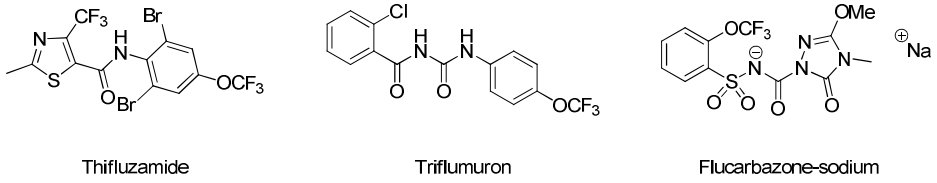


Figure 2.1 : Pesticides bearing a –OCF_3 substituent

The same conclusion can be drawn for pharmaceuticals. Indeed, Riluzole (Sanofi Aventis), a drug treating amyotrophic lateral sclerosis and Celikalim, a drug preventing cardiovascular diseases contain a trifluoromethoxy substituent, but not on their heteroaromatic part (Figure 2.2).

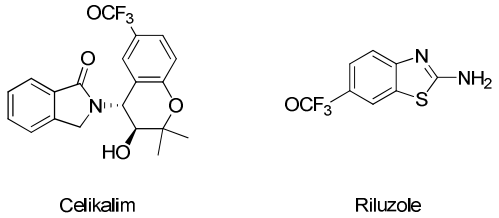


Figure 2.2: Pharmaceuticals bearing a –OCF_3 substituent

Given the importance of such pyrazole and pyridine building-blocks and the novel properties that a trifluoromethoxy group could confer to them, it is conceivable that developing a general method for their obtention would be very important for the synthesis of new bioactive molecules.

2.1. Properties of the trifluoromethoxy substituent

It has been explained earlier that the advantage of introducing fluorinated compounds into a molecule is due to its electron-withdrawing properties and to its short van der Waals radius. This influences the biological properties of molecules such as lipophilicity, p*K*a and preferred conformation. What about the $-OCF_3$ group?

We have already stated that comparison of trifluoromethoxy benzene and methoxy benzene showed that they adopt different conformations. Indeed, anisole adopts a planar conformation when there is no *ortho* substituent, whereas the trifluoromethoxy group is twisted of ca. 90° compared to the aromatic ring in trifluoromethoxy benzene.[4]

Similar conclusions have been drawn with the X-Ray single crystal analysis of several trifluoromethoxy pyridines (Figure 2.3).

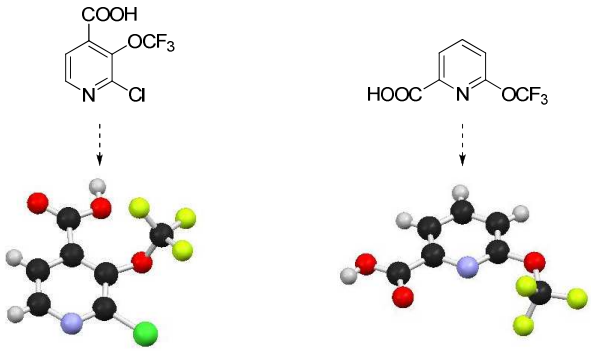


Figure 2.3: X-Ray crystal structures of OCF_3-pyridines

When the trifluoromethoxy substituent is at the 3-position of the pyridine ring, the trifluoromethoxy is perpendicular to the pyridine plane. In contrast, when it is at the 2-position, it is coplanar with the pyridine ring.[5]

Entry	Atom/group	Pauling electronegativity	Hydrophobicity π
1	H	2,1	0
2	F	4	0,14
3	Cl	3	0,71
4	Br	2,8	0,86
5	I	2,5	1,12
6	CH_3	2,3	0,56
7	*tert*-Butyl	2,3	1,98
8	CF_3	3,5	0,88
9	OCH_3	2,7	-0,02
10	OCF_3	3,7	1,04
11	SCF_3	-	1,44
12	Ph	-	1,96
13	SF_5	-	1,23

Table 2-1: Electronegativities and Hydrophobic parameters for several substituents

In terms of electronic properties, the trifluoromethoxy group is more electronegative and lipophilic than the methoxy group. It presents a high hydrophobic substituent parameter,[6]

situated between that of a CF_3 and a SCF_3 group (Table 2-1, entries 8, 10 and 11). In contrast, it is far more hydrophobic than halogens (fluorine and chlorine, entries 2 and 3). Thus, it has the ability to increase lipid solubility of molecules.

A closer look to the electron-withdrawing properties (Table 2-1) of the trifluoromethoxy group (entry 10) shows that it is comparable to chlorine or fluorine (entries 2 and 3). In addition, we can outline that it is also more electronegative than the methoxy group (entry 9). Thus, it can be predicted that due to the presence of the three fluorine atoms, the electron-withdrawing properties the $-OCF_3$ group influences the electronic distribution of molecules. In addition, the presence of the oxygen and the possibility of delocalisation of its lone-pair electrons makes that the trifluoromethoxy substituent can be considered as a π-donating substituent.

Detailed studies on benzoic acids and phenols bearing a trifluoromethoxy substituent[7] showed that the p*K*as were decreased. These electron-withdrawing properties are comparable to those of a chlorine atom. Finally, the trifluoromethoxy group present similar electronic properties to those of a chlorine or a fluorine atom.[8] In addition, studies on the p*K*a of trifluoromethoxy pyridines[5] revealed that similar conclusions could be drawn. Indeed, calculations showed that the p*K*a of 2- and 3-OCF_3 pyridines were comparable to those of fluoro, chloro and trifluoromethyl pyridines.

Hence, the trifluoromethoxy substituent has been called a super-[7b] and a pseudo-halogen[9] because of the similar electronic properties it confers to molecules compared to fluoro and chloro substituents.

2.2. State of the art

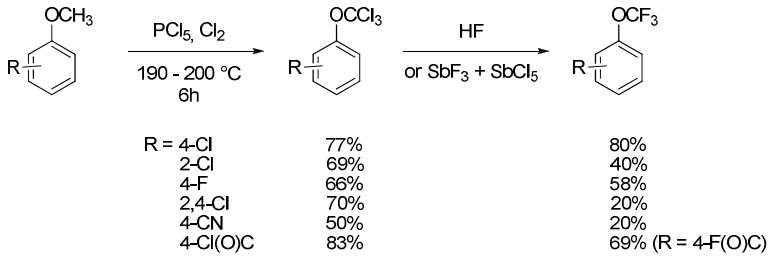
The literature reveals several methods for the introduction of trifluoromethoxy groups and most of them have been detailed in a recent review by F. R. Leroux *et al.*[10] The proportion of aromatic trifluoromethyl ethers is much higher than that of aliphatic trifluoromethyl ethers, and very few methods report on the synthesis of the latter ones. In addition, approaches for the preparation of trifluoromethoxy heteroaromatics are still very rare. For instance, syntheses of trifluoromethoxy pyridines are scarce, and the synthesis of trifluoromethoxy pyrazoles has still not been reported.

2.2.1. Preparation of trifluoromethyl ethers

2.2.1.1. Nucleophilic fluorination

Several methods have been detailed for the preparation of trifluoromethoxy groups, most of them using nucleophilic fluoride reagents for the introduction of fluorine.

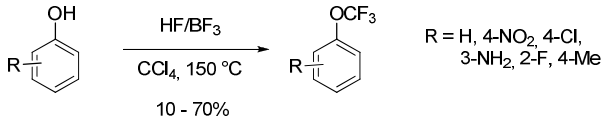
The first method for the synthesis of aromatic trifluoromethyl ethers was reported in 1955 by L. M. Yagupol'skii.[11] Starting from substituted electron-deficient anisoles, chlorination with PCl_5 and chlorine at elevated temperatures proceeded smoothly (Scheme 2.1). However, in the case of non-substituted anisole, chlorination of the aromatic ring was preferred to radical chlorination of the methoxy group.



Scheme 2.1: Chlorination/fluorination sequence developed by Yagupol'skii

Subsequent displacement of chlorine by fluorine was performed either with anhydrous HF or with antimony trifluoride (Swart's reagent) in presence of catalytic antimony pentachloride in 20-80% yield, depending on the substitution pattern of the anisole.[12] Unsubstituted anisole could be converted into the corresponding trichloromethyl ether by photochlorination in tetrachloromethane at reflux in presence of chlorine.[13]

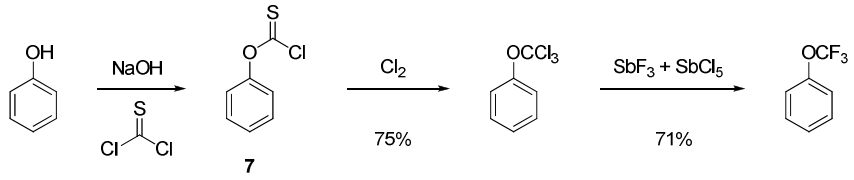
More recently, A. E. Feiring reported on the direct conversion of phenols into trifluoromethoxy-substituted aromatics.[14] Heating the starting material with anhydrous HF and boron trifluoride in tetrachloromethane in a closed pressure vessel provided the desired trifluoromethyl ethers in 10-70% yield (Scheme 2.2).



Scheme 2.2: Direct trifluoromethoxylation of phenols

However, this reaction cannot be performed on substrates which present substituents capable of hydrogen-bonding at the *ortho* position to the hydroxy group.

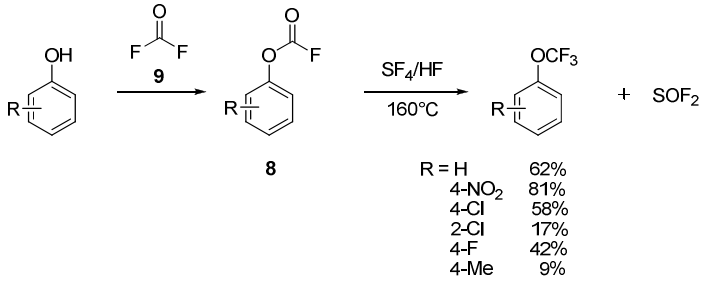
N. N. Yarovenko *et al.* described the obtention of trichloromethoxy benzene from phenol *via* chlorothionoformate **7** (Scheme 2.3). Subsequent fluorination with Swart's reagent in presence of catalytic antimony pentachloride led to the corresponding trifluoromethoxy compound in a good 71% yield.[12a]



*Scheme 2.3: Obtention of trifluromethoxy benzene via chlorothionoformate **7***

It was shown that direct fluorination of chlorothionoformates can be performed with molybdenum hexafluoride.[15] The main disadvantage of this method is the high percutaneous toxicity of the chlorothionoformate **7**.

In 1964, W. A. Sheppard showed that the synthesis of aryl trifluoromethoxy compounds was possible by an *in situ* acylation/fluorination sequence. The fluorination of fluoroformates **8** was carried out with sulphur tetrafluoride at 160 °C (Scheme 2.4).[16]



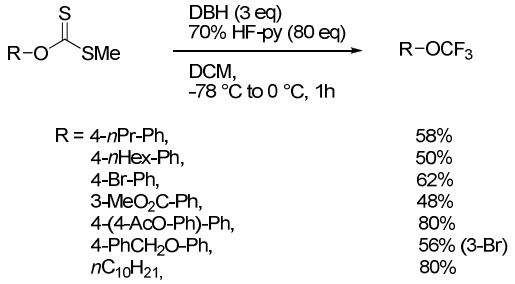
Scheme 2.4: Fluorination of fluoroformates

The fluoroformates were not isolated, and this one-pot procedure provided the trifluoromethoxy compounds in moderate to good yields. Once again, it can be underlined that the reaction proceeds more readily with electron-deficient aromatics. In addition, the process implies the use of highly toxic fluorophosgene **9** which represents an important drawback.

To conclude, we detailed several methods for the preparation of trichloromethyl ethers and their fluorination. Displacement of the chlorine atoms by fluorine with nucleophilic fluoride reagents has proven to be very efficient, and different methods using phenols or anisoles as starting materials have been developed. However, their applicability to aromatics bearing electron-withdrawing groups narrows the scope of the reaction but avoids aromatic ring chlorination. It can also be noticed that using highly toxic reagents or intermediates can be a problem. In addition, harsh conditions in terms of temperatures can be an issue with some substrates.

2.2.1.2. Fluorodesulphurisation approaches

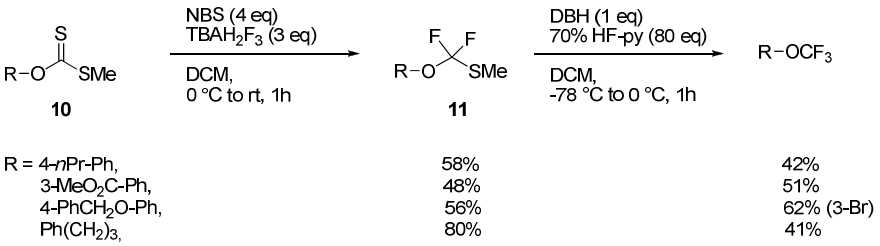
More recently, T. Hiyama *et al.* developed the synthesis of trifluoromethyl ethers from *S*-methyl dithiocarbamates (xanthogenates).[17] The latter underwent an oxidative desulphurisation-fluorination in presence of *N,N*-dimethyl-1,3-dibromohydantoin (DBH) and a large excess of 70% HF/pyridine (40-80 equivalents), which led to the corresponding trifluoromethyl ethers in moderate to very good yields (Scheme 2.5).



Scheme 2.5: Oxidative desulphurisation-fluorination of xanthogenates

To prevent bromination of the aromatic ring, only the necessary 3 equivalents of DBH for the formation of the trifluoromethoxy substituents should be used. In the case of aromatics bearing an alkoxy group, one more equivalent was necessary in order to complete the reaction. For example, the 4-benzyloxyphenyl xanthate was converted into 4-benzyloxy-3-bromo-1-trifluoromethoxy benzene in presence of 4 equivalents of DBH and 80 equivalents of HF/pyridine (Scheme 2.5).

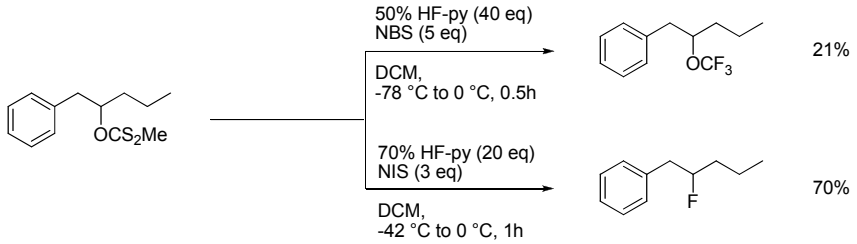
The dithiocarbamates **10** were also fluorinated with tetrabutylammonium dihydrogentrifluoride and *N*-bromosuccinimide to form difluoro(methylthio)methyl ethers **11** in moderate yields (Scheme 2.6).



Scheme 2.6: Formation of difluoro(methylthio)methyl ethers

The compounds **11** could then be transformed into the corresponding trifluoromethyl ethers in moderate yields using the previous reaction conditions with only one equivalent of DBH. For this step, bromination of the phenyl ring occurred in presence of 2 equivalents of DBH in the case of the 4-benzyloxyphenyl xanthogenate as it had been observed for the formation of the trifluoromethoxy compound.

In presence of 5 equivalents of *N*-bromosuccinimide and 40 equivalents of 50% HF/pyridine, secondary trifluoromethyl ethers were prepared from *S*-methyl dithiocarbamates (Scheme 2.7).[18] Using the same substrates with 70% HF/pyridine (20 equivalents) and *N*-iodosuccinimide, the $-OCS_2Me$ group was displaced by a fluorine atom.



Scheme 2.7: Control of the reaction of fluorination or trifluoromethoxylation

The postulated mechanism of oxidative desulphurisation-fluorination is based on the oxidation of sulphur by one of the electrophilic bromine atoms of DBH (Figure 2.4). It generates the cationic species **12** which then undergoes nucleophilic attack of a fluoride to form a C-F bond. A second reaction of an electrophilic bromine atom with the sulphur atom followed by nucleophilic attack of a fluoride anion yields the isolated difluoro(methylthio)methyl ether **11**. Subsequent oxidation/fluorination sequence on the difluoro compound provides the desired trifluoromethyl ether **13**.

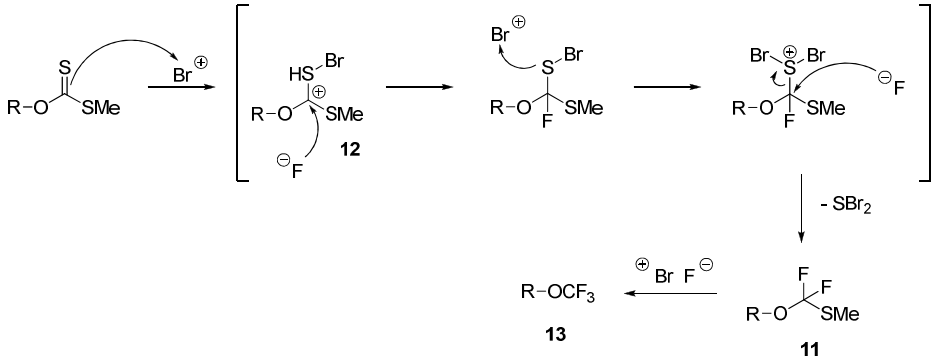


Figure 2.4: Mechanism for the oxidative fluorodesulphurisation

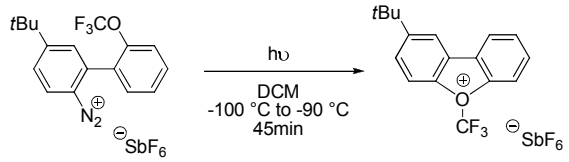
In 1999, S. Rozen and coworkers disclosed that the oxidative desulphurisation-fluorination sequence was applicable using bromine trifluoride as the source of electrophilic bromine and nucleophilic fluoride.[19] Several aliphatic compounds were successfully synthesised in excellent 78-90% yields.

As a conclusion, we can claim that oxidative fluorodesulphurisation methods are very efficient approaches for the preparation of trifluoromethoxy compounds. The mild reaction conditions are a real advantage of this method, the reaction can indeed be applied to various aliphatic and aromatic substrates without altering them. However, the use of either a huge excess of HF/pyridine or the very toxic bromine trifluoride make this method difficult to scale-up.

2.2.1.3. Electrophilic trifluoromethyl reagents

More recently, there has been a real breakthrough in study of trifluoromethyl-transfer reagents.[20],[21] It should be mentioned that the term "electrophilic trifluoromethyl transfer reagent" does not imply the fact that "CF_3^+" cations can be found in solution, but that nucleophilic entities can attack at the electrophilic CF_3 carbon to create a Nu-carbon bond.

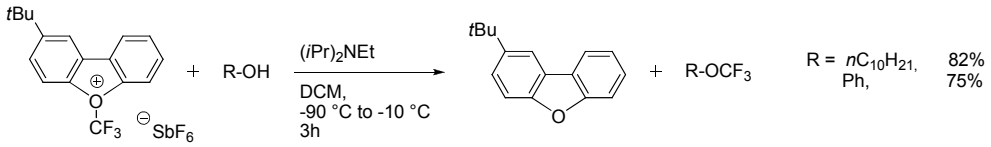
T. Umemoto reported on the synthesis of trifluoromethyl ethers *via* the use of *O*-(trifluoromethyl)dibenzofuranium salts[22] and their preparation. These compounds are unstable above -90 °C, and must be prepared *in situ* at -100 °C by photochemical cyclisation of 2-(trifluoromethoxy)biphenylyl-2'-diazonium salts **14** (Scheme 2.8).



14

Scheme 2.8: Preparation of dibenzofuranium salts

A study of the reactivity of 2-*tert*-butyl-*O*-(trifluoromethyl)dibenzofuranium hexafluoroantimonate **14** revealed that trifluoromethyl ethers could be prepared in very good yields from alcohols in presence of a base in dichloromethane at -90 °C (Scheme 2.9).

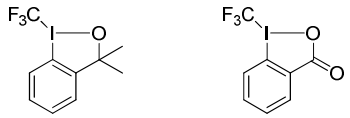


14

Scheme 2.9: Umemoto's oxonium reagent as –CF_3 transfer reagent

This method allows the synthesis of aliphatic and aromatic trifluoromethyl ethers under mild conditions, but the stability and tedious preparation of the dibenzofuranium salts limit further applications.

More recently, A. Togni *et al.* described the use of hypervalent iodine reagents as electrophilic $-CF_3$ transfer agents. Their preparation has been detailed,[23] and their reactivity towards numerous types of nucleophiles (*C*-, *O*-, *S*-, *N*- and *P*- nucleophiles) has been studied, revealing a broad scope of application. Among the several reagents that have been studied, two of them revealed to be the most active (Figure 2.5).

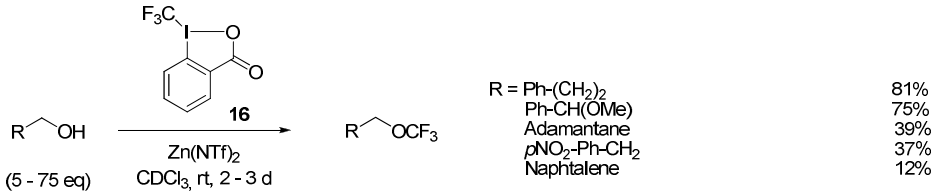


15 **16**

Figure 2.5: Togni's trifluoromethyl transfer reagents

3,3-Dimethyl-1-trifluoromethyl-1,3-dihydro-1,2-benzodioxole **15** has been mostly used to form S-, N-, P- and C-CF_3 bonds, whereas 1-trifluoromethyl-1,2-benzodioxol-3(1*H*)-one **16** has been essentially used for the formation of O-CF_3 bonds, and in a few cases for the formation of P-CF_3 bonds.[21]

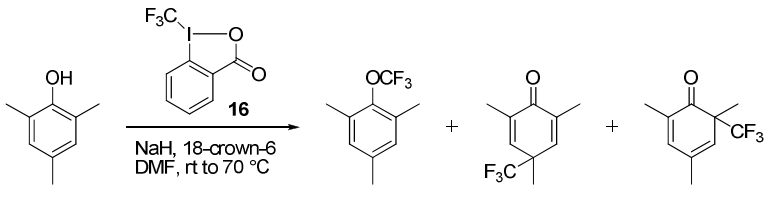
The trifluoromethylation of several aliphatic alcohols has been accomplished in low to good yields (Scheme 2.10), by reaction with **16** and one equivalent of zinc bis(triflimide) ($Zn(NTf)_2$).[24] However, so far this reagent does not allow the synthesis of aromatic and heteroaromatic trifluoromethoxy derivatives.



*Scheme 2.10: Trifluoromethylation of aliphatic alcohols with **16***

This efficient method using mild reaction conditions makes of Togni's reagent a reagent of choice for sensitive substrates. However, the protocol requires a large excess of alcohol which can be an issue.

Several aromatic substrates have been studied for trifluoromethylation with **16**,[25] and the results revealed that *O*-trifluoromethylation was in competition with aromatic trifluoromethylation. Among all the tested phenols, only 2,4,6-trimethylphenol led to *O*-trifluoromethylation product **18** in a low 15% yield under optimum reaction conditions (Scheme 2.11). In addition, the reaction was very messy.



*Scheme 2.11: Trifluoromethylation of 2,4,6-trimethylphenol with **16***

Togni's reagent has proven to have a high reactivity towards several nucleophiles for the formation of trifluoromethyl ethers, particularly aliphatic alcohols which are the most difficult to obtain.[26] However, reactions with aromatic substrates are at an early stage, and do not represent a suitable method for *O*-trifluoromethylation of phenols.

2.2.1.4. Nucleophilic trifluoromethoxy transfer reagents

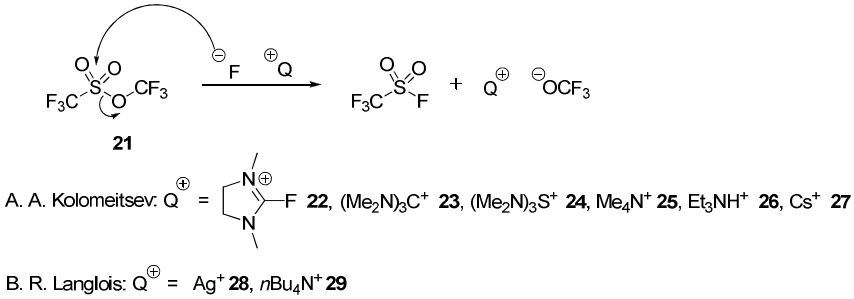
Several methods for the preparation of trifluoromethyl ethers *via* nucleophilic $-OCF_3$ transfer reagents have been reported recently. As it has been pointed out for "CF_3^+", "$^-OCF_3$" anions do not exist in solution, and must be stabilised by voluminous counter-ions in order to avoid their facile decomposition into fluoride and fluorophosgene.

Firstly, "$^-OCF_3$" anions have been generated from fluorophosgene in presence of tris(dimethylammonium) difluoro trimethylsilicate in THF at -78 °C.[27] They proved to be able to react with bromides and triflates to provide trifluoromethyl ethers.[28] However, this method requires the use of highly toxic fluorophosgene in large amounts and under pressure.

Very recently, an alternative with the use of trifluoromethyl trifluoromethanesulfonate **21** (TFMT) for the generation of trifluoromethoxide salts has been proposed.

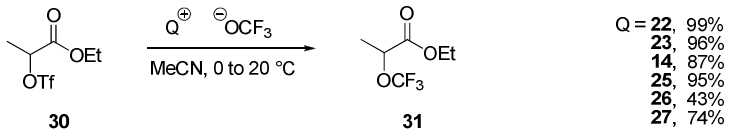
Independently and simultaneously, A. A. Kolomeitsev *et al.* and B. R. Langlois and coworkers reported on the preparation of such salts from various fluoride or difluoro triphenylsilicate salts and TFMT (Scheme 2.12).[29,30] Unlike other triflates, TFMT cannot be considered as a "$^-OCF_3$" transfer reagent by reaction with hard nucleophiles. As they usually attack on the harder electrophilic site of TFMT, which is the sulphur atom, fluoride anions were employed. Hence, nucleophilic trifluoromethoxide anions are released along with fluoride triflate (Scheme 2.12).

The use of bulky counter-ions such as tris(dimethylamino) sulfonium, dihydro imidazolium and cesium(I),[30] silver(I) and tetrabutylammonium[29] avoids the decomposition of the anion and allows its use as a nucleophilic OCF_3-transfer agent.



Scheme 2.12: Preparation of trifluoromethoxide salts

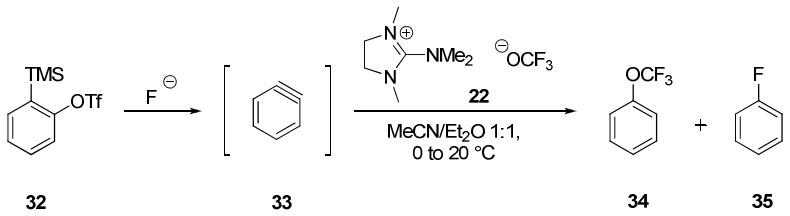
The trifluoromethoxide anion is prepared *in-situ*, and A. A. Kolomeitsev showed that subsequent reaction with the aliphatic triflate **30** provided the corresponding trifluoromethyl ether **31** in moderate to very good yields, depending on the counter-ion.



*Scheme 2.13: Trifluoromethoxylation of **30** according to Kolomeitsev*

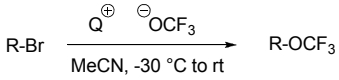
The reaction has been extended to other substrates such as electron-rich benzyl bromides and aliphatic iodides, still in very good yields. However, its application onto nitro- and chloro-aromatic substrates led to fluorination by S_NAr with 81 to 87% yield.

Interestingly, formation of the aryne **33** from Kobayashi's reagent **32** and subsequent trifluoromethoxylation in presence of the complex **22** provided a mixture of trifluoromethoxy benzene **34** and fluorobenzene **35** with 72% yield in a 85:15 ratio (Scheme 2.14). Trifluoromethoxylation of the corresponding naphthalene reagent has also been performed in 63% yield.[30]



Scheme 2.14: Trifluoromethoxylation of arynes

B. R. Langlois *et al.* observed the same kind of reactivity for tetrabutylammonium and silver(I) trifluoromethoxide salts **29** and **28**. Preparation of trifluoromethyl ethers from aliphatic bromides has been performed in moderate to very good yields (Scheme 2.15). [29]

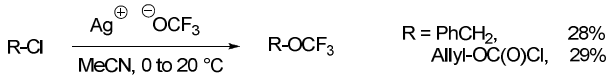


Q = nBu$_4$N, **29**		Q = Ag, **28**	
R = $PhCH_2$,	75%	R = $PhCH_2$,	100%
$Ph(CH)_2CH_2$,	53%	$Ph(CH)_2CH_2$,	57%
$PhC(O)CH_2$,	41%	$PhC(O)CH_2$,	47%
PhC(O),	100%	PhC(O),	92%
PhCH(Me),	11%	PhCH(Me),	74%
2-cyclohexene,	40%	2-cyclohexene,	44%

Scheme 2.15: Use of Langlois's silver(I) and nBu_4N trifluoromethoxide salts

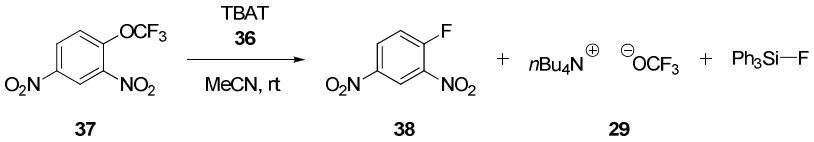
In addition, several aliphatic iodides have also been converted into trifluoromethoxy compounds by reaction with **28** and **29** in 33 to 85% yield. As a general tendency, silver(I) salt **28** led to trifluoromethyl ethers in higher yields than tetrabutylammonium salt **29**.

Finally, chlorides underwent trifluoromethoxylation in presence of the silver salt **28**. Although yields were moderate (Scheme 2.16), this proves that these reagents are powerful tools for nucleophilic trifluoromethoxy transfer onto aliphatic substrates.



*Scheme 2.16: Trifluoromethoxylation of chlorides by **28***

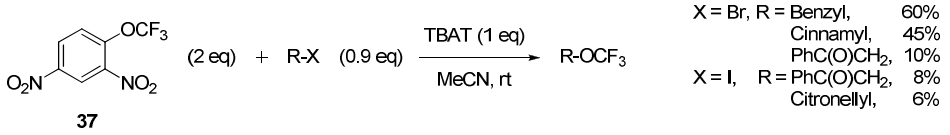
These methods proved to be very efficient for the preparation of trifluoromethyl ethers from aliphatic halides, but the reaction is limited to bench-scale as TFMT is quite expensive. Looking for an alternative, B. R. Langlois *et al.* demonstrated that *in-situ* formation of the trifluoromethoxide salt **29** by reaction of tetrabutylammonium difluorotriphenylsilicate (TBAT) **36** with 2,4-dinitro(trifluoromethoxy) benzene **37** was possible.[31]



37 **38** **29**

*Scheme 2.17: Formation of trifluoromethoxide salts via **37***

Nucleophilic attack of fluoride onto the electron-poor trifluoromethoxy benzene leads to release of a trifluoromethoxide anion and the formation of 2,4-dinitro-1-fluoro benzene **38** *via* an aromatic nucleophilic substitution (Scheme 2.17). Subsequent addition of various aliphatic bromides led to the corresponding trifluoromethyl ethers in low to good yields (Scheme 2.18).



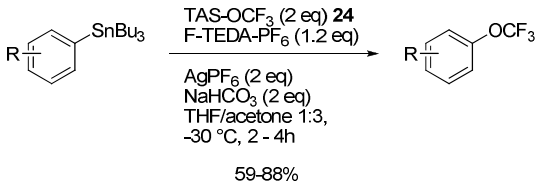
37

*Scheme 2.18: Preparation of trifluoromethyl ethers via **37***

In consequence, this alternative does not work as with TFMT to generate the trifluoromethoxide salts, but it avoids its expensive use.

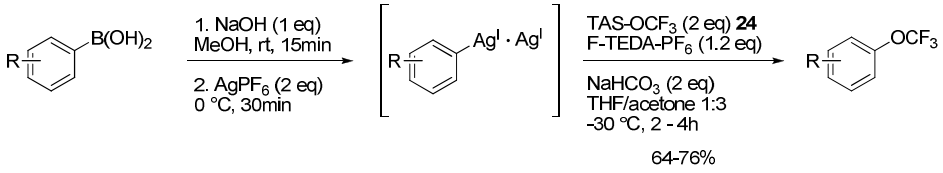
In 2011, T. Ritter *et al.* reported on a silver-mediated trifluoromethoxylation of aryl boronic acids and aryl stannanes.[32] On the same principle, a tris(dimethylamino)sulfonium trifluoromethoxide salt **24** (TAS-OCF_3) is generated *in situ* by reaction of TFMT with tris(dimethylamino) sulphonium difluorotrimethyl silicate (TASF). Treatment of aryl stannanes with **24**, silver(I) hexafluorophosphate ($AgPF_6$) and F-TEDA-PF_6 in a 1:3 THF/acetone mixture at -30 °C led to the corresponding aryl trifluoromethyl ethers in very good yields (Scheme 2.19).

5-Trifluoromethoxy-*N*-Boc indole has been prepared in 72% yield, making this protocol one of the rare trifluoromethoxylations of heteroaromatic structures, even if the fluorinated substituent is located on the aromatic moiety. In addition, this process is mild enough for the preparation of trifluoromethoxy analogues of natural products, such as a morphine derivative (59% yield) and amino acids (*N*-boc-4-OCF_3-*L*-phenylalanine methyl ester has been obtained in 75% yield).



Scheme 2.19: Silver-mediated trifluoromethoxylation of aryl stannanes

The preparation of aryl trifluoromethoxy compounds has also been obtained from boronic acids. In this case, an aryl silver complex is firstly formed by reaction of the aryl boronic acid with $AgPF_6$ in presence of sodium hydroxide (Scheme 2.20). Subsequent addition of the trifluoromethoxide salt **24** and the additive F-TEDA-PF_6 led to the desired compounds in 64 to 76% yields.



Scheme 2.20: Silver-mediated trifluoromethoxylation of aryl boronic acids

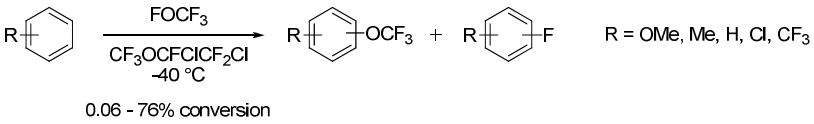
Finally, this synthesis presents a lot of advantages and is very efficient, but the uses of the expensive additive F-TEDA-PF6 and of TFMT represent a drawback.

In conclusion, these methods which have been developed only very recently, are very interesting for the preparation of aliphatic and aromatic trifluoromethyl ethers. However, the synthesis of aromatic substrates leads to fluorination of the aromatic ring unless in the case of a silver-mediated protocol. But this reaction is impossible to scale-up, as TFMT and F-TEDA-PF_6 are very expensive. In addition, an alternative to the use of trifluoromethyl triflate has been found with 2,4-dinitrotrifluoromethoxy benzene, which can be scaled-up.

2.2.1.5. Radical trifluoromethoxylation

A few years ago, S. Rozen reported that the addition of trifluoromethyl hypofluorite (F_3COF) to olefins led to the formation of aliphatic trifluoromethyl ethers *via* a radical mechanism.[33] However, the use of aromatic substrates only led to fluorination of the phenyl ring.

Very recently, W. Navarrini *et al.* described the trifluoromethoxylation of aromatic compounds by trifluoromethyl hypofluorite *via* a radical mechanism.[34] The reported results showed that trifluoromethyl ethers were obtained in a mixture with the fluorinated compounds, and conversions of the starting materials were never complete (Scheme 2.21).

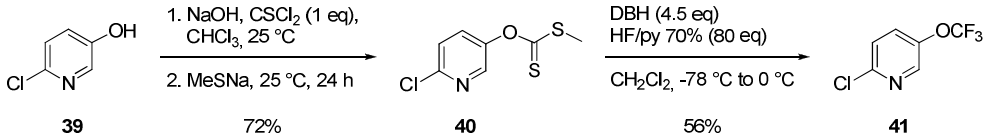


Scheme 2.21: Reaction of aromatic substrates with $FOCF_3$

Despite the interesting properties of trifluoromethyl hypofluorite, its high toxicity and the fact that it is a potential explosive are major drawbacks for further investigations.

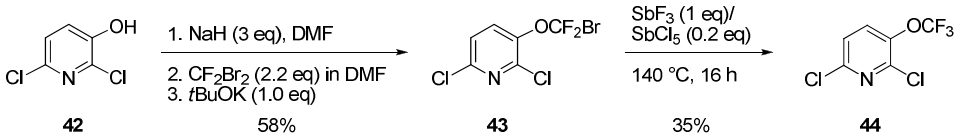
2.2.2. Synthesis of trifluoromethoxy aromatic substrates

In 2010, our group reported the first modular preparation of trifluoromethoxy pyridines.[5, 35] Firstly, construction of the *S*-methyl dithiocarbamate **40** has been performed in 72% yield from 2-chloro-5-hydroxy pyridine **39** (Scheme 2.22) by deprotonation with sodium hydroxide followed by alkylation with thiophosgene and sodium methanethiolate. Then, a desulphurisation-fluorination sequence has been applied with 80 equivalents of HF/pyridine in presence of 4.5 equivalents of DBH and provided 2-chloro-5-trifluoromethoxy pyridine **41** in 56% yield.



Scheme 2.22: Oxidative fluorodesulphurisation sequence applied to pyridines

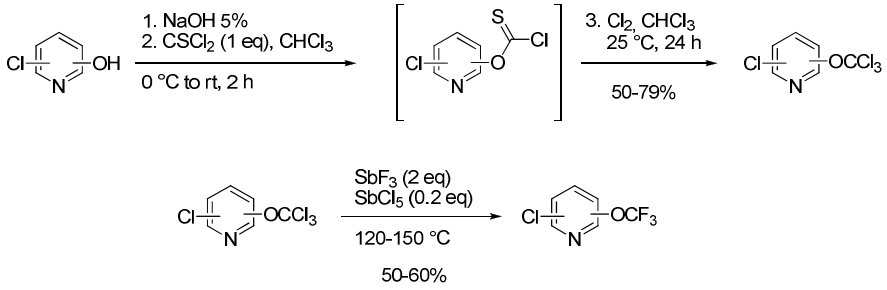
The huge excess of HF/pyridine used during the fluorination step limited the scale-up, so another approach has been studied. It consisted in the *O*-alkylation of 2,6-dichloro-5-hydroxy pyridine **42** by dibromodifluoromethane to lead to the corresponding $-OCF_2Br$ derivative **43**. Subsequent introduction of the third fluorine atom with SbF_3 in presence of catalytic $SbCl_5$ provided 2,6-dichloro-5-trifluoromethoxy pyridine **44** in 20% yield over two steps (Scheme 2.23).



Scheme 2.23: O*-alkylation with freons*

Once again, this method was not suitable for a scale-up, as freons have been recently classified as ozone-depleting substances. In addition, the low overall yield was a drawback.

Thus, another approach was investigated, based on N. N. Yarovenko's observation that phenyl chlorothionoformate **7**[12a] can be submitted to chlorination to form trichloromethoxy benzene. It was successfully applied to pyridines (Scheme 2.24): chloro-hydroxy pyridines underwent *O*-alkylation with thiophosgene, and subsequent chlorination led to the trichloromethoxy compounds in 50 to 79% yield.



Scheme 2.24: chlorodesulphurisation-fluorination sequence

The trichloromethoxy compounds were successfully converted into the corresponding trifluoromethyl ethers by reaction with antimony trifluoride and catalytic antimony pentachloride in 50 to 64% yield, depending on the position of the trifluoromethoxy substituent on the heteroaromatic ring.

It has to be noticed that the presence of the chlorine atom at the α-position to the pyridine nitrogen atom is crucial, as any of the detailed reactions occur in its absence, or when it is not at the 2-position. The presence of another halogen atom (fluorine or bromine) led to degradation of the starting material during the fluorination step.

The reactivity of these new trifluoromethoxy pyridines has been studied. By means of organometallic reagents, the building blocks bearing a trifluoromethoxy substituent at the 2-, 3-

and 4-positions have been regioexhaustively functionalised with carboxylic acids, amines, and halogen substituents.[10]

To the best of our knowledge, this approach is the only general method providing trifluoromethoxy heteroaromatic compounds which is straightforward and suitable for an industrial scale.

A few other literature examples describe the synthesis of heteroaromatic trifluoromethyl ethers, but they are only performed on selected substrates. They use Hiyama's oxidative desulphurisation-fluorination sequence[36] or *O*-alkylation with freons (difluorodibromomethane and chlorodifluoromethane) and subsequent introduction of the third fluorine atom,[37] or formation of trichloromethyl ethers followed by fluorination.[38]

2.2.3. Conclusion

We have detailed the existing methods for the preparation of trifluoromethyl ethers. Several methods have been developed, and trifluoromethoxy aromatic and aliphatic compounds are now easily accessible.

Among them, nucleophilic fluorinations represent one of the most widely used methods for the preparation of aromatic derivatives. The fluorination can be performed onto trichloromethyl ethers, fluoroformates or directly from phenols in presence of carbon tetrachloride.

The oxidative desulphurisation-fluorination sequence developed by T. Hiyama represents a good alternative under mild conditions for the construction of the trifluoromethoxy substituent. It has proven to be efficient on aliphatic and aromatic substrates. Later, S. Rozen proved that this could be performed in presence of bromine(III) trifluoride. However, the fluorinating reagent is used in large excess, and it is highly toxic.

More recently, protocols of electrophilic trifluoromethylation have been developed, based on CF_3-transfer agents. T. Umemoto used trifluoromethyl dibenzofuranium salts which proved to be efficient for the trifluoromethylation of aromatic and aliphatic alcohols. However, these reagents are unstable above -90 °C and must be prepared *in situ* by photochemical ring-closure which makes their use quite tedious and not suitable for a scale-up. A. Togni reported on the use of hypervalent iodine(III) reagents for the transfer of electrophilic trifluoromethyl groups. This allowed the preparation of several alkyl trifluoromethoxy compounds in good yields, but the reagent revealed to be unselective towards phenols which provided a mixture of *O*- and *C*-trifluoromethylation.

The development of novel nucleophilic trifluoromethoxy transfer reagents provided a new tool for the preparation of trifluoromethyl ethers. It is based on the release of a trifluoromethoxide anion, followed by trapping by bulky counter-ions to form trifluoromethoxide salts avoiding its decomposition into fluorophosgene and fluoride. Subsequent addition on substrates bearing leaving groups such as halogens and triflates provides the corresponding trifluoromethyl ethers. A. A. Kolomeitsev and B. R. Langlois successfully applied this to aliphatic substrates, but failed to prepare aromatic compounds which underwent fluorination of the aromatic ring *via* a S_NAr mechanism.

Very recently, T. Ritter *et al.* developed a silver-mediated version of this reaction which allowed the access to aromatic trifluoromethoxy compounds from stannanes and boronic acids. The mild reaction conditions are suitable for sensitive substrates, but the high prices of the

reagents, especially TFMT which is only commercially available at bench scale, are the main drawback.

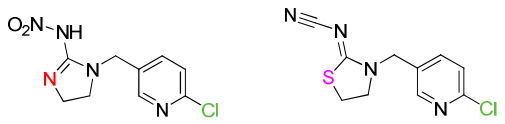
A few examples deal with the preparation of aliphatic trifluoromethyl ethers by reaction with trifluoromethyl hypofluorite. A recent description of the use of this reagent onto aromatic substrates has been reported, but the reaction is not selective. In addition, $FOCF_3$ is highly toxic and a potential explosive.

Only few references report in details the synthesis of trifluoromethoxy heteroaromatic compounds. A chlorodesulphurisation-fluorination sequence has been developed on several pyridine building-blocks, and it can be scaled-up.

With this overview of the recent literature, one can notice that the methods for the preparation of heteroaromatic building blocks bearing a trifluoromethoxy substituent are still scarce. Thus, the development of such methods is very important in order to provide new tools to synthetic chemists for the discovery of new pharmaceuticals and agrochemicals. With this aim in mind, we have used the chlorodesulphurisation-fluorination approach for the synthesis of molecules of biological interest, and we have investigated the synthesis of pyrazoles bearing a trifluoromethoxy substituent.

2.3. Towards a trifluoromethoxy analogue of Imidacloprid

Imidacloprid **45** and Thiacloprid **46** are systemic insecticides which belong to the class of neonicotinoids (Figure 2.6). They exhibit a high affinity for insect nicotinic acetylcholine receptors (nAChRs), which are located in the central nervous system of insects. In presence of Imidacloprid, these receptors are overstimulated and hence blocked, resulting in paralysis and subsequent death of the insects.



Imidacloprid **45** Thiacloprid **46**

Figure 2.6: Imidacloprid and Thiacloprid structures

Compounds **45** and **46** are active on numerous insects, but were primarily used as aphicides. Due to its broad range of bioactivity, Imidacloprid is one of the key insecticides of Bayer CropScience, and represents the most widely used insecticide in the world. Contrary to nicotine which is not selective, all the molecules from this class, including Imidacloprid and Thiacloprid have a low affinity for mammalian nAChRs, and that high selectivity makes them very attractive for agrochemical applications.

These molecules present the same pyridine core with a chlorine atom at the 2-position, and an azole moiety bearing a nitrogen-rich substituent (Figure 2.6). The only difference between the two molecules is that the azole core is an imidazoline bearing a nitroamine substituent in compound **45**, and a thiazolidine bearing a cyanamide substituent in compound **46**.

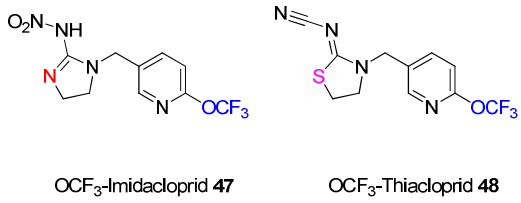
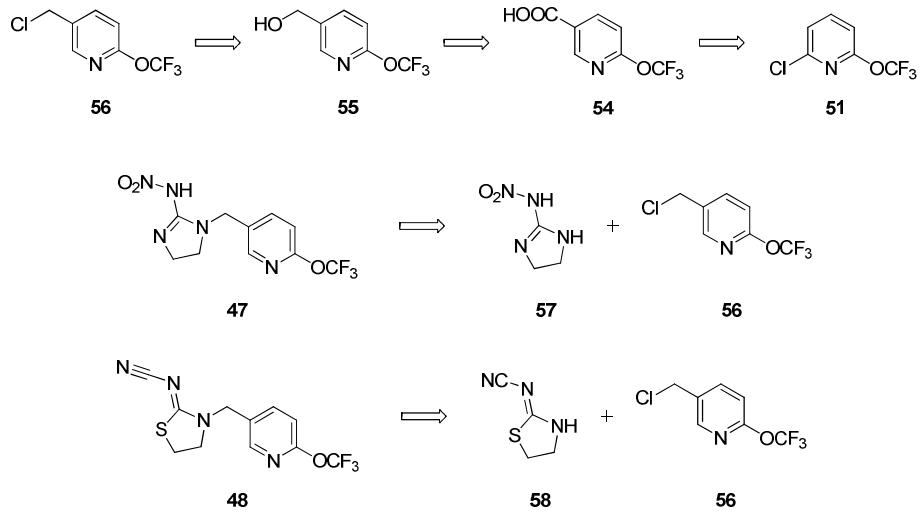


*Figure 2.7: Trifluoromethoxy analogues of **47** and **48***

Having developed an access to trifluoromethoxy pyridines, we were interested in the synthesis of trifluoromethoxy analogues **47** and **48** of Imidacloprid and Thiacloprid **45** and **46** (Figure 2.7). Given that the trifluoromethoxy substituent can be considered as a pseudo-halogen, replacing the pyridine chlorine atom with a trifluoromethoxy group would allow the comparison of biological activities.

2.3.1. Synthesis of 3-chloromethyl-6-trifluoromethoxy pyridine

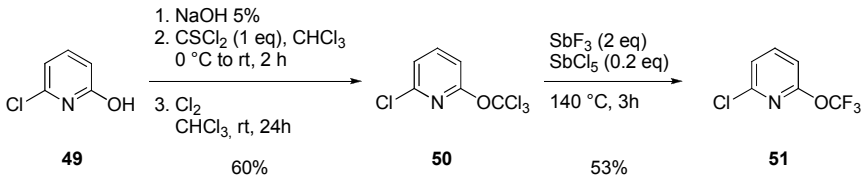
In order to access both compounds **47** and **48** (Figure 2.7), the synthesis of only one trifluoromethoxy pyridine was necessary. Indeed, Imidacloprid can be obtained by a simple deprotonation of the nitrogen atom of **58** and nucleophilic substitution of the chlorine atom of **56** (Scheme 2.25).



*Scheme 2.25: Retrosynthetic analysis of OCF3-Imidacloprid **47** and OCF3-Thiacloprid **48***

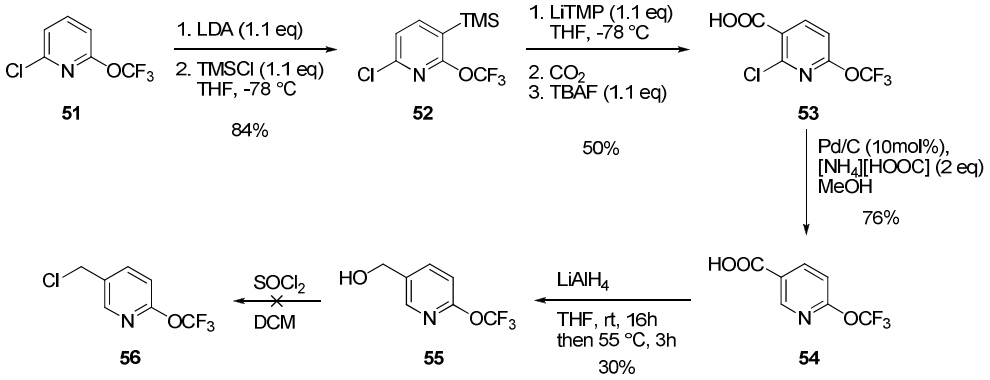
Compound **56** could be synthesised by chlorination of the primary alcohol in presence of thionyl chloride, and the primary alcohol **55** could be accessed *via* reduction of the 2-trifluoromethoxy nicotinic acid **54** with lithium aluminum hydride (LAH). Given the methodology around the synthesis of trifluoromethoxy pyridines and their functionalisation which had been previously developed in our laboratory,[16] the access to 2-trifluoromethoxy nicotinic acid **54** was easy from 2-chloro-6-trifluoromethoxy pyridine **51**.

Starting with 2-chloro-6-hydroxy pyridine **49**, the preparation of the chlorothionoformate and subsequent chlorination in presence of chlorine in chloroform at room temperature yielded the corresponding trichloromethyl ether **50** in 60% yield (Scheme 2.26). Subsequent fluorination in presence of antimony trifluoride and catalytic antimony pentachloride provided 2-chloro-6-trifluoromethoxy pyridine **51** in 53% yield.



*Scheme 2.26: Preparation of 2-chloro-6-trifluoromethoxy pyridine **51***

Now that we had prepared the trifluoromethoxy pyridine **51**, we wanted to access 5-chloromethyl-2-trifluoromethoxy pyridine **56**. The position 3 of the pyridine **51** was protected with a TMS group by metallation with lithium diisopropyl amide (LDA) and subsequent trapping with trimethylsilyl chloride (TMSCl, Scheme 2.27). Synthesis of the nicotinic acid **53** was performed by deprotonation with lithium tetramethyl piperidide (LiTMP) followed by trapping with carbon dioxide and direct deprotection of the TMS group in 50% yield.

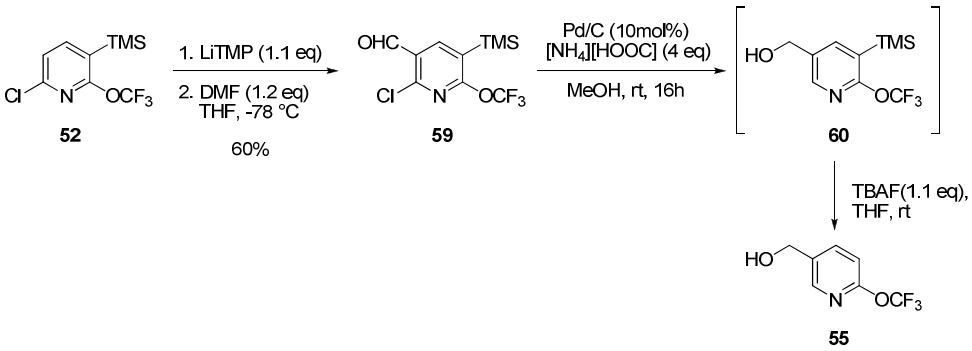


*Scheme 2.27: Synthesis of **57** via reduction with LAH*

Palladium-catalysed dechlorination to afford the 2-trifluoromethoxy nicotinic acid **54** was performed with 76% yield and reduction of the carboxylic acid into the corresponding primary alcohol **55** occurred with 30% yield, affording the desired product in a very small amount (8% yield over 5 steps). Unfortunately, chlorination of the alcohol **55** in presence of thionyl chloride did not provide the target product **56**. Although it was present according to the ^{1}H NMR spectrum, we were not able to isolate it.

Hence, after this first attempt, we had to solve two problems: the reduction had to be improved, and we had to find a way to isolate product **56** after chlorination.

In order to increase the overall yield, we tried to prepare the aldehyde **59** instead of the nicotinic acid **53** (Scheme 2.28). Indeed, this could allow us to avoid the reduction of the nicotinic acid **54**, as the reduction of the aldehyde should be possible during the catalytic reductive dechlorination. Therefore, the position 3 of the 6-chloro-2-trifluoromethoxy pyridine **51** was protected by a trimethylsilyl group under the same conditions. On the second step of the synthesis, metallation of the 5-position of the pyridine ring using LiTMP and trapping with DMF afforded the corresponding aldehyde **59** in 60% yield.

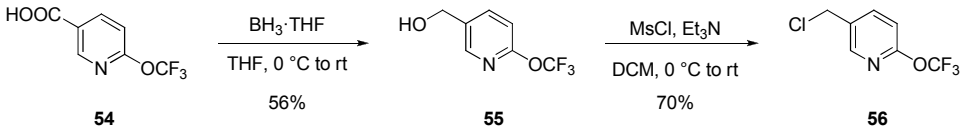


*Scheme 2.28: Preparation of **55** via the aldehyde **59***

We performed the combined reduction of the aldehyde **59** into the primary alcohol **60** and the dechlorination in presence of Pd/C and ammonium formate. The product **60** was not isolated and brought directly to the next step. Deprotection of the TMS substituent with TBAF occurred, as the presence of the desired product was confirmed by ^{1}H NMR. However, a lot of byproducts had been formed, and we could not isolate **55**.

Therefore, we had to find an alternative approach in order to obtain the chloromethyl trifluoromethoxy pyridine **56** in a reasonable yield. We decided to optimise the first approach by changing the means of reduction and chlorination, instead of modifying completely the strategy.

2-Trifluoromethoxy nicotinic acid **54** was synthesised from 6-chloro-2-trifluoromethoxy pyridine **51** (Scheme 2.27). In the previous attempts to synthesise this molecule, the problem was to find a convenient way to reduce the acid in a satisfying yield and to perform its chlorination in order to obtain the desired product **56**.



Scheme 2.29: Optimised conditions for the reduction and the chlorination steps

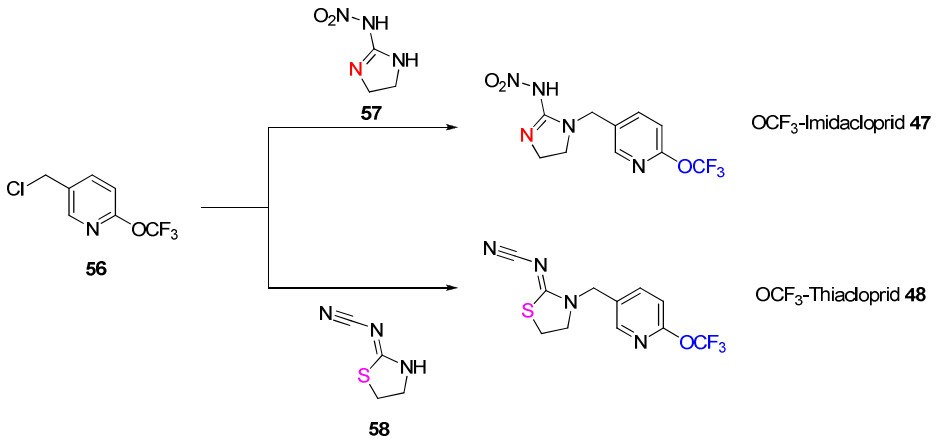
The reduction of the acid into the corresponding primary alcohol was performed with 56% yield using previously described conditions with BH_3·THF[39] on a nicotinic acid. The expected chlorinated product **56** was obtained by an *in situ* mesylation-chlorination described on a secondary alcohol[40] with 56% yield. Therefore, we could obtain the desired product with 12.5% overall yield over five steps.

2.3.2. Conclusion

In conclusion, we found appropriate reaction conditions for the obtention of 3-(chloromethyl)-5-trifluoromethoxy pyridine **56**. The desired product was synthesised in five steps from 2-chloro-6-trifluoromethoxy pyridine **51** in 12.5% overall yield. Optimising the reaction conditions allowed us to improve the reduction and the chlorination steps in order to afford the product in reasonable amounts.

Finally, this chlorinated building block was sent to Bayer CropScience in Monheim, where they performed the couplings with the imidazoline **57** bearing a nitroamine substituent and the

thiazolidine **58** bearing a cyanamide substituent to afford Imidacloprid **47** and Thiacloprid **48** (Scheme 2.30).



*Scheme 2.30: Preparation of OCF_3-Imidacloprid **47** and Thiacloprid **48***

In vitro tests on nicotinic acetylcholine receptors (or nAChRs), and *in vivo* on *Myzus Persicae*, which is the green peach aphid have been performed. Unfortunately, the synthesised trifluoromethoxy analogues of Imidacloprid and Thiacloprid revealed a lower biological activity than their chlorinated counterparts. Even if in this case the biological activity was decreased by the presence of a trifluoromethoxy group, in other cases it could enhance it. Still, this test showed that the presence of this substituent had an influence on its binding to the biological receptor.

2.4. Synthesis of trifluoromethoxy "Magic Pyridine"

2.4.1. Around "Magic Pyridine" and its utilities

"Magic Pyridine" is the 2,3-dichloro-5-trifluoromethyl pyridine. This building-block is very important, especially for the design of bioactive molecules. Indeed, as it is highly functionalisable, it presents many options for the addition of electrophiles and nucleophiles (Figure 2.8).

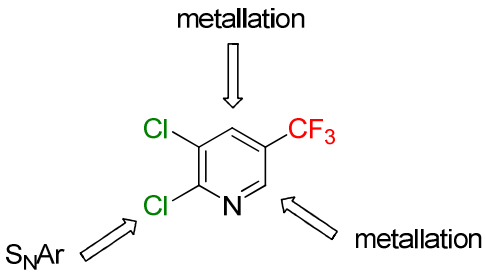


*Figure 2.8: Magic Pyridine **61***

For instance, the 2-position can be functionalised with an amino group by a palladium-catalysed amination or by nucleophilic aromatic substitution of the chlorine atom by a bromine atom, followed by a bromine-lithium exchange to functionalise it. The 4-position can be metallated with LDA, and subsequently functionalised with a carboxylic acid, a halogen or an amine. By protection of this position with a TMS group for example; the 6-position can then be

reached by metallation and subsequent trapping with any electrophile.[5] The 3-position can remain chlorinated, or it can be freed *via* a reductive palladium-catalysed dechlorination with palladium on charcoal.

"Magic Pyridine" **61** is part of the synthesis pathway of the fungicide Fluopyram **65** (Figure 2.9). Fluopyram **65** can be prepared by peptide coupling between the amine **63** and 2-trifluoromethyl benzoic acid **64**. The amine itself can be obtained by a saponification /decarboxylation sequence followed by reduction of the nitrile function of **62**. Nucleophilic aromatic substitution of the chlorine atom of **61** at the 2-position by cyano acetate can lead to the pyridine **62**.

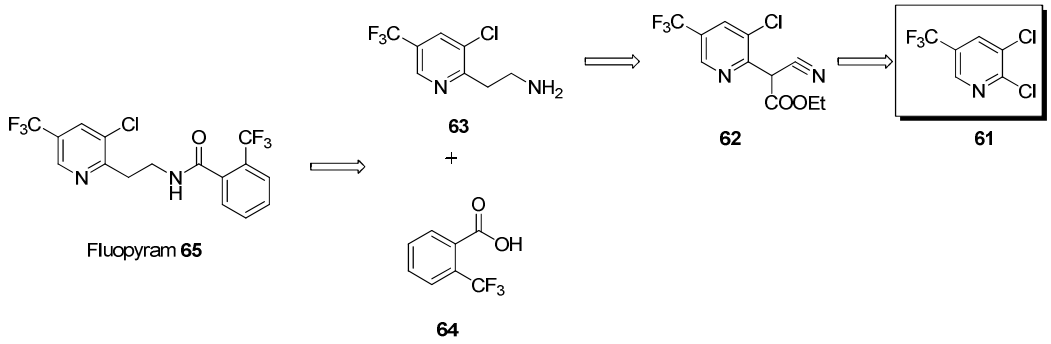
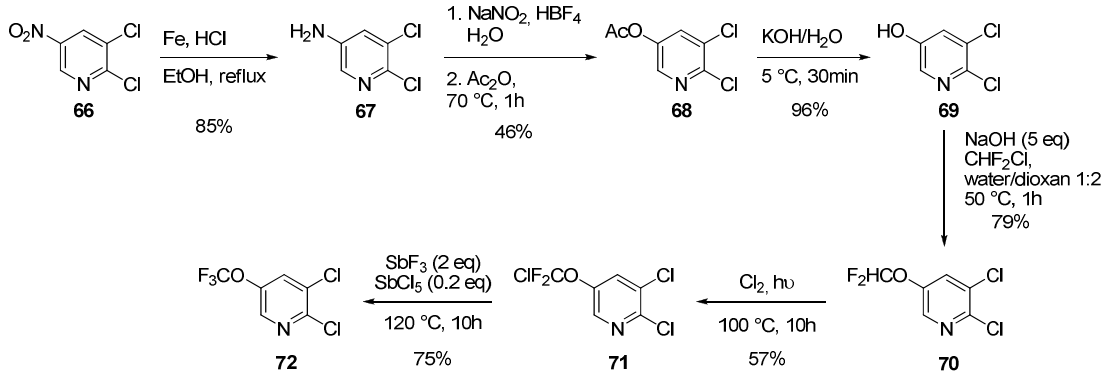


*Figure 2.9: Retrosynthetic analysis of Fluopyram **65** with "Magic Pyridine" **61***

Hence, we thought that developing a methodology for the preparation of a trifluoromethoxy "Magic Pyridine" could be interesting. The wide variety of possibilities that this building-block presents can provide many options for the preparation of novel active ingredients containing a pyridine core.

Trifluoromethoxy "Magic Pyridine" **72** has already been described, but the reaction pathway was long and tedious.[37a,41] 2,3-Dichloro-5-nitro pyridine **66** had to be previously prepared, as it was not commercially available at the time. We will not detail this here, and will focus on the synthesis of 2,3-dichloro-5-trifluoromethoxy pyridine **72** from **66**.



*Scheme 2.31: Koch's synthesis of 2,3-dichloro-5-trifluoromethoxy pyridine **72***

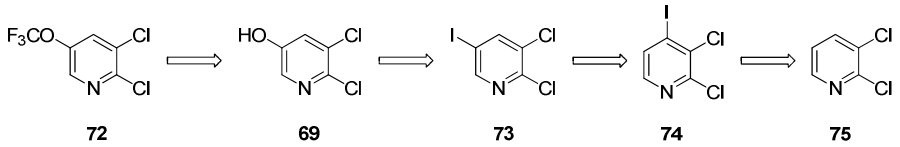
Reduction of the nitro group of **66** in presence of iron(0) and HCl led to the aminopyridine **67** with 85% yield. Then, diazotation of the amine **67** in presence of sodium nitrite and fluoroboric acid followed by addition of acetic anhydride provided the acetylated compound **68** in 46% yield. Subsequent deprotection of the alcohol occurred in 96% yield, and the alcohol **69**

underwent *O*-alkylation in presence of chlorodifluoromethane (F22) with 79% yield. The difluoromethoxy pyridine **70** was then chlorinated under UV activation to provide the chlorodifluoromethoxy pyridine **71**. Finally, introduction of the third fluorine atom by reaction with antimony trifluoride in presence of catalytic antimony pentachloride led to the desired trifluoromethoxy pyridine **72** in 75% yield. Hence, 2,3-dichloro-5-trifluoromethoxy pyridine **72** was prepared from 2,3-dichloro-5-nitro pyridine in six steps.

Given the difficulty and the sometimes low yields of this synthesis, we wanted to propose a shorter alternative to this process. In addition, this could valorise the two-step protocol we had developed for the synthesis of trifluoromethoxy pyridines from hydroxy derivatives.[35]

2.4.2. Preparation of 2,3-dichloro-5-trifluoromethoxy pyridine

In order to improve the access to the 2,3-dichloro-5-trifluoromethoxy pyridine **72**, we had imagined two pathways. The first one was based on the "halogen dance" (Figure 2.10).[42] 2,3-Dichloro-5-trifluoromethoxy pyridine **72** could be obtained from the 5-hydroxy compound **69** *via* the chlorodesulphurisation-fluorination sequence we had developed. The hydroxy function could be introduced performing a borylation-oxidation sequence on **73**. 2,3-dichloro-5-iodopyridine **73** would itself be the product of an iodine migration from the 4-position to the 5-position of the pyridine ring, and compound **74** could be obtained after deprotonation of 2,3-dichloro pyridine **75** and trapping with iodine.

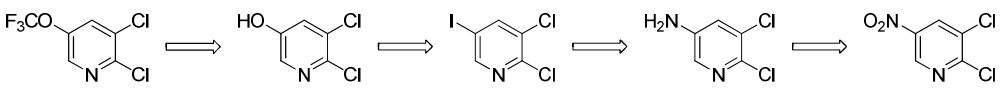


72 **69** **73** **74** **75**

*Figure 2.10: Migration pathway to trifluoromethoxy "Magic Pyridine" **72***

This sequence includes five steps from the commercially available 2,3-dichloro pyridine **75**. Except for the fluorination step, we could anticipate good yields, as metallation of pyridines using lithium reagents has been widely studied.[43]

The second pathway we had imagined was in fact an improvement of the one described earlier (Scheme 2.31). We envisaged the construction of the trifluoromethoxy group of **72** from 5-iodo pyridine **73** as in the "migration pathway". In this case, 2,3-dichloro-5-iodopyridine **73** could be obtained from 2,3-dichloro-5-amino pyridine **67** *via* a Sandmeyer reaction. Contrary to what was described by V. Koch *et al.*,[41] we decided to synthesise the 5-iodo pyridine **73** instead of preparing the hydroxy compound immediately because of the low yields obtained. Finally, the amino pyridine **67** could be prepared by reduction of the 5-nitro pyridine **66** which is now commercially available.



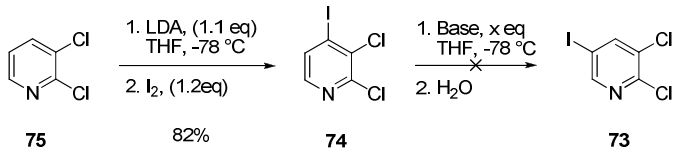
72 **69** **73** **67** **66**

*Figure 2.11: Diazotation pathway to trifluoromethoxy "Magic Pyridine" **72***

This pathway also contains five steps, but we could not predict the outcome of the diazotation/iodination and the fluorination steps. Nevertheless, we investigated both approaches simultaneously in order to compare their efficiency.

2.4.2.1. Migration approach

The first step consisted in the iodination of 2,3-dichloro pyridine **75** at the 4-position, which was successfully performed by deprotonation with LDA followed by addition of iodine with 82% yield (Table 2-2). Unfortunately, the second step which consisted in the migration of the iodine atom to the position 5 did not occur.



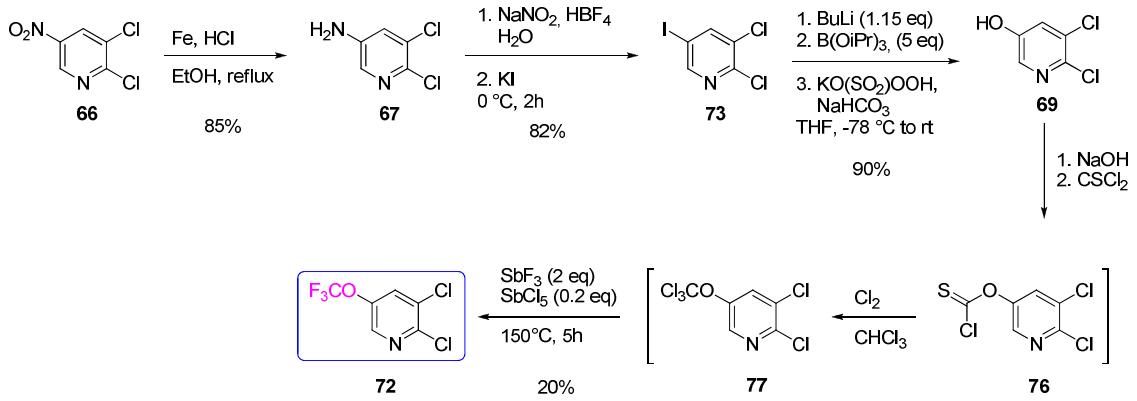
Entry	Base	Equiv.	Metallation time	Observations
1	LDA	1,2	2h	No desired product observed
2	LDA	1,2	4h	"
3	LDA	1,5	2h	"
4	LiTMP	2	2h	"

Table 2-2: Conditions for iodine migration

We could observe that the nature of the base, the metallation time and the number of base equivalents had no influence on the outcome of the reaction. Hence, we decided to abandon this route and to focus on the other one.

2.4.2.2. Diazotation approach

The second synthetic path to "Magic Pyridine" was already partly described, but we tried to improve it. Starting from the commercially available 2,3-dichloro-5-nitro pyridine **66**, the first step was the reduction of the nitro group in presence of iron(0) and HCl, which afforded the amino pyridine **77** with 85% yield (Scheme 2.32).



*Scheme 2.32: Preparation of **72** via the diazotation approach*

The amine **67** was converted to the iodo-compound **73** *via* the diazonium salt, yielding 82%. The product underwent a borylation and oxidation to provide the desired hydroxy

pyridine **69** with 90% yield, using oxone® as the oxidizing agent under basic conditions[44] instead of 56% when using hydrogen peroxide under acidic conditions.

Finally, *O*-alkylation with thiophosgene followed by the chlorodesulphurisation-fluorination sequence provided the final 2,3-dichloro-5-trifluoromethoxy pyridine **72**, but only in 20% yield from the hydroxy compound **69**. This represented a 12.5% yield over five steps.

2.4.3. Conclusion

The aim of this project was to develop a straightforward and efficient access to 2,3-dichloro-5-trifluoromethoxy pyridine **72** in order to open an access to a great variety of potentially active molecules containing a trifluoromethoxy pyridine core. We have successfully managed to isolate the final building block **72** in 12.5% yield over five steps.

The first approach failed, as we could not perform the iodine migration. An improved version of the synthesis of this building-block has been developed. The low yield of the chlorodesulphurisation-fluorination sequence is the weakness of our approach, as the overall yield has not been increased. However, this sequence made our approach shorter than the one previously described, and we improved the outcome of the Sandmeyer reaction *via* an iodination followed by a borylation/oxidation sequence performed in high yields.

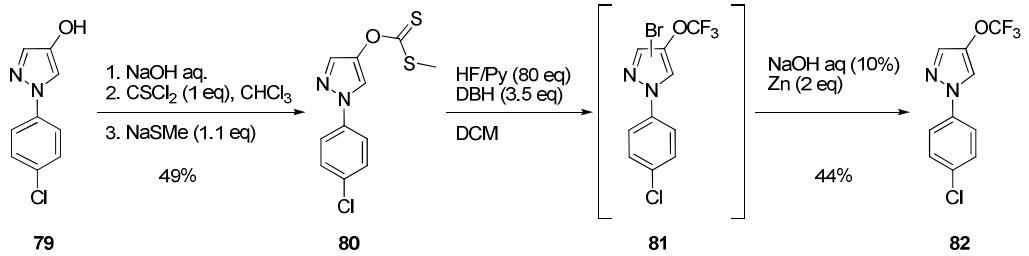
It should be noticed that according to the Montreal protocol, the use of Freon 22 will be prohibited by 2020. Hence, the method we have developed is more suitable for the synthesis of 2,3-dichloro-5-trifluoromethoxy pyridine **72**. Finally, we can claim that we could develop an efficient access to this building block, which can be adaptable to an industrial scale.

2.5. Towards 5-trifluoromethoxy pyrazoles

The methodology developed by our team was very efficient and straightforward for the synthesis of trifluoromethoxy pyridines, providing many options for their functionalisation. We decided to construct such a fluorinated group on pyrazoles.

2.5.1. Introduction and objectives

Our group showed that the construction of a trifluoromethoxy group onto a pyrazole was possible.[45] Starting from 4-hydroxy pyrazole **79**, the xanthogenate **80** was prepared in 49% yield, and an oxidative desulphurisation-fluorination onto the *S*-methyl dithiocarbamate **80** provided the 4-trifluoromethoxy pyrazole **82** (Scheme 2.33). However, the pyrazole was brominated on the aromatic ring during the fluorination step.



Scheme 2.33: Synthesis of a 4-trifluoromethoxy pyrazole

The pyrazole **81** was not isolated, and underwent readily a reductive debromination in presence of zinc(0), which led to the 4-trifluoromethoxy pyrazole **82** in 44% yield. This is the very first report on the synthesis of a trifluoromethoxy pyrazole. Hence, we wanted to investigate this in order to develop a general method for the synthesis of trifluoromethoxy pyrazoles.

We started by studying the literature for the synthesis of 4-hydroxy pyrazoles bearing a *N*-protecting group which could be deprotected later, as the phenyl one was not. However, we found that the methods for the preparation of unsubstituted 4-hydroxy pyrazoles are scarce and essentially concern the synthesis of *N*-phenyl pyrazoles. Hence, we realised that preparation of 4-hydroxy pyrazoles should be more efficient by the use of trifluoromethoxylated precursors, and we decided to study 3- and 5-trifluoromethoxy pyrazoles.

The aim was to try to construct a trifluoromethoxy group at the 3- or 5-position of the pyrazole ring. We decided to start the study with 5-trifluoromethoxy pyrazoles, as the preparation of 3-OCF_3 pyrazoles is similar. Ideally, the pyrazole would be unsubstituted at the 3- and 4-positions in order to provide many options for further functionalisation by means of organometallic reagents. Furthermore, we wanted to obtain *N*-H pyrazoles to be able to functionalise the nitrogen atom with any group on demand.

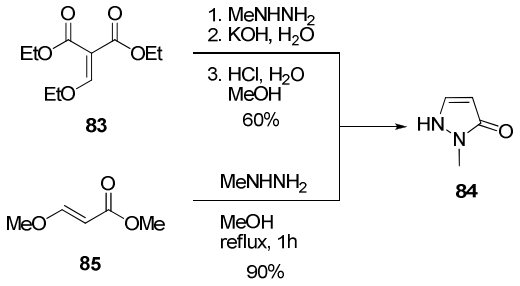
For the construction of the trifluoromethoxy group, two options were selected: on one hand, we could use the oxidative desulphurisation-fluorination which had successfully provided 4-OCF_3 pyrazoles. On the other hand, we could apply the alkylation/chlorodesulphurisation/ fluorination sequence which had been successfully developed by our group on pyridines.[5, 35]

2.5.2. Oxidative fluorodesulphurisation approach

As our first aim was to provide an access to 5-OCF_3 pyrazoles which were unsubstituted at the 3- and 4- positions, we started with the preparation of 5-hydroxy pyrazoles. Indeed, we had to find a way to perform *O*-alkylation on these pyrazoles in order to prepare the xanthogenate before the fluorination step. Several methods exist in order to afford 5-hydroxy pyrazoles, but few of them allow an access to pyrazoles which are not functionalised.

2.5.2.1. Preparation of 5-(*S*-methyl) dithiocarbamate pyrazoles

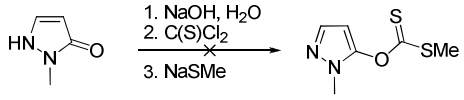
We found two convenient protocols in the literature. The first attempt consisted in the synthesis of pyrazoles by reaction of methyl hydrazine on diethyl (ethoxymethylene)malonate[46] **83** and subsequent saponification and decarboxylation to afford the corresponding *N*-methyl 5-pyrazolone **84** (Scheme 2.34). The yields were around 60% over two steps.



Scheme 2.34: Synthesis of unsubstituted 5-pyrazolone

Then, a more convenient one-step procedure was tried: it consisted in the reaction of hydrazine with methyl *trans*-3-methoxyacrylate **85**[47] in methanol and gave the desired pyrazole **84** in 90% yield. This method gives an access to several pyrazolones bearing different *N*-protecting groups.

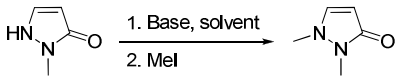
The next step was to try an *O*-methylation in order to synthesise the xanthogenate **86**. Several attempts were done, first using the described conditions for pyridines (Scheme 2.35), but this method revealed to be inefficient.



84 **86**

*Scheme 2.35: Attempt of construction of the xanthogenate on **84***

As the acidity of the proton of the hydroxy pyrazole **84** might be lower than the one of hydroxy pyridines, we decided to do a screening of several conditions in order to obtain the desired product (Table 2-3). We trapped the anion with methyl iodide instead of thiophosgene for the optimisation of the conditions. Neither the solvent nor the base had an influence on the outcome of the reaction. Indeed, according to ^{1}H NMR, we only afforded the *N*-methylation product **87**.

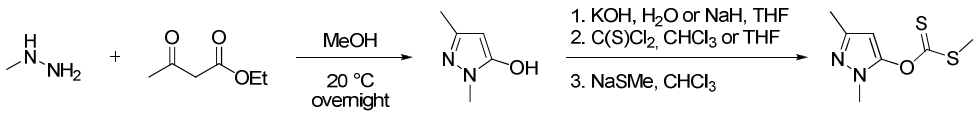


84 **87**

Entry	Base	Solvent	Trapping reagent	Observations
1	MeONa	MeOH	MeI	Complete conversion
2	K_2CO_3	DMF	MeI	Complete conversion
3	NaH	MeOH	MeI	Complete conversion
4	NaH	DMF	MeI	Complete conversion

*Table 2-3: Attempts of O-alkylation of 5-pyrazolone **84***

In order to favour *O*-alkylation over *N*-alkylation, we decided to introduce a substituent at the 3-position of the pyrazole. Hence, we chose to prepare 3-methyl and 3-halogeno pyrazoles as they had been reported in the literature to undergo *O*-alkylation.[48, 49]

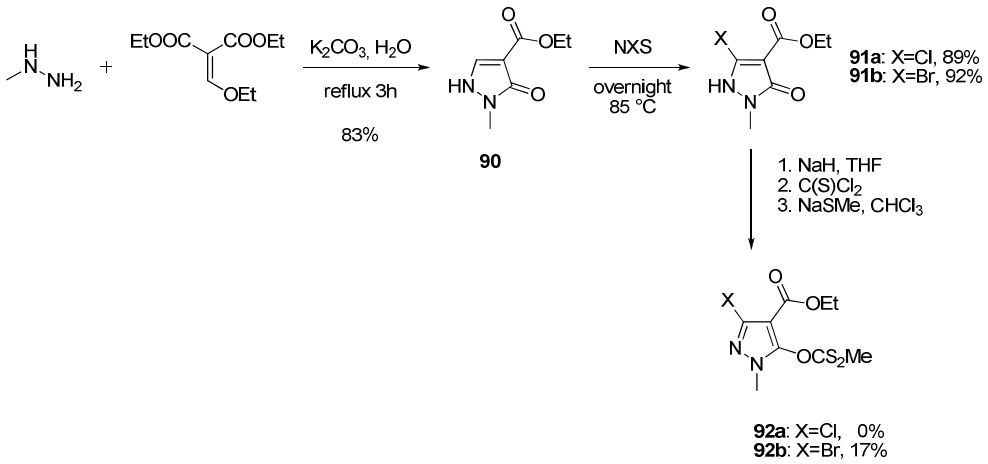


92% **88** 6 or 5% **89**

*Scheme 2.36: Preparation of **88** and of the xanthogenate **89***

1,3-Dimethyl-5-hydroxy pyrazole **88** was obtained by reaction of methyl hydrazine with ethyl acetoacetate in 92% yield[50] (Scheme 2.36). *O*-alkylation in presence of thiophosgene and sodium methane thiolate to prepare the dithiocarbamate **89** provided the desired product in very low yields. Given that the nature of the base and the solvent did not influence the yield, and that we had not obtained enough material to try a fluorination, we decided to concentrate our efforts on 3-halogeno pyrazoles.

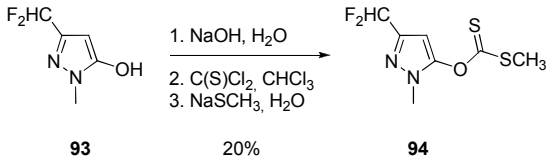
We focused again on Hiyama's method in order to obtain the 5-trifluoromethoxy pyrazoles. We found a convenient route to 3-chloro pyrazoles, which had been reported to undergo *O*-alkylation in presence of isopropyl iodide and potassium carbonate in DMF with 73% yield.[49] We applied this protocol to our compounds and decided to prepare simultaneously the chlorinated and the brominated compounds (Scheme 2.37).



*Scheme 2.37: Synthesis of 3-halogeno pyrazoles **91***

The pyrazolone **90** was synthesised by reaction of methyl hydrazine with diethyl (ethoxymethylene)malonate in presence of potassium carbonate with 83% yield. The pyrazole ring was then chlorinated with *N*-chlorosuccinimide to afford **91a** with 89% yield, but we were not able to convert it to the corresponding xanthogenate **92a**.

In consequence, we prepared the brominated derivative **91b** by reaction with NBS. In addition, a bromine atom would be more useful for further functionalisation of the pyrazole ring after construction of the trifluoromethoxy group. The bromination of the ring was successfully performed in 92% yield, and subsequent reaction with thiophosgene and sodium methane thiolate provided the xanthogenate **92b** in 17% yield. Despite the low yield, the reactivity was enhanced compared to 3-methyl pyrazoles.



*Scheme 2.38: Construction of the xanthogenate **94***

Simultaneously, we had received 1-methyl-3-difluoromethyl-5-hydroxy pyrazole **93** from Bayer CropScience (Scheme 2.38). The presence of an electron-withdrawing-group might have a positive influence on the outcome of the reaction. We decided to try the construction of the xanthogenate substituent on this compound in order to compare the yields. Thus, **93** was deprotonated with sodium hydroxide, and subsequent addition of thiophosgene followed by sodium methane thiolate provided compound **94** in 20% yield.

Finally, the substituent of the pyrazole ring did not have an important influence on the outcome of the reaction, as the yield was not improved by the presence of the difluoromethyl

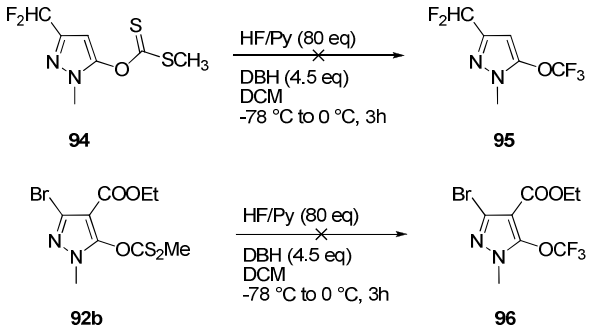
group. It should be noticed that the conversion of the hydroxy pyrazoles to the chlorothionoformates was in each case complete. Hence, in our case, the problem came from the reactivity of sodium methane thiolate towards 5-pyrazolones. We decided to test fluorination conditions on the brominated and the difluoromethylated compounds. Indeed, if the fluorination step was successful, we could study the influence of other parameters later in order to optimise the *O*-alkylation step.

2.5.2.2. Towards 5-trifluoromethoxy pyrazoles

Hence, we performed oxidative fluorodesulphurisation conditions on the 3-bromo and 3-difluoromethyl dithiocarbamates **92b** and **94**. Those conditions had been applied for the preparation of 4-trifluoromethoxy pyrazole[45] and use 80 equivalents of HF/pyridine and 4.5 equivalents of *N,N*-dibromohydantoin in dichloromethane (Scheme 2.39).

Unfortunately, these reaction conditions led to very messy reaction mixtures. We could observe the bromination of the pyrazole ring in the case of the 3-CHF_2 pyrazole **94**. Many byproducts were formed in the two cases and changing the reaction time and the temperature of the fluorination step did not influence the outcome of the reaction.

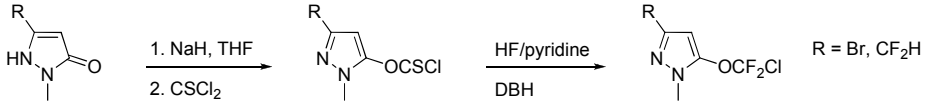
In conclusion, this route was inadaptable to the preparation of 5-trifluoromethoxy pyrazoles, so we had to find an alternative. As we had realised that the conversion of hydroxy pyrazoles to the corresponding chlorothionoformates was total, we decided to investigate this route.



*Scheme 2.39: Attempts of trifluoromethoxylation of compounds **92b** and **94***

2.5.2.3. Reactivity of chlorothionoformates

Deprotonation of 5-hydroxy pyrazoles with a base and subsequent addition of thiophosgene leads to chlorothionoformates quantitatively. As we had to find an alternative, we decided to study the reactivity of chlorothionoformates under Hiyama's conditions. In this case, we could obtain the corresponding chlorodifluoromethyl ethers, on which the third fluorine atom could subsequently be introduced (Scheme 2.40).

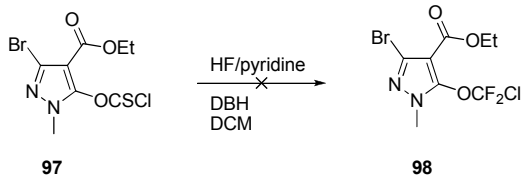


Scheme 2.40: Proposed fluorination of chlorothionoformates

Consequently, we decided to apply this route to 3-bromo-5-hydroxy pyrazole **97**. Several reaction conditions were tried for the fluorination step (Table 2-4), and this led either to total

recovery of the starting material (entries 1 to 3) or to very messy reaction mixtures (entries 4 and 5).

We think that if fluorination occurred, the synthesised products were not stable enough to be isolated properly. Finally, the oxidative fluorodesulphurisation conditions revealed to be inappropriate for the preparation of chlorodifluoromethyl and trifluoromethyl ethers at the 5-position of pyrazoles.



97 **98**

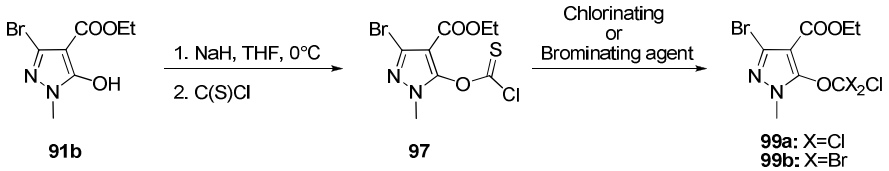
Entry	Eq. of DBH	Temperature	Time	Observations
1	3	0 °C	2h	/
2	3	0 °C to rt	overnight	/
3	4.5	0 °C	2h	/
4	4.5	0 °C	4h	Not interpretable
5	4.5	0 °C to rt	overnight	Not interpretable

*Table 2-4: Attempts of fluorination of chlorothionoformate **97***

As all the conditions we had studied had been unsuccessful, we chose to change the strategy completely, and to perform a chlorodesulphurisation-fluorination sequence on pyrazoles.

2.5.3. Chlorodesulphurisation-fluorination sequence

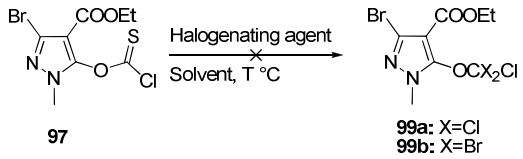
We thought that we could use the alkylation/chlorodesulphurisation/fluorination sequence developed on pyridines.[5] We had already developed an access to the chlorothionoformate **97**. During the chlorination step, there is a risk of chlorination of the electron-rich pyrazole ring when all the positions are not functionalised. Therefore, we investigated several chlorination and bromination methods in order to obtain the halogenated compounds **99a** and/or **99b** under milder conditions than the use of gaseous chlorine (Scheme 2.41).



91b **97** **99a:** X=Cl **99b:** X=Br

Scheme 2.41: Access to O-alkylated pyrazoles

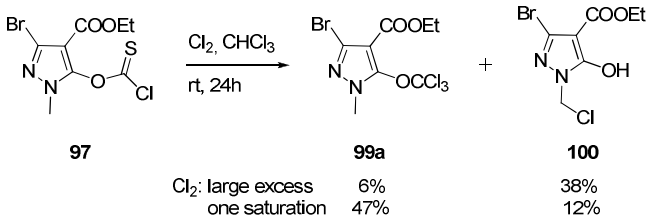
We tested several halogenating reagents (Table 2-5), and realised that the nature of the halogenating reagent had no influence on the outcome of the reaction (entries 1, 2, 5 and 6). Increasing the temperature and changing the solvent (entries 1, 3 and 4) did not lead to conversion of the starting material. Unfortunately, none of these methods provided the desired trihalogeno methyl ethers, and we always recovered the starting material.



Entry	Halogenating agent	Temperature	Solvent	Time	Observations
1	NBS	-75 °C to rt	$CHCl_3$	16h	Total recovery of **97**
2	NCS	"	"	"	"
3	NBS	"	CH_2Cl_2	16h	"
4	NBS	85 °C	/	16h	"
5	Trichloroisocyaniuric acid	Reflux	$CHCl_3$	16h	"
6	Br_2	rt	CCl_4	3 days	"

*Table 2-5: Reaction conditions for the obtention of the pyrazoles **99a** and **99b***

We then decided to perform the chlorination step under the conditions described for pyridines. The chlorothionoformate pyrazole **97** was dissolved in chloroform without further purification after the alkylation step, and the solution was saturated with gaseous chlorine twice. A change of the colour of the solution and total disappearance of the starting material were observed. Two products had been formed, and after purification we could isolate the trichloromethyl ether **99a**, but only in 6% yield. The major product being the pyrazole **100** (Scheme 2.42) obtained in 38% yield.



*Scheme 2.42: Chlorination of the thioniochloroformate **97** with chlorine*

Surprisingly, the chlorination of the *N*-methyl substituent had occurred, and the *O*-alkyl group had been eliminated. The formation of **100** proved that the alkyl group introduced onto the 5-hydroxy pyrazole can be removed in presence of nucleophilic halogens. The reaction was carried out again, but saturating the solution only once with gaseous chlorine. After one night, the major product isolated was the trichloromethyl ether **99a** with 47% yield.

After obtention of this chlorinated pyrazole, we performed a chlorine/fluorine exchange using antimony trifluoride and a catalytic amount of antimony pentachloride at 150 °C.[5] But the high temperatures needed for this reaction only led to decomposition of the pyrazole. We decreased gradually the fluorination temperature until 100 °C, and we observed every time a complete degradation of the starting material. Attempts to perform the fluorination in presence of milder reagents such as HF/pyridine or HF/triethylamine led to total recovery of the starting material.

We concluded that these reaction conditions were not suitable for the preparation of 5-OCF_3 pyrazoles. As we had tried all the convenient approaches that had been reported for the preparation of aryl trifluoromethoxy derivatives, we decided to abandon this project.

2.5.4. Conclusion and perspectives

In conclusion, despite all the efforts put into the study of various approaches we were not able to prepare and isolate 5-OCF_3 pyrazoles. The study started on the basis that 4-trifluoromethoxy pyrazoles had been obtained by oxidative fluorodesulphurisation on the corresponding xanthogenate.[45] We thought that the xanthogenate could be constructed onto 5-hydroxy pyrazoles and that subsequent fluorination under Hiyama's conditions could lead to 5-OCF_3 pyrazoles.

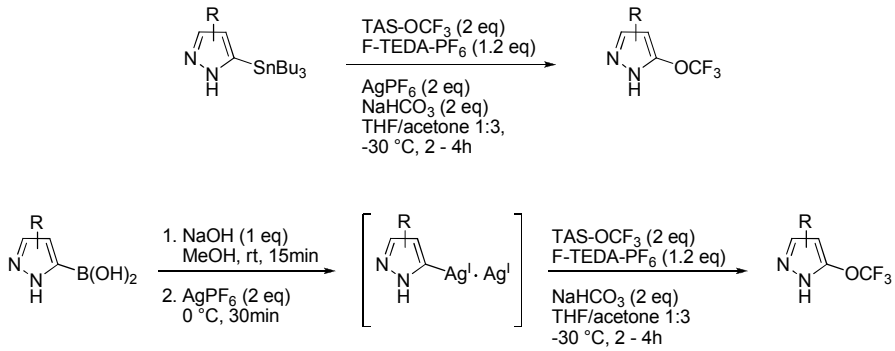
However, when we tried to construct the xanthogenate substituent on 5-hydroxy pyrazoles, we either obtained *N*-methylation, or low *O*-methylation yields. Variations around the pyrazole substitution pattern did not afford the dithiocarbamates above 20% yield. Even though the obtention of the pyrazole xanthogenates was not satisfactory, we performed oxidative fluorodesulphurisation on the 3-difluoromethyl and 3-bromo compounds. Unfortunately, this did not lead to the trifluoromethyl ethers but to complex reaction mixtures.

Hence, as the conversion of 3-bromo-5-hydroxy pyrazole into chlorothionoformate was complete, we studied its reactivity under "Hiyama-like" conditions. This could lead to 5-chlorodifluoromethyl ethers, and open an access to 5-trifluoromethoxy pyrazoles. Once again, this either led to complete recovery of the starting material or to messy reaction mixtures with no detection of the desired product, depending on the reaction conditions.

Finally, as oxidative desulphurisation-fluorination conditions were not applicable to 5-hydroxy pyrazoles, we decided to change the strategy. We chose to apply an alkylation/chlorodesulphurisation/fluorination sequence that had been developed on pyridines for the obtention of trifluoromethyl ethers. In order to achieve this, we had to find a way to obtain trichloro or chlorodibromo methyl ethers from chlorothionoformates in order to perform a halogen/fluorine exchange on these substrates. After several attempts, we could obtain 5-trichloromethoxy pyrazoles by chlorination with gaseous chlorine in 47% yield. However, fluorination with a SbF_3/SbF_5 mixture proved to be too harsh for the substrates and led to degradation of the trichloromethoxy pyrazoles. Changing the fluorination reagent for HF/pyridine and HF/triethylamine led to complete recovery of the starting material.

In conclusion, all the experiments we have performed showed that the obtention of 5-OCF_3 pyrazoles was not possible under the conditions we had chosen. This might be due to the sensitivity of these substrates, which degraded under harsh conditions. The fail of this method could also be explained by a lack of stability of the formed trifluoromethyl ethers. Indeed, we observed the elimination of the alkyl group during the formation of the trichloromethoxy compound, when chlorine was used in a large excess. There could be a similar reaction in presence of fluorine, and partial elimination of the alkyl group, leading to the complex mixtures we observed.

When we studied the synthesis of 5-trifluoromethoxy pyrazoles, the obtention of aromatic trifluoromethyl ethers from stannanes and boronic acids in presence of silver(I) hexafluorophosphate ($AgPF_6$) and F-TEDA-PF_6 and TAS·OCF_3 had not been reported yet. It could be interesting to apply these conditions to pyrazoles in order to see if this mixture is efficient for the preparation of 5-trifluoromethoxy pyrazoles (Scheme 2.43).



Scheme 2.43: Possible approaches towards 5-trifluoromethoxy pyrazoles

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Chapter 3. Pyridine α-Fluoro Ethers

The development of synthetic methods for the preparation of diversely fluorinated heteroaromatic building blocks is very important for life-sciences oriented research. In the past decades, many methods have been reported for the preparation of pyridine building blocks bearing fluorinated substituents,[1,2] most of which are a single fluorine atom and/or a trifluoromethyl substituent. Fewer methods for the preparation of pyridines bearing perfluoroalkyl groups are reported (C_nF_{2n+1}, n>1).

More recently, the preparation of pyridines containing emerging fluorinated groups has attracted a lot of attention. Among them, the introduction of difluoromethyl[3] and trifluoromethoxy[4] groups onto pyridines has been described and these building blocks will find an application in the design of new bioactive agents. As these fluorinated substituents are scarcely described, their potential influence on biological activity remains unexplored.

Fluorinated methyl ethers are present in agrochemicals and pharmaceuticals (Figure 3.1), as it has been detailed in the previous chapter. For instance, Riluzole (Sanofi-Aventis) contains a trifluoromethoxy substituent, the plant growth regulator Primisulfuron-methyl (Ciba Geigy) a difluoromethyl ether, and the anaesthetic Sevoflurane (Abbott Laboratories) a monofluoromethoxy group.

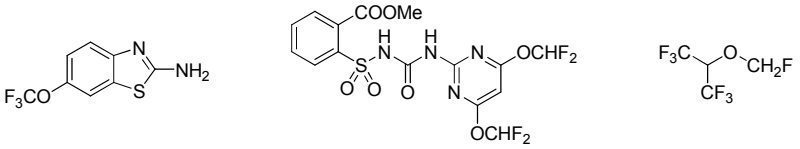


Figure 3.1: Bioactive compounds bearing fluorinated methyl ethers

In contrast, mixed chloro/fluoro methyl ethers have been scarcely described. These fluorinated groups have been considered as intermediates for the preparation of trifluoromethoxy[5] and difluoromethoxy[6] substituents for a long time, as chlorine-fluorine exchange is the most widely used method for the synthesis of fluorinated molecules.[7] Recently, they have attracted interest as they might confer unprecedented biological activities to molecules.

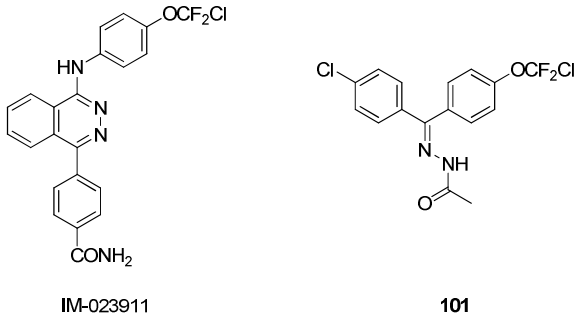


Figure 3.2: Bioactive molecules containing an –OCF_2Cl group

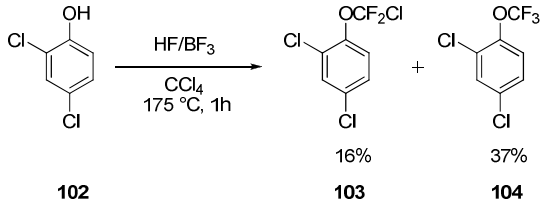
Molecules containing an -OCF_2Cl have been reported to have potential anti-cancer activity[8,9] for IM-023911 and insecticidal properties[10] for **101** (Figure 3.2). OCF_2Cl- and $OCFCl_2$-containing methyl ethers have been described as anaesthetic agents.[11] However, these fluorinated methyl ethers are constructed onto aromatic molecules and in the literature the references concerning heteroaromatic compounds remain scarce. Preparing OCF_2Cl- and $OCFCl_2$-containing heteroaromatics still constitutes a challenge. Therefore, we decided to study the possibility of constructing such fluorinated substituents on pyridines.

3.1. State of the art

3.1.1. Preparation of –OCF_2Cl and –$OCFCl_2$ aromatic compounds

All the methods reporting the preparation of mixed chloro/fluoro methyl ethers consist in fluorination of chlorinated precursors.

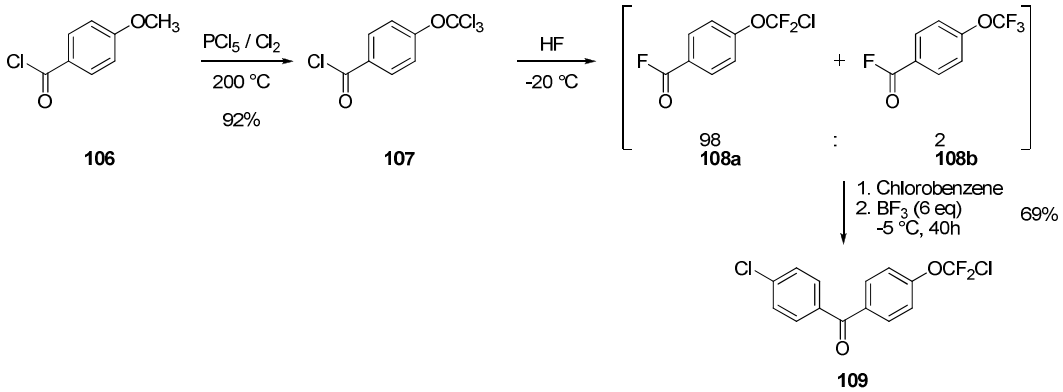
In 1979, A. E. Feiring described the preparation of 2,3-dichloro chlorodifluoromethoxy benzene **103** by reaction of 2,3-dichloro phenol **102** in presence of tetrachloromethane and *in-situ* fluorination with anhydrous HF.[12] Here, the aim was to obtain trifluoromethyl ethers, so hydrogen fluoride was used in a large excess in presence of boron trifluoride. The chlorodifluoromethoxy compound **103** was obtained as a side-product and as a mixture with the trifluoromethoxy benzene **104** (Scheme 3.1).



Scheme 3.1: Obtention of chlorodifluoromethyl ethers from phenols

Conversion of phenols into –OCF_2Cl groups has also been described by *O*-alkylation with diphosgene followed by fluorination with HF,[13] and by *O*-alkylation with $CHClF_2$ followed by photochlorination.[14] However, these products were described as side-products in the preparation of trifluoromethoxy compounds.

More recently, A. Pascual and coworkers reported the preparation of chlorodifluoromethoxy benzophenones.[15] The *p*-anisyl acyl chloride **106** was converted into the trichloromethoxy compound **107** in presence of PCl_5 and gaseous chlorine (Scheme 3.2). Fluorination in presence of anhydrous HF at -20 °C led to the insertion of two fluorine atoms generating the corresponding chlorodifluoromethoxy compound **108a**.

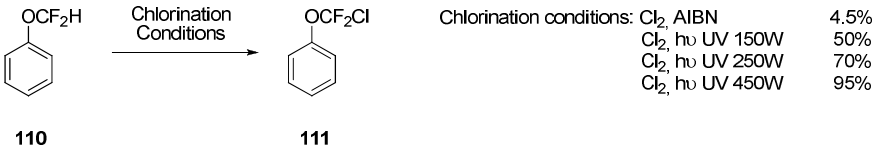


*Scheme 3.2: Preparation of –OCF_2Cl benzophenone **109***

The acyl fluoride **108b** was simultaneously generated and was submitted without isolation to electrophilic aromatic substitution in presence of chlorobenzene and boron trifluoride to provide the benzophenone **109** in 69% yield from **108a** and **108b** as a 98:2

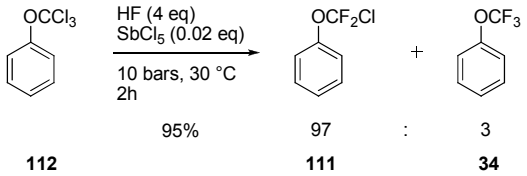
mixture of the -OCF_2Cl and -OCF_3 derivatives. In addition, this method is scalable and the insertion of only two fluorine atoms is controlled performing the reaction at low temperature.

The preparation of chlorodifluoromethoxy benzenes by chlorination of difluoromethyl ethers has been studied by A. I. Shipilov *et al*.[16] This study has shown that the initiation of the reaction has a huge influence on its outcome. Indeed, difluoromethyl ethers did not undergo chlorination in presence of PCl_5, but under radical conditions. The difluoromethoxy benzene **110** provided the corresponding –OCF_2Cl compound **111** in better yields by UV-initiated chlorination, and the yields depended on the intensity of the UV irradiation (Scheme 3.3).



Scheme 3.3: Chlorination of aromatic difluoromethyl ethers

The conversion of trichloromethoxy benzene **112** into –OCF_2Cl is also possible by nucleophilic fluorination in liquid HF under pressure in presence of catalytic antimony pentachloride.[17] Depending on the temperature, difluorination or trifluorination have been observed, providing either chlorodifluoromethoxy or trifluoromethoxy benzenes **111** and **34** (Scheme 3.4). The reaction provided the same result in absence of antimony pentachloride at 50 °C for one hour.

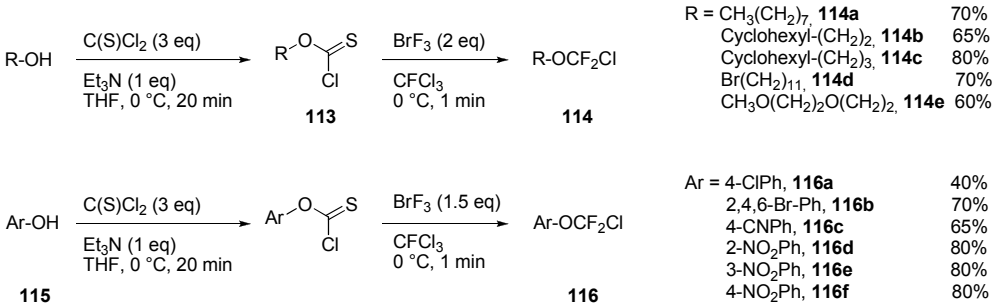


Scheme 3.4: Fluorination of trichloromethoxy benzene with HF/$SbCl_5$

These reaction conditions are selective and provide the chlorodifluoromethoxy benzene **111** in very good yields and are scalable, but they necessitate a safety equipment at a laboratory scale.

S. Rozen *et al.* reported that aryl and alkyl chlorodifluoromethyl ethers could be prepared by reaction of chlorothionoformates with bromine trifluoride.[18] Deprotonation of alkyl primary alcohols with triethylamine followed by *O*-alkylation with thiophosgene led to the chlorothionoformates **113a** to **113e** (Scheme 3.5). Subsequent fluorination in presence of two equivalents of bromine trifluoride provided the chlorodifluoromethoxy compounds **114a** to **114e** in 60 to 80% yield.

Similarly, phenols **115a** to **115f** were converted into the chlorodifluoromethoxy compounds **116a** to **116f** in 40 to 80% yield. Adding three equivalents of bromine trifluoride led to formation of the –OCF_2Cl products along with bromination of the aromatic ring. Despite its efficiency, this method has proven to be only applicable to aromatic substrates containing strong electron-withdrawing groups, and forces the use of highly toxic bromine trifluoride.

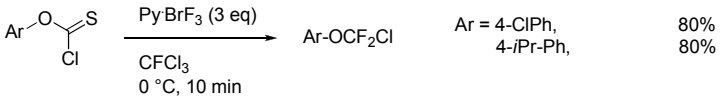


Scheme 3.5: Preparation of –OCF_2Cl compounds by fluorination of chlorothionoformates with BrF_3

The same research group described the preparation of the corresponding difluoromethyl ethers by reduction of the chlorodifluoromethoxy substituent under radical conditions.[6] This was only described once on an aromatic compound and the nitro group had to be reduced into the amino function before the dechlorination step was performed (Scheme 3.6).

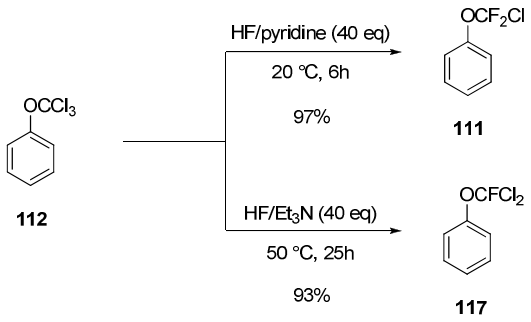
Scheme 3.6: Reductive preparation of difluoromethoxy compounds

More recently, the preparation of a pyridine-bromine trifluoride complex and its use as a fluorinating reagent has been reported.[19] In a similar reaction, chlorodifluoromethoxy compounds are synthesised from the corresponding chlorothionoformates with the Py·BrF_3 complex. Using this reagent, the preparation of aromatic chlorodifluoromethoxy compounds was performed with no side-bromination on the aromatic ring, and it has even been performed on an aromatic substrate bearing an electron-donating group (Scheme 3.7).



Scheme 3.7: Fluorination of aromatic chlorothionoformates with Py·BrF_3

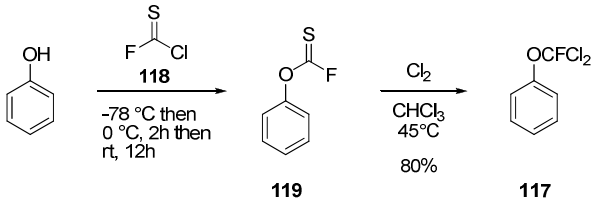
In 2006, L. Saint-Jalmes reported on the preparation of various aromatic mixed chloro/fluoro methyl ethers and thioethers.[20] This method was more applicable to a laboratory scale, as it described the selective chlorine/fluorine exchange on trichlorinated precursors with HF/pyridine and HF/triethylamine (Scheme 3.8).



Scheme 3.8: Controlled insertion of fluorine by reaction with HF/Py and HF/Et_3N

Trichloromethoxy benzene **112** provided chlorodifluoromethoxy benzene **111** in 97% yield with 40 equivalents of HF/pyridine, and dichlorofluoromethoxy benzene **117** in 93% yield with 40 equivalents of HF/triethylamine. This method presents the main advantage of using milder reagents such as HF/pyridine and HF/triethylamine instead of anhydrous HF.

To the best of our knowledge, only one other method has been reported for the obtention of dichlorofluoromethoxy aromatic compounds.[21] *O*-alkylation of phenol with carbonothioic chloride fluoride **118** (Scheme 3.9) provided the fluorothionoformate **119**, which was chlorinated in presence of gaseous chlorine to obtain the corresponding dichlorofluoromethoxy benzene **117** in 80% yield.



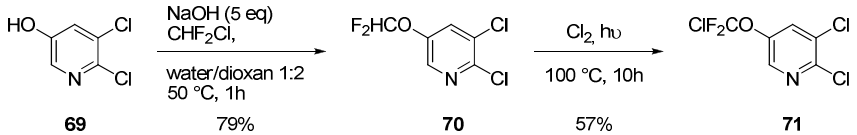
*Scheme 3.9: Chlorination of fluorothionoformate **119***

Despite its great efficacy, this method presents the drawback that very toxic and difficult-to-handle products are used, and that **118** is not commercially available.

Overviewing all the detailed methods, we can conclude that nucleophilic fluorination is a key step for the obtention of mixed chloro/fluoro methyl ethers. The preparation of chlorodifluoromethoxy compounds has been widely described, whereas the dichlorofluoromethoxy ones were only reported twice by mono-fluorination of the corresponding trichloromethoxy compound in presence of HF/triethylamine and by chlorination of a fluorothionoformate.

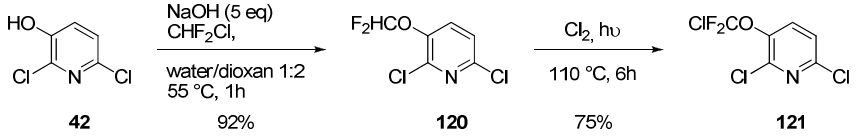
3.1.2. Preparation of –OCF_2Cl heteroaromatic compounds

The synthesis of heteroaromatic structures bearing mixed chloro/fluoro methyl ethers has scarcely been reported, and concerns OCF_2Cl-pyridines. The first reference described[22] the obtention of the pyridine **71** *via O*-alkylation of the hydroxy pyridine **69** with $CHClF_2$ (Freon 22) in 79% yield and subsequent photochlorination with 57% yield (Scheme 3.10).



Scheme 3.10: Preparation of 2,3-dichloro-5-OCF_2Cl pyridine

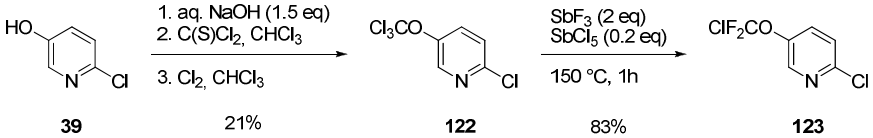
This has been reported to work only on chlorinated pyridines, as the alkylation step did not occur in the absence of chloro-susbtituents.[4] The same sequence applied to 2,6-dichloro-3-hydroxy pyridine **69** provided the final product **71** in comparable yields (Scheme 3.11).



42 92% **120** 75% **121**

Scheme 3.11: Preparation of 2,6-dichloro-3-OCF_2Cl pyridine

Recently, the obtention of an $-OCF_2Cl$ pyridine has been described *via* nucleophilic fluorination with antimony trifluoride in presence of catalytic antimony pentachloride.[23] 2-Chloro-5-hydroxy pyridine **39** was converted into the trichloromethoxy pyridine **122** (Scheme 3.12) by *O*-alkylation with thiophosgene and chlorination with gaseous chlorine in 21% yield. Subsequent fluorination led to the desired chlorodifluoromethoxy pyridine **123** in 83% yield.



39 21% **122** 83% **123**

*Scheme 3.12: Fluorination of the trichloromethoxy pyridine **122** with SbF_3*

Surprisingly, the fluorination provided only the difluorinated product **123**, which has been described to be very difficult to isolate in pure form.[24] Indeed, fluorination under these conditions usually leads to an unseparable mixture of the mono-, di- and trifluorination products. Nevertheless, this method proved to be very efficient, as the fluorination yield is excellent.

To the best of our knowledge, no method for the preparation of dichlorofluoromethyl ethers onto heteroaromatic compounds has yet been reported.

3.2. Objectives

In conclusion, almost all the described methods for the preparation of aromatic and aliphatic chlorodifluoromethyl ethers involve nucleophilic fluorination of the chlorinated precursor. The source of nucleophilic fluoride can be anhydrous HF, with sometimes addition of a Lewis acid such as antimony pentachloride or boron trifluoride. It can also be bromine trifluoride, which has provided chlorodifluoromethoxy arenes bearing strong electron-withdrawing groups and electron-rich $-OCF_2Cl$ benzenes when used as a complex with pyridine. Finally, milder reagents such as HF/pyridine can be used for the preparation of chlorodifluoromethoxy-substituted aromatic compounds.

An alternative to nucleophilic fluorination allows the synthesis of these building blocks: *O*-alkylation with $CHClF_2$ (Freon 22) followed by photochlorination provides the corresponding aromatic chlorodifluoromethyl ether.

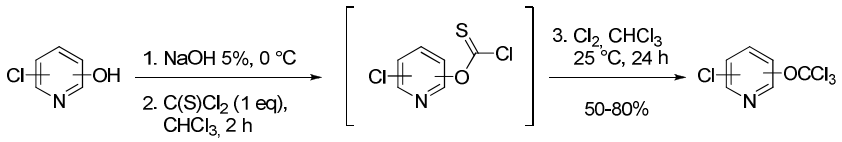
In contrast, only two methods have been described for the preparation of dichlorofluoromethoxy benzene. This compound was obtained by fluorination of trichloromethoxy benzene in presence of HF/triethylamine and by chlorination of fluorothionoformate.

The construction of $-OCF_2Cl$ and $-OCFCl_2$ groups onto heteroaromatic structures has been less studied. The preparation of chlorodifluoromethoxy pyridines has been described by

chlorination of difluoromethyl ethers and by fluorination of trichloromethoxy compounds in presence of antimony trifluoride and catalytic antimony pentachloride. However, the first method includes the use of Freon 22 which has limited commercial availability, and the second one often leads to an inseparable mixture of mono-, di- and trifluorinated products. To the best of our knowledge, dichlorofluoromethoxy-substituted heteroaromatic compounds have never been reported.

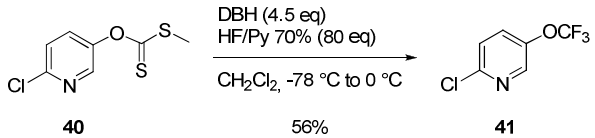
To conclude, we realised that there were very few existing methods for the preparation of mixed chloro/fluoro methyl ethers of heteroaromatic compounds and that they could be dramatically improved. Thus, we decided to study the preparation of such compounds, as they could be useful for the synthesis of molecules with potential biological activity. In some cases, they also could open a new access to trifluoromethoxy-functionalised heteroaromatic structures. A detailed study on the preparation of trifluoromethoxy pyridines has recently been described by our group,[4] which revealed the high interest in pyridines, present in numerous bioactive compounds.[25] Therefore, we decided to study the preparation of mixed chloro/fluoro methyl ethers on pyridines.

As a starting point, the previous study on trifluoromethoxy pyridines had provided an access to chlorothionoformates and to trichloromethoxy pyridines (Scheme 3.13) in moderate to very good yields from commercially available hydroxy pyridines. We decided to use these intermediates for the preparation of dichlorofluoro- and chlorodifluoro methyl ethers on pyridines. Thus, we decided to work with chlorinated pyridines, as they undergo *O*-alkylation readily. In addition, the presence of chlorine on the pyridine ring would not be an issue, as it can be easily removed by palladium-catalysed dechlorination (see chapter 2).



Scheme 3.13: Access to chlorothionoformates and trichloromethoxy pyridines from hydroxy pyridines

In 1992, T. Hiyama *et al.* described and oxidative desulphurisation-fluorination which led to aliphatic and aromatic trifluoromethoxy compounds.[26] These conditions had successfully been adapted to pyridine substrates (Scheme 3.14).[4]

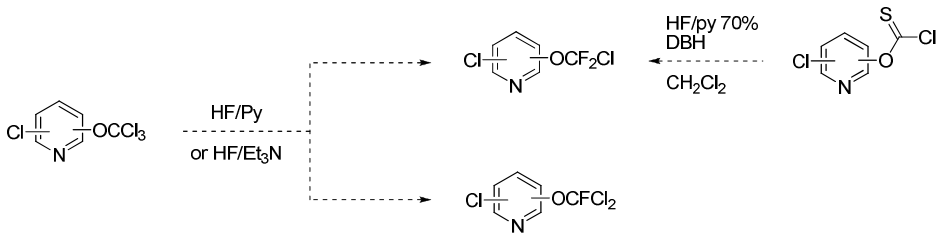


*Scheme 3.14: Obtention of **41** under oxidative fluorodesulphurisation conditions*

We chose to apply the oxidative desulphurisation-fluorination conditions to chlorothionoformates. This would allow us to control the insertion of fluorine, which is not the case when fluorination is performed on trichloromethoxy-substituted substrates with antimony trifluoride.

Another convenient approach was to adapt the reaction conditions described by L. Saint-Jalmes[20] on aromatic compounds, and to use them on pyridines in order to access mixed

chloro/fluoro methyl ethers. We decided to study the reactivity of trichloromethoxy pyridines towards HF/pyridine and HF/triethylamine. Thus, we could either obtain chlorodifluoro- or dichlorofluoromethoxy compounds (Scheme 3.15).



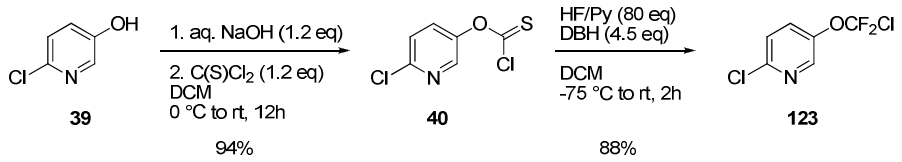
Scheme 3.15: Two possible pathways for the obtention of –OCF_2Cl and –$OCFCl_2$ pyridines

Therefore, we had selected two possible pathways for the synthesis of chlorodifluoromethoxy pyridines, and one for dichlorofluoromethoxy pyridines. We started our investigation with the oxidative fluorodesulphurisation.

3.3. Oxidative fluorodesulphurisation

The aim was to adapt the reaction conditions which had been described for the preparation of trifluoromethoxy pyridines from the corresponding *S*-methyl dithiocarbamate, which were different from Hiyama's conditions for aliphatic and aromatic substrates. The conversion of chloro hydroxy pyridines into chlorothionoformates was complete in each case, so we did not have to optimise this step. Finally, we decided to study the reactivity of 2-chloro-5-hydroxy pyridine **39** and to improve the reaction conditions on this substrate.

2-Chloro-5-hydroxy pyridine **39** was submitted to *O*-alkylation with thiophosgene in presence of aqueous sodium hydroxide in 94% yield (Scheme 3.16). Because chlorothionoformates have a high percutaneous toxicity they were isolated, but were not purified further, as crude ^{13}C and ^{1}H NMR showed that the conversion was complete and that the product was pure enough to be used for the next step.

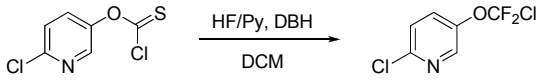


*Scheme 3.16: Preparation of chlorodifluoromethoxy pyridine **123** via **40***

The chlorothionoformate **40** underwent fluorination readily with eighty equivalents of HF/pyridine in presence of 4.5 equivalents of *N,N*-dibromohydantoin in dichloromethane to yield the chlorodifluoromethoxy pyridine **123** with 88% yield. No trace amounts of the $-OCF_3$ byproduct have been detected.

Given this positive result, we decided to optimise the reaction conditions. Indeed, the large amount of HF/pyridine which is used under these conditions considerably limits the scale-up of the reaction. Thus, we decreased the amount of HF/pyridine used for the reaction, as well as the equivalents of DBH used (Table 3-1).

Decreasing the amount of HF/pyridine from 80 equivalents to 40 equivalents did not have a great influence on the yield of the reaction (entries 1 and 2). In contrast, lowering to 20 and 10 equivalents of HF/pyridine had a detrimental effect on the yield (entries 3 and 5) and increased the reaction time.



40 **123**

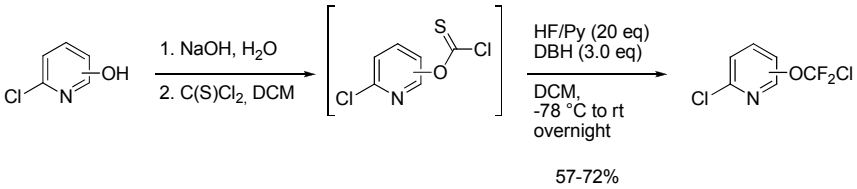
Entry	HF/pyridine	DBH	Reaction time	Yield	Observations
1	80 eq	4.5 eq	2h	88%	/
2	40 eq	4.5 eq	2h	92%	/
3	20 eq	4.5 eq	4h	76%	/
4	20 eq	3.0 eq	4h	72%	/
5	10 eq	4.5 eq	12h	57%	/
6	10 eq	2.0 eq	12h	56%	/
7	5 eq	4.5 eq	4 days	/	Uncomplete conversion

*Table 3-1: Optimisation of the fluorination of chlorothionoformate **40***

With only 5 equivalents of HF/pyridine, the conversion was not complete after four days (entry 7). Lowering the amount of DBH from 4.5 to 3.0 or 2.0 equivalents had no influence on the outcome of the reaction (entries 3 to 6).

Finally, we decided to use 20 equivalents of HF/pyridine, and 3.0 equivalents of DBH. Indeed, despite a diminished efficiency (entries 4 vs 2), it was the best compromise between the amount of reagent used and the yield.

In order to study the scope of the reaction, we decided to perform it with several hydroxy pyridines (Table 3-2). The chlorodifluoromethoxy pyridines **123**, **124** and **125** were obtained in 57 to 72% yield in one step from the corresponding hydroxy pyridines.



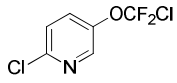
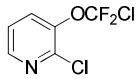
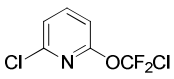
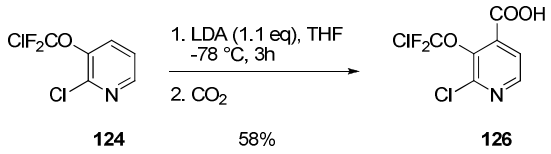
Entry	Substrate	No	Yield
1		**123**	72%
2		**124**	69%
3		**125**	57%

Table 3-2: Preparation of –OCF_2Cl pyridines via *chlorothionoformates*

With the optimised reaction conditions, we could decrease the amount of reagents used during the fluorination step. In this way, we developed an efficient and selective access to

chlorodifluoromethoxy pyridines in one step from the commercially available hydroxy compounds.

In order to access building blocks for further studies, one of these pyridines was submitted to metallation with LDA followed by trapping with carbon dioxide affording the carboxylic acid **126** (Scheme 3.17) with 58% yield.



124 58% **126**

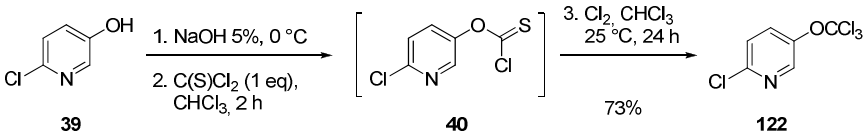
*Scheme 3.17: Carboxylation of chlorodifluoromethoxy pyridine **124***

This metallation reaction led to the desired carboxylic acid **126** in a moderate yield. This allowed us to show that these compounds could be accessed *via* a metallation reaction, and thus be used as building blocks for further synthesis. However, in order to obtain better yields the reaction conditions should be optimised changing the base or increasing the metallation time. Due to lack of time, these studies could not be performed.

To conclude, we developed an efficient synthesis of chlorodifluoromethoxy pyridines in one step from the commercially available hydroxy substrates. Functionalisation with a carboxylic acid was performed in low to moderate yields. The reactivity of these substrates could be further studied by functionalisation with other substituents such as amines and halogens in order to allow their use for the preparation of bioactive molecules as shown previously by our group with trifluoromethoxy pyridines.

3.4. Fluorination of trichloromethoxy pyridines

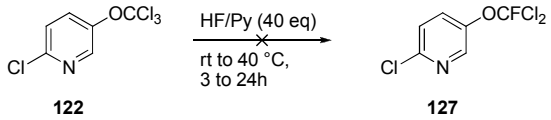
The second aim of this project was to study the reactivity of trichloromethoxy pyridines towards mild fluorinating agents: HF/pyridine and HF/triethylamine. As we had started the previous study with 2-chloro-5-hydroxy pyridine **39**, we decided to use the same substrate for the optimisation of the reaction conditions. The corresponding trichloromethyl ether **122** was prepared in one step with 73% yield by *O*-alkylation with thiophosgene and subsequent chlorination with gaseous chlorine (Scheme 3.18), in accordance with the method developed by our group.[4]



39 **40** 73% **122**

*Scheme 3.18: Preparation of 2-chloro-5-trichloromethoxy pyridine **122***

Once we had prepared the trichloromethyl ether **122**, we started the study of its reactivity. The first reagent we tested was HF/pyridine. Unfortunately, the substrate revealed to be inert towards this reagent (Scheme 3.19). We could not heat above 40 °C because according to its MSDS, HF/pyridine is not stable above 50 °C, and total recovery of the starting material was observed.

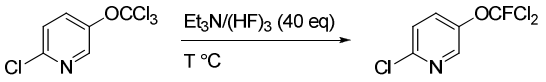


122 **127**

*Scheme 3.19: Attempt of fluorination of **122** with HF/pyridine*

We then performed the reaction with HF/triethylamine (Table 3-3), which is known to be less reactive than HF/pyridine but more stable at higher temperatures.[20] At room temperature, no reaction was observed (entry 1). When the temperature was gradually increased (entries 2 and 3) still no conversion was observed. Finally, at 90 °C for 24 h, the conversion into the dichlorofluoromethoxy compound **127** was complete (entry 4), and it was isolated with 84% yield.

The reaction was monitored by GC-analysis, and we observed a clean conversion to the monofluoromethyl ether. No byproduct was formed, and this was confirmed when we isolated the product. Therefore, thank to the use of HF/triethylamine, we could perfectly control the insertion of a single fluorine atom into the trichloromethoxy group. As outlined before this is rare, as generally the first and second fluorine introductions onto $-CCl_3$ derivatives are fast and the third is the rate-determining step.[17a]



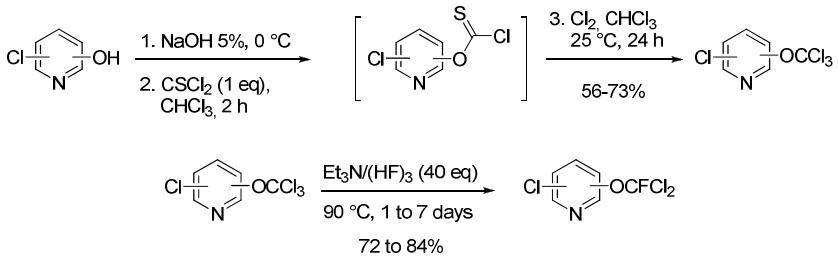
122 **127**

Entry	Temperature	Reaction time	Yield
1	rt	24 h	/
2	40 °C	12 h	/
3	60 °C	12 h	/
4	90 °C	24 h	84%

*Table 3-3: Optimisation of the fluorination of **122** with HF/triethylamine*

Now that the reaction conditions had been optimised and that a good yield had been reached, the reaction was performed with two other substrates in order to study its scope (Table 3-4). We prepared dichlorofluoromethoxy pyridines **127**, **128** and **129** bearing the fluorinated substituent at the 2- and 3-position of the aromatic ring in good 72 to 84% yields.

The mixed chlorine/fluorine methyl ethers were prepared in two steps from the commercially available hydroxy compounds, in moderate to good 43 to 62% overall yields.



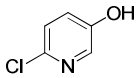
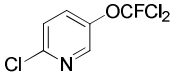
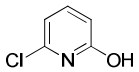
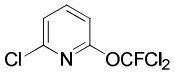
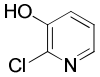
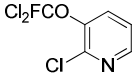
Entry	Starting material	Chlorination yield	Fluorination time	Final product	No	Fluorination yield
1		73%	24h		**127**	84%
2		56%	48h		**128**	76%
3		63%	7 days		**129**	72%

Table 3-4: Preparation of dichlorofluoromethyl ethers in two steps from the hydroxy pyridines

3.5. Conclusion

The literature that has been detailed showed that several methods for the preparation of mixed chloro/fluoro methoxy substituents onto aromatic compounds have been reported. Most of these methods consist in chlorine/fluorine exchange using nucleophilic fluorinating agents such as anhydrous HF, antimony trifluoride, bromine trifluoride, HF/pyridine and HF/triethylamine. *O*-Alkylation of hydroxy compounds leading to the difluoromethyl ether and subsequent chlorination to obtain the corresponding chlorodifluoromethoxy derivatives has also been reported. But this method using Freon 22 is not suitable because of its high global warming potential, which limits its commercial availability.

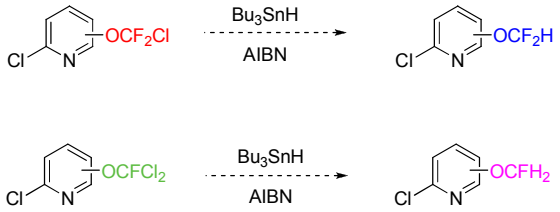
In contrast, the preparation of heteroaromatic structures bearing such fluorinated groups has been scarcely described. In each case, the product is an isolated example, and no general method has been reported. The aim of this project was to develop an access to pyridine building blocks bearing chlorodifluoromethyl and dichlorofluoromethyl ethers.

We first focused on applying Hiyama's oxidative fluorodesulphurisation conditions to a pyridine bearing a chlorothionoformate substituent. This provided the chlorodifluoromethoxy pyridine **123** in a good yield. After optimisation of the reaction conditions in order to reduce the amount of reagents used, the chlorodifluoromethoxy pyridines **123**, **124** and **125** were prepared in 57 to 72% yield. This was performed in one step from the commercially available hydroxy compounds. Finally, a carboxylation of these compounds was carried out in 58% yield.

Afterwards, we studied the reactivity of trichloromethoxy pyridines towards HF/pyridine and HF/triethylamine. We could perform the selective monofluorination with HF/triethylamine at 90 °C towards dichlorofluoromethoxy pyridines **127**, **128** and **128** in 72 to 84% yield. The final fluorinated methyl ethers were obtained in two steps with 43 to 62% yield from the starting hydroxy pyridines.

Hence, we provided an efficient, straightforward and selective access to chlorodifluoromethoxy and dichlorofluoromethoxy-substituted pyridines in one or two steps from commercially available starting materials. The fluorination steps have been performed in fair yields, and this represents the first general route to heteroaromatic compounds bearing this kind of fluorinated substituents.

This could lead to other fluorinated substituents: trifluoromethoxy compounds could be obtained by fluorination, and difluoromethoxy or fluoromethoxy substituents could be prepared *via* a reductive dechlorination under radical conditions (Scheme 3.20).



Scheme 3.20: Reduction of mixed chloro-/fluoro methyl ethers

Another outlook is the study of the reactivity of these building blocks. Their selective functionalisation by means of organometallic methods as demonstrated by our group on similar derivatives would allow the preparation of building blocks for agrochemical or pharmaceutical ingredients.

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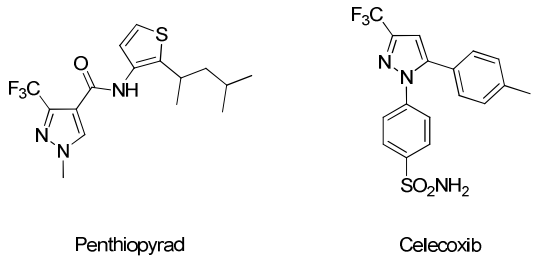
Chapter 4. Synthesis of 3,5-bis(fluoroalkyl) Pyrazoles

4.1. State of the art

The synthesis of fluoroalkyl pyrazoles has attracted considerable interest during the last decades. Indeed, their potential enhanced biological properties make them very attractive for the preparation of pharmaceutical and agrochemical ingredients.[1] Pyrazoles bearing a fluorinated group are present in numerous marketed bioactive molecules such as the fungicide Penthiopyrad (Mitsui chemicals) and Celecoxib (Pfizer), an anti-inflammatory agent (Figure 4.1).



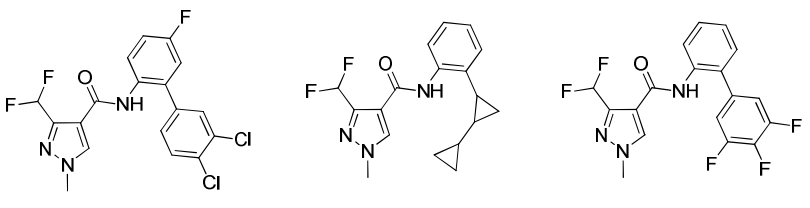
Penthiopyrad Celecoxib

Figure 4.1: Examples of bioactive fluoroalkyl pyrazoles

Several methods are described in the literature to prepare fluoroalkyl pyrazoles. Most of them consist in the use of fluorinated precursors and subsequent cyclisation. These fluorinated building blocks can be submitted to cyclocondensation with hydrazines to give the desired compounds (e.g., 1,3-diketones, α,β-unsaturated ketones, enaminones), or to 1,3-dipolar cycloadditions in the presence of diazomethane. Another way to obtain fluorinated pyrazoles is the construction of the fluoroalkyl group on the pyrazole ring.

It can also be noticed that the introduction of a single fluorine atom or a trifluoromethyl substituent have been widely studied, whereas the synthesis of difluoromethyl-substituted derivatives is scarcely described.[1] The most common perfluoroalkyl derivatives are those in which the fluorinated substituent is a trifluoromethyl group. In 2009, J. F. Sanz-Cervera *et al.* published a review on recent advances in the synthesis of pyrazoles, and a whole chapter is dedicated to the synthesis of trifluoromethylated pyrazoles.[2]

In agrochemistry, difluoromethyl pyrazoles represent a huge interest. Indeed, if they present a carbonyl function at the 4-position, they are key intermediates for the synthesis of carboxamide compounds (Figure 4.2). Pyrazole-carboxamides belong to the class of succinate-dehydrogenase inhibitors (SDHI) fungicides. Three major agrochemical companies recently marketed molecules from this class of fungicides, which shows the importance of the difluoromethyl pyrazole pattern.



Bixafen (Bayer CropScience) Sedaxane (Syngenta) Fluxapyroxad (BASF)

Figure 4.2: Pyrazole-carboxamides bearing a difluoromethyl substituent

In this context, we will first summarize the existing methods allowing the introduction of difluoromethyl substituents on pyrazole rings.

4.1.1. Synthesis of pyrazoles bearing one fluorinated group

4.1.1.1. From 1,3-diketones

Among the existing methods for the synthesis of pyrazoles, the use of diketones is widespread. Indeed, many of them are commercially available, and when it is not the case, their synthesis is possible *via* a *pseudo*-Claisen condensation.

This pathway is commonly used for the synthesis of Celecoxib analogues[3]. These molecules belong to the class of non-steroidal anti-inflammatory agents, and are cyclooxygenase-2 (COX-2) inhibitors. The pattern includes a pyrazole core, with aromatic substituents at the 1- and 5-positions, and a fluorinated substituent at the 3-position (Figure 4.3).

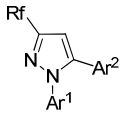
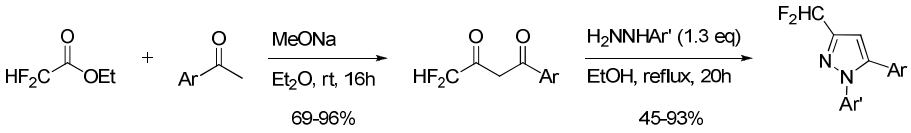


Figure 4.3 : Common pattern for COX-2 inhibitors

The cyclisation of 1-fluoroalkyl-3-aryl propanediones with aryl hydrazines leads to highly functionalised compounds in one step. The use of 1-difluoromethyl-3-aryl 1,3-diketones for the synthesis of pyrazoles has proven to be very efficient.[4] Indeed, several aromatic derivatives can be used, and the cyclisation yields are modest to very good (Scheme 4.1).

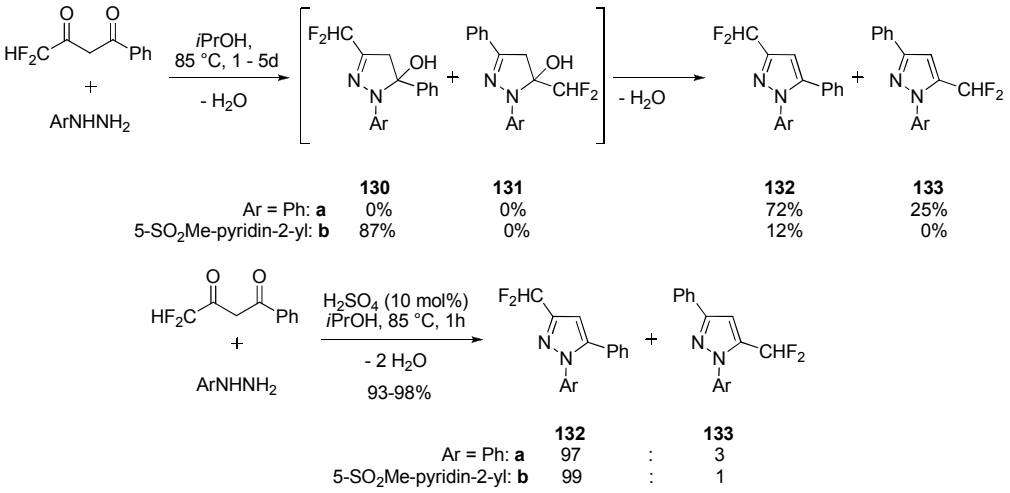


Scheme 4.1: Use of 1-CHF_2-3-aryl-1,3-propanedione

However, no regioselectivity issue is discussed, despite the well known problems of the reaction of hydrazines with 1,3-diketones.[5] It is also interesting to note that for this process the 1,3-diketones have to be prepared previsouly, not always in very good yields.

Similarly, T. Norris *et al.* described the synthesis of 3-CHF_2 pyrazoles[6] from the reaction of 1,3-diketones and aryl hydrazines (Scheme 4.2). When the reaction is carried out in isopropanol at 85 °C for one to five days under neutral conditions, depending on the nitrogen-substituent, either the formation of 3- and 5- difluoromethyl pyrazoles **132a** and **133a** (72% and 25% yield, respectively), or the formation of 3-difluoromethyl-5-hydroxy pyrazoline **130b** (87% yield) along with 3-difluoromethyl pyrazole **132b** (12%) has been observed.

The challenge working under neutral conditions is thus the regioselective formation of the hydroxy pyrazoline **130** and secondly its dehydration. Better results were obtained when 10mol% of concentrated H_2SO_4 were added to the reaction mixture. No un-dehydrated intermediates **130** and **131** have been observed, and the 3-/5- isomer ratios are of 97:3 and 99:1 depending on the aryl hydrazine. In addition, similar yields were obtained (93 and 98% respectively).

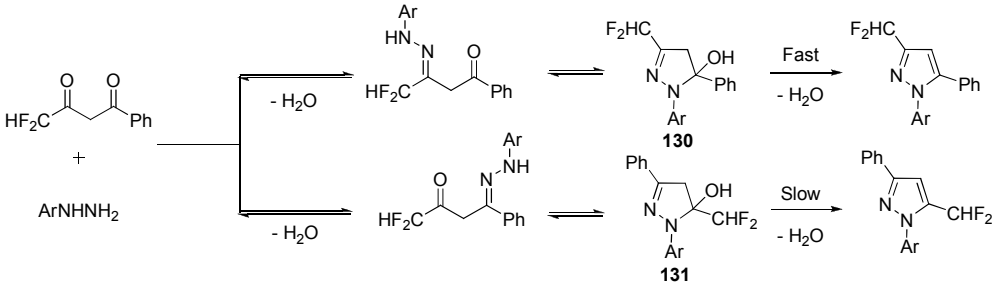


	130	131	132	133
Ar = Ph: **a**	0%	0%	72%	25%
5-SO_2Me-pyridin-2-yl: **b**	87%	0%	12%	0%

	132		133
Ar = Ph: **a**	97	:	3
5-SO_2Me-pyridin-2-yl: **b**	99	:	1

Scheme 4.2 : Synthesis of 3-CHF_2 pyrazoles by T. Norris et al.

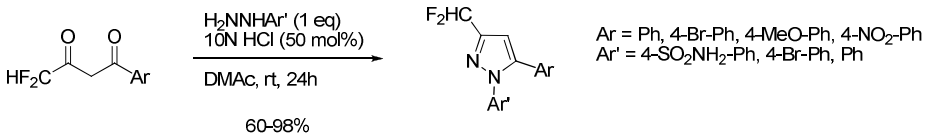
In order to explain this, the authors postulate different dehydration rates between both hydroxy pyrazolines **130** and **131** (Scheme 4.3). As previously explained by J. Elguero *et al.*,[5a] due to the electron withdrawing properties of the fluoroalkyl substituent, the second dehydration step is disfavoured when the hydroxy group is at the α-position to the -CHF_2-group compared to the other isomer.



Scheme 4.3 : Formation of one predominant regioisomer due to dehydration rates

Nevertheless, and certainly with the aim of synthesizing COX2-inhibitors (Celecoxib analogues), the study only refers to aryl hydrazines and aryl-fluoroalkyl 1,3-diketones in which the carbonyl groups have very different reactivities.

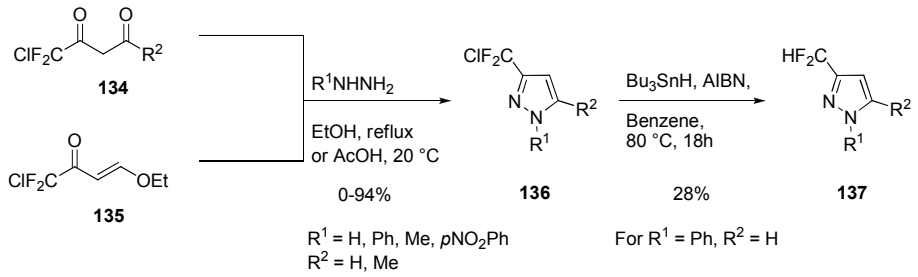
These conclusions were confirmed by F. Gosselin *et al.*, who observed that the addition of 50mol% of 10N HCl to the medium improves the regioselectivity.[7] Ratios from 86:14 to 99.8:0.2 for the 3-CFH_2/5-CHF_2 isomers have been observed. The yields are fair to excellent, between 60 and 98% depending on the diketone and the hydrazine used (Scheme 4.4). Once again, the study only refers to aryl hydrazines, and aryl-fluoroalkyl 1,3-diketones.



Scheme 4.4 : Influence of acidic medium on the regiochemistry

More recently, P. Langer and V. Iaroshenko reported on the synthesis of various bicyclic heterocycles (pyrazolo-, imidazolo-, pyrrolo- and thiazolo-pyridines) bearing a -CF_2Cl group on the pyridine moiety.[8] The authors converted the -CF_2Cl group into a -CF_2allyl or -CF_2H substituent by means of radical reactions initiated by AIBN with, respectively, Bu_3Sn(allyl) or

Bu_3SnH. Fair to good yields were obtained, depending on the nature of the heterocycle and its substitution pattern. Only a few examples concerning monocyclic heteroaromatic structures like pyrimidines and pyrazoles have been reported.



Scheme 4.5 : Radical reduction of the -CF_2Cl group into -CF_2H

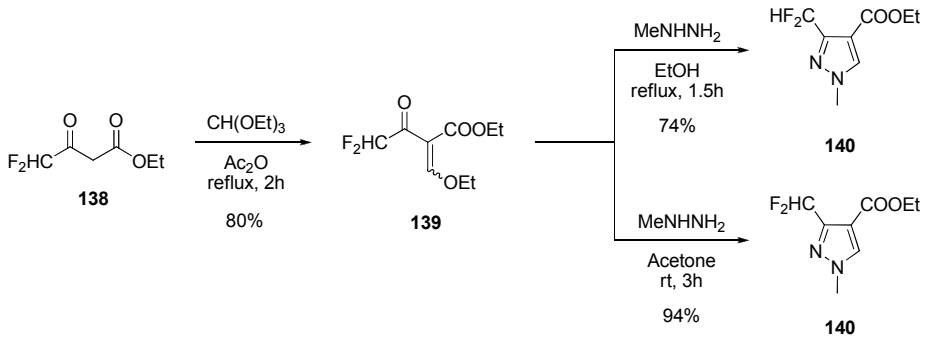
The synthesis starts with chlorodifluoromethyl 1,3-diketones **134** and enone **135** affording the corresponding pyrazoles **136** (Scheme 4.5). The conversion of the -CF_2Cl group into -CF_2H was only performed onto a *N*-phenyl pyrazole and led to the desired product **137** in a poor 28% yield.

To conclude this access route, some efficient methods have been developed to synthesise pyrazoles bearing a difluoromethyl group starting from 1,3-diketones. But regioselectivity remains an important issue because it cannot be predicted before the preparation of the heterocycle, even if some very good results have been obtained in isolated cases.

4.1.1.2. <u>From α,β-unsaturated ketones</u>

Given the unpredictable nature of heterocyclisations using 1,3-diketones, other routes towards difluoromethyl pyrazoles have been investigated. α,β-Unsaturated ketones appeared to be a convenient solution, as a great variety of them is accessible bearing an ethoxy methylene or a dialkylamino methylene fragment and have mainly been reported in patent applications.

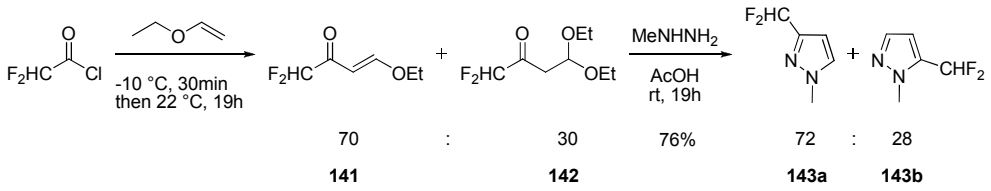
The first synthesis of ethyl difluoromethyl pyrazole carboxylate which has been reported starts from ethyl difluoro acetoacetate **138** which is converted into ethyl 2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate **139**.[9] The desired product **140** was obtained after cyclisation with hydrazine in a good 74% yield, but no information was given about the regioselectivity (Scheme 4.6).



Scheme 4.6 : First described synthesis from α,β-unsaturated ketones

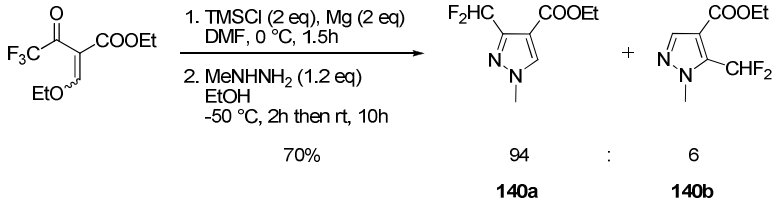
However, the difficult access to ethyl difluoroacetoacetate **138** at that time and the lack of regioselectivity of the cyclisation with hydrazine made the product rather expensive. Hence, there was a need to find a better alternative for the synthesis of pyrazoles, or to improve the existing process. When the cyclisation was carried out in acetone[10] at room temperature instead of ethanol, the yield was increased to 94% with complete regioselectivity (Scheme 4.6).

Fluorinated enones can be obtained by reaction of difluoroacetyl chloride with ethyl vinyl ether.[11] No yields are reported, but a side product **142** is obtained along with the desired enone **141** in a 70:30 ratio (Scheme 4.7). After cyclisation with methyl hydrazine, a 72:28 mixture of 3- and 5- isomers **143a** and **143b** has been observed. Further bromination of the heterocycle can allow functionalisation at the 4-position of the pyrazole ring.



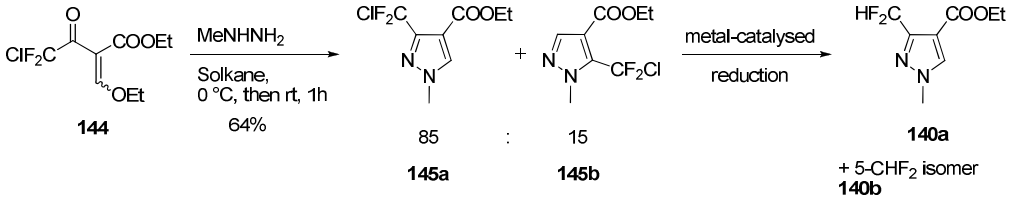
Scheme 4.7 : Starting from difluoroacetyl chloride

The reductive defluorination of trifluoromethyl enone with activated magnesium and trimethylsilyl chloride[12] and subsequent cyclisation with methyl hydrazine afforded the ethyl difluoromethyl-4-carboxylate pyrazole **140** in 70% yield. The 3-CHF_2 isomer **140a** has been obtained in a 94:6 ratio with the 5-difluoromethyl isomer **140b** (Scheme 4.8).



Scheme 4.8 : Reductive defluorination followed by cyclisation

M. Braun and J. Jaunzems recently developed an original access to difluoromethyl pyrazoles.[13] It consists in the cycloaddition of chlorodifluoromethyl enone **144** with methyl hydrazine followed by metal-catalysed reductive dechlorination of the -CF_2Cl substituent (Scheme 4.9).

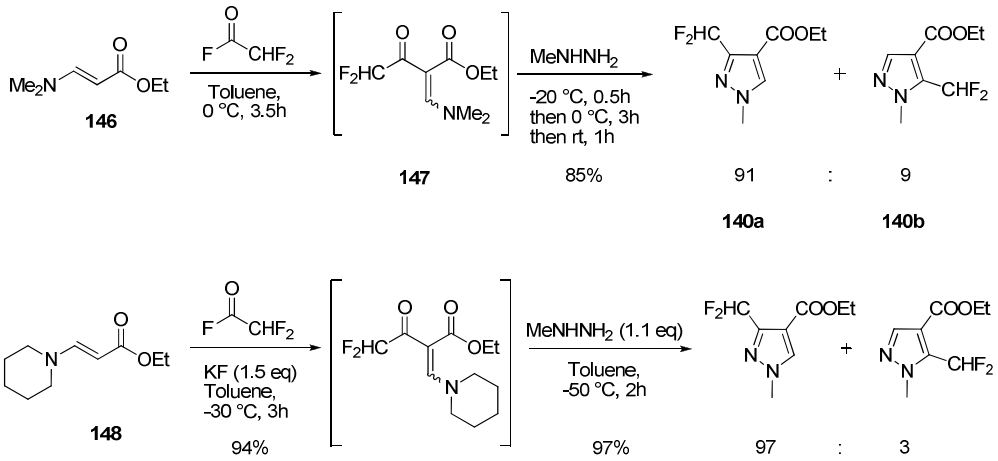


Scheme 4.9 : Catalytic dechlorination of the chlorodifluoromethyl substituent

The cyclisation was performed in a fluorinated solvent (Solkane®) in 64% yield and the product was obtained in a 85:15 ratio between the 3- and 5-chlorodifluoromethyl isomers **145a** and **145b**. It is interesting to note that the reduction of the -CF_2Cl substituent was performed under different conditions: Zn/CsF in EtOH/water 9:1 (97% yield), 20% Pd/C (1mol%) in presence of Borax (79% yield), and with Raney-Ni and Rh/Al_2O_3 catalysts, but in the last two

cases the product **140** was formed along with the reduced -CH_3 product. This approach provides an alternative to rather expensive difluoromethyl starting materials, but the yields and regiochemistry should be improved to make it competitive.

Di(alkyl)amino acrylates **146** are widely used, and the introduction of the fluorinated substituent can be done by reaction with difluoromethyl acyl fluoride to provide the desired adduct **147** (Scheme 4.10). Addition of methyl hydrazine to the dimethylamino adduct **147** affords the desired 3-difluoromethyl pyrazole **140** in 85% yield.[14] The regioselectivity is rather good: the 3- and 5-difluoromethyl isomers **140a** and **140b** are obtained in a 91:9 ratio.

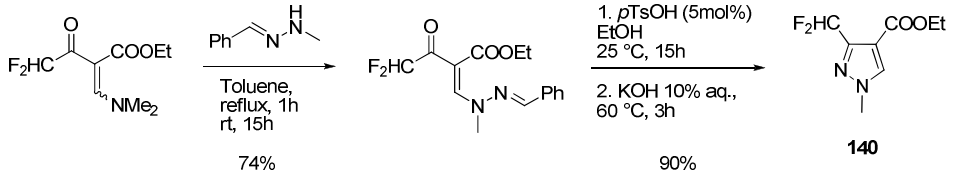


Scheme 4.10 : Use of acylfluorides and dimethylamino acrylates

The yield and selectivity of this method can be improved[15] by the use of the piperidinyl derivative **148**, the addition of potassium fluoride for the preparation of the fluorinated enone, and the lower temperature for the cyclisation step. The starting material is commercially available, but it is synthesised on demand involving very high prices.

Although these one-pot syntheses of 3-CHF_2 pyrazoles are rather efficient, their main drawback is the use of very toxic and volatile acyl fluorides.

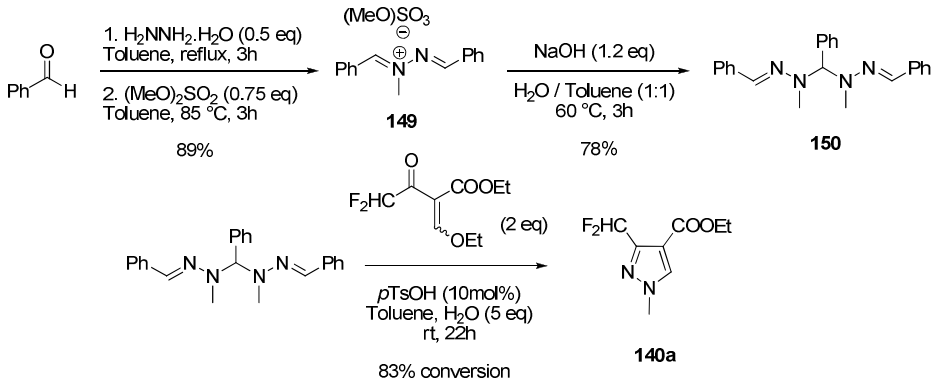
In order to have a better control on the regiochemistry of the reaction, the protection of hydrazines with a benzylidene group has been successfully studied,[16] and cyclisation provided the 3-difluoromethyl isomer **140a** as a single product in 90% yield (Scheme 4.11).



Scheme 4.11 : Cyclisation using benzylidene hydrazones

In a similar manner, hydrazine hydrate was transformed into dibenzaldazine by reaction with two equivalents of benzaldehyde (Scheme 4.12), and then methylated in presence of dimethyl sulphate to yield **149** in 89% (one-pot).[17] The conversion into the aminal **150** in a basic medium followed by cyclocondensation with the difluoromethyl enone yielded the desired 3-difluoromethyl pyrazole-4-carboxylate **140a** as a single isomer.

A very elegant one-pot procedure from the hydrazine to the saponified pyrazolic acid was performed in 64% yield, which is remarkable given the number of steps. Nevertheless, the process is quite tedious and an easier method would be preferable.[17]

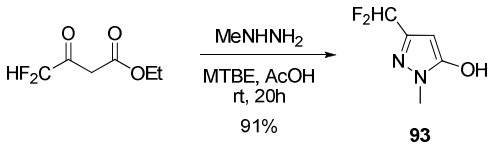


Scheme 4.12 : Cyclisation via *dibenzaldazine*

It should be mentioned that all the methods detailed here are based on the utilisation of difluoromethyl α,β-unsaturated ketones. Hence, they require a commercial access to the main starting material for their preparation: difluoroacetic acid or ethyl difluoroacetate.

4.1.1.3. From β-keto esters

Surprisingly, only one approach was detailed for the use of β-keto esters to obtain fluoroalkyl hydroxy pyrazoles. β-Keto esters are known to react with hydrazines to give the corresponding hydroxy pyrazoles,[18] but once again, the regioselectivity is an issue as two regioisomers can be formed.



Scheme 4.13 : From difluoromethyl acetoacetate

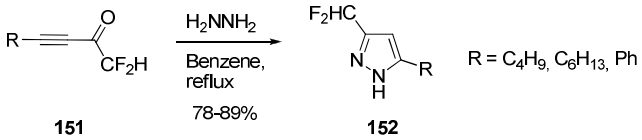
It has been shown[19] that in presence of an acid (acetic or formic acid), the regioselectivity of the cyclisation is total in favour of the 3-difluoromethyl-5-hydroxy pyrazole **93** (Scheme 4.13). The reaction was carried out in methyl-*tert*-butyl ether at room temperature. In the described process, all reagents are commercially available, and the cyclisation yields are high (>90%).

4.1.1.4. From perfluoro acetylenes

Acetylenic carbonyl derivatives can be considered as equivalent to enones. Their use in the synthesis of pyrazoles is less common, and fluoroalkyl acetylenes are most often used in 1,3-dipolar cycloaddition reactions with diazomethane.[20] No such process is described for the synthesis of difluoromethyl pyrazoles. Instead, β-acetylenic ketones and β-acetylenic esters have been used for cyclocondensations with hydrazines to provide respectively difluoromethylated pyrazoles and hydroxy pyrazoles.

The first reference[21] reporting on the synthesis of 3-difluoromethyl pyrazoles from acetylenes describes a cyclisation in benzene by azeotropic removal of water in good yields (Scheme 4.14).

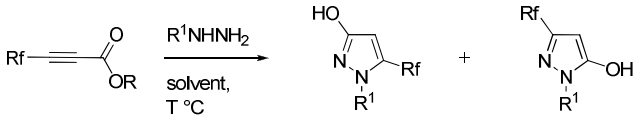
The mechanism can imply two pathways: either the nucleophilic attack of hydrazine on the carbonyl function of **151** or *via* a Michael-type addition followed by ring closure and aromatisation to form the pyrazole **152**. Given that the reaction has only been performed with hydrazine, the mechanism has not been identified.



151 **152**

Scheme 4.14 : Use of β-keto acetylenes

The reaction of acetylenic esters for the preparation of 3- and 5-hydroxy pyrazoles has been detailed by B. C. Hamper *et al.*[22] Depending on the solvents and temperatures, 3- and/or 5-difluoromethyl isomers can be obtained. When the reaction is performed in a 1:1 mixture of methanol and water at 0 °C, the ratio **154 a/b** is 35:65 (entry 4), whereas in dichloromethane at 25 °C, the **154 a/b** ratio is 5:95, with unchanged yields (Table 4-1).



153 **154a** **154b**

Entry	Rf	R^1	**a/b** Ratios		Yield (%) [c]
			H_2O/CH_3OH [a]	CH_2Cl_2 [b]	
1	C_2F_5	CH_3	98:2	98:2	98
2	CF_3	CH_3	94:6	71:29	80
3	CF_2Cl	CH_3	95:5	95:5	79
4	CF_2H	CH_3	35:65	5:95 [d]	22 [e]
5	CF_3	*tert*-butyl	0:100	/	n. d.

[a] MeOH/H_2O 1:1, 0 °C. [b] -78 °C. [c] Except as noted, yields from isolated products **154** of the reaction in methanol/water. [d] 25 °C. [e] Isolated yield obtained from the reaction in dichloromethane.

Table 4-1: Use of acetylenic esters

As this study has been made on different fluorinated substituents, the results obtained show that, in a 1:1 mixture of methanol and water, the amount of 3-Rf isomer increases when the electron-withdrawing properties and the size of the fluorinated substituent decrease. The regioselectivity is only totally controlled with a trifluoromethyl substituent and a bulky alkyl group on the hydrazine (entry 5).

4.1.1.5. By introduction of the fluorinated group *via* the hydrazine

Another way towards difluoromethyl pyrazoles is *via* the introduction of a fluorinated substituent on the hydrazine itself to form the corresponding hydrazone. One of the significant advantages of this approach is a better control of the regioselectivity during the cyclisation step.

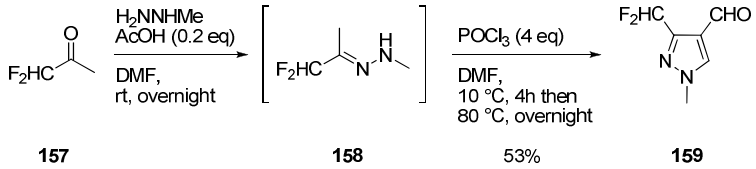
In this perspective, M. Bowden *et al.* chose to use methyl difluoroacetate **155** to introduce the fluorinated substituent instead of the acetylene.[23] After reaction with hydrazine (Scheme

4.15) the obtained hydrazide **156** was methylated exclusively at the NH_2 position in presence of Pt/C, H_2, and dimethyl formamide in 36% yield.

Scheme 4.15 : Use of difluoromethyl acetate

Cyclisation occurs by reaction with ethyl propargylate in DMF to form the desired 3-difluoromethyl pyrazole **140a**. No yield is given for this step but the regioselectivity is total.

Similarly, the difluoromethyl methyl ketone **157** can be converted into the hydrazone **158** and subsequently cyclised under Vilsmeier-Haack conditions[24] to yield 1-methyl-3-difluoromethyl-4-carbaldehyde **159** in 53% yield as a single isomer (Scheme 4.16).



Scheme 4.16 : Use of 1,1-difluoroacetone

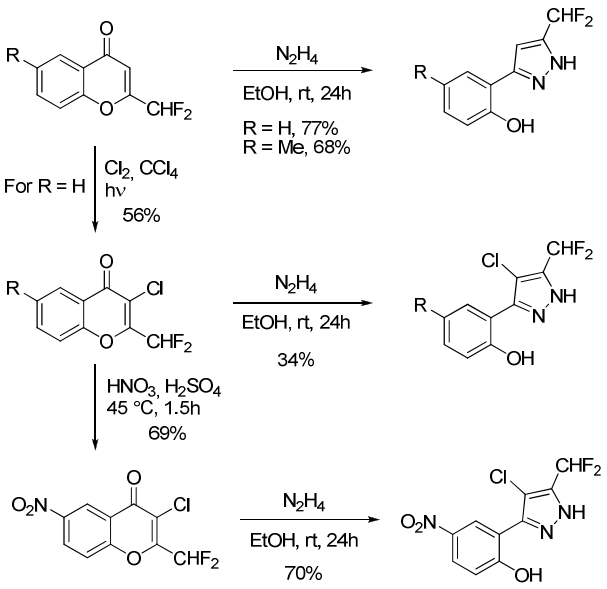
This product can be further oxidised to the carboxylic acid in presence of H_2O_2 and sodium hydroxide, and thus be used in the formation of carboxamides.

These strategies present several advantages: they provide only one isomer of difluoromethyl pyrazoles, and the starting materials (difluoromethyl acetate and difluoroacetone) are commercially available at reasonable prices. But the main weakness is the relatively low yields, and these processes can difficultly be used on an industrial scale.

4.1.1.6. From Chromones

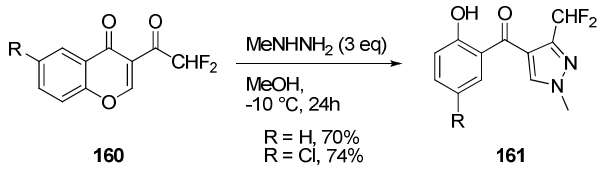
The research group of V. Ya. Sosnovskikh reported on the reactivity of fluorinated chromones, which can lead to fluorinated pyrazoles by ring transformation.[25] Chromones can be compared to "hidden" aryloxy enones, and they react readily with hydrazine to give fluoroalkyl pyrazoles bearing an aryl group at the 3-position.

This study is mostly focused on trifluoromethyl pyrazoles, but a few examples with difluoromethyl substituents have been mentioned (Scheme 4.17). The desired pyrazoles have been obtained in moderate to good yields, depending on the substituent on the aromatic ring.



Scheme 4.17 : Reactivity of fluorinated chromones

The reactivity of fluoroacyl chromones towards several hydrazines has also been studied (Scheme 4.18). In two examples, difluoromethyl starting materials **160** exclusively yielded the 3-difluoromethyl isomer **161** by reaction with methyl hydrazine in reasonable 70% (R = H) and 74% (R = Cl) yields.



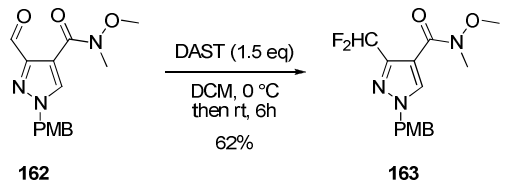
Scheme 4.18 : Reactivity of fluoroacyl chromones

This method opens an access to already functionalised difluoromethyl pyrazoles in moderate to good yields.

4.1.1.7. <u>By fluorination on the pyrazole ring</u>

When fluorinated starting materials are not easily accessible, an alternative is the construction of the fluorinated substituent on the heteroaromatic structure. Ideally, this step should present high yields and mild conditions since pyrazoles are quite sensitive substrates.

DAST (diethylaminosulfur trifluoride) usually employed for the conversion of alcohols and aldehydes into fluoroalkyl and difluoroalkyl compounds[26] has been used for this purpose on pyrazoles.[27] Pyrazolic aldehydes **162** have been converted into the difluoromethyl substituent **163** with DAST in 62% yield (Scheme 4.19).

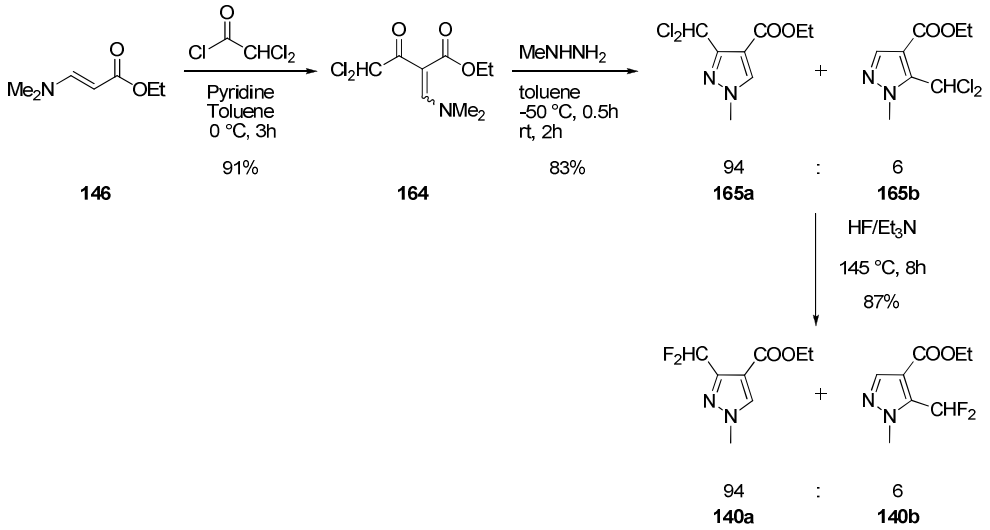


Scheme 4.19 : Fluorination of pyrazolic aldehydes with DAST

This method does not require the preparation of fluorinated precursors, but necessitates a reasonable synthetic pathway towards the pyrazolic aldehyde before fluorination.

Another option for the synthesis of difluoromethyl substituents on pyrazoles is the displacement of chlorine atoms using nucleophilic fluorination reagents. The reaction conditions have been found to be ideal with the use of a selective and mild fluorinating reagent such as triethylamine trishydrofluoride (TREAT-HF).

In this context, the regioselective synthesis of the 3-dichloromethyl pyrazole **165** from the enaminone **146** has been described[28] (Scheme 4.20). Its conversion into the corresponding chlorinated dimethylamino acetoacetate **164** by reaction with dichloromethyl acetyl chloride was achieved in high yield. Subsequent cyclisation with methyl hydrazine in toluene led to the desired 3-dichloromethyl-4-carboxylate pyrazole **165a** along with its 5-dichloromethyl isomer **165b** in a 94:6 ratio, and in a good 83% yield.

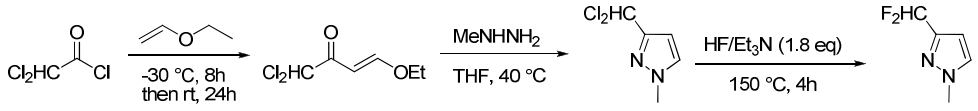


Scheme 4.20 : Fluorination of dichloromethyl pyrazole with TREAT-HF

The dichloromethyl pyrazole **165** was finally fluorinated in presence of TREAT-HF in 87% yield. The synthesis of the difluoromethyl pyrazole **140** was also reported using directly difluoromethyl acetyl chloride, but this led to lower yields, and to a mixture of 3/5 isomers in a 89:11 ratio.

In 2009, O. C. Kappe proposed a microwave-assisted fluorination[29] of similar substrates. The highly polar properties of TREAT-HF proved to be compatible with microwave irradiation, and the fluorination of **165** was completed within five minutes at 250 °C in 69% yield. However, the desired product was formed along with ca. 10% of the saponification product. The use of methoxymethyl(dimethylamino) acrylate[30] instead of ethyl(dimethylamino) acrylate led to a lower yield for the cyclisation step, and a comparable fluorination yield.

A similar method has been employed later,[31] starting from the dichloroacetyl chloride **166**, which yields 63% of the ethoxy enone **167** by reaction with ethyl vinyl ether (Scheme 4.21). Unfortunately, neither the yields nor the 3-/5-dichloromethyl isomer ratio were reported. Fluorination with TREAT-HF provided the desired pyrazole **143a** in 51% yield.



*Scheme 4.21 : Cyclisation of dichloromethyl ethoxy enone **167***

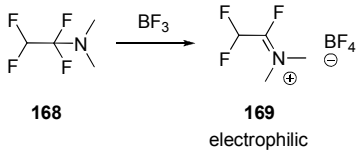
The fluorination of the dichloromethyl group of pyrazoles using TREAT-HF, either by thermal heating or microwave-assisted has proven to be very efficient. This represents a good alternative to the construction of the heterocycle with fluorinated precursors. However, the pyrazole moiety has to be compatible with the fluorination conditions.

4.1.1.8. <u>*Via* the use of FAR</u>

In the bibliographic data which has been detailed until now, several methods for the construction of difluoromethyl pyrazoles have been outlined. Most of them use fluorinated precursors, which are derivatives of difluoro acetic acid: esters, acyl chlorides or acyl fluorides. Additional possibilities are nucleophilic fluorinations: utilisation of chlorinated derivatives and subsequent reaction with TREAT-HF and fluorination of aldehydes using DAST.

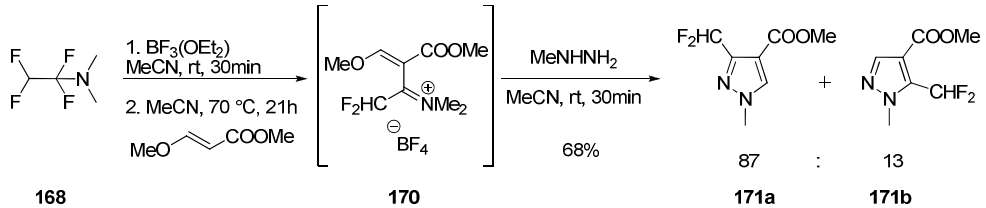
Another approach has been developed employing polyfluorinated amines, also called FAR (fluoroalkyl amino reagents). This class of reagents is commonly used for the fluorination of alcohols and activated carbonyls. More precisely, the use of 1,1,2,2-tetrafluoroethyl dimethylamine (TFEDMA) has been widely studied. We will discuss this topic more thoroughly in a following paragraph (4.1.4).

C. Wakselman *et al.* showed that by reaction with BF_3, this reagent can be activated[32] (Scheme 4.22). Thus, under these conditions, the ammonium salt of TFEDMA **168** can be considered as an electrophilic difluoromethyl-transfer reagent, and has been used for this purpose in the synthesis of difluoromethylated pyrazoles.



Scheme 4.22: Activation of TFEDMA

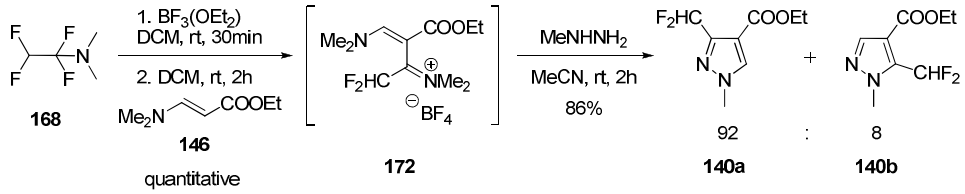
It appeared in the literature[33] that the ammonium salt **169** of TFEDMA can be attacked by methyl methoxyacrylate to give the corresponding adduct **170** (Scheme 4.23). Addition of methyl hydrazine to the reaction mixture yields the desired pyrazole **171** (68%) in a 87:13 mixture of the 3-CHF_2 and the 5-CHF_2 isomers respectively.



Scheme 4.23 : Reaction of TFEDMA with methoxy acrylate

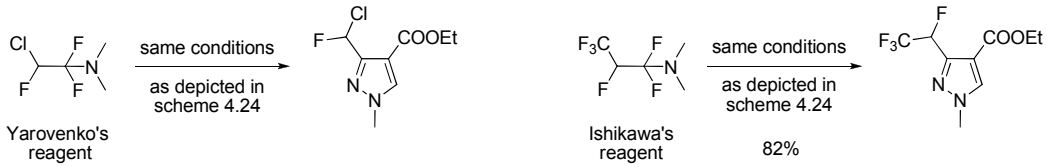
S. Pazenok *et al.*[34] also reported on the use of TFEDMA **168**. After activation with $BF_3(OEt_2)$ it reacted with dimethylamino acrylate **146** affording the intermediate **172**.

Cyclisation with methyl hydrazine led to 3- and 5-difluoromethyl pyrazoles **140a** and **140b** in 86% yield. It has to be outlined that the regiochemistry has been increased from 87:13 for the methoxy acrylate to 92:8 for the dimethylamino acrylate (Scheme 4.24).



*Scheme 4.24 : Use of TFEDMA with the dimethylamino acrylate **146***

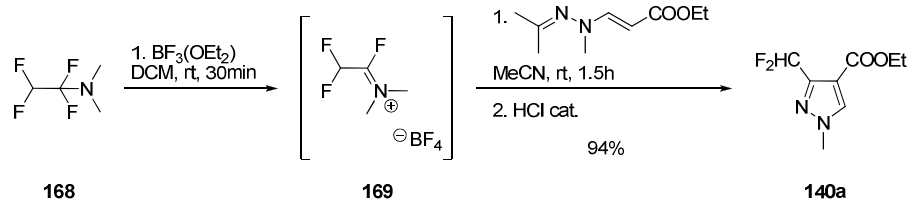
This approach is very versatile as other FAR can be used either to introduce a chlorofluoromethyl group or a 1,2,2,2-tetrafluoroethyl substituent at the position 3 of the pyrazole (Scheme 4.25).[34]



Scheme 4.25 : Use of other FAR

Although the cyclisation yield with Yarovenko's reagent is not given and the regioselectivities are not specified, this method is one of the most efficient and straightforward. Indeed, the fluorinated precursors are commercially available, and do not need any transformation before being used for the preparation of fluoroalkyl pyrazoles.

In order to enhance the regioselectivity of the cyclisation step, the reaction of the dimethylamino acrylate with a methyl hydrazone can be performed[35] (Scheme 4.26). It is coupled with the introduction of the fluorinated group *via* TFEDMA **168** to give the desired 3-difluoromethyl pyrazole **140a** in a high 94% yield and as the only regioisomer.



Scheme 4.26 : Coupling of TFEDMA with a methyl hydrazone

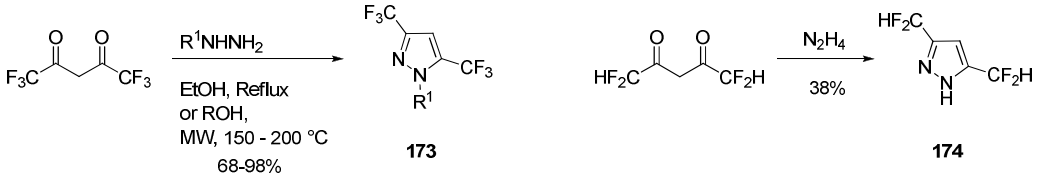
Having detailed all the principal methods for the obtention of 3-difluoromethyl pyrazoles, we can summarize that among these processes, most of them are using derivatives of difluoroacetic acid, others involve nucleophilic fluorinating reagents, or FAR. On a practical point of view, methods using DAST or chromones could difficultly be brought to an industrial scale. Most of the described synthetic pathways using 1,3-diketones provide highly functionalised pyrazoles. Difluoromethyl pyrazole building blocks can be produced in high yields, but the regioselectivity of the cyclisation reactions remains a challenge.

4.1.2. Synthesis of pyrazoles bearing two fluorinated groups

The synthesis of pyrazoles bearing two fluorinated groups is far less described, and is also more developed for -CF_3 derivatives. However, some approaches have been developed, as 3,5-bis(fluoroalkyl) pyrazoles represent an important pattern for bioactive molecules.[36]

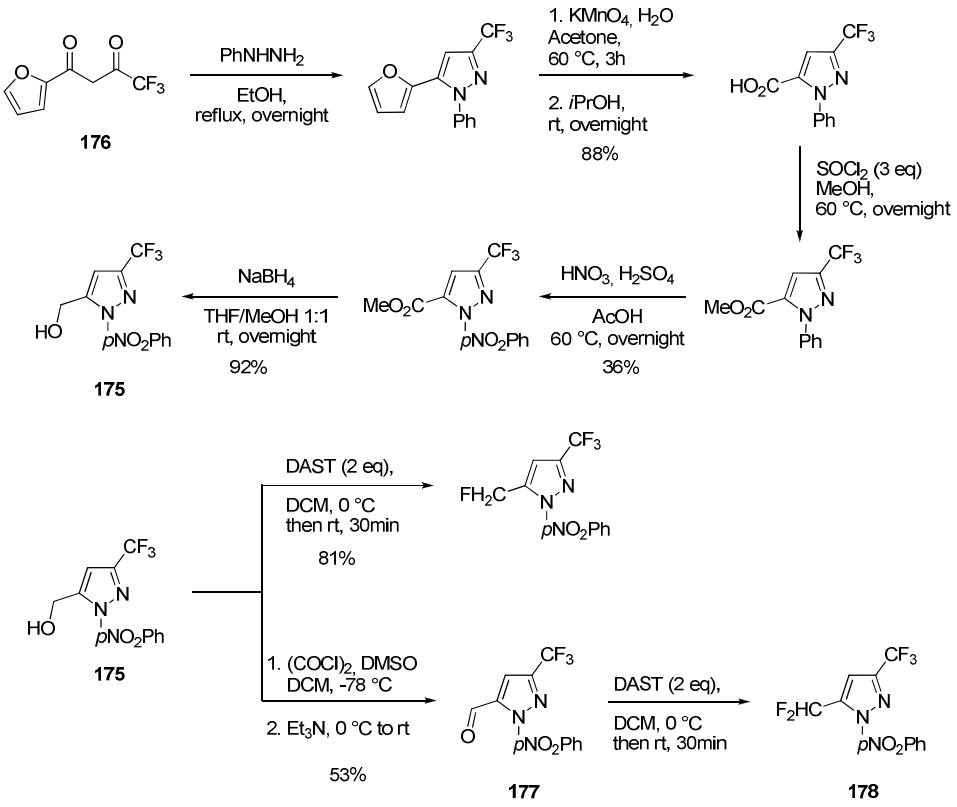
4.1.2.1. 3,5-Bis(fluoroalkyl) pyrazoles

Most of the reports found in the literature describe the synthesis of 3,5-bis(trifluoromethyl) pyrazoles **173** from 1,3-bis(trifluoromethyl) diketone.[37,5b] They are either obtained by [2+3] cycloaddition followed by dehydration in ethanol or isopropanol at reflux, or by microwave irradiation (Scheme 4.27). A few patents and only one journal article[38] describe the obtention of 3,5-bis(difluoromethyl) pyrazole **174** starting from symmetrical 1,3-difluoromethyl diketone.



Scheme 4.27: Synthesis of symmetrical 3,5-bis(fluoroalkyl) pyrazoles

To the best of our knowledge, only one protocol for the synthesis of unsymmetrical 3,5-bis(fluoroalkyl) pyrazoles has been reported.[36b] First, the 5-CF_3-substituted pyrazole **175** is synthesised from 1,3-diketone **176** in five steps (Scheme 4.28).



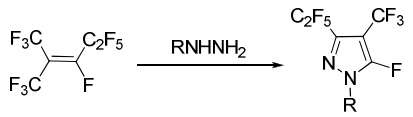
Scheme 4.28: Preparation of 5-trifluoromethyl intermediates and their fluorination

Subsequently, the hydroxymethyl group at the 3-position of pyrazole **175** is transformed into a -CFH_2 in 81% yield. It can also be oxidised under Swern conditions to yield 53% of aldehyde **177**, which is transformed into a -CF_2H group in presence of DAST to form pyrazole **178** (no yield is given for the conversion of the aldehyde) (Scheme 4.28).

This method is very efficient, and presents good yields for the fluorination steps. However, the main drawback is the tedious preparation of the alcohol **175** and aldehyde **177**. Indeed, this multistep synthesis presents restrictive stages, and the yields are not always given.

4.1.2.2. 3,4-Bis(fluoroalkyl) pyrazoles

Some syntheses are reported for 3,4-fluoroalkyl pyrazoles **180** by reaction of perfluoro-2-methylpent-2-ene[39] **179** (Scheme 4.29). Depending on the hydrazine, the *N*-substituent can be fluorinated or not, and sometimes its deprotection occurs during the cyclisation to give the free *N*-H pyrazoles. But among all these references, none of them details the presence of a difluoromethyl substituent at any position of the pyrazole ring.



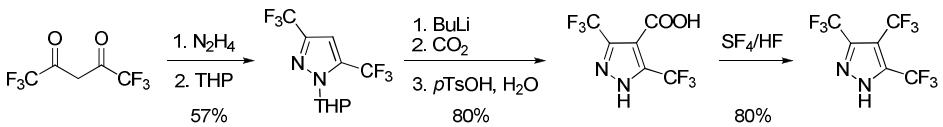
179 **180**

Scheme 4.29: 3,4-Bis(perfluoroalkyl) pyrazoles

After having examined all literature references, we can claim that a straightforward, reproducible and efficient method for the synthesis of pyrazoles bearing two fluorinated groups is severely missing. The development of such a tool would be very useful for the synthesis of new active ingredients, as we have seen before that the pyrazole core is present in numerous agrochemical and pharmaceutical compounds.

4.1.3. Synthesis of pyrazoles bearing three fluorinated groups

Only one recent literature reference mentions the synthesis of pyrazoles bearing three fluorinated substituents[40] (Scheme 4.30).



181 **182** **183**

Scheme 4.30 : Synthesis of 3,4,5-Tris(trifluoromethyl) Pyrazole

3,4,5-Tris(trifluoromethyl) pyrazole **183** was synthesised by cyclisation of the fluorinated 1,3-diketone with hydrazine. Subsequent protection of the nitrogen atom followed by metallation in presence of butyllithium, trapping with carbon dioxide and deprotection led to the carboxylic acid **182**. Finally, fluorination of the carboxylic function with sulphur tetrafluoride in presence of HF afforded 3,4,5-tris(trifluoromethyl) pyrazole **183** in 80% yield. The multistep synthesis presents an overall yield of 36% over five steps. It can be scalable, and brought to industrial scale.

We can conclude that methods for the synthesis of pyrazoles bearing more than one fluorinated substituent are very rare, and that the ones existing are almost impossible to scale up, mainly because of their cost. Furthermore, only one method depicts the preparation of pyrazole building blocks containing different fluoroalkyl substituents. At the beginning of our study, there was a real need for a new straightforward method for the synthesis of pyrazoles bearing two different fluorinated substituents.

Fluoroalkyl amino reagents are commonly used as fluorinating reagents. Their use, more precisely the use of 1,1,2,2-tetrafluoroethyl dimethylamine (TFEDMA) as difluoromethyl-transfer reagent has showed to be very efficient. The regioselectivity can be controlled, and high cyclisation yields have been observed.

4.1.4. α,α-Fluoroalkyl Amino Reagents (FAR)

FAR are selective fluorinating agents, commonly used for the synthesis of alkyl fluorides and *gem*-difluorides by reaction with alcohols and activated carbonyls. A wide variety of FAR have been developed, but the most commonly used are Yarovenko's and Ishikawa's reagents, as well as 1,1,2,2-tetrafluoroethyl dimethylamine (TFEDMA).

In 1959, N. N. Yarovenko and M. A. Raksha[41] introduced the first FAR **184** (Figure 4.4), then R. V. Lindsey and coworkers reported on the preparation of TFEDMA[42] **168**, and finally N. Ishikawa developed his own reagent **185** in 1979[43].

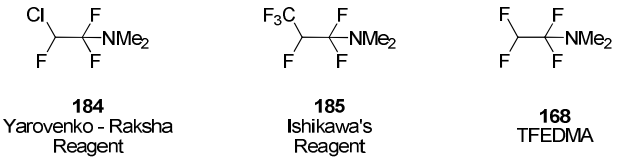
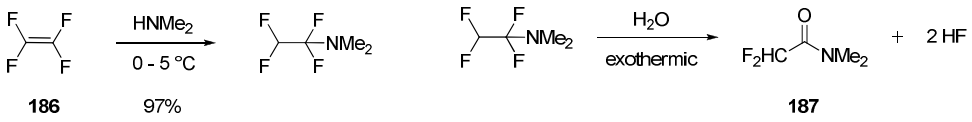


Figure 4.4 : Fluoroalkyl Amino Reagents

These reagents are very similar, and their preparation is quite trivial.[44] They are commonly prepared by reaction of the corresponding fluoro-olefin with dimethylamine. TFEDMA derives from the cheap tetrafluoroethylene **186** (TFE), whereas Ishikawa's and Yarovenko's reagents derive respectively from the more expensive hexafluoropropene and chlorotrifluoroethylene (Scheme 4.31).



Scheme 4.31 : Synthesis of TFEDMA

For TFEDMA, the reaction is performed with no solvents, yields are almost quantitative, and the reaction involves no side product. In contrast to the reaction of tetrafluoroethylene **186** (TFE) with diethylamine which is performed at high temperatures affording many byproducts and a moderate yield (ca. 60%), dimethylamine reacts readily and cleanly with TFE at low temperatures. FAR react violently with water to give the corresponding amide **187** and two molecules of HF (Scheme 4.31).

TFEDMA and Ishikawa's reagent are stable at room temperature, when stored protected from moisture. In contrast, Yarovenko's reagent has to be prepared freshly before its use. For these reasons, among FAR, TFEDMA is the most practical and cheapest reagent. It is very

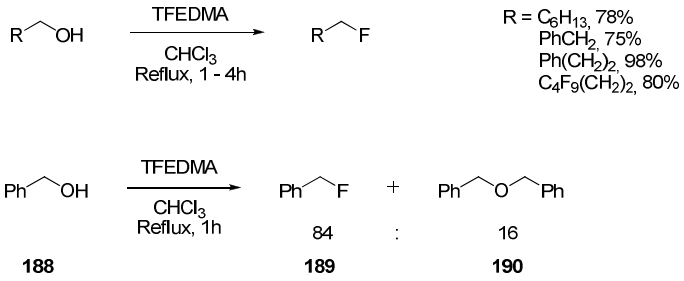
attractive for industrial purposes, as a fluorinating agent or as a difluoromethyl-transfer reagent, for the synthesis of pharmaceutical and agrochemical fluorinated intermediates. We will now focus on the reactivity of this reagent.

4.1.4.1. Uses as fluorinating reagent

a. Fluorination of alcohols

TFEDMA reacts readily with alcohols to yield the corresponding alkyl fluorides. It is important to notice that the reaction with primary alcohols has to be performed at elevated temperatures, whereas secondary and tertiary derivatives are much more reactive.[45]

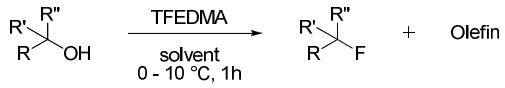
The reactivity of a wide range of alcohols has been studied, and the results show that primary alcohols are fluorinated in moderate to good yields (Scheme 4.32), and very selectively: no formation of byproducts has been observed. The reaction can be carried out in inert solvents such as dichloromethane, chloroform, ethers and acetonitrile, or without any solvent. The substrates can be linear primary alcohols, phenyl ethanol and propanol, benzyl alcohol, and fluoroalcohols.



Scheme 4.32 : Fluorination of primary alcohols

In the case of benzyl alcohol **188**, the product **189** is formed along with benzyl ether **190** in a 84:16 ratio. This side product **190** does not appear anymore when the alcohol is slowly added to the reaction mixture.

Secondary and tertiary alcohols have higher reactivities towards TFEDMA, thus reaction conditions are usually milder with these substrates. However, the reaction is less selective: olefin byproducts due to water elimination are often observed (Table 4-2).



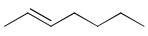
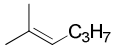
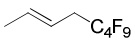
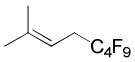
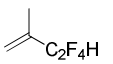
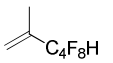
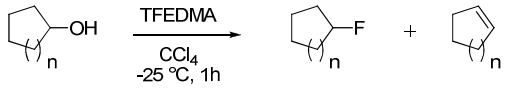
Entry	R	R'	R''	Solvent	Fluoride/olefin ratio	Major olefin formed
1	C_5H_{11}	CH_3	H	CCl_4	65:35	
2	C_4H_9	CH_3	CH_3	CCl_4	55:45	
3	$C_4F_9(CH_2)_2$	CH_3	H	/	97:3	
4	$C_4F_9(CH_2)_2$	CH_3	CH_3	/	78:22	
5	$H(CF_2)_2$	CH_3	CH_3	/	0:100 (47% yield)	
6	$H(CF_2)_4$	CH_3	CH_3	/	0:100 (71% yield)	

Table 4-2 : Fluorination of secondary and tertiary alcohols

We can remark that the major olefins formed are internal ones. We can also point out that the reactivity of TFEDMA towards secondary and tertiary alcohols is comparable to Yarovenko's and Ishikawa's reagents.[41,43] In general, TFEDMA is less selective for these substrates than sulphur tetrafluoride and DAST. For instance reaction of TFEDMA with tertiary fluoroalcohols, only leads to olefins (entries 5 and 6).

Similarly, cyclic alcohols can also be fluorinated in presence of TFEDMA. They react rapidly and at low temperatures to yield a mixture of the dehydrated product and the corresponding fluoride.



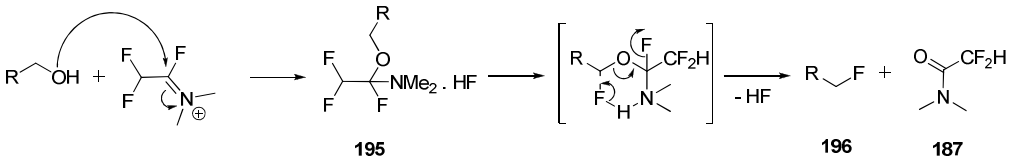
192	n=1	78	:	22
193	n=2	9	:	91
194	n=3	78	:	22
195	n=4	45	:	55

Scheme 4.33 : Fluorination of cyclic alcohols

Depending on the size of the carbocycle, the olefin/fluoride ratios vary significantly. Five and seven member rings **191** and **193** are less prone to dehydration and provide fluorinated products in majority. For cyclohexanol **192**, cyclohexene is the major product. The reaction of cyclooctanol **194** produces an almost equal mixture of fluorinated and dehydrated compounds. The reaction is carried out at low temperature to minimize the amount of olefin, but its formation cannot be avoided.

When the cyclic alcohol cannot undergo dehydration, the fluorination is straightforward. Indeed, the reaction of 1- and 2-adamantanol with TFEDMA provides the desired fluoro adamantanes in 85 and 97% yield respectively.

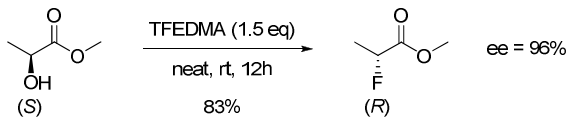
It is postulated that the mechanism of fluorination of alcohols in presence of TFEDMA is a two-step process. The first step is the formation of **195** by addition of the alcohol on TFEDMA (Scheme 4.34). The second step consists in the decomposition of **195** and formation of the amide **187** and the fluoride **196**.



195 **196** **187**

Scheme 4.34: Mechanism of TFEDMA-assisted fluorination of alcohols

N. Lui and coworkers reported on the fluorination of chiral (*R*)- and (*S*)-methyl lactates **197** in presence of TFEDMA (Scheme 4.35). This reaction yields chiral 2-fluoropropionates **198** in high yields. The high enantiomeric excesses (96-97% ee)[46] prove that the inversion of configuration is total.



197 **198**

Scheme 4.35 : Enantioselective fluorination of alcohols

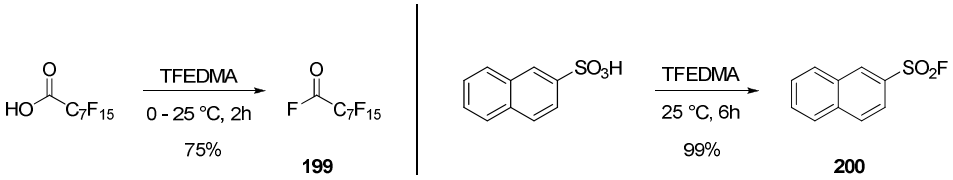
As fluorination of optically active alcohols by TFEDMA has been reported to proceed with inversion of configuration, the carbon-fluorine bond is reasonably thought to be formed *via* a S_N2 process.

To conclude, it has been outlined that TFEDMA is a selective and effective reagent for the fluorination of alcohols. Primary alcohols react at high temperatures in a selective manner. As for secondary and tertiary alcohols, their reactivity is higher, but the reaction is much less selective with the formation of olefin side products.

b. Fluorination of activated carbonyl groups

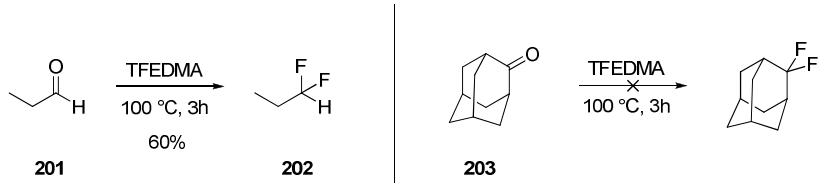
TFEDMA can also be used for the fluorination of carbonyl compounds. The reactivity of the reagent towards ketones, aldehydes and carboxylic acids allows the fluorination of these substrates to some extent.

In the case of carboxylic acids, FAR are convenient reagents. TFEDMA reacts with carboxylic acids and sulfonic acids at ambient temperature to give the acyl and sulfonyl fluorides[44] **199** and **200** in good to excellent yields (Scheme 4.36).



Scheme 4.36 : Fluorination of acids

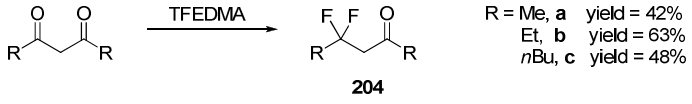
Perfluoro-octanoic acyl fluoride **199** and naphthalene-2-sulfonic fluoride **200** were prepared in 75% and 99% yield by reaction with TFEDMA at room temperature for two or six hours. Generally, TFEDMA is less active with carbonyl functions than SF_4 and DAST. Nevertheless, the preparation of difluorides is possible with activated substrates at elevated temperatures.[45]



Scheme 4.37 : Fluorination of carbonyl compounds

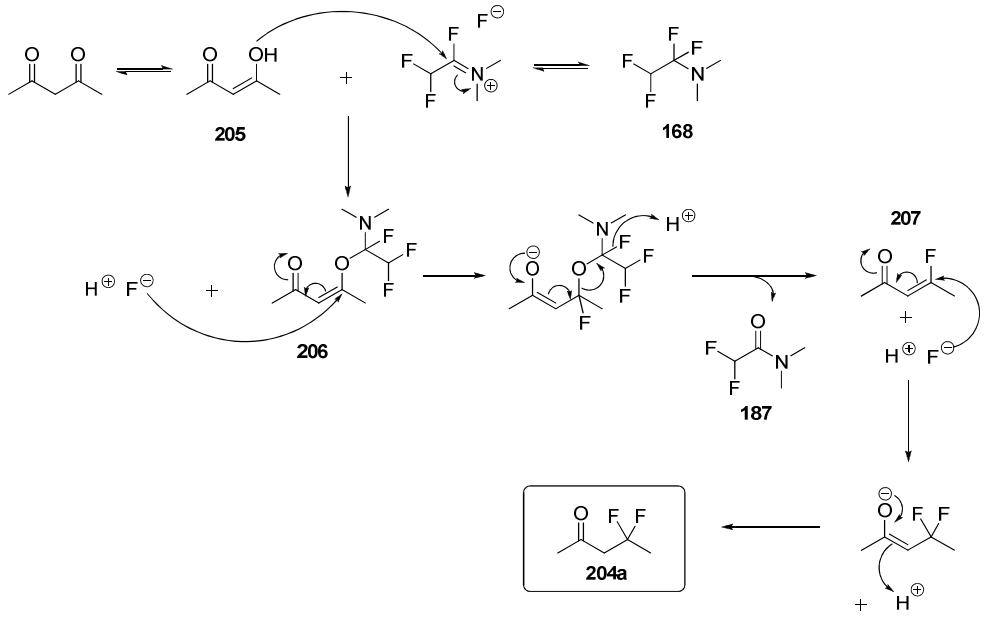
Hence, propionyl aldehyde **201** was converted into the corresponding difluoromethyl compound **202** in 60% yield,[44] but the unactivated 2-adamantone **203** did not react with TFEDMA (Scheme 4.37).

The reaction of 1,3-diketones with TFEDMA has also been the subject of a study. 1,3-diketones[44] yielded 42 to 63% of the desired difluorides **204a**, **204b** and **204c** in presence of TFEDMA at 50 to 80 °C for 6h (Scheme 4.38). Since TFEDMA does not react with unactivated ketones, V. A. Petrov *et al.* studied its reactivity towards linear and cyclic β-dicarbonyls.[47]



Scheme 4.38 : Fluorination of 1,3-pentadione

The reaction was performed on a few substrates, and showed moderate yields. The supposed mechanism is comparable to the one for the fluorination of alcohols. The oxygen of the enol tautomer **205** attacks the electrophilic carbon of TFEDMA to form the adduct **206** (Scheme 4.39).



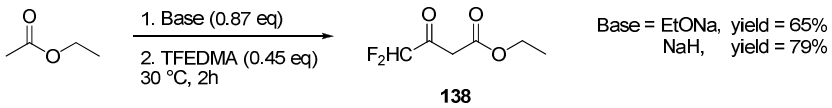
Scheme 4.39 : Mechanism for the fluorination of 1,3-diketones

The intermediate **206** is then fluorinated *via* 1,4-addition of fluoride, and subsequent elimination of acetamide **187** provides enone **207**. Another nucleophilic attack of fluoride on the double bond induces the formation of the desired β,β-difluoro ketone **204a**. Although free hydrogen fluoride is represented on the scheme, it is likely to be complexed to the amide **187** in solution.

4.1.4.2. Introduction of a fluorinated substituent

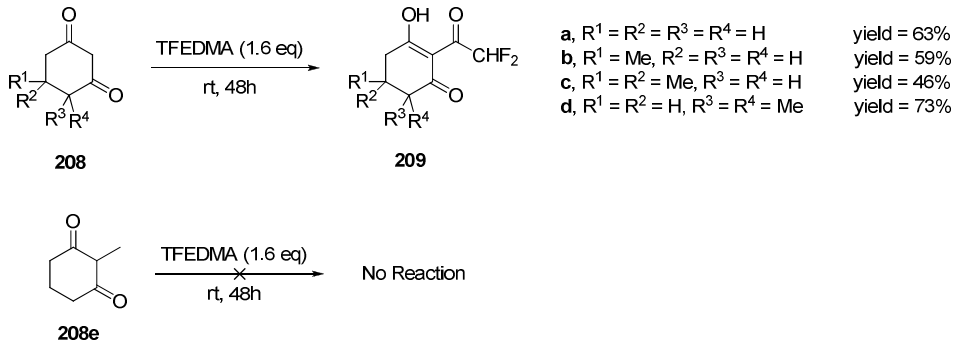
The use of TFEDMA as a fluorinating agent has been reported, and several methods for its application have been developed.

In 2008, S. Pazenok *et al.* described that ethyl difluoro acetoacetate **138** can be prepared from ethyl acetate in presence of TFEDMA and a base.[48] The reaction was achieved in good yields, depending on the base (Scheme 4.40).



Scheme 4.40 : Synthesis of difluoro acetoacetate via TFEDMA

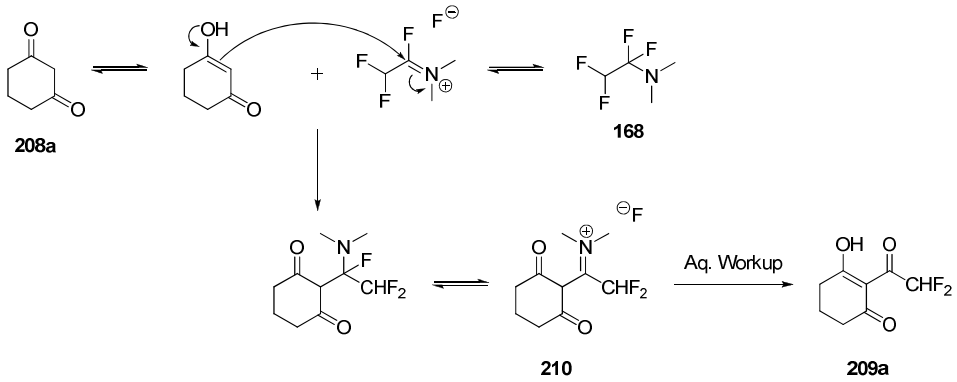
Recently, V. A. Petrov *et al.* detailed the reaction of TFEDMA with 1,3-diketones. However, when the reaction was then attempted on cyclic diketones,[47] acylation rather than fluorination occurred (Scheme 4.41).



Scheme 4.41 : Acylation of cyclic 1,3-diketones

Indeed, depending on reaction conditions, electrophiles can be attacked either by the carbon or by the oxygen atom of **208**. During the reaction of TFEDMA with cyclic 1,3-diketones at room temperature, the only observed product was the acylation product **209**. Thus, in this case, TFEDMA can be considered as a difluoroacetyl transfer reagent.

The reaction mechanism is different from the one postulated for the fluorination of linear diketones. It consists in the nucleophilic attack of the carbon of **208a** at the electrophilic carbon of TFEDMA (Scheme 4.42).



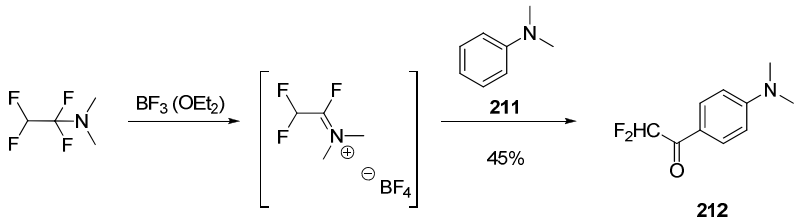
Scheme 4.42: Mechanism for the acylation with TFEDMA

Given that a new carbon-carbon bond has been formed, and unlike with linear substrates, elimination of the amide is not possible. Hence, it is likely that the iminium cation **210** is hydrolysed during aqueous workup. The equilibrium is then displaced to the formation of the iminium **210**, and the reaction leads to the acylation product **209a**.

In order to prove that the carbon which is active is the one between the two carbonyl groups, an experiment with the cyclic 1,3-diketone **208e** bearing a methyl substituent at the 2-position was performed (Scheme 4.41). The lack of reactivity and total recovery of the starting material represented an evidence that this carbon is involved into the mechanism.

Earlier, C. Wakselman *et al.* showed that TFEDMA is able to acylate aromatic substrates.[32] Indeed, the action of boron trifluoride makes it an electrophilic reagent which can undergo electrophilic aromatic substitution. Reaction with dimethyl aniline **211** yields 45% of the corresponding acylated product **212** (Scheme 4.43).

Furthermore, TFEDMA has attracted a lot of interest in the last few years as it can be used as a difluoromethyl-transfer reagent. Its importance for the synthesis of difluoromethylated pyrazoles has been outlined and detailed earlier.



Scheme 4.43 : Acylation of aromatic substrates

All the literature which has been detailed here confirms that TFEDMA is a versatile reagent which can be used for several purposes: fluorination of alcohols, acids, activated carbonyls, or introduction of a fluorinated substituent. To a certain extent, its reactivity as a difluoromethyl-transfer reagent represents important possibilities for further investigation.

4.1.5. Objectives

In the first part, we have detailed the several existing methods for the synthesis of difluoromethyl pyrazoles bearing one, two and three fluorinated substituents. Difluoromethyl pyrazoles can be synthesised from fluorinated 1,3-diketones, enones, β-keto esters, acetylenes and chromones. The fluoroalkyl substituent can be introduced *via* the reaction of hydrazines with carbonyl derivatives followed by cyclisation, or *via* the use of TFEDMA as a difluoromethyl transfer reagent. Although scarcely reported, the construction of the fluorinated group on the pyrazole ring is possible by conversion of chlorinated derivatives in presence of TREAT-HF.

Pyrazoles bearing more than one fluorinated substituent are hardly described, and only one method reports on the synthesis of unsymmetrical pyrazoles. As a matter of fact, the synthetic approach for pyrazole precursors is tedious, which makes the access to 3,5-bis(fluoroalkyl) products very difficult. Numerous methods have been developed for pyrazoles bearing one fluorinated substituent, whereas 3,5-(bis)fluoroalkyl pyrazoles are scarcely described.

Besides, the regioselectivity of the cyclisation step remains an issue, even if a few methods allow its control. Among them, the protection of methyl hydrazine as a hydrazone before cyclisation provides good results, but is not compatible with the concept of atom economy.

In a second part, the reactivity of TFEDMA has been detailed, and showed a wide range of possibilities. It can be used for the fluorination of alcohols, acids and activated carbonyls, as well as for the introduction of fluorinated substituents into molecules. The latter possibility presents many opportunities for investigation. Indeed, using TFEDMA for the introduction of a fluorinated moiety can lead to products bearing either a difluoromethyl or a difluoroacetyl substituent, but this has not been described extensively. In addition, its facile and low-cost preparation from tetrafluoroethylene makes it a reagent of choice for further industrial applications.

A careful study of the literature revealed that there is a crucial lack of straightforward, regioselective and reproducible methods for the synthesis of pyrazoles bearing two fluoroalkyl substituents at the 3- and 5- positions. A process allowing the access to this class of compounds *via* a short synthetic pathway in high yields would be very useful for the preparation of new active ingredients. For instance, these pyrazole building blocks could confer enhanced biological properties by replacement in known bioactive molecules.

Given that literature did not provide satisfying procedures, we were intrigued by the possibility of opening a new route to unsymmetrical 3,5-bis(fluoroalkyl) pyrazoles. The main idea was to design a straightforward and versatile method, which could be customized to lead to any fluorinated substituent on demand. After considering several synthetic pathways, two principal strategies emerged. They should allow the differentiation of the fluorinated substituents, and the route should be short enough to be competitive.

The first one consisted in the use of α,β-unsaturated ketones. As it has been demonstrated, the cyclisation of these compounds leads to pyrazoles in very good yields. Since it is one of the most common routes to pyrazoles, the reactivity of enones towards hydrazine is well described, thus predictable, and the regioselectivity can be controlled. The idea was to use fluorinated enones to synthesise 3,5-disubstituted pyrazoles. The second fluorinated substituent would be introduced later by a bromination/fluorination sequence (approach A, Figure 4.5), either on the enone precursor or on the cyclised pyrazole (approach B).

The advantage of this route is the easy access to fluorinated enones **213**, which has already been reported. For instance, the trifluoromethyl enone **213a** can be obtained in very good yields by reaction of 2-methoxy propene with trifluoromethyl acyl chloride or trifluoroacetic anhydride.[49] Therefore, we have chosen this approach as a starting point to prepare the enones **213** bearing a methyl group at one end, and a fluoroalkyl substituent at the other end (Figure 4.5).

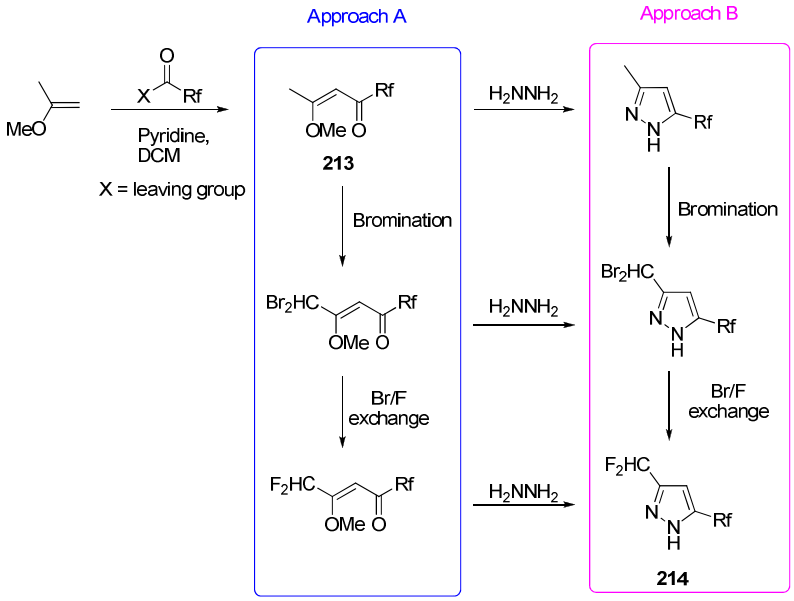


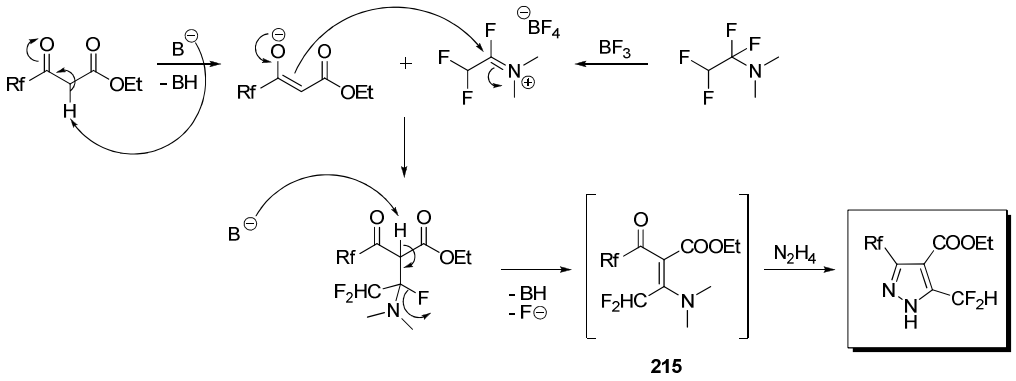
Figure 4.5 : First strategy for the synthesis of 3,5-bis(fluoroalkyl) pyrazoles

From this enone, the strategy exhibits many possibilities. The aim was to introduce bromine atoms on the methyl substituent and ensuing bromine-fluorine exchange, to open an access to difluoromethylated compounds. The bromination is therefore a key step of this synthesis.

Two approaches emerged: the first one, approach A, was based on working on the bromination of the enone **213** and subsequent cyclisation followed by fluorination to lead to the desired pyrazole **214**. Approach B consisted in direct cyclisation of enone **213** followed by bromination and bromine-fluorine exchange onto the cyclised pyrazole leading to the final compound **214**.

The second strategy was based on the use of TFEDMA as a difluoromethyl-transfer reagent. As it has been described, TFEDMA is a convenient reagent for the synthesis of 3-difluoromethyl pyrazoles (Scheme 4.24). If a fluorinated precursor is used, the access to 3,5-bis(fluoroalkyl) pyrazoles can be developed.

It is known that fluorinated β-keto esters can be easily deprotonated in the presence of weak bases, and that the activation of TFEDMA by reaction with boron trifluoride makes it a good electrophile. By nucleophilic attack, a difluorinated enone adduct **215** could be formed, and subsequent cyclisation could lead to the desired 3,5-bis(fluoroalkyl) pyrazoles (Scheme 4.44).



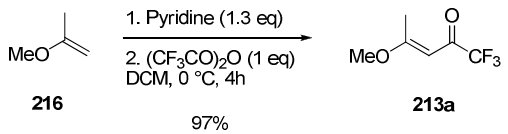
Scheme 4.44: Use of TFEDMA on β-keto esters

The synthetic path leads to a fluorinated dimethylamino acrylate **215**, and this class of compounds has demonstrated a good reactivity towards hydrazines. Once again, the method can provide fluorinated substituents on demand. Indeed, several fluorinated acetoacetates are commercially available or can be easily synthesised by Claisen condensation. Moreover, the use of other FAR having the same reactivity (Yarovenko or Ishikawa's reagents) supplies further possibilities for the second fluorinated substituent.

These two approaches could allow the preparation of 3,5-bis(fluoroalkyl) pyrazoles in a few steps, avoiding the tedious synthetic pathways that had been reported before. Both synthetic approaches have been investigated, and we will now present our results.

4.2. Fluorination of alkyl pyrazoles

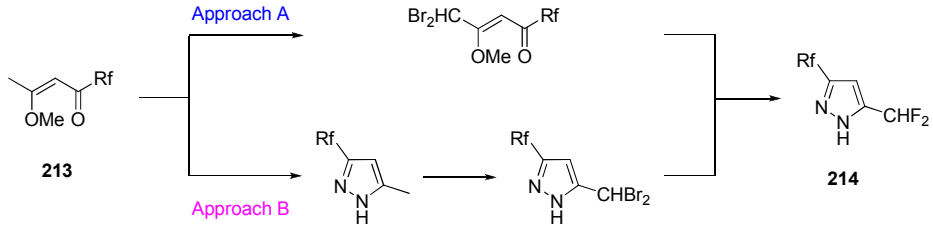
At the beginning of our study, we decided to start with trifluoromethyl enones, as their reactivity and preparation are widely described in the literature. In addition, such starting materials are commercially available and among the cheapest fluorinated starting materials. The first step of our synthetic route, which was the synthesis of 1,1,1-trifluoro-4-methoxypent-3-en-2-one **213a**, had been reported by reaction of trifluoroacetic acyl chloride with 2-methoxy propene **216** by I. I. Gerus *et al.*[50] We applied this process to trifluoroacetic anhydride with success, and the pure fluorinated enone was obtained in 97% yield (Scheme 4.45).



Scheme 4.45 : Synthesis of 1,1,1-trifluoro-4-methoxypent-3-en-2-one

The approach consisting in bromination followed by fluorination of the enone precursor was immediately put aside. Indeed, fluorinated compounds tend to be more volatile than their alkyl counterparts. We thought that a molecule such as **213**, containing two fluorinated substituents, would be very difficult to handle. Approaches A and B were investigated simultaneously.

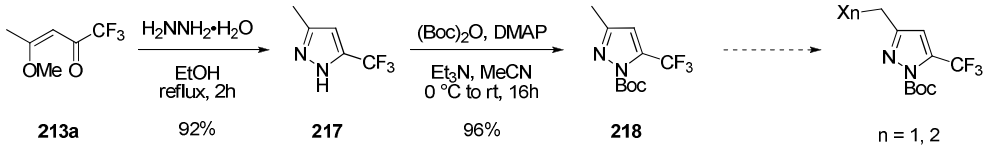
The bromination of the synthesised enone **213** had been described, so we tried to reproduce this procedure. The aim was to obtain the mono and dibrominated products in order to synthesise two pyrazoles bearing a difluoro or a monofluoromethyl substituent in addition to the trifluoromethyl group. In parallel, direct cyclisation of the trifluoromethyl enone followed by bromination was tried in order to construct the second fluorinated group directly on the pyrazole ring (Scheme 4.46).



Scheme 4.46 : Two envisaged synthetic pathways

4.2.1. Towards 3-halogenoalkyl pyrazoles

Having the trifluoromethyl enone **213a** in hand (Scheme 4.47), we started with the approach B (Scheme 4.46). We performed the cyclocondensation in presence of hydrazine hydrate in ethanol at reflux to yield 92% of the desired pyrazole **217**. Subsequent protection in presence of Boc_2O, triethylamine and DMAP provided the *N*-Boc pyrazole **218** in 96% yield. The latter could then be used for halogenation tests (bromination and chlorination).

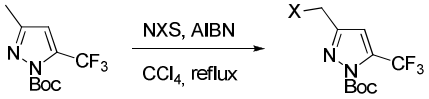


*Scheme 4.47 : Synthesis of N-Boc pyrazole **218** from **213a***

Halogenation of methyl pyrazoles has been reported several times in the literature by different processes. It should be noticed that dihalogenation of methyl pyrazoles has never been described. Halogenation reactions can be performed in presence of bromine, as well as under radical conditions initiated by AIBN in presence of *N*-bromo or *N*-chloro succinimide (NBS or NCS).

However, bromination of methyl pyrazoles containing a fluorinated substituent has only been described twice.[51] It has been performed in carbon tetrachloride, in presence of NBS either on a *N*-phenyl pyrazole initiated by benzoyl peroxide at reflux for 21h or on a *N*-methyl pyrazole initiated by AIBN at reflux for 30 minutes.

As the product in the second example had a substitution pattern closer to ours, we decided to try to reproduce these conditions on our compound (Table 4-3). The first tested conditions were exactly the ones described earlier. As only 33% conversion was observed on the crude NMR spectrum, we tried to improve the conditions. The conversion had to be total, as the brominated product and the starting material are obtained in an unseparable mixture.



Entry	Halogenating agent	Eq NXS	Eq AIBN	Concentration	Reaction time	Observations
1	NBS	1,15	0,1	0,16 M	12h	33% conversion
2	NBS	1,5	0,1	0,8 M	6h	40% conversion
3	NBS	1,8	0,1	0,72 M	6h	40% conversion
4	NBS	2,3	0,1	0,16 M	12h	5 spots on TLC
5	NBS	1,15	0,1 + 0,1	0,16 M	24h	Degradation
6	NBS	1,15	0,1	0,32 M	12h	50% conversion
7	NBS	1,2	0,1	0,72 M	12h	Degradation
8	NBS	1,2	0,1	1,44 M	12h	Degradation
9	NBS	1,2	0,1	0,72 M	4h	50% conversion
10	NBS	1,2	0,1	0,75 M	3h	45% conversion[a]
11	NCS	1,2	0,1	0,72 M	6h	5 spots on TLC + SM

[a] *Reagent used: N-methyl pyrazole*

Table 4-3 : Conditions for the halogenation of the 3-methyl-5-trifluoromethyl pyrazole

We realised that increasing the number of equivalents of NBS (entries 2, 3 and 4), influenced the conversion, and when we reached 2.3 equivalents the reaction became very messy. A second addition of radical initiator after one night at reflux (entry 5) only led to degradation of the starting material. Increasing the concentration of the reaction mixture gave better results (entries 6, 7 and 8) at first, but when the mixture was too concentrated the starting material was degraded.

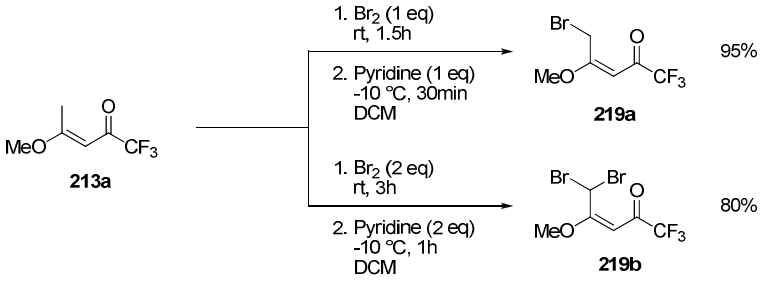
Finally, the best conversions were observed with relatively higher concentrations and shorter reaction times (entry 9) or lower concentrations and longer reaction times (entries 1 and 6). The substituent on the nitrogen atom had no influence on the reaction rate (entry 10), and the use of NCS instead of NBS produces an uninterpretable result (entry 11).

Several reaction conditions were tested, always leading to either degradation of the starting material or to an unseparable mixture of starting material and brominated compound. As we obtained no encouraging results, we decided to concentrate our efforts on the option of performing a bromination on the enone precursor before cyclisation (approach A, Scheme 4.46).

4.2.2. Synthesis of brominated enones

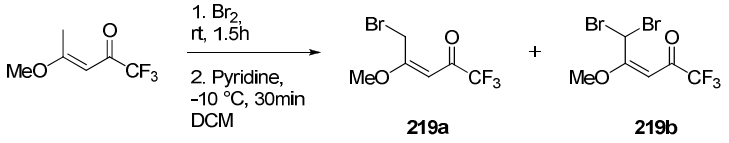
Given that the strategy of bromination of the cyclised pyrazole did not provide positive results, we started to investigate the bromination of the fluorinated enone **213a**. The aim was to be able to perform a mono and a di-bromination on the methyl substituent of the enone. Both procedures have been described,[52] but as the results could not be reproduced, we had to optimise the reaction conditions.

According to the literature, the reaction was carried out by slow addition of 1 equivalent of bromine onto a 1,1,1-trifluoro-4-methoxypent-3-en-2-one **213a** solution in dichloromethane at room temperature (Scheme 4.48). Subsequent quenching with pyridine at -10 °C provided the desired product in excellent yields.



Scheme 4.48 : Mono and dibromination conditions according to M. A. P. Martins et al.

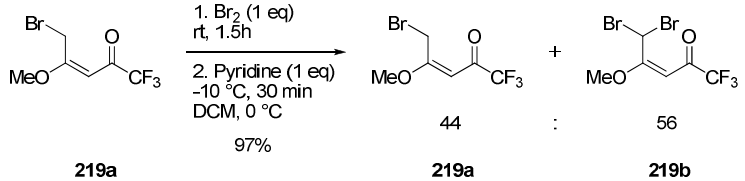
When we performed the reaction on the same scale a 86:14 mixture of the desired product **219a** and the dibrominated byproduct **219b** was obtained in 88% yield (Table 4-4).



Entry	Eq. Br_2	Reaction time	Yield	**219a/219b** Ratios
1	1	2h	/	86:14
2	1,2	2h	/	71:29
3	0,9	2h	90%	100:0
4	2	3h	/	27:73
5	2,5	3h	/	16:84

*Table 4-4 : Optimisation of the bromination of **213a***

When we used 0.9 equivalents of bromine, we could isolate the desired monobrominated enone in 90% yield (entry 3). We also wanted to synthesise the dibrominated compound in order to access the difluoromethyl pyrazole. Unfortunately, our attempts to perform the dibromination failed completely. Even when we tried to force the reaction conditions (entry 5) using 2.5 equivalents of bromine, we observed a mixture of mono and dibrominated products **219a** and **219b** on the crude NMR spectra. As this mixture was unseparable by column chromatography or by distillation, we decided to perform a bromination of the isolated mono brominated product **219a** (Scheme 4.49).

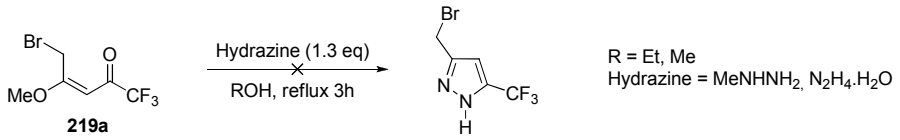


*Scheme 4.49 : Attempt of bromination of the brominated fluoroenone **219a***

One equivalent of bromine was added dropwise over 1.5 h onto the brominated enone **219a** in solution in dichloromethane at room temperature. After quenching with one equivalent of pyridine at -10 °C, the crude NMR spectrum showed a 44:56 mixture of mono and dibromo products.

As we had successfully isolated the mono brominated enone **219a**, we tried thus to condense it with hydrazine in order to perform a fluorination on the bromo methyl pyrazole. 5-Bromo-1,1,1-trifluoro-4-methoxypent-3-en-2-one **219a** was diluted in ethanol and heated to

reflux for 3h in presence of 1.3 equivalents of hydrazine hydrate (Scheme 4.50). The reaction was messy, and many byproducts were formed. The hydrazine and the solvent had no influence on the outcome of the reaction. No improvement was observed with the use of methyl hydrazine and/or methanol instead of ethanol.



*Scheme 4.50 : Attempts of cyclisation of the brominated fluoroenone **219a***

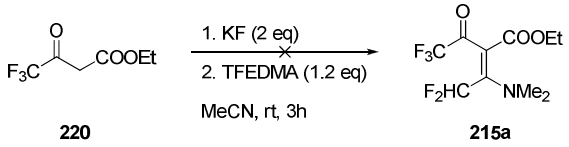
The cyclocondensation seems to be disfavoured when the methyl group is brominated due to the bulkiness and the electronic influence of the bromine atom. Given these unsuccessful results, we decided to concentrate our efforts on the "TFEDMA strategy".

4.3. Synthesis of 3,5-bis(fluoroalkyl) pyrazoles *via* the use of TFEDMA

4.3.1. Preparation of 3,5-bis(fluoroalkyl) pyrazoles

We started our studies with the addition of β-keto esters on TFEDMA. Once again, the trifluoromethyl derivative (ethyl trifluoroacetoacetate) was chosen for the optimisation of the reaction as it is commercially available, and among the cheapest fluorinated acetoacetates. The synthesis of the adduct **215** and its isolation will help us to confirm the reaction pathway in accordance with the one we had envisaged.

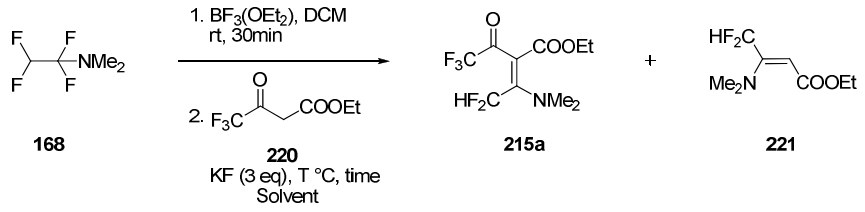
When TFEDMA was added onto ethyl trifluoroacetoacetate **220** and potassium fluoride in acetonitrile, no desired product **215a** was detected (Scheme 4.51) and the starting material was completely recovered. We decided to use boron trifluoride in order to activate TFEDMA.



*Scheme 4.51 : Reaction of ethyl trifluoroacetoacetate **220** with TFEDMA*

When TFEDMA was previously activated with $BF_3(OEt_2)$ and added onto ethyl trifluoroacetoacetate in presence of potassium fluoride, the formation of the adduct **215a** was observed, along with the byproduct **221** (Table 4-5).

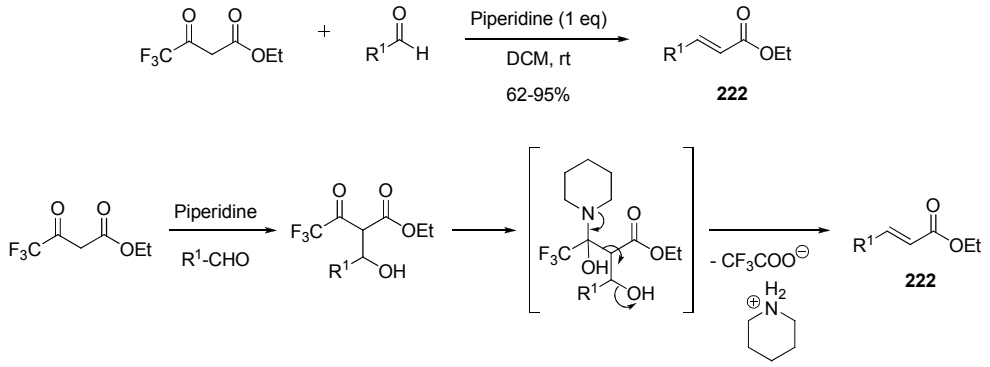
In dichloromethane (entry 1), no reaction was observed, probably due to the fact that activated TFEDMA is not soluble in this solvent. We thus changed for DMF and DMAc, which led to the disappearance of the starting material but the reaction was very messy and the results were uninterpretable (entries 2 and 3). In acetonitrile, we could observe the formation of the desired adduct **215a** along with a side product **221** (entries 4, 5 and 6).



Entry	Solvent	Reaction time	Temperature	Observations
1	DCM	overnight	rt	No reaction
2	DMF	overnight	rt	Observation of a side product, no desired product
3	DMAc	overnight	rt	No desired product, uninterpretable
4	MeCN	overnight	rt	Mixture **220/215a/221** 36:21:43
5	MeCN	1h	0 °C	Mixture **220/215a/221** 10:68:22
6	MeCN	3h	-30 °C	Mixture **220/215a/221** 8:75:17

*Table 4-5 : Optimisation of the formation of adduct **215a***

The dimethyl amino α,β-unsaturated ester **221** is the result of the loss of the trifluoroacetyl group. A similar reaction has been reported,[53] where the attack of deprotonated trifluoro acetoacetate onto an aldehyde provided the α,β-unsaturated ester **222** (Scheme 4.52). The postulated mechanism implies attack of the base at the electrophilic carbon of the trifluoroacetyl group, and this induces the elimination of trifluoroacetate and the formation of the α,β-unsaturated ester **222**.



Scheme 4.52 : Possible mechanism for trifluoroacetyl elimination described by Suman et al.

Given that our adduct is very similar to this one, we can imagine that the fluoride anions in solution are nucleophilic enough to attack the electrophilic carbonyl group, leading to the formation of the α,β-unsaturated ester **221** after elimination of the trifluoroacetyl group.

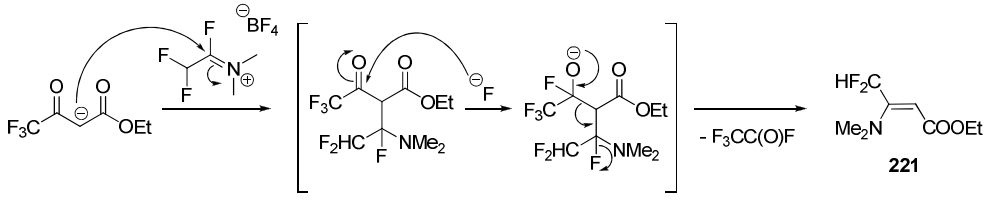


*Figure 4.6: Possible mechanism for the formation of the byproduct **221***

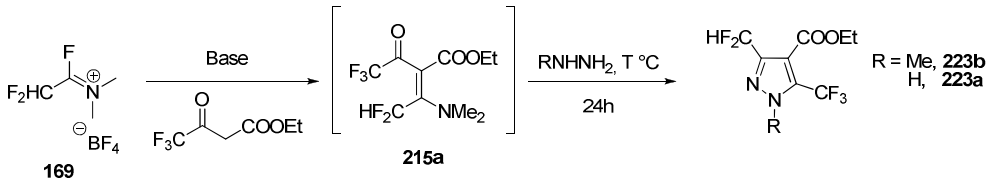
In order to avoid this side reaction, we carried the reaction out in acetonitrile and we decreased the temperature, which led to improved **215a/221** ratios (entries 5 and 6). The best

result was obtained when the reaction was performed at -30 °C for 3h (entry 6) which provided a **220/215a/221** ratio of 8:75:17. Besides, the reaction must be performed in a completely dry reaction medium, as TFEDMA and its activated form are very sensitive to the presence of water and decompose immediately to form the corresponding amide **187**.

Given that the adduct **215a** is rather unstable, every attempt to isolate it failed. In consequence, we decided to employ it directly in the cyclisation with hydrazine. Performing the adduct formation under optimised conditions, hydrazine was added onto the reaction mixture. Several attempts were necessary before good yields were reached (Table 4-6).

First, the adduct **215a** had been prepared and stirred overnight at room temperature. The methyl hydrazine or hydrazine hydrate (entries 1 and 2) were added to the mixture and stirred for 24h at room temperature. The desired pyrazoles **223a** and **223b** were obtained in 31% and 20% yields (entries 1 and 2). The regioselectivity was completely controlled, as we only observed the formation of 3-difluoromethyl-5-trifluoromethyl pyrazoles.

Others experiments were performed with the same reaction times, unless specified. Methyl hydrazine was chosen to optimise the reaction. Different inorganic bases (entry 3) or reversing the order of addition (entry 9) did not lead to the desired product. Decreasing gradually the temperature of addition from room temperature to -30 °C (entries 4 to 8) led to lower yields. Heating the mixture to 90 °C for 3h after hydrazine addition led to no product formation at all (entry 9).



Entry	R	Eq.	Base	T °C hydrazine addition	T °C reaction	Yield (%)	Observations
1	H	1,2	KF (3eq)	rt	rt	31	/
2	CH_3	1,2	KF (3eq)	rt	rt	20	/
3	CH_3	1,2	Cs_2CO_3 (3eq)	rt	rt	/	No desired product observed
4	CH_3	1,2	KF (3eq)	0 °C	rt	16	/
5	CH_3	1,2	KF (3eq)	-30 °C	rt	9	/
6	CH_3	1,5	KF (3eq)	0 °C	rt	18	/
7	CH_3	1,5	KF (3eq)	-10 °C	rt	10	/
8	CH_3	1,2	KF (2eq)	-30 °C	rt	9	Slightly acidic medium
9	CH_3	1,2	KF (3eq)	-30 °C	90 °C	/	Reverse addition and 3h at reflux, no desired product observed

Table 4-6 : Optimisation of the cyclisation step

We could conclude that the number of equivalents of hydrazine has no influence on the yield (entry 6), and that a slightly acidic medium did not favour cyclisation (entry 8).

Finally, after having studied the influence of various parameters in order to improve the yield of the reaction, we thought that the low yields could be due to a lack of reactivity of the adduct **215a**. Therefore, addition of an azaphilic lewis acid should help us to increase its reactivity and thus reach higher yields (Figure 4.7).

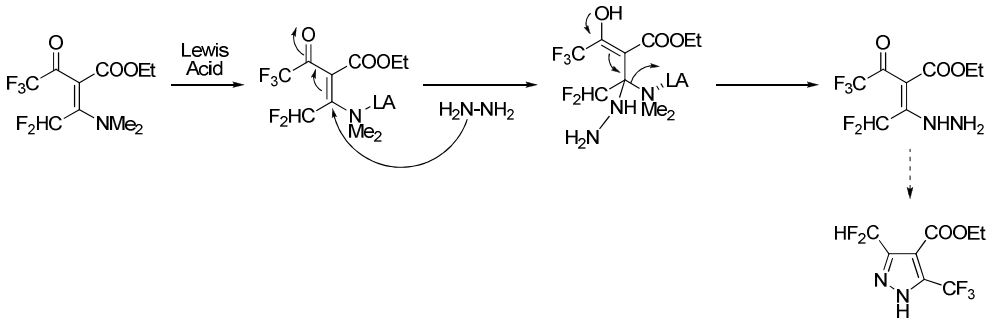
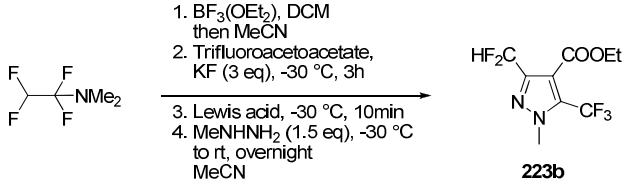


Figure 4.7 : Use of an azaphilic Lewis acid

The addition of an azaphilic Lewis acid shall increase the electrophilicity of the carbon α to the -NMe_2 group and facilitate the Michael-type addition of hydrazine onto our adduct.

Several Lewis acids have been classified[54] according to their preferences for oxygen or nitrogen (selectivity), and their activity (yield). We selected some of them and we tested them during the cyclisation step (Table 4-7). $FeCl_3$ is described as a very active and mildly selective Lewis acid, $CuCl_2$, $Cu(OTf)_2$ and CuCl as very selective for nitrogen and mildly active, and finally $Yb(OTf)_3$ as the most selective but weakly active Lewis acid.

The formation of the adduct **215a** was performed under the previously described conditions (Table 4-5). The Lewis acid was added onto the adduct *in situ* and stirred for 10 minutes at -30 °C. Methyl hydrazine was then added onto the reaction mixture, and stirred from -30 °C to room temperature overnight.



Entry	Lewis Acid	Eq.	Yield	Observations
1	/	/	20%	No Lewis acid in the reaction medium
2	$CuCl_2$	1	27%	/
3	$CuCl_2$	1	/	Overnight at rt then 1h at 80 °C in MW. Disappearance of **223b** after MW irradiation.
4	$CuCl_2$	0.2	16%	/
5	$CuCl_2$	5	13%	/
6	CuCl	1	/	No DP observed[a]
7	$FeCl_3$	1	/	No DP observed[a]
8	$Yb(OTf)_3$	0.2	13%	/
9	$Cu(OTf)_2$	1	22%	/
10	$TiCl_4$	1	/	No DP observed[a]

[a]*DP = desired product*

Table 4-7 : Study of the influence of Lewis acids on the cyclisation step

The results obtained emphasise that addition of 1 equivalent of $CuCl_2$ allowed us to reach 27% yield (entry 2) instead of 20% under the previous cyclisation conditions (entry 1). Addition of 0.2 or 5 equivalents of copper(II) chloride (entries 4 and 5) lowered the yield, and addition of 1 equivalent of copper(II) chloride and subsequent heating in the microwave oven (entry 3) led to degradation of the desired product. When we introduced one equivalent of $FeCl_3$ into the reaction mixture, no desired product was detected. This might be due to the strong oxidative properties of this complex. Ytterbium(III) and copper(II) triflates did not improve the yield compared to $CuCl_2$ (entries 9 and 10). It has to be noticed that the addition of Lewis acids did not change the regioselectivity of the reaction, as the same regioisomer was obtained under these conditions.

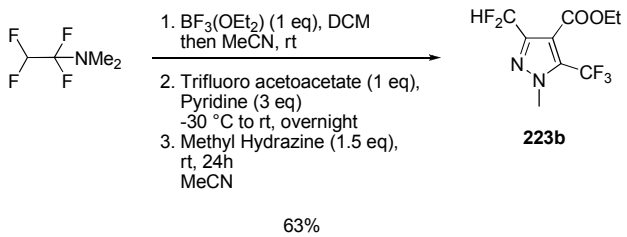
In order to compare the results, we also tested titanium tetrachloride as an oxophilic Lewis acid. Unfortunately, no product was detected in presence of one equivalent of this complex. To conclude, the only positive effect of azaphilic Lewis acids observed was in presence of copper(II) chloride.

At this point, although we had slightly increased the yield, the results were not satisfactory. So far, only one factor had not been modified in the optimisation study. The base had only been changed once (Table 4-6), and only inorganic bases had been used.

A possible explanation for the low yields of the cyclisation could be the use of potassium fluoride. Indeed, for the formation of the adduct, ethyl trifluoroacetoacetate was mixed with 3 equivalents of potassium fluoride. This means that during deprotonation of the β-keto ester, two molecules of HF were released (Scheme 4.44), and that the reaction medium was slightly acidic. Hence, we thought that using an organic base which could in addition trap the HF that was released during cyclisation could increase the yield.

In addition, the literature reports in same cases on the synthesis of pyrazoles from β-keto esters or α,β-unsaturated ketones under basic conditions. In this case, the most common organic bases are amines.[33,55] Consequently, we chose to perform the reaction in presence of pyridine, which could deprotonate the fluorinated β-keto esters and simultaneously play the role of trapping reagent for HF.

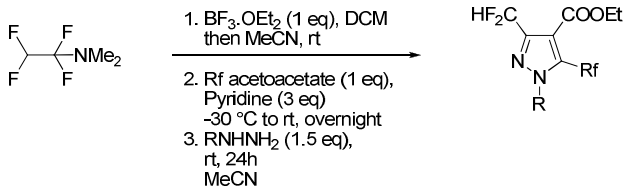
Hence, the reaction was performed with ethyl trifluoroacetoacetate. First, TFEDMA was activated with $BF_3(OEt)_2$, and it was added onto ethyl trifluoroacetoacetate and dry pyridine in MeCN at -30 °C (Scheme 4.53). After one night at room temperature, methyl hydrazine was added onto the reaction mixture, and it was stirred for one day to afford the desired 3-difluoromethyl-5-trifluoromethyl pyrazole **223b** in 63% yield.



Scheme 4.53 : Optimised conditions for the cyclisation from ethyl trifluoroacetoacetate

In this way, we had been able to triple the cyclisation yield. The reaction was working well, and now that we had reached a reasonable yield we decided to perform the reaction on several fluorinated acetoacetates in order to study the scope of the reaction. Hence, we accomplished the reaction with commercially available ethyl difluoro-, trifluoro- and pentafluoroethyl-acetoacetates **138**, **220**, **224** and synthesised ethyl chlorodifluoroacetoacetate **225** by Claisen

condensation.[56] We also studied different hydrazines in order to compare their reactivity towards the adducts we had synthesised: hydrazine hydrate, methyl, phenyl and *tert*-butyl hydrazines (Table 4-8).



Entry	Number	Rf	R	Yield
1	**223a**	CF_3	H[a]	67%
2	**226a**	CF_2H	H[a]	29%
3	**227a**	CF_2Cl	H[a]	63%
4	**228a**	C_2F_5	H[a]	46%
5	**223b**	CF_3	CH_3	63%
6	**226b**	CF_2H	CH_3	39%
7	**227b**	CF_2Cl	CH_3	72%
8	**228b**	C_2F_5	CH_3	83%
9	**223c**	CF_3	Phenyl	67%
10	**226c**	CF_2H	Phenyl	43%
11	**227c**	CF_2Cl	Phenyl	53%
12	**228c**	C_2F_5	Phenyl	85%
13	**223d**	CF_3	*tert*-Butyl[b]	53%
14	**226d**	CF_2H	*tert*-Butyl[b]	30%
15	**228d**	C_2F_5	*tert*-Butyl[b]	33%

[a] *Reagent: hydrazine hydrate* [b] *Reagent:* t*BuNHNH*$_2$*.HCl*

Table 4-8 : Scope of the cyclisation reaction

A careful observation of the obtained results leads to the conclusion that the reaction is substrate-dependent. The 3-difluoromethyl pyrazoles **223a** to **228d** are obtained in moderate to very good yields: from 29 to 85% depending on the fluorinated alkyl group and the hydrazine employed.

The influence of the hydrazine is obvious. Indeed, lower yields have been obtained with *tert*-butyl hydrazine and hydrazine hydrate than with methyl and phenyl hydrazines. It has to be noticed here that *tert*-butyl hydrazine and hydrazine are not used pure: *tert*-butyl hydrazine is a hydrochloride salt and hydrazine is used as a hydrate. This might have an influence on the reactivity.

The first results obtained with *tert*-butyl hydrazine hydrochloride afforded the pyrazoles **223d** and **228d** in 16% and 33% yield, respectively. Quenching the hydrochloride in presence of potassium hydroxide (1 equivalent) in methanol before cyclisation significantly increased the yield (entry 13). However, due to lack of time, this could not be tested for the cyclisation of **228d** and **226d**.

Furthermore, it should be noticed that the nature of the fluorinated acetoacetate also has an influence on the cyclisation yields. The trifluoromethyl-substituted starting material **220** provided the more consistent results, as yields are between 53 and 67%. Mostly, difluoromethyl-substituted acetoacetate **138** led to lower yields (between 29 and 43%), and pentafluoroethyl

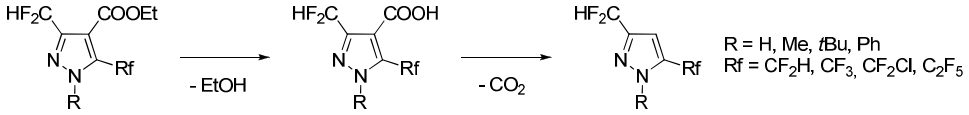
acetoacetate **224** to higher yields (between 33 and 85%). In consequence, we can point out that the general tendency is that the yields increase with the electron-withdrawing properties and the size of the fluorinated substituent.

Finally, neither the nature of the hydrazine nor the starting fluorinated acetoacetate has an influence of the regioselectivity of the cyclisation reaction, as the desired pyrazoles are always obtained as a single 3-difluoromethyl regioisomer.

To conclude, we can say that we developed a straightforward method for the synthesis of ethyl 3,5-bis(fluoroalkyl)-4-carboxylate pyrazoles **223a** to **228d** bearing two different fluorinated groups. Despite the low yields for the 3,5-bis(difluoromethyl) pyrazoles **226**, the method is applicable to several fluorinated groups and scalable. In addition, it allows obtaining pyrazoles bearing different fluoroalkyl substituents at the 3- and 5-positions in a one-step process, which had never been described. Only a multi-step synthetic approach has been reported for the preparation of such products.[36b]

4.3.2. Towards 4-unsubstituted pyrazoles

In order to enlarge the scope of functionalisation of these pyrazole building blocks, we wanted to transform the carboxylate at the 4-position of the pyrazole ring. With this purpose in mind, we investigated several reaction conditions for the obtention of pyrazole carboxylic acids and their decarboxylation towards 4-unsubstituted pyrazoles (Scheme 4.54).



Scheme 4.54 : Synthetic path for the obtention of 4-H pyrazoles

Indeed, the carboxylic acids could allow the coupling for the formation of amides, the transformation into a cyano group or nucleophilic substitutions by reduction to the primary alcohol and subsequent chlorination. The obtention of the free 4-position could lead to other functionalised pyrazoles by means of organometallic reagents.

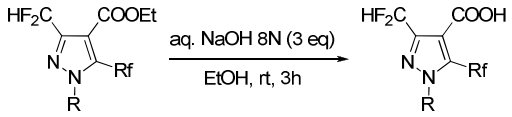
4.3.2.1. Saponification and decarboxylation at the 4-position

First, we had to find mild reaction conditions for the decarboxylation due to the sensitivity of the pyrazole ring.

We started with the study of common saponification conditions with 3 equivalents of sodium hydroxide (aqueous solution) in ethanol at room temperature. Fortunately, these conditions provided the desired carboxylic acids in very high yields (Table 4-9). All saponification yields were almost quantitative, and the obtained products were all crystalline and did not need any further purification. This made this method very practical, straightforward and adaptable to scale-up.

However, saponification of the free *N*-H pyrazoles did not occur, and in every case the starting material was completely recovered. At this point, we decided to work with *tert*-butyl pyrazoles as the *N*-*t*Bu group can be deprotected under strong acidic conditions. Developing an access to 3,5-difluoroalkyl pyrazoles having a free nitrogen atom was very important for us.

Indeed, this can provide further options for a functionalisation of the pyrazole nitrogen on demand.



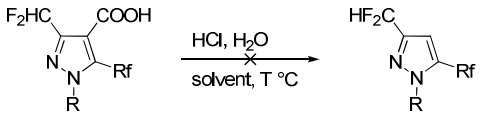
Entry	Number	R	Rf	Yield
1	**229b**	CH_3	CF_2H	97%
2	**230b**	CH_3	CF_3	98%
3	**231b**	CH_3	CF_2Cl	90%
4	**232b**	CH_3	C_2F_5	97%
5	**229c**	Phenyl	CF_2H	98%
6	**230c**	Phenyl	CF_3	94%
7	**231c**	Phenyl	CF_2Cl	99%
8	**232c**	Phenyl	C_2F_5	98%
9	**229d**	*tert*-Butyl	CF_2H	97%
10	**230d**	*tert*-Butyl	CF_3	94%
11	**232d**	*tert*-Butyl	C_2F_5	99%

Table 4-9 : Saponification of ethyl 4-carboxylate pyrazoles

After having optimised the saponification step and obtained all desired pyrazoles in high yields, we wanted to perform the decarboxylation of these compounds in order to access the corresponding 4-H pyrazoles. We thought that this step would be easily achieved, but it revealed to be problematic.

To the best of our knowledge, only one reference reports on the decarboxylation of pyrazoles bearing fluoroalkyl groups.[57] G. Daidone *et al.* described the decarboxylation of a 3-trifluoromethyl pyrazole with 30% yield by heating it to its melting point for 5 minutes. Unfortunately, applying these conditions to our products led to total degradation. Then, we began applying common decarboxylation conditions which were described on pyrazoles.

Decarboxylation in presence of HCl is one of the mostly reported conditions. We tried different concentrations, solvents and temperatures on our compounds. This led either to total recovery of the starting material or its degradation (Table 4-10).

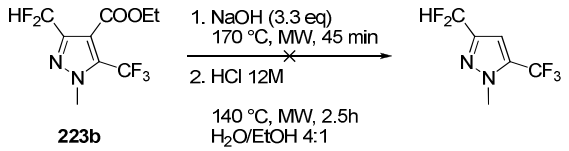


Entry	Conc. HCl	Solvent	Temperature	Observations
1	1M (3 eq)	H_2O	rt then reflux 3h	No reaction
2	1M (3 eq)	H_2O/EtOH 3:1	reflux 3h	No reaction
3	6M	H_2O/EtOH 3:1	reflux overnight	No reaction
4	12M	MeCN	reflux overnight	No reaction
5	12M	H_2O	1h 130 °C MW	Degradation of SM

Table 4-10 : Attempts of decarboxylation in presence of HCl

Considering these negative results, we decided to try to perform a tandem saponification/decarboxylation approach.[58] The principle of the sequence was a saponification in presence of sodium hydroxide followed by acidification of the reaction medium with

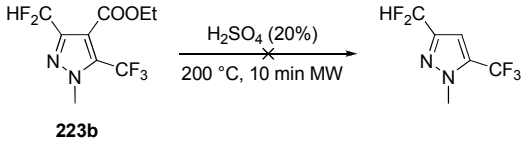
concentrated HCl and subsequent decarboxylation in a water/ethanol 4:1 mixture under microwave irradiation (Scheme 4.55).



Scheme 4.55 : Tandem saponification/decarboxylation

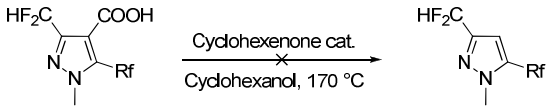
Heating the first step in the microwave oven under basic conditions, a total conversion of the ester **223b** into the carboxylic acid **230b** was observed. After acidification of the reaction medium, we completely recovered the starting material: the ethanol present in the mixture led to esterification of the pyrazole carboxylic acid. The procedure was repeated without ethanol, and it led to complete degradation of the starting material.

As saponification of the ester can occur under acidic conditions, we tried to heat the carboxylate **223b** in H_2SO_4 (20% wt) for 10 minutes at 200 °C under microwave irradiation. Once again, this led to complete degradation of the starting material (Scheme 4.56).



Scheme 4.56 : Acid-promoted tandem reaction

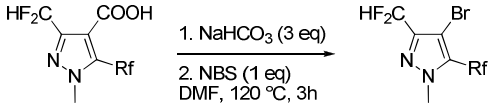
These results indicate that milder conditions for the decarboxylation of these pyrazoles are required, as strong acidic conditions only degraded the starting materials. A decarboxylation has been reported on 4-hydroxy-L-proline in cyclohexanol and in presence of catalytic cyclohexenone (14 mol%) without epimerisation of the asymmetric carbon.[59] Hence, we applied these reaction conditions to our pyrazole carboxylic acids, and observed no reaction. We repeated the procedure in presence of a stoichiometric amount of cyclohexenone, and we still could not detect any formation of a new product (Scheme 4.57). Even when the reaction was stirred for 24h at reflux, no conversion of the starting material was observed, so we abandoned this method.



Scheme 4.57 : Reaction conditions in presence of cyclohexenone

In order to be sure that we did not lose the product of decarboxylation because of volatility we decided to try a tandem decarboxylation/electrophilic bromination described for pyrazolo-pyridines[60] and in one case for a pyrazole[61] bearing alkyl substituents.

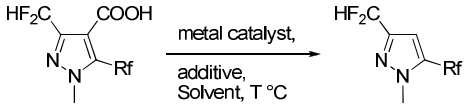
The presence of the bromine atom on the desired pyrazole could have several advantages: it decreases the volatility of the product, and allows further functionalisation of the building block. The pyrazole carboxylic acid was heated in presence of $NaHCO_3$ and *N*-bromosuccinimide in DMF at 120 °C for 3h (Scheme 4.58).



Scheme 4.58 : Decarboxylation/electrophilic bromination conditions

We performed the reaction in a sealed tube in order to avoid any loss of the product due to its volatility. We detected a small amount of the desired product by GCMS, along with several unidentified byproducts and a very low conversion of the starting material. When the reaction mixture was heated for 24h, we still did not reach total conversion of the starting material. Therefore, we had to find another approach.

Several metal-promoted decarboxylation reactions have been recently developed, and we decided to test some of them. So far, none of these reactions have been tested on pyrazoles. Mostly silver and copper salts have been employed with additives like potassium carbonate, phenanthroline, acetic acid, etc. Generally high boiling-point solvents such as DMF, DMSO, NMP and quinoline have been used (Table 4-11).[62-66]



Entry	Metal Catalyst	Additive	Solvent	T °C	Reaction time	Observations
1	CuO (1 eq)	/	DMF	160	16h	No reaction
2	CuO (1 eq)	/	DMF	220	3h	Microwave irradiation, no reaction
3	Cu (6 eq)	/	NMP	180	3h	No reaction
4	Cu (7 eq)	/	Quinoline	240	3h	No reaction
5	CuI (6 eq)	/	NMP	180	3h	No reaction
6	Ag_2CO_3 (10mol%)	AcOH (5mol%)	DMSO	120	3h	MW, no reaction
7	AgOAc (10mol%	K_2CO_3 (15mol%)	NMP	120	16h	No reaction
8	AgOAc (1 eq)	K_2CO_3 (1.5 eq)	NMP	120	16h	No reaction
9	$MgCl_2.6H_2O$ (1 eq)	/	DMF	160	16h	No reaction
10	Cu_2O (5mol%)	Phenanthroline (10mol%)	NMP/quinoline 3:1	160	16h	Complete conversion and detection of the desired product in GCMS

Table 4-11 : Metal-promoted conditions for the decarboxylation

As copper salts are known to promote decarboxylations,[62] we tried to carry the reactions out in presence of copper(I) oxide, copper(II) oxide, copper(0) and copper(I) iodide in stoichiometric amounts (entries 1 to 5). In NMP or DMF as a solvent, even under harsh conditions (entry 2 and 4), no reaction has been observed.

I. Larrosa *et al.* have reported on the decarboxylation of several heteroaromatic compounds in presence of a catalytic amount of silver carbonate and acetic acid in DMSO.[63] Although no pyrazoles were described, we decided to test these conditions on our compounds (entry 5). Unfortunately, when we performed the reaction at 120 °C under microwave irradiation for 3h, the starting material was completely recovered.

It is known that protodecarboxylation of various aromatic carboxylic acids can occur in presence of a silver acetate/potassium carbonate catalytic system.[64] This has been described on electron-rich and electron-poor aromatic systems, and a few examples regarding the decarboxylation of heteroaromatic systems can be found. Once again, no pyrazoles have been studied. Nevertheless, we applied these conditions to our products. The reaction was accomplished in presence of 10 mol% of silver acetate and 15 mol% of potassium carbonate in NMP at 120 °C for 16 h, but no reaction was observed (entry 7). Repeating the procedure in presence of a stoichiometric amount of the catalyst and 1.5 equivalent of potassium carbonate had no influence on the outcome of the reaction (entry 8).

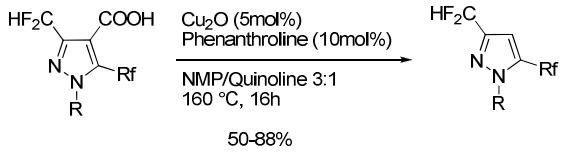
As magnesium chloride has proven to promote decarboxylation on natural products,[65] we used the described conditions on our fluorinated pyrazoles. The reaction was carried out in DMF at 160 °C for 3 h with 1 equivalent of magnesium (II) chloride hexahydrate (entry 9). Even after prolonged reaction time, no reaction was observed.

Finally, after having tried almost all decarboxylation reactions described in the literature, we decided to use a copper(I) oxide/phenanthroline catalytic system in NMP/quinoline 3:1 as solvent recently reported by Goossen *et al.*[66] The pyrazolic acid was stirred in this solvent mixture with 5 mol% of Cu_2O and 10 mol% of phenanthroline at 160 °C for 16 h (entry 10). The desired product was now detected in GCMS as the major product and with complete conversion.

The reactivity of 3,5-bis(fluoroalkyl) pyrazoles regarding their decarboxylation caused numerous problems, but finally with the above approach we found a way to obtain the desired products. Nevertheless, purification of the decarboxylated 3,5-bis(fluoroalkyl) pyrazoles required many efforts.

As it has been specified earlier, the synthesised products are very volatile, and we had to isolate them from the reaction mixture. When we tried the isolation of the desired product directly by distillation under reduced pressure of the reaction mixture, we obtained a mixture of the product along with NMP and quinoline. As most of the products were nitrogen-containing molecules, we were able to extract them with an aqueous acidic medium. The organic phase had to be thoroughly washed, as the boiling points are close to the one of NMP. Diethyl ether, used for the extraction, had to be distilled at atmospheric pressure with a Vigreux column, and the product was finally distilled under reduced pressure to be obtained in pure form. In a few cases, a small amount of quinoline and/or diethyl ether was still detectable after purification.

Nevertheless, the isolation of the desired products in moderate to good yields was achieved (Table 4-12). No general tendency concerning the substitution pattern of the fluorinated pyrazoles on the outcome of the reaction can be observed. Heavier pyrazoles, such as *N*-phenyl pyrazoles (entries 4 and 5) provided the desired decarboxylated products in excellent yields. In contrast, *N*-methyl pyrazoles (entries 1 to 3) afforded generally lower yields except for the bis-difluoromethyl pyrazole. Finally, *N*-*tert*-butyl derivatives were obtained in good yields (entries 6 to 8).



Entry	Number	R	Rf	Yield (%)
1	**233b**	CH_3	CHF_2	78
2	**234b**	CH_3	CF_3	50
3	**235b**	CH_3	C_2F_5	63
4	**233c**	Phenyl	CHF_2	87
5	**234c**	Phenyl	CF_3	84
6	**235c**	Phenyl	C_2F_5	88
7	**233d**	*tert*-Butyl	CHF_2	64
8	**234d**	*tert*-Butyl	CF_3	83
9	**235d**	*tert*-Butyl	C_2F_5	46[a]

[a]*Yield of the corresponding N-H pyrazole (see text)*

Table 4-12 : Copper-catalysed decarboxylation of 3,5-bis (fluoroalkyl) pyrazoles

Surprisingly, the 5-pentafluoroethyl pyrazole **232d** (entry 9) underwent deprotection during the saponification step, which was not observed with other *N*-*tert*-butyl pyrazoles. We could thus obtain the *N*-H pyrazole **235d** in a moderate 46% yield, but in only one step from the *N*-*tert*-butyl compound **232d**. In conclusion, the major difficulty in this synthesis is the high volatility of the products and the precautions that have to be taken. The conversions are total in each case.

When the same decarboxylation was performed on 5-CF_2Cl derivatives, the results were quite different. Indeed, for methyl derivatives, the conversion was not complete, and we were not able to isolate the products which had been formed. For *N*-phenyl compounds, the conversion was complete, but we could detect the formation of a lot of byproducts. We were not able to isolate pure products and given that the reaction was very messy, we did not try further experiments to decarboxylate these pyrazoles as we had already tried many procedures which had not given any positive results.

To conclude, we have been able to develop an efficient method for the synthesis of 3,5-bis(difluoromethyl) pyrazoles. Unfortunately, we were not able to perform the decarboxylation of 5-CF_2Cl pyrazoles. However, this three-step pathway leading to pyrazoles building-blocks having the 4-position free is straightforward and more efficient than the method which had been developed earlier.[36b] Furthermore, the reaction conditions which are used are scalable, and thus can be suitable for an industrial application. But to broaden the scope of our method, we wanted to develop an access to these building blocks bearing no protecting group on the nitrogen atom.

4.3.2.2. Obtention of *N*-H pyrazoles

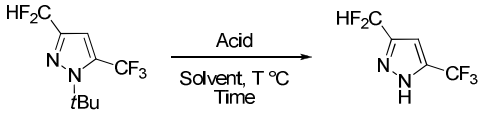
In order to obtain *N*-H pyrazoles, the use of a *tert*-butyl group appeared to be a suitable approach. Indeed, the compounds can be easily purified as they are less volatile. Additionally, they readily undergo the saponification and the decarboxylation steps. Therefore, developing an access to *N*-H pyrazoles was essential, as afterwards any substituent could be introduced at the

nitrogen atom, and the design of new active ingredients containing 3,5-fluoroalkyl pyrazoles would be much easier to customise.

The literature contains numerous procedures for the deprotection of *tert*-butyl groups on pyrazoles, but only one is described on a pyrazole bearing a fluorinated substituent.[67] Most of the procedures concern bicyclic pyrazoles: pyrazolo-pyridines or pyrazolo-pyrimidines.

The deprotection is mainly carried out in a strong acidic medium (formic or trifluoroacetic acids), and frequently at elevated temperatures. The procedure which had been applied to a fluorinated pyrazole was in formic acid as solvent, at 90 °C for one hour. Therefore, we submitted *N-tert*-butyl-3-difluoromethyl-5-trifluoromethyl pyrazole **234d** to this protocol.

Different temperatures have been tested, starting from room temperature (Table 4-13). But even heating at 90 °C for 4 h did not lead to the deprotection of the pyrazole, and the starting material was completely recovered (entries 1 and 2).



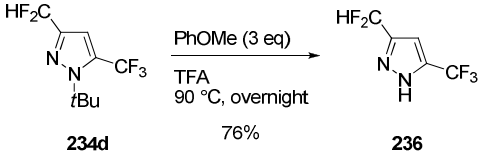
234d **236**

Entry	Acid	Eq.	Additive	Solvent	Temperature	Reaction time	Observations
1	HCOOH	/	/	HCOOH	rt	16h	No reaction
2	HCOOH	/	/	HCOOH	90 °C	4h	No reaction
3	TFA	3	/	DCM	rt	5 days	No reaction
4	TFA	3	/	DCM	50 °C	16h	No reaction
5	TFA	30	/	DCM	50 °C	1h	No reaction
6	TFA	30	/	DCM	50 °C	16h	No reaction
7	TFA	/	/	TFA	rt	16h	No reaction
8	TFA	/	/	TFA	90 °C	16h	Degradation
9	TFA	/	PhOMe (3 eq)	TFA	90 °C	16h	Complete conversion

Table 4-13: Reaction conditions for the deprotection of N-tert-*butyl pyrazoles*

Afterwards, the acidic medium has been changed for trifluoroacetic acid. It was reported that it can either be used as a reagent in solution in dichloromethane, as the solvent, or in presence of anisole.[68] The first attempts were carried out in dichloromethane (entries 3 to 6). With 3 equivalents of TFA at room temperature, then heating to 50 °C overnight, and with 30 equivalents of TFA at 50 °C overnight, we entirely recovered the starting material.

Therefore, TFA has been used as the solvent at room temperature (entry 7), and again no reaction occurred. When the reaction mixture was heated at 90 °C overnight, the starting material degraded to produce a black residue (entry 8). When the reaction was carried out in presence of 3 equivalents of anisole in TFA and heated at 90 °C overnight (entry 9), we observed complete conversion of the starting material, and only a slight coloration of the reaction mixture. GCMS indicated the presence of the desired deprotected product, of anisole and of *para-tert*-butyl anisole. After purification, the desired deprotected pyrazole **236** was obtained in 76% yield (Scheme 4.59).



*Scheme 4.59: Deprotection of tert-butyl pyrazole **234d** in presence of TFA and anisole*

We performed this procedure on the 3,5-bis(difluoromethyl pyrazole), and after one night in presence of 3 equivalents of anisole, in TFA at 90 °C, GCMS showed similar results. Unfortunately, the desired deprotected pyrazole could not be isolated from the reaction mixture. Nevertheless, we could observe total conversion of the starting material to the desired product.

In summary, we were able to isolate two *N*-deprotected pyrazoles, and to deprotect one without isolation of the final product. We could open an access to unsymmetrical 3,5-bis(fluoroalkyl) *N*-H pyrazoles *via* an efficient and cheap method that uses commercially available starting materials. Unfortunately, we could not isolate the chlorodifluoromethyl derivatives, which did not undergo decarboxylation in presence of Cu_2O and phenanthroline.

4.3.3. Mechanistic aspects and regiochemistry

As it has been underlined before, the cyclisation step towards ethyl 4-carboxylate pyrazoles is completely regioselective. Indeed, with every hydrazine used (*N*-methyl, *N*-phenyl or *N*-*tert*-butyl) and every fluorinated substituent, the only regioisomer which has been detected was the 3-difluoromethyl-5-fluoroalkyl pyrazole.

The regiochemistry of the reaction can be guided by two principal factors:

- On one hand, the nucleophilicity of the nitrogen atoms of the hydrazines plays an important role. For alkyl hydrazines, the nitrogen bearing the alkyl group is believed to be more nucleophilic than the other one and attacks first. For aryl hydrazines, the $-NH_2$ is supposed to be more nucleophilic than the one bearing the aryl group.[5] Thus, when one uses alkyl and aryl hydrazines, a different regiochemistry should be observed.

- On the other hand, the electrophilicity of the carbon influences the outcome of the reaction. In our case, two sites can be potentially attacked. A 1,2-attack of the hydrazine onto the carbonyl bearing the fluoroalkyl substituent or a 1,4-"Michael-type addition" on the carbon bearing the difluoromethyl group. Then, depending on the hydrazine nucleophilicity, two different regioisomers can possibly be detected.

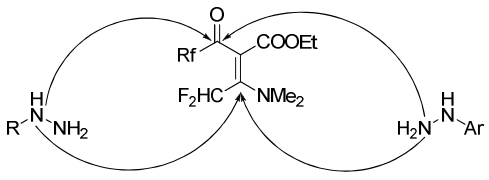


Figure 4.8: Possible nucleophilic attacks of hydrazines

In the case of the formation of ethyl 1-methyl-3-CHF_2-5-CF_3-4-carboxylate pyrazole **223b**, when we interpreted the NMR spectra of our experiments, we realised that only one regioisomer had been formed during the cyclisation. First of all, the ^1H NMR spectrum revealed only one regioisomer of compound **223b**. The ^{13}C NMR spectrum showed that the carbon of the

N-methyl group undergoes a coupling with the fluoroalkyl group which is at the 5-position of the pyrazole ring to form a quadruplet (Figure 4.9, $^{4}J_{C\text{-}F}$ = 3.3 Hz). Hence, we deducted that the trifluoromethyl group was at the 5-position. In the other case, the *N*-methyl group's signal would have been a triplet.

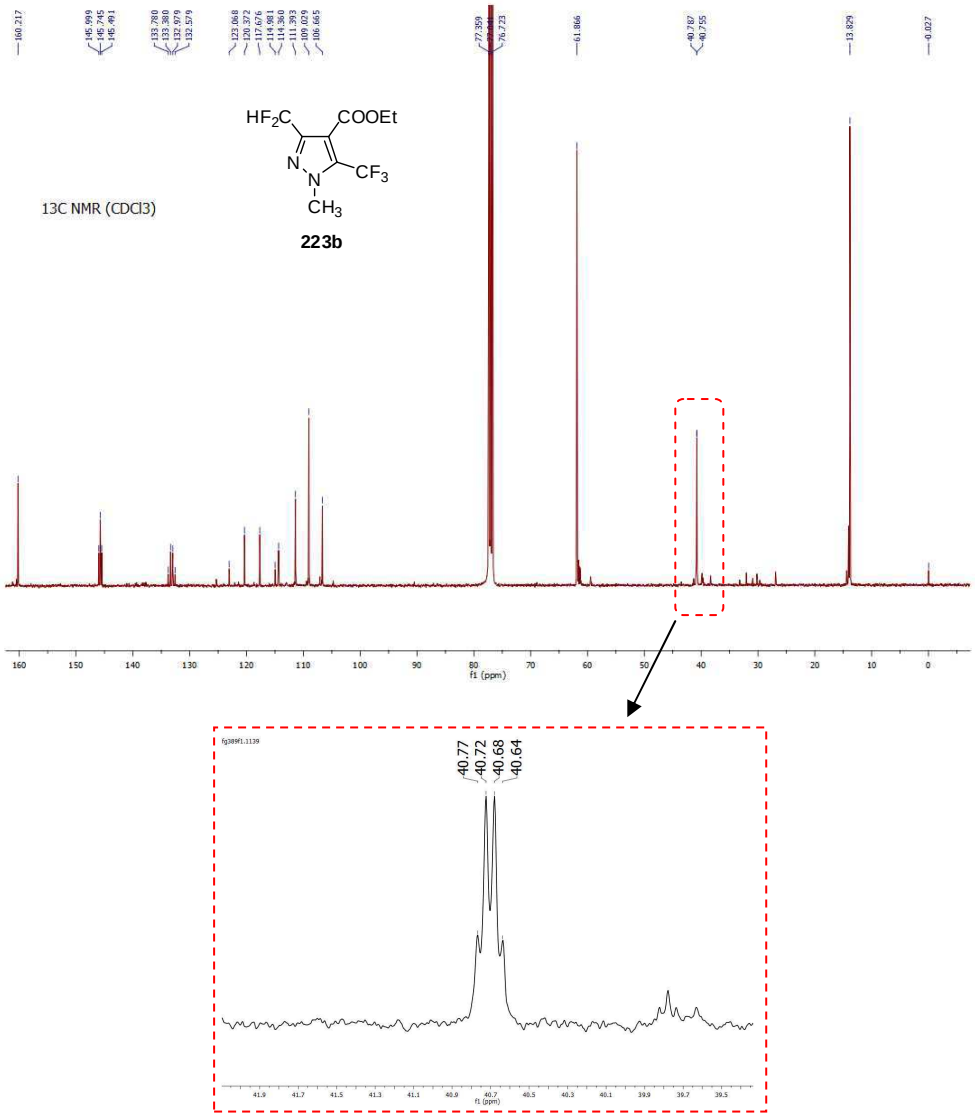


*Figure 4.9: ^{13}C NMR of compound **223b***

Although these observations confirmed undoubtedly the regiochemistry of our compounds, we were able to perform a single crystal X-ray analysis of the carboxylic acid **230b** (Figure 4.10), which confirmed our claims: the formed regioisomer is the 3-difluoromethyl-5-trifluoromethyl isomer.

Similar results were obtained for all other compounds, when the *N*-substituent was a methyl, a *tert*-butyl or a phenyl, as well as with any fluorinated substituent. In almost all cases, we could observe C-F coupling of the substituent at the nitrogen with the adjacent fluoroalkyl group in ^{13}C NMR, with a characteristic coupling pattern. We concluded that the only regioisomers are those bearing the difluoromethyl substituent from TFEDMA at the 3-position of the pyrazole ring.

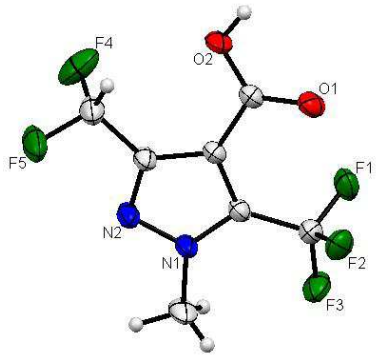
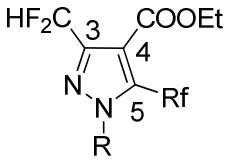


*Figure 4.10: ORTEP diagram of compound **230b***

In addition, we could compare the ^{13}C NMR shifts of the $-CHF_2$ carbon, and of the aromatic carbon bearing the CHF_2 group (C-3). We can observe that for compounds having the same *N*-substituent, similar shifts are observed for both $-CHF_2$ and C-3 carbons (Table 4-14). For instance, for *N*-methyl pyrazoles (entries 1 to 4), the $-CHF_2$ carbon has a shift of ca. 109 ppm, and the aromatic one of ca. 145.5 ppm. Similarly, the C-F couplings are identical.



Entry	Compound	Rf	R	Shift -CHF_2 (ppm)	$J_{C\text{-}F}$ (Hz)	Shift C-3 (ppm)	$^2J_{C\text{-}F}$ (Hz)
1	**223b**	CF_3	CH_3	109,0	237,9	145,7	25,6
2	**226b**	CF_2H	CH_3	109,1	237,6	145,3	24,9
3	**227b**	CF_2Cl	CH_3	109,1	237,8	145,3	25,7
4	**228b**	C_2F_5	CH_3	109,1	238,1	146,1	25,6
5	**223c**	CF_3	Ph	109,2	238,4	146,7	26,2
6	**226c**	CF_2H	Ph	109,4	238,2	146,6	25,3
7	**227c**	CF_2Cl	Ph	109,3	238,4	146,5	26,3
8	**228c**	C_2F_5	Ph	109,4	238,6	147,6	25,8
9	**223d**	CF_3	*t*Bu	109,9	236,7	141,9	27,8
10	**226b**	CF_2H	*t*Bu	109,9	237,3	143,4	25,5
11	**228d**	C_2F_5	*t*Bu	110,0	237,2	142,8	27,3

Table 4-14 : ^{13}C NMR shifts of 3-CHF_2 Pyrazoles

All $-CHF_2$ carbons have comparable shifts, i.e. similar electronic environments. If we compare the shifts of the two $-CHF_2$ carbons of compound **226b** (Figure 4.11), we can see that one carbon has a shift of 109.1 ppm, and the other one has a shift of 107.2 ppm. Thus, by analogy with compound **223b**, we deduce that the 3-CHF_2 carbon has a shift of 109.1 ppm, and that the 5-CHF_2 carbon has a shift of 107.2 ppm.

As the regiochemistry of compound **223b** (entry 1) has been confirmed by X-Ray crystallography, we can conclude that all pyrazoles probably have the same regiochemistry.

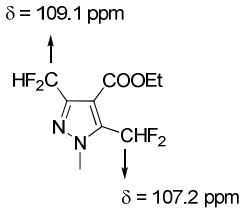


*Figure 4.11: ^{13}C NMR shifts of **226b***

These observations concerning the regiochemistry allowed us to postulate the following reaction mechanism. As shown earlier, the resulting heterocycle can be obtained by nucleophilic attack of one of the nitrogen atoms of the hydrazine onto one of the two electrophilic carbons of the enone entity, which implies four possible regioisomers.

One has to keep in mind that the most nucleophilic nitrogen of methyl hydrazine is the one bearing the methyl group.[5] Then, the first mechanism envisaged involves firstly the nucleophilic attack of the NHMe group of methyl hydrazine onto the adduct **215a**. This adduct can either undergo a Michael-addition or a direct nucleophilic addition onto the trifluorocarbonyl substituent.

In the first case, when the most nucleophilic nitrogen of methyl hydrazine attacks the Michael-acceptor, cyclisation leads to the 3-CF_3-5-CF_2H isomer, after elimination of dimethylamine and water.

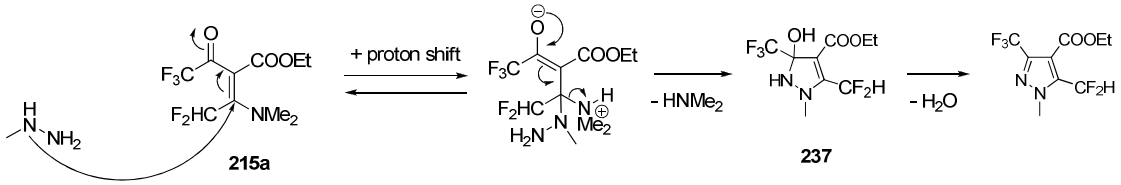


Figure 4.12: Mechanism of the Michael-addition of –NHMe onto the adduct

However, this isomer is not the one we observed (Figure 4.12), and we can conclude that the mechanism of the cyclisation does not involve a Michael-addition of the NHMe onto the adduct.

The other option is the direct attack of the NHMe group on the trifluoromethyl carbonyl group (Figure 4.13). As in this case, the hydrazone cannot be formed, this should give rise to the corresponding hydroxy pyrazoline **239** after attack of the NH_2 on the "Michael-acceptor" **215a**.

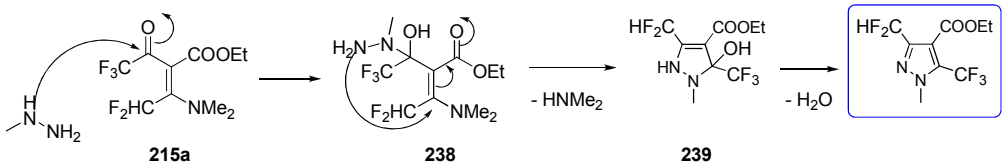


Figure 4.13: Mechanism of the attack of –NHMe onto the trifluoromethyl carbonyl

Dehydration then leads to the isomer we have isolated. However, previous literature[5] dealing with the mechanism for pyrazoles formation reported that usually a dehydration leading to elimination of the hydroxy group next to the trifluoromethyl substituent is disfavoured, and that most of the time the hydroxy pyrazoline is the isolated product. In our case, we never observed the formation of this pyrazoline, but this pathway cannot be totally excluded, as this

pyrazoline might be formed and undergo elimination of water very quickly despite the literature precedents.

As these two approaches did not lead to satisfying conclusions, we considered the pathway *via* attack of the NH_2 substituent of methyl hydrazine. Once again, this can lead to 1,2-attack on the trifluoromethyl carbonyl group, or attack on the Michael-acceptor. In the first case, the attack of the NH_2 substituent directly onto the trifluorocarbonyl group would lead to the formation of the corresponding hydrazone **240** and loss of a molecule of water. Subsequent cyclisation by attack of the NHMe group on the "Michael-acceptor" would provide the 3-trifluoromethyl-5-difluoromethyl isomer (Figure 4.14).

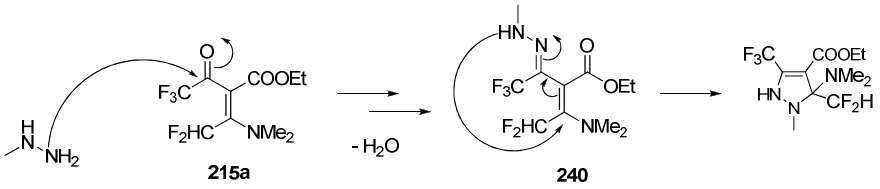


Figure 4.14: Mechanism of the attack of –NH_2 on the trifluorocarbonyl

Hence, we can conclude that in our case, the cyclisation pathway does not proceed *via* the formation of the hydrazone on the trifluorocarbonyl substituent of adduct **215a**. Examining the last possibility led to the conclusion that this mechanism was the most plausible of all. Indeed, the Michael-addition of the NH_2 nitrogen on the adduct would provoke the formation of the desired isomer after elimination of dimethylamine and water (Figure 4.15).

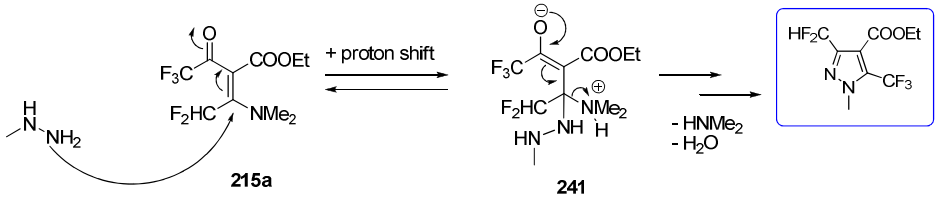


Figure 4.15: Plausible mechanism via *Michael-addition of –NH_2 onto the adduct*

Furthermore, a similar reaction has been reported by M. A. P. Martins *et al.* who observed the formation of a pyrazole by reaction of *tert*-butyl hydrazine with an enaminodiketone.[69] They postulate the addition of the NH_2 nitrogen of the *tert*-butyl hydrazine onto the Michael-acceptor. Subsequent elimination of dimethylamine and cyclisation with elimination of water provided the desired pyrazole. Comparable regioselectivity was observed, and as in our case, the formation of only one regioisomer was detected.

Given all this corroborating information we could conclude on a possible mechanism for the formation of the 3,5-bis(fluoroalkyl) pyrazoles as single isomers. The most plausible pathway is *via* the NH_2 nitrogen Michael-addition on the adduct **215a** followed by cyclisation and elimination of water to provide the desired pyrazole (Figure 4.16). This would be satisfying for the reactivity of *N*-phenyl hydrazine, in which the NH_2 nitrogen is the most nucleophilic one. Regarding *N-tert*-butyl hydrazine, this mechanism is also the most plausible for steric hindrance reasons.

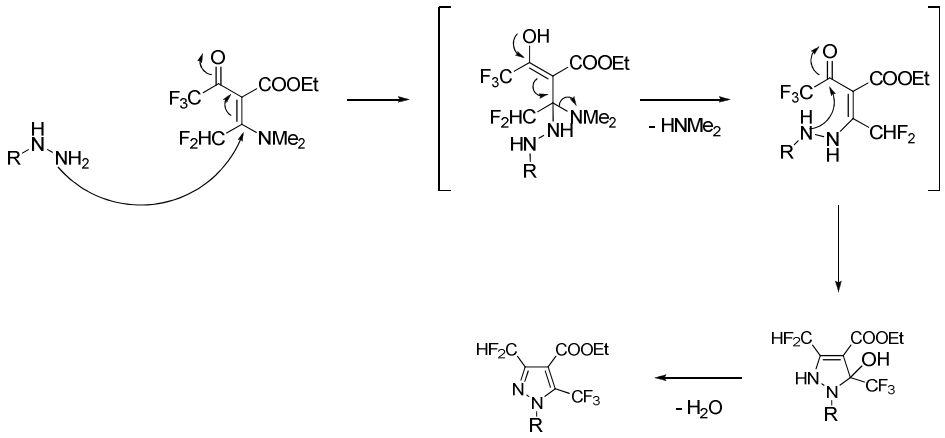


Figure 4.16: Postulated mechanism for the synthesis of 3,5-bis(fluoroalkyl) pyrazoles

However, doubts are still present concerning the *N*-methyl hydrazine, as the NHMe nitrogen atom is believed to be the most nucleophilic one. The results obtained allowed us to eliminate two pathways that led to the wrong isomer. The one which occurs should either be the attack of the NHMe nitrogen onto the trifluoromethyl carbonyl with rapid dehydration of the final product **239** (Figure 4.13) or the Michael-addition of the NH_2 nitrogen on the adduct **215a**. In order to elucidate this reaction pathway, it is necessary to characterise the products of addition **241** (Figure 4.15) or **238** (Figure 4.13).

To conclude, we can claim that ^{13}C NMR and single crystal X-ray diffraction analyses allowed us to undoubtedly determine the regiochemistry of the isomer formed during the cyclisation step. These observations allowed us to postulate a reasonable mechanism. We observed complete regioselectivity in all cases, which is not usually the case.[69] The mechanism is still not clear for the reaction of *N*-methyl hydrazine, but it leads to the same isomer as for the other hydrazine derivatives.

4.4. Conclusion and perspectives

At the beginning of our project, only one existing method for the synthesis of unsymmetrical 3,5-bis(fluoroalkyl) pyrazoles had been reported. Starting with the use of TFEDMA and commercially available fluorinated β-keto esters, we developed a practical method for the synthesis of 3,5-bis(fluoroalkyl) pyrazoles allowing further scale-up. Our investigations resulted in the development of a direct and efficient access to these building blocks. Despite the problems encountered during our studies, we could reach our goal with almost all derivatives.

Thus, we could firstly perform and optimise the cyclisation step in order to obtain several *N*-substituted fluoroalkyl pyrazoles in moderate to very good yields, and observe the influence of the size and the electron-withdrawing properties of the fluorinated group on the yield. The optimised reaction conditions provided the desired pyrazoles regioselectively. The results allowed us to postulate a reasonable reaction mechanism for the formation of these buildingblocks.

Then, a suitable protocol for the saponification of the ethyl carboxylate derivatives was found which gave very good yields. However, the reaction conditions were not convenient for *N*-H pyrazoles, and we had to circumvent this lack of reactivity by synthesising *N*-*tert*-butyl

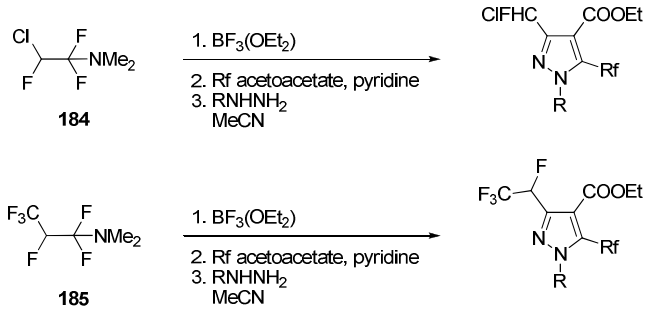
pyrazoles and deprotect them afterwards. Theferore, we were able to access pyrazoles with no substituent at the 4-position after decarboxylation.

Various conditions have been tested before the optimum protocol *i.e.* Cu_2O (5 mol%) and phenanthroline (10 mol%) in a 3:1 mixture of NMP and quinoline, promoted decarboxylation in moderate to good yields. During this reaction, we realised that the volatility was the major factor that had an influence on the yield. However, 5-chlorodifluoro pyrazoles did not undergo decarboxylation in any of the tested conditions.

Finally, we could access *N*-H pyrazoles by deprotection of the *tert*-butyl *N*-substituent in presence of TFA and anisole. These conditions were adapted to 3-CHF_2-5-CF_3 and 3,5-bis(CHF_2) pyrazoles **233d** and **234d**, even if the 3,5-bis(CHF_2) deprotected pyrazole was not isolated. Moreover, we could obtain 3-CHF_2-5-C_2F_5 pyrazole **235d** which was deprotected during the decarboxylation step. It allowed the economy of one step, which is an advantage despite the moderate 46% yield.

The method which has been developed during this investigation provided an efficient and straightforward access to diversely (fluoroalkyl) substituted pyrazoles. We could open an access to unsymmetrical 3,5-bis(fluoroalkyl) pyrazoles bearing an ethyl carboxylate, a carboxylic acid or no substituent at the 4-position of the pyrazole ring. Moreover, the good reactivity of the TFEDMA-acetoacetate adducts towards hydrazines allows the synthesis of several *N*-substituted pyrazoles. This pathway presents a wide range of possibilities for the synthesis of pyrazole building blocks, thus the possibility of a fine tuning for the preparation of new bioactive ingredients. This work has been filed on two patent applications.

Given the encouraging results we obtained during this study, we imagined that other FAR could be used for the synthesis of pyrazoles. This could give another dimension to the choice of the fluorinated group at the 3-position of the pyrazole ring. We could then introduce a -$CHFCF_3$ group if we use Ishikawa's reagent or a -CHFCl substituent with the Yarovenko-Raksha reagent (Scheme 4.60).



Scheme 4.60: Use of other FAR in the synthesis of 3,5-bis(fluoroalkyl) pyrazoles

In order to broaden the scope of synthetic applications of the TFEDMA-β-keto ester adduct **215a**, we had a close look to the literature. We found a lack of existing methods for the preparation of several heteroaromatic building blocks bearing two different fluorinated substituents. Interestingly, the dimethylamino adducts could have a good reactivity towards hydroxylamine for the preparation of isoxazoles, as well as towards urea and thiourea for the synthesis of pyrimidines (Figure 4.17). These studies are currently under investigation in our group.

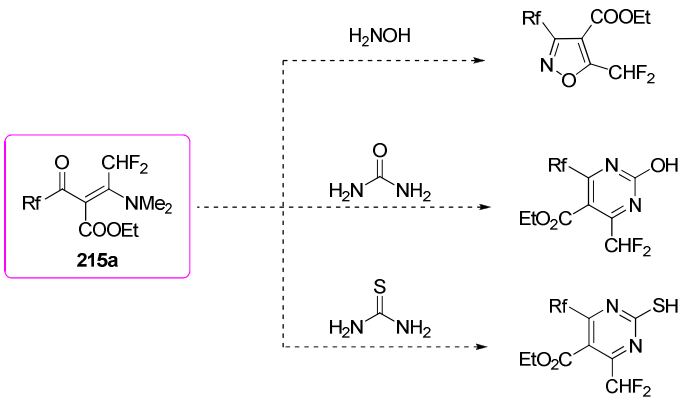


Figure 4.17: Outlook for the synthesis of various heteroaromatic structures

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Chapter 5. General Conclusion

The importance of fluorine in life-sciences oriented research has been outlined, because fluorine dramatically influences the reactivity and bioavailability of active ingredients. The aim of synthetic chemists is thus to open new routes to fluorinated compounds. The large use of heterocycles in agrochemistry as well as in pharmaceutical research requires a constant improvement of the existing methods for the preparation of heterocycles bearing fluorinated substituents. Thus, developing accesses to heterocyclic building blocks with high potential for further functionalisation is essential.

In this manuscript, we have detailed the development of an access to two kinds of heteroaromatic structures: pyridines and pyrazoles. In the first chapter, value has been added to the previously reported method for the preparation of trifluoromethoxy pyridines.

Preparing trifluoromethoxylated analogues of the well-know insecticides Imidacloprid and Thiacloprid proved that these building blocks could be used for the preparation of active ingredients (Figure 5.1).

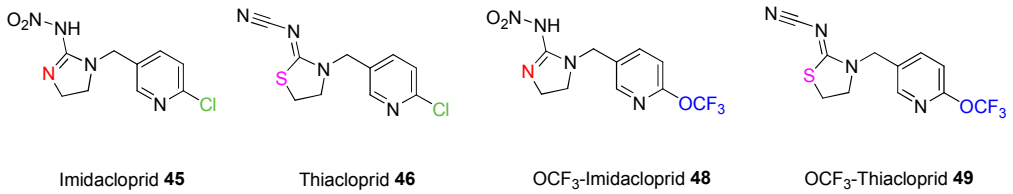


Figure 5.1: Trifluoromethoxy analogues of Imidacloprid and Thiacloprid

Even though the biological tests showed lower activities for these compounds compared to the chlorinated ones, this will not mean that OCF_3-derivatives are in general less active. This simply proved that $-OCF_3$, frequently called a pseudo-halogen, implied a drastic change of activity from chlorine to trifluoromethoxy. Therefore, we can expect that in another case replacing a substituent by a trifluoromethoxy could have a positive effect on the biological activity of the compound.

The preparation of the "OCF_3-Magic Pyridine" represented a big challenge (Figure 5.2). This pyridine is very useful for synthetic chemists because it is highly functionalisable and thus provides many options for a structure-activity relationship study.

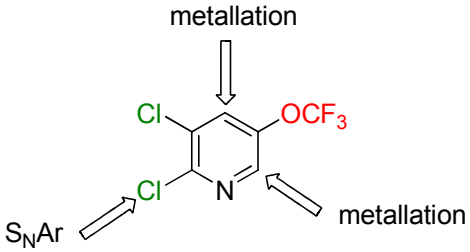
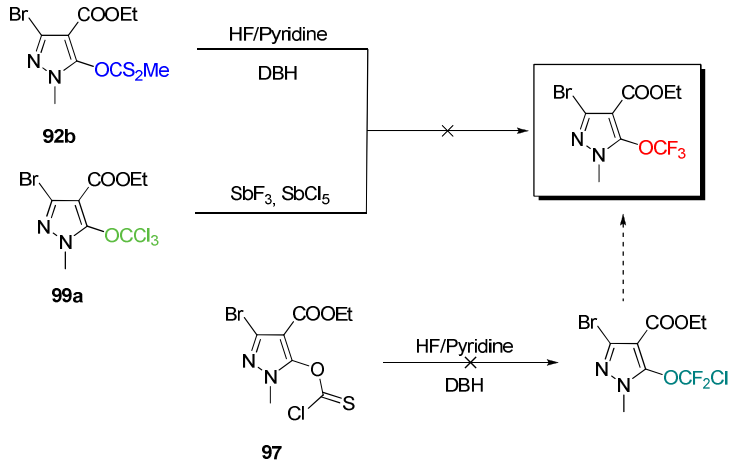


Figure 5.2: OCF_3-Magic Pyridine

The existing method described the use of CHF_2Cl as an *O*-alkylating agent. Subsequent photochlorination and insertion of the third fluorine atom led to the trifluoromethoxy compound. By applying our alkylation/chlorodesulphurisation/fluorination method for the synthesis of "OCF_3-Magic Pyridine", we improved the synthesis of this building block reducing the number of steps.

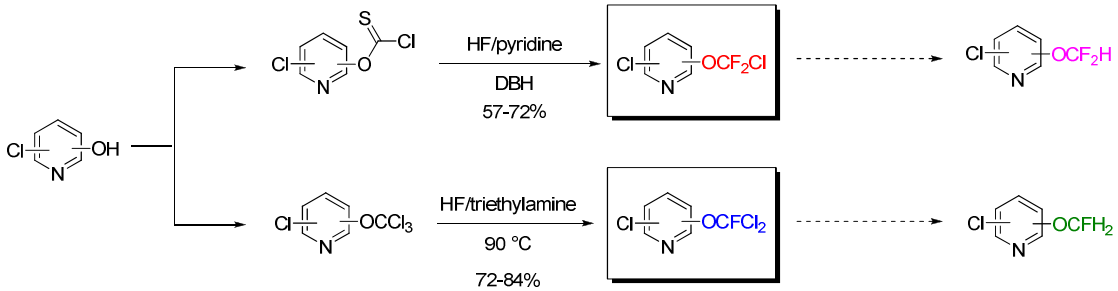
A study on the preparation of 5-trifluoromethoxy pyrazoles was performed, and despite several attempts, we could not reach the desired compound. The aim here was to prepare an unsubstituted pyrazole, but we realised that *N*-alkylation was preferred over *O*-alkylation on these compounds. We tried to perform *O*-alkylation on pyrazoles bearing a methyl or a halogen on the aromatic ring, and this provided slightly better results.



Scheme 5.1: Different approaches for the preparation of 5-OCF_3 pyrazoles

Finally, we realised that oxidative fluorodesulphurisation conditions were not suitable for this kind of pyrazole (Scheme 5.1), so we tried to obtain pyrazoles from the 5-trichloromethoxy compound **99a**. This method did not provide any positive results and we decided to abandon this project.

In a second chapter, we detailed the development of a synthetic route towards chlorodifluoromethoxy and dichlorofluoromethoxy pyridines. This was inspired by the previously developed access to trifluoromethoxy pyridines, which had opened an access to trichloromethoxy pyridines based on chlorothionoformates as starting point of our synthetic routes (Scheme 5.2).



Scheme 5.2: Preparation of –OCF_2Cl and –$OCFCl_2$ pyridines

Chlorodifluoromethoxy pyridines have been obtained selectively in one step from the hydroxy compounds with fair 57 to 72% yields. Fluorination occurred under oxidative fluorodesulphurisation conditions, and the reaction conditions have been optimised with the intention of reducing the amount of HF/pyridine and DBH used.

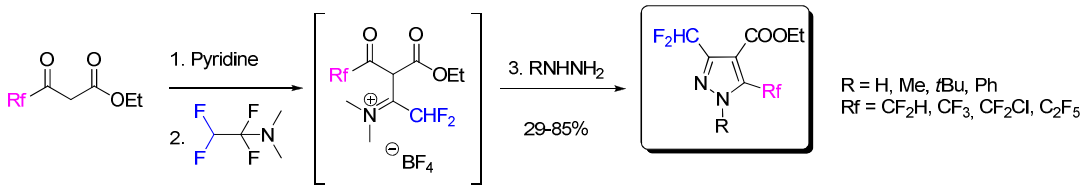
Dichlorofluoromethoxy pyridines have been prepared selectively *via* fluorination of the trichloromethoxy compounds in two steps from the commercially available hydroxy compounds

with good 72 to 84% yields. The fluorination step was performed in presence of HF/triethylamine, with a perfect control of the insertion of a single fluorine atom.

An outlook for this project could be the preparation of difluoro- and fluoro-methyl ethers by reductive dechlorination under radical conditions.

In the third chapter, we detailed our study on the preparation of 3,5-bis(fluoroalkyl) pyrazoles. On one hand, after a careful study of the existing methods for the synthesis of 3-difluoromethyl pyrazoles, we realised that very few methods allowed the preparation of these compounds in good yields and in a totally regioselective way. On the second hand, we were attracted by the use of TFEDMA as a difluoromethyl-transfer reagent. Indeed, its low cost and the fact that the regioselective preparation of 3-difluoromethyl pyrazoles with this reagent had been reported were two big advantages.

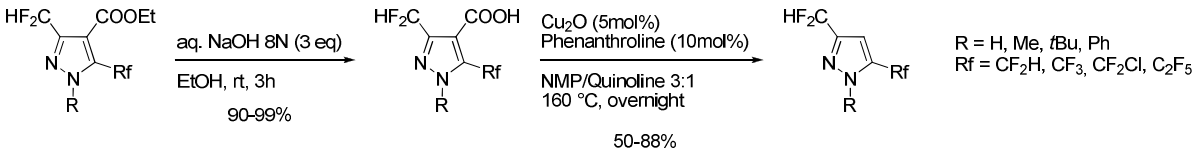
Thus, we used TFEDMA for the introduction of a difluoromethyl group onto an acetoacetate already bearing a fluorinated substituent (Scheme 5.3). This led to the adduct **215a** which could be cyclised in presence of hydrazine to provide the pyrazoles **223a** to **228d** in 29 to 85% yields, depending on the acetoacetate and the hydrazine. In addition, we realised that the cyclisation was completely regioselective, as the only regioisomer formed was the 3-CHF_2-5-Rf pyrazole in each case.



Scheme 5.3: Synthesis of 3,5-bis(fluoroalkyl)-4-carboxylate pyrazoles

^{13}C NMR spectroscopy and a single-crystal X-Ray analysis allowed us to identify the regioisomer which had been formed, and to postulate a reasonable mechanism for the cyclisation step.

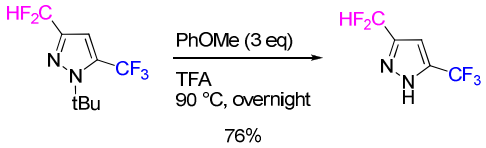
The aim was to develop an access to 4-unsubstituted pyrazoles, so we found a suitable approach for a saponification/decarboxylation sequence (Scheme 5.4). Saponification occurred under basic conditions using three equivalents of sodium hydroxide in ethanol in almost quantitative yields.



Scheme 5.4: Saponification/decarboxylation sequence

Decarboxylation of the pyrazoles has been performed in presence of Cu_2O and phenanthroline, in a 3:1 NMP/quinoline mixture at 160 °C overnight. 4-Unsubstituted products have been obtained in 50 to 88% yield, depending on the *N*-substituent and on the 5-fluorinated substituent. However, with 5-CF_2Cl pyrazoles, the decarboxylation did not occur.

Unfortunately, *N*-H pyrazoles had not undergone saponification, so we had to find a way to isolate 4-unsubstituted 3,5-bis(fluoroalkyl)pyrazoles which were also unsubstituted at the nitrogen atom. Indeed, these building blocks are very important, as they allow any functionalisation at the 4-position and at the nitrogen atom for a structure-activity relationship study. These pyrazoles were accessed by deprotection of *tert*-butyl pyrazoles under strong acidic conditions (TFA) in presence of anisole (Scheme 5.5). Pyrazole **236** was isolated in 76% yield, and the 3,5-bis(CHF_2) pyrazole was deprotected but we were unable to isolate it.



Scheme 5.5: Deprotection of N-tert-butyl 3-CHF_2-5-CF_3 pyrazole

The positive results of this study led to further applications. Indeed, there is a lack of existing methods for the preparation of isoxazoles and pyrimidines bearing two different fluorinated groups. Hence, a study is under development in our group in order to use the TFEDMA/β-keto ester adduct for the preparation of these building blocks.

Scientific production

Oral communications :

- Journées de Chimie Organique, Palaiseau, France (21-23 Septembre 2010)

Title: "First general approach towards functionalised Trifluoromethoxy Pyridines: synthesis, X-Ray analysis and quantum chemistry studies".
Authors: Baptiste Manteau, Pierre Genix, Florence Giornal, Jean-Pierre Vors, Sergiy Pazenok, and Frédéric R. Leroux.

- 8th French Colloquium on Organofluorine Chemistry, Obernai, France (20-24 Mars 2011)

Title: "Synthesis and functionalisation of Trifluoromethoxy Pyridines".
Authors: Baptiste Manteau, Pierre Genix, Florence Giornal, Jean-Pierre Vors, Sergiy Pazenok, and Frédéric R. Leroux.

- SECO 48, Agde, France (22-28 Mai 2011)

Title : "Synthèse et fonctionnalisation de Trifluoromethoxy Pyridines".
Authors: Baptiste Manteau, Pierre Genix, Florence Giornal, Jean-Pierre Vors, Sergiy Pazenok, and Frédéric R. Leroux.

Patents :

- F. Leroux, F. Giornal, S. Pazenok, J.-P. Vors, "*Verfahren zur Herstellung von 3,5-bis(fluoralkyl)-pyrazol-4-carbonsäure-Derivaten und 3,5-bis(fluoralkyl)-pyrazolen*". No 12356001.3-2117 (Bayer CropScience AG / CNRS / Université de Strasbourg; filed 1/2/2012).

- F. Leroux, F. Giornal, S. Pazenok, J.-P. Vors, "Procedure for the decarboxylation of 3,5-bis(haloalkyl)-pyrazole-4-carboxylic acid derivatives". (Bayer CropScience AG / CNRS / Université de Strasbourg; filed 1/2/2012).

Publications :

- B. Manteau, P. Genix, L. Brelot, J.-P. Vors, S. Pazenok, F. Giornal, C. Leuenberger, F. R. Leroux, *Eur. J. Org. Chem.* **2010**, 6043.

- F. Giornal, S. Pazenok, L. Rodefeld, N. Lui, J.-P. Vors, F. R. Leroux *J. Fluorine Chem.,* Accepted.

Chapter 6. Experimental section

6.1. General methods

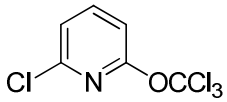
Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Diethyl ether, toluene and tetrahydrofurane were dried by distillation from sodium after the characteristic blue colour of sodium diphenyl ketyl (benzephenone-sodium "radical-anion") had been found to persist. Dichloromethane was dried by distillation from calcium hydride. *N,N*-Dimethyl formamide (DMF) was dried by distillation from magnesium sulphate and stored over molecular sieve (4Å). Acetonitrile was purchased dry from Aldrich and stored over molecular sieve (4Å). Melting ranges (mp) given were found to be reproducible after recrystallisation, unless stated otherwise ("decomp."), and are uncorrected. Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulphate. Water was twice distilled and passed through a Millipore apparatus. Thin-Layer chromatography (TLC) was carried out on 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualised with UV light or iodine. Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 63-210 μm. The solid support was suspended in hexanes and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3 – 5 cm above the support layer, the dry powder, obtained by adsorption of the crude mixture to some 25 mL of silica and subsequent evaporation of the solvent, was poured on top of the column. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 or 300 and 101 or 75 MHz, respectively. ^{19}F NMR was recorded at 282 MHz. Chemical shifts are reported in δ units, parts per million (ppm) and were measured relatively to the signals for residual deuterated solvents or to tetramethylsilane (TMS). Coupling constants (*J)* are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), tq (triplet of quartets), qt (quartet of triplets), m (multiplet), and brs (broad singlet). Gas chromatography monitoring was performed with HP 6890 Series apparatus, capillary column HP-5 (5% phenylmethylsiloxane), FID detector (250 °C), with the following program: 60 °C for 3 minutes, 30 °C/minute until 300 °C, 300 °C for 5 minutes, injector (230 °C). Butyllithium and *tert*-butyllithium were used as solutions in hexanes or pentane and their concentrations were determined following the Wittig-Harborth double titration method[1] ((Total base) – (Residual base after reaction with 1,2-dibromoethane)). Organometallic reagents were usually checked by Gilman tests 1 (all organolithiums) and 2 (only for alkyllithiums).[2]

[1] G. Wittig, G. Harborth *Ber. Dtsch. Chem. Ges.* **1944**, *77*, 315-325.

[2] H. Gilman, J. Swiss *J. Am. Chem. Soc.* **1940**, *62*, 1847-1849.

6.2. Trifluoromethoxy-Imidacloprid

2-Chloro-6-trichloromethoxy pyridine (50)

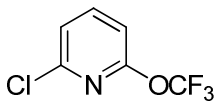


Thiophosgene (4.5 g, 3.0 mL, 39 mmol, 1 equiv.) in dichloromethane (24 mL) was added dropwise to a solution of 2-chloro-6-hydroxypyridine (5.0 g, 39 mmol) in aqueous sodium hydroxide (5%, 34 mL) at 0 °C. The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with 1M HCl (20 mL) and water (20 mL) and dried with sodium sulphate before being evaporated. The crude product was taken up in chloroform (40 mL) and the reaction mixture was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated. The crude pale yellow oil was distilled under reduced pressure to afford pure 2-chloro-6-trichloromethoxy pyridine (5.7 g, 23 mmol, 60%) as a colourless oil which crystallised on standing (b.p. = 80–82 °C, 1 mbar). ^{1}H and ^{13}C NMR were in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.70 (t, 1 H, J = 7.9 Hz, H-4), 7.19 (d, 1 H, J = 7.7 Hz, H-5), 7.02 (d, J = 8.1 Hz, 1 H, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 151.8 (C), 149.0 (C), 141.7 (CHarom), 122.2 (CHarom), 112.7 (CHarom), 109.1 ($OCCl_3$) ppm.

2-Chloro-6-trifluoromethoxy pyridine (51)

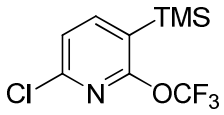


2-Chloro-6-trichloromethoxy pyridine (5.9 g, 24 mmol, 1 equiv.) was added dropwise at 120 °C to a mixture of SbF_3 (8.7 g, 48 mmol, 2 equiv.) and $SbCl_5$ (1.4 g, 0.60 mL, 4.8 mmol, 0.2 equiv.) and the mixture was stirred for 3 h at 140 °C. GC monitoring indicated 100% conversion and disappearance of the -OCF_2Cl byproduct. The mixture was then cooled to room temperature and dissolved in dichloromethane (100 mL). The solution was washed with 2M HCl (150 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude product was distilled under reduced pressure to afford pure 2-chloro-6-trifluoromethoxy pyridine (2.5 g, 13 mmol, 53%) as a colourless oil (b.p. = 42–44 °C, 20 mbar). ^{1}H and ^{13}C NMR were in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.67 (t, 1 H, J = 7.9 Hz, H-4), 7.18 (d, 1 H, J = 7.7 Hz, H-5), 6.87 (d, 1 H, J = 8.0 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 155.6 (C), 149.3 (C), 142.0 (CHarom), 122.2 (CHarom), 119.8 (q, $J_{C\text{-}F}$ = 262.1 Hz, OCF_3), 111.1 (CH) ppm.

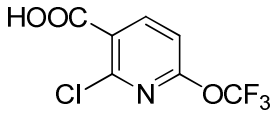
2-Chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (52)



Butyllithium (1.56 M in hexanes, 5.7 mL, 8.9 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.90 g, 1.2 mL, 8.9 mmol, 1.1 equiv.) in THF (15 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine (1.6 g, 8.1 mmol, 1 equiv.) in THF (5 mL) was added dropwise at -78 °C, and the reaction mixture was stirred for 2 h at this temperature. Chlorotrimethylsilane (1.0 g, 8.9 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to reach 25 °C before being neutralised with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The crude product was distilled under reduced pressure to afford pure 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (1.5 g, 5.5 mmol, 68%) as a colourless oil (b.p. = 89–93 °C, 14 mbar). ^{1}H NMR was in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.78 (d, 1 H, J = 7.6 Hz, H-3), 7.22 (d, 1 H, J = 7.6 Hz, H-4), 0.34 (s, 9 H, $SiMe_3$) ppm.

2-Chloro-6-trifluoromethoxy nicotinic acid (53)

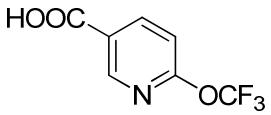


Butyllithium (1.56 M in hexanes, 3.7 mL, 5.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of 2,2,6,6-tetramethylpiperidine (0.8 g, 1.0 mL, 5.7 mmol, 1.1 equiv.) in THF (10 mL). A solution of 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (1.4 g, 5.2 mmol, 1 equiv.) in THF (5 mL) was added dropwise at -78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 10 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH = 1 by dropwise addition of 6M HCl (4 mL). After extraction with ethyl acetate (3 x 10 mL), the combined organic layers were dried over sodium sulphate and evaporated. The crude oil was treated with tetrabutylammonium fluoride (1M in THF, 5.7 mL, 5.7 mmol, 1.1 equiv.) for 20 h at 25 °C. The mixture was then neutralised by addition of 2M HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated to afford pure 2-chloro-6-(trifluoromethoxy) nicotinic acid (0.92 g, 3.7 mmol, 70%) as a colourless

powder. ^{1}H NMR was in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.44 (d, 1H, *J* = 8.3 Hz, H-4), 7.21 (d, 1 H, *J* = 8.3 Hz, H-5) ppm.

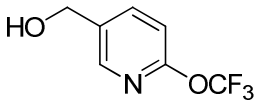
6-Trifluoromethoxy nicotinic acid (54)



Palladium (10% on charcoal, 2.1 g, 2.0 mmol, 10 mol%) was added at 25 °C with stirring to a solution of 2-chloro-6-trifluoromethoxy nicotinic acid (4.8 g, 20 mmol, 1 equiv.) and ammonium formate (2.5 g, 40 mmol, 2 equiv.) in methanol (40 mL). The reaction mixture was stirred for 16 h at room temperature before being filtered on celite, the filtrate was concentrated and the residue was taken up in ethyl acetate (50 mL). The organic layer was washed with 2M HCl (2 x 20 mL) and water (20 mL). The organic layer was dried over sodium sulphate and evaporated *in vacuo* to afford pure 6-(trifluoromethoxy) nicotinic acid (3.2 g, 15 mmol, 76%) as a colourless powder. ^{1}H NMR was in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.91 (d, 1 H, *Jm* = 2.3 Hz, H-2), 8.48 (dd, 1 H, *Jo* = 8.4, *Jm* = 2.3 Hz, H-4), 7.24 (d, 1 H, *Jo* = 8.4 Hz, H-5) ppm.

(6-(Trifluoromethoxy)pyridin-3-yl)methanol (55)



Method A: $LiAlH_4$ (1M in THF, 1.47 mL, 1.47 mmol, 1.5 equiv.) was added dropwise to 6-trifluoromethoxy nicotinic acid (207 mg, 1.00 mmol, 1 equiv.) in solution in THF (5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and at 55 °C for 3 h. It was quenched with saturated ammonium chloride (5 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulphate and the solvent was distilled off. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether (7:3 to 1:1) as eluent, which afforded **55** (60.0 mg, 0.310 mmol, 31%) as a colourless oil.

Method B: BH_3·THF (1M in THF, 36 mL, 36 mmol, 5 equiv.) was added dropwise to the 6-trifluoromethoxy nicotinic acid (1.5 g, 7.3 mmol, 1 equiv.) in solution in THF (25 mL) at 0 °C. The reaction mixture was stirred 30 min at this temperature, and allowed to reach room temperature overnight. It was quenched with methanol (25 mL), diluted with diethyl ether (100 mL) and the organic layer was washed with brine (2 x 100 mL). The combined organic layers were dried with sodium sulphate and the solvent was distilled off. The crude product was

purified by column chromatography on silica gel with pentane/diethyl ether (6:4 to 3:7) as eluent, which afforded **55** (1.0 g, 5.0 mmol, 70%) as a colourless oil.

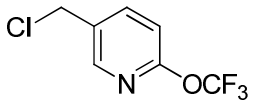
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.28 (d, J = 2.4 Hz, 1 H, H-2), 7.82 (dd, 1 H, Jo = 8.4 Hz, Jm = 2.4 Hz, H-4), 7.03 (d, 1 H, J = 8.4 Hz, H-5), 4.73 (s, 2H, CH_2), 2.36 (brs, 1H, -OH) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 156.5 (C-6), 146.7 (C-2), 139.7 (C-4), 135.6 (C-3), 120.6 (q, $J_{C\text{-}F}$ = 259.2 Hz, OCF_3), 62.1 (CH_2) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -56.7 ppm.

HRMS (ESI Positive) for $C_7H_7F_3NO_2$ [M+H]: calcd. 194.043; found 194.044.

3-(Chloromethyl)-6-(trifluoromethoxy) pyridine (56)



Mesyl chloride (0.28 mL, 0.42 g, 3.6 mmol, 1.5 equiv.) was added dropwise to a solution of (6-(trifluoromethoxy)pyridin-3-yl)methanol (0.50 g, 2.4 mmol, 1 equiv.) in dichloromethane (8 mL) in presence of triethylamine (0.60 g, 5.7 mmol, 2.4 equiv.) at 0 °C. The reaction mixture was allowed to reach room temperature overnight. It was then poured into a saturated solution of sodium hydrogen carbonate (10 mL). The aqueous layer was extracted with dichloromethane (3 x 15 mL) and washed with water (2 x 10 mL). The combined organic layers were dried over sodium sulphate and the solvent was distilled off. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent, which afforded **56** (0.31 g, 1.4 mmol, 56%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.32 (d, 1 H, J = 2.4 Hz, H-2), 7.85 (dd, 1 H, Jm = 2.4 Hz, Jo = 8.4 Hz, H-4), 7.03 (d, 1 H, J = 8.4 Hz, H-5), 4.59 (s, 2H, CH_2) ppm.

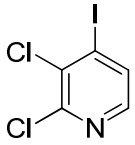
^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 156.5 (C-6), 147.4 (C-2), 140.6 (C-4), 131.6 (C-3), 120.0 (q, OCF_3, $J_{C\text{-}F}$ = 260.1 Hz), 42.0 (CH_2) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -56.6 ppm.

MS (EI): m/z = 211.1 [M^+], 176.0 [M^+-Cl].

6.3. Trifluoromethoxy "Magic Pyridine"

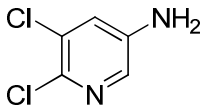
2,3-Dichloro-4-iodo pyridine (74)



Butyllithium (1.59 M in hexanes, 14.1 mL, 22.4 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (2.30 g, 3.20 mL, 22.4 mmol, 1.1 equiv.) in THF (20 mL). A solution of 2,3-dichloro pyridine (3.00 g, 20.4 mmol, 1 equiv.) in THF (10 mL) was added dropwise at –75 °C, followed after 2 h by a solution of iodine (6.22 g, 24.5 mmol, 1.2 equiv.) in THF (12 mL). The reaction mixture was allowed to reach 25 °C before being diluted with diethyl ether (60 mL). The organic layer was washed with a saturated aqueous solution of sodium sulphite (2 x 30 mL), water (15 mL) and brine (15 mL). The combined organic layers were dried over sodium sulphate prior to concentration. The crude product was recrystallised from methanol to afford pure 2,3-dichloro-4-iodo pyridine (4.54 g, 16.7 mmol, 82%). ^{1}H NMR in accordance with the literature (K. Snegaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros, F. Mongin *Chem. Eur. J.* **2011**, *17*, 13284 – 13297.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.90 (d, 1H, J = 5.1 Hz, H-6), 7.74 (d, 1H, J = 5.1 Hz, H-5) ppm.

2,3-Dichloro-5-amino pyridine (67)

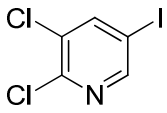


Iron (11.5 g, 207 mmol, 4 equiv.) was added portionwise to 2,3-dichloro-5-nitro pyridine (10.0 g, 52.0 mmol, 1 equiv.) diluted in a 4:1 ethanol/HCl mixture (50 mL). The reaction mixture was heated to reflux for 1 h. The reaction mixture was allowed to reach room temperature and adjusted to pH = 8 with a 5% aqueous solution of sodium hydrogen carbonate (500 mL). Ethyl acetate (500 mL) was added and the reaction mixture was filtered through celite. The organic layer was washed with water (2 x 150 mL), brine (2 x 150 mL), dried over sodium sulphate and evaporated under vacuum to afford pure 2,3-dichloro-5-amino pyridine (7.10 g, 44.0 mmol, 85%) as a white solid. ^{1}H and ^{13}C NMR in accordance with the literature (V. Koch, S. Schnatterer *Synthesis* **1990**, 499-501.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.75 (d, 1H, J = 2.7 Hz, H-6), 7.10 (d, 1H, J = 2.7 Hz, H-4), 3.87 (brs, 2H, NH_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 142.7 (C-5), 137.4 (C-2), 134.2 (C-6), 130.1 (C-3), 124.1 (C-4) ppm.

2,3-Dichloro-5-iodo pyridine (73)



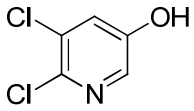
To a solution of 2,3-dichloro-5-aminopyridine (10.0 g, 61.7 mmol, 1 equiv.) in HBF_4 (100 mL) and water (100 mL) was added dropwise a solution of sodium nitrite (6.40 g, 92.6 mmol, 1.5 equiv.) in water (50 mL) at -5 °C. After 20 min, a solution of potassium iodide (20.5 g, 123 mmol, 2 equiv.) in water (55 mL) was added, and the reaction mixture was stirred for one hour at -5 °C. Solid potassium carbonate was added until the pH of the reaction mixture reached 10. The aqueous layer was extracted with ethyl acetate (3 x 200 mL), the combined organic layers were washed with saturated sodium sulphate (2 x 100 mL) and water (100 mL) before being dried over magnesium sulphate and evaporated under vacuum. The brownish crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (100:0 to 98:2) as eluent, which afforded the title compound (13.8 g, 50.6 mmol, 82%) as an orange solid, m.p. [56.9-57.4] °C.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.50 (d, 1H, J = 2.1 Hz, H-6), 8.08 (d, 1H, J = 2.1 Hz, H-4) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 153.2 (C-6), 148.9 (C-2), 146.1 (C-4), 131.5 (C-3), 90.2 (C-5) ppm.

HRMS (ESI Positive) for $C_5H_3Cl_2IN$ [M+H]: calcd. 273.869; found 273.869.

2,3-Dichloro-5-hydroxy pyridine (69)

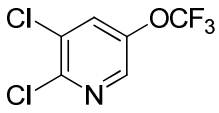


Butyllithium (1.60 M in hexanes, 13.2 mL, 21.1 mmol, 1.1 equiv.) was added dropwise at -78 °C to a solution of 2,3-dichloro-5-iodo pyridine (5.00 g, 18.3 mmol, 1 equiv.) in THF (500 mL). After 5 min, triisopropyl borate (17.2 g, 21.1 mL, 91.5 mmol, 5 equiv.) was added dropwise and the reaction mixture was allowed to reach room temperature. At 0 °C, oxone (11.3 g, 18.3 mmol, 1 equiv.) and 60 mL of a saturated aqueous solution of sodium hydrogen carbonate were added. The reaction mixture was stirred for 30 min at this temperature, and allowed to reach room temperature over 1 h. A saturated solution of sodium thiosulfate (125 mL) was added dropwise, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (7:3 to 1:1) as eluent, which afforded 2,3-dichloro-5-hydroxy pyridine (2.70 g, 16.6 mmol, 90%) as a white solid. 1H and 13C NMR were in accordance with the literature (V. Koch, S. Schnatterer *Synthesis* **1990**, 499-501.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 10.82 (brs, 1H, OH), 7.94 (d, 1H, J = 2.7 Hz, H-6), 7.49 (d, 1H, J = 2.7 Hz, H-4) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 153.9 (C2), 136.6 (C5), 135.9 (C6), 128.7 (C3), 125.7 (C4) ppm.

2,3-Dichloro-5-trifluoromethoxy pyridine (72)



Thiophosgene (4.6 g, 3.0 mL, 40 mmol, 1 equiv.) in chloroform (24 mL) was added dropwise at 0 °C to a solution of 2,3-dichloro-5-hydroxy pyridine (6.4 g, 40 mmol) in aqueous sodium hydroxide (5%, 34 mL). The reaction mixture was vigorously stirred for 12 h at room temperature before being extracted with chloroform (3 x 20 mL). The combined organic layers were washed with water (20 mL) and dried over sodium sulphate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated to afford 2,3-dichloro-5-trichloromethoxy pyridine (9.3 g, 33 mmol, 83%). The crude pale yellow oil was directly added dropwise at 120 °C to a mixture of SbF_3 (12 g, 66 mmol, 2 equiv.) and $SbCl_5$ (2.0 g, 0.9 mL, 6.6 mmol, 0.2 equiv.) and the mixture was stirred for 5 h at 150 °C. GC monitoring indicated 100% conversion and disappearance of the -OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (100 mL). The solution was washed with 2M HCl (100 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried with sodium sulphate and the solvent was distilled off. The crude product was distilled under reduced pressure to afford pure 2,3-chloro-5-trifluoromethoxy pyridine (1.5 g, 6.5 mmol, 20%) as a colourless oil (b.p. 65–68 °C, 13 mbar).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.29 (d, 1H, J = 2.1 Hz, H-6), 7.49 (dd, 1H, J_{H-H} = 2.7 Hz, J_{H-F} = 0.6 Hz, H-4) ppm.

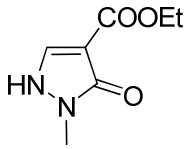
^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (C-2), 144.8 (C-5), 140.2 (C-6), 131.5 (C-4), 131.1 (C-3), 120.3 (q, J_{C-F} = 259.2 Hz, OCF_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -58.5 ppm.

HRMS (ESI Positive) for $C_6H_3Cl_2F_3NO$ [M+H]: calcd. 231.954; found 231.954.

6.4. Towards 5-trifluoromethoxy pyrazoles

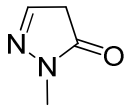
Ethyl 1-methyl-5-oxo pyrazole-4-carboxylate (90)



To a solution of methyl hydrazine (3.5 g, 3.9 mL, 76 mmol, 1 equiv.) in water (300 mL) with K_2CO_3 (11 g, 76 mmol, 1 equiv.) was added dropwise diethyl (ethoxymethylene)malonate (16 g, 15 mL, 76 mmol, 1 equiv.). The reaction mixture was heated to reflux for 3 h. At room temperature, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The aqueous layer was then adjusted to pH = 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). These combined organic layers were washed with water (150 mL) and dried over sodium sulphate before being filtered and evaporated *in vacuo* to afford pure ethyl 1-methyl-5-oxo pyrazole-4-carboxylate (11 g, 63 mmol, 83%) as a white solid. ^{1}H NMR was in accordance with the literature (L. F. Tietze, T. Brumby, M. Pretor, G. Remberg *J. Org. Chem.* **1988**, *53*, 810-820.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.59 (s, 1H, Harom), 4.32 (q, 2H, J = 7.1 Hz, CH_2), 3.67 (s, 3H, N-CH_3), 1.36 (t, 3H, J = 7.2 Hz, CH_3) ppm.

1-Methyl-1*H*-pyrazol-5-one (84)



Method A:
Methyl hydrazine (0.50 g, 11 mmol, 1.1 equiv.) was added dropwise to diethyl (ethoxymethylene)malonate (2.2 g, 10 mmol, 1 equiv.) in methanol (7 mL), and the reaction mixture was heated to reflux for 4 h. The solvent was evaporated, and the resulting solid washed with diethyl ether (3 x 10 mL). After being dried, the crude mixture was dissolved with KOH (1.7 g, 30 mmol, 3 equiv.) in a water/ethanol 1:1 mixture (10 mL). The resulting red solution was heated at 100 °C for 2 h and allowed to cool to room temperature and then 0 °C. 12M HCl was added dropwise until the pH reached 1, and the reaction mixture was heated at 100 °C overnight. The solvent was evaporated to dryness, and the KCl/product mixture was washed several times with ethyl acetate (5 x 20 mL). The filtrate was dried over sodium sulphate and evaporated *in vacuo* to afford pure 1-methyl-1*H*-pyrazol-5-one (0.6 g, 6.0 mmol, 60%) as a colourless solid. ^{1}H NMR was in accordance with the literature (L. F. Tietze, T. Brumby, M. Pretor, G. Remberg *J. Org. Chem.* **1988**, *53*, 810-820.).

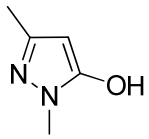
Methob B:
Methyl hydrazine (1.5 g, 33.0 mmol, 1.1 equiv.) was added to methyl 3-methoxyacrylate (3.5 g, 30 mmol, 1 equiv.) in methanol (3 mL), and the mixture was heated to reflux for 1 h. The solvent

was evaporated *in vacuo*, and the resulting solid was recrystallised from diethyl ether to afford pure 1-methyl-1*H*-pyrazol-5-one (2.7 g, 27 mmol, 90%) as a white solid. ^{1}H and ^{13}C NMR were in accordance with the literature (G. A. Eller, W. Holzer *Molbank* **2006**, M464.).

^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 7.65 (s, 2H, CH_2), 5.75 (s, 1H, CH), 3.75 (s, 3H, N-CH_3) ppm.

^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 157.7 (CH_2), 136.1 (CH), 91.9 (CO), 32.7 (N-CH_3) ppm.

1,3-Dimethyl-1*H*-pyrazol-5-ol (88)

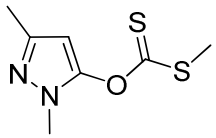


Ethyl acetoacetate (10 g, 10 mL, 80 mmol, 1 equiv.) was added dropwise to a solution of methyl hydrazine (3.7 g, 4.2 mL, 80 mmol, 1equiv.) in methanol (40 mL) cooled to 0 °C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure to afford pure 1,3-dimethyl-1*H*-pyrazol-5-ol (8.6 g, 76 mmol, 95%) as a slightly yellow solid. ^{1}H and ^{13}C NMR were in accordance with the literature (J. Gonzalez, T. M. Jewell, A. Linton, T. H. Tatlock, K. Ruddock PCT Int. appl. *WO* 2006018725 (Pfizer Inc., **2006**)).

^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ = 10.64 (brs, 1H, OH), 5.11 (s, 1 H), 3.38 (s, 3 H, N-CH_3), 2.00 (s. 3 H, CH_3) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C): δ = 155.3 (C-5), 145.5 (C-3), 87.0 (C-4), 32.0 (N-CH_3), 13.6 (CH_3) ppm.

***S*-Methyl 1,3-dimethyl-1*H*-pyrazol-5-dithiocarbamate (89)**



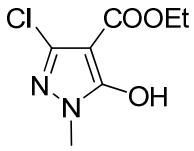
Method A: Thiophosgene (2.1 g, 1.4 mL, 18 mmol, 1 equiv.) in chloroform (15 mL) was added dropwise at 0 °C to a solution of 1,3-dimethyl-1*H*-pyrazol-5-ol (2.0 g, 18 mmol) in aqueous potassium hydroxide (5%, 20 mL). The reaction mixture was then vigorously stirred overnight at room temperature before being extracted with chloroform (3 x 10 mL). The combined organic layers were washed with water (10 mL), and were dried with sodium sulphate before being filtered. To a 21% solution of sodium methanethiolate in water (6.5 mL, 22 mmol, 1.1 equiv.) was added the filtrate at 25 °C, and the reaction mixture was vigorously stirred at this temperature for 20 h. The aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were dried over sodium sulphate and evaporated under vacuum. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate (9:1) as eluent, which afforded **89** (0.20 g, 1.1 mmol, 6%) as a yellow oil.

Method B: To 1,3-dimethyl-1*H*-pyrazol-5-ol (2.0 g, 18 mmol, 1 equiv.) in THF (10 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 1.1 g, 27 mmol, 1.5 equiv.) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 45 minutes and thiophosgene (2.1 g, 1.4 mL, 18 mmol, 1 equiv.) in chloroform (15 mL) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature. It was quenched with dropwise addition of water (15 mL) before being extracted with chloroform (3 x 10 mL). The combined organic layers were washed with water (10 mL), and were dried over sodium sulphate before being filtered. The filtrate was added to a 21% solution of sodium methanethiolate in water (6.5 mL, 22 mmol, 1.1 equiv.) at 25 °C and the reaction mixture was vigorously stirred 20 h. The aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate (9:1 to 3:7) as eluent, which afforded **89** (0.25 g, 1.3 mmol, 7%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 5.80 (s, 1 H, Harom), 3.59 (s, 3 H, N-CH_3), 2.68 (s, 3 H, S-CH_3), 2.25 (s, 3 H, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 212.6 (C=S), 147.1 (C3, C5), 94.9 (CH), 34.6 (N-CH_3), 20.4 (S-CH_3), 14.5 (CH_3) ppm.

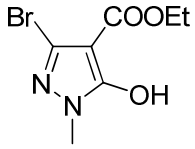
Ethyl 3-chloro-5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate (91a)



N-Chlorosuccinimide (2.0 g, 15 mmol, 2.5 equiv.) was combined with Ethyl 1-methyl-5-oxo pyrazole-4-carboxylate **90** (1.0 g, 5.9 mmol, 1 equiv.) and the mixture was heated at 85 °C overnight. The reaction temperature was lowered to 60 °C and the mixture was taken up in tetrachloromethane (15 mL) and washed twice with saturated aqueous sodium carbonate (2 x 10 mL), followed by water (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulphate and filtered. The solvent was evaporated *in vacuo* to provide pure ethyl 3-chloro-5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate (1.1 g, 5.3 mmol, 89%) as a yellow oil. ^{1}H NMR was in accordance with the literature (M. A. Hanagan, T. P. Selby, P. L. Sharpe, R. B. Sheth, T. M. Stevenson PCT Int. Appl. *WO* 2005070889 (Dupont De Nemours and company, **2005**)).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.35 (m, 2H, CH_2), 3.40 (s, 3H, N-CH_3), 1.32 (t, 3H, CH_3) ppm.

Ethyl 3-bromo-5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate (91b)



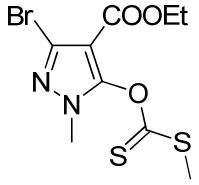
N-Bromosuccinimide (26.2 g, 147 mmol, 2.5 equiv.) was combined with Ethyl 1-methyl-5-oxo pyrazole-4-carboxylate **90** (10.0 g, 59.0 mmol, 1 equiv.) and the mixture was heated at 90 °C for 4.5 h. The reaction temperature was lowered to 60 °C, the mixture was taken up in tetrachloromethane (150 mL) and washed twice with saturated aqueous sodium carbonate (2 x 100 mL), followed by water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulphate and filtered, and the solvent was evaporated *in vacuo* to provide pure ethyl 3-bromo-5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate (14.1 g, 56.2 mmol, 96%) as an orange oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.40-4.28 (m, 2H, CH_2), 3.41 (s, 3H, N-CH_3), 1.32 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.7 (COOEt), 160.0 (C_5-OH), 134.4 (C-4), 64.9 (CH_2), 55.4 (C-3), 32.5 (N-CH_3), 13.9 (CH_3) ppm.

HRMS (ESI positive) for $C_7H_8BrN_2NaO_3$ [M+Na]: calcd. 269.961; found 269.962.

Ethyl 3-bromo-1-methyl-5-(methylthiocarbonothioyloxy)-1*H*-pyrazole-4-carboxylate (92b)



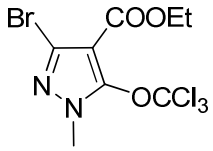
Ethyl 3-bromo-5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate(2.5 g, 10 mmol, 1 equiv.) in THF (5 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 0.6 g, 15 mmol, 1.5 equiv.) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 45 min and thiophosgene (1.2 g, 0.82 mL, 10 mmol, 1 equiv.) in THF (8 mL) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature. It was quenched by dropwise addition of water (8 mL) before being extracted with chloroform (3 x 5 mL). The combined organic layers were washed with water (10 mL), and were dried over sodium sulphate before being filtered. The filtrate was added to a 21% solution of sodium methanethiolate in water (3.7 mL, 11 mmol, 1.1 equiv.) at 25 °C, and the reaction mixture was vigorously stirred for 20 h. The aqueous layer was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate (9:1 to 2:8) as eluent, which afforded **92b** (0.62 g, 1.7 mmol, 17%) as a brown oil which crystallised on standing.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.16 (q, 2H, J = 7.2 Hz, CH_2), 3.60 (s, 3H, N-CH_3), 2.63 (s, 3H, S-CH_3) 1.20 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 211.4 (C=S), 159.9 (C=O), 148.4 (C-5), 126.8 (C-3-Br), 102.9 (C-4), 60.4 (CH_2), 35.5 (N-CH_3), 20.6 (S-CH_3), 14.1 (CH_3) ppm.

MS(EI): m/z = 291 [M-SCH_3],

Ethyl 3-bromo-1-methyl-5-(trichloromethoxy)-1*H*-pyrazole-4-carboxylate (99a)



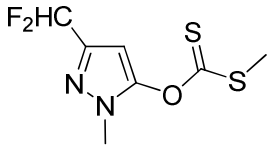
Ethyl *N*-methyl-3-bromo-5-hydroxy pyrazole-4-carboxylate (10.0 g, 40.2 mmol, 1 equiv.) in THF (20 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 2.43 g, 60.3 mmol, 1.5 equiv.) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 45 min and thiophosgene (5.30 g, 3.75 mL, 48.2 mmol, 1.2 equiv.) in THF (30 mL) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature. It was quenched by dropwise addition of water (20 mL) before being extracted with chloroform (3 x 30 mL). The combined organic layers were washed with water (30 mL), and were dried over sodium sulphate before being filtered and evaporated under vacuum. The crude product was taken up in chloroform (90 mL) and the reaction mixture was saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated. The crude pale yellow oil was purified by chromatography on silica gel with cyclohexane/ethyl acetate (95:5) as eluent, which afforded **99a** (6.93 g, 18.8 mmol, 47%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.29 (q, 2H, J = 7.2 Hz, CH_2), 3.88 (s, 3H, N-CH_3), 1.35 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.5 (C=O), 145.6 (C-5), 127.1 (C-3-Br), 114.3 ($OCCl_3$), 105.8 (C-4), 61.3 (CH_2), 37.8 (N-CH_3), 14.3 (CH_3) ppm.

HRMS (ESI positive) for $C_8H_8BrCl_3N_2NaO_3$ [M+Na]: calcd. 386.868; found 386.868.

3-Difluorometyl-1-methyl-5-(methylthiocarbonothioyloxy)-1*H*-pyrazole (94)



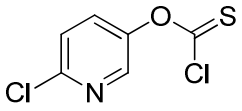
Thiophosgene (1.6 g, 1.0 mL, 14 mmol, 1 equiv.) in chloroform (10 mL) was added dropwise at 0 °C to a solution of *N*-methyl-3-difluoromethyl-5-hydroxy pyrazole **93** (2.0 g, 14 mmol) in aqueous sodium hydroxide (5%, 12 mL). The reaction mixture was then vigorously stirred for 2 h at room temperature before being extracted with chloroform (3 x 10 mL). The combined organic layers were washed with water (10 mL), and dried over sodium sulphate before being filtered. The filtrate was added to a 21% solution of sodium methanethiolate in water (4.6 mL, 15 mmol, 1.1 equiv.) at 25 °C, and the reaction mixture was vigorously stirred for 2 days. The aqueous layer was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate (8:2) as eluent, which afforded **94** (0.69 g, 2.7 mmol, 20%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.58 (t, 1H, $J_{H\text{-}F}$ = 56.3 Hz, CHF_2), 6.25 (s, 1H, H), 3.69 (s, 3H, N-CH_3), 2.70 (s, 3H, S-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 212.0 (C=S), 147.41 (C-5), 144.96 (t, $^{2}J_{C\text{-}F}$ = 30.1 Hz, C-3), 111.3 (t, $J_{C\text{-}F}$ = 237.4 Hz, CHF_2), 93.4 (C-4), 35.5 (N-CH_3), 20.4 (S-CH_3) ppm.

6.5. Pyridines bearing –$OCFCl_2$ and –OCF_2Cl substituents

2-Chloro-5-(chlorothionoformate) pyridine

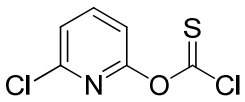


Thiophosgene (1.1 g, 9.3 mmol, 1.2 equiv.) in dichloromethane (5 mL) was added dropwise at 0 °C to a solution of 2-chloro-5-hydroxy pyridine (1.0 g, 7.7 mmol) in aqueous sodium hydroxide (5%, 7.5 mL, 1.2 equiv.). The reaction mixture was vigorously stirred for 12 h at room temperature until the pH of the aqueous phase reached 1. It was then diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (20 mL) and dried over sodium sulphate before evaporated to afford the desired product (1.5 g, 7.3 mmol, 94%) as a brownish solid. The product was not isolated for toxicity reasons.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.25 (d, 1H, *Jm* = 2.8 Hz, H-6), 7.50 (dd, 1H, *Jo* = 8.7 Hz, *Jm* = 2.8 Hz, H-4), 7.42 (d, 1H, *Jo* = 8.7 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 185.2 (C=S), 150.1 (C-5), 149.6 (C-2), 142.9 (C-6), 133.2 (C-4), 125.3 (C-3) ppm.

2-Chloro-6-(chlorothionoformate) pyridine

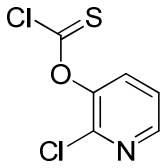


Thiophosgene (10.7 g, 93.0 mmol, 1.2 equiv.) in dichloromethane (50 mL) was added dropwise at 0 °C to a solution of 2-chloro-6-hydroxy pyridine (10.0 g, 77.2 mmol) in aqueous sodium hydroxide (5%, 75.0 mL, 1.2 equiv.). The reaction mixture was vigorously stirred for 12 h at room temperature until the pH of the aqueous phase reached 1. It was then diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (50 mL) and dried over sodium sulphate before evaporated to afford the desired product (11.9 g, 57.2 mmol, 74%) as a brownish solid. The product was not isolated for toxicity reasons.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.85 (t, 1H, *J* = 7.9 Hz, H-4), 7.36 (d, 1H, *J* = 7.8 Hz, H-3), 7.07 (d, 1H, *J* = 7.9 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 183.8 (C=S), 158.6 (C-6), 150.0 (C-2), 142.6 (C-4), 124.2 (C-3), 114.7 (C-5) ppm.

2-Chloro-3-(chlorothionoformate) pyridine

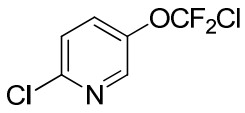


Thiophosgene (10.7 g, 93.0 mmol, 1.2 equiv.) in dichloromethane (50 mL) was added dropwise at 0 °C to a solution of 2-chloro-6-hydroxy pyridine (10.0 g, 77.2 mmol) in aqueous sodium hydroxide (5%, 75.0 mL, 1.2 equiv.). The reaction mixture was vigorously stirred for 12 h at room temperature until the pH of the aqueous phase reached 1. It was then diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (50 mL) and dried over sodium sulphate before evaporated to afford the desired product (15.8 g, 76.0 mmol, 99%) as a yellow solid. The product was not isolated for toxicity reasons.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.39 (dd, 1H, *Jo* = 4.7 Hz, *Jm* = 1.6 Hz, H-6), 7.60 (dd, 1H, *Jo* = 8.0 Hz, *Jm* = 1.6 Hz, H-4), 7.40 (dd, 1H, Jo_1 = 8.0 Hz, Jo_2 = 4.8 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 183.5 (C=S), 148.0 (C-3), 147.0 (C-2), 143.7 (C-5), 132.0 (CHarom), 114.7 (CHarom) ppm.

2-Chloro-5-chlorodifluoromethoxy pyridine (123)



To a suspension of *N,N*-dibromohydantoin (18.5 g, 64.8 mmol, 4.5 equiv.) in dry dichloromethane (45 mL) at -78 °C was added 70% HF/pyridine (7.50 mL, 288 mmol, 20 equiv.) and the reaction mixture was stirred for 30 minutes. 2-Chloro-5-(chlorothionoformate) pyridine (3.00 g, 14.4 mmol, 1 equiv.) in dichloromethane (20 mL) was added to the reaction mixture. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was diluted with dry diethyl ether (50 mL) and cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the red colour disappeared. The aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layer were washed with 1M HCl (3 x 50 mL), water (50 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-5-chlorodifluoromethoxy pyridine (2.40 g, 11.0 mmol, 76%) as a colourless liquid.

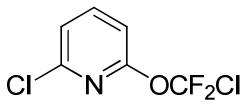
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.27 (d, 1H, *Jm* = 2.5 Hz, H-6), 7.49 (dd, 1H, *Jo* = 8.7 Hz, *Jm* = 2.9 Hz, H-4), 7.32 (d, 1H, *J* = 8.7 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.4 (C-2), 146.0 (t, $J_{C\text{-}F}$ = 2.1 Hz, C-5), 143.2 (t, $J_{C\text{-}F}$ = 1.3 Hz, C-6), 131.9 (CH arom), 125.1 (CHarom), 125.1 (t, $J_{C\text{-}F}$ = 290.2 Hz, CF_2Cl) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -26.9 ppm.

HRMS (ESI positive) for $C_6H_4Cl_2F_2NO$ [M+H]: calcd. 213.963; found 213.965.

2-Chloro-6-chlorodifluoromethoxy pyridine (125)



To a suspension of *N,N*-dibromohydantoin (18.5 g, 64.8 mmol, 4.5 equiv.) in dry dichloromethane (45 mL) at -78 °C was added 70% HF/pyridine (7.50 mL, 288 mmol, 20 equiv.) and the reaction mixture was stirred for 30 minutes. 2-Chloro-6-(chlorothionoformate) pyridine (3.00 g, 14.4 mmol, 1 equiv.) in dichloromethane (20 mL) was added to the reaction mixture. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was diluted with dry diethyl ether (50 mL) and cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the red colour disappeared. The aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layer were washed with 1M HCl (3 x 50 mL), water (50 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-5-chlorodifluoromethoxy pyridine (1.80 g, 8.10 mmol, 57%) as a slightly yellow liquid.

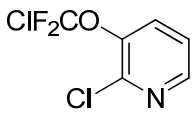
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.27 (d, 1H, *Jm* = 2.5 Hz, H-6), 7.49 (dd, 1H, *Jo* = 8.7 Hz, *Jm* = 2.9 Hz, H-4), 7.32 (d, 1H, *Jo* = 8.7 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.4 (C-2), 146.0 (t, $J_{C\text{-}F}$ = 2.1 Hz, C-5), 143.2 (t, $J_{C\text{-}F}$ = 1.3 Hz, C-6), 131.9 (CH arom), 125.1 (CHarom), 125.1 (t, $J_{C\text{-}F}$ = 290.2 Hz, CF_2Cl) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -25.8 ppm.

HRMS (ESI positive) for $C_6H_4Cl_2F_2NO$ [M+H]: calcd. 213.964; found 213.964.

2-Chloro-3-chlorodifluoromethoxy pyridine (124)



To a suspension of *N,N*-dibromohydantoin (18.5 g, 64.8 mmol, 4.5 equiv.) in dry dichloromethane (45 mL) at -78 °C was added 70% HF/pyridine (7.5 mL, 288 mmol, 20 equiv.) and the reaction mixture was stirred for 30 minutes. 2-Chloro-3-(chlorothionoformate) pyridine (3.00 g, 14.4 mmol, 1 equiv.) in dichloromethane (20 mL) was added to the reaction mixture. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was diluted with dry diethyl ether (50 mL) and

cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the red colour disappeared. The aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layer were washed with 1M HCl (3 x 50 mL), water (50 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-5-chlorodifluoromethoxy pyridine (2.10 g, 10.0 mmol, 70%) as a slightly yellow liquid.

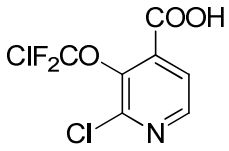
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.33 (dd, 1H, *Jo* = 4.7 Hz, *Jm* = 1.5 Hz, H-6), 7.80 (dd, 1H, *Jo* = 8.2 Hz, *Jm* = 1.5 Hz, H-4), 7.33 (dd, 1H, Jo_1 = 8.2 Hz, Jo_2 = 4.3 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.5 (C-6), 145.0 (C-2), 143.3 (t, $J_{C\text{-}F}$ = 1.9 Hz, C-3), 130.9 (t, $J_{C\text{-}F}$ = 1.3 Hz, C-4), 125.4 (t, $J_{C\text{-}F}$ = 292.6 Hz, CF_2Cl), 123.4 (C-5) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -26.1 ppm.

HRMS (ESI positive) for $C_6H_4Cl_2F_2NO$ [M+H]: calcd. 213.963; found 213.963.

2-Chloro-3-chlorodifluoromethoxy isonicotinic acid (126)



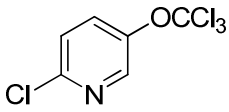
Butyllithium (1.56 M in hexanes, 3.3 mL, 5.2 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.52 g, 0.73 mL, 5.2 mmol, 1.1 equiv.) in THF (8 mL). A solution of 2-chloro-3-chlorodifluoromethoxy pyridine (1.0 g, 4.7 mmol, 1 equiv.) in THF (2.5 mL) was added dropwise at -78 °C, and the reaction mixture was stirred for 3 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 10 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH = 1 by dropwise addition of 6M HCl (4 mL). After extraction with ethyl acetate (3 x 10 mL), the combined organic layers were dried with sodium sulphate and evaporated to afford pure 2-chloro-6-chlorodifluoromethoxy isonicotinic acid (0.70 g, 2.7 mmol, 58%) as a slightly yellow powder, m.p. 162-163 °C.

^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.51 (d, 1H, *J* = 4.9 Hz, H-6), 7.78 (d, 1H, *J* = 4.9 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.4 (COOH), 149.8 (CHarom), 148.3 (C_{IV}arom), 141.4 (t, $J_{C\text{-}F}$ = 2.0 Hz, C-4), 139.6 (C_{IV}arom), 127.3 (t, $J_{C\text{-}F}$ = 292.9 Hz, OCF_2Cl), 125.2 (CHarom) ppm.

HRMS (ESI negative) for $C_7H_2Cl_2F_2NO_3$ [M-H]: calcd. 255.937; found 255.938.

2-Chloro-5-trichloromethoxy pyridine (122)

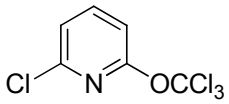


2-Chloro-5-(chlorothionoformate) pyridine (3.00 g, 14.4 mmol, 1 equiv.) was diluted in chloroform (30 mL). The solution was saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated to afford pure 2-chloro-5-trichloromethoxy pyridine (2.62 g, 10.5 mmol, 73%) as a yellow oil. ^{1}H and ^{13}C NMR were in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.41 (dd, 1H, *Jm* = 3.0 Hz, H-6), 7.71 (dd, 1H, *Jo* = 8.7 Hz, *Jm* = 3.0 Hz, H-4), 7.38 (d, 1H, *Jo* = 8.7 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.3 (C-5), 147.8 (C-2), 144.1 (C-6), 132.7 (CH arom), 125.2 (CHarom), 112.2 (CCl_3) ppm.

2-Chloro-6-trichloromethoxy pyridine

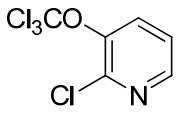


2-Chloro-6-(chlorothionoformate) pyridine (3.0 g, 14 mmol, 1 equiv.) was diluted in chloroform (30 mL). the solution was saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated to afford pure 2-chloro-6-trichloromethoxy pyridine (2.0 g, 8.1 mmol, 56%) as a yellow oil. ^{1}H and ^{13}C NMR were in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.72 (t, 1H, *J* = 7.9 Hz, H-4), 7.22 (d, 1H, *J* = 7.8 Hz, H-3), 7.05 (d, 1H, *J* = 7.9 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 151.9 (C-5), 149.0 (C-6), 141.7 (C-2), 122.2 (C-4), 113.0 (C-3), 112.6 (CCl_3) ppm.

2-Chloro-3-trichloromethoxy pyridine

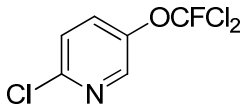


2-Chloro-3-(chlorothionoformate) pyridine (10 g, 48 mmol, 1 equiv.) was diluted in chloroform (100 mL). The solution was saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of argon and the solution was concentrated to afford pure 2-chloro-3-trichloromethoxy pyridine (7.5 g, 30 mmol, 63%) as a yellow oil. ^{1}H and ^{13}C NMR were in accordance with the literature (B. Manteau PhD Thesis, Université de Strasbourg, 2009).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.35 (dd, 1H, *Jo* = 4.7 Hz, *Jm* = 1.6 Hz, Harom), 8.05 (dd, 1H, *Jo* = 8.2 Hz, *Jm* = 1.5 Hz, Harom), 7.35 (dd, 1H, Jo_1 = 8.2 Hz, Jo_2 = 4.7 Hz, H-5) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.2 (C-6), 145.5 (C-3), 145.4 (C-2), 130.6 (CHarom), 123.0 (CHarom), 112.0 (CCl_3) ppm.

2-Chloro-5-dichlorofluoromethoxy pyridine (127)



2-Chloro-5-trichloromethoxy pyridine (2.00 g, 8.10 mmol, 1 equiv.) was mixed with HF/Et_3N (17.6 mL, 108 mmol, 40 equiv.) and heated to 90 °C for 24 h. The reaction mixture was diluted with dry diethyl ether (50 mL) and cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the pH of the aqueous phase reached 7. It was adjusted to pH = 9 with an aqueous NaOH solution (10%, 20 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 1M HCl (3 x 30 mL), water (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-5-dichlorofluoromethoxy pyridine (1.63 g, 6.82 mmol, 84%) as a colourless oil.

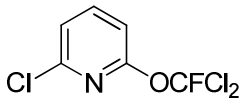
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.39 (d, 1H, *Jm* = 2.9 Hz, H-6), 7.62 (dd, 1H, *Jo* = 8.7 Hz, *Jm* = 2.9 Hz, H-4), 7.40 (d, 1H, *Jo* = 8.7 Hz, H-3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.4 (C-2), 147.0 (d, $J_{C\text{-}F}$ = 0.9 Hz, C-5), 143.6 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-6), 132.4 (d, $J_{C\text{-}F}$ = 1.3 Hz, C-4), 125.0 (C-3), 123.6 (d, $J_{C\text{-}F}$ = 312.7 Hz, $CFCl_2$) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -8.5 ppm.

HRMS (ESI positive) for $C_6H_4Cl_3FNO$ [M+H]: calcd. 229.934; found 229.932.

2-Chloro-6-dichlorofluoromethoxy pyridine (128)



2-Chloro-6-trichloromethoxy pyridine (2.43 g, 9.50 mmol, 1 equiv.) was mixed with HF/Et_3N (20.7 mL, 127 mmol, 40 equiv.) and heated to 90 °C for 48 h. The reaction mixture was diluted with dry diethyl ether (50 mL) and cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the pH of the aqueous phase reached 7. It was adjusted to pH = 9 with an aqueous NaOH solution (10%, 20 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 1M HCl (3 x 30 mL), water (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-5-dichlorofluoromethoxy pyridine (1.73 g, 7.20 mmol, 76%) as a slightly yellow oil.

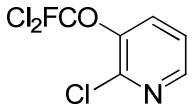
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.77 (t, 1H, *J* = 7.9 Hz, H-4), 7.30 (d, 1H, *J* = 7.7 Hz, Harom), 7.05 (d, 1H, *J* = 8.1 Hz, Harom) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 156.9 (d, $^3J_{C\text{-}F}$ = 2.0 Hz, C-6), 149.2 (C-2), 142.0 (CHarom), 122.5 (CHarom), 121.7 (d, $J_{C\text{-}F}$ = 312.7 Hz, $CFCl_2$), 112.5 (d, $^4J_{C\text{-}F}$ = 1.9 Hz, C-5) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -9.1 ppm.

HRMS (ESI positive) for $C_6H_4Cl_3FNO$ [M+H]: calcd. 229.935; found 229.934.

2-Chloro-6-dichlorofluoromethoxy pyridine (129)



2-Chloro-3-trichloromethoxy pyridine (3.00 g, 12.0 mmol, 1 equiv.) was mixed with HF/Et_3N (26.4 mL, 162 mmol, 40 equiv.) and heated to 90 °C for 7 days. The reaction mixture was diluted with dry diethyl ether (50 mL) and cooled to 0 °C. It was quenched with an aqueous saturated $NaHCO_3$ solution (100 mL) and then solid $NaHCO_3$ until the pH of the aqueous phase reached 7. It was adjusted to pH = 9 with an aqueous NaOH solution (10%, 20 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 1M HCl (3 x 30 mL), water (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure 2-chloro-3-dichlorofluoromethoxy pyridine (2.00 g, 8.83 mmol, 72%) as a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.37 (dd, 1H, *Jo* = 4.7 Hz, *Jm* = 1.5 Hz, Harom), 7.80 (dt, 1H, *Jo* = 8.2 Hz, *Jm* = 1.6 Hz, Harom), 7.35 (dd, 1H, Jo_1 = 8.2 Hz, Jo_2 = 4.3 Hz, H-5) ppm.

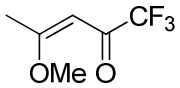
^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.3 (C-6), 145.2 (d, J_{C-F} = 0.9 Hz, C-3), 144.4 (C-2), 131.0 (d, J_{C-F} = 2.1 Hz, C-4), 123.7 (d, J_{C-F} = 314.9 Hz, $CFCl_2$), 123.1 (C-5) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -6.6 ppm.

HRMS (ESI positive) for $C_6H_4Cl_3FNO$ [M+H]: calcd. 229.935; found 229.935.

6.6. (3,5)-Bis(fluoroalkyl) pyrazoles

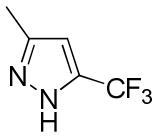
1,1,1-Trifluoro-4-methoxypent-3-en-2-one (213a)



Trifluoroacetic anhydride (9.1 g, 6.1 mL, 43 mmol, 1 equiv.) in dry dichloromethane (20 mL) was added to 2-methoxypropene (3.6 g, 50.0 mmol, 1.15 equiv.) and pyridine (4.5 g, 57 mmol, 1.3 equiv.) in dry dichloromethane (40 mL) at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and diluted with dichloromethane (75 mL). The organic layer was washed with water (3 x 30 mL), 1M HCl (3 x 30 mL), and brine (30 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by distillation under reduced pressure to afford pure 1,1,1-trifluoro-4-methoxypent-3-en-2-one (7.0 g, 42 mmol, 97%) as a yellow liquid. ^{1}H NMR was in accordance with the literature (K. V. Tarashenko, O. V. Manoylenko, V. P. Kukhar, G.-V. Röschenthaler, I. I. Gerus *Tetrahedron Lett.* **2010**, *51*, 4623-4626.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 5.68 (s, 1H, Hvinylic), 3.80 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3) ppm.

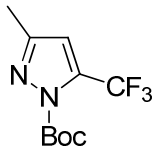
3-Methyl-5-trifluoromethyl-1*H*-pyrazole (217)



Hydrazine hydrate (2.7 g, 55 mmol, 1.3 equiv.) was added to 1,1,1-trifluoro-4-methoxypent-3-en-2-one (7.0 g, 42 mmol, 1 equiv.) in ethanol (21 mL). The reaction mixture was heated to reflux during 2 h then allowed to cool to room temperature and evaporated *in vacuo*. The resulting crude product was taken up in isopropyl ether (40 mL) and evaporated under reduced pressure to afford pure 3-methyl-5-(trifluoromethyl)-1*H*-pyrazole (5.8 g, 39 mmol, 92%) as a slightly yellow solid. ^{1}H NMR was in accordance with the literature (M. A. P. Martins, D. N. Moreira, C. P. Frizzo, K. Longhi, N. Zanatta, H. G. Bonacorso *J. Braz. Chem. Soc.* **2008,** *19*, 1361-1368.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.31 (s, 1H, Harom), 2.33 (s, 3H, CH_3) ppm.

tert-Butyl 3-methyl-5-trifluoromethyl-1*H*-pyrazole-1-carboxylate (218)



3-Methyl-5-(trifluoromethyl)-1*H*-pyrazole (2.0 g, 13 mmol, 1 equiv.) was diluted in acetonitrile (20 mL) with triethylamine (1.5 g, 15 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (0.32 g, 2.7 mmol, 0.2 equiv.) at 0 °C. Di-*tert*-butyl dicarbonate dissolved in acetonitrile (10 mL) was added to the reaction mixture, and it was stirred overnight at room temperature. Acetonitrile was evaporated *in vacuo* and the crude mixture was taken up in dichloromethane (50 mL). The organic layer was washed with water (30 mL), and the aqueous layer was acidified to pH = 1 with 1M HCl. The organic layer was washed again with the acidified aqueous layer, with brine (30 mL), dried over magnesium sulphate and the solvent was evaporated to afford pure *tert*-butyl 3-methyl-5-trifluoromethyl-1*H*-pyrazole-1-carboxylate (3.0 g, 12 mmol, 92%) as a yellow oil. The title compound was obtained as a 93:7 ratio between the 3-methyl and the 5-methyl isomers (NMR ratios), only the major compound is described.

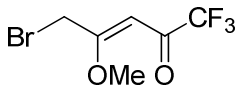
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.37 (s, 1H, Harom), 2.56 (s, 3H, CH_3), 1.66 (s, 9H, Boc-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.8 (C=O), 145.3 (C_{IV}arom), 144.96 (q, $^{2}J_{C\text{-}F}$ = 38.6 Hz, C_{IV}arom), 120.6 (q, $J_{C\text{-}F}$ = 269.7 Hz, CF_3), 107.0 (q, $^{3}J_{C\text{-}F}$ = 1.7 Hz, CHarom), 86.5 (C_{IV}*t*Bu), 27.8 (*t*BuCH_3), 14.5 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -64.3 ppm.

HRMS (ESI positive) for $C_{10}H_{13}F_3N_2NaO_2$ [M+Na]: calcd. 273.082; found 273.084.

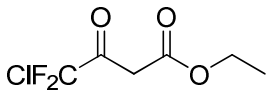
5-Bromo-1,1,1-trifluoro-4-methoxypent-3-en-2-one (219a)



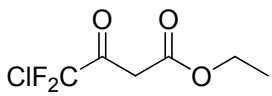
Bromine (2.1 g, 0.74 mL, 13 mmol, 0.9 equiv.) was added over 30 min to 1,1,1-trifluoro-4-methoxypent-3-en-2-one (2.5 g, 15 mmol, 1 equiv.) in dry dichloromethane (120 mL) at 0 °C and stirred for 2 h. Pyridine (1.1 g, 13 mmol, 0.9 equiv.) was added at 0 °C and stirred for 30 minutes before water was added (100 mL). The aqueous phase was extracted with dichloromethane (2 x 50 mL), the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford the title compound (3.3 g, 13 mmol, 90%) as a brown-orange oil. ^{1}H NMR was in accordance with the literature (M. A. P. Martins, A. P. Sinhorin, A. Da Rosa, A. F. C. Flores, A. D. Wastowski, C. M. P. Pereira, D. C. Flores, P. Beck, R. A. Freitag, S. Brondani, W. Cunico, H. G. Bonacorso, N. Zanatta *Synthesis* **2002**, 2353-2358.).

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 5.74 (s, 1H, Hvinylic), 4.45 (s, 2H, CH_2Br), 3.88 (s, 3H, OCH_3) ppm.

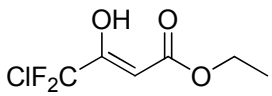
Ethyl 4-chloro-4,4-difluoro-3-oxobutanoate (225)



Butyllithium (1.53 M in hexanes, 52.3 mL, 80.0 mmol, 2 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (8.16 g, 11.3 mL, 80.0 mmol, 2 equiv.) in diethyl ether (30 mL). A solution of dry ethyl acetate (7.06 g, 80.0 mmol, 2 equiv.) in diethyl ether (5 mL) was added dropwise at –78 °C, followed directly by a solution of ethyl chlorodifluoro acetate (6.29 g, 40.0 mmol, 1 equiv.) in diethyl ether (4 mL). The reaction mixture was stirred for 4 h at this temperature, and quenched with a saturated ammonium chloride solution (50 mL) before being allowed to reach room temperature. The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 1M HCl (50 mL), brine (50 mL) and dried with sodium sulphate prior to concentration. Distillation under reduced pressure afforded pure title compound (5.83 g, 28.9 mmol, 72%) as a slightly yellow liquid (b.p. = 94-97 °C, 93 mbar). ^{1}H NMR was in accordance with the literature (T. Kitazume, M. Asai, T. Tsukamoto, T. Yamazaki *J. Fluorine Chem.* **1992**, *56*, 271-284.). The desired product was obtained in a mixture between the keto form (isomer a) and the enol form (isomer b).



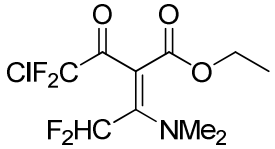
isomer a



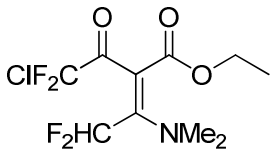
isomer b

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.02 (brs, 0.5H, -OH), 5.58 (s, 0.5H, Hvinylic), 4.33-4.24 (m, 2H, CH_2), 3.78 (s, 1H, CH_2), 1.36-1.27 (m, 3H, CH_3) ppm.

Ethyl 2-(2-chloro-2,2-difluoroacetyl)-3-(dimethylamino)-4,4-difluorobut-2-enoate (215c)

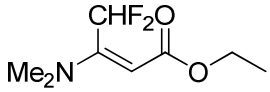


$BF_3(OEt_2)$ (0.1 mL, 1.0 mmol, 1 equiv.) was added to a solution of TFEDMA (0.1 mL, 1.0 mmol, 1 equiv.) in dry dichloromethane (1 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry deuterated acetonitrile (1 mL). In another Teflon flask, ethyl 4-chloro-4,4-difluoroacetoacetate (0.2 g, 1.0 mmol, 1 equiv.) was added to a solution of potassium fluoride (0.2 g, 3.0 mmol, 3 equiv.) in dry deuterated acetonitrile (2 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was then analysed by ^{1}H and ^{13}C NMR spectroscopy. The title compound was obtained in a 2:1 mixture (^{1}H NMR) with ethyl 3-(dimethylamino)-4,4-difluorobut-2-enoate.



^{1}H NMR (CD_3CN, 300 MHz, 25 °C): δ = 6.36 (t, 1H, $J_{H\text{-}F}$ = 53.2 Hz, CHF_2), 4.21 (q, 2H, J = 7.2 Hz, CH_2), 3.07 (t, 3H, $^{5}J_{H\text{-}F}$ = 1.2 Hz, NMe), 2.95 (t, 3H, $^{5}J_{H\text{-}F}$ = 1.2 Hz, NMe), 1.26 (t, 3H, J = 7.2 Hz, CH_3) ppm.

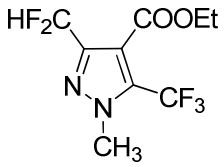
^{13}C NMR (CD_3CN, 75 MHz, 25 °C): δ = 185.3 (F_2ClC-$\underline{C}O$), 164.9 (CO), 161.7 (t, $^{2}J_{C\text{-}F}$ = 25.1 Hz, $\underline{C}_{IV}$-NMe_2), 119.4 (t, $J_{C\text{-}F}$ = 304.3 Hz, CF_2Cl), 108.1 (t, $J_{C\text{-}F}$ = 244.4 Hz, CHF_2), 98.1 (t, $^{3}J_{C\text{-}F}$ = 4.8 Hz, C_{IV}), 61.9 (CH_2), 35.0 (N-$\underline{Me}_2$), 13.3 (CH_3) ppm.



^{1}H NMR (CD_3CN, 300 MHz, 25 °C): δ = 6.65 (t, 1H, $J_{H\text{-}F}$ = 51.9 Hz, CHF_2), 5.70 (s, 1H, CH), 4.31 (q, 2H, J = 7.1 Hz, CH_2), 3.91 (t, 3H, $^{5}J_{H\text{-}F}$ = 0.8 Hz, NMe), 3.22 (t, 3H, $^{5}J_{H\text{-}F}$ = 1.2 Hz, NMe), 1.31 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR (CD_3CN, 75 MHz, 25 °C): δ = 171.3 (CO), 163.4 (t, $^{2}J_{C\text{-}F}$ = 21.3 Hz, $\underline{C}_{IV}$-NMe_2), 110.5 (t, $J_{C\text{-}F}$ = 246.7 Hz, CHF_2), 91.1 (t, $^{3}J_{C\text{-}F}$ = 4.4 Hz, C_{IV}), 61.2 (CH_2), 36.4 (N-Me_2), 13.3 (CH_3) ppm.

Ethyl 1-methyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (223b)



Method A:
$BF_3(OEt_2)$ (0.62 mL, 5.0 mmol, 1 equiv.) was added to a solution of TFEDMA (0.59 mL, 5.0 mmol, 1 equiv.) in dry dichloromethane (5 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (5 mL). In another Teflon flask, ethyl 4,4,4-trifluoroacetoacetate (0.73 mL, 5.0 mmol, 1 equiv.) was added to a solution of potassium fluoride (0.88 g, 15 mmol, 3 equiv.) in 10 mL of dry acetonitrile and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach -10 °C over one hour. Methyl hydrazine (0.32 mL, 6.0 mmol, 1.2 equiv.) was added dropwise at -30 °C, the cooling bath was removed and the reaction mixture was stirred at room temperature overnight. The solution was filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 8:2) as eluent to afford the pure title compound **223b** (0.29 g, 1.1 mmol, 21%) as a yellow oil.

Method B:

$BF_3(OEt_2)$ (6.2 mL, 50 mmol, 1 equiv.) was added to a solution of TFEDMA (5.9 mL, 50 mmol, 1 equiv.) in dry dichloromethane (50 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (50 mL). In another Teflon flask, ethyl 4,4,4-trifluoroacetoacetate (9.2 g, 50 mmol, 1 equiv.) was added to a solution of pyridine (12 mL, 150 mmol, 3 equiv.) in dry acetonitrile (100 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Methyl hydrazine (3.9 mL, 75 mmol, 1.5 equiv.) was added dropwise at room temperature and the reaction mixture was stirred for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (100 mL). The organic phase was washed with HCl 1M (3 x 50 mL), brine (50 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 8:2) as eluent to afford the pure title compound **223b** (8.5 g, 31 mmol, 63%) as a yellow oil.

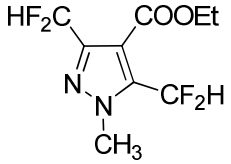
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.00 (t, 1H, $J_{H\text{-}F}$ = 54 Hz, CHF_2), 4.37 (q, 2H, J = 7.2 Hz, CH_2), 4.12 (s, 3H, N-CH_3), 1.37 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.2 (CO), 145.7 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_{IV}arom), 133.2 (q, $^2J_{C\text{-}F}$ = 40.3 Hz, C_{IV}arom), 119.0 (q, $J_{C\text{-}F}$ = 271.2 Hz, CF_3), 114.4 (C_{IV}arom), 109.0 (t, $J_{C\text{-}F}$ = 237.9 Hz, CHF_2), 61.9 (CH_2), 40.8 (q, $^4J_{C\text{-}F}$ = 3.2 Hz, N-CH_3), 13.8 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -57.6 (CF_3), -116.4 (CHF_2) ppm.

$C_9H_9F_5N_2O_2$ (272): calcd. (%) C 39.72, H 3.33, N 10.29; found C 39.03, H 3.33, N 10.26.

Ethyl 1-methyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (226b)



$BF_3(OEt_2)$ (1.24 mL, 10.0 mmol, 1 equiv.) was added to a solution of TFEDMA (1.20 mL, 10.0 mmol, 1 equiv.) in dry dichloromethane (10 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (10 mL). In another Teflon flask, ethyl 4,4-difluoroacetoacetate (1.03 mL, 10.0 mmol, 1 equiv.) was added to a solution of pyridine (1.60 mL, 20.0 mmol, 2 equiv.) in dry acetonitrile (20 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Methyl hydrazine (0.790 mL, 15.0 mmol, 1.5 equiv.) was added dropwise at room temperature the reaction mixture was stirred for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (25 mL). The organic phase was washed with HCl 1M (3 x 20 mL), brine (20 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0

to 8:2) as eluent to afford the pure title compound **226b** (0.840 g, 3.31 mmol, 33%) as a colourless oil which crystallised on standing, m.p. 53-54 °C.

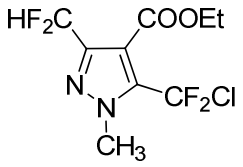
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.48 (t, 1H, $J_{H\text{-}F}$ = 52.6 Hz, CHF_2), 7.04 (t, 1H, $J_{H\text{-}F}$ = 53.8 Hz, CHF_2), 4.38 (q, 2H, J = 7.1 Hz, CH_2), 4.12 (s, 3H, N-CH_3), 1.39 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.1 (CO), 145.3 (t, $^2J_{C\text{-}F}$ = 24.9 Hz, C_{IV}arom), 138.2 (t, $^2J_{C\text{-}F}$ = 24.1 Hz, C_{IV}arom), 112.9 (m, C_{IV}arom), 109.1 (t, $J_{C\text{-}F}$ = 237.6 Hz, CHF_2), 107.2 (t, $J_{C\text{-}F}$ = 236.3 Hz, CHF_2), 61.5 (CH_2), 39.6 (t, $^4J_{C\text{-}F}$ = 3.1 Hz, N-CH_3), 13.9 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -117.00 (d, $J_{F\text{-}H}$ = 53.8 Hz, CHF_2), -117.04 (d, $J_{F\text{-}H}$ = 52.6 Hz, CHF_2) ppm.

$C_9H_{10}F_4N_2O_2$ (254): calcd. (%) C 42.53, H 3.97, N 11.02; found C 42.50, H 4.05, N 11.18.

Ethyl 1-methyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (227b)



$BF_3(OEt_2)$ (1.24 mL, 10.0 mmol, 1 equiv.) was added to a solution of TFEDMA (1.20 mL, 10.0 mmol, 1 equiv.) in dry dichloromethane (10 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (10 mL). In another Teflon flask, ethyl 4-chloro-4,4-difluoroacetoacetate (2.00 g, 10.0 mmol, 1 equiv.) was added to a solution of pyridine (2.42 mL, 30.0 mmol, 3 equiv.) in dry acetonitrile (20 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Methyl hydrazine (0.79 mL, 15.0 mmol, 1.5 equiv.) was added dropwise at room temperature the reaction mixture was stirred for 24 h. The solution was filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 8:2) as eluent to afford pure ethyl 1-methyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (2.07 g, 7.18 mmol, 72%) as a colourless liquid.

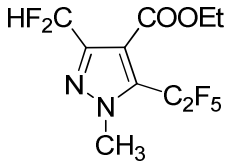
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.97 (t, 1H, $J_{H\text{-}F}$ = 53.9 Hz, CHF_2), 4.37 (q, 2H, J = 7.1 Hz, CH_2), 4.10 (t, 3H, $^5J_{H\text{-}F}$ = 2.2 Hz, N-CH_3), 1.38 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.3 (CO), 145.3 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_{IV}arom), 137.5 (t, $^2J_{C\text{-}F}$ = 33.3 Hz, C_{IV}arom), 119.9 (t, $J_{C\text{-}F}$ = 288.8 Hz, CF_2Cl), 112.7 (C_{IV}arom), 109.1 (t, $J_{C\text{-}F}$ = 237.8 Hz, CHF_2), 61.8 (CH_2), 40.6 (t, $^4J_{C\text{-}F}$ = 4.6 Hz, N-CH_3), 13.7 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -47.9 (CF_2Cl), -116.7 (d, $J_{F\text{-}H}$ = 53.9 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_9H_9ClF_4N_2NaO_2$ [M+Na]: calcd. 311.018; found 311.018.

Ethyl 1-methyl-3-difluoromethyl-5-pantafluoroethyl-1*H*-pyrazole-4-carboxylate (228b)



$BF_3(OEt_2)$ (1.24 mL, 10.0 mmol, 1 equiv.) was added to a solution of TFEDMA (1.20 mL, 10.0 mmol, 1 equiv.) in dry dichloromethane (10 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (10 mL). In another Teflon flask, ethyl 4,4,5,5,5-pentafluoroacetoacetate (1.75 mL, 10.0 mmol, 1 equiv.) was added to a solution of pyridine (2.42 mL, 30.0 mmol, 3 equiv.) in dry acetonitrile (20 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Methyl hydrazine (0.790 mL, 15.0 mmol, 1.5 equiv.) was added dropwise at room temperature the reaction mixture was stirred for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with HCl 1M (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 8:2) as eluent to afford pure ethyl 1-methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (2.42 g, 7.52 mmol, 75%) as a colourless liquid.

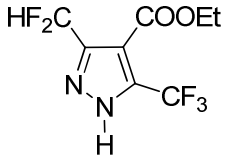
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.00 (t, 1H, $^2J_{H\text{-}F}$ = 53.9 Hz, CHF_2), 4.35 (q, 2H, J = 7.1 Hz, CH_2), 4.10 (t, 3H, $^5J_{H\text{-}F}$ = 2.2 Hz, N-CH_3), 1.35 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.2 (CO), 146.1 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_{IV}arom), 131.1 (t, $^2J_{C\text{-}F}$ = 29.6 Hz, C_{IV}arom), 118.6 (qt, $^1J_{C\text{-}F}$ = 287.1 Hz, $^2J_{C\text{-}F}$ = 37.7 Hz, $CF_2\underline{CF_3}$), 116.3 (C_{IV}arom), 109.98 (tq, $^1J_{C\text{-}F}$ = 192.0 Hz, $^2J_{C\text{-}F}$ = 41.7 Hz, $\underline{CF_2}CF_3$), 109.1 (t, $J_{C\text{-}F}$ = 238.1 Hz, CHF_2), 61.9 (CH_2), 41.0 (t, $^4J_{C\text{-}F}$ = 4.3 Hz, N-CH_3), 13.8 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -83.7 ($CF_2\underline{CF_3}$), -109.5 ($\underline{CF_2}CF_3$), -116.8 (d, $J_{F\text{-}H}$ = 53.9 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{10}H_9F_7N_2NaO_2$ [M+Na]: calcd. 345.044; found 345.046.

Ethyl 3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (223a)



Method A:

$BF_3(OEt_2)$ (0.31 mL, 2.5 mmol, 1 equiv.) was added to a solution of TFEDMA (0.30 mL, 2.5 mmol, 1 equiv.) in dry dichloromethane (2.5 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (2.5 mL). In another Teflon flask, ethyl 4,4,4-trifluoroacetoacetate (0.37 mL, 2.5 mmol, 1 equiv.) was added to a solution of potassium fluoride (0.44 g, 7.5 mmol, 3 equiv.) in dry acetonitrile (5 mL) and stirred at room temperature for 15 min. The content of the first flask was added dropwise, and the reaction mixture was stirred at room temperature overnight. Hydrazine hydrate (0.15 mL, 3.0 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solution was filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 7:3) as eluent to afford pure ethyl 3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (0.20 g, 0.77 mmol, 31%) as a yellow oil which crystallised on standing.

Method B:

$BF_3(OEt_2)$ (2.7 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.6 mL, 22 mol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4,4-trifluoroacetoacetate (2.9 mL, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.8 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. The content of the first flask was added dropwise, and the reaction mixture was stirred at room temperature overnight. Hydrazine hydrate (1.5 mL, 30.0 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with HCl 1M (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 7:3) as eluent to afford the pure title compound **223a** (3.4 g, 13 mmol, 66%) as a yellow oil which crystallised on standing, m.p. 63-64 °C.

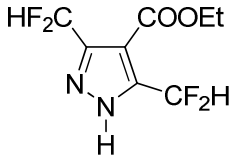
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.07 (brs, 1H, NH), 7.22 (t, 1H, $J_{H\text{-}F}$ = 53.5 Hz, CHF_2), 4.39 (q, 2H, J = 6.9 Hz, CH_2), 1.38 (t, 3H, J = 6.9 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.4 (CO), 142.2 (t, $^2J_{C\text{-}F}$ = 18.3 Hz, C_{IV}arom), 142.2 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, C_{IV}arom), 119.7 (q, $J_{C\text{-}F}$ = 268.1 Hz, CF_3), 111.7 (C_{IV}arom), 107.4 (t, $J_{C\text{-}F}$ = 237.5 Hz, CHF_2), 62.0 (CH_2), 13.7 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -62.5 (CF_3), -117.1 (d, $J_{F\text{-}H}$ = 53.5 Hz, CHF_2) ppm.

$C_8H_7F_5N_2O_2$ (258): calcd. (%) C 37.22, H 2.73, N 10.85; found C 37.27, H 2.91, N 10.61.

Ethyl 3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (226a)



Method A:
$BF_3(OEt_2)$ (1.85 mL, 15.0 mmol, 1 equiv.) was added to a solution of TFEDMA (1.76 mL, 15.0 mmol, 1 equiv.) in dry dichloromethane (15 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (15 mL). In another Teflon flask, ethyl 4,4-difluoroacetoacetate (1.55 mL, 15.0 mmol, 1 equiv.) was added to a solution of potassium fluoride (2.61 g, 45.0 mmol, 3 equiv.) in dry acetonitrile (30 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Hydrazine hydrate (1.10 mL, 22.5 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solution was filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 7:3) as eluent to afford pure ethyl 3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (0.370 g, 1.54 mmol, 10%) as a colourless solid.

Method B:
$BF_3(OEt_2)$ (2.7 mL, 20 mmol, 1 equiv.) was added to a solution of TFEDMA (2.6 mL, 20 mmol, 1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4-difluoroacetoacetate (3.3 g, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.7 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Hydrazine hydrate (1.5 mL, 30.0 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 7:3) as eluent to afford the pure title compound **226a** (1.5 g, 5.8 mmol, 29%) as a colourless solid, m.p. 88-89 °C.

^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.15 (t, 2H, $J_{H\text{-}F}$ = 53.6 Hz, CHF_2), 4.39 (q, 2H, J = 7.1 Hz, CH_2), 1.39 (t, 3H, J = 7.1 Hz, CH_3) ppm.

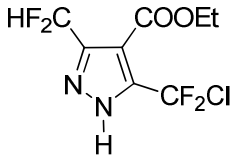
^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.1 (CO), 143.8 (t, $^2J_{C\text{-}F}$ = 23.1 Hz, C_{IV}arom), 111.6 (C_{IV}arom), 108.2 (t, $J_{C\text{-}F}$ = 238.4 Hz, CHF_2), 61.7 (CH_2), 13.9 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -117.3 (d, J_{F-H} = 53.6 Hz, CHF_2) ppm.

MS (ESI positive): m/z = 263.04 [M+Na].

HRMS (ESI positive) for $C_8H_8F_4N_2NaO_2$ [M+Na]: calcd. 263.041; found 263.043.

Ethyl 3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (227a)



$BF_3(OEt_2)$ (0.62 mL, 5.0 mmol, 1 equiv.) was added to a solution of TFEDMA (0.59 mL, 5.0 mmol, 1 equiv.) in dry dichloromethane (5 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (5 mL). In another Teflon flask, ethyl 4-chloro-4,4-difluoroacetoacetate (1.0 g, 5.0 mmol, 1 equiv.) was added to a solution of pyridine (1.2 g, 15 mmol, 3 equiv.) in dry acetonitrile (10 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Hydrazine hydrate (0.37 mL, 7.5 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (20 mL). The organic phase was washed with 1M HCl (3 x 10 mL), brine (10 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1 to 7:3) as eluent to afford pure ethyl 3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (0.66 g, 2.4 mmol, 48%) as a slightly yellow oil which crystallised on standing, m.p. 78-79 °C.

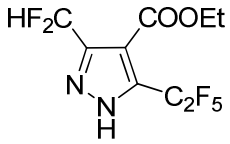
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.62 (brs, 1H, NH), 7.25 (t, 2H, J_{H-F} = 53.5 Hz, CHF_2), 4.41 (q, 2H, J = 7.1 Hz, CH_2), 1.41 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.6 (CO), 146.3 (t, $^2J_{C-F}$ = 32.3 Hz, C_{IV}arom), 142.7 (t, $^2J_{C-F}$ = 29.3 Hz, CHF_2), 121.3 (t, J_{C-F} = 287.3 Hz, CF_2Cl), 110.8 (C_{IV}arom), 109.1 (t, J_{C-F} = 240.2 Hz, CHF_2), 62.0 (CH_2), 13.6 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -49.6 (CF_2Cl), -116.8 (d, J_{F-H} = 53.5 Hz, CHF_2) ppm.

$C_8H_7ClF_4N_2O_2$ (274.6): calcd. (%) C 35.00, H 2.57, N 10.20; found C 35.22, H 2.67, N 9.95.

Ethyl 3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (228a)



$BF_3(OEt_2)$ (1.24 mL, 10.0 mmol, 1 equiv.) was added to a solution of TFEDMA (1.20 mL, 10.0 mmol, 1 equiv.) in dry dichloromethane (10 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (10 mL). In another Teflon flask, ethyl 4,4,5,5,5-pentafluoroacetoacetate (1.75 mL, 10.0 mmol, 1 equiv.) was added to a solution of pyridine (2.42 mL, 30.0 mmol, 3 equiv.) in dry acetonitrile (20 mL) and stirred at room temperature for 15 min. At -30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -30 °C for 2 h and allowed to reach room temperature overnight. Hydrazine hydrate (0.740 mL, 15.0 mmol, 1.5 equiv.) was added dropwise at room temperature the reaction mixture was stirred for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (30 mL). The organic phase was washed with 1M HCl (3 x 20 mL), brine (20 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (10:0 to 7:3) as eluent to afford pure ethyl 3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (1.43 g, 4.60 mmol, 46%) as a colourless oil.

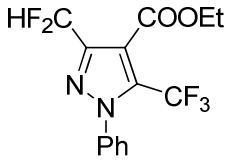
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.69 (brs, 1H, N-H), 7.26 (t, 1H, $J_{H\text{-}F}$ = 53.5 Hz, CHF_2), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 1.39 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.6 (CO), 141.8 (t, $^2J_{C\text{-}F}$ = 25.9 Hz, C_{IV}arom), 141.1 (t, $^2J_{C\text{-}F}$ = 31.7 Hz, C_{IV}arom), 118.7 (qt, $^1J_{C\text{-}F}$ = 286.6 Hz, $^2J_{C\text{-}F}$ = 36.3 Hz, $CF_2\underline{CF_3}$), 113.2 (C_{IV}arom), 110.1 (tq, $^1J_{C\text{-}F}$ = 252.9 Hz, $^2J_{C\text{-}F}$ = 39.5 Hz, $\underline{CF_2}CF_3$), 107.5 (t, $J_{C\text{-}F}$ = 238.8 Hz, CHF_2), 62.0 (CH_2), 13.6 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -83.2 ($CF_2\underline{CF_3}$), -110.1 ($\underline{CF_2}CF_3$), -117.2 (d, $J_{F\text{-}H}$ = 53.5 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_9H_7F_7N_2NaO_2$ [M+Na]: calcd. 331.029; found 331.031.

Ethyl 1-phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (223c)



$BF_3(OEt_2)$ (2.5 mL, 20 mmol, 1 equiv.) was added to a solution of TFEDMA (2.4 mL, 20 mmol, 1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl

4,4,4-trifluoroacetoacetate (2.8 mL, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.7 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. Phenyl hydrazine (3.0 mL, 30 mmol, 1.5 equiv.) was added dropwise at room temperature and the reaction mixture was stirred 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent followed by recrystallisation from hexane to afford pure ethyl 1-phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (4.5 g, 13 mmol, 67%) as a colourless solid, m.p. 58-59 °C.

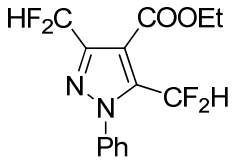
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55-7.42 (m, 5H, N-Ph), 7.05 (t, 1H, J_{H-F} = 53.7 Hz, CHF_2), 4.42 (q, 2H, J = 7.1 Hz, CH_2), 1.40 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.3 (CO), 146.7 (t, $^{2}J_{C-F}$ = 26.2 Hz, C_{IV}arom), 138.8 (N-C_{IV} Phenyl), 133.8 (q, $^{2}J_{C-F}$ = 40.1 Hz, C_{IV}arom), 130.4 (CH Phenyl), 129.3 (CH Phenyl), 125.9 (CH Phenyl), 118.6 (q, J_{C-F} = 271.9 Hz, CF_3), 115.0 (C_{IV}arom), 109.2 (t, J_{C-F} = 238.4 Hz, CHF_2), 62.0 (CH_2), 13.8 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -56.8 (CF_3), -117.3 (CHF_2) ppm.

$C_{14}H_{11}F_5N_2O_2$ (334): calcd. (%) C 50.31, H 3.32, N 8.38; found C 50.34, H 3.40, N 8.51.

Ethyl 1-phenyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (226c)



$BF_3.OEt_2$ (2.6 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.7 mL, 22 mmol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4-difluoroacetoacetate (3.3 g, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.7 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. Phenyl hydrazine (3.0 mL, 30 mmol) was added dropwise at room temperature and the reaction mixture was stirred 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent followed by recrystallisation from hexane to afford pure ethyl 1-phenyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (3.0 g, 9.4 mmol, 47%) as a colourless solid, m.p. 54-55 °C.

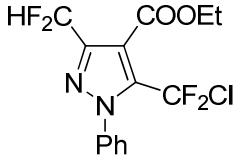
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.57-7.51 (m, 5H, N-Ph), 7.44 (t, 1H, J_{H-F} = 52.5 Hz, CHF_2), 7.13 (t, 1H, J_{H-F} = 53.7 Hz, CHF_2), 4.43 (q, 2H, J = 7.1 Hz, CH_2), 1.43 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.2 (CO), 146.6 (t, $^{2}J_{C-F}$ = 25.3 Hz, C_{IV}arom), 139.0 (N-C_{IV} Phenyl), 138.9 (t, $^{2}J_{C-F}$ = 24.8 Hz, C_{IV}arom), 130.1 (CH Phenyl), 129.1 (CH Phenyl), 125.9 (CH Phenyl), 113.8 (C_{IV}arom), 109.4 (t, J_{C-F} = 238.2 Hz, CF_2H), 106.9 (t, J_{C-F} = 238.4 Hz, CHF_2), 61.8 (CH_2), 14.0 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -114.3 (d, J_{F-H} = 52.5 Hz, CHF_2), -117.7 (d, J_{F-H} = 53.7 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{14}H_{12}F_4N_2NaO_2$ [M+Na]: calcd. 339.073; found 339.075.

Ethyl 1-phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (227c)



$BF_3(OEt_2)$ (2.6 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.7 mL, 22 mmol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4-chloro-4,4-difluoroacetoacetate (4.0 g, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.7 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. Phenyl hydrazine (3.0 mL, 30 mmol) was added dropwise at room temperature and the reaction mixture was stirred 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent followed by recrystallisation from hexane to afford pure ethyl 1-phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate (3.7 g, 11 mmol, 53%) as a colourless solid, m.p. 70-71 °C.

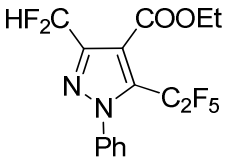
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55-7.45 (m, 5H, N-Ph), 7.03 (t, 1H, J_{H-F} = 53.7 Hz, CHF_2), 4.42 (q, 2H, J = 7.1 Hz, CH_2), 1.41 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.5 (CO), 146.5 (t, $^{2}J_{C-F}$ = 26.3 Hz, C_{IV}arom), 138.9 (N-C_{IV} Phenyl), 138.3 (t, $^{2}J_{C-F}$ = 32.7 Hz, C_{IV}arom), 130.3 (CH Phenyl), 129.2 (CH Phenyl), 126.2 (CH Phenyl), 119.5 (t, J_{C-F} = 290.0 Hz, CF_2Cl), 115.6 (C_{IV}arom), 109.3 (t, J_{C-F} = 238.4 Hz, CHF_2), 62.0 (CH_2), 13.9 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -46.6 (CF_2Cl), -117.3 (CHF_2) ppm.

$C_{14}H_{11}ClF_4N_2O_2$ (350.7): calcd. (%) C 47.95, H 3.16, N 7.99; found (%) C 47.86, H 3.20, N 7.73.

Ethyl 1-phenyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (228c)



$BF_3(OEt_2)$ (2.5 mL, 20 mmol, 1.8 equiv.) was added to a solution of TFEDMA (2.4 mL, 20 mmol, 1.8 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4,5,5,5-pentafluoroacetoacetate (3.5 mL, 12 mmol, 1 equiv.) was added to a solution of pyridine (2.7 g, 35 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. Phenyl hydrazine (2.0 mL, 20 mmol, 1.8 equiv.) was added dropwise at room temperature and the reaction mixture was stirred 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent followed by recrystallisation from hexane to afford pure ethyl 1-phenyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (3.7 g, 9.7 mmol, 85%) as a beige solid, m.p. 93-94 °C.

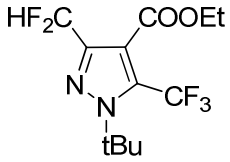
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.58-7.35 (m, 5H, N-Ph), 7.04 (t, 1H, $J_{H\text{-}F}$ = 53.8 Hz, CHF_2), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 1.38 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 147.6 (t, $^2J_{C\text{-}F}$ = 25.8 Hz, C_{IV}arom), 138.7 (N-C_{IV} Phenyl), 135.1 (q, $^2J_{C\text{-}F}$ = 40.4 Hz, C_{IV}arom), 130.6 (CH Phenyl), 129.4 (CH Phenyl), 125.9 (CH Phenyl), 118.4 (qt, $^1J_{C\text{-}F}$ = 287.5 Hz, $^2J_{C\text{-}F}$ = 37.5 Hz, $CF_2\underline{CF_3}$), 116.4 (C_{IV}arom), 109.6 (tq, $^1J_{C\text{-}F}$ = 255.3 Hz, $^2J_{C\text{-}F}$ = 41.6 Hz, $\underline{CF_2}CF_3$), 109.4 (t, $J_{C\text{-}F}$ = 238.6 Hz, CHF_2), 62.1 (CH_2), 13.7 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -83.6 ($CF_2\underline{CF_3}$), -107.1 ($\underline{CF_2}CF_3$), -117.3 (CHF_2) ppm.

$C_{15}H_{11}F_7N_2O_2$ (384): calcd. (%) C 46.88, H 2.88, N 7.29; found (%) C 46.84, H 3.00, N 7.11.

Ethyl 1-*tert*-butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (223d)



$BF_3(OEt_2)$ (2.7 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.5 mL, 22 mmol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4,4-trifluoroacetoacetate (2.8 mL, 20 mmol, 1 equiv.) was added to a solution of pyridine (7.1 g, 90 mmol, 4.5 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. *tert*-Butyl hydrazine hydrochloride (3.7 g, 30 mmol, 1.5 equiv.) was added to a solution of potassium hydroxide (1.7 g, 30 mmol, 1.5 equiv.) in methanol (10 mL) and stirred at room temperature for 30 min. This mixture was then added to the reaction medium at room temperature and the resulting reaction mixture was stirred 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent to afford pure ethyl 1-*tert*-butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (3.3 g, 11 mmol, 53%) as a yellow oil.

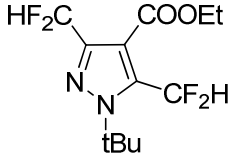
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.80 (t, 1H, $J_{H\text{-}F}$ = 54.0 Hz, CHF_2), 4.37 (q, 2H, J = 7.1 Hz, CH_2), 1.70 (s, 9H, *t*Bu), 1.36 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.5 (CO), 141.9 (t, $^2J_{C\text{-}F}$ = 27.8 Hz, C_{IV}arom), 131.5 (q, $^2J_{C\text{-}F}$ = 40.6 Hz, C_{IV}arom), 119.3 (q, $J_{C\text{-}F}$ = 270.7 Hz, CF_3), 116.9 (C_{IV}arom), 109.9 (t, $J_{C\text{-}F}$ = 236.7 Hz, CHF_2), 66.0 (N-C_{IV} *t*Bu), 62.0 (CH_2), 29.9 (q *t*Bu, $^5J_{C\text{-}F}$ = 2.4 Hz, CH_3), 13.8 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -53.3 (CF_3), -114.4 (d, $J_{F\text{-}H}$ = 54.0 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{12}H_{15}F_5N_2NaO_2$ [M+Na]: calcd. 337.095; found 337.097.

Ethyl 1-*tert*-butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (226d)



$BF_3(OEt_2)$ (2.7 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.5 mL, 22 mol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl

4,4-difluoroacetoacetate (3.3 g, 20 mmol, 1 equiv.) was added to a solution of pyridine (7.1 g, 90 mmol, 4.5 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2 h and allowed to reach room temperature overnight. *tert*-Butyl hydrazine hydrochloride (3.7 g, 30 mmol, 1.5 equiv.) was added to a solution of potassium hydroxide (1.7 g, 30 mmol, 1.5 equiv.) in methanol (10 mL) and stirred at room temperature for 30 minutes. This mixture was then added to the reaction medium at room temperature and the resulting reaction mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent to afford pure ethyl 1-*tert*-butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate (1.8 g, 6.0 mmol, 30%) as an orange oil.

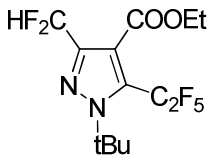
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.71 (t, 1H, $J_{H\text{-}F}$ = 52.9 Hz, CHF_2), 6.97 (t, 1H, $J_{H\text{-}F}$ = 54.0 Hz, CHF_2), 4.37 (q, 2H, J = 7.1 Hz, CH_2), 1.71 (s, 9H, *t*Bu), 1.39 (t, 3H, J = 7.1 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.9 (CO), 143.4 (t, $^{2}J_{C\text{-}F}$ = 25.5 Hz, C_{IV}arom), 137.9 (t, $^{2}J_{C\text{-}F}$ = 24.8 Hz, C_{IV}arom), 114.5 (C_{IV}arom), 109.9 (t, $J_{C\text{-}F}$ = 237.3 Hz, CHF_2), 106.8 (t, $J_{C\text{-}F}$ = 238.3 Hz, CHF_2), 65.3 (N-C_{IV} *t*Bu), 61.5 (CH_2), 30.0 (t, $^{5}J_{C\text{-}F}$ = 3.4 Hz, *t*Bu CH_3), 14.0 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -111.5 (CHF_2), -116.0 (CHF_2) ppm.

HRMS (ESI positive) for $C_{12}H_{16}F_4N_2NaO_2$ [M+Na]: calcd. 319.104; found 319.104.

Ethyl 1-*tert*-butyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (228d)



$BF_3(OEt_2)$ (2.7 mL, 22 mmol, 1.1 equiv.) was added to a solution of TFEDMA (2.5 mL, 22 mmol, 1.1 equiv.) in dry dichloromethane (20 mL) under Argon in a Teflon flask. The solution was stirred for 15 min at room temperature, and dichloromethane was removed under reduced pressure. The mixture was taken up in dry acetonitrile (20 mL). In another Teflon flask, ethyl 4,4,5,5,5-pentafluoroacetoacetate (4.7 g, 20 mmol, 1 equiv.) was added to a solution of pyridine (4.7 g, 60 mmol, 3 equiv.) in dry acetonitrile (40 mL) and stirred at room temperature for 15 min. At -40 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at -40 °C for 2h and allowed to reach room temperature overnight. *tert*-Butyl hydrazine hydrochloride (3.7 g, 30 mmol, 1.5 equiv.) was added to the reaction mixture and was stirred at room temperature overnight. The solution was evaporated under reduced pressure and taken up in diethyl ether (50 mL). The organic phase was washed with 1M HCl (3 x 30 mL), brine (30 mL), dried over sodium sulphate and evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (9:1)

as eluent to afford pure ethyl 1-*tert*-butyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate (2.4 g, 6.6 mmol, 33%) as a colourless oil.

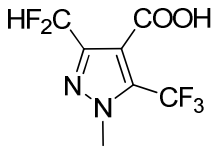
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.83 (t, 1H, J_{H-F} = 54.1 Hz, CHF_2), 4.35 (q, 2H, J = 7.1 Hz, CH_2), 1.69 (s, 9H, *t*Bu), 1.34 (t, 3H, J = 7.2 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.2 (CO), 142.8 (t, $^2J_{C-F}$ = 27.3 Hz, C_{IV}arom), 130.0 (q, $^2J_{C-F}$ = 31.0 Hz, C_{IV}arom), 118.6 (qt, $^1J_{C-F}$ = 287.8 Hz, $^2J_{C-F}$ = 38.3 Hz, $CF_2\underline{CF_3}$), 118.5 (C_{IV}arom), 110.8 (tq, $^1J_{C-F}$ = 258.1 Hz, $^2J_{C-F}$ = 41.0 Hz, $\underline{CF_2}CF_3$), 110.0 (t, J_{C-F} = 237.2 Hz, CHF_2), 67.6 (N-C_{IV} *t*Bu), 62.0 (CH_2), 30.5 (t, $^5J_{C-F}$ = 3.6 Hz, CH_3 *t*Bu), 13.7 (CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -80.7 ($CF_2\underline{CF_3}$), -100.8 ($\underline{CF_2}CF_3$), -115.5 (d, J_{F-H} = 54.1 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{13}H_{15}F_7N_2NaO_2$ [M+Na]: calcd. 387.091; found 387.091.

1-Methyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (230b)



To a solution of ethyl 1-methyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate **223b** (0.50 g, 1.8 mmol, 1 equiv.) in ethanol (3 mL) was slowly added a 8M aqueous solution of sodium hydroxide (0.70 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (10 mL). The aqueous layer was extracted with diethyl ether (10 mL), and acidified to pH = 1 with 1M HCl before being extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-methyl-5-trifluoromethyl-3-difluoromethyl-1*H*-pyrazole-4-carboxylic acid (0.44 g, 1.8 mmol, 98%) as a yellow solid, m.p. 116-117 °C.

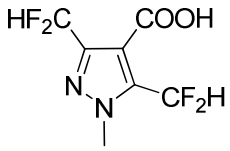
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.08 (t, 1H, J_{H-F} = 53.5 Hz, CHF_2), 4.16 (s, 3H, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.5 (CO), 146.7 (t, $^2J_{C-F}$ = 18.8 Hz, C_{IV}arom), 134.4 (q, $^2J_{C-F}$ = 30.8 Hz, C_{IV}arom), 118.8 (q, J_{C-F} = 202.5 Hz, CF_3), 112.9 (C_{IV}arom), 108.7 (t, J_{C-F} = 177.0 Hz, CHF_2), 41.1 (q, $^4J_{C-F}$ = 2.3 Hz, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -57.9 (CF_3), -117.3 (d, J_{F-H} = 53.5 Hz, CHF_2) ppm.

$C_7H_5F_5N_2O_2$ (244): calcd. (%) C 34.44, H 2.06, N 11.48; found (%) C 34.44, H 2.19, N 11.13.

1-Methyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (229b)



To a solution of ethyl 1-methyl-3,5-difluoromethyl-1*H*-pyrazole-4-carboxylate **226b** (0.50 g, 2.0 mmol, 1 equiv.) in ethanol (3 mL) was slowly added a 8M aqueous solution of sodium hydroxide (0.75 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 2 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (10 mL). The aqueous layer was extracted with diethyl ether (10 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-methyl-3,5-difluoromethyl-1*H*-pyrazole-4-carboxylic acid (0.44 g, 2.0 mmol, 97%) as a colourless solid, m.p. 131-132 °C.

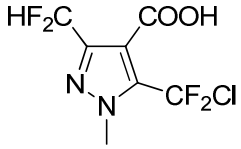
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.16 (brs, 1H, COOH), 7.48 (t, 1H, J_{H-F} = 52.4 Hz, CHF_2), 7.08 (t, 1H, J_{H-F} = 53.6 Hz, CHF_2), 4.16 (s, 3H, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.9 (CO), 146.4 (t, $^{2}J_{C-F}$ = 25.1 Hz, C_{IV}arom), 139.2 (t, $^{2}J_{C-F}$ = 24.4 Hz, C_{IV}arom), 111.5 (C_{IV}arom), 108.8 (t, J_{C-F} = 238.1 Hz, CHF_2), 106.9 (t, J_{C-F} = 237.0 Hz, CHF_2), 39.9 (t, $^{4}J_{C-F}$ = 3.1 Hz, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -117.1 (d, J_{F-H} = 52.6 Hz, CHF_2), -117.3 (d, J_{F-H} = 53.7 Hz, CHF_2) ppm.

$C_7H_6F_4N_2O_2$ (226): calcd. (%) C 37.18, H 2.67, N 12.39; found C 37.19, H 2.84, N 12.00.

1-Methyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylic acid (231b)



To a solution of ethyl 1-methyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate **227b** (0.50 g, 1.7 mmol, 1 equiv.) in ethanol (3 mL) was slowly added a 8M aqueous solution of sodium hydroxide (0.65 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 2 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (10 mL). The aqueous layer was extracted with diethyl ether (10 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-methyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylic acid (0.36 g, 1.4 mmol, 80%) as a colourless solid, m.p. 111-112 °C.

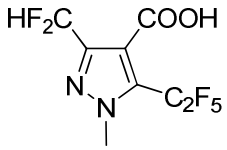
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.15 (brs, 1H, COOH), 7.07 (t, 1H, J_{H-F} = 53.6 Hz, CHF_2), 4.15 (t, 3H, $^{5}J_{H-F}$ = 2.1 Hz, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 146.4 (t, $^{2}J_{C-F}$ = 25.3 Hz, C_{IV}arom), 138.9 (t, $^{2}J_{C-F}$ = 33.6 Hz, C_{IV}arom), 119.6 (t, J_{C-F} = 289.4 Hz, CF_2Cl), 111.15 (C_{IV}arom), 108.8 (t, J_{C-F} = 238.4 Hz, CHF_2), 41.0 (t, $^{4}J_{C-F}$ = 4.9 Hz, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -48.1 (CF_2Cl), -117.2 (d, J_{F-H} = 53.6 Hz, CHF_2) ppm.

$C_7H_5ClF_4N_2O_2$ (260.6): calcd. (%) C 32.27, H 1.93, N 10.75; found C 32.53, H 2.13, N 10.38.

1-Methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylic acid (232b)



To a solution of ethyl 1-methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate **228b** (0.50 g, 1.6 mmol, 1 equiv.) in solution in ethanol (3 mL) was slowly added a 8M aqueous solution of sodium hydroxide (0.60 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (10 mL). The aqueous layer was extracted with diethyl ether (5 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylic acid (0.44 g, 1.5 mmol, 97%) as a colourless solid, m.p. 138-139 °C.

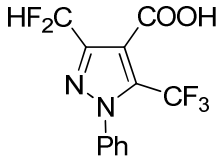
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.16 (brs, 1H, COOH), 7.09 (t, 1H, J_{H-F} = 53.6 Hz, CHF_2), 4.15 (t, 3H, $^{5}J_{H-F}$ = 2.4 Hz, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.2 (CO), 147.2 (t, $^{2}J_{C-F}$ = 25.2 Hz, C_{IV}arom), 132.5 (t, $^{2}J_{C-F}$ = *29.8* Hz, C_{IV}arom), 118.5 (qt, $^{1}J_{C-F}$ = 287.0 Hz, $^{2}J_{C-F}$ = 37.5 Hz, $CF_2\underline{CF_3}$), 114.6 (C_{IV}arom), 109.9 (tq, $^{1}J_{C-F}$ = 258.0 Hz, $^{2}J_{C-F}$ = 41.7 Hz, $\underline{CF_2}CF_3$), 108.8 (t, J_{C-F} = 238.6 Hz, CHF_2), 41.4 (t, $^{4}J_{C-F}$ = 4.8 Hz, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -83.2 ($CF_2\underline{CF_3}$), -108.9 ($\underline{CF_2}CF_3$), -116.8 (d, J_{F-H} = 53.6 Hz, CHF_2) ppm.

$C_8H_5F_7N_2O_2$ (294): calcd. (%) C 32.67, H 1.71, N 9.52; found C 32.82, H 1.86, N 9.30.

1-Phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (230c)



To a solution of ethyl 1-phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate **223c** (3.0 g, 9.0 mmol, 1 equiv.) in solution in ethanol (15 mL) was slowly added a 8M aqueous solution of sodium hydroxide (3.4 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (2.6 g, 8.4 mmol, 94%) as a colourless solid, m.p. 154-155 °C.

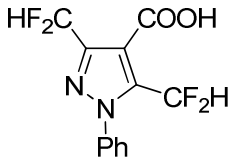
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.53 (brs, 1H, COOH), 7.58-7.44 (m, 5H, N-Phenyl), 7.15 (t, 1H, $J_{H\text{-}F}$ = 53.5 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 147.6 (t, $^{2}J_{C\text{-}F}$ = 25.8 Hz, C_{IV}arom), 138.7 (N-C_{IV} Phenyl), 135.1 (q, $^{2}J_{C\text{-}F}$ = 40.4 Hz, C_{IV}arom), 130.6 (CH Phenyl), 129.4 (CH Phenyl), 125.9 (CH Phenyl), 118.4 (q, $J_{C\text{-}F}$ = 272.3 Hz, CF_3), 114.3 (C_{IV}arom), 108.9 (t, $J_{C\text{-}F}$ = 239.0 Hz, CHF_2) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -56.8 (CF_3), -117.8 (CHF_2) ppm.

$C_{12}H_7F_5N_2O_2$ (306): calcd. (%) C 47.07, H 2.30, N 9.15; found C 47.24, H 2.40, N 8.89.

1-Phenyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (229c)



To a solution of ethyl 1-phenyl-3,5-(bis)difluoromethyl-1*H*-pyrazole-4-carboxylate **226c** (2.6 g, 8.2 mmol, 1 equiv.) in ethanol (15 mL) was slowly added a 8M aqueous solution of sodium hydroxide (3.1 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude product obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-phenyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (2.3 g, 8.1 mmol, 99%) as a colourless solid, m.p. 169-170 °C.

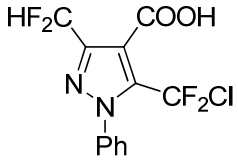
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.59-7.49 (m, 5H, N-Phenyl), 7.43 (t, 1H, J_{H-F} = 52.3 Hz, CHF_2), 7.16 (t, 1H, J_{H-F} = 53.5 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.3 (CO), 147.4 (t, $^{2}J_{C-F}$ = 25.5 Hz, C_{IV}arom), 139.8 (t, $^{2}J_{C-F}$ = 24.9 Hz, C_{IV}arom), 138.8 (N-C_{IV} Phenyl), 130.3 (CH Phenyl), 129.2 (CH Phenyl), 125.9 (CH Phenyl), 112.3 (t, $^{3}J_{C-F}$ = 3.5 Hz, C_{IV}arom), 109.0 (t, J_{C-F} = 238.7 Hz, CHF_2), 106.6 (t, J_{C-F} = 239.2 Hz, CHF_2) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -113.4 (CHF_2), -117.0 (CHF_2) ppm.

$C_{12}H_8F_4N_2O_2$ (288): calcd. (%) C 50.01, H 2.80, N 9.72; found C 50.28, H 3.04, N 9.59.

1-Phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylic acid (231c)



To a solution of ethyl 1-phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1*H*-pyrazole-4-carboxylate **227c** (3.0 g, 8.6 mmol, 1 equiv.) in solution in ethanol (15 mL) was slowly added a 8M aqueous solution of sodium hydroxide (3.2 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure *N*-phenyl-3-difluoromethyl-5-chlorodifluoromethyl-4-carboxylic acid pyrazole (2.7 g, 8.5 mmol, 99%) as a colourless solid, m.p. 155-156 °C.

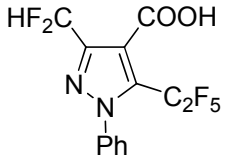
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.57-7.47 (m, 5H, N-Phenyl), 7.12 (t, 1H, J_{H-F} = 53.5 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.9 (CO), 147.4 (t, $^{2}J_{C-F}$ = 25.8 Hz, C_{IV}arom), 139.8 (t, $^{2}J_{C-F}$ = 33.0 Hz, C_{IV}arom), 138.9 (N-C_{IV} Phenyl), 130.5 (CH Phenyl), 129.3 (CH Phenyl), 126.2 (CH Phenyl), 119.2 (t, J_{C-F} = 290.6 Hz, CF_2Cl), 112.1 (C_{IV}arom), 108.9 (t, J_{C-F} = 239.0 Hz, CHF_2) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -46.9 (CF_2Cl), -117.8 (CHF_2) ppm.

$C_{12}H_7ClF_4N_2O_2$ (322.6): calcd. (%) C 44.67, H 2.19, N 8.68; found C 44.83, H 2.34, N 8.32.

1-Phenyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylic acid (232c)



To a solution of ethyl 1-phenyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxyate **228c** (3.0 g, 7.8 mmol, 1 equiv.) in solution in ethanol (15 mL) was slowly added a 8M aqueous solution of sodium hydroxide (3.0 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure *N*-phenyl-3-difluoromethyl-5-pentafluoroethyl-4-carboxylic acid pyrazole (2.7 g, 7.6 mmol, 98%) as a colourless solid, m.p. 187-188 °C.

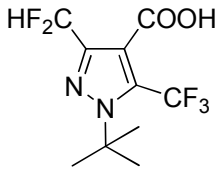
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.60-7.37 (m, 5H, N-Phenyl), 7.14 (t, 1H, $J_{H\text{-}F}$ = 53.6 Hz, CHF_2) ppm.

^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 164.0 (CO), 148.6 (t, $^{2}J_{C\text{-}F}$ = 25.6 Hz, C_{IV}arom), 141.4 (N-C_{IV} Phenyl), 133.4 (CH Phenyl), 133.1 (t, $^{2}J_{C\text{-}F}$ = 29.1 Hz, C_{IV}arom), 131.7 (CH Phenyl), 130.0 (CH Phenyl), 120.6 (qt, $^{1}J_{C\text{-}F}$ = 287.6 Hz, $^{2}J_{C\text{-}F}$ = 37.9 Hz, $CF_2\underline{CF_3}$), 120.1 (C_{IV}arom), 112.3 (t, $J_{C\text{-}F}$ = 236.4Hz, CHF_2), 112.1 (tq, $^{1}J_{C\text{-}F}$ = 262.5 Hz, $^{2}J_{C\text{-}F}$ = 40.5 Hz, $\underline{CF_2}CF_3$) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -83.5 ($CF_2\underline{CF_3}$), -107.1 ($\underline{CF_2}CF_3$), -117.9 (CHF_2) ppm.

$C_{13}H_7F_7N_2O_2$ (356): calcd. (%) C 43.84, H 1.98, N 7.86; found C 44.02, H 2.10, N 7.62.

1-*tert*-Butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (230d)



To a solution of ethyl 1-*tert*-butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate **223d** (2.5 g, 7.9 mmol, 1 equiv.) in solution in ethanol (15 mL) was slowly added a 8M aqueous solution of sodium hydroxide (3.0 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-*tert*-butyl-3-difluoromethyl-5-

trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (2.2 g, 7.5 mmol, 94%) as a yellow solid, m.p. 126-127 °C.

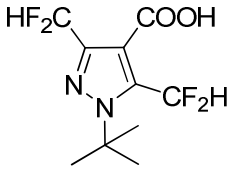
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.92 (t, 1H, J_{H-F} = 53.8 Hz, CHF_2), 1.74 (s, 9H, *t*Bu) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.8 (CO), 142.9 (t, $^{2}J_{C-F}$ = 26.9 Hz, C_{IV}arom), 132.9 (q, $^{2}J_{C-F}$ = 41.1 Hz, C_{IV}arom), 119.1 (q, J_{C-F} = 271.1 Hz, CF_3), 115.1 (C_{IV}arom), 109.5 (t, J_{C-F} = 237.5 Hz, CHF_2), 66.7 (N-C_{IV} *t*Bu), 29.9 (q, $^{5}J_{C-F}$ = 2.5 Hz, CH_3 *t*Bu) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -54.0 (CF_3), -116.0 (CHF_2) ppm.

HRMS (ESI negative) for $C_{10}H_{10}F_5N_2O_2$ [M-H]: calcd. 285.066; found 285.0.67.

1-*tert*-Butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (229d)



To a solution of ethyl 1-*tert*-butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylate **226d** (3.40 g, 11.5 mmol, 1 equiv.) in solution in ethanol (23 mL) was slowly added a 8M aqueous solution of sodium hydroxide (4.30 mL, 3 equiv.). The reaction mixture was stirred at room temperature overnight until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-*tert*-butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (3.00 g, 11.2 mmol, 97%) as a pink solid, m.p. 159-160 °C.

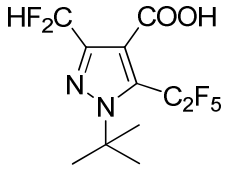
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.72 (t, 1H, J_{H-F} = 52.7 Hz, CHF_2), 7.06 (t, 1H, J_{H-F} = 53.7 Hz, CHF_2), 1.75 (s, 9H, *t*Bu) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.3 (CO), 144.5 (t, $^{2}J_{C-F}$ = 25.3 Hz, C_{IV}arom), 138.8 (q, $^{2}J_{C-F}$ = 25.1 Hz, C_{IV}arom), 113.0 (C_{IV}arom), 109.4 (t, J_{C-F} = 237.7 Hz, CF_2H), 106.5 (t, J_{C-F} = 238.8 Hz, CHF_2), 65.9 (N-C_{IV} *t*Bu), 30.0 (t, $^{5}J_{C-F}$ = 3.5 Hz, CH_3 *t*Bu) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -112.5 (CHF_2), -117.4 (CHF_2) ppm.

HRMS (ESI negative) for $C_{10}H_{11}F_4N_2O_2$ [M-H]: calcd. 267.076; found 267.076.

1-*tert*-Butyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylic acid (232d)



To a solution of ethyl 1-*tert*-butyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylate **228d** (2.0 g, 5.5 mmol, 1 equiv.) in solution in ethanol (10 mL) was slowly added a 8M aqueous solution of sodium hydroxide (2.0 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h until completion of the reaction. The solvents were evaporated and the crude solid obtained was taken up in water (40 mL). The aqueous layer was extracted with diethyl ether (20 mL), and acidified to pH = 1 with 6M HCl before being extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-*tert*-butyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole-4-carboxylic acid (1.8 g, 5.4 mmol, 99%) as a yellow solid, m.p. 97-98 °C.

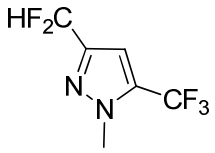
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.4 (brs, 1H, COOH), 7.01 (t, 1H, $J_{H\text{-}F}$ = 53.9 Hz, CHF_2), 1.78 (s, 9H, *t*Bu) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.5 (CO), 143.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz, C_{IV}arom), 131.5 (q, $^{2}J_{C\text{-}F}$ = 31.0 Hz, C_{IV}arom), 120.0 (qt, $^{1}J_{C\text{-}F}$ = 288.1 Hz, $^{2}J_{C\text{-}F}$ = 38.1 Hz, $CF_2\underline{CF_3}$), 117.4 (C_{IV}arom), 110.6 (tq, $^{1}J_{C\text{-}F}$ = 258.7 Hz, $^{2}J_{C\text{-}F}$ = 41.2 Hz, $\underline{CF_2}CF_3$), 109.5 (t, $J_{C\text{-}F}$ = 237.9 Hz, CHF_2), 68.3 (N-C_{IV} *t*Bu), 30.6 (t, $^{5}J_{C\text{-}F}$ = 3.7 Hz, CH_3 *t*Bu) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -80.3 ($CF_2\underline{CF_3}$), -100.4 ($\underline{CF_2}CF_3$), -116.3 (d, $J_{F\text{-}H}$ = 53.9 Hz, CHF_2) ppm.

HRMS (ESI negative) for $C_{11}H_{10}F_7N_2O_2$ [M-H]: calcd. 335.064; found 335.065.

1-Methyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (234b)



A Schlenk tube was charged the carboxylic acid **230b** (2.1 g, 8.6 mmol, 1 equiv.), Cu_2O (65 mg, 0.45 mmol, 5mol%), and 1,10-phenanthroline hydrate (176 mg, 0.90 mmol, 10mol%) NMP (15 mL), quinoline (5 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was distilled off over a Vigreux column at atmospheric pressure. The crude material obtained was purified by distillation under reduced pressure to

afford 1-methyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (0.85 g, 4.3 mmol, 50%) as a colourless liquid (b.p. = 45-46°C, 27 mbar).

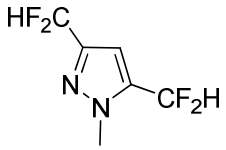
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.84 (s, 1H, Harom), 6.66 (t, 1H, J_{H-F} = 55 Hz, CHF_2), 4.02 (s, 3H, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 145.6 (t, $^{2}J_{C-F}$ = 30 Hz, C_{IV}arom), 133.3 (q, $^{2}J_{C-F}$ = 39.6 Hz, C_{IV}arom), 119.5 (q, J_{C-F} = 267.2 Hz, CF_3), 110.3 (t, J_{C-F} = 233.2 Hz, CHF_2), 105.2 (q, $^{3}J_{C-F}$ = 2.0 Hz, CHarom), 38.3 (q, $^{4}J_{C-F}$ = 1.6 Hz, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -61.5 (CF_3), -113.0 (CHF_2) ppm.

HRMS (ESI positive) for $C_6H_6F_5N_2$ [M+H]: calcd. 201.045 found 201.045.

1-Methyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (233b)



A Schlenk tube was charged with the carboxylic acid **229b** (2.0 g, 8.9 mmol, 1 equiv.), Cu_2O (65 mg, 0.45 mmol, 5mol%), and 1,10-phenanthroline hydrate (176 mg, 0.90 mmol, 10mol%). NMP (15 mL), quinoline (5 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was distilled off over a Vigreux column at atmospheric pressure. The crude product obtained was purified by distillation under reduced pressure to afford 1-methyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (1.3 g, 6.9 mmol, 78%) as a colourless liquid (b.p. = 78-80°C, 28 mbar).

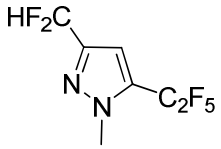
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.73 (t, 1H, CHF_2, J_{H-F} = 53.4 Hz), 6.69 (s, 1H, Harom), 6.66 (t, 1H, CHF_2, J_{H-F} = 54.9 Hz), 4.01 (s, 3H, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 145.6 (t, C_{IV}arom, $^{2}J_{C-F}$ = 30.0 Hz), 136.5 (t, C_{IV}arom, $^{2}J_{C-F}$ = 26.6 Hz), 110.6 (t, CHF_2, J_{C-F} = 234.1 Hz), 108.2 (t, CHF_2, J_{C-F} = 236.5 Hz), 104.7 (m, CHarom), 38.1 (s, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -112.5 (CHF_2, J_{F-H} = 54.9 Hz), -113.7 (d, J_{F-H} = 53.3 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_6H_7F_4N_2$ [M+H]: calcd. 183.054 found 183.055.

1-Methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole (235b)



A Schlenk tube was charged with the carboxylic acid **232b** (2.0 g, 6.8 mmol, 1 equiv.), Cu_2O (49 mg, 0.34 mmol, 5mol%), and 1,10-phenanthroline hydrate (135 mg, 0.68 mmol, 10mol%). NMP (12 mL), quinoline (4 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was distilled off over a Vigreux column at atmospheric pressure. The crude material was purified by distillation under reduced pressure to afford 1-methyl-3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole (1.07g, 4.28 mmol, 63%) as a colourless liquid (b.p. = 53-54°C, 28 mbar).

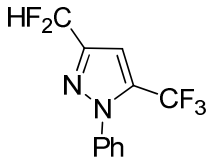
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.84 (s, 1H, Harom), 6.67 (t, 1H, $J_{H\text{-}F}$ = 54.8 Hz, CHF_2), 4.05 (s, 3H, N-CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.0 (t, $^2J_{C\text{-}F}$ = 30.1 Hz, C_{IV}arom), 131.2 (t, $^2J_{C\text{-}F}$ = 28.9 Hz, C_{IV}arom), 118.5 (qt, $^1J_{C\text{-}F}$ = 285.7 Hz, $^2J_{C\text{-}F}$ = 37.3 Hz , $CF_2\underline{CF_3}$), 110.2 (t, $J_{C\text{-}F}$ = 234.8 Hz, CHF_2), 109.8 (tq, $^1J_{C\text{-}F}$ = 252.7 Hz, $^2J_{C\text{-}F}$ = 40.6 Hz, $\underline{CF_2}CF_3$), 106.9 (brs, CHarom), 39.2 (brs, N-CH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -84.4 ($CF_2\underline{CF_3}$), -111.1 ($\underline{CF_2}CF_3$), -113.0 (d, $J_{F\text{-}H}$ = 54.8 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_7H_6F_7N_2$ [M+H]: calcd. 251.042; found 251.042.

1-Phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (234c)



A Schlenk tube was charged with the carboxylic acid **230c** (2.0 g, 6.5 mmol, 1 equiv.), Cu_2O (47 mg, 0.33 mmol, 5mol%), and 1,10-phenanthroline hydrate (131 mg, 0.66 mmol, 10mol%). NMP (12 mL), quinoline (4 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (95:5) as eluent to afford pure 1-phenyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (1.4 g, 5.5 mmol, 84%) as a colourless oil.

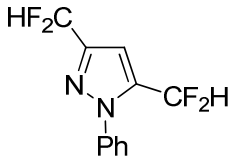
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55-7.48 (m, 5H, phenylH), 7.07 (brs, 1H, Hpyrazole), 6.78 (t, 1H, J_{H-F} = 54.6 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.9 (t, $^{2}J_{C-F}$ = 30.5 Hz, C_{IV}pyrazole), 138.4 (s, N-C_{IV}phenyl), 134.2 (q, $^{2}J_{C-F}$ = 40.0 Hz, C_{IV}pyrazole), 130.0 (s, CHphenyl), 129.3 (s, CHphenyl), 125.7 (s, CHphenyl), 119.2 (q, J_{C-F} = 269.4 Hz, CF_3), 110.4 (t, J_{C-F} = 235.1 Hz, CHF_2), 106.4 (brs, CHpyrazole) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -58.4 (CF_3), -112.9 (d, J_{F-H} = 54.6 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{11}H_8F_5N_2$ [M+H]: calcd. 263.061; found 263.060.

1-Phenyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (233c)



A Schlenk tube was charged with the carboxylic acid **229c** (2.0 g, 6.9 mmol, 1 equiv.), Cu_2O (50 mg, 0.35 mmol, 5mol%), and 1,10-phenanthroline hydrate (137 mg, 0.69 mmol, 10mol%). NMP (12 mL), quinoline (4 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 95:5) as eluent to afford pure 1-phenyl-3,5-(bis)difluoromethyl-1*H*-pyrazole (1.5 g, 6.0 mmol, 87%) as a colourless oil.

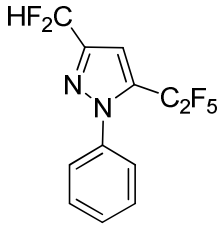
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54-7.46 (m, 5H, N-Phenyl), 6.97 (s, 1H, CHarom), 6.76 (t, 1H, J_{H-F} = 54.8 Hz, CHF_2), 6.61 (t, 1H, J_{H-F} = 53.4 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (t, $^{2}J_{C-F}$ = 30.2 Hz, C_{IV}arom), 138.2 (N-C_{IV} Phenyl), 137.8 (t, $^{2}J_{C-F}$ = 30.3 Hz, C_{IV}arom), 129.62 (CH Phenyl), 129.60 (CH Phenyl), 125.1 (CH Phenyl), 110.7 (t, J_{C-F} = 234.8 Hz, CHF_2), 107.9 (t, J_{C-F} = 236.6 Hz, CHF_2), 104.8 (s, CHarom)ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = -110.6 (CHF_2), -112.2 (CHF_2) ppm.

HRMS (ESI positive) for $C_{11}H_9F_4N_2$ [M+H]: calcd. 245.070; found 245.070.

1-Phenyl-3-difluoromethyl -5-pentafluoroethyl-1*H*-pyrazole (235c)



A Schlenk tube was charged with the carboxylic acid **232c** (2.0 g, 5.6 mmol, 1 equiv.), Cu_2O (40 mg, 0.28 mmol, 5mol%), and 1,10-phenanthroline hydrate (111 mg, 0.56 mmol, 10mol%). NMP (12 mL), quinoline (4 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (95:5) as eluent to afford pure 1-phenyl -3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole (1.5 g, 4.9 mmol, 88%) as a colourless oil.

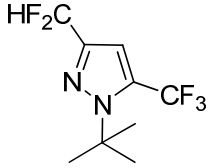
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54-7.43 (m, 5H, phenylH), 7.03 (brs, 1H, Hpyrazole), 6.76 (t, 1H, J_{H-F} = 54.6 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (t, $^2J_{C-F}$ = 30.4 Hz, C_{IV}pyrazole), 139.1 (s, N-C_{IV}phenyl), 132.4 (t, $^2J_{C-F}$ = 28.1 Hz, C_{IV}pyrazole), 130.2 (s, CHphenyl), 129.1 (s, CHphenyl), 126.7 (s, CHphenyl), 118.5 (qt, $^1J_{C-F}$ = 286.3 Hz, $^2J_{C-F}$ = 36.8 Hz, $CF_2\underline{CF_3}$), 110.4 (t, J_{C-F} = 235.3 Hz, CHF_2), 109.5 (tq, $^1J_{C-F}$ = 252.0 Hz, $^2J_{C-F}$ = 40.4 Hz, $\underline{CF_2}CF_3$), 107.5 (brs, CHpyrazole) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -83.9 ($CF_2\underline{CF_3}$), -107.1 ($\underline{CF_2}CF_3$), -113.0 (d, J_{F-H} = 54.6 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_{12}H_8F_7N_2$ [M+H]: calcd. 313.058; found 313.058.

1-*tert*-Butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (234d)



A Schlenk tube was charged with the carboxylic acid **230d** (2.0 g, 7.0 mmol, 1 equiv.), Cu_2O (51 mg, 0.35 mmol, 5mol%), and 1,10-phenanthroline hydrate (134 mg, 0.70 mmol, 10mol%). NMP (15 mL), quinoline (5 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1M HCl (4 x 30 mL), brine (30 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by distillation under reduced pressure to afford 1-*tert*-butyl-3-

difluoromethyl -5-trifluoromethyl-1*H*-pyrazole (1.4 g, 5.6 mmol, 83%) as a colourless liquid (b.p. = 68-69°C, 32 mbar).

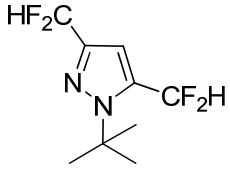
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.94 (brs, 1H, Harom), 6.68 (t, 1H, $J_{H\text{-}F}$ = 54.8 Hz, CHF_2), 1.69 (s, 9H, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 143.5 (t, $^{2}J_{C\text{-}F}$ = 30.4 Hz, C_{IV}arom), 132.7 (q, $^{2}J_{C\text{-}F}$ = 40.1 Hz, C_{IV}arom), 119.9 (q, $J_{C\text{-}F}$ = 268.9 Hz, CF_3), 110.8 (t, $J_{C\text{-}F}$ = 233.9 Hz, CHF_2), 108.0 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, CHarom), 64.2 (s, C_{IV}*t*Bu), 29.8 (q, $^{5}J_{C\text{-}F}$ = 2.1 Hz, *t*Bu CH_3) ppm.
ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = = -55.6 (CF_3), -112.3 (d, $J_{F\text{-}H}$ = 54.9 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_9H_{12}F_5N_2$ [M+H]: calcd. 243.092 found 243.094.

1-*tert*-Butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (233d)



A Schlenk tube was charged with the carboxylic acid **229d** (3.0 g, 11.2 mmol, 1 equiv.), Cu_2O (86 mg, 0.60 mmol, 5mol%), and 1,10-phenanthroline hydrate (238 mg, 1.20 mmol, 10mol%). NMP (27 mL), quinoline (9 mL), and H_2O (3 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (50 mL) and water (50 mL). The organic layer was washed with 1M HCl (4 x 50 mL), brine (50 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by distillation under reduced pressure to afford 1-*tert*-butyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (1.6 g, 7.2 mmol, 64%) as a colourless liquid (b.p. = 90-91 °C, 24 mbar).

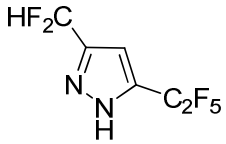
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.96 (t, 1H, $J_{H\text{-}F}$ = 54.4 Hz, CHF_2), 6.82 (brs, 1H, Harom), 6.68 (t, 1H, $J_{H\text{-}F}$ = 55.0 Hz, CHF_2), 1.67 (s, 9H, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 143.9 (t, $^{2}J_{C\text{-}F}$ = 30.1 Hz, C_{IV}arom), 137.2 (t, $^{2}J_{C\text{-}F}$ = 29.7 Hz, C_{IV}arom), 111.1 (t, $J_{C\text{-}F}$ = 233.5 Hz, CF_2H), 108.4 (t, $J_{C\text{-}F}$ = 236.9 Hz, CHF_2), 105.5 (t, $^{3}J_{C\text{-}F}$ = 4.5 Hz, CHarom), 62.6 (s, C_{IV}*t*Bu), 30.0 (s, *t*BuCH_3) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -110.2 (d, $J_{F\text{-}H}$ = 54.5 Hz, CHF_2), -112.5 (d, $J_{F\text{-}H}$ = 55.0 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_9H_{13}F_4N_2$ [M+H]: calcd. 225.102; found 225.101.

3-Difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole (235d)



A Schlenk tube was charged with the *t*Bu-protected pyrazole carboxylic acid **232d** (1.0 g, 3.0 mmol, 1 equiv.), Cu_2O (22 mg, 0.15 mmol, 5mol%), and 1,10-phenanthroline hydrate (60 mg, 0.30 mmol, 10mol%). NMP (6 mL), quinoline (2 mL), and H_2O (2 drops) were added *via* syringe. The vessel was sealed, and the resulting mixture was stirred at 160 °C overnight. It was then diluted with Et_2O (10 mL) and water (10 mL). The organic layer was washed with 1M HCl (4 x 10 mL), brine (10 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by distillation under reduced pressure to afford 3-difluoromethyl-5-pentafluoroethyl-1*H*-pyrazole (0.31 g, 1.3 mmol, 44%) as a colourless solid (b.p. = 63-65°C, 55 mbar).

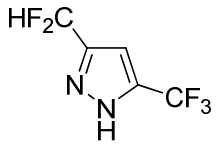
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.87 (brs, 1H, NH), 6.87 (brs, 1H, Harom), 6.80 (t, 1H, $J_{H\text{-}F}$ = 54.7 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 141.5 (brs, C_{IV}arom), 139.5 (brs, C_{IV}arom), 118.4 (qt, $^1J_{C\text{-}F}$ = 285.4 Hz, $^2J_{C\text{-}F}$ = 37.3 Hz, $CF_2\underline{CF_3}$), 109.9 (tq, $^1J_{C\text{-}F}$ = 252.2 Hz, $^2J_{C\text{-}F}$ = 40.1 Hz, $\underline{CF_2}CF_3$), 108.4 (t, $J_{C\text{-}F}$ = 238.2 Hz, CHF_2), 104.9 (brs, CHpyrazole) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -85.1 ($CF_2\underline{CF_3}$), -113.5 ($\underline{CF_2}CF_3$), -113.8 (d, $J_{F\text{-}H}$ = 54.7 Hz, CHF_2) ppm.

HRMS (ESI positive) for $C_6H_4F_7N_2$ [M+H]: calcd. 237.026 found 237.026.

3-Difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (236)



A mixture of 1-*tert*-butyl-3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole **234d** (0.10 g, 0.41 mmol, 1 equiv.), anisole (0.13 g, 0.14 ml, 1.2 mmol, 3 equiv.) and trifluoroacetic acid (2 ml) was stirred and heated to 90 °C for 16 h. The reaction mixture was cooled to ambient temperature, neutralised by the addition of a solution of sodium hydroxide (8.4 g, 0.21 mol) in water (30 mL) until pH = 8. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (gradient 10:0 to 5:5) as eluent to afford pure 3-difluoromethyl-5-trifluoromethyl-1*H*-pyrazole (0.47 g, 2.5 mmol, 76%) as a colourless solid, m.p. 72-73 °C.

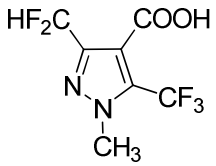
^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 13.38 (brs, 1H, N-H), 6.84 (s, 1H, Harom), 6.79 (t, 1H, J_{H-F} = 54.7 Hz, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 141.1 (brs, C_{IV}arom, C-1 and C-3), 120.1 (q, J_{C-F} = 268.8 Hz, CF_3), 108.3 (t, J_{C-F} = 238.2 Hz, CHF_2), 103.6 (d, $^{3}J_{C-F}$ = 1.6 Hz, CHarom) ppm.

^{19}F NMR ($CDCl_3$, 282 MHz, 25°C): δ = -62.3 (CF_3), -114.2 (CHF_2) ppm.

HRMS (ESI positive) for $C_5H_4F_5N_2$ [M+H]: calcd. 187.029; found 187.029.

6.7. Single Crystal Analysis Data



230b

Crystal data

$C_7H_5F_5N_2O_2$	$F(000)$ = 488
M_r = 244.13	
Triclinic, *P*	D_x = 1.812 Mg m^{-3}
Hall symbol: -P 1	
a = 7.9652 (7) Å	Mo *K*α radiation, λ = 0.71073 Å
b = 8.6230 (8) Å	Cell parameters from 2478 reflections
c = 14.1843 (12) Å	θ = 2.7–27.8°
α = 77.877 (2)°	μ = 0.20 mm^{-1}
β = 73.801 (2)°	*T* = 173 K
γ = 75.338 (2)°	Plate, colourless
V = 894.84 (14) Å^3	0.35 × 0.16 × 0.05 mm
Z = 4	

Data collection

Bruker APEX-II CCD diffractometer	4316 independent reflections
Radiation source: sealed tube	3009 reflections with $I > 2\sigma(I)$
triumph	R_{int} = 0.018
Detector resolution: pixels mm^{-1}	θ_{max} = 28.1°, θ_{min} = 2.5°
φ and ω scans	*h* = −10 9
Absorption correction: multi-scan sadabs	*k* = −11 11

T_{min} = 0.934, T_{max} = 0.990	l = −18 17
7894 measured reflections	

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.043	H-atom parameters constrained
$wR(F^2)$ = 0.114	$w = 1/[\sigma^2(F_o^2) + (0.0502P)^2 + 0.4238P]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 1.02	$(\Delta/\sigma)_{max} < 0.001$
4316 reflections	$\Delta\rho_{max}$ = 0.32 e Å^{-3}
293 parameters	$\Delta\rho_{min}$ = −0.31 e Å^{-3}
0 restraints	Extinction correction: none
constraints	Extinction coefficient:
Primary atom site location: structure-invariant direct methods	

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Novel Access to Heteroaromatic Building Blocks bearing Diversely Fluorinated Substituents

Résumé

Dans un contexte où il est préférable de limiter les quantités de principes actifs, aussi bien dans les médicaments que dans les produits phytosanitaires, il est important de développer des produits dont l'activité biologique est augmentée. Pour ce faire, il est possible d'utiliser des hétérocycles aromatiques contenant des groupements fluorés. Ainsi, nous nous sommes intéressés au développement de voies d'accès à des building blocks hétéroaromatiques portant divers groupements fluorés afin de fournir de nouvelles possibilités pour la préparation de composés d'intérêt thérapeutique et phytosanitaire. Trois projets ont été réalisés, et ont résulté en la préparation efficace de pyridines comportant des groupements trifluorométhoxy, chlorodifluorométhoxy et dichlorofluorométhoxy. Une voie de synthèse régiosélective de 3,5-bis(fluoroalkyl) pyrazoles a également été mise au point. Tous ces méthodes de synthèse ont été développées de manière à obtenir les produits en peu d'étapes à partir de produits commerciaux et sont transposables à grande échelle.

Mots Clés : Hétérocycles aromatiques, Fluor, Activité Biologique, building blocks

Résumé en anglais

The current trend is to lower the amounts of active ingredients used, in pharmaceutical chemistry and in agrochemistry. Therefore, it is important to produce molecules which are more biologically active. It is known that heterocycles are bioactive, and that fluorine can enhance this activity. With this aim in mind, we have taken an interest in the development of heteroaromatic building blocks bearing diversely fluorinated substituents in order to provide new options for the preparation of bioactive compounds. Three projects have resulted in the opening of new synthetic routes towards pyridines bearing trifluoromethoxy, chlorodifluoromethoxy and dichlorofluoromethoxy substituents. A regioselective method for the preparation of 3,5-bis(fluoroalkyl) pyrazoles has also been developed. All these routes have been studied with the aim of obtaining the building blocks in a few steps from commercially available products and are transposable to an industrial scale.

Keywords: Aromatic Heterocycles, Fluorine, Bioactivity, building blocks