Synthesis of 3-fluoro-oxindoles and phenyl fluoroacetic acid derivatives

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A Thesis Entitled

Synthesis of 3-fluoro-oxindoles and phenyl fluoroacetic acid derivatives

Submitted by

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Declaration

The work presented within this thesis was carried out at Durham University between October 2011 and August 2012. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree.

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Statement of copyright

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Abbreviations

Å	Ångstrom
Ac	Acetyl
aHF	Anhydrous Hydrogen Fluoride
Ar	Aryl
Boc	*tert*-Buyloxycarbonyl
bp	Boiling Point
Bu	Butyl
Cbz	Carboxybenzyl
d	Days
DABCO	1,4-diazabyciclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylidene Acetone
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DeoxoFluor®	Bis(2-methoxyethyl)aminosulfur trifluoride
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric Excess
Et	Ethyl
EtOH	Ethanol
EWG	Electron Withdrawing Group
FEP	Fluorinated Ethylene Propylene
Fluorlead™	4-*tert*-Butyl-2,6-dimethylphenylsulfur trifluoride
GPCR	G Protein-Coupled Receptor

h	hours
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mp	Melting Point
NFSI	N-Fluorodibenzenesulfonamide
NMR	Nuclear Magnetic Resonance
OTf	Trifluoromethanesulfonate
Pd/C	Palladium on Carbon
Ph	Phenyl
ppm	Parts Per Million
Pr	Propyl
RAF	Rapidly Accelerated Fibrosarcoma
Rf	Retention Factor
Rt	Room Temperature
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)
S_NAr	Nucleophilic Aromatic Substitution
TBDMS	*tert*-Butyldimethylsilyl
TBS	Tributylsilyl
*t*Bu	*tert*-Butyl
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
XtalFluor-E®	N,N-Diethyl-S,S-difluorosulfiliminium tetrafluoroborate

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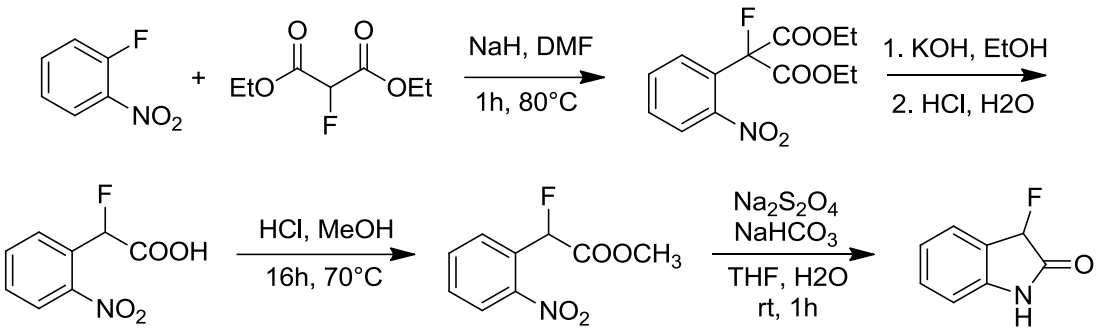
Abstract

Fluorinated heterocycles are potentially interesting compounds for the pharmaceutical and agrochemical industry.[1] Fluorinated indole and oxindole derivatives are generally synthesised by late stage fluorination methodologies (Selectfluor™[2], NFSI[3]). Here, a new method for the synthesis of 3-fluorooxindoles starting from 1-fluoro-2-nitrobenzenes and diethyl fluoromalonate is presented.



The S_NAr reaction is very efficient: 2-aryl-2-fluoromalonates are obtained in quantitative yields and are used without any purification in the hydrolysis step. Following esterification and reduction 3-fluorooxindoles are obtained in moderate yield. The reduction is the most challenging step in the reaction sequence, as the most commonly used metal based techniques (catalytic hydrogenation, dissolving metals) eliminate the benzylic fluorine. This is the first reported example of aromatic nucleophilic substitution using fluoromalonates and is a simple and potentially scalable route to 2-aryl-2-fluoroacetic acids and derivatives. As the anion derived from diethyl fluoromalonate is a weak nucleophile, only fluorobenzenes with strong deactivating groups are suitable substrates for this reaction.

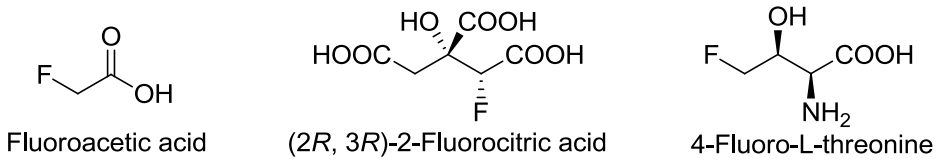
Chapter 1: The chemistry of fluoromalonates

1.1. Introduction to organofluorine chemistry

Although fluorine is the most abundant element of the halogen group in nature, it almost exclusively occurs in inorganic compounds. The most important minerals are fluorite (CaF_2), cryolite (Na_3AlF_6) and fluorapatite ($Ca_5(PO_4)_3F$)[4], which are the sources of hydrogen fluoride (HF), the starting material of fluorine chemistry. All inorganic and organic fluorine containing compounds can be derived from HF.

The isolation of the pure element F_2 was one of the greatest challenges for 19th century chemists and it was late in that century (1886) when Henry Moissan reported his first method of F_2 generation. Moissan's process was a low temperature (-24 °C) electrolysis of KF in aHF (anhydrous HF) in a platinum cell. Today's industrial fluorine cells are all based on the Moissan cell, however, they operate at higher temperatures and are built from more economical structural materials.[4]

Despite the high natural abundance of fluorine, only a handful of naturally occurring organofluorine compounds are known (e.g. Figure 1).



Fluoroacetic acid (2*R*, 3*R*)-2-Fluorocitric acid 4-Fluoro-L-threonine

Figure 1: *Naturally occurring organofluorine compounds.*[5]

In spite of the small number of these compounds, there is an enormous number of synthetic organofluorine molecules and the huge interest in fluorinated compounds can be explained by the unique properties of the fluorine atom. In organic molecules fluorine atoms are only 20 % larger than hydrogen atoms (van der Waals radius: 1.20 Å (H), 1.47 Å (F); CH_3-X bond length: 1.087 Å (H), 1.382 Å (F)) and this small difference enables fluorinated structures to mimic the hydrogenated analogues in biochemical reactions where the molecular recognition is mostly based on steric

interactions.[5] Another important property of fluorinated structures is their enhanced metabolic stability. The metabolically oxidised sites of a structure can be blocked by the introduction of a fluorine atom at these positions.[6]

Lipophilicity plays a key role in the absorption and the distribution of bioactive molecules in an organism and fluorine, or fluorine containing functional groups, can increase the lipophilicity of organic substrates, especially that of aromatic molecules. It is obvious, that the introduction of fluorine - the element with the highest electronegativity value - into a structure will significantly change the physicochemical properties of the molecule as well. For example, fluorine can affect the acidity of carboxylic acids as well as the basicity of amino groups.[5]

All the above properties have encouraged pharmaceutical researchers to incorporate fluorine into their lead structures. Today approximately 20% of pharmaceutical molecules have at least one fluorine atom incorporated into their structure, in agrochemicals this rate can even reach 30%.[7] A recent report from the U.S. Food and Drug Administration reveals that 7 (20%) from the 35 new drug compounds registered by the office in 2011 have fluorine in their structure.[8] Five of these compounds have at least one aromatic C-F bond which indicates that aromatic fluorination methods are of interest.

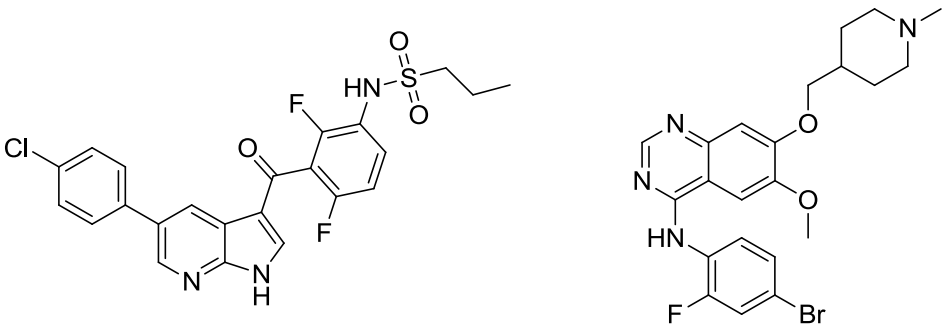


Figure 2: *Aromatic fluorine containing drugs introduced in 2011. Zelboraf® for the treatment of late stage melanoma and Caprelsa® for the treatment of small cell lung cancer.*[8]

Since only a very few molecules bearing a C-F bond are present in nature, all organofluorine compounds are produced synthetically. There are two general methods for the synthesis of complex fluorinated structures: late stage C-F bond formation and C-C bond formation using fluorinated building blocks, but both pathways require the use of fluorinating reagents at one stage.

Although recently several efficient late stage fluorination methodologies have been developed,[9] these reactions are mostly designed for discovery chemists. Whenever a complex fluorinated structure has to be synthesised on industrial scale, the use of fluorinated building blocks is generally favoured. Fluorinated aromatic structures are usually synthesised using either the Balz-Schiemann reaction (1-3 fluorine atoms)[10] or halogen exchange reaction (3+ fluorine atoms)[11].

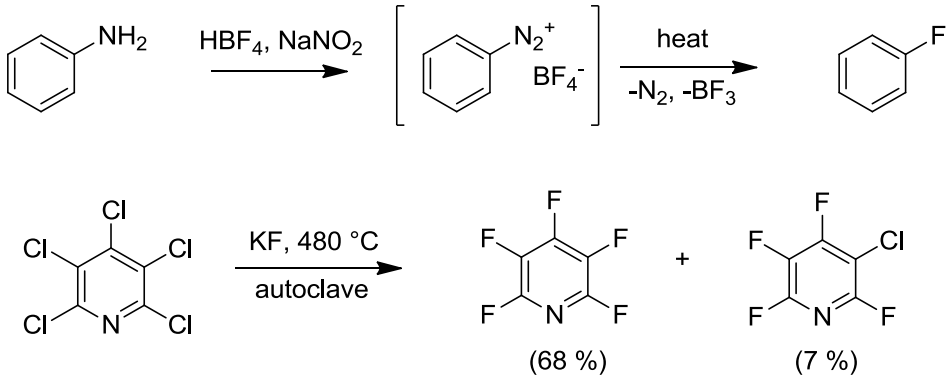


Figure 3: *Aromatic fluorination methods: the Balz-Schieman reaction (top) and halogen exchange reaction (bottom).*

These reactions are efficient, but they require several synthetic steps and usually harsh reaction conditions and therefore, are mostly suitable for the synthesis of simple structures.

There are fluorinated heterocyclic systems that are very inefficient to synthesise using any of the above mentioned reactions, these are usually made by direct fluorination (eg. 5-fluorouracil) or from aliphatic building blocks. 2-Fluoro 1,3 dicarbonyl compounds are efficiently prepared using elemental fluorine and can be used in the synthesis of various heterocycles such as 4-fluoropyrazoles[12] or 4-fluoropyrimidines[13].

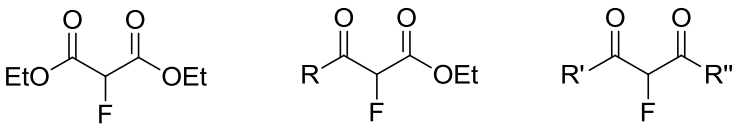


Figure 4: *2-Fluoro-1,3-dicarbonyl compounds.*

The synthesis of 2-fluoro-1,3-dicarbonyl compounds (diketones, keto-esters and malonates) is well documented, but despite of the large literature of the non-fluorinated analogues, only a few types of reactions have been reported using fluorodicarbonyls.

In this work our aim was to demonstrate the versatility of diethyl (dialkyl) 2-fluoromalonate as a fluorinated building block through the detailed discussion of its already established chemistry and the presentation of its new S_NAr reaction.

1.2. Chemistry of fluoromalonates

Derivatives of malonic acid (1,3-propanedioic acid) are widely used intermediates in organic synthesis. The chemistry of malonates includes a large range of reactions from their alkylation to heterocycle synthesis and many industrial processes use malonate derivatives to manufacture agrochemicals, pharmaceuticals (eg. Barbituric acids) or other fine chemicals.[14]

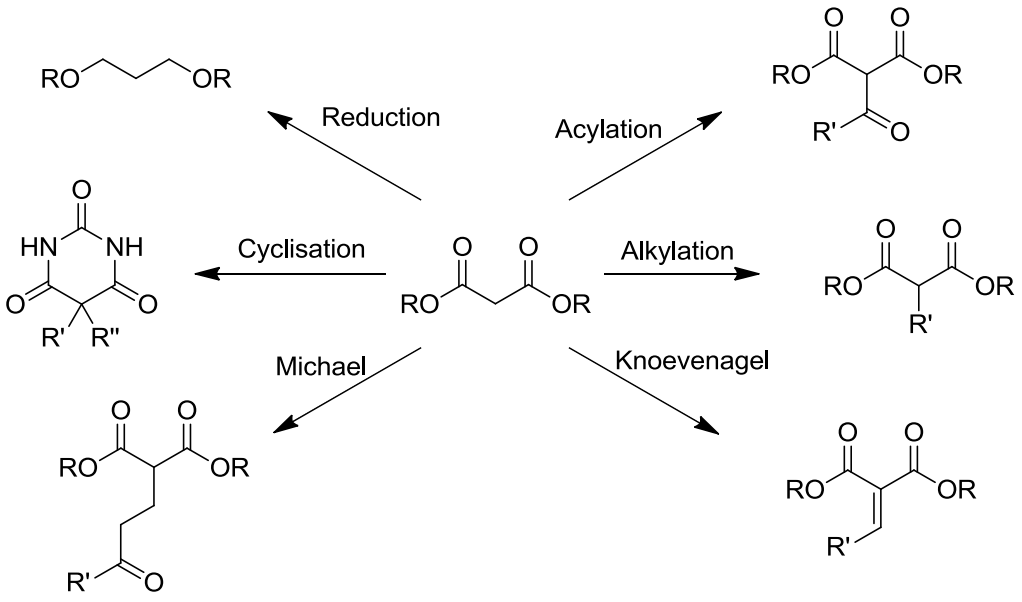


Figure 5: *Selected reactions of dialkyl malonates.*[14]

As malonates are such versatile building blocks, their fluorinated analogues could be utilised to synthesize a large range of fluorinated chemicals that are potentially interesting for the chemical industry. Although dialkyl 2-fluoromalonates were discovered a long time ago, their chemistry is not as developed as that of the parent compounds. The main goal of this chapter is to review the synthesis and the few reported reactions of dialkyl fluoromalonates.

1.2.1. Synthesis of dialkyl 2-fluoromalonates

As dialkyl fluoromalonates are potentially desirable building blocks in organic chemistry, their practical synthesis has been a research subject for decades. Over the last 50-60 years, several procedures were developed, always using the most current fluorinating methods[15] of the time.

1.2.1.1. Fluorination of malonic esters

Malonic esters have acidic protons in the 2 position so deprotonation is possible with bases such as sodium ethoxide or sodium hydride. The generated anion is in equilibrium with the enolate form and reacts readily with electrophiles to give 2-substituted malonates.

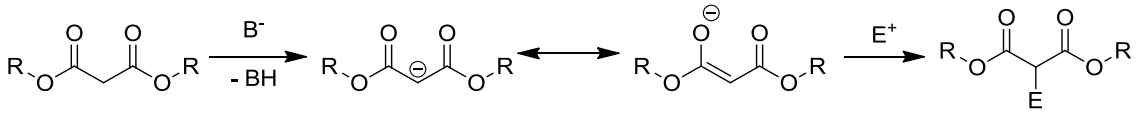
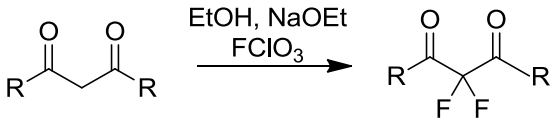
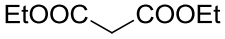
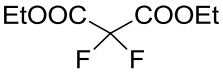
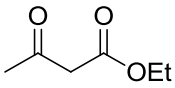
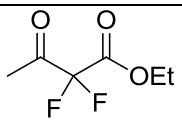
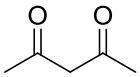
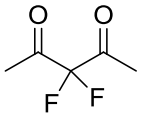
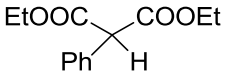
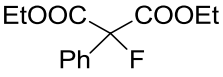


Figure 6: *Reaction of dialkyl malonates with electrophiles (E+).*

The fluorination of malonic esters requires the use of electrophilic fluorinating reagents. The first example of the fluorination of malonates was published in 1958 and used perchloryl fluoride ($FClO_3$) as the fluorinating reagent.[16] When $FClO_3$ was added to the ethanolic solution of sodium diethyl malonate in equimolar ratio, a 50 : 50 mixture of diethyl malonate and diethyl 2,2-difluoromalonate was obtained instead of the expected diethyl 2-fluoromalonate. When two equivalents of NaOEt and $FClO_3$ were used, pure diethyl 2,2-difluoromalonate was obtained in high yield. This fluorination methodology can be extended to 2-substituted malonic esters and to different 1,3-dicarbonyl systems and the results are summarised in Table 1.

Table 1: *Fluorination of 1,3-dicarbonyl systems with perchloryl fluoride.*[16]



Starting material	Product	Yield (%)
		84
		59
		77
		93

Although the yields suggest a potentially useful synthetic method, this fluorination methodology has not been applied because of the safety problems related to perchloryl fluoride and the eventual side product organic perchlorates (highly oxidising, potentially explosive compounds).

In the 1980's, the development of novel fluorinating reagents has seen an unprecedentedly productive period. Over this decade, the hypofluorite and N-F type reagents were discovered and their chemistry was investigated in detail. The main purpose of these reagents was to 'tame' elemental fluorine.

Acetyl hypofluorite (CH_3COOF), discovered by Rozen *et al.*, was the first successful reagent to monofluorinate 1,3-dicarbonyl systems in reasonable yield and purity.[17] It is discussed in the paper, that the previously used reagents (CF_3OF, CF_3COOF, F_2) were too reactive with dicarbonyls, usually resulting in low yield of the desired product and large amount of tar.

The possible reason why this reagent did not find wide spread applications is that it has to be used immediately after being prepared using elemental fluorine.

Another reagent that was developed at the same time is N-fluoro-2-pyridone which can conveniently be prepared from 2-trimethylsiloxy pyridine with elemental fluorine (5% in N_2). [18] This reagent is also capable of fluorinating sodium dialkyl malonates, but the yields are poor, it reaches 30% only in the case of diethyl 2-phenylmalonate. When diethyl malonate sodium salt is treated with N-fluoro-2-pyridone, the monofluorinated product is only formed in a disappointing 9% yield. The low yield combined with the large amount of recovered starting material makes this reaction unpractical.

An interesting and long studied fluorinating reagent is xenon difluoride (XeF_2). This compound is one of the first noble gas compounds ever isolated[19] and is a powerful fluorinating reagent. The fluorination of carbanions was described using a mixture of XeF_2, dimethyl sulphide and $BF_3.Et_2O$.[20] This mixture possibly forms an ionic intermediate (Figure 7) which can transfer fluorine to a carbanion.

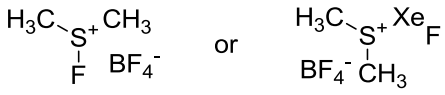


Figure 7: *Proposed intermediates.*[20]

When sodium diethyl malonate was reacted with the pre-made fluorinating reagent (Figure 7), diethyl 2-fluoromalonate was obtained in fair (40%) yield and this reaction can be extended to other 2 substituted malonates. Although this reaction is a good example of the chemistry of noble gas compounds, it is not of practical importance, mostly because of the difficult and expensive preparation of XeF_2 related reagents.

A very important fluorinating reagent family is that of N-fluoropyridinium salts. By changing the substituents attached to the pyridine ring a range of reagents can be synthesised with different reactivity.[21] For the fluorination of carbanions N-fluoro-2,4,6-trimethylpyridinium triflate (trifluoromethyanesulfonate) was found to be the most effective. Diethyl malonate sodium salt gave diethyl 2-fluoromalonate in high yield (73%) and other, substituted malonates also gave the fluorinated product in high yield as well (which will be discussed in detail in Chapter 1.2.2.1.). This reagent family is a valuable tool for discovery chemists and several of these reagents are commercially available.

The direct fluorination of malonates with elemental fluorine was believed to be impractical until it was demonstrated by Purrington *et al.* that it is possible to fluorinate TMS-malonate derivatives with it.[22] The starting material in this case was the corresponding silyl enol ether that was fluorinated with dilute (5% in N_2) fluorine gas in an inert solvent ($CFCl_3$).

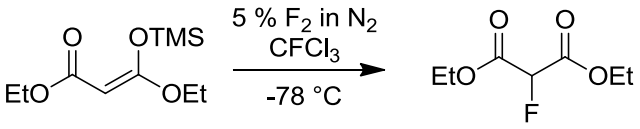


Figure 8: *First synthesis of diethyl 2-fluoromalonate using elemental fluorine.*[22]

Although the yield is good (59%) and this reaction can be extended to other silyl enol ethers, this method is not very practical as the starting material is moisture and acid sensitive and the used solvent ($CFCl_3$) is banned by the Montreal Protocol.

The use of elemental fluorine in the synthesis of this product was also described by Chambers *et al*.[23] In their paper, the fluorination of several dialkyl sodio-malonates was described including that of the parent compound diethyl malonate. Using this method, the product mixture contains mono and difluorinated product as well and their relative ratio depends on the amount of base used. With one equivalent of NaH, 37 % mono- and 23 % difluorinated product was obtained (yields determined by NMR) while when adding 2.25 equivalents of NaH, the difluorinated product was the major product (37 %) with 14 % monofluoro malonate. This method clearly demonstrated that elemental fluorine can fluorinate simple malonate derivatives, but with diethyl malonate the selectivity remains an unsolved problem.

When diethyl malonate was fluorinated in a continuous flow microreactor, several mono- and difluorinated products were detected with low selectivity.[24] The change of substrate to Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) increased the selectivity and the conversion as well; after treatment with ethanol, diethyl mono- and difluoromalonate were isolated.

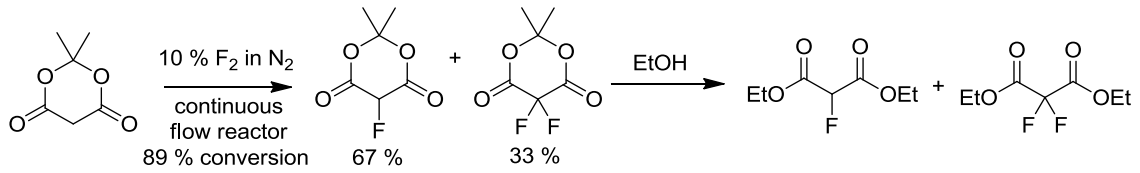


Figure 9: *Continuous flow fluorination of Meldrum's acid.*[24]

The selectivity problem was solved, when it was discovered that the addition of catalytic amount of copper nitrate ($Cu(NO_3)_2$. 2.5 H_2O) can replace the base and activate the malonate for fluorination.[25]

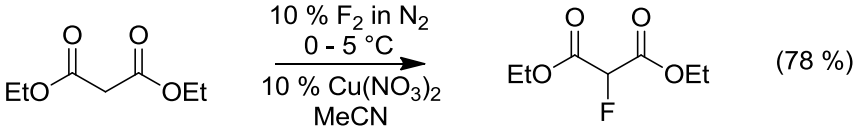


Figure 10: *Cu catalysed fluorination of diethyl malonate.*[25]

Using this method 100 % conversion of the starting material and 78 % yield can be achieved with a trace amount of 2,2-difluoromalonate. This reaction can be extended to several 1,3-dicarbonyl systems as well. Although the selectivity and high yield make this reaction very appealing for potential scale up, the use of elemental fluorine requires specialised equipment and highly trained personnel.

Dialkyl 2-formyl malonates mostly exist in their tautomeric enol form and they readily undergo fluorination with elemental fluorine to yield dialkyl 2-fluoro-2-formyl malonates that can easily be deformylated.[26]

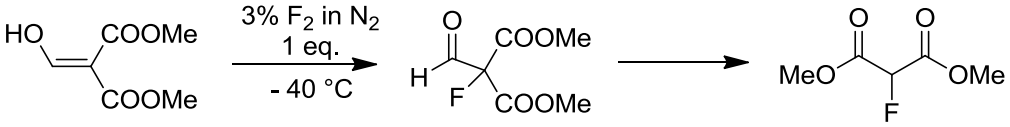


Figure 11: *Fluorination of dimethyl 2-formyl malonate.*[26]

This reaction yields exclusively the monofluorinated product in good yield (78 %). The limitation of this reaction is that only non-functionalised malonates can be prepared.

From the several different fluorination methodologies only the elemental fluorine based reactions are potentially useful for the preparation of non-substituted dialkyl malonates and they have the potential for industrial scale application.

1.2.1.2. Halogen exchange reactions

The substitution of heavier halogens with fluoride is one of the most important reactions in industrial fluorine chemistry. The most frequently used fluoride sources are KF and anhydrous HF. Halogen exchange reaction was used in an early synthesis of fluoromalonates[27], but a later investigation revealed that in the reaction of diethyl bromomalonate and KF only diethyl difluoromalonate is formed in low yield[28].

The negative results using KF discouraged researchers from developing this reaction until in the early 2000s' several patents were filed by Bayer[29] and Solvay[30]. These methods both use amine-hydrogen fluoride complexes with diethyl chloromalonate.

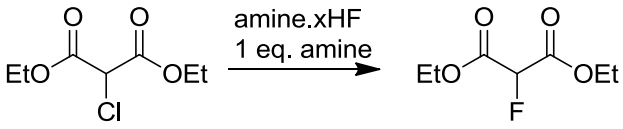


Figure 12: *Halogen exchange with amine.xHF reagents.*

The only difference between the reactions is the base, as Bayer's procedure uses triethylamine and triethylamine.3HF to give diethyl 2-fluoromalonate in 82 % yield while Solvay's process uses DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) HF complex as fluoride source to prepare diethyl 2-fluoromalonate in 92% yield and good purity.

These processes both have the potential for large scale applications as they operate with cost effective reagents and produce the desired product in good selectivity and yield. The safety issues concerning the use of HF reagents make these reactions hazardous, but it is possible to overcome these problems.

1.2.1.3. Miscellaneous preparations

The condensation of fluoroacetic acid derivatives with alkyl chloroformate is another possible route to dialkyl fluoromalonates. An early procedure uses this methodology to prepare diethyl fluoromalonate.[28] Ethyl chloroformate was added to the sodium enolate of ethyl fluoroacetate while cooling. Following workup and fractional distillation, diethyl 2-fluoromalonate was obtained in low yield (21 %).

A similar procedure was developed using the less toxic ethyl bromofluoroacetate[31] which was reacted with tributylphosphine to form an ylide that can be acylated with acid chlorides, in this case with ethyl chloroformate, to give diethyl 2-fluoromalonate in 50 % yield.

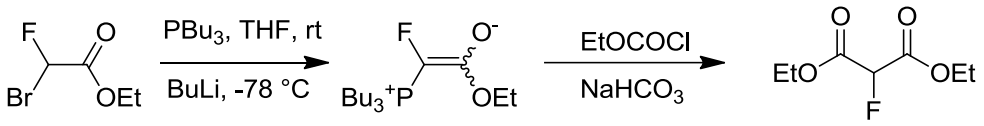


Figure 13: *Acylation of the fluorinated ylide generated from ethyl bromofluoroacetate.*

Although it is possible to prepare fluoromalonate using these reactions, it is not practical, using monofluorinated acetic acid derivatives is not desirable as they are very toxic and the esters are volatile as well.

The sequential solvolysis of hexafluoropropene also gives dialkyl 2-fluoromalonates in good yield. This method was published by Japanese authors in the early 1980s.[32] As hexafluoropropene is manufactured on a large scale for the production of various fluoropolymers, it is a convenient inexpensive starting material. When it is reacted with an alcoholic solution of sodium alkoxide conjugate addition of an alcohol leads to an ether that can be hydrolysed with concentrated sulfuric acid to alkyl 2,3,3,3-tetrafluoropropanoate. When this ester is reacted with an alcoholic alkoxide solution, HF elimination gives the corresponding acrylic acid derivative that immediately undergoes another conjugate addition that is followed by another acidic hydrolysis to give the desired dialkyl fluoromalonate.

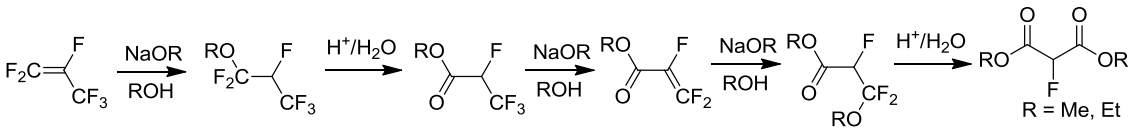


Figure 14: *Sequential solvolysis of hexafluoropropene.*[32b]

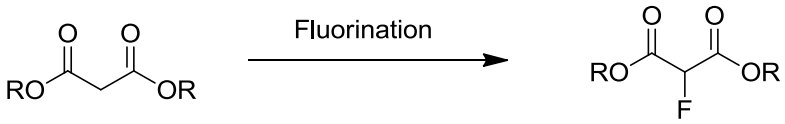
This method was the first potentially scalable synthesis of dialkyl fluoromalonates and has potential for industrial scale usage.

1.2.1.4. Conclusion

As dialkyl fluoromalonates are potentially important building blocks for the synthesis of more complex fluorinated structures, their efficient synthesis has long

been the target of chemists. The following table summarises the results of the discussed reactions.

Table 2: *Syntheses of dialkyl fluoromalonates.*



Reagent	Malonate ester (R)	Yield (%)	Reference
CH_3COOF	CH_3	52	17
N-fluoro-2-pyridone	CH_2CH_3	9 (+ 5% difluoro)	18
$XeF_2/Me_2S/BF_3$	CH_2CH_3	42	20
N-fluoro-2,4,6-trimethylpyridinium triflate	CH_2CH_3	73	21
F_2 (TMS enolate)	CH_2CH_3	59	22
F_2 (Na dialkylmalonate)	CH_2CH_3	37 (+ 23% difluoro)	23
F_2 (in flow)	CH_2CH_3	66	24
F_2 ($Cu(NO_3)_2$)	CH_2CH_3	78	25
F_2 (2-formylmalonate)	CH_3	81	26
NEt_3.xHF	CH_2CH_3	82	29a
DBN.xHF	CH_2CH_3	92	30
Ethyl fluoroacetate	CH_2CH_3	21	28
Ethyl bromofluoroacetate	CH_2CH_3	50	31
Hexafluoropropene	CH_2CH_3	51	32b
Hexafluoropropene	CH_3	49	32b

The results clearly demonstrate that there already are processes that are highly efficient in producing dialkyl fluoromalonates. From these methods the copper catalysed direct fluorination and the halogen exchange reactions with amine.xHF

reagents clearly stand out as being high yielding and having the potential for industrial scale production.

1.2.2. Synthesis of 2-substituted-2-fluoromalonates

2-Substituted malonic esters are frequently the precursors of 2-substituted acetic acids, as the decarboxylation of malonic acids is often easily performed by heating in aqueous acid. The synthesis of 2-alkyl and 2-aryl fluoromalonates has been a challenging subject for a long time and therefore several approaches have been investigated. This chapter will include the fluorination of 2-substituted malonates and the alkylation/arylation of dialkyl fluoromalonates. Several other reactions of fluoromalonates will be discussed in Chapter 1.2.3.

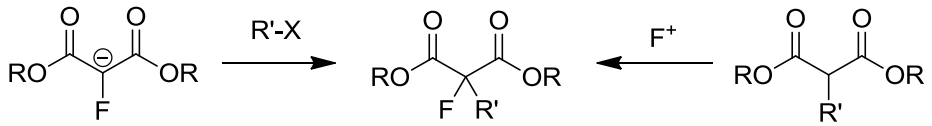


Figure 15: *Different routes to 2-substituted 2-fluoromalonates.*

1.2.2.1. Fluorination of dialkyl 2-substituted malonates

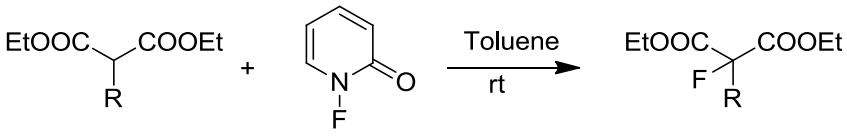
A thoroughly investigated approach to the synthesis 2-substituted 2-fluoromalonates is the fluorination of the non-fluorinated analogues. The same electrophilic fluorination strategy was used with these substrates as in the case of non-substituted malonates. Having a substituent in the 2 position makes the fluorinations more effective and usually higher yielding because there is no difluorinated side product.

The use of perchloryl fluoride[16] is described in detail previously (Chapter 1.2.1.1.) and it will not be discussed here. This fluorination method was used in the synthesis of antiherpetic agents when fluorinating diethyl allylmalonate, a key intermediate[33].

N-Fluoro-2-pyridone[18] was introduced in a previous chapter and it was demonstrated that it can fluorinate carbanions. When it was reacted with 2-substituted (R) malonates, fluorination occurred in reasonable yield (up to 40 %), but

two equivalents of fluorinating reagent was used and significant amount of unreacted starting material was recovered as well.

Table 3: *Fluorination of diethyl 2-R malonates with N-fluoro-2-pyridone.*[18]

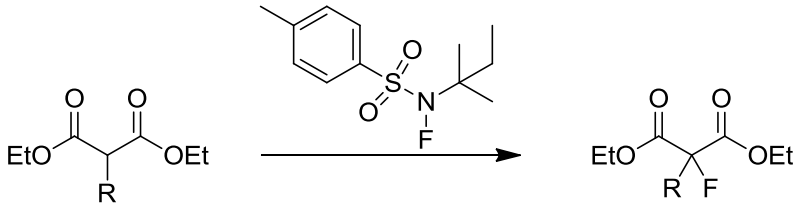


R substituent	Reaction time (h)	Yield (%)
Ph	16	39
CH_2Ph	16	30
CH_3	1.7	17

Considering these results, the usefulness of this reagent is limited, especially because separation of the fluorinated products from the starting material is often difficult.

N-Fluoro-N-alkylsulfonamides are remarkable electrophilic fluorinating reagents that were introduced by Barnette[34] in the early 1980s. N-fluoro-N-alkyl-*p*-toluenesulfonamides were prepared simply by passing dilute (3-5 % in N_2) fluorine gas through a solution of the starting sulfonamide in an inert solvent. Their fluorinating power was demonstrated by reaction with a series of carbanions, most of which gave the desired monofluorinated product in good yield.

Table 4: *Fluorination of malonates with N-fluoro-N-neopentyl-p-toluenesulfonamide.*[34]



Compound	Base	Yield (%)
$PhCH(COOEt)_2$	NaH	81
$CH_3CH(COOEt)_2$	NaH	53

Following these results, DesMarteau's group synthesised a range of very powerful electrophilic fluorinating reagents and investigated their reactivity.[35] N-Fluoro-perfluoroalkylsulfonimides were made from the sulfonimides using pure elemental fluorine. The possibly most useful reagent of this family is N-fluorobis(trifluoromethylsulfonyl)imide which is a clear liquid that has to be handled carefully in a fluoropolymer container. These reagents readily react with electron rich aromatics and with carbanions and essentially give the fluorinated product in quantitative yield (96 % for diethyl 2-methylmalonate). These reagents would potentially be useful if they were commercially available, but their extremely hazardous preparation (use of neat fluorine that is liquefied during the reaction) makes it unlikely.

More recently another class of N-fluoro sulfonamide was developed that use oxathiazione dioxides (for example Acesulfame K) as easily accessible starting materials.[36] The most stable and promising fluorinating reagent is benz-1,2,3-oxathiazin-4-(3-F)-one 2,2-dioxide which was used to fluorinate various carbon nucleophiles.

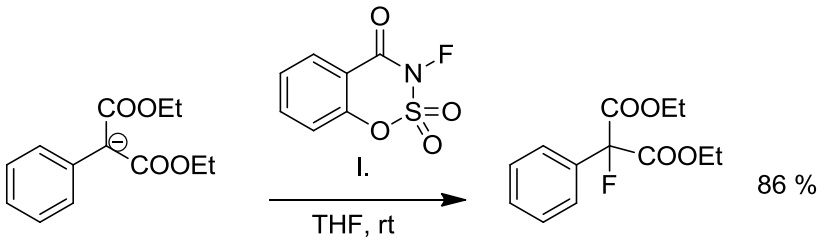


Figure 16: *Fluorination of diethyl 2-phenylmalonate with I.*[36]

Although this reagent gives good yields with several carbon nucleophiles and is convenient to prepare, this reagent family did not find lots of applications, possibly because simultaneously several other, commercially available fluorinating reagents appeared.

An important, commercially available fluorinating reagent is N-fluorobenzenesulfonimide (NFSI). This powerful reagent is used in several fluorinations, including the asymmetric fluorination of prochiral malonate esters.[37]

The Banks group has made an enormous contribution to this field with discovering and developing the azabicyclooctane (quinuclidine and DABCO) based electrophilic fluorinating reagent family following early results with N-fluoro-perfluoropiperidine[38]

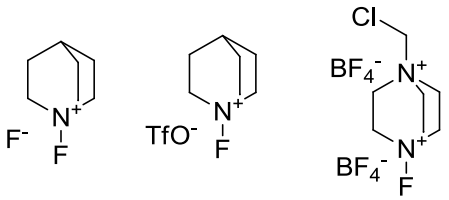


Figure 17: *Fluorinating reagents developed by the Banks group.*

The first isolated compound of this family was N-fluoroquinuclidinium fluoride[39]. The fluorinating capability of this compound was demonstrated by reaction with ionic carbon nucleophiles (diethyl 2-phenylmalonate: 56 % yield). However the biggest problem with this compound was that it is a very hygroscopic solid.

The problems arising from the difficult handling of this reagent were easily overcome by changing the counterion to a non-nucleophilic ion such as triflate ($^{-}$OTf) or tetrafluoroborate (BF_4^-).[40] Although these reagents react selectively with several nucleophiles, the yields are usually low and the reagent is not very efficient.

In the next generation of fluorinating reagents having the bicyclooctane structure quinuclidine was replaced by DABCO.[41] To increase the reactivity an electron withdrawing group was added to the 4 position and the chloromethyl group was chosen for its convenient availability.

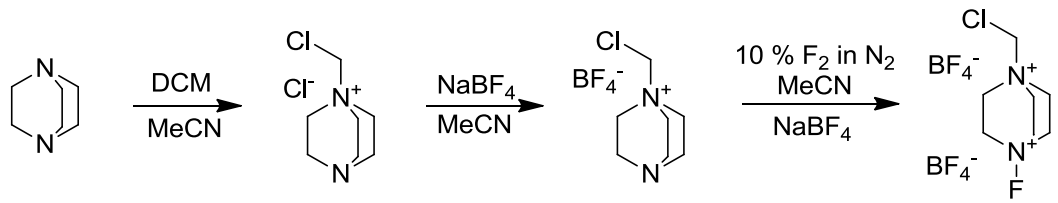


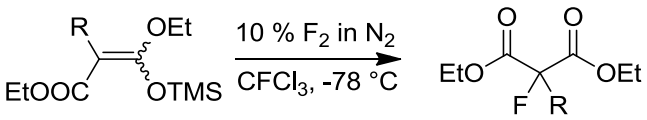
Figure 18: *Synthesis of Selectfluor™.*

This reagent (Selectfluor™) has much better properties than any previously developed reagents. It is much more reactive than the quinuclidine based reagents and

it is a very stable, non-hygroscopic solid. The fluorination of the deprotonated diethyl 2-phenylmalonate afforded the fluorinated product in almost quantitative yield (93 %). This reagent is probably the most widely used commercially available fluorinating reagent, but its use is mainly limited to laboratory scale mostly because its price and low atom efficiency (only 5.3 % by weight is active fluorine). This fluorination reagent has been used in several fluoromalonate syntheses, for example that of novel liquid crystal compounds[42] and potential pharmaceutical target compounds[43].

Elemental fluorine is obviously the most economic electrophilic fluorinating reagent. Its usefulness has already been demonstrated in the previous chapter in the synthesis of dialkyl 2-fluoromalonates.

Table 5: *Fluorination of TMS enolates of malonic esters.* [22]

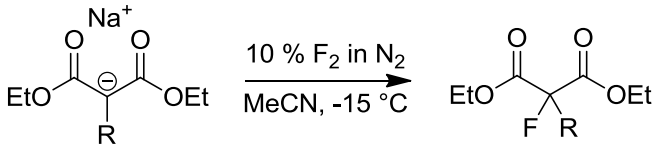


R	Yield (%)
CH_3	68
C_6H_5 (Ph)	73

Substituted malonate ester enolates can be fluorinated using Purrington's method[22] as it is described in Chapter 1.2.1.1. Although substituted fluoromalonate derivatives are synthesised in good yields using this method, this method did not find much use because of the already discussed reasons.

When fluorinating substituted dialkyl sodio-malonates with elemental fluorine, the selectivity is better than with the unsubstituted malonate, as the main competing reaction, difluorination, is not possible.[23]

Table 6: *Fluorination of malonates with elemental fluorine.*[23]



R	Conversion (%)	Yield (%)
CH_3	74	59
^{n}Bu	66	69
OCH_3	75	51
NO_2	100	73
Cl	97	40
Ph	72	41

The table above summarises the results of this fluorination methodology. In several cases the conversion is only approximately 70 % which is possibly due to the protonation of the reactive carbanions. The most probable proton source is HF which is an impurity of F_2 (only 1-2%) and that is also generated in the unavoidable reaction of F_2 and acetonitrile. The high conversion of the nitro and chloro derivatives is probably due to the high acidity of the protonated form. This hypothesis is supported by the fact that when dry KF was used as base, the conversion of diethyl 2-nitromalonate was as high as 80%.[23] The incomplete conversion unfortunately leaves a product mixture that is difficult to purify, therefore, this method is not practical without further optimisation.

The addition of copper catalyst proved very useful in the case of the non-substituted malonate (Chapter 1.2.1.1.), but with substituted malonates the efficiency of the catalysis declined. The only suitable substrates that were fluorinated with copper nitrate catalysis were diethyl 2-nitromalonate (100 % conversion, 76 % yield) and diethyl 2-chloromalonate (38 % conversion, 78 % yield).[25] This later reacted more slowly than the parent diethyl malonate and diethyl 2-nitromalonate. Despite the discouraging results with substituted malonates, this reaction may have potential with the right combination of substrate and catalyst.

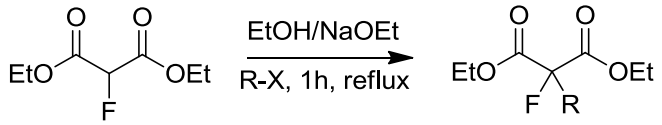
The fluorination of substituted malonate esters on laboratory scale is not a challenging problem anymore mostly due to the commercial availability of effective electrophilic fluorinating reagents such as Selectfluor and NFSI. For the large scale synthesis of substituted fluoromalonate esters there is no available direct fluorination method and, therefore, the development of a reliable process would be potentially useful.

1.2.2.2. Alkylation and arylation of fluoromalonates

One of the first reactions an undergraduate chemistry student comes across in their organic chemistry studies is the alkylation of dialkyl malonates with alkyl halides under basic (NaH or NaOEt) conditions. This reaction is a potentially obvious route to substituted fluoromalonate esters as well.

The alkylation of fluoromalonate esters with simple alkyl halides was demonstrated, using diethyl fluoromalonate and high yields of diethyl 2-alkyl-2-fluoromalonates were obtained.[32]

Table 7: *Alkylation of diethyl fluoromalonate.*[32a]



R-X	Yield (%)
CH_3-I	74
CH_3CH_2-Br	79
n-Bu-Br	85

The authors highlighted that the reaction proceeded more slowly than with the non-fluorinated malonate and they attributed this observation to the low stability and low nucleophilicity of the generated fluoromalonate ion.

This alkylation methodology was used to introduce the fluoromalonate moiety into more complex structures (Figure 19).

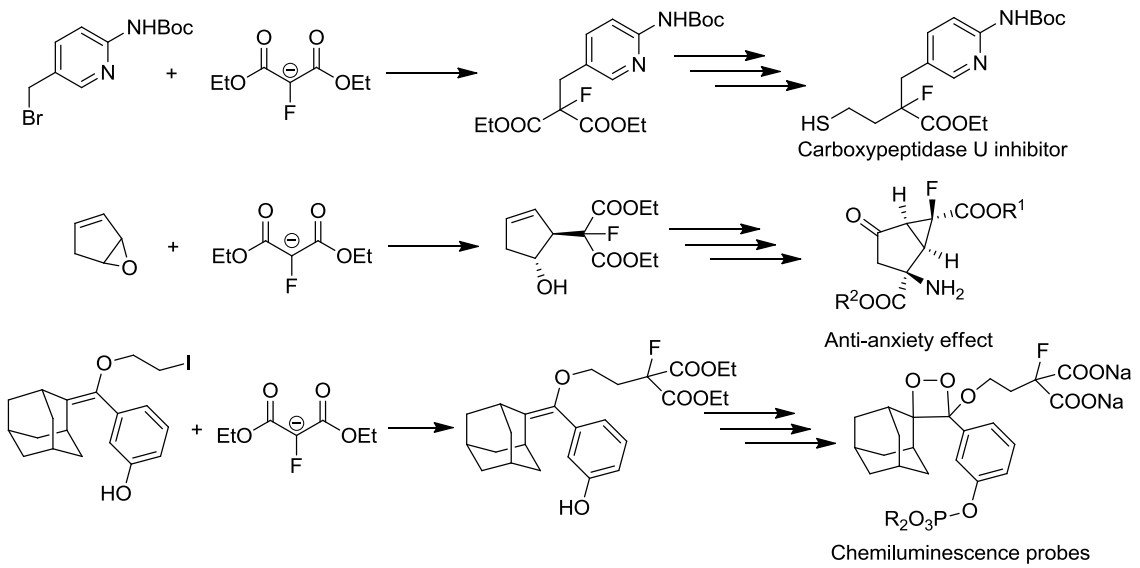


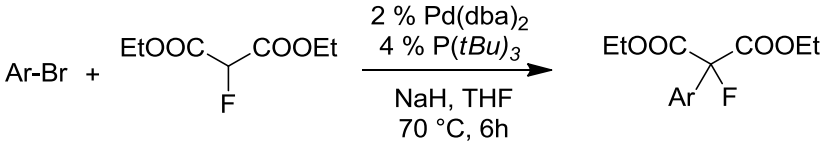
Figure 19: *Bioactive compounds synthesised via fluoromalonate alkylation.*

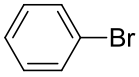
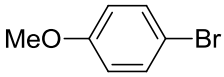
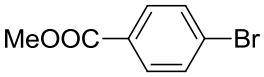
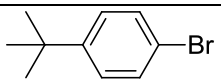
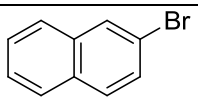
Dialkyl fluoromalonates are alkylated with alkyl halides in the case of the carbopeptidase U inhibitor[44] and the enzymatically triggered chemiluminescent probes[45]. The synthesis of bicyclo[3.1.0]hexane based anti-anxiety drug candidates involves an early stage epoxide opening step[46,47] with diethyl fluoromalonate.

The above presented examples clearly demonstrate the potential importance of dialkyl fluoromalonates and the practicality of its alkylation reactions.

Although 2-aryl-2-fluoromalonates are potential precursors of several monofluorinated compound classes including arylacetic acids and various heterocycles, there are very few examples of the arylation of dialkyl fluoromalonates. There is only one published procedure for the arylation of diethyl fluoromalonate that involves the use of a palladium catalyst, therefore, potentially useful for discovery chemists.[48] In this reaction, diethyl fluoromalonate is deprotonated with NaH and coupled with aryl bromides in the presence of a Pd(0) catalyst.

Table 8: *Pd catalysed arylation of diethyl fluoromalonate.*[48]



Aryl bromide	Yield (%)
	84
	88
	89
	86
	79

This methodology is a good example of the versatility of palladium catalysed chemistry, but obviously this method is mostly suitable for laboratory scale applications. This methodology has already been employed in the synthesis of novel fluorinated arylamide derivatives that are potential cancer treatment drug candidates.[43a]

As dialkyl aryl fluoromalonates are potentially useful intermediates in the synthesis of more complex fluorinated structures, the development of an efficient, readily scalable synthetic method would be important.

1.2.3. Reactions of dialkyl 2-fluoromalonates

Dialkyl 2-fluoromalonates are potentially very versatile building blocks in organic synthesis and may be used in the synthesis of more complex fluorinated structures. The most important applications of fluoromalonates are the synthesis of different heterocyclic structures and the synthesis of chiral fluorinated molecules.

1.2.3.1. Synthesis of 5-fluoropyrimidine systems

One of the earliest heterocycle syntheses using diethyl fluoromalonate was the preparation of 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine in the reaction of diethyl fluoromalonate, S-ethyl *iso*thiouronium bromide and sodium ethoxide.[28]

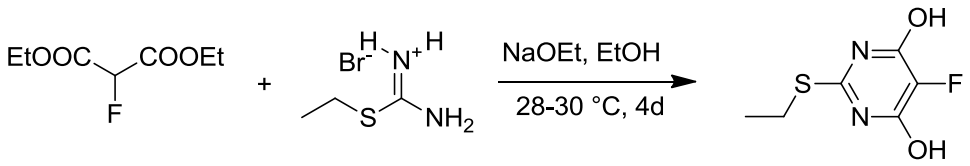


Figure 20: *Synthesis of 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine.*[28]

This condensation reaction has been employed since in the synthesis of several fluoropyrimidine derivatives. As any amidine derivative can be condensed with fluoromalonate, several substituents can be placed in the 2 position. 4,6-Dihydroxypyrimidines can easily be converted to the corresponding dichloropyrimidines using phosphorus based halogenating reagents such as PCl_3, $POCl_3$, PCl_5.[49]

During the last decade (since approximately 2005) several pharmaceutical and agrochemical patents discussed the introduction of this 5-fluoropyrimidine structure into complex bioactive molecules. In most of these cases compounds are derived from 4,6-dichloro-5-fluoropyrimidine, examples include Janus kinase inhibitors[50], orexin receptor modulators[51], anti-cancer drugs[52], GPCR inhibitors[53], RAF kinase inhibitors[54], calcium channel antagonists[55] and chronic obstructive pulmonary disease treatment drugs[56].

Although 5-fluoropyrimidine is present in the above mentioned applications, in all those cases it is only one of the many examples presented in patents. In 2009 a novel antibacterial drug family was patented by GlaxoSmithKline where 5-fluoropyrimidine is a main component of the structure.[57]

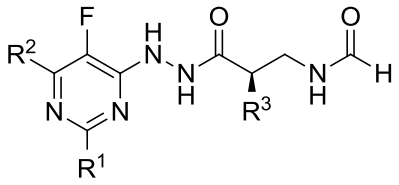


Figure 21 : *5-Fluoropyrimidine based antibacterial drug family.*[57]

The synthesis of this drug family is based on the already described condensation of dialkyl fluoromalonates with an amidine followed by halogenation to give a 2-substituted 4,6-dichloro-5-fluoropyrimidine that can be further functionalised using standard synthetic transformations.

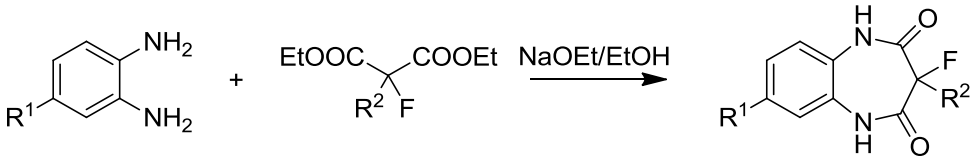
The above demonstrated examples clearly identify 5-fluoropyrimidines as potential building blocks in pharmaceutical research. At present the only practical route to these pyrimidine building blocks is the condensation of dialkyl fluoromalonates with amidines. Interestingly a detailed study discussing the reactions of 4,6-dihalo-5-fluoropyrimidines has not been reported to date.

1.2.3.2. Synthesis of other fluorinated heterocyclic systems

Malonic esters are involved in the synthesis of several different heterocyclic systems besides pyrimidines, for example, barbituric acids, benzodiazepines, etc. In contrast to non-fluorinated malonates, only a small number of examples have been reported about the use of fluoromalonates in the synthesis of non-pyrimidine heterocycles.

Fluorinated 1,4-benzodiazepines were successfully synthesised from diethyl fluoromalonates when reacted with 1,2-diaminobenzenes.[32b,58]

Table 9: *Synthesis of fluorinated benzodiazepines using fluoromalonates.*[58]



R^1	R^2	Yield (%)
H	CH_3	59
H	C_2H_5	62
H	*n*-C_4H_9	48
H	H	61
Cl	H	41
NO_2	H	52
CH_3	H	72

Dimethyl 2-fluoromalonate was used in the large scale synthesis of 3-fluoroquinoline derivatives that were used in the synthesis of novel anti-bacterial drug candidates.[59]

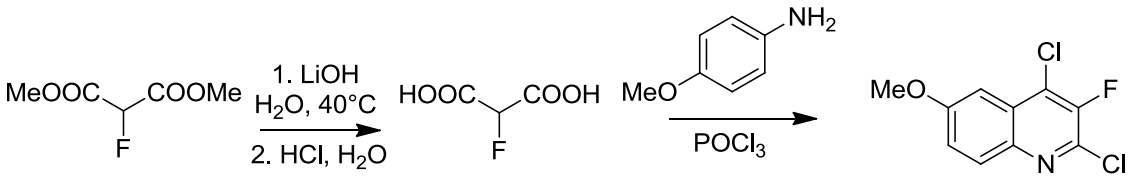


Figure 22: *Synthesis of 3-fluoro-6-methoxyquinoline using dimethyl fluoromalonate.*[59]

This synthesis was performed on several hundred grams scale, demonstrating that the reactions of fluoromalonates are safe to scale up and they usually behave in a very similar way to the parent non-fluorinated malonates.

A recent patent publication from Takeda Pharmaceuticals discusses the synthesis of 3,5-disubstituted 6-fluoro-8-methylpyrido[2,3-d]pyrimidine-4,7-(3H,8H)-diones, active pharmaceutical ingredients for the synthesis of different drug candidates. The multistep synthesis of the condensed heterocyclic structure is presented in Figure 23.[60]

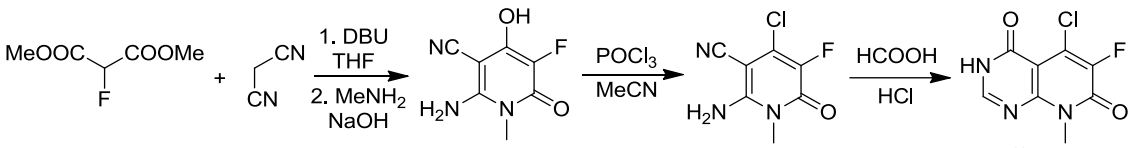


Figure 23: *Synthesis of 6-fluoro-8-methylpyrido[2,3-d]pyrimidine-4,7-(3H,8H)-dione.*[60]

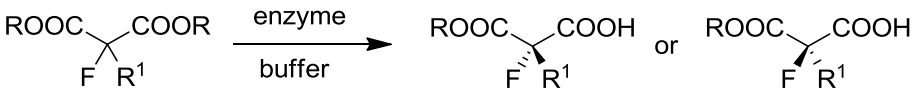
Although dialkyl fluoromalonates have a great potential in the synthesis of monofluorinated heterocycles, their chemistry has not been developed to a great extent. The above mentioned procedures cover the available literature of this area. It is possible, that the relative underdevelopment of this field is due to the fact that fluoromalonates have been available mostly to organofluorine chemists for a long time who were more interested in synthesising these compounds than discovering their chemistry. The increasing number of industrial publications suggests that since dialkyl fluoromalonates became commercially available, they immediately found applications.

1.2.3.3. Biochemical synthesis of chiral synthons

The development of enantioselective fluorinating methods has been an intensively researched area for decades. The achievements of this field were reviewed most recently by O'Hagan[61] but it is important to note that synthetic reactions are rarely as efficient and selective as biochemical transformations.

The first reported use of fluoromalonates in the synthesis of chiral building blocks was the enantioselective enzymatic hydrolysis of malonate esters to malonate monoesters.[62] For these studies esterase (*Candida Cylindracea*) and cellulase (*Trichoderma Viride*) enzymes were selected.

Table 10 : *Enzymatic asymmetric hydrolysis of fluoromalonates.*[62]



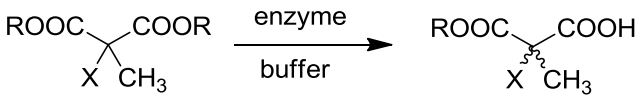
Substrate	Origin of enzyme	Yield (%)	Direction of optical rotation	Optical purity (%ee)
$MeCF(COOEt)_2$	*Candida Cylindracea*	87	(-)	91
$MeCF(COOEt)_2$	*Trichoderma Viride*	60	(+)	56
$MeCF(COOMe)_2$	*Candida Cylindracea*	74	(-)	95
$MeCF(COOMe)_2$	*Trichoderma Viride*	83	(+)	46
$EtCF(COOEt)_2$	*Candida Cylindracea*	87	(-)	93
$EtCF(COOEt)_2$	*Trichoderma Viride*	No reaction		-
$EtCF(COOMe)_2$	*Candida Cylindracea*	87	(-)	99
$EtCF(COOMe)_2$	*Trichoderma Viride*	No reaction		-
$CHF(COOEt)_2$	*Candida Cylindracea*	70	(+)	62
$CHF(COOEt)_2$	*Trichoderma Viride*	51	(+)	58
n-$PrCF(COOEt)_2$	*Candida Cylindracea*	No reaction		-
n-$BuCF(COOEt)_2$	*Candida Cylindracea*	No reaction		-

The results clearly indicate that, with the selection of the appropriate enzyme, chiral fluoromalonate monoesters can be obtained in excellent yield and enantiopurity. Using different enzymes, both enantiomers were synthesised, but the lipase from *Candida Cylindracea* is a more efficient catalyst for this transformation. The scope of this reaction is very limited as alkyl chains longer then ethyl completely inhibit the reaction probably because of steric effects.

The absolute configurations were determined by reducing (+)-2-fluoromalonate monoethyl ester to the corresponding (+) ethyl 2-fluoropropionate which was known to be the R isomer.[63]

The same group also investigated the mimic effect of fluorine in the same hydrolysis reaction and proved that the substitution of a hydrogen atom with fluorine does not affect the highly stereo-controlled enzymatic reactions.[64]

Table 11: *Mimic effect of fluorine.*[64]



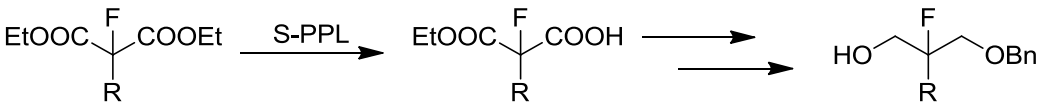
X	Yield (%)	Optical purity (% ee)	Van der Waals radius (Å)
H	83	Racemisation	1.20
F	60	91	1.35
Cl	No reaction		1.80
Br	No reaction		1.95
CH_3	No reaction		2.00

This result is a very important example of the mimic effect of fluorine in biological reactions. It is unfortunate that the scope of this reaction is very limited because the high yields and excellent enantiopurities make this process very appealing for large scale applications.

2-Aryl-2-fluoromalonates are not suitable substrates for the above mentioned reaction, but different approaches were developed for asymmetric modifications of these substrates.

A practical approach to asymmetric 2-aryl-2-fluoro-1,3-propanediol monoacetates was developed using enzymatic hydrolysis of 2-aryl-2-fluoromalonate esters.[65] In this reaction Celite supported porcine pancreatic lipase (S-PPL) was used for the asymmetric hydrolysis that was followed by several steps to give 1-(O)-benzyl-2-aryl-2-fluoro-1,3-propanediols with good enantiopurity. The substrate scope was later extended to 2-methoxy systems as well, but in this case a different enzyme was used (microbial lipase Amano AY, (AYL)).[66]

Table 12: *Asymmetric hydrolysis of 2-substituted fluoromalonates.*[66]



R	Lipase	Conversion (%)	Yield (%)	Enantiomeric excess (%)
Phenyl	S-PPL	64	60	96
2-Naphtyl	S-PPL	13	5*	-
3-Thienyl	S-PPL	50	77	96
OCH_3	AYL	50	63	96

***** *Decarboxylation of the monoester was immediate and the main isolated product was ethyl 2-fluoro-2-naphtylacetate.*

This hydrolysis methodology has a very narrow demonstrated scope, but with the substrates demonstrated above excellent selectivity was observed.

Enantiopure 2-fluoro-2-phenylacetic acid can be used as chiral derivatising agent to determine enantiomeric excess by ^{19}F NMR.[67] A very efficient and selective synthesis of (R)-2-fluoro-2-phenylacetic acid was developed by Japanese researchers when an arylmalonate decarboxylase enzyme (expressed from *E. coli* JM 109) is used to decarboxylate dipotassium 2-fluoro-2-phenylmalonate.[68]

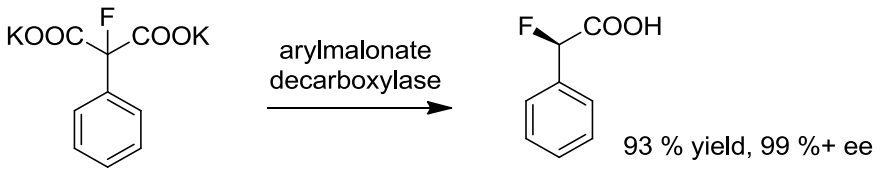


Figure 24: *Asymmetric dexarboxylation of 2-fluoro-2-phenylmalonate.*

The crude product of the reaction already was 99.1% pure R isomer, but after one recrystallization (69% recovery) enantiopure product was obtained.

Although there are few examples of enzymatic asymmetrisation of fluoromalonates, with the right enzyme it is possible to achieve good yields and excellent enantiopurities. Unfortunately there is no general enzyme for these reactions, but as fluorine can mimic hydrogen in biochemical processes, several enzymes, tested on non-fluorinated products, have the potential to be effective with fluoromalonates.

1.2.3.4. Synthesis of α-fluorocarboxylic acid derivatives

A very important property or malonate esters is that, after hydrolysis, one of the carboxylic groups can be removed simply by heating the compound in aqueous acidic medium. This reaction enables the simple synthesis of longer chain carboxylic acids from alkyl (or aryl) halides. As dialkyl fluoromalonates can easily be alkylated (the arylation is less convenient), these products are potential precursors of longer chain 2-fluoroalkanecarboxylic acids and 2-fluoroarylacetic acids.

Despite the simplicity of these reactions, only a few documented examples of this chemistry are available. Early publications discuss the synthesis of 2-fluoroalkanoic acids[17,69] and 2-fluoro-2-phenylacetic acid[22].

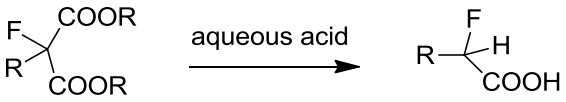


Figure 25: *Acid hydrolysis of fluoromalonates.*

This acid hydrolysis usually gives the desired α-fluoro carboxylic acids in high yield and purity. The application of this chemistry can be found in several industrial syntheses of bioactive compounds in the patent literature such as anti-cancer 2-fluoro-6-benzothiophenyl acetic acid[43a, 70] and 2-aryl-5-fluoromethyl-1,3,4-oxadiazol[43b] derivatives , 3-aryldifluoromethylpyridazines[71] and α-fluorovalerolactone containing steroids[72].

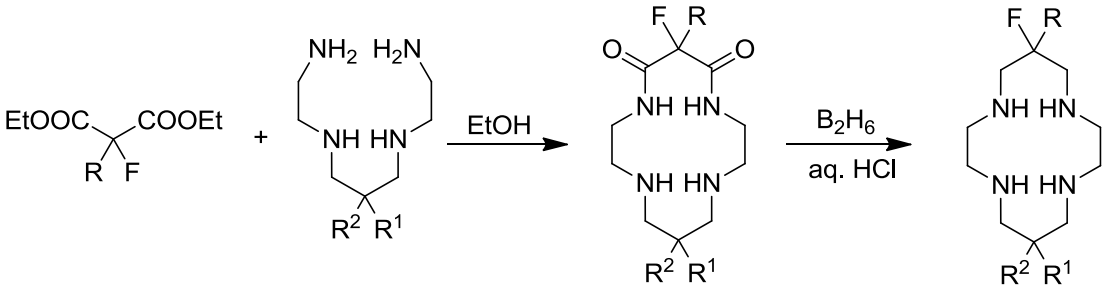
Although arylacetic acids are versatile intermediates in the synthesis of several bioactive systems, the chemistry of 2-aryl-2-fluoromalonates (and related aryl fluoroacetic acids) has not been fully explored.

1.2.3.5. Synthesis of fluoromalonamides and 2-fluoro-1,3-diamines

Malonamides and propane 1,3-diamines are practical building blocks in the synthesis of more complex structures such as heterocycles and macrocycles. The fluorinated analogues can easily be prepared from dialkyl fluoromalonates by reaction with amines and reducing the amides if the diamine is needed.

An early example of this chemistry was the synthesis of several fluorinated cyclams (1,4,8,11-tetraazacyclotetradecanes) that are useful reagents in the formation of metal ion complexes.[73]

Table 13: *Synthesis of fluorinated cyclames.*[74]



R	R^1	Yield (%) (2 steps)
H	H	28
H	F	22
F	F	15

Although the yields are low, it is due to the low efficiency of the cyclisation (generally aprox. 30 % yield for the first step), since the reduction proceeded effectively. This reaction was one of the earliest examples of the synthesis of fluorinated malonamides and their subsequent reduction to the corresponding diamine. Recently 2,2-difluoro-propane-1,3-diamine based cobalt and rhodium complexes were used in photocatalytic hydrogen production from water.[75]

The incorporation of 2-fluoro- or 2,2-difluoro-1,3-diaminopropyl segments into complex bioactive structures is documented in several cases. Potential antitumor[76, 77, 78], Alzheimer's disease treatment[79] and cardiovascular disease treatment[80] compounds have been synthesised with examples containing these structural elements.

N,N'-Disubstituted 2-fluoromalonamides can be synthesised easily even in the case when the two substituents are different. When the two substituents are the same, dialkyl fluoromalonates are simply heated with excess amine to produce the diamide in good yield, but when non-symmetrically substituted malonamides are desired the stepwise synthesis is more practical.

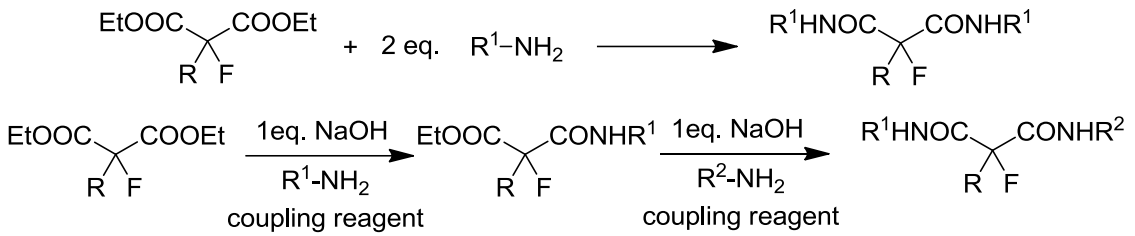


Figure 26: *Synthesis of N,N'-disubstituted fluoromalonamides.*

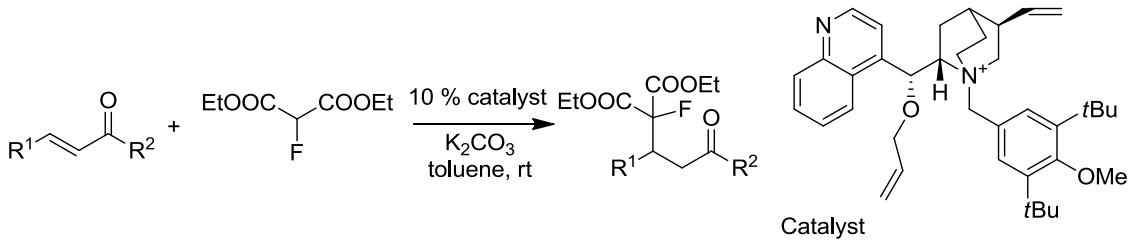
Although these reactions are very simple and effective, there are only a few documented applications, all of which are selected examples from pharmaceutical patents. These compounds have various biological effects such as immunosuppressant activity[81], different enzyme inhibition[82] or potential treatment of Alzheimer's disease[83].

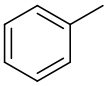
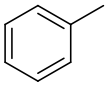
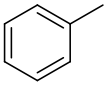
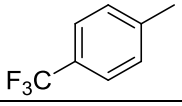
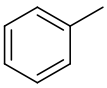
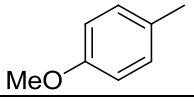
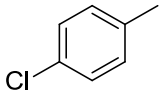
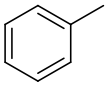
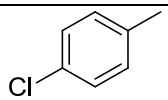
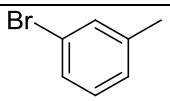
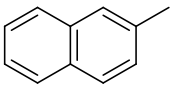
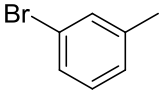
1.2.3.6. Conjugate addition of fluoromalonates to double bonds

A very important C-C bond forming reaction is the conjugate (Michael) addition of carbon nucleophiles to α-β unsaturated carbonyl compounds. Several methodologies have been developed since the discovery of this synthesis in the late 19th century.

The enantioselective addition of dialkyl fluoromalonates to different Michael-acceptors is possibly their most intensively researched reaction by academic researchers. The first example uses a cinchonine derived quaternary ammonium salt catalyst which is efficient, but the enantioselectivty of the reaction remains mediocre.[84]

Table 14: *Enantioselective Michael addition of diethyl fluoromalonate to chalcones.*[84]

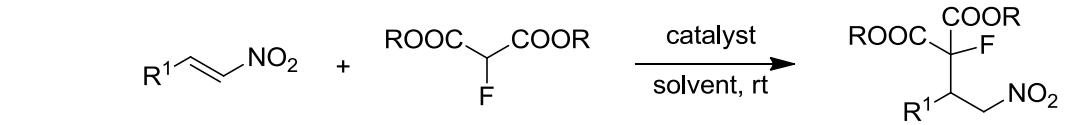


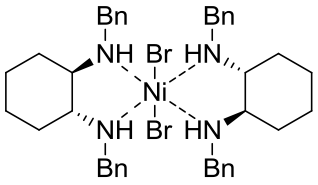
R1	R2	Reaction time (h)	Yield (%)	Enantiomeric excess (%)
		15	63	39
		18	60	45
		18	58	47
		18	77	37
		18	64	37
		18	76	47

Despite the good yields this reaction is not appealing as the enantiopurity of the products is low and the reactions were conducted only on 0.1 mmol scale which does not show the potential usefulness of this reaction.

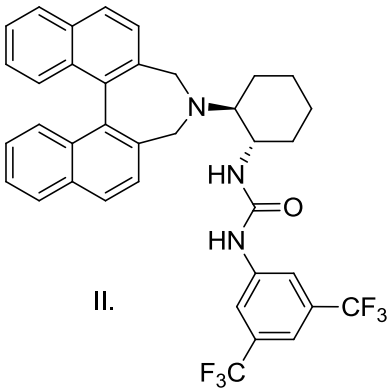
Nitroolefins are also potential Michael-acceptors that are often used in the testing of novel chiral catalyst systems. In 2009, three different catalysts were shown to be very effective and selective in the addition of fluoromalonates to nitroolefins. The catalysts and the results are presented in Table 15.

Table 15: *Enantioselective addition of dialkyl fluoromalonates to nitroolefins.*[85-87]

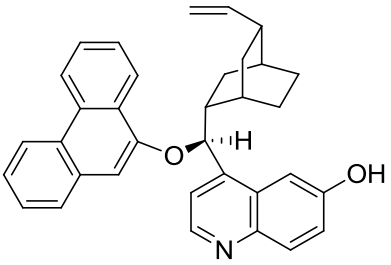




I.



II.



III.

R	R^1	Catalyst (mol %)	Time (h)	Solvent	Yield (%)	Ee % (Optical rotation)
Et	C_6H_5	I.[85] (5)	20	Toluene	97	97 (+)
Et	4-F-C_6H_4	I. (5)	11	Toluene	92	93 (n.a.*)
Et	4-MeO-C_6H_4	I. (5)	10	Toluene	91	95 (n.a.)
Et	2-Cl-C_6H_4	I. (5)	13	Toluene	96	97 (n.a.)
Et	C_6H_5	II.[86](10)	48	DCM	93	96 (+)
Et	4-F-C_6H_4	II. (10)	120	DCM	80	98 (n.a.)
Et	4-Br-C_6H_4	II. (10)	72	DCM	78	95 (n.a.)
Et	2-Furyl	II. (10)	96	DCM	80	97 (n.a.)
Me	2-NO_2-C_6H_4	II. (10)	120	DCM	85	97 (n.a.)
Me	C_6H_5	III.[87] (20)	24	Chloroform	97	97 (+)
Me	2-MeO-C_6H_4	III. (20)	168	Chloroform	82	91 (+)
Me	3-Br-C_6H_4	III. (20)	24	Chloroform	91	94 (+)
Me	2-Thienyl	III. (20)	12	Chloroform	99	98 (+)
Me	*n*-C_5H_{11}	III. (20)	168	Chloroform	65	88 (+)

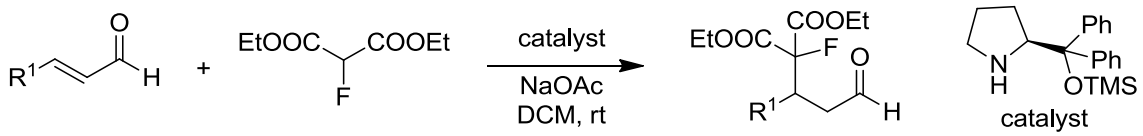
** N.a. means that the information is not available in the publications.*

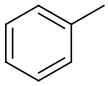
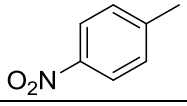
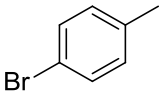
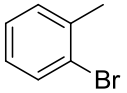
The results demonstrate that several catalysts are capable of catalysing the same reaction with similar efficiency and selectivity. Although the yields and enantiopurities are very similar, it is important to note that the Ni complex is more

effective than the organocatalysts as the reaction times are significantly shorter and the catalyst load (5 mol% vs 10 and 20) is lower as well. It is not surprising that both ethyl and methyl fluoromalonates react with the same result, but while the organocatalysts react slowly with *ortho*-substituted benzene derivatives, the nickel catalyst is not affected by steric effects. The high selectivity of these catalysts compared to the example previously described is possibly due to the sterically demanding substituents close to their active sites. The absolute configuration of these products was found to be (S) in all cases so, therefore, when the other isomer is needed, different catalysts must be applied.

α-β Unsaturated aldehydes are interesting substrates for this reaction as aldehydes usually undergo Knoevenagel condensation with malonates to give unsaturated products. The enantioselective addition of diethyl fluoromalonate to α-β unsaturated aldehydes was carried out in the presence of a simple prolinol organocatalyst that produced good yields and enantiopurities.[88]

Table 16: *Enantioselective addition of diethyl fluoromalonate to unsaturated aldehydes.*[88]

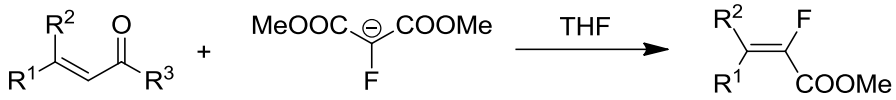


R^1	Reaction time (d)	Yield (%)	Ee (%)
	1	66	96
	3	69	94
	3	75	95
	2	78	96

Although the yields are good and the enantioselectivity is excellent, in this method, 2 equivalents of aldehyde was reacted with one fluoromalonate that means low atom economy which is not desirable especially in the case of costly substrates.

The use of dialkyl fluoromalonates is not limited to the above demonstrated reactions. A very efficient 2-fluoroacrylate ester synthesis is based on a domino reaction where the first step is the addition of fluoromalonate to a Michael-acceptor followed by elimination to give fluoroacrylate.[89]

Table 17: *Synthesis of fluoroacrylates from fluoromalonates.*[89]



R^1	R^2	R^3	Yield (%)	E / Z ratio
Me	H	*t*-Bu	30	0 : 100
Et	H	*t*-Bu	71	2 : 98
i-Pr	H	*t*-Bu	63	0 : 100
t-Bu	H	*t*-Bu	29	0 : 100
Ph	H	*t*-Bu	60	0 : 100
CH_3CH(OTBS)	H	*t*-Bu	58	9 : 91
CH_3CH(Ph)	H	*t*-Bu	94	3 : 97
Me	H	Me	(59)*	-
Ph	H	Me	73	0 : 100
Ph	Me	*t*-Bu	n.r.*	-

** This reaction gave the accepted Michael adduct; n.r.: no reaction observed.*

The above presented examples clearly demonstrate the usefulness of this synthetic strategy. Although the yields vary from poor to excellent, the E/Z selectivity of the reaction is very good. Unfortunately when the Michael-acceptor is disubstituted (R^1 and R^2 are not H) only unreacted starting materials were recovered. The proposed mechanism of this reaction is presented in Figure 27.

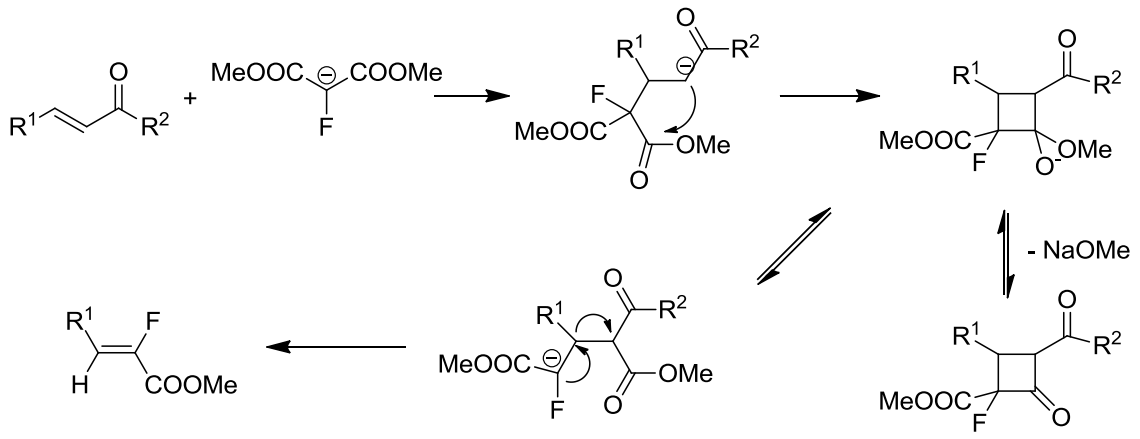


Figure 27: *Proposed mechanism of the fluoroacrylate synthesis.*[89]

Besides the already presented reactions, the Michael addition of fluoromalonates has been used in the synthesis of several complex monofluorinated structures. Examples include the synthesis of α-fluoro-γ-aminoacids[90], 4-fluoroglutamates[91] and 4-fluoro-5,5'-dihydroxyleucine[92]. Several chemicals with potential bioactivity were prepared this way such as herbicides[93], anti-inflammatory drug candidates[94], immunomodulators[95] and potassium channel deactivator compounds[96].

The above mentioned examples also demonstrate the versatility and usefulness of this type of reaction of fluoromalonates. The conjugate addition of fluoromalonate esters is a very mild and selective way to introduce one fluorine atom into complex structures, but this chemistry has not been developed to its full potential.

Another important reaction of fluoromalonates is their addition to carbon heteroatom double bonds, especially C=O and C=N bonds. These reactions are potentially useful in the synthesis of β-fluoro alcohols and amines.

An early example of this chemistry is the synthesis of fluorinated acrylic esters for polymerisation reactions.[97] Where 2-fluoroacrylic chloride was prepared in three steps from dimethyl 2-fluoromalonate and was consecutively used in the synthesis of its esters.

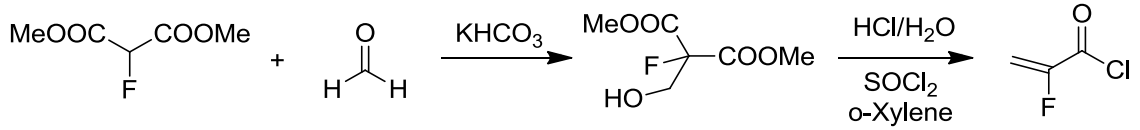
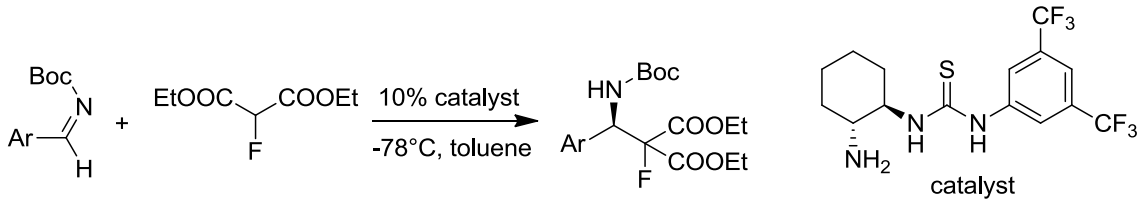


Figure 28: *Synthesis of 2-fluoroacrylic chloride form dimethyl fluoromalonate.*[97]

This 2-fluoroacrylate synthesis can be extended to other aldehydes, and was used in the synthesis of fluorinated porphobilinogens.[98]

When 2-fluoromalonates are added to C=N bonds the products are α-fluoro-β-aminoacid precursors. This important compound class is effectively generated from aldimines or their synthetic equivalents. The enantioselective addition of diethyl fluoromalonate to N-Boc aldimines was performed using a chiral thiourea based organocatalyst.[99]

Table 18: *Asymmetric Mannich type reaction of diethyl fluoromalonate.*[99]



Ar	Time (d)	Yield (%)	Ee (%)
C_6H_5	3.8	86	96
2-F-C_6H_4	5.7	81	97
4-MeO-C_6H_4	7.5	85	96
4-Cl-C_6H_4	5.5	86	96
1-Naphthyl	6.0	82	95

Although the yields and the enantioselectivity is excellent, it comes at a cost as the reactions were carried out at low temperature (-78 °C) and the reaction times are long (several days) which is inconvenient.

A simple synthesis of racemic 2-fluoro-2-(α-Cbz-aminobenzyl)malonates used diethyl fluoromalonate and α-amido p-tolylsulphones as Mannich base equivalent reagents.[100]

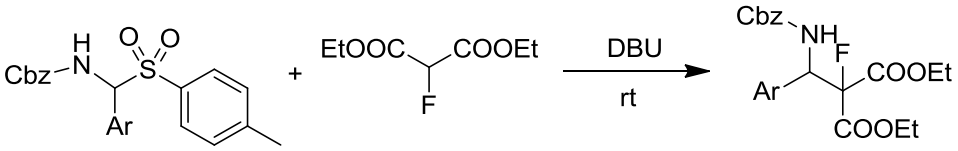


Figure 29: *Solvent free reaction of fluoromalonate and α-amido p-tolylsulfones.*[100]

This reaction proceeds without any added solvent in the presence of catalytic amount of added base, but it is important to note that 6 equivalents of fluoromalonate was used that can act as solvent (although its cost is higher than that of any other solvent). The scope of this reaction is very similar to the above mentioned enantioselective method and the yields are generally good (60 – 80 %), but without the recovery of the excess malonate this is not a practical method.

In conclusion, the nucleophilic addition of fluoromalonate esters is potentially a very versatile tool in the synthesis of more complex monofluorinated structures.

1.2.3.7. Miscellaneous reactions of fluoromalonates

A useful, but not yet discussed reaction of fluoromalonates is their Claisen condensation with methyl ketones to yield various polycarbonyl compounds. When dimethyl difluoromalonate is reacted with 2-acetylnaphthalene in the presence of methoxide as base the symmetrical tetraketone and the diketo-ester are both isolated in poor yield.[101]

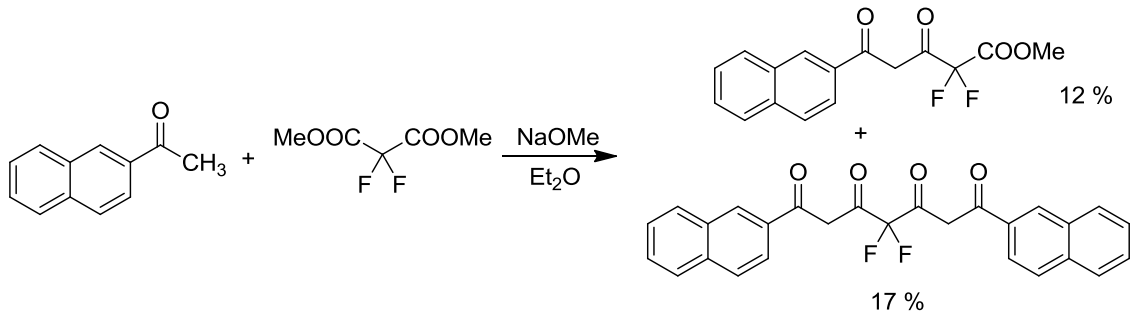


Figure 30: *Claisen condensation of difluoromalonate and 2-acetylnaphtalene.*

Another example is the synthesis of a 3-difluoromethylpyrazole system that is a key intermediate of an eye disease treatment drug family.[102]

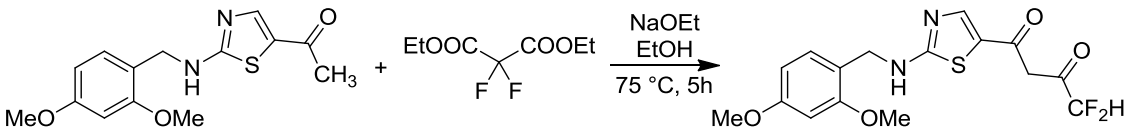


Figure 31: *Synthesis of the 1-aryl-5-difluoromethyl-2,4-diketone, precursor of a bioactive pyrazole.*[102]

Although this reaction has only this reported use, it could potentially be generalised to aryl-methyl ketones that could lead to 1-aryl-5,5-difluoro-1,3-diketones, precursors of several heterocyclic systems.

Possibly the only practical synthesis of 2-fluoro-1,3-propanediols is the reduction of substituted fluoromalonates. There are few examples where these diols were prepared and used in the synthesis of more complex structures. The reported reducing reagents were diborane in tetrahydrofuran[103] and calcium borohydride[104].

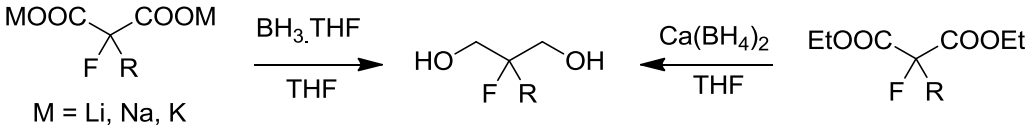


Figure 32: *Reduction of fluoromalonate derivatives to diols.*

Fluoromalonates can be reduced to 2-fluoro-3-hydroxypropanoates as well if the monoester is prepared by partial hydrolysis of the diesters.[105]

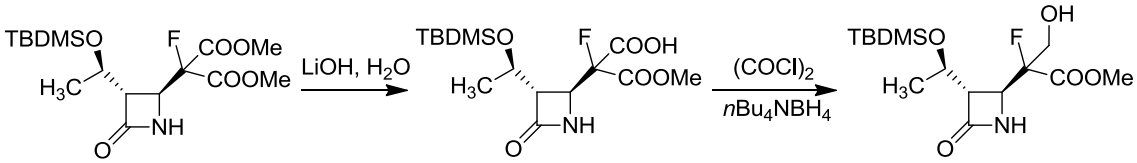


Figure 33: *Reduction of a fluoromalonate monoester.*

Although the reduction of fluoromalonates can lead to fluorinated alcohols that are otherwise very difficult to synthesise there are only few applications of this chemistry.

1.2.4. Conclusion

The role of fluorine in modern organic chemistry is unquestionable and well demonstrated by the high number of fluorine containing biologically active compounds, but the synthetic chemistry of organofluorine compounds is usually less developed than that of the non-fluorinated analogues

The chemistry of fluoromalonate esters has not been reviewed before. This area of chemistry has been reviewed comprehensively here using all accessible sources of information.

The above chapters describe a wide variety of reactions about the synthesis of fluoromalonates and their use in the synthesis of complex, often biologically active structures. Most of the basic reactions of fluoromalonates (alkylation, addition, reduction, etc.) are not particularly well documented in the literature and there are several potential uses that have never been investigated.

The goal of our research is to further develop the chemistry of dialkyl fluoromalonates especially their use in the synthesis of heterocyclic compounds that are not practically available otherwise and this will be discussed in Chapter 2.

Chapter 2: Synthesis of 3-fluorooxindole derivatives using diethyl 2-fluoromalonate

2.1. Aims

The goal of this research project is to develop new reactions of 2-fluoro-1,3-dicarbonyl compounds, especially fluoromalonates and to use the obtained multifunctional, selectively fluorinated compounds for the synthesis of novel structures.

2-Aryl-2-fluoromalonates can be obtained by fluorination of 2-arylmalonates using a range of electrophilic fluorinating reagents (Chapter 1.2.2.1.) or by palladium mediated substitution of electron rich bromoarenes with diethyl fluoromalonate[48]. As electron deficient fluoroarenes readily undergo S_NAr reactions with dialkyl malonates, we aimed at exploring the reactivity of diethyl 2-fluoromalonate with aryl electrophiles, as an alternative efficient method for preparing 2-aryl-2-fluoromalonates.

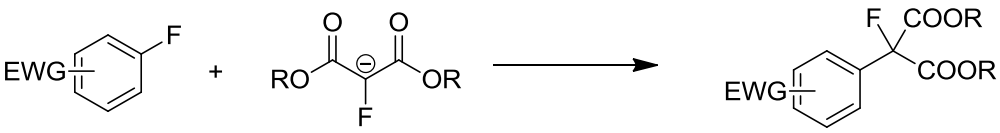


Figure 34: *Planned S_NAr reaction with fluoromalonate ion.*

Some of our target compounds were nitroaryl substituted fluoromalonates as they can potentially be reduced and undergo cyclisation to 3-fluoroindole derivatives.

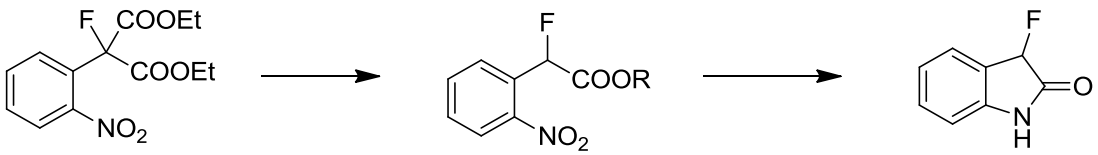


Figure 35: *Planned synthetic route to 3-fluorooxindoles.*

Our intention was to find a suitable reduction method that enables the transformation of 2-(2-nitrophenyl)-2-fluoroacetic acid derivatives to 3-fluoro-3-hydro-oxindoles, a compound class previously not reported in the literature.

2.2. Synthesis of 2-fluoro-2-(*o*-nitrophenyl)acetic acid derivatives

To compare the already existing methods for the synthesis of 2-aryl-2-fluoromalonates with our planned reaction, a model compound had to be chosen. The 2-nitrophenyl derivative was identified as an ideal compound as the non-fluorinated analogue has been prepared previously[106] and it is also a multifunctional scaffold for the synthesis of various compounds[107].

2.2.1. Two step synthesis of diethyl 2-fluoro-2-(2-nitrophenyl)malonate

The first step was the reproduction of a previously reported procedure[106] when 1-chloro-2-nitrobenzene was reacted with diethyl malonate sodium salt to give the desired diethyl 2-(2-nitrophenyl malonate) via nucleophilic aromatic substitution.

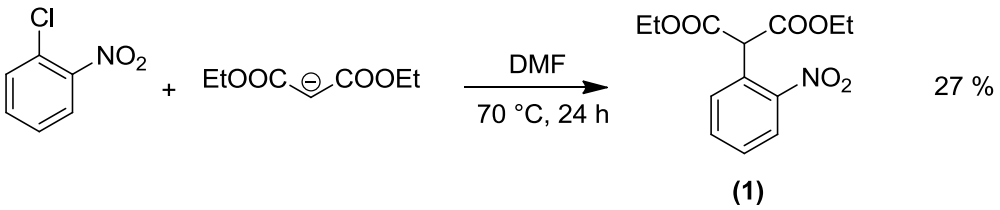
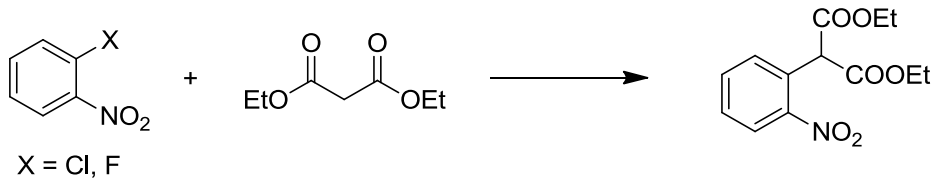
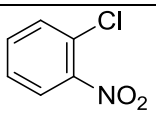
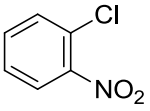
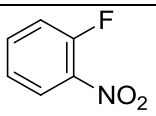
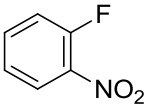
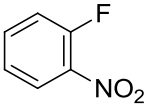


Figure 36: *Synthesis of malonate (1).*

Under the literature reaction conditions the desired malonate **(1)** was obtained in a disappointing 27 % yield. Further investigation revealed that with one equivalent of malonate ester approximately 50 % conversion can be achieved. This may be explained by the difference of pKa-s of diethyl malonate and the product malonate that has a strong electron withdrawing substituent in that position. If malonate **(1)** is in equilibrium with the enolate of diethyl malonate, it can prevent it from further reaction. With two equivalents of diethyl malonate full conversion was not achieved even after heating for 48 hours at 80 °C. The final modification was to use the more reactive 1-fluoro-2-nitrobenzene as electrophile for trapping the malonate anion. The results of this optimisation are summarised in Table 19.

Table 19: *Optimisation of the synthesis of malonate* **(1)**.



1-Halo-2-nitrobenzene	Equivalent malonate	Reaction time (h)	Yield (%)
	1.2	24	27
	2.0	48	58
	1.0	19	46
	2.0	18	89
	2.1	18	96

The table shows that this reaction was best carried out with an excess (2.1 equivalent) of diethyl malonate sodium enolate with 1-fluoro-2-nitrobenzene as starting material. The purification of the product was conveniently achieved by Kugelrohr vacuum distillation that removes the more volatile diethyl malonate and the traces of unreacted 1-fluoro-2-nitrobenzene. The reaction was scaled up to 30 g scale without experiencing difficulties.

Dialkyl 2-arylmalonates can conveniently be fluorinated using several different electrophilic fluorinating reagents such as Selectfluor, NFSI or N-fluoro-2,4,6-trimethylpyridinium triflate. Because of its availability Selectfluor was chosen for the fluorination of malonate **(1).** The synthesis was conducted as previously reported by Banks[108]: the malonate was deprotonated with NaH and added to the cooled solution of the fluorinating reagent.

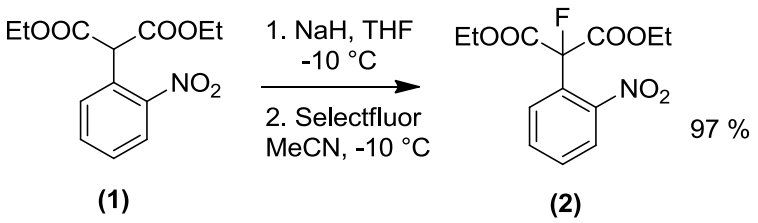


Figure 37*: Fluorination of malonate* **(1)** *with Selectfluor.*

The reaction proceeded as expected and produced the desired fluoromalonate in excellent yield and purity as after workup no further purification was necessary. The structure of the product was confirmed by ^{1}H, ^{19}F and ^{13}C NMR as well as X-ray crystallography.

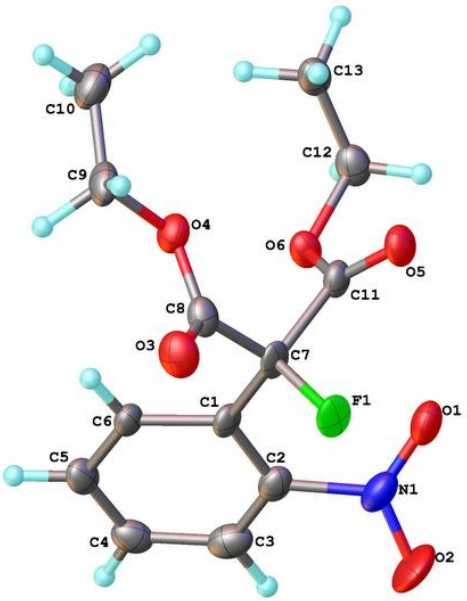


Figure 38: *X-ray structure of diethyl 2-fluoro-2-(2-nitrophenyl)malonate* **(1)**.

Elemental fluorine can be used for the fluorination of malonate esters and this method was examined as well. Chambers and co-workers reported[23] the fluorination of diethyl 2-phenylmalonate with F_2 and their method was applied to **(1)**. In this reaction **(1)** was deprotonated with NaH in acetonitrile and 10 % F_2 in N_2 was introduced at 15 ml /min rate.

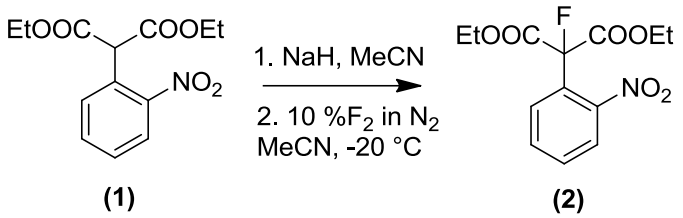


Figure 39: *Fluorination of **(1)** with F_2.*

Although the conversion of **(1)** was good (66 %) and competing aromatic fluorination was not detected, this reaction was not further developed. If the synthesis of **(2)** should be scaled up, this reaction may be worth re-examining possibly using continuous fluorination techniques.

Using this two-step synthesis, diethyl 2-fluoro-2-(2-nitrophenyl)malonate can be synthesised in excellent yield, but the reaction is not economic mainly due to the fluorinating reagent. If atom economy (one of the twelve principles of green chemistry[109]) is considered, the excess reagents make this reaction less desirable. With a model 2-fluoro-2-arylmalonate synthesised, we turned our attention to develop the use of diethyl 2-fluoromalonate for the synthesis of these systems.

2.2.2. S_NAr reaction of diethyl fluoromalonate

Arylation of diethyl 2-fluoromalonate is a potential replacement of the above described two-step process, but it has only been reported for reactions of electron rich aryl bromides with palladium catalysis[48]. The above described S_NAr reaction of 1-fluoro-2-nitrobenzene was attempted with diethyl 2-fluoromalonate, to simplify the synthesis of **(2)** and was followed by ^{19}F NMR spectroscopy.

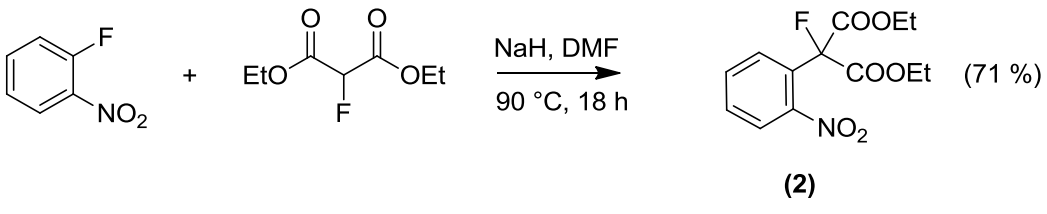


Figure 40: *One step synthesis of* **(2)** *from diethyl 2-fluoromalonate.*

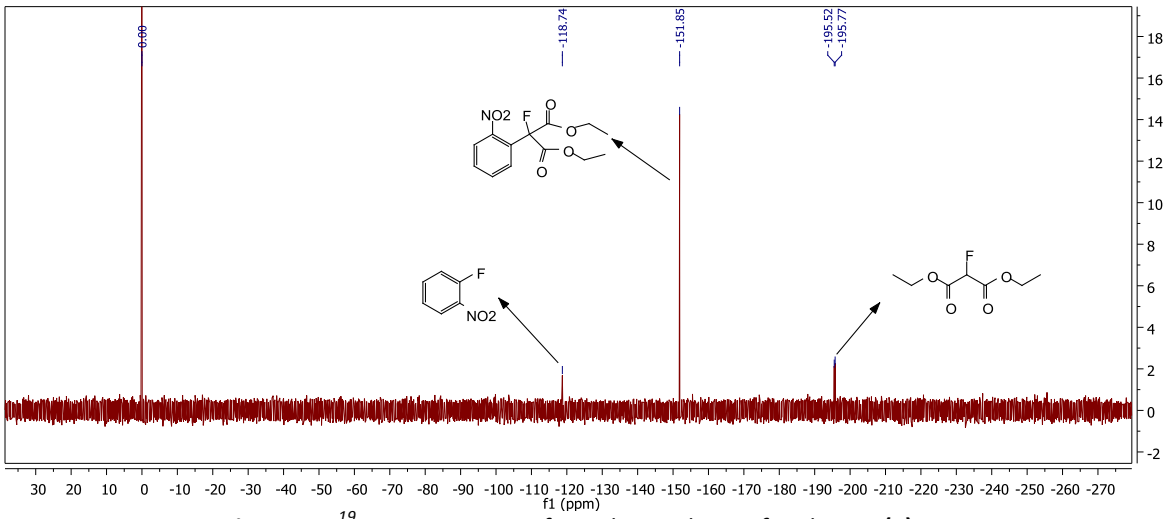
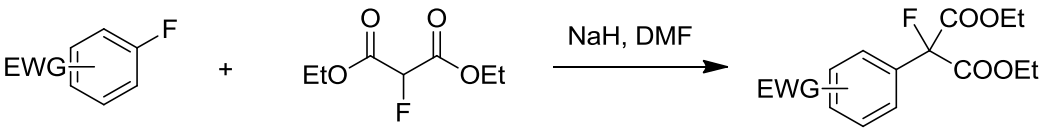


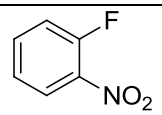
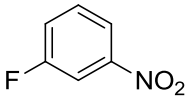
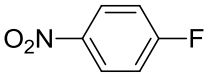
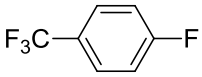
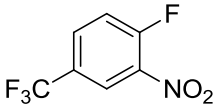
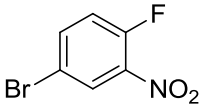
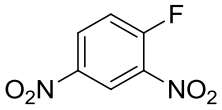
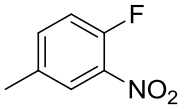
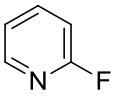
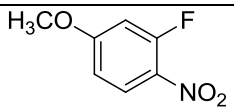
Figure 41: *^{19}F NMR spectrum from the synthesis of malonate* **(2)**.

The singlet around -150 ppm is the characteristic peak of the 2-aryl-2-fluoromalonate is distinct from the starting fluorobenzene (singlet at -119 ppm) and the fluoromalonate (doublet at -195 ppm, can also be detected as the enolate at -190 ppm). After workup and Kugelrohr distillation, **(2)** was obtained in good yield (71 %) which is lower than that of the two-step process, but **(2)** is more volatile than the non-fluorinated compound and some of it was lost during the distillation.

To investigate the scope of this reaction, several electron deficient fluoroarenes were reacted with diethyl fluoromalonate under similar conditions. The following table summarises the ^{19}F NMR based conversions, when clean reaction was observed they were used in the next step without any purification.

Table 20: *S_NAr reaction of fluoromalonate with electron deficient fluoroarenes.*



Ar-F	Conditions	Conversion	Ar-F	Conditions	Conversion
	80 °C, 1 h	100 %		120 °C, 4 h	0 %
	80 °C, 1 h	90 %		100 °C, 24 h	0 %
	80 °C, 1 h	100 %		80 °C, 1 h	100 %
	80 °C, 1 h	100 %		80 °C, 1 h	75 %
	120 °C, 4 h	0 %		80 °C, 1 h	100 %
	80 °C, 10 h	100 %			

These results suggest, that the presence of a nitro group *ortho* or *para* to the fluorine leaving group is necessary to achieve any conversion of the starting fluoroarene, pyridine or CF_3 group alone are not sufficiently activating. There were cases when even this condition was not enough to reach complete conversion and side reactions occurred.

When an *ortho* nitro group was present in the fluoroarene, complete conversion was observed after a short reaction time. In the case of 3-fluoro-4-nitroanisole, where a strong electron donating substituent is present, the reaction proceeds more slowly, but full conversion can be achieved.

Para-fluoronitrobenzene reacted with diethyl fluoromalonate to give a complex mixture of unidentified porducts. ^{19}F NMR shows 3 singlets in the region where aryl-fluoromalonates can be expected (1:2:4 ratio) and also two, less intensive doublets as well as unreacted starting materials (fluorobenzene and fluoromalonate as well).

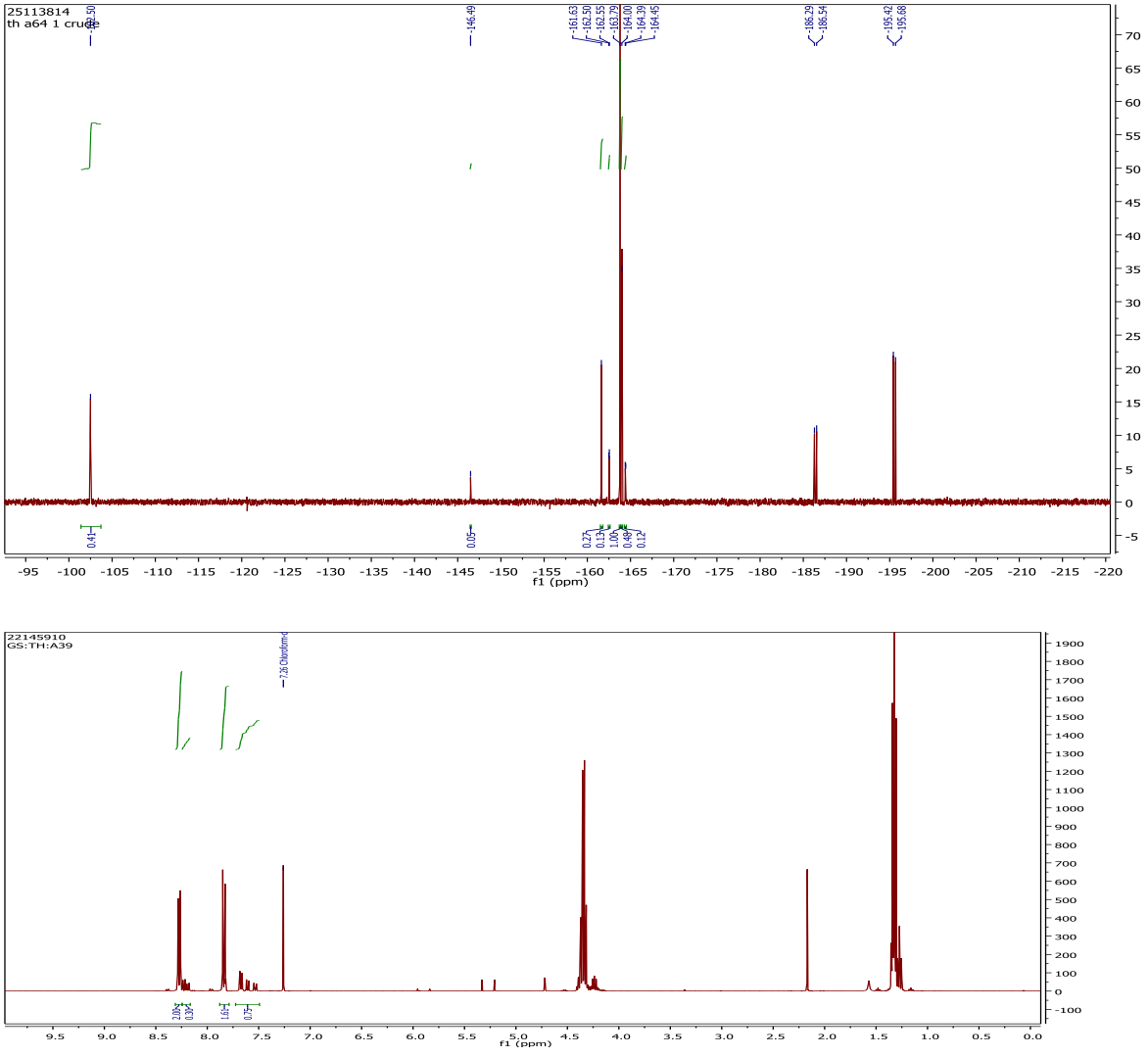


Figure 42: *^{19}F NMR spectrum of the product mixture from the reaction of 4-fluoronitrobenzene with diethyl fluoromalonate (top) and ^{1}H NMR spectrum of the isolated main component (bottom).*

Unfortunately no pure products were isolated from this reaction as the two major products co-eluted with all tested solvent systems on TLC and column chromatography only resulted in the separation these two compounds from the other side products. A possible explanation of the poor selectivity of this reaction is a competing benzyne intermediate which would result in the formation of both isomers (1,3 and 1,4 substituted derivatives) of the product and potentially other side products as well.

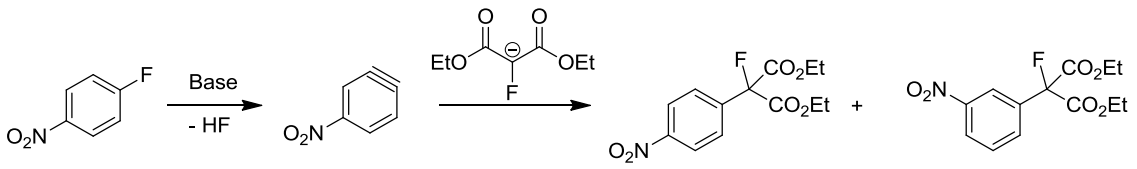


Figure 43: *Possible side reaction of the reaction of 4-fluoronitrobenzene with diethyl fluoromalonate.*

3-Fluoro-4-nitrotoluene is another example where complete conversion was not achieved. In this case several experiments were run with different amounts of NaH and diethyl fluoromalonate, but complete conversion did not occur under any experimental conditions. It is possible that the deprotonation of the methyl group is in equilibrium with the fluoromalonate enolate.

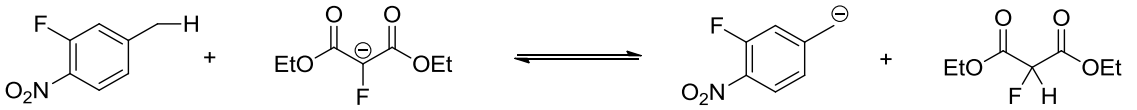


Figure 44: *Possible equilibrium between fluoromalonate and 3-fluoro-4-nitrobenzyl carbanions.*

The *para*-nitrobenzyl anion is possibly more stable than the fluoromalonate anion that is why even long reaction times did not lead to complete conversion.

In conclusion, S_NAr reaction of diethyl fluoromalonate with electron deficient fluoroarenes such as 2-fluoronitrobenzenes is possible and was demonstrated on several examples for the first time.

2.2.3. Hydrolysis and decarboxylation of 2-aryl-2-fluoromalonates

One potential use of fluoromalonates is the synthesis of α-fluorocarboxylic acids that would be more complicated to obtain otherwise. 2-Aryl-2-fluoroacetic acids are usually synthesised either from their enolates with an electrophilic fluorinating reagent such as Selectfluor[110] or from the corresponding mandelic acids using deoxofluorinating reagents such as DAST[111]. The next step of our research plan was the hydrolysis and decarboxylation of **(2)** to give 2-fluoro-2-(2-nitrophenyl)acetic acid **(3)** in a scalable, simple process.

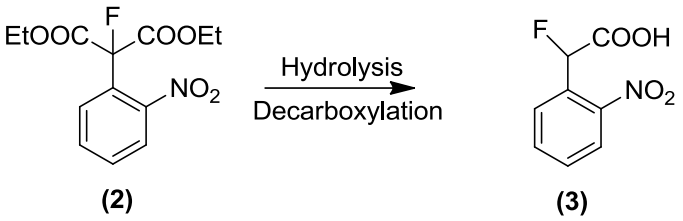


Figure 45: *Synthesis of* **(3)** *from fluoromalonate* **(2).**

Previously 2-fluoro-2-phenylacetic acid has been prepared from the corresponding malonate using acid hydrolysis in good yield[22], therefore, our first attempt was the acid hydrolysis of **(2)**. The malonate was dissolved in a mixture of acetic acid, water and concentrated sulfuric acid and heated to 100 °C for 18 hours. This method produced **(3)** in 71 % yield after purification, but it was not possible to reproduce this yield, the average yield for the other runs was approximately 50 %. Basic hydrolysis was conducted using KOH dissolved in anhydrous ethanol which after isolation of the potassium salt, acidification and extraction produced **(3)** in 81 % yield which was reproduced in other runs and required significantly shorter reaction times than the acid hydrolysis.

The crude reaction mixture was examined by ^{19}F NMR spectroscopy to show that it is a 7 : 1 mixture of potassium 2-fluoro-2-(2-nitrophenyl)acetate and potassium 2-fluoro-2-(2-nitrophenyl)malonate. After acidification and extraction from aqueous solution, only pure **(3)** was isolated showing that the decarboxylation was completed in acidic solution.

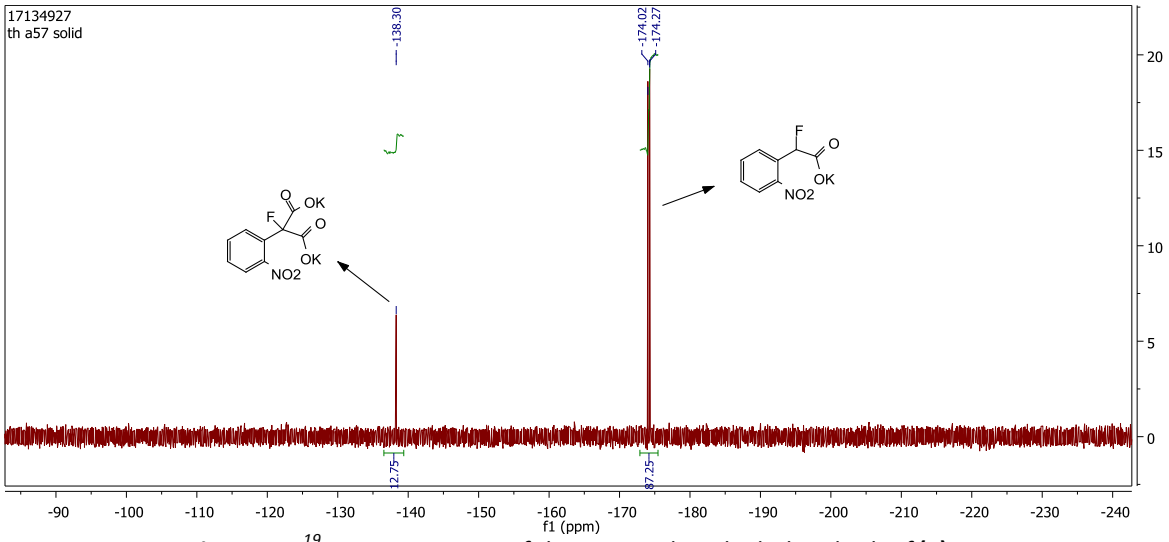
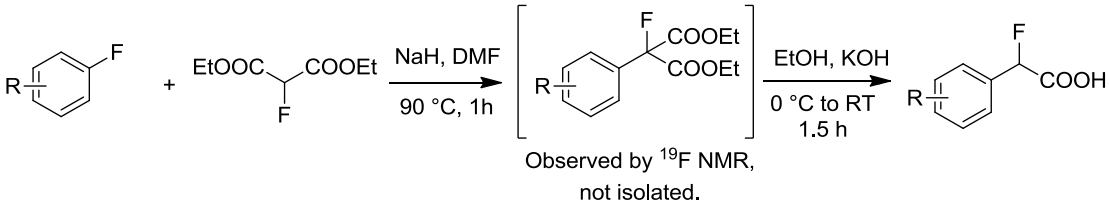
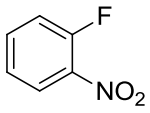
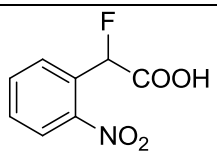
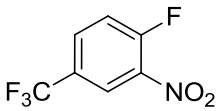
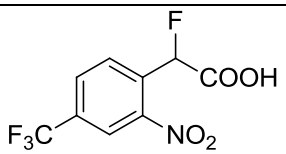
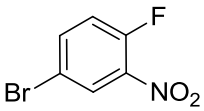
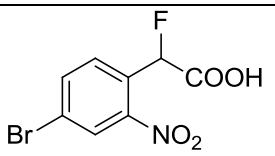
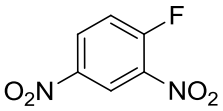
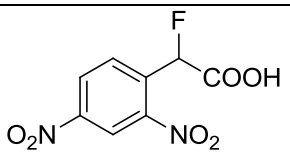
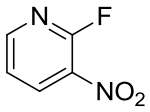
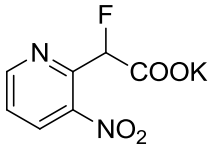
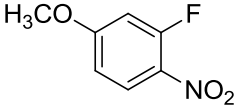
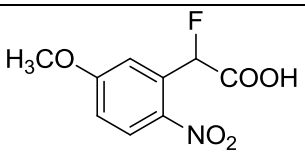


Figure 46: *^{19}F NMR spectrum of the intermediate hydrolysed salt of* **(2)**.

The hydrolysis of **(2)** is possible without the purification of the crude fluoromalonate product without affecting the overall yield and purity of the reaction. Those 2-aryl-2-fluoromalonates that were obtained with complete conversion of the starting fluoroarene (Table 21) were converted to the corresponding 2-aryl-2-fluoroacetic acids.

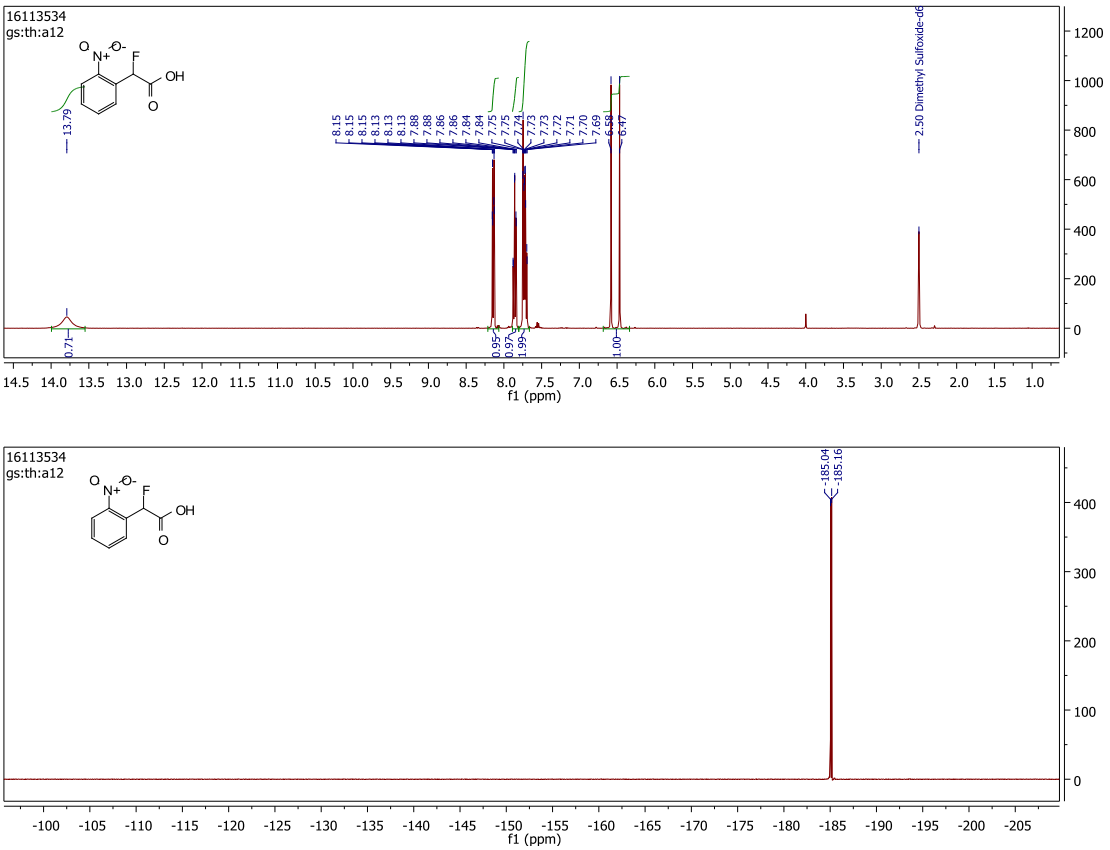
Table 21: *Synthesis of 2-aryl-2-fluoroacetic acids.*



Fluoroarene	Product	Yield (%)
		62
		77
		83
		56
		86
		60

The base hydrolysis of the 2,4-dinitro derivative did not result in a pure product and it was not possible to obtain pure acid even after multiple recrystallizations. Therefore, acid hydrolysis was tried and this method delivered the desired acid in good purity and acceptable yield. The pyridine derivative was isolated and characterised as the potassium salt because when an attempt was made to neutralise the compound, nothing could be recovered from the aqueous phase.

In the ^{1}H NMR spectrum the most characteristic peak of these compounds, for example 2-fluoro-2-(2-nitrophenyl)acetic acid, is a doublet with 50 Hz H-F coupling constant at 6.5 ppm which corresponds to the benzylic hydrogen of the CHF group. This group also shows a doublet with the same coupling constant in the ^{19}F NMR spectrum at -184.5 ppm. The same group also shows a doublet in the ^{13}C NMR spectrum at 86.6 ppm with a large 180 Hz coupling constant.



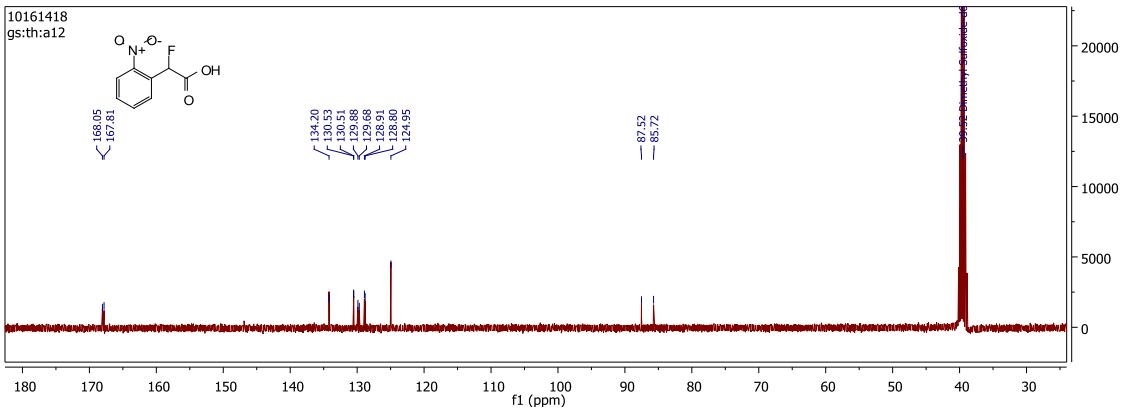


Figure 47: *^{1}H, ^{19}F and ^{13}C NMR spectra of 2-fluoro-2-(2-nitrophenyl)acetic acid.*

Overall, this two-step method is a practical way to prepare 2-fluoro-2-(2-nitrophenyl)acetic acids and this class of compounds have not been synthesised before. Several reactions were repeated on 5 grams scale without experiencing any difficulty or change in yield and purity.

An attempt was made to extend this reaction to ethyl 2-fluoroacetoacetate, but even after 24 hours of heating only low conversion (5 %) of the starting fluoroarene was observed without any desired product.

2.3. Synthesis of 3-fluorooxindoles

Fluorinated heterocycles are important compounds in drug discovery, but their efficient and scalable synthesis is often complicated. 3-Fluorooxindoles are an interesting class of fluoroheterocycles and this is due to a potential drug candidate, MaxiPost™ (BMS-204352) that was developed for post-stroke neuroprotection.[112]

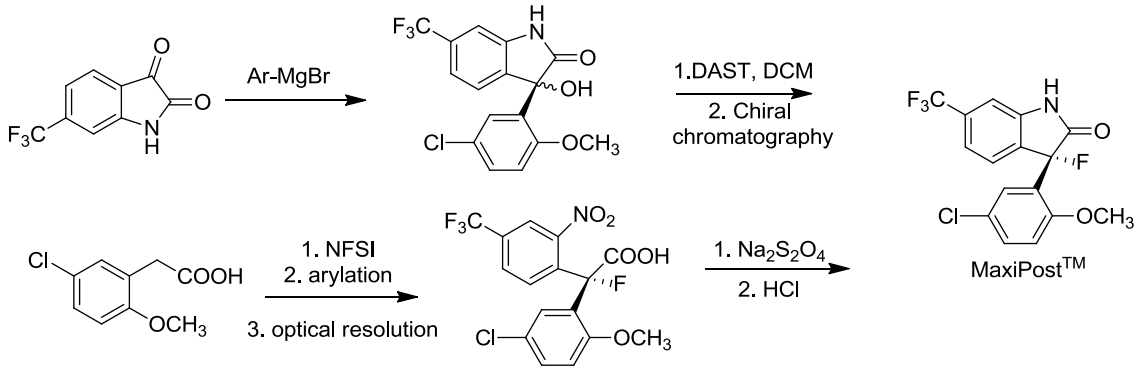


Figure 48: *Synthetic routes to MaxiPost™.*[112]

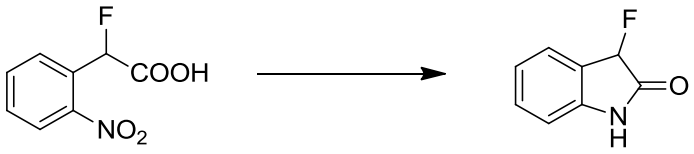
The synthesis of 3-fluoro- and 3,3-difluorooxindoles is generally carried out using deoxofluorinating reagents (DAST, Deoxofluor®, XtalFluor-E®, Fluolead™, etc.) as presented in the synthesis of MaxiPost™ although not many derivatives have been reported. Interestingly, the synthesis of 3-fluoro-3-hydrooxindoles have not been reported to date.

2.3.1. Testing of reduction methods

The first reduction that was attempted was the reduction of 2-fluoro-2-(2-nitrophenyl)acetic acid with $Na_2S_2O_4$ as reported with MaxiPost™.[112] In this case complete reduction was observed by TLC, but it was impossible to isolate the produced amino acid intermediate from the aqueous reaction mixture.

The problems associated with aqueous reductions were overcome by using non-aqueous reducing methods. The synthesis of non-fluorinated oxindole was reported using several transition metal catalysed hydrogenation reactions and of the reported catalysts Pd/C[113] was tried first.

Table 22: *Attempted reductive cyclisations of* **(3)**.



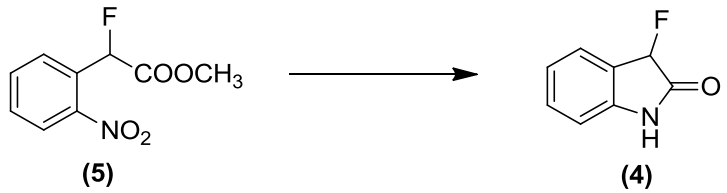
(3) **(4)**

Reducing system	Conditions	Result
$Na_2S_2O_4$	THF, H_2O, $NaHCO_3$, rt, 1h	Not possible to isolate
5% Pd/C, $N_2H_4.H_2O$	EtOH, 60 °C, 30 min	No fluorinated material detected
Raney Ni, $N_2H_4.H_2O$	EtOH, 60 °C, 30 min	No fluorinated material detected
5 % Pd/C, H_2 (40 psi)	AcOH, rt, 1 h	Trace amount isolated (< I %)
5 % Pt/C, H_2 (40 psi)	AcOH, rt, 1 h	No fluorinated material detected

All attempts to reduce and cyclise **(3)** to form oxindole **(4)** failed: no fluorinated material was detected by ^{19}F NMR due to defluorination of the starting material. It was decided that the starting acid had to be transformed to its ester to enable the use of

aqueous reduction methodologies. Methyl ester **(5)** was obtained in good yield after refluxing acid **(3)** in HCl containing methanol followed by vacuum distillation. Several reduction methods were tested with the methyl ester to obtain the desired 3-fluorooxindole **(4)**.

Table 23: *Reductive cyclisations of* **(5)**.



(5) **(4)**

Reducing system	Conditions	Result
Fe, AcOH	80 °C, 2 h	2 % product isolated
Fe, NH_4Cl	H_2O, 80 °C, 3 h	No fluorinated material detected
5% Pd/C,$HCOONH_4$	MeOH, 70 °C, 2 h	No fluorinated material detected
$Na_2S_2O_4$	1.THF, H_2O, $NaHCO_3$, rt, 1h 2. EtOAc, HCl, 70 °C, 3 h	32 % yield of **(4)**

In the case of methyl ester **(5)**, defluorination was also a serious problem. All metal based reduction methods gave the defluorinated amino ester as the major product. The originally tested $Na_2S_2O_4$ reduction conditions provided fluorooxindole **(4)** in acceptable yield. The product was isolated using column chromatography and characterised using ^{1}H, ^{19}F and ^{13}C NMR as well as MS and IR.

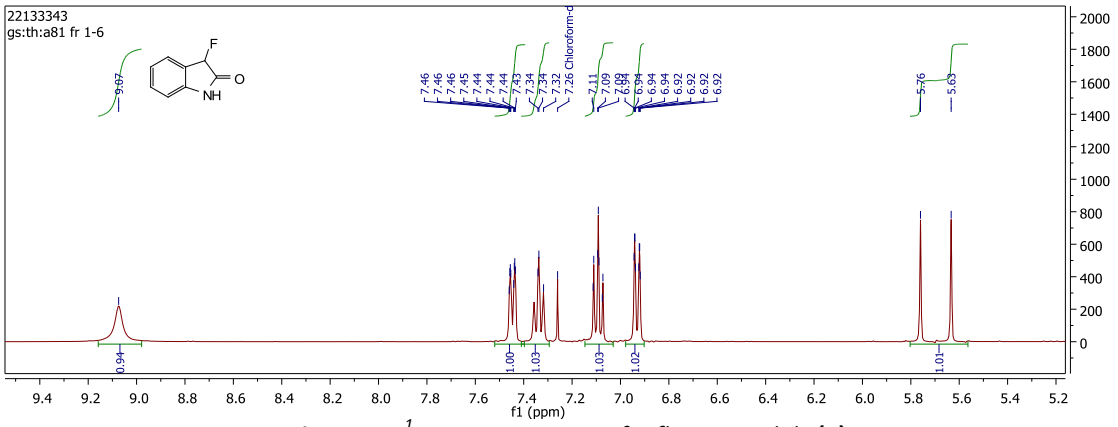


Figure 49: *^{1}H NMR Spectrum of 3-fluorooxindole* **(4)**.

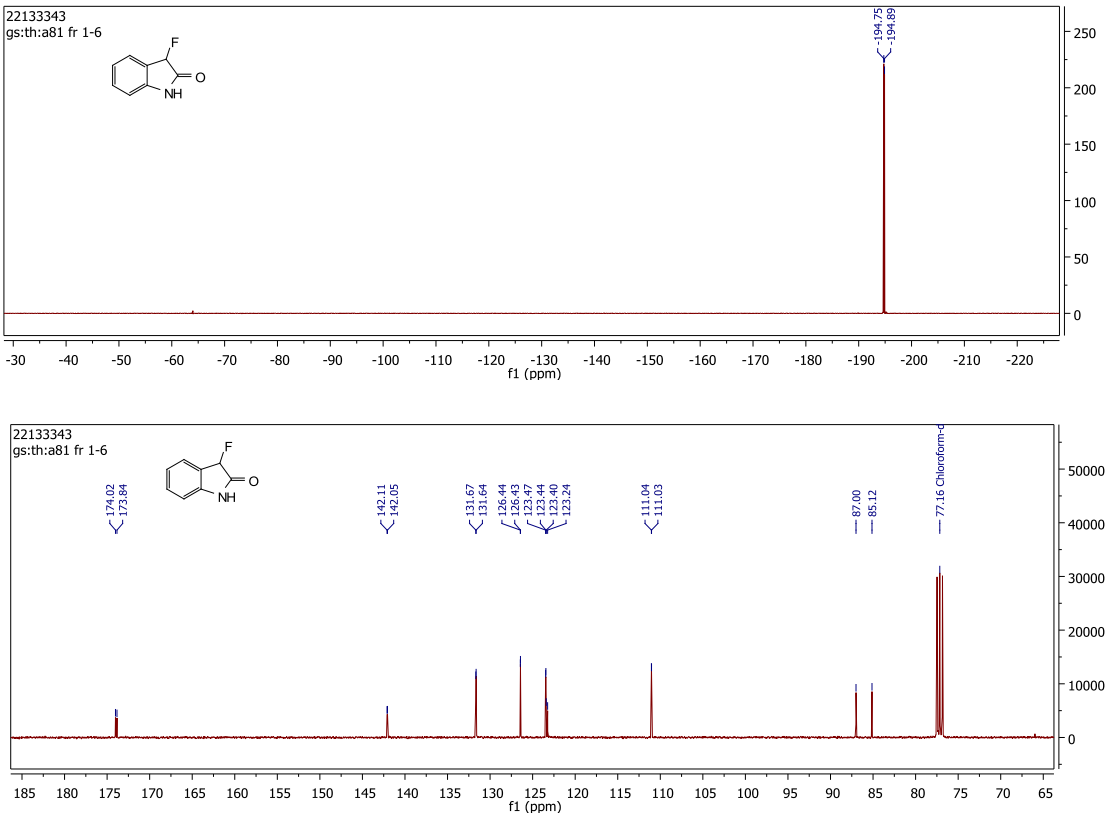


Figure 50: *^{19}F and ^{13}C NMR spectra of 3-fluorooxindole* **(4)**.

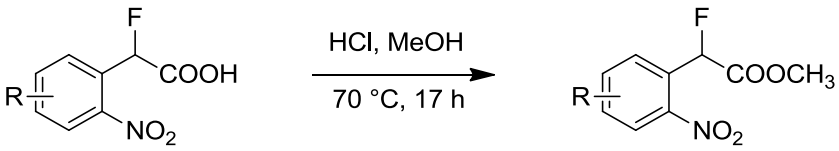
Compared to aryl-fluoroacetic ester **(5)** the characteristic doublet is 0.9 ppm upfield at 5.7 ppm ($^{2}J_{HF}$ 51 Hz) in the ^{1}H spectrum and also a broad NH singlet is detected at 9.0 ppm. The shift of the doublet (-194.8 ppm) in the ^{19}F NMR spectrum also shows 10 ppm difference from the starting ester. In the ^{13}C spectrum the biggest change in chemical shift belongs to the carbonyl group (5 ppm) but the most characteristic peak is still the doublet of the CHF group at 85.9 ppm.

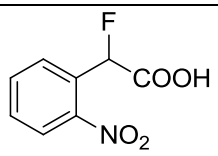
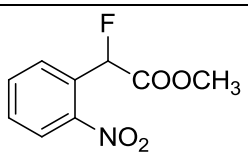
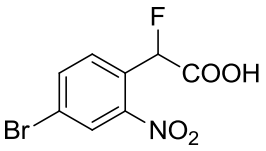
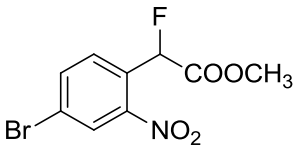
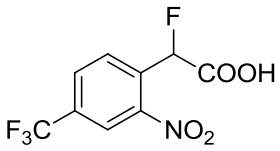
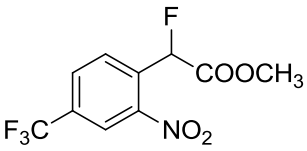
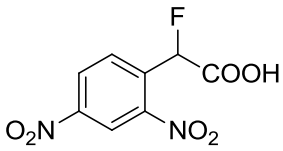
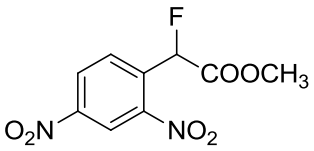
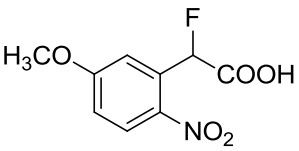
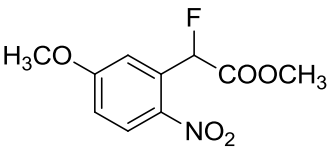
After finding an acceptable method, several other 3-fluorooxindoles were prepared without trying to optimise the conditions.

2.3.2. Synthesis of 3-fluorooxindoles

After finding a suitable method for the reduction and cyclisation of methyl 2-fluoro-2-(2-nitrophenyl)acetate, several other derivatives were subjected to the same process. Firstly the acids had to be transformed to their methyl esters using HCl in methanol.

Table 24: *Esterification of 2-fluoro-(2-nitrophenyl)acetic acids.*



2-Aryl-2-fluoroacetic acid	Methyl ester	Yield (%)
		88
		97
		98
		65
		98

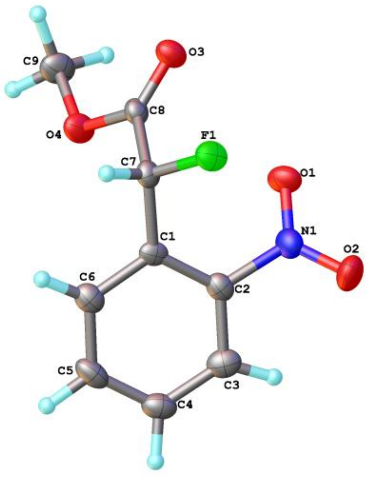
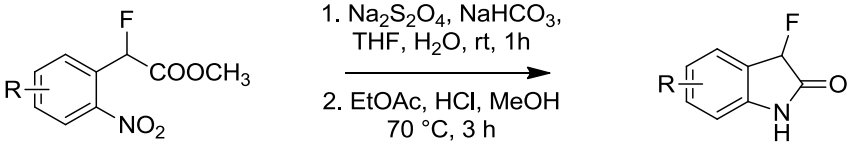


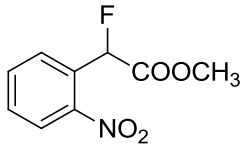
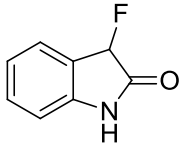
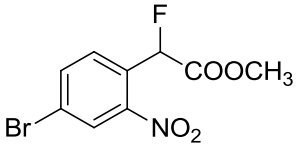
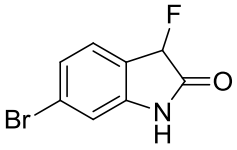
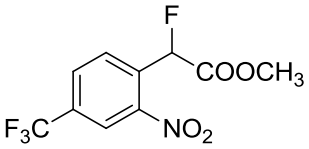
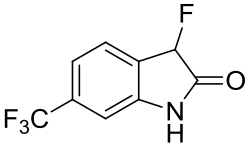
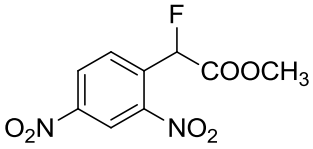
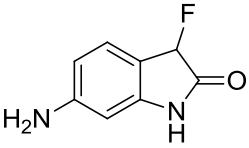
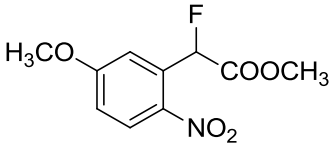
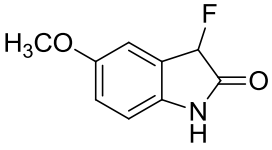
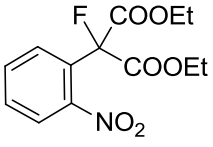
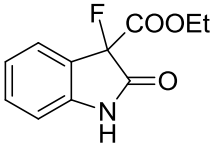
Figure 51: *X-ray structure of methyl 2-fluoro-2-(2-nitrophenyl)acetate.*

This esterification procedure gave the desired esters in excellent yield and good purity. The only exception was the 2,4-dinitrophenyl derivative where the lower yield was due to the impure starting acid and the necessary use of column chromatography to purify the ester. Methyl 2-fluoro-2-(2-nitrophenyl)acetate was further characterised by X-ray crystallography (Figure 51).

These esters were subjected to the reductive cyclisation reaction which was described above. Diethyl 2-fluoro-2-(2-nitrophenyl)malonate was also subjected to this reaction.

Table 25: *Synthesis of 3-fluorooxindole derivatives.*



Starting ester	Product	Yield (%)
		32
		57
		82
		0
		30
		37

There is no general trend why the yields vary between 0 and 82 %, but the ^{19}F NMR examination of the 0 % reaction showed a very strong F^- peak (at -124 ppm). In that case instead of the usual 3 equivalents of $Na_2S_2O_4$, 6 equivalents were used to reduce both nitro groups. As the reduction mechanism is obscure only speculative explanations can be made. In the literature reaction mechanisms for different hydrosulfite reductions usually propose radical intermediates.[114]

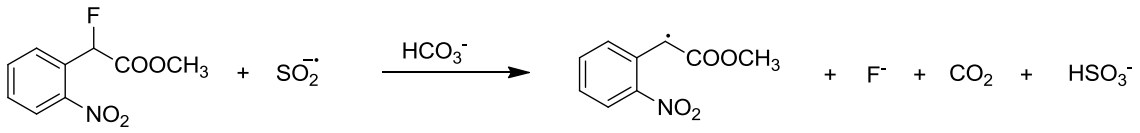


Figure 52: *Possible mechanism of the defluorination reaction.*

The reaction mechanism was not investigated in detail, but it is interesting to note that non-fluorinated oxindole has not been observed in any of the cases. The above scheme describes a possible radical defluorination pathway. The benzyl radical can recombine with another benzyl radical or extract a proton from the solvent with an electron from the reducing agent (in this case defluorinated product would be observed).

Overall it has been demonstrated that 3-fluoro-oxindoles can be synthesised in varying yield from 2-fluoro-2-(2-nitrophenyl)acetic esters. This is the first reported synthesis of this compound class and the direct comparison of their chemistry with the non-fluorinated analogues is now potentially possible.

2.4. Synthesis of benzyl-fluoride systems

During the synthesis of the already mentioned intermediates the formation of benzyl fluorides was observed in two different cases.

Firstly, when toluene was evaporated from crude 2-fluoro-2-(2,4-dinitrophenyl)acetic acid to remove residual water, a significant change in appearance was observed (dark solid instead of the starting brown oil). ^{19}F NMR analysis showed the complete conversion of the starting fluoroacetic acid (doublet at -190.4 ppm) to the benzyl fluoride (triplet at -219.9 ppm).

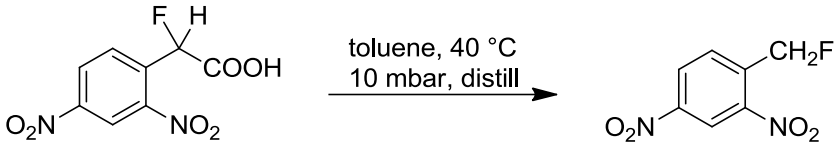


Figure 53: *Unexpected synthesis of 2,4-dinitrobenzyl fluoride.*

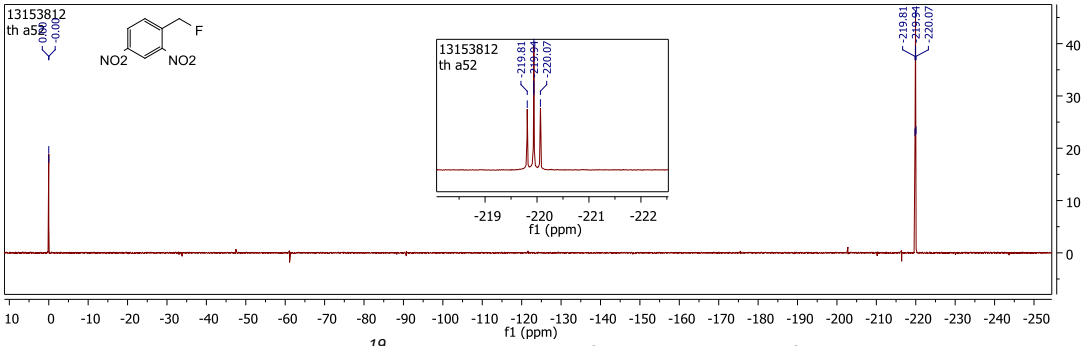


Figure 54: *^{19}F NMR spectrum of 2,4-dinitrobenzyl fluoride.*

After purification by column chromatography pure 2,4-dinitrobenzyl fluoride was obtained in 61 % yield (from 2,4-dinitrofluorobenzene). This second decarboxylation was not observed with 2-fluoro-2-(2-nitrophenyl)acetic acid even when it was refluxed in toluene. Generally decarboxylations are easier with strong electron withdrawing groups as observed in this case. The use of fluoromalonates as aromatic monofluoromethyl group precursors has not been reported previously.

Another reaction where fluoromethyl group formation was observed was when the esterification of potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate was attempted with HCl in methanol. During the overnight heating the reaction mixture was heterogenous and the release of a gas was observed.

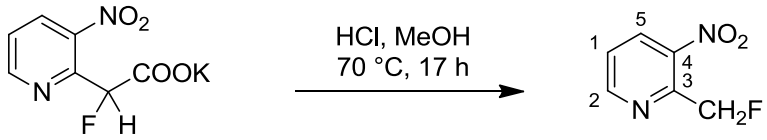


Figure 55: *Synthesis of 2-fluoromethyl-3-nitropyridine.*

^{19}F NMR analysis of the crude red solid confirmed the complete conversion of the starting material (doublet at -180.3 ppm) to the fluoromethyl pyridine (triplet at -221.8 ppm).

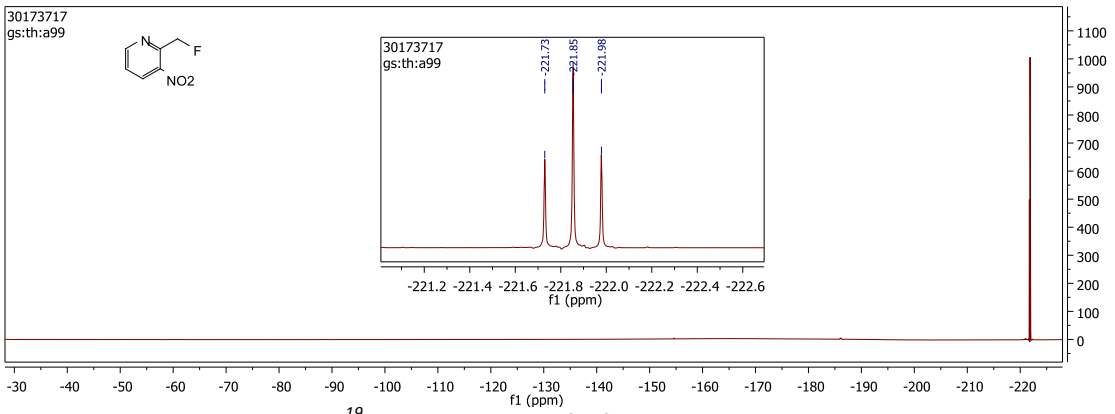


Figure 56: *^{19}F NMR spectrum of 2-fluoromethyl-3-nitropyridine.*

After purification of the crude material by column chromatography, 2-fluoromethyl-3-nitropyridine was isolated in 68 % yield. The product produced large crystals when crystallised and X-ray analysis also confirmed its structure.

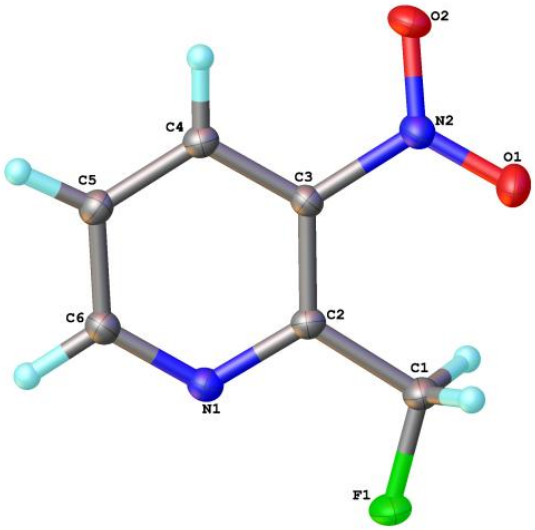


Figure 57: *X-ray structure of 2-fluoromethyl-3-nitropyridine.*

In this chapter the use of diethyl fluoromalonate as an aromatic fluoromethyl group precursor was demonstrated. This reaction is possibly limited to electron deficient systems, but is potentially safer than the existing fluoromethyl group forming reactions.

2.5. Conclusions

The S_NAr reaction of diethyl fluoromalonate and fluoroarenes was demonstrated and reported for the first time. The scope of the reaction was investigated and several 1-fluoro-2-nitrobenzenes were found to be excellent substrates for this reaction.

A two-step simple method was introduced to synthesise 2-fluoro-2-(2-nitroaryl)acetic acids with one purification step. The reactions provide these products in good yield without using any expensive fluorinating reagents.

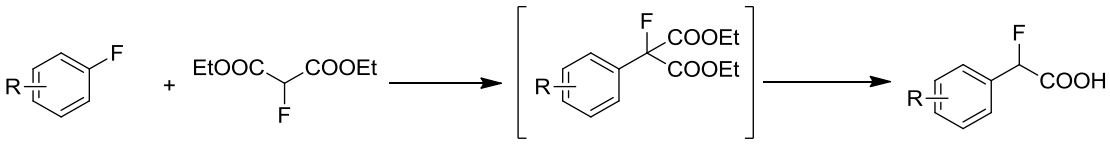


Figure 58: *Two step synthesis of 2-fluoro-2-arylacetic acids.*

The reduction of 2-fluoro-2-(2-nitrophenyl)acetic acid to 3-fluorooxindole was investigated in detail and a simple method was found to provide the desired product in acceptable yield.

2-Fluoro-2-(2-nitroaryl)acetic acids were esterified in excellent yield and were used subsequently in the reductive cyclisation step. This way previously not reported 3-fluoro-3-hydro oxindoles were obtained in moderate to good yield.

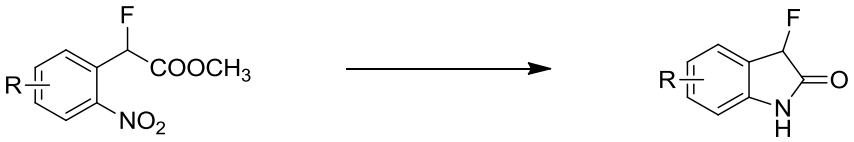


Figure 59: *Reductive cyclisation of 2-fluoro-2-(2-nitroaryl)acetic esters.*

Previously unknown monofluoromethylation with diethyl fluoromalonate was also discovered. This reaction in the observed cases provides the monofluoromethylated products in good yield.

The structures were confirmed by all available analytical techniques. ^{19}F NMR is the most useful tool for the analysis of these transformations. Some structures were confirmed by single crystal X-ray crystallography as well.

2.6. Future work

The synthesised 2-fluoro-2-(2-nitroaryl)acetic acids are potential multifunctional building blocks for the synthesis of other heterocyclic systems. For example the corresponding acid chlorides might be used in Friedel-Crafts acylation followed by reduction and cyclisation to 2-aryl-3-fluoroindoles.

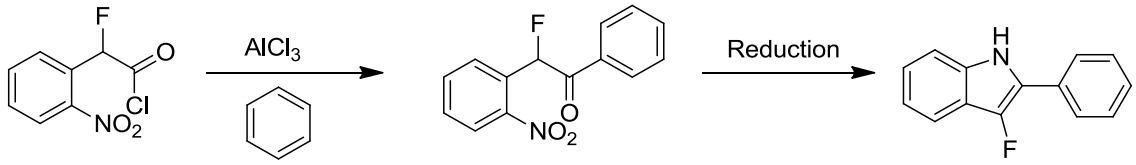


Figure 60: *Possible synthesis of 2-aryl-3-fluoroindoles.*

As this work describes the synthesis of previously unknown 3-fluoro-3-hydro oxindoles, it provides an opportunity to explore their potential chemistry. The reactions of the benzene ring, the benzylic position or the carbonyl may be affected by the fluorine substituent, therefore, the investigation of these reactions would provide useful information about the stability of benzyl fluorides.

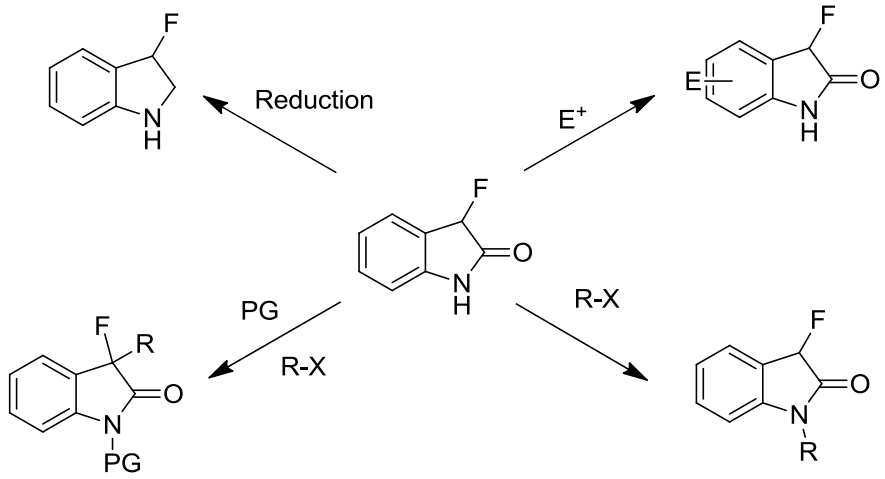


Figure 61: *Potentially interesting transformations of 3-fluorooxindole systems.*

Chapter 3: Experimental

3.1. General information

Chemicals were purchased from Fluorochem, Apollo Scientific (diethyl 2-fluoromalonate), Alfa Aesar or Sigma Aldrich and, unless otherwise stated, were used without any further purification. Dry solvents were obtained using an Innovative Technology Inc. Solvent Purification System. All column chromatography was carried out using Silicagel LC60A (40–63 micron) purchased from Fluorochem.

Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on either a Varian Mercury 400 or a Bruker 400 Ultrashield (^{1}H NMR at 400 MHz; ^{13}C NMR at 100 MHz; ^{17}F NMR at 376 MHz) spectrometer with residual solvent peaks as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz) and assignment.

GC-MS analysis was performed on a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode. Accurate mass analysis was achieved with a Xevo QtoF mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP).

Elemental analysis (C, H and N) was performed on an Exeter Analytical CE-440 Elemental Analyser.

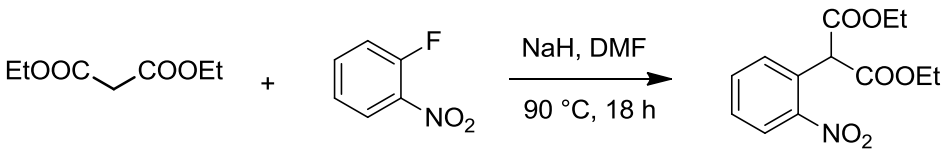
Infra-red (IR) spectra were recorded on a Perkin Elmer 1600 Series FTIR fitted with an ATR probe.

Crystallographic data was recorded with a Rigaku R-Axis SPIDER IP diffractometer equipped with a Cryostream (Oxford Cryosystems) low temperature device at 120 K.

Melting points were measured with a Gallenkamp apparatus at atmospheric pressure and are uncorrected.

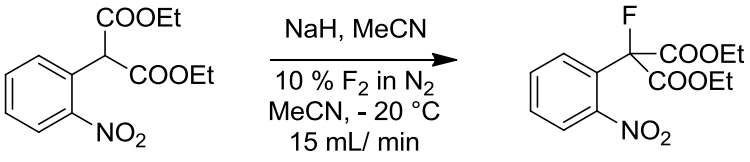
3.2. Experimental

Diethyl 2-(2-nitrophenyl)malonate



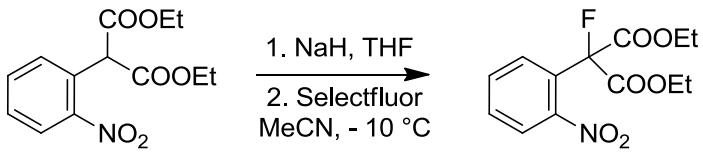
NaH (3.60 g, 90 mmol, 60 % in mineral oil) was washed free from oil with hexane (3x30 mL) and dried under vacuum in a 250 mL round bottom flask. The flask was filled with argon and NaH was suspended in dry DMF (80 mL). Diethyl malonate (12.81 g, 80 mmol) was dissolved in dry DMF (30 mL) and added dropwise to the NaH suspension with a syringe. After stirring at room temperature for 30 minutes, 1-fluoro-2-nitrobenzene (5.64 g, 40 mmol) was added in one portion followed by DMF (20 mL). The mixture was heated overnight at 90 °C (18 h, turned dark red), TLC analysis showed complete conversion of 1-fluoro-2-nitrobenzene. The mixture was poured into crushed ice (200 mL) and water (100 mL) was added. The mixture was acidified with HCl (5 ml, 37 % aq. solution) and extracted with diethyl ether (3x150 mL), the organic phase was washed with saturated aqueous $NaHCO_3$ solution (1x100 mL) and saturated brine (2x100 mL) than dried over Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure to leave a yellow oil (15.90 g). The residue was subjected to Kugelrohr distillation to remove the more volatile impurities (10 mbar, 150 °C) to leave *diethyl 2-(2-nitrophenyl)malonate* (10.06 g, 89 %) as a yellow oil. (Found: C 55.41, H 5.54, N 4.96 %. $C_{13}H_{15}NO_6$ requires: C 55.51, H 5.38, N 4.98 %); δ_H ($CDCl_3$, 400 MHz) 1.28 (6H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 4.26 (4H, q, $^3J_{HH}$ 7.2 Hz, CH_2), 5.29 (1H, s, CH), 7.49-7.54 (2H, m, Ar-H), 7.62-7.68 (1H, m, Ar-H), 8.04-8.08 (1H, m, Ar-H); δ_C ($CDCl_3$, 100 MHz) 14.12 (CH_3), 54.62 (CH_2), 62.41 (CH), 125.35 (Ar), 128.36 (Ar), 129.33 (Ar), 131.40 (Ar), 133.63 (Ar), 148.93 (C-NO_2), 167.36 (COO); m/z (EI^+) 235 (50 %, $[M\text{-}NO_2]^+$), 207 (24 %, $[M\text{-}NO_2\text{-}C_2H_4]^+$), 92 (100 %, $[M\text{-}NO_2\text{-}2xCO_2Et+2H_2]^+$). All data in agreement with previously reported[115].

Fluorination of diethyl 2-(2-nitrophenyl)-malonate with F_2



NaH (92 mg, 2.3 mmol, 60 % in mineral oil) was suspended in dry acetonitrile (5 mL) in a 25 mL FEP fluorination reactor and diethyl 2-(2-nitrophenyl)-malonate (0.56 g, 2 mmol dissolved in 5 mL acetonitrile) was added dropwise. The deep red solution was cooled to -20 °C and purged with N_2 for 15 minutes. 10 % F_2 in N_2 was introduced at 15 mL/min rate for 45 minutes (disappearance of the initial colour). After purging with nitrogen for 15 minutes, the mixture was diluted with water (40 mL), extracted with diethyl ether (3x30 mL), washed with saturated $NaHCO_3$ solution (1x20 mL) and saturated brine (1x20 mL) than dried on $MgSO_4$. The solvent was evaporated under reduced pressure to leave a yellow oil (0.55 g) that was examined by ^{19}F and ^{1}H NMR. Estimated yield (^{19}F NMR): 60 %. δ_F ($CDCl_3$, 376 MHz) - 153.04 (s, C-F); δ_H ($CDCl_3$, 400 MHz) 1.28 (3.2H, t, $^{3}J_{HH}$ 7.2 Hz, CH_3, starting material), 1.33 (6H, t, $^{3}J_{HH}$ 7.1 Hz, CH_3, product).

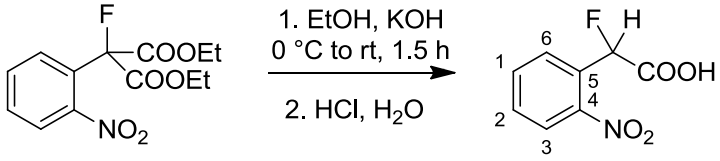
Fluorination of diethyl 2-(2-nitrophenyl)-malonate with Selectfluor



NaH (0.44 g, 11 mmol, 60 % in mineral oil) was washed free from oil with hexane (3x10 mL) and was suspended in dry THF (20 mL) under argon. Diethyl 2-(2-nitrophenyl)malonate (2.81 g, 10 mmol) in THF (30 mL) was added dropwise and stirred at room temperature for 20 minutes than cooled to -10 °C. Selectfluor (3.55 g, 10 mmol) was dissolved in dry acetonitrile (100 mL) and cooled to -10 °C. The THF solution was added to the Selectfluor solution dropwise at -10 °C and was allowed to warm to room temperature (2 hours). The solution was diluted with diethyl ether (300 mL) washed with dilute acetic acid (0.1 M, 1x100 mL), saturated $NaHCO_3$ solution (1x100 mL) and saturated brine (1x100 mL) than dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave *diethyl 2-fluoro-2-(2-nitrophenyl)malonate* (2.90 g, 97 %) as an orange solid. M.p. 48-49 °C; IR (neat, cm^{-1}) 2996, 1755, 1530, 1276, 1103; δ_H ($CDCl_3$, 400 MHz) 1.33 (6H, t, $^{3}J_{HH}$ 7.1 Hz, CH_3), 4.31 – 4.43 (4H, m, CH_2), 7.57 – 7.63 (2H, m, Ar-H), 7.66 – 7.71 (1H, m, Ar-H), 8.04 (1H, d, $^{3}J_{HH}$ 8.0 Hz, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 152.98 (s, C-F); δ_C ($CDCl_3$, 100 MHz) 14.01 (CH_3), 63.55 (CH_2), 94.05 (d, $^{1}J_{CF}$ 198.7 Hz, C-F), 125.87 (Ar), 128.60 (d, $^{3}J_{CF}$ 11.5 Hz, Ar), 128.78

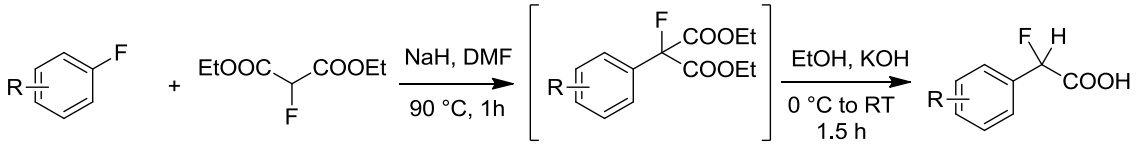
(d, $^{2}J_{CF}$ 21.6 Hz, Ar), 130.97 (Ar), 133.30 (Ar), 147.88 (Ar-NO_2) 164.68 (d, $^{2}J_{CF}$ 25.1 Hz, COO). m/z (ASAP): 226.0 (85%, $[M\text{-}CO_2Et]^+$), 134.0 (100%, $[M\text{-}2xCO_2Et\text{-}F]^+$. Crystals suitable for X-ray crystallography were obtained by crystallisation from EtOH/H_2O (1:1 mixture), crystallography data is in the digital appendix.

2-Fluoro-2-(2-nitrophenyl)acetic acid



Diethyl 2-fluoro-2-(2-nitrophenyl)malonate (3.00 g, 10 mmol) was dissolved in absolute ethanol (30 mL) and cooled to -10 °C. KOH (1.40 g, 25 mmol) was dissolved in ethanol (10 mL), added to the malonate solution dropwise and stirred for 1.5 hours. A yellow precipitate was formed; hexane (150 mL) was added, stirred for further 30 minutes and filtered. The solid was washed with hexane : ethanol (1 : 1 mixture, 15 mL) on the sinter. The solid was dissolved in water (50 mL), acidified with concentrated HCl (5 mL), extracted with DCM (4x20 mL) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure to leave *2-fluoro-2-(2-nitrophenyl)acetic acid* (1.61 g, 81 %) as a tan powder. Mp. 119-121 °C; (Found: C 48.16, H 2.98, N 6.93. $C_8H_6FNO_4$ requires: C 48.25, H 3.04, N 7.03 %); IR (neat, cm^{-1}) 3014 (br), 1732, 1530, 1340, 1204, 1063; δ_H (DMSO d_6, 400 MHz) 6.52 (1H, d, $^{2}J_{HF}$ 45.5 Hz, C-H), 7.70-7.75 (2H, m, Ar-H), 7.86 (1H, t, $^{3}J_{HH}$ 7.6 Hz, Ar-H), 8.14 (1H, d, $^{3}J_{HH}$ 7.6 Hz, Ar-H), 13.40 (1H, bs, COO-H); δ_F (DMSO d_6, 376 MHz) - 185.10 (d, $^{2}J_{HF}$ 45.5 Hz, CH-F); δ_C (DMSO d_6, 100 MHz): 86.62 (d, $^{1}J_{FC}$ 181.7 Hz, CHF), 124.96 (C3), 128.85 (d, $^{3}J_{FC}$ 11.0 Hz, C6), 129.79 (d, $^{2}J_{FC}$ 20.3 Hz, C5), 132.52 (d, $^{4}J_{FC}$ 1.6 Hz, C1), 134.20 (d, $^{5}J_{FC}$ 1.1 Hz, C2), 146.91 (C4), 169.94 (d, $^{2}J_{FC}$ 24.2 Hz, COO); m/z (ESI): 154 (100%, $[M\text{-}COOH]^+$, 104 (23%, $[M\text{-}COOH\text{-}NO_2]^+$. Synthesis has been reported but without any characterisation.[110]

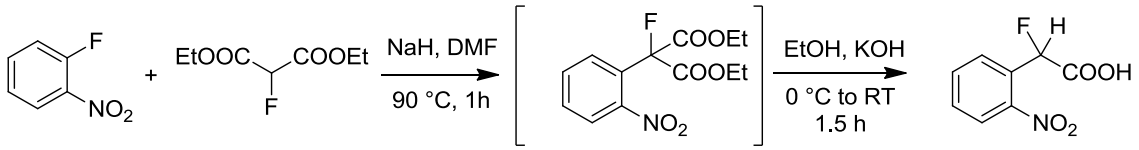
Synthesis of 2-aryl-2-fluoroacetic acids: general procedure.



NaH (0.32 g, 8.0 mmol, 60 % in mineral oil) was washed with hexane (3x10 mL) to remove the oil and was suspended in dry DMF (10 mL). Diethyl fluoromalonate (1.07 g, 6.0 mmol) was dissolved in DMF (5 mL), added dropwise to the NaH suspension and stirred at room temperature for 20 minutes. Fluoroarene (5.0 mmol) in dry DMF (10 mL) was added and the mixture was heated to 80 °C until ^{19}F NMR showed completion of the reaction. The mixture was poured into crushed ice (150 mL), acidified with conc. HCl (5mL) and extracted with diethyl ether (3x30 mL). The organic phase was washed with saturated $NaHCO_3$ solution (25 mL) and saturated brine (2x25 mL) and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed under pressure. ^{1}H and ^{19}F NMR analysis confirmed the formation of the intermediate aryl-fluoromalonate (δ_F – 150) which was used in the next step without any further purification.

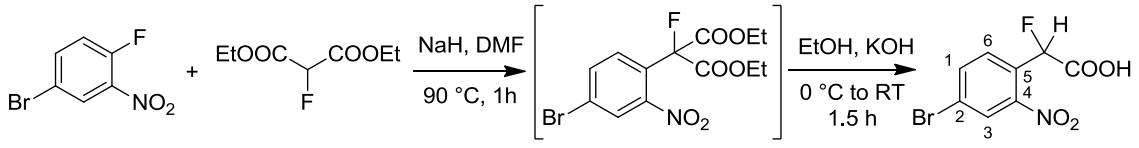
The malonate was dissolved in anhydrous ethanol (40 mL) and KOH (0.68 g, 12.0 mmol) in ethanol (10 ml) was added dropwise while cooling in ice-water bath. The mixture was stirred for 1 hour, hexane (50 mL) was added, stirred for further 30 minutes than filtered and washed with hexane : ethanol (20 mL, 1 : 1 mixture). The solid was dissolved in water (40 mL), acidified with conc. HCl (5 mL) and extracted with ethyl acetate (3x30 mL). The organic phase was washed with saturated brine (2x20 ml) and dried over Na_2SO_4. After filtration the solvent was evaporated under reduced pressure to obtain the pure product which was purified by recrystallization from aqueous ethanol if required.

2-Fluoro-2-(2-nitrophenyl)-acetic acid



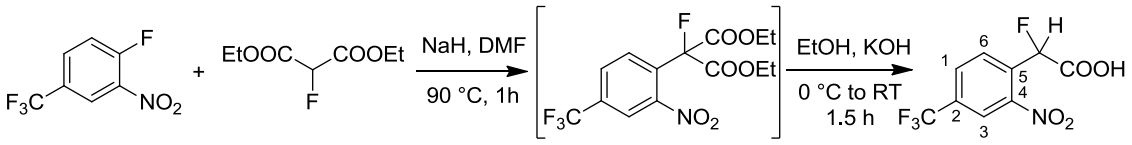
1-Fluoro-2-nitrobenzene (0.71 g, 5 mmol) gave *2-fluoro-2-(2-nitrophenyl)-acetic acid* (0.62 g, 62 %) as a yellow powder. Analytical data described above.

2-Fluoro-2-(2-nitro-4-bromophenyl)-acetic acid



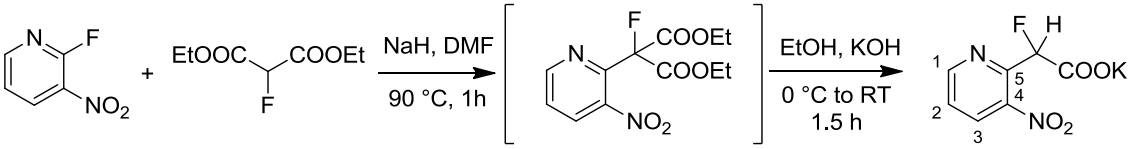
4-Bromo-1-fluoro-2-nitrobenzene (1.10 g, 5.0 mmol) gave *2-fluoro-2-(2-nitro-4-bromophenyl)-acetic acid* (1.15 g, 83 %) as a tan powder. Mp. 155 - 158 °C; (Found: C 34.46, H 1.79, N 4.86. $C_8H_5BrFNO_4$ requires: C 34.56, H 1.81, N 5.04 %); IR (neat, cm^{-1}) 3084 (br), 2360, 1693, 1537, 1339, 1205, 1060; δ_H (CD_3OD, 400 MHz) 6.51 (1H, d, $^2J_{HF}$ 46.4 Hz, C-H), 7.65 (1H, d, $^3J_{HH}$ 8.4 Hz, Ar-H), 7.94 (1H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HF}$ 2.0 Hz, Ar-H), 8.27 -8.29 (1H, m, Ar-H); δ_F (CD_3OD, 376 MHz) - 189.70 (d, $^2J_{HF}$ 46.4 Hz); δ_C (CD_3OD, 100 MHz) 87.66 (d, $^1J_{FC}$ 182.9 Hz, CH-F), 124.19 (d, $^4J_{CF}$ 1.9 Hz, C1), 129.02 (C3), 130.80 (d, $^3J_{CF}$ 13.3 Hz, C6), 130.98 (d, $^2J_{CF}$ 21.4 Hz, C5), 137.99 (d, $^5J_{CF}$ 1.5 Hz, C2), 149.10 (C4), 169.47 (d, $^2J_{FC}$ 24.3 Hz, COO); m/z (asap) 234 (96 %, $[M(^{81}Br)\text{-}CO_2H]^+$), 232 (100 %, $[M(^{79}Br)\text{-}CO_2H]^+$).

2-Fluoro-2-(2-nitro-4-trifluoromethylphenyl)-acetic acid



4-Fluoro-3-nitrobenzotrifluoride (1.05 g, 5.0 mmol) gave *2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)-acetic acid* (1.03 g, 77 %) as an off white powder. Mp. 110 - 112 °C; (Found: C 40.22, H 1.87, N 5.10. $C_9H_5F_4NO_4$ requires: C 40.47, H 1.89, N 5.24 %); IR (neat, cm^{-1}) 3018 (br), 1736, 1549, 1319, 1196, 1131, 1096, 1059; δ_H (CD_3OD, 400 MHz) 6.63 (1H, d, $^2J_{HF}$ 46.3 Hz, C-H), 7.96 (1H, d, $^3J_{HH}$ 8.4 Hz, Ar-H), 8.09 (1H, d, $^3J_{HH}$ 8.4 Hz, Ar-H), 8.41 (1H, s, Ar-H); δ_F (CD_3OD, 376 MHz) - 67.11 (3F, CF_3), - 192.48 (1F, d, $^2J_{HF}$ 46.3 Hz, CH-F); δ_C (CD_3OD, 100 MHz): 87.88 (d, $^1J_{CF}$ 186.3 Hz, CHF), 123.32 (q, $^3J_{CF}$ 4.0 Hz, C3), 124.27 (q, $^1J_{CF}$ 271.5 Hz, CF_3), 130.24 (d, $^3J_{CF}$ 14.4 Hz, C6), 131.52-131-54 (m, C1), 133.19 (q, $^2J_{CF}$ 33.6 Hz, C2), 136.00 (d, $^3J_{CF}$ 21.3 Hz, C5), 148.77 (C4), 169.06 (d, $^2J_{CF}$ 24.3 Hz, COO); m/z (asap): 222 (100 %, $[M\text{-}CO_2H]^+$).

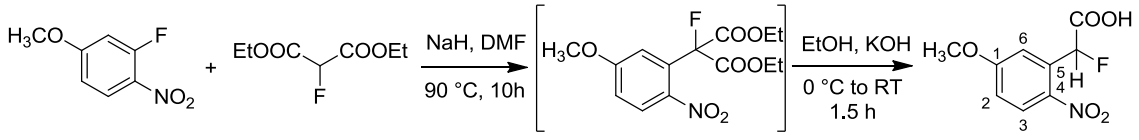
Potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate



2-Fluoro-3-nitropyridine (0.72 g, 5.0 mmol) gave *potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate* (1.03 g, 86 %) as a deep red powder after filtration and drying. Mp.

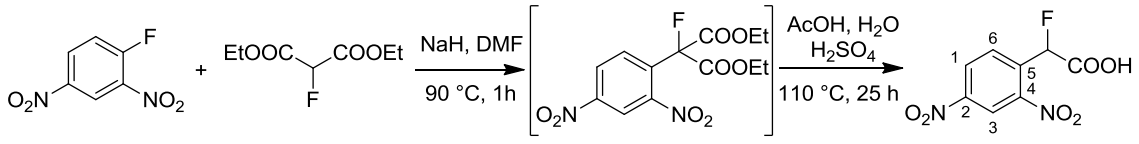
>140 °C (decomposes); IR (neat, cm^{-1}) 1654, 1523, 1359; δ_H (D_2O, 400 MHz) 6.32 (1H, d, $^2J_{HF}$ 47.7 Hz, CF-H), 7.69 – 7.73 (1H, m, Ar-H), 8.52 (1H, d, $^3J_{HH}$ 8.4 Hz, Ar-H), 8.80 (1H, dd, $^3J_{HH}$ 4.9 Hz, $^4J_{HF}$ 1.4 Hz, Ar-H); δ_F (D_2O, 376 MHz) - 180.27 (d, $^2J_{HF}$ 47.7 Hz, CH-F); δ_C (D_2O, 100 MHz) 87.91 (d, $^1J_{CF}$ 185.2 Hz, CHF), 124.29 (d, $^5J_{CF}$ 1.6 Hz, C2), 133.25 (C3), 143.85 (C1), 148.27 (d, $^2J_{CF}$ 20.0 Hz, C5), 151.82 (C4), 171.86 (d, $^2J_{CF}$ 21.6 Hz, COO); m/z (asap) 155 (8 %, $[M\text{-}CO_2K]^+$), 137 (100 %, $[M\text{-}CO_2K\text{-}F+H]^+$).

2-Fluoro-2-(2-nitro-5-methoxyphenyl)-acetic acid



3-Fluoro-4-nitroanisole (1.0 g, 5.8 mmol) gave *2-fluoro-2-(2-nitro-5-methoxyphenyl)-acetic acid* (0.80 g, 60 %) as a tan powder. Mp. 129 – 131 °C; (Found: C 46.86, H 3.52, N 6.11. $C_9H_7FKNO_5$ requires: C 47.17, H 3.52, N 6.11 %); IR (neat, cm^{-1}) 2848 (br), 1724, 1582, 1324, 1283, 1235, 1087; δ_H (DMSO d_6, 400 MHz) 3.92 (3H, s, CH_3), 6.52 (1H, d, $^2J_{HF}$ 46.0 Hz, CF-H), 7.18-7.24 (2H, m, Ar-H), 8.22 (1H, d, $^3J_{HH}$ 8.9 Hz, Ar-H), 13.73 (1H, s, COOH); δ_F (DMSO d_6, 376 MHz) - 185.36 (d, $^2J_{HF}$ 46.0 Hz, CH-F); δ_C (DMSO d_6, 100 MHz) 56.37 (CH_3), 87.39 (d, $^1J_{CF}$ 183.2 Hz, CHF), 114.18 (d, $^3J_{CF}$ 13.5 Hz, C6), 114.45 (C2), 128.10 (s, C3), 133.21 (d, $^2J_{CF}$ 19.8 Hz, C5), 139.45 (d, $^3J_{CF}$ 1.9 Hz, C4), 163.58 (d, $^4J_{CF}$ 1.4 Hz, C1), 167.73 (d, $^2J_{CF}$ 23.5 Hz, COO); m/z (asap) 184 (100 %, $[M\text{-}CO_2H]^+$), 164 (24 %, $[M\text{-}CO_2H\text{-}HF]^+$).

2-Fluoro-2-(2,4-dinitrophenyl)-acetic acid

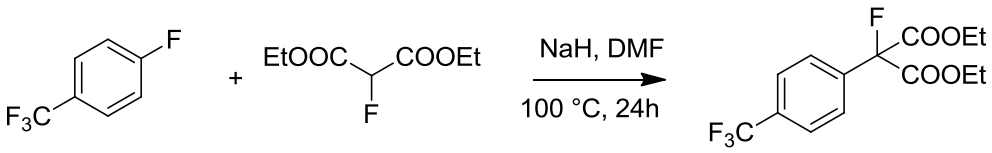


1-Fluoro-2,4-dinitrobenzene (1.50 g, 8 mmol) was used to synthesise the crude fluoromalonate which was dissolved in glacial acetic acid (25 mL) and water (15 mL), concentrated sulphuric acid (4 mL) was added and the mixture was heated at 100 °C (bath temperature) for 25 hours. The mixture was poured on crushed ice (350 mL), extracted with DCM (3x100 mL) that was evaporated under reduced pressure. The

residue was dissolved in saturated $NaHCO_3$ solution (60 mL) and extracted with DCM (2x30 mL) to remove the non-acidic impurities. The aqueous solution was acidified to pH 1 with concentrated HCl and extracted with DCM (3x50 mL). The organic phase was dried with Na_2SO_4, filtered and evaporated under reduced pressure to leave *2-fluoro-2-(2,4-dinitrophenyl)-acetic acid* (1.10 g, 56 %) as an orange solid. Mp. 74 - 77 °C; IR (neat, cm^{-1}) 3585, 3109, 2481, 1715, 1521, 1354, 1093; δ_H ($CDCl_3$, 400 MHz) 6.80 (1H, d, $^2J_{HF}$ 46.5 Hz, C-H), 8.05 (1H, d, $^3J_{HH}$ 8.5 Hz, Ar-H), 8.59 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{FH}$ 2.4 Hz, Ar-H), 8.72 (1H, bs, COOH), 9.00 – 9.01 (1H, m, Ar-H); δ_F ($CDCl_3$, 376 MHz): - 190.37 (d, $^2J_{HF}$ 46.5 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 86.16 (d, $^1J_{CF}$ 189.4 Hz, CHF), 120.88 (C3), 128.38 (q, $^4J_{CF}$ 2.3 Hz, C1), 129.29 (d, $^3J_{CF}$ 15.9 Hz, C6), 136.06 (d, $^2J_{CF}$ 21.5 Hz, C5), 147.14 (C-NO_2), 148.51 (C-NO_2), 169.21 (d, $^2J_{CF}$ 23.6 Hz, COO); m/z (asap) 199 (55 %, $[M\text{-}CO_2H]^+$), 179 (44 %, $[M\text{-}CO_2H\text{-}HF]^+$).

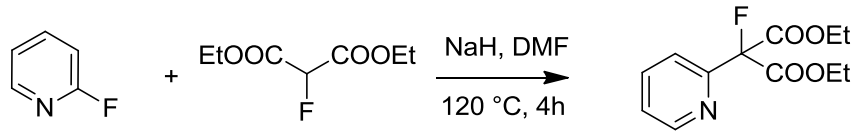
Attempted arylation of fluoromalonate

4-Fluorobenzotrifluoride



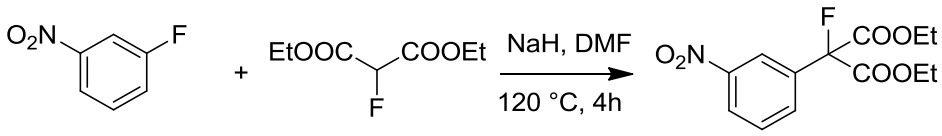
4-Fluorobenzotrifluoride (1.31 g, 8 mmol) was heated in DMF (35 mL) with diethyl 2-fluoromalonate sodium salt (9 mmol from 1.60 g diethyl 2-fluoromalonate and 0.48 g NaH (60 % in mineral oil), 12 mmol) in a 100 °C bath for 24 hours. No products were observed by ^{19}F NMR analysis of the reaction mixture.

2-Fluoropyridine



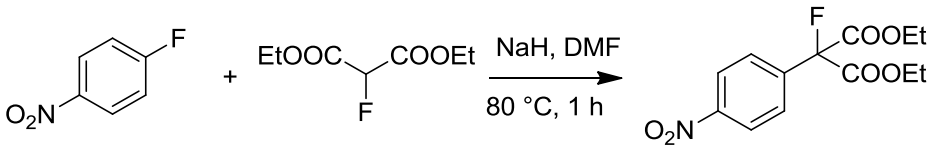
2-Fluoropyridine (0.49 g, 5 mmol) was heated in DMF (35 mL) with diethyl 2-fluoromalonate sodium salt (6 mmol from 1.06 g diethyl 2-fluoromalonate and 0.32 g NaH (60 % in mineral oil), 8 mmol) in a 120 °C bath for 4 hours. No products were observed by ^{19}F NMR analysis of the reaction mixture.

1-Fluoro-3-nitrobenzene



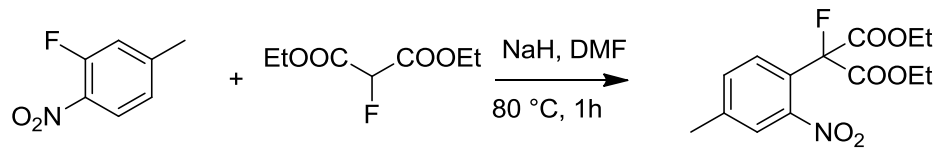
1-Fluoro-3-nitrobenzene (0.71 g, 5 mmol) was heated in DMF (35 mL) with diethyl 2-fluoromalonate sodium salt (6 mmol from 1.06 g diethyl 2-fluoromalonate and 0.32 g NaH (60 % in mineral oil), 8 mmol) in a 120 °C bath for 4 hours. No products were observed by ^{19}F NMR analysis of the reaction mixture.

1-Fluoro-4-nitrobenzene



1-Fluoro-4-nitrobenzene (0.71 g, 5 mmol) was heated in DMF (35 mL) with diethyl 2-fluoromalonate sodium salt (6 mmol from 1.06 g diethyl 2-fluoromalonate and 0.32 g NaH (60 % in mineral oil), 8 mmol) in an 80 °C bath for 1 hour. The mixture was poured into crushed ice (200 mL), acidified with concentrated HCl (2 mL) and extracted with diethyl ether (3x40 mL). The ether phase was washed with saturated $NaHCO_3$ (2x20 mL) and saturated brine (20 mL) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure and the crude product was analysed with ^{19}F NMR. The fluorine spectrum showed the presence of several major products, most of which were aryl fluoromalonate derivatives. The purification of this mixture was not possible even with chromatography on silica gel with hexane : ethyl acetate (5 : 1).

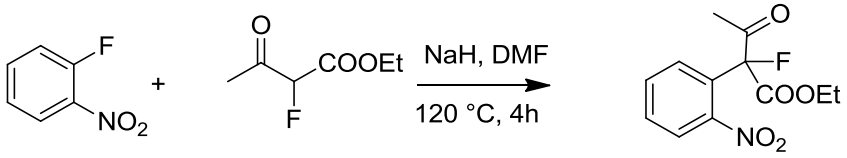
3-Fluoro-4-nitrotoluene



3-Fluoro-4-nitrotoluene (0.78 g, 5 mmol) was heated in DMF (35 mL) with diethyl 2-fluoromalonate sodium salt (6 mmol from 1.06 g diethyl 2-fluoromalonate and 0.32 g NaH (60 % in mineral oil), 8 mmol) in 80 °C bath for 1 hour. The reaction

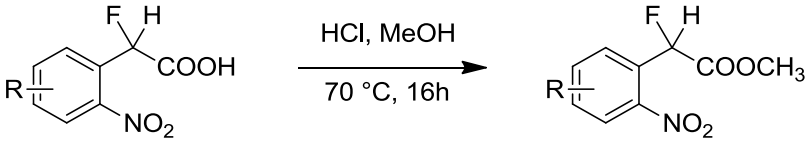
mixture was analysed with ^{19}F NMR spectroscopy and approximately 75 % conversion was detected. As complete conversion was not achieved even after prolonged heating, this reaction was not pursued any further.

Reaction of 1-fluoro-2-nitrobenzene with ethyl 2-fluoroacetoacetate



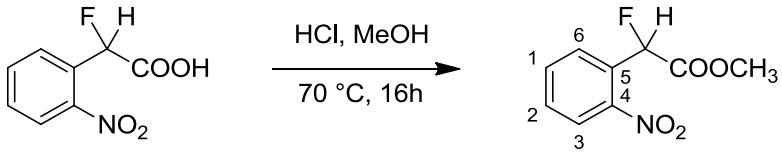
NaH (1.19 g, 30 mmol, 60 % in mineral oil) was washed with hexane (3x20 mL) to remove the oil and was suspended in DMF (40 mL). Ethyl 2-fluoroacetoacetate (3.10 g, 22 mmol) was dissolved in DMF (30 mL) and added to the NaH suspension dropwise at room temperature. After stirring for 20 hours in a 90 °C bath, ^{19}F NMR analysis showed a low conversion (10 %) of starting material and the presence of several unidentified products and no further purification was attempted.

Synthesis of methyl esters: general procedure



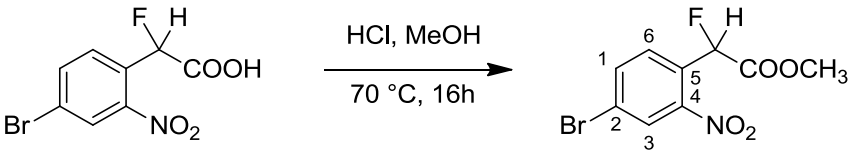
2-Fluoro-2-arylacetic acid (20 to 30 mmol) was dissolved in methanol (50 mL) and HCl in methanol (1.4 M, 10 ml, 14 mmol) was added. The mixture was refluxed for 16 hours than the solvent was removed under reduced pressure. The resulting oil was partitioned between DCM (50 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with DCM (2x20 mL), the combined organic phase was washed with saturated brine (20 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left the desired methyl 2-fluoro-2-arylacetate derivative that was purified by distillation or column chromatography if necessary.

Methyl 2-fluoro-2-(2-nitrophenyl)acetate



2-Fluoro-2-(2-nitrophenyl)acetic acid (5.98 g, 30 mmol) after vacuum distillation gave *methyl 2-fluoro-2-(2-nitrophenyl)acetate* (5.67 g, 88 %) as a yellow crystalline solid. Mp. 41 - 43 °C; bp. 110-112 °C (5 mbar); ($[M+H]^+$; 214.0500. $C_9H_9FNO_4$ requires: $[M]^+$, 214.0516); IR (neat, cm^{-1}) 1749, 1526, 1348, 1216, 1022; δ_H ($CDCl_3$, 400 MHz) 3.76 (3H, s, CH_3), 6.57 (1H, d, $^2J_{HF}$ 46.7 Hz, CF-H), 7.55-7.59 (1H, m, Ar-H), 7.70-7.75 (2H, m, Ar-H), 8.12 (1H, d, $^3J_{HH}$ 8.4 Hz, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 188.04 (d, $^2J_{HF}$ 46.7 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.07 (CH_3), 86.60 (d, $^1J_{CF}$ 185.4 Hz, CHF), 125.07 (C2), 127.80 (d, $^3J_{CF}$ 15.1 Hz, C6), 130.12 (d, $^4J_{CF}$ 1.3 Hz, C1), 130.17 (d, $^2J_{CF}$ 21.1 Hz, C5), 134.21 (d, $^4J_{CF}$ 1.9 Hz, C3), 146.82 (d, $^3J_{CF}$ 3.2 Hz, C4), 167.13 (d, $^2J_{CF}$ 25.0 Hz, COO); m/z (asap) 214 (4 %, $[M+H]^+$), 194 (8 %, $[M-F]^+$), 154 (100 %, $[M-COOCH_3]^+$). Crystals suitable for X-ray crystallography were obtained from the solidified melt, crystallography data is in the digital appendix.

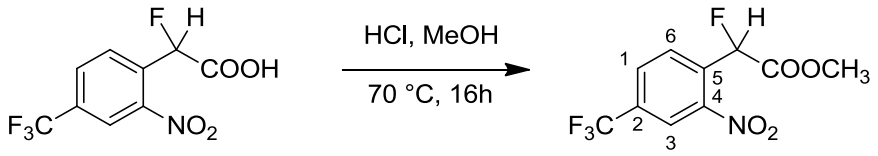
Methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate



2-Fluoro-2-(2-nitro-4-bromophenyl)acetic acid (5.83 g, 21 mmol) gave *methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate* (5.93 g, 97 %) as a tan powder. Mp. 78 - 79 °C; ($[M+H]^+$, 291.9641. $C_9H_8[^{79}Br]FNO_4$ requires: $[M]^+$, 291.9621); IR (neat, cm^{-1}) 1744, 1525, 1345, 1214, 1021, 986; δ_H ($CDCl_3$, 400 MHz) 3.79 (3H, s, CH_3), 6.56 (1H, d, $^2J_{HF}$ 46.5 Hz, CF-H), 7.65 (1H, d, $^3J_{HH}$ 8.6 Hz, Ar-H), 7.86 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.0 Hz, Ar-H), 8.29 (1H, s, Ar-H). δ_F ($CDCl_3$, 376 MHz) -188.89 (d, $^2J_{HF}$ 46.5 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.38 (CH_3), 86.39 (d, $^1J_{CF}$ 185.4 Hz, CHF), 123.70 (d, $^5J_{CF}$ 2.0 Hz, C2), 128.31 (C3), 129.23 (d, $^3J_{CF}$ 14.8 Hz, C6), 129.39 (d, $^2J_{CF}$ 21.7 Hz, C5), 137.27 (d, $^4J_{CF}$ 1.7 Hz, C1), 147.28 (C4), 166.73 (d, $^2J_{CF}$ 24.7 Hz, COO); m/z (asap) 292 (6 %, $[M(^{79}Br)+H]^+$), 294 (6 %,

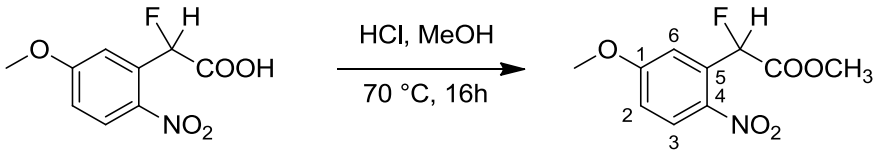
[M(^{81}Br)+H]$^+$), 272 (15 %, [M(^{79}Br)-F]$^+$), 274 (15 %, [M(^{81}Br)-F]$^+$), 232 (100%, [M(^{79}Br)-$COOCH_3$]$^+$), 234 (96%, [M(^{81}Br)-$COOCH_3$]$^+$).

Methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate



2-Fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetic acid (5.91 g, 22 mmol) gave *methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate* (6.10 g, 98 %) as a brown oil. ([M+H]$^+$, 282.0394. $C_{10}H_8F_4NO_4$ requires: [M]$^+$, 282.0389); IR (neat, cm^{-1}) 1752, 1543, 1324, 1179, 1133, 1095; δ_H ($CDCl_3$, 400 MHz) 3.81 (3H, s, CH_3), 6.70 (1H, d, $^2J_{HF}$ 46.4 Hz, CF-H), 7.96-8.05 (2H, m, Ar-H), 8.44 (1H, s, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 64.09 (3F, s, CF_3), - 189.74 (1F, d, $^2J_{HF}$ 46.4 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.55 (CH_3), 86.54 (d, $^1J_{CF}$ 186.2 Hz, CHF), 122.65 (q, $^1J_{CF}$ 272.6, CF_3), 122.66 (q, $^3J_{CF}$ 3.7 Hz, C3),128.70 (d, $^3J_{CF}$ 16.0 Hz, C6), 130.77-130.85 (m, C1), 132.80 (q, $^2J_{CF}$ 34.8 Hz, C2), 134.25 (d, $^2J_{CF}$ 21.8 Hz, C5), 146.97 (C5), 166.41 (d, $^2J_{CF}$ 24.0 Hz, COO); m/z (asap) 282 (13 %, [M+H]$^+$), 222 (100%, [M-$COOCH_3$]$^+$).

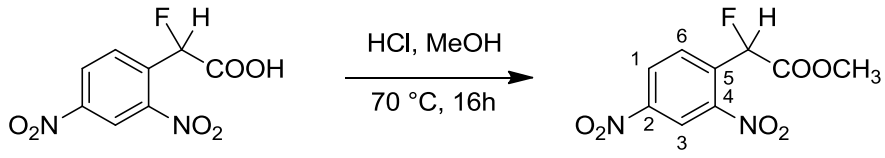
Methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate



2-Fluoro-2-(2-nitro-5-methoxyphenyl)acetic acid gave *methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate* (4.35 g, 98 %) as a brown oil. ([M+H]$^+$, 244.0598. $C_{10}H_{11}FNO_5$ requires: [M]$^+$, 244.0621); IR (neat, cm^{-1}) 2956, 1751, 1582, 1514, 1340, 1288, 1238; δ_H ($CDCl_3$, 400 MHz) 3.76 (3H, s, CH_3), 3.90 (3H, s, CH_3), 6.57 (1H, d, $^2J_{HF}$ 46.9 Hz, CF-H), 6.97 (1H, dd, $^3J_{HH}$ 9.3 Hz, $^4J_{HH}$ 2.8 Hz, Ar-H), 7.18 (1H, d, $^4J_{HH}$ 3.0 Hz, Ar-H), 8.17 (1H, dd, $^3J_{HH}$ 9.3 Hz, $^5J_{HH}$ 1.0 Hz, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 187.68 (d, $^2J_{HF}$ 46.9 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.06 (CH_3), 56.16 (CH_3), 87.18 (d, $^1J_{CF}$ 183.5 Hz, CHF), 112.66 (d, $^3J_{CF}$ 16.8 Hz, C6), 114.41 (C2), 128.03 (C3), 133.42 (d, $^2J_{CF}$ 20.6 Hz, C5), 139.53 (d, $^3J_{CF}$ 3.0 Hz, C4), 164.06 (d, $^4J_{CF}$ 2.4 Hz, C1) 166.92 (d, $^2J_{CF}$ 24.5 Hz, COO); m/z

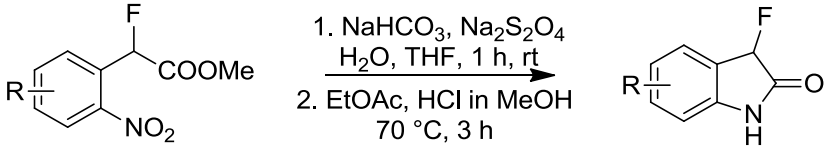
(asap) 244 (7 %, $[M+H]^+$), 212 (24 %, $[M-OCH_3]^+$), 198 (17 %, $[M+H-NO_2]^+$), 184 (100%, $[M-COOCH_3]^+$).

Methyl 2-fluoro-2-(2,4-dinitrophenyl)acetate



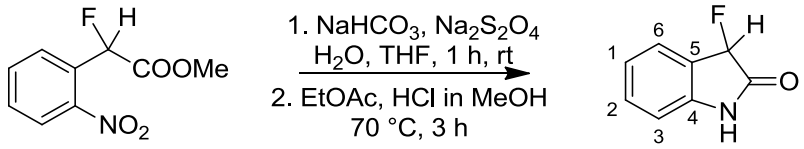
2-Fluoro-2-(2,4-dinitrophenyl)acetic acid (4.69 g, 19 mmol, 90 % pure) after purification with column chromatography (hexane : ethyl acetate, 3 : 1 on silica, Rf: 0.36) gave *methyl 2-fluoro-2-(2,4-dinitrophenyl)acetate* (3.21 g, 65 %) as a yellow oil. ($[M+H]^+$, 259.0372. $C_9H_8FN_2O_6$ requires: $[M]^+$, 259.0366); IR (neat, cm^{-1}) 3101, 1760, 1530, 1349, 1228, 1087; δ_H ($CDCl_3$, 400 MHz) 3.82 (3H, s, CH_3), 6.74 (1H, d, $^2J_{HF}$ 46.8 Hz, CF-H), 8.06 (1H, d, $^3J_{HH}$ 8.6 Hz, Ar-H), 8.59 (1H, dd, $^3J_{HH}$ 8.6 Hz, $^4J_{HH}$ 2.3 Hz, Ar-H), 9.00-9.02 (1H, m, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 189.83 (d, $^2J_{HF}$ 46.8 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 53.73 (CH_3), 86.56 (d, $^1J_{CF}$ 187.8 Hz, CHF), 120.77 (C3), 128.31 (d, $^4J_{CF}$ 2.3 Hz, C1), 129.17 (d, $^3J_{CF}$ 16.7 Hz, C6), 136.66 (d, $^2J_{CF}$ 21.4 Hz, C5), 147.17 (C-NO_2), 148.39 (C-NO_2), 165.95 (d, $^2J_{CF}$ 23.7 Hz, COO); m/z (asap) 259 (10 %, $[M+H]^+$), 212 (54 %, $[M-NO_2^+]$), 199 (100 %, $[M-COOCH_3]^+$).

Reductive cyclisation: general procedure



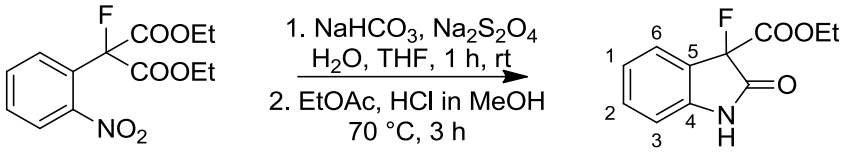
Methyl 2-fluoro-2-(2-nitroaryl)acetate (5 mmol) was dissolved in THF (20mL) and water (20 mL). $NaHCO_3$ (1.68 g, 20 mmol) was added and the mixture was stirred vigorously. $Na_2S_2O_4$ (2.61 g, 15 mmol) was added in small portions over 40 minutes and the mixture was stirred for 20 minutes. Ethyl acetate (40 mL) was added, the aqueous layer was removed, HCl in methanol (3 mL, 1.4 M, 4.2 mmol) was added and the mixture was refluxed for 3 hours. The solution was cooled to ambient temperature, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane : ethyl acetate (5 : 1) as eluent.

3-Fluorooxindole



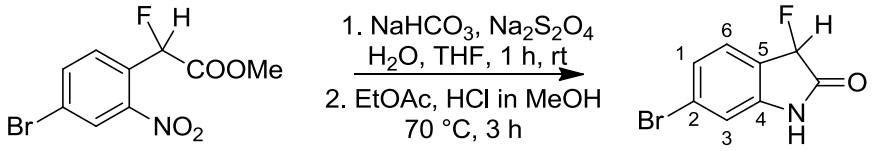
Methyl 2-fluoro-2-(2-nitrophenyl)acetate (1.06 g, 5 mmol) gave *3-fluorooxindole* (0.24 g, 32 %) as a yellow powder; Rf: 0.21. Mp. 92 - 94 °C; ($[M+H]^+$, 152.0496. C_8H_7FNO requires: $[M]^+$, 152.0512); IR (neat, cm^{-1}) 3188, 1772, 1642, 1050; δ_H ($CDCl_3$, 400 MHz) 5.70 (1H, d, $^2J_{HF}$ 51.0 Hz, CF-H), 6.91 (1H, d, $^3J_{HH}$ 7.8 Hz, Ar-H), 7.11 (1H, t, $^3J_{HH}$ 7.6 Hz Ar-H), 7.35 (1H, t, $^3J_{HH}$ 7.8 Hz, Ar-H), 7.46 (1H, d, $^3J_{HH}$ 7.4 Hz, Ar-H), 8.42 (1H, bs, N-H); δ_F ($CDCl_3$, 376 MHz); - 194.56 (d, $^2J_{HF}$ 51.0 Hz, CH-F); δ_C ($CDCl_3$, 100 MHz) 85.87 (d, $^1J_{CF}$ 189.4 Hz, CHF), 110.84 (d, $^5J_{CF}$ 1.5 Hz, C2), 123.36 (d, $^2J_{CF}$ 16.4 Hz, C5), 123.52 (d, $^4J_{CF}$ 3.0 Hz, C3), 126.57 (d, $^4J_{CF}$ 1.7 Hz, C1), 131.68 (d, $^3J_{CF}$ 3.3 Hz, C6), 141.92 (d, $^3J_{CF}$ 5.5 Hz, C4), 173.39 (d, $^2J_{CF}$ 17.9 Hz, CO); m/z (asap) 152 (100 %, $[M+H]^+$), 132 (53 %, $[M-F]^+$).

Ethyl 3-fluoro-3-oxindolocarboxylate



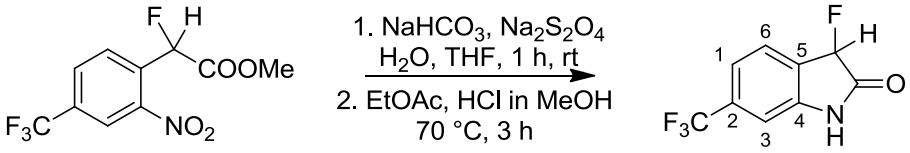
Diethyl 2-fluoro-2-(2-nitrophenyl)malonate (0.90 g, 3mmol) gave *ethyl 3-fluoro-3-oxindolocarboxylate* (0.25 g, 37 %) as a tan powder; Rf: 0.32. Mp. 86 - 88 °C; ($[M-H]^+$, 222.0578. $C_{11}H_9FNO_3$ requires: $[M]^+$, 222.0566); IR (neat, cm^{-1}) 3082, 1702, 1618, 1342, 1271, 1078; δ_H ($CDCl_3$, 400 MHz) 1.16 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 4.15-4.30 (2H, m, CH_2), 7.15-7.21 (2H, m, Ar-H), 7.38 (1H, d, $^3J_{HH}$ 7.4 Hz, Ar-H), 7.49 (1H, t, $^3J_{HH}$ 7.8 Hz, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 168.09 (s, C-F); δ_C ($CDCl_3$, 100 MHz) 13.91 (CH_3), 63.43 (CH_2), 89.21 (d, $^1J_{CF}$ 207.4 Hz, CF), 109.88 (C3), 120.21 (d, $^2J_{CF}$ 19.8 Hz, C5), 124.50 (C2), 124.88 (d, $^4J_{CF}$ 2.3 Hz, Ar), 132.76 (d, $^4J_{CF}$ 2.8 Hz, Ar), 142.69 (d, $^3J_{CF}$ 4.3Hz, C4), 164.53 (d, $^2J_{CF}$ 31.4 Hz, CO), 166.92 (d, $^2J_{CF}$ 22.2 Hz, CO); m/z (asap) 222 (94 %, $[M-H]^+$), 204 (76 %, $[M-F]^+$), 174 (100 %, $[M-F-C_2H_5]^+$).

3-Fluoro-7-bromooxindole



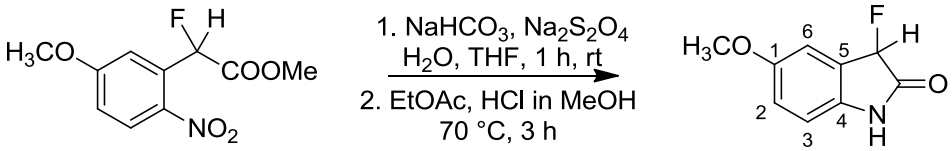
Methyl 2-fluoro-2-(2-nitro-4-bromophenyl)acetate (1.45 g, 5 mmol) gave *3-fluoro-7-bromooxindole* (0.65 g, 57 %) as a white solid; Rf: 0.18. Mp. 207 - 208 °C (decomposes); ([M]$^+$, 228.9534. $C_8H_5{}^{79}BrFNO$ requires: [M]$^+$, 229.9539); IR (neat, cm^{-1}) 3136, 1728, 1617, 1451, 1048; δ_H (DMSO d_6, 400 MHz) 5.85 (1H, d, $^2J_{HF}$ 50.3 Hz, CF-H), 7.01 – 7.02 (1H, m, Ar-H), 7.23 (1H, dm, $^3J_{HH}$ 8.0 Hz, Ar-H), 7.40 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 2.0 Hz, Ar-H), 10.78 (1H, bs, N-H); δ_F (DMSO d_6, 376 MHz) - 193.44 (d, $^2J_{HF}$ 50.2 Hz, CH-F); δ_C (DMSO d_6, 100 MHz) 85.49 (d, $^1J_{CF}$ 183.9 Hz, CHF), 113.23 (C3), 122.63 (d, $^2J_{CF}$ 16.1 Hz, C5), 124.02 (d, $^5J_{CF}$ 4.0 Hz, C2), 124.85 (d, $^3J_{CF}$ 2.9 Hz, C6), 127.99 (C1), 144.99 (d, $^3J_{CF}$ 5.8 Hz, C4), 172.16 (d, $^2J_{CF}$ 17.4 Hz, CO); m/z (asap) 232 (92 %, [M(^{81}Br)+H]$^+$), 230 (100 %, [M(^{79}Br)+H]$^+$), 229 (26 %, [M(^{79}Br)]$^+$),212 (86 %, [M(^{81}Br)-F]$^+$), 210 (91 %, [M(^{79}Br)-F]$^+$).

3-Fluoro-7-trifluoromethyloxindole



Methyl 2-fluoro-2-(2-nitro-4-trifluoromethylphenyl)acetate (1.41 g, 5 mmol) gave *3-fluoro-7-trifluoromethyloxindole* (0.90 g, 82 %) as a pale yellow powder; Rf: 0.17. Mp. 175 – 177 °C; ([M]$^+$, 219.0305. $C_9H_5F_4NO$ requires: [M]$^+$, 219.0307); IR (neat, cm^{-1}) 3143, 1753,1698, 1317, 1292, 1257, 1114, 1054; δ_H (DMSO d_6, 400 MHz) 5.99 (1H, d, $^2J_{HF}$ 49.5 Hz, CF-H), 7.08 (1H, s, Ar-H), 7.41 (1H, d, $^3J_{HH}$ 7.6 Hz, Ar-H), 7.68 (1H, d, $^3J_{HH}$ 7.6 Hz, Ar-H), 10.91 (1H, bs, N-H); δ_F (DMSO d_6, 376 MHz) - 62.55 (3F, s, CF_3), - 195.89 (1F, d, $^2J_{HF}$ 49.5 Hz, CH-F); δ_C (DMSO d_6, 100 MHz) 85.44 (d, $^1J_{CF}$ 184.9 Hz, CHF), 106.50 (m, C3), 119.11 (m, C1), 123.70 (q, $^1J_{CF}$ 271.5 Hz, CF_3), 126.99 (C6), 127.67 (d, $^2J_{CF}$ 15.6 Hz, C5), 131.48 (qd, $^2J_{CF}$ 32.1 Hz, $^4J_{CF}$ 3.1 Hz, C2), 144.24 (d, $^3J_{CF}$ Hz, C4), 172.06 (d, $^2J_{CF}$ 17.4 Hz, COO); m/z (asap) 220 (100 %, [M+H]$^+$), 219 (21 %, [M]$^+$), 200 (95 %, [M-F]$^+$), 191 (24 %, [M-CO]$^+$).

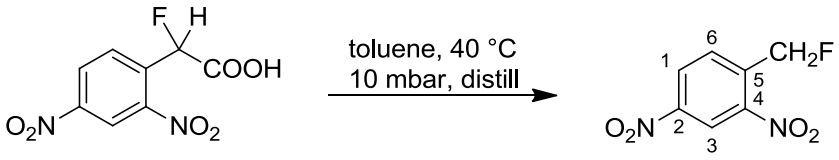
3-Fluoro-6-methoxyoxindole



Methyl 2-fluoro-2-(2-nitro-5-methoxyphenyl)acetate (1.15 g, 5 mmol) gave *3-fluoro-6-methoxyoxindole* (0.25 g, 30 %) as a tan powder; Rf: 0.20. Mp. 130-132 °C; ($[M+H]^+$, 182.0612. $C_9H_9FNO_2$ requires: $[M]^+$, 182.0617); IR (neat, cm^{-1}) 3192, 1716, 1486, 1309, 1206, 1050; δ_H (DMSO d_6, 400 MHz) 3.72 (3H, s, CH_3), 5.84 (1H, d, $^2J_{HF}$ 50.5 Hz, CF-H), 6.78 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HF}$ 1.4 Hz, Ar-H), 6.91 (1H, dt, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.3 Hz Ar-H), 7.10 (1H, t, $^4J_{HH}$ 2.3 Hz, Ar-H), 10.45 (1H, bs, N-H); δ_F (DMSO d_6, 376 MHz) - 193.13 (d, $^2J_{HF}$ 50.5 Hz);. δ_C (DMSO d_6, 100 MHz) 55.60 (CH_3), 86.40 (d, $^1J_{CF}$ 183.6 Hz, CHF), 110.92 (Ar), 112.69 (Ar), 116.25 (d, $^4J_{CF}$ 3.8 Hz, C3), 124.37 (d, $^2J_{CF}$ 15.9 Hz, C5), 136.36 (d, $^3J_{CF}$ 5.9 Hz, C4), 155.11 (d, $^4J_{CF}$ 3.3 Hz, C1), 172.21 (d, $^2J_{CF}$ 17.5 Hz, CO) m/z (asap) 182 (37 %, $[M+H]^+$), 162 (100 %, $[M-F]^+$).

Synthesis of fluoromethyl nitroarenes

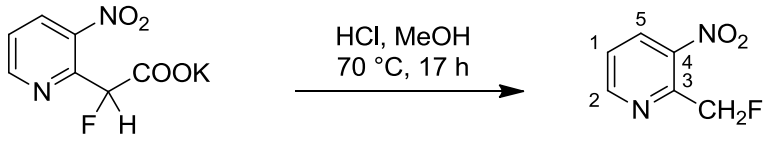
2,4-Dinitrobenzyl fluoride



2-Fluoro-2-(2,4-dinitrophenyl)acetic acid was synthesised according to the general procedure from 2,4-dinitrofluorobenzene (0.93 g, 5 mmol). The crude acid (dark oil) was dissolved in toluene (40 mL) that was removed under reduced pressure (10 mbar) in a 40 °C water bath to leave a dark solid that was purified by column chromatography (hexane : ethyl acetate, 4 : 1 on silica, Rf: 0.19) to leave *2,4-dinitrobenzyl fluoride* (0.61 g, 61 %) as an off white solid. Mp. 68 – 70 °C; (Found: C 42.11, H 2.53, N 13.82; $C_7H_5FN_2O_4$ requires: C 42.01, H 2.52, N 14.00 %); ($[M+H]^+$, 201.0298. $C_7H_6FN_2O_4$ requires: $[M]^+$, 201.0312), IR (neat, cm^{-1}) 2360, 1522, 1341, 1027; δ_H ($CDCl_3$, 400 MHz) 5.97 (2H, d, $^2J_{HF}$ 47.8 Hz, CF-H), 8.08 (1H, d, $^3J_{HH}$ 8.7 Hz, Ar-H), 8.60 (1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{FH}$ 2.4 Hz Ar-H), 9.08 (1H, s, Ar-H); δ_F ($CDCl_3$, 376 MHz) - 219.93 (t, $^2J_{HF}$ 47.8 Hz, CH_2-F); δ_C ($CDCl_3$, 100 MHz) 81.93 (d, $^1J_{CF}$ 176.4 Hz), 120.58 (C3), 128.51 (d,

$^{3}J_{CF}$ 12.7 Hz, C6), 128.56 (d, $^{4}J_{CF}$ 3.5 Hz, C1), 140.97 (d, $^{2}J_{CF}$ 19.2 Hz, C5), 145.66 (C-NO_2), 147.64 (C-NO_2); m/z (asap) 201 (100 %, $[M+H]^+$), 181 (43 %, $[M-F]^+$), 123 (55 %, $[M-F-NO_2]^+$).

2-Fluoromethyl-3-nitropyridine



Potassium 2-fluoro-2-(3-nitro-2-pyridinyl)acetate (6.00 g, 25 mmol) was suspended in methanol (100 mL), HCl in methanol (1.4 M, 50 mL, 70 mmol) was added and the mixture was refluxed for 17 hours. After cooling to ambient temperature, the solvent was removed under reduced pressure and the solid residue was partitioned between dichloromethane (100 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic layer was washed with saturated brine (25 mL) and dried on Na_2SO_4. After filtration the solvent was removed under reduced pressure to leave a brown solid (3.50 g) that was purified by column chromatography (hexane: ethyl acetate, 2 : 1 on silica, Rf: 0.27) to leave *2-fluoromethyl-3-nitropyridine* (2.66 g, 68 %) as an orange crystalline solid. Mp. 74 – 76 °C; ($[M+H]^+$, 157.0406. $C_6H_6FN_2O_2$ requires: $[M]^+$, 157.0413); IR (neat, cm^{-1}) 2358, 1598, 1522, 1349, 1022; δ_H ($CDCl_3$, 400 MHz) 5.83 (2H, d, $^{2}J_{HF}$ 47.3 Hz, CF-H), 7.53 (1H, dd, $^{3}J_{HH}$ 8.3 Hz, $^{3}J_{HH}$ 4.8 Hz, Ar-H), 8.41 (1H, dt, $^{3}J_{HH}$ 8.3 Hz, $^{4}J_{HH}$ 1.2 Hz Ar-H), 8.88 (1H, dm, $^{3}J_{HH}$ 4.8 Hz Ar-H); δ_F ($CDCl_3$, 376 MHz) - 221.85 (t, $^{2}J_{HF}$ 47.0 Hz, CH_2-F); δ_C ($CDCl_3$, 100 MHz) 82.16 (d, $^{1}J_{CF}$ 175.7 Hz, CH_2F), 124.06 (d, $^{4}J_{CF}$ 1.8 Hz, C2), 132.97 (C1), 144.04 (C5), 151.02 (d, $^{2}J_{CF}$ 17.1 Hz, C3), 153.47 (C4); m/z (asap) 157 (100 %, $[M+H]^+$), 137 (46 %, $[M-F]^+$). Crystals suitable for X-ray crystallography were grown by slow evaporation of chloroform, crystallography data is in the digital appendix.

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Appendix

Contents of the attached CD:

Crystallography data of 2-fluoromethyl-3-nitropyridine.

Crystallography data of methyl 2-fluoro-2-(2-nitrophenyl)acetate.

Crystallography data of diethyl 2-fluoro-2-(2-nitrophenyl)malonate.

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