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Elemental fluorine. Part 9[1] Catalysis of the direct fluorination of 2-substituted carbonyl compounds[2]

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Abstract

Catalysis of the reaction between fluorine and a range of 2-substituted carbonyl compounds has been investigated. Most notably, the preparation of diethyl-2-fluoromalonate has been achieved in high yield by fluorination of diethylmalonate in the presence of hydrated copper nitrate. Reactions between fluorine and carbanions derived from 2-substituted carbonyl compounds, including phosphonates, sulphones and nitriles, are also discussed.

1. Introduction

2-Substituted-2-fluoro carbonyl compounds are valuable 'building blocks' for the preparation of many compounds having potentially useful biological activity and much effort has been devoted to their preparation [2]. The ease with which fluorine can be introduced into the parent 2-substituted carbonyl compounds is related to the nature and disposition of other groups attached to the 2-carbon. Thus, many 1,3-diketones and 1,3-ketoesters can be fluorinated directly with a variety of electrophilic fluorinating agents [3–12], including fluorine [13], and high conversions and yields of the corresponding 2-fluoro-compounds have been obtained. Under comparable conditions, dialkyl malonates are resistant to fluorination and in order to obtain the 2-fluoro-derivatives, it has been usual to treat the parent malonates with base (most commonly, sodium hydride) and then expose the derived carbanions to the various fluorinating agents [6–8,10,11,14–19], again, including fluorine [20].

Copper (II) salts have been used to promote the bromination of 1,3-ketoesters [21] and this led us to investigate whether the direct fluorination of dialkyl malonates, and other compounds where direct fluorination is inconveniently slow, could be catalysed. We are now able to report that catalysis can be achieved for the fluorination of many substrates although in some cases the effect is modest and, in others, complicating side reactions arise. In these latter situations, alternative methods of promoting reaction will be described.

1.1. Fluorination of dialkyl malonates

Diethyl 2-fluoromalonate (**4**) is potentially a particularly valuable 'building block' and a significant body of its chemistry has already been described in the literature [6,14,22–36]. However, the lack of a viable route to the compound has hindered the realisation of its true potential in synthesis.

We have now re-examined the reaction of diethyl malonate (**1**) with fluorine using both formic acid and acetonitrile as solvents (i.e. conditions under which ethyl acetoacetate can be efficiently fluorinated) and have confirmed that reaction is indeed very slow with only a few percent of the substrate being converted into products after some hours of exposure to fluorine. Interestingly, in neither solvent was replacement of the 2-hydrogen the main reaction. When formic acid was used as the solvent, the ^{19}F spectrum of the reaction product showed a doublet of quartets at −123 ppm (J_{HF}=55 and 20.9 Hz) and a triplet of triplets at −225 ppm (J_{HF}=47.4 and 28.7 Hz) in approximately equal intensities, and a much smaller doublet at −195 ppm (J_{HF}=48.2 Hz) which is consistent with the presence of the compounds $CH_3CHFOCO{\cdot}CH_2CO{\cdot}OC_2H_5$

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[1] See Ref. [1]

[2] Dedicated to Professor Klaus Burger on the occasion of his 60th birthday.

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$$(EtOOC)_2CH_2 \longrightarrow (EtOOC)_2CHF$$

1 **4**

1, (20mmol)/ catalyst, (0.4mmol)/ F_2, (32mmol over 2 hrs.)/CH_3CN, (50ml)/ ca. 5 °C

Scheme 1.

Table 1
Catalysis of the fluorination of diethyl malonate

	Catalyst	Conversion (%)
1	$Cu(NO_3)_2 \cdot 2.5H_2O$	88
2	$Ni(NO_3)_2 \cdot 3H_2O$	70
3	$Cr(NO_3)_3 \cdot 9H_2O$[a]	ca. 5%
	$Mn(NO_3) \cdot 6H_2O$	
	$Fe(NO_3)_3 \cdot 6H_2O$	
	$Co(NO_3)_3 \cdot 6H_2O$	
	$Zn(NO_3)_2 \cdot 6H_2O$	
4	$CuCl_2 \cdot 2H_2O$	ca. 5%
	$Cu(OOC \cdot CH_3)_2 \cdot H_2O$	
	$CuSO_4 \cdot 5H_2O$[a]	

[a]Only partially soluble.

Table 2

	Substrate	Catalyst (%)	Conversion (%)	Yield(%)
1a	$CH_2(COOEt)_2$ (**1**)	10	100	78 (**4**)
1b	**1**	–	ca. 6	–
2a	$HC(NO_2)(COOEt)_2$ (**5**)	10	100	76 (**8**)
2b	**5**	–	12	
3a	$HC(Me)(COOEt)_2$ (**6**)	10	ca. 30	[a]
3b	**6**	–	ca. 5	–
4a	$HC(Cl)(COOEt)_2$ (**7**)	10	38	78 (**10**)
4b	**7**	–	ca. 5	–
5a	$HC(F)(COOEt)_2$ (**4**)	10	ca. 5	–
5b	**4**	–	ca. 5	–

[a]See text.

(**2**), $FCH_2CH_2OCO \cdot CH_2CO \cdot OC_2H_5$ (**3**), and CH_3CH_2O-$CO \cdot CHFCO \cdot OC_2H_5$ (**4**), respectively. When the reaction was carried out in acetonitrile, the same products were obtained but here, attack was more site-specific with **2** representing some 80% of the product. The reaction in formic acid was then carried out in the presence of a range of salts of transition metals but no significant difference in the course of the reaction was observed. However, when the fluorination in acetonitrile was carried out in the presence of a catalytic amount of hydrated copper (II) nitrate, a clean, rapid reaction occurred and 88% of the starting material was converted into **4** in over 80% yield (Scheme 1, Table 1, Entry 1) – a most remarkable catalysis.

Using diethyl malonate as a model, hydrated nitrates of chromium, manganese, iron, cobalt, nickel and zinc were evaluated as catalysts for the fluorination but, of these salts, only nickel(II) nitrate·$6H_2O$ displayed catalysis (Table 1, Entries 2 and 3). Similarly, other salts of copper were evaluated but they did not show catalytic activity (Table 1, Entry 4) and, furthermore, **2** was the main product as in the case of fluorination in the absence of catalyst. An important feature of the catalysed fluorination of diethyl malonate is that scarcely any difluorination occured (vide infra). This is very important in the context of the development of a viable commercial process for production of diethyl fluoromalonate, and is in contrast to the fluorination of the sodium salt of diethyl malonate which gave a mixture of mono- and difluoro-compounds [20].

In the light of these findings, the effect of hydrated copper(II) nitrate on 2-substituted dialkyl malonates was investigated (Scheme 2, Table 2).

The experiments outlined in Table 2 do not reveal the relative reactivity of diethyl malonate **1** and diethyl nitromalonate **5**. However, a competition experiment in which equimolecular amounts of **1** and **5** were treated with a deficiency of fluorine in the presence of hydrated copper(II) nitrate established that **5** is the more reactive compound. Thus, from this experiment and results given in Table 2, it can be deduced that reactivity is in the order EtOOCCH·NO_2COOEt>$EtOOCCH_2COOEt$>EtOOCCH·ClCOOEt>

$$(EtOOC)_2CHX \longrightarrow (EtOOC)_2CXF$$

1 X = H
5 X = NO_2
6 X = Me
7 X = Cl
4 X = F

4 X = H
8 X = NO_2
9 X = Me
10 X = Cl
4 X = F

Substrate, (20mmol)/F_2, (64mmol over 4 hrs.)/$Cu(NO_3)2.5H_2O$/CH_3CN, (50ml)/ ca. 5 °C

Scheme 2.

$YCHXCO.CH_3 \longrightarrow YCFXCO.CH_3$

12, X = H, Y = EtO.OC
13, X = Cl, Y = EtO.OC
14, X = Me, Y = EtO.OC
15, X = H, Y = Et_2N.OC

16, X = H, Y = EtO.OC
17, X = Cl, Y = EtO.OC
18, X = Me, Y = EtO.OC
19, X = H, Y = Et_2N.OC

12 - 15, (20mmol)/ catalyst, (0.4mmol)/ F_2, (32mmol over 2 hrs.)/ CH_3CN, (50ml)/ ca. 5 °C

Scheme 3.

EtOOCCH·FCOOEt. Significant fluorination of diethyl nitromalonate occurs in the absence of a catalyst and the 2-hydrogen is replaced almost exclusively (Entry 2b). This behaviour is in sharp contrast to that of **1**, **6**, **7**, and **4** where replacement of hydrogen in the ethyl group (dq in ^{19}F NMR spectum at ca. −123 ppm) is the main process in the absence of a catalyst.

The catalysed fluorination of diethyl-2-methylmalonate (**6**) is not a useful method for the preparation of its 2-fluoro-derivative (**9**)* (Table 2, Entry 3a). Not only is the process relatively slow but also, a mixture of products is obtained in which the main components, deduced from the ^{19}F NMR spectrum, arise from fluorination at the ethyl group to give the two diasterioisomers of $CH_3CHF{\cdot}OCO{\cdot}CH(CH_3){\cdot}COOCH_2CH_3$ (**11**) (two doublets of quartets at −123.79 and −123.95 ppm, J_{HF}=57.9 and 20.9 Hz).

1.2. Fluorination of 1,3-ketoesters

The results of our investigation into the catalysis of the fluorination of 1,3-ketoesters and the related *N,N*-diethyl acetoacetamide (**15**) are outlined in Scheme 3, Table 3. Clearly, hydrated copper(II) nitrate catalysed the fluorination of **12–15** to a significant extent in acetonitrile but compared to the corresponding dialkyl malonates, the process was less efficient. Furthermore, **14** and to a lesser extent **13** gave more complicated mixtures of products than when fluorination was carried out in formic acid [13].

Like the fluorination of dialkyl malonates, attempts to catalyse the fluorination of 1,3-ketoacetates, and indeed all other substrates discussed in this paper, using formic acid as the solvent were unsuccessful, with the exception of ethyl chloroacetoacetate (**13**). We have previously shown that, in formic acid, the enol content of **13** is circa 15% and that when solutions of this compound in formic acid are treated with fluorine, fluorination is rapid until all the enol tautomer is consumed. After this, fluorination is extremely slow due to the slow enolisation of the compound in this medium [13]. We have now found that in contrast to fluorinations in acetonitrile where only copper and nickel nitrates display catalysis, the fluorination of **13** in formic acid is catalysed by salts of manganese, iron, cobalt, nickel, copper and zinc to give the fluorinated product in >85% yield. Furthermore, catalysis is not sensitive to the nature of the anion in the salt (Scheme 4, Table 4).

$EtO.OCCHClCO.CH_3 \longrightarrow EtO.OCFClCO.CH_3$

13 **17**

13, (20mmol)/ catalyst, (0.4mmol)/ F_2, (32mmol over 2 hrs.)/ Formic Acid, 97%, (50ml)/ ca. 5 °C

Scheme 4.

1.3. Fluorination of other 2-substituted carbonyl compounds

Using acetonitrile as the solvent, the catalysed fluorination of other 2-substituted carbonyl compounds has also been investigated (Scheme 5, Table 5). It is clear that

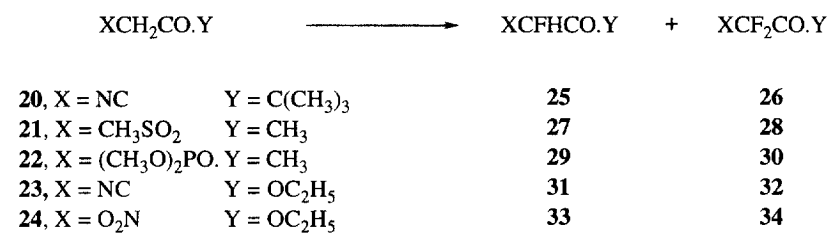
Table 3

	Substrate	Catalyst (%)	Conversion (%)
1a	$EtO{\cdot}OCCH_2CO{\cdot}CH_3$ (**12**)	2	45
1b	**12**	–	23
2a	$EtO{\cdot}OCCHClCO{\cdot}CH_3$ (**13**)	2	40
2b	**13**	–	20
3a	$EtO{\cdot}OCCHCH_3CO{\cdot}CH_3$ (**14**)	2	90[a]
3b	**14**	–	5
4a	$Et_2N{\cdot}OCCH_2CO{\cdot}CH_3$ (**15**)	2	60
4b	**15**	–	46

[a]Although $EtOOCCFCH_3CO{\cdot}CH_3$ (**18**) was the main product, there were many other minor products resulting from fluorination at other sites.

Table 4

Catalyst	Conversion (%)
–	16
$Cr(NO_3)_3{\cdot}9H_2O$	16
$Mn(NO_3){\cdot}H_2O$	60
$Fe(NO_3)_3{\cdot}6H_2O$	54
$Co(NO_3)_3{\cdot}6H_2O$	85
$Ni(NO_3)_2{\cdot}3H_2O$	53
$Cu(NO_3)_2{\cdot}2.5H_2O$	90
$CuCl_2{\cdot}2H_2O$	86
$Cu(OOC{\cdot}CH_3)_2{\cdot}H_2O$	84
$CuSO_4{\cdot}5H_2O$	82
$Zn(NO_3)_2{\cdot}6H_2O$	62



Scheme 5.

Table 5

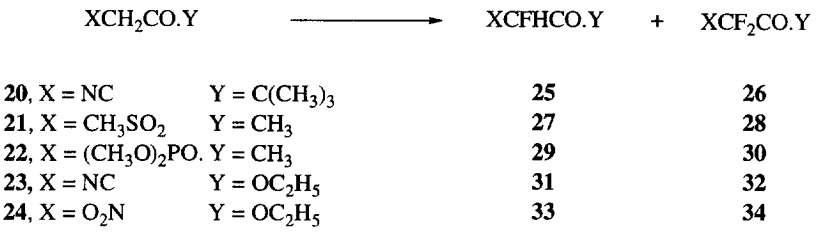
	Substrate	Catalyst (%)	Conversion (%)	Yield (%)
1a	$NCCH_2CO{\cdot}C(CH_3)_3$ (**20**)	10	70	52 (**25**) 13 (**26**)
1b	**20**	–	15	–
2a	$CH_3SO_2CH_2CO{\cdot}CH_3$ (**21**)	10	87	45 (**27**) 5 (**28**)
2b	**21**	–	14	–
3a	$(CH_3O)_2PO{\cdot}CH_2CO{\cdot}CH_3$ (**22**)	10	95	20 (**29**) 5 (**30**)
3b	**22**	–	<5	–
4a	$NCCH_2CO{\cdot}OC_2H_5$ (**23**)	10	46	50 (**31**) 8 (**32**)
4b	**23**	–	12	–
5a	$O_2NCH_2CO{\cdot}OC_2H_5$ (**24**)	10	54	52 (**33**) 20 (**34**)
5b	**24**	–	12	–

fluorination of all these compounds is catalysed by hydrated copper(II) nitrate and, with the exception of phosphonate (**22**) fair to good yields of mono and difluorinated products were obtained. The lower yields of **29/30** can in part be attributed to C–P bond cleavage because doublets at $\delta_F=-86$ ppm, $J_{FP}=980$ Hz, and at $\delta_P=-6.9$ ppm, $J_{FP}=980$ Hz, in the NMR spectra of the reaction mixture indicate the formation of P–F bonds. It is probable that there was corresponding C–S bond cleavage in the fluorination of **21.** Yields from the fluorination of **20**, **23**, and **24** were almost certainly reduced by some of the volatile difluorinated derivatives **26**, **32** and **34** being swept from the reaction vessel over the course of the fluorination process. The fluorination of compounds **20–24** could also be promoted by excess potassium fluoride (see fluorination of diethyl nitromalonate [20]) (Scheme 6, Table 6) but neither

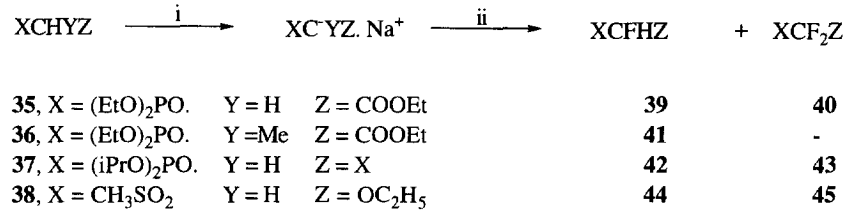
Table 6

	Substrate	Conversion (%)	Yield (%)
1	$CNCH_2CO{\cdot}C(CH_3)_3$ (**20**)	100	45 (**25**) 6 (**26**)
2	$CH_3SO_2CH_2CO{\cdot}CH_3$ (**21**)	90	43 (**27**) 4 (**28**)
3	$(CH_3O)_2PO{\cdot}CH_2CO{\cdot}CH_3$ (**22**)	70	43 (**29**) 7 (**30**)
4	$NCCH_2CO{\cdot}OC_2H_5$ (**23**)	62	40 (**31**) 25 (**32**)
5	$O_2NCH_2CO{\cdot}OC_2H_5$ (**24**)	100	50 (**33**) 7 (**34**)

of these methods gave satisfactory yields of products when the substrates were triethyl phosphonoacetate (**35**), triethyl phosphonopropionate (**36**), tetraisopropyl methylene diphosphonate (**37**) and ethyl methanesulphonyl acetate (**38**). However, when anions of **35–38**, prepared by reaction of the parent compounds with sodium hydride were, in their



Scheme 6.



Scheme 7.

Table 7

	Substrate	Conversion (%)	Yield (%)
1	$(EtO)_2PO{\cdot}CH_2CO{\cdot}OEt$ (**35**)	90	35 (**39**) 15 (**40**)
2	$(EtO)_2PO{\cdot}CH(CH_3)CO{\cdot}OEt$ (**36**)	70	35 (**41**)
3	$\{(i\text{-}PrO)_2PO{\cdot}\}_2CH_2$ (**37**)	73	50 (**42**) 10 (**43**)
4	$MeSO_2CH_2CO{\cdot}OEt$ (**38**)	62	36 (**44**) 7 (**45**)

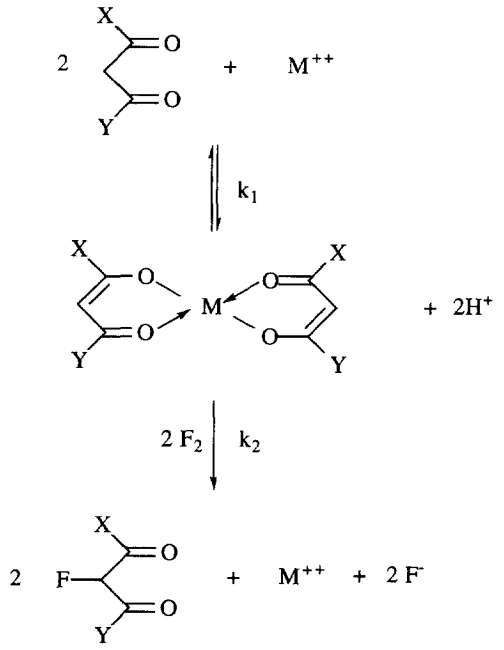
turn, treated with fluorine (i.e. the method that we have already described for the fluorination of dialkyl malonates [20]), fair yields of the desired fluoro-compounds were obtained (Scheme 7, Table 7). Again, C–P cleavage (P–F in NMR) reduced the yields but of course, optimisation of the reaction conditions might be expected to give improvements.

2. Mechanism

In the fluorination of dicarbonyl compounds such as 1,3-diketones and 1,3-ketoesters, fluorine reacts with the enol forms of the compounds and the rate of enolisation is the rate determining step [13]. The catalytic activity of a salt therefore must stem from the ability of the cation to accelerate formation of the enolate. Equally important for the process to be catalytic is the rapid release of the metal cation so that it can again complex with the starting material and complete the cycle. The overall rate is, of course, dependant on k_1 and k_2 (Scheme 8) which are influenced by factors such as the nature of X, Y, the anion, the cation and the solvent. However, the interplay of these various factors is complex and it is not surprising that a simple pattern of catalytic activity does not emerge.

3. Summary

1,3-dicarbonyl compounds, such as in 1,3-diketones and 1,3-ketoesters can react with fluorine to yield the corresponding 2-fluoro- compounds directly [13,37]. However, when the combined effects of a carbonyl group and other groups attached to the 2-carbon atom are less activating, other approaches to preparing the required 2-fluoro-derivatives are required. We have previously shown that fluorination of carbanions derived from dialkyl malonates yields the corresponding 2-fluoro compounds [20], and in this paper, we have demonstrated that this methodology can be used for the synthesis of other 2-fluoro-2-substituted carbonyl compounds. Additionally, we have shown that the fluorination of many 2-substituted carbonyl compounds, most spectacularly diethyl malonate, can be catalysed by certain salts of transition metals. Although the reactions described in this paper have not been optimised, the results clearly demonstrate practical methodologies which are available for the direct fluorination of an ever widening range of potentially useful 'chemical building blocks'.



Scheme 8.

4. Experimental

Except where indicated otherwise, ^1H, ^{19}F and ^{31}P NMR spectra were recorded on a Bruker AC250 spectrometer operating at 250 MHz for hydrogen, 235 MHz for fluorine or 101 MHz for phosphorus. ^{13}C NMR spectra were mea-

sured on a Varian VXR 400 spectrometer operating at 100 MHz or a Varian Gemini 200 spectrometer operating at 50 MHz. Chemical shifts ($CDCl_3$) are recorded in ppm from tetramethyl silane, fluorotrichloromethane and phosphoric acid, and coupling constants are in Hz. Mass spectra were measured on a Fisons Trio 1000 mass spectrometer coupled to a Hewlett Packard 5890 II gas chromatograph fitted with a silicone elastomer coated column (SE 30; 25 m; 0.2 mm i.d.). Accurate mass measurements were determined at the EPSRC Mass Spectrometry Service Centre, Swansea, UK. Pure samples were isolated by GC (4 m SE30) unless indicated otherwise.

In these experiments two basic procedures, 'a' and 'b', were used.

4.1. Procedure 'a'

A glass reaction vessel fitted with a PTFE coated mechanical stirrer, a FEP thermocouple well, a FEP gas delivery tube and an exit tube to a scrubber filled with soda lime was charged with diethyl malonate (3.2 gm, 20 mmol), cupric nitrate $2.5H_2O$ (0.46 gm, 2.0 mmol) and acetonitrile (50 ml) before being cooled to 5–8°C. The vessel was purged with nitrogen and then fluorine diluted to 10% v/v with nitrogen was passed through the stirred solution at a rate of 16 mmol h^{-1} for 4 h. When the fluorine supply had been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then poured into water and extracted with dichloromethane. A weighed amount of trifluoromethylbenzene was added to the extracts whose ^{19}F NMR spectrum was then measured. The dried extracts were evaporated and the residue was analysed by GLC and or ^1H NMR. From this information, the amount of substrate converted (conversion) and yield of product, based on the amount of substrate converted, were calculated. A sample of pure product was obtained by preparative scale GC and identified as diethyl-2-fluoromalonate.

4.2. Procedure 'b'

A similar vessel to that described in 'a' was purged with nitrogen and charged with degreased sodium hydride (0.72 gm, 30 mmol). Dry acetonitrile (35 ml) was added to the hydride followed by the dropwise addition, with stirring, of triethyl-2-phosphonopropionate (4.47 gm, 20 mmol) in dry acetonitrile (15 ml). After addition of the substrate, the mixture was stirred for ca. 1 h before 10% fluorine in nitrogen was passed through it for 4 h as described above. When fluorination was finished and the reaction vessel purged, water was slowly added to hydrolyse excess hydride. Extraction and the remaining work up was as described in 'a'.

Fluorination of diethyl malonate (**1**). Diethyl-2-fluoromalonate, $C_2H_5O{\cdot}OCCHFCO{\cdot}OC_2H_5$ (**4**) [38], δ_H=1.41 (3H, t, J=7.1, CH_3), 4.4 (2H, q, J=7.2, CH_2), 5.36 (1H, d, J_{HF}=48.3, CHF); δ_F=−196.5 (d, J_{HF}=48.3); δ_C=13.9 (s, CH_3), 62.7 (s, CH_2), 85.3 (d, $^1J_{CF}$=196.6, CHF), 163.9 (d, $^2J_{CF}$=24.1, CO); m/z (CI^+, NH_3) 196 ($(M+NH_4)^+$, 100%).

Fluorination of diethyl 2-nitromalonate (**5**). Diethyl-2-fluoro-2-nitromalonate, $C_2H_5O{\cdot}OCCF(NO_2)CO{\cdot}OC_2H_5$ (**8**) [8], δ_H=1.40 (3H, t, J_{HH}=7.1, CH_3), 4.47 (2H, q, J_{HH}=7.12, CH_2); δ_F=−127.3 (s); δ_C=13.7 (s, CH_3), 65.2 (s, CH_2), 106.3 (d, $^1J_{CF}$=261.7, CNO_2F), 157.9 (d, $^2J_{CF}$=25.2, CO).

Fluorination of diethyl 2-chloromalonate (**7**). Diethyl 2-chloro-2-fluoromalonate, $C_2H_5O{\cdot}OCCFClCO{\cdot}OC_2H_5$ (**9**) [7], δ_H=1.35 (3H, t, J_{HF}=7.0, CH_3), 4.39 (2H, q, J_{HF}=7.0, CH_2); δ_F=−121.0 (s); m/z (CI^+, NH_3) 230 ($(M+NH_4)^+$, 100%) for ^{35}Cl.

Fluorination of ethyl acetoacetate (**12**). Ethyl 2-fluoroacetoacetate, $CH_3COCHFCOOC_2H_5$ (**16**) [10,39], δ_H=1.34 (3H, t, J_{HH}=7.2, CH_3CH_2) 2.35 (3H, d, J_{HH}=4.0, $COCH_3$) 4.32 (2H, q, J_{HH}=7.1, OCH_2) 5.2 (1H, d, J_{HF}=49.3, CHF); δ_F=−193.7 (d, J_{HF}=49.4); m/z 148 (M^+) 106 (M-CH_2CO) 43 (CH_3CO).

Fluorination of ethyl 2-chloroacetoacetate (**13**). Ethyl 2-chloro-2-fluoroacetoacetate, $CH_3COCClFCOOC_2H_5$ (**17**) [8], δ_H=1.36 (3H, t, J_{HH}=7.1, CH_3CH_2), 2.46 (3H, d, J_{HF}=2.6, CH_3CO), 4.39 (2H, q, J_{HH}=7.3, CH_3CH_2); δ_F=−123.5 (m); m/z 183 (M+1) 43 (CH_3CO) for ^{35}Cl.

Fluorination of ethyl 2-methylacetoacetate (**14**). Ethyl 2-fluoro-2-methylacetoacetate, $CH_3COCF(CH_3)COOC_2H_5$ (**18**) [10], δ_H=1.31 (3H, t, J_{HH}=7.1, CH_3CH_2), 1.69 (3H, d, J_{HF}=22.2, CH_3CF), 2.33 (3H, d, J_{HF}=4.6, $COCH_3$), 4.28 (2H, q, J_{HH}=7.1, CH_2); δ_F=−157.7 (qq, J_{HF}=22.1, J_{HF}=4.5); m/z 163 (M^++1) 120 (M-CH_2CO) 43 ($COCH_3$).

Fluorination of *N,N*-diethyl acetoacetamide (**15**). Purification by column chromatography (SiO_2/ethyl acetate) gave *N,N*,-diethyl-2-fluoroacetoacetamide, CH_3COCHF-$CO{\cdot}N(C_2H_5)_2$ (**19**) (nc), (Found: C, 54.3; H, 8.1; N, 7.8. $C_8H_{14}NO_2$ requires C, 54.8; H, 8.0; N, 8.0%); δ_H=1.00 (3H, t, J_{HH}=7.0, CH_2CH_3), 1.08 (3H, t, J_{HH}=7.2, CH_2CH_3), 2.18 (3H, d, J=4.0, CH_3COCHF), 3.26 (4H, m, $N(CH_2CH_3)_2$), 5.3 (1H, d, J_{HF}=49.9, CHF); δ_F=−188.7 (dd, J_{HF}=49.5, J_{HF}=4.3); δ_C 12.20 (s, CH_2CH_3), 13.90 (s, CH_2CH_3), 25.73 (s, CH_3CO), 40.41 (s, CH_2CH_3), 41.47 (s, CH_2CH_3), 91.25 (d, $^1J_{CF}$=194.9, CHF), 162.8 (d, $^2J_{CF}$ 20.2, CO.N<), 201.7 (d, $^2J_{CF}$=24.0, CH_3COCHF); m/z 175(M^+).

Fluorination of 4,4-dimethyl-3-oxo-pentane nitrile (**20**). 4,4-dimethyl-3-oxo-2-fluoropentane nitrile, $CNCHFCO{\cdot}C(CH_3)_3$ (**25**) (nc), (HRMS (NH_3/CI), Found: 161.1090; $C_7H_{14}FN_2O$ $(M+NH_4)^+$ requires 161.1090); δ_H=1.31 (9H, s), 5.69 (1H, d, J_{HF}=47.0); δ_F=−192.3 (d, J_{HF}=47.0); δ_C=25.76 (d, $^4J_{CF}$=2.3, CH_3), 44.29 (d, $^3J_{CF}$=2.7, $(CH_3)_3C$), 79.08 (d, $^1J_{CF}$=199.2, CFH), 112.29 (d, $^2J_{CF}$=29.7, CN), 200.59 (d, $^2J_{CF}$=17.9, CO); m/z (CI^+, NH_3) 161 $(M+NH_4)^+$ 11%, 101 (100). 4,4-dimethyl-3-oxo-2,2-difluoropentane nitrile, $CNCF_2CO.C(CH_3)_3$ (**26**) (not pure), δ_H=1.34 (s); δ_F=−94.2 (s); δ_C=30.02 (s, CH_3), 47.68 (s, $(CH_3)_3C$), 109.63 (t, $^1J_{CF}$=262.47 CF_2), 114.25 (t, $^2J_{CF}$=42.14, CN), 200.40 (t, $^2J_{CF}$=25.34, CO); m/z (CI^+, CH_4) 162 $(M+1)^+$ 22%, 85 (100).

Fluorination of 1-methanesulphonylpropan-2-one (**21**). 1-Fluoro-1-methanesulphonylpropan-2-one, CH_3SO_2CHF-$CO{\cdot}CH_3$ (**27**) (nc), (Found: C, 31.0; H, 4.4. $C_4H_7FO_3S$ requires C, 31.2; H, 4.5%, HRMS, Found; $(M+NH_4)^+$ 172.0444 $C_4H_{11}FNO_3S$ requires 172.04437); δ_H=2.5 (3H, d, $^4J_{HF}$=3.6, $CO{\cdot}CH_3$), 3.1 (3H, d, $^4J_{HF}$=2.2, $SO{\cdot}CH_3$), 5.6 (1H, d, $^2J_{HF}$=48.0, CHF); δ_F=−183.7 (dm, $^2J_{HF}$=47.0); δ_C=27.8 (s, CH_3S), 38.1 (s, CH_3C), 100.4 (d, $^1J_{CF}$=231, CHF), 196.0 (d, $^2J_{CF}$=20.4, CO); *m/z* (CI^+, NH_3) 172 ($(M+NH_4)^+$, 100%). 1,1-Difluoro-1-methanesulphonylpropan-2-one, $MeSO_2CF_2CO{\cdot}Me$ (**28**) (not pure), δ_F=−113.3 (s); *m/z* (CI^+, NH_3) 190 ($(M+NH_4)^+$, 100%).

Fluorination of dimethyl-2-oxypropyl phosphonate (**22**). Dimethyl-1-fluoro-2-oxypropyl phosphonate, $(CH_3O)_2$-$PO{\cdot}CHFCO{\cdot}CH_3$ (**29**) (nc), (HRMS, Found: $(M+NH_4)^+$ 202.0644. $C_5H_{14}FNO_4P$ requires 202.0644); δ_H=2.39 (3H, d, $^4J_{HF}$=4.5, $CO{\cdot}CH_3$), 3.9 (6H, d, d, $^2J_{HP}$=10.8, J=2.9, CH_3OP), 5.25 (1H, d,d, $^2J_{HF}$=47.7, $^2J_{HP}$=14.4, CHF); δ_F=−208 (ddq, $^2J_{FP}$=71.3, $^2J_{HF}$=47.8, $^4J_{HF}$=4.5); δ_P=12.7 (d, $^2J_{FP}$=71.2); δ_C=(50 MHz) 26.5 (s, $CH_3O{\cdot}C$), 54.2 (dd, $^2J_{CP}$=6.6, $^4J_{CF}$=2.0, CH_3OP), 91.0 (dd, $^1J_{CF}$=196.5, $^1J_{CP}$=152.5 CHF), 200.5 (d, $^2J_{CF}$=20.2, CFHCO); *m/z* (CI^+, NH_3) 202 ($(M+NH_4)^+$, 10%). Dimethyl-1,1-difluoro-2-oxypropyl phosphonate, $(CH_3O)_2$-$PO{\cdot}CF_2CO{\cdot}CH_3$ (**30**) (not pure), δ_F=−117.7 (d, $^2J_{FP}$=97); δ_P=5.9 (d, $^2J_{FP}$=97); *m/z* (CI^+, NH_3) 220 ($(M+NH_4)^+$, 100%).

Fluorination of ethyl cyanoacetate (**23**). Ethyl cyanofluoroacetate, $NCCHFCO{\cdot}OC_2H_5$ (**31**) [40], (HRMS (NH_3/CI), Found: 149.0730; $C_5H_{10}FN_2O_2$ $(M+NH_4)^+$ requires 149.0726); δ_H=1.39 (3H, t, J_{HH}=7.14, CH_3), 4.42 (2H, q, J_{HH}=7.14, CH_2), 5.50 (1H, d, J_{HF}=46.3, CHF); δ_F=−194.6 (d, J_{HF}=46.3); δ_C=13.89 (s, CH_3), 64.31 (s, (CH_2), 74.28 (d, $^1J_{CF}$=196.8, CFH), 111.62 (d, $^2J_{CF}$=29.8, CN), 160.64 (d, $^2J_{CF}$=24.7, CO); *m/z* (CI^+, NH_3) 149 $(M+NH_4)^+$ 3%, 61 (100). Ethyl cyanodifluoroacetate, $NCCF_2CO{\cdot}OC_2H_5$ (**32**) (not pure), δ_F=−97.4 s); *m/z* (CI^+, CH_4) 150$(M+1)^+$ 46%, 122 (100).

Fluorination of ethyl nitroacetate (**24**). Ethyl fluoronitroacetate, $O_2NCHFCO{\cdot}OC_2H_5$ (**33**) [41], (HRMS (CH_4/CI), Found: 152.0312; $C_4H_7FNO_4$ $(M+1)^+$ requires 152.0391); δ_H=1.38 (3H, t, J_{HH}=7.1, CH_3), 4.42 (2H, q, J_{HH}=7.1, CH_2), 6.06 (1H, d, J_{HF}=46.4, CHF); δ_F=−150.5 (d, J_{HF}=48.4); δ_C=13.75 (s, CH_3), 64.58 (s, CH_2), 102.72 (d, $^1J_{CF}$=248.9, CFH), 159.0 (d, $^2J_{CF}$=24.8, CO); *m/z* (CI^+, CH_4) 152$(M+1)^+$ 21%, 124 (100). Ethyl difluoronitroacetate, $O_2NCF_2CO{\cdot}OC_2H_5$ (**34**) [41,42], δ_H=1.41 (3H, t, J_{HH}=7.1, CH_3), 4.49 (2H, q, J_{HH}=7.1, CH_2); δ_F=−92.8 (s); δ_C=13.6 (s, CH_3), 65.8 (s, (CH_2), 112.9 (t, $^1J_{CF}$=297.5, CF_2), 155.9 (t, $^2J_{CF}$=31.3, CO); *m/z* (CI^+, CH_4) 170$(M+1)^+$ 16%, 74 (100).

Fluorination of triethyl phosphonoacetate (**35**). (SiO_2/Ethyl acetate) Triethyl 1-fluorophosphonoacetate, $(C_2H_5O)_2PO{\cdot}CHFCO{\cdot}OC_2H_5$ (**39**) [12,43,44], (HRMS, Found: $(M+NH_4)^+$ 260.1063; $C_8H_{20}FNO_5P$ requires 260.1063); δ_H=1.3 (9H, m), 4.3 (6H, m), 5.2 (1H, dd, J_{HF}=46.8, J_{HP}=11.7); δ_F=−211 (dd, $^2J_{FP}$=71.9, J_{HF}=46.8); δ_P=10.3 (d, J_{FP}=71.9); δ_C=(100 MHz) 13.5 (s, $COOCH_2CH_3$), 15.8 (d, $^3J_{CP}$=5.7, OCH_2CH_3), 61.8 (s, $COOCH_2CH_3$), 63.7 (t, $^2J_{CP}$ =^{4} J_{CF}=6.3, OCH_2CH_3), 84.4 (dd, $^1J_{CF}$=195, $^1J_{CP}$=158, CHF), 164.3 (d, $^2J_{CF}$=21.7, CO); *m/z* (CI^+, NH_3) 260 ($(M+NH_4)^+$ 100%). Triethyl 1,1-difluorophosphonoacetate, $(C_2H_5O)_2PO{\cdot}CF_2CO{\cdot}C_2H_5$ (**40**) (nc), (HRMS, Found: $(M+NH_4)^+$ 278.0969. $C_8H_{19}F_2NO_5P$ requires 278.0969); δ_H=1.4 (3H, m), 4.4 (2H, m); δ_P=2.96 (t, J_{FP}=96.2); δ_F=−117 (d, $^2J_{FP}$=96.2); δ_C=(100 MHz) 13.4 (s, $COOCH_2CH_3$), 15.9 (d, $^3J_{CP}$=5.3, OCH_2CH_3), 63.4 (s, $COOCH_2CH_3$), 65.2 (d, $^2J_{CP}$=6.5, OCH_2CH_3), 110.7 (dt, $^1J_{CF}$=271, $^1J_{CP}$=203, CF_2), 161.4 (q, $^2J_{CF}$=18.3, CO); *m/z* (CI^+, NH_3) 278 ($(M+NH_4)^+$ 100%).

Fluorination of triethyl 2-phosphonopropionate (**36**). (SiO_2/Ethyl acetate) Triethyl 2-fluoro-2-phosphonopropionate, $(C_2H_5O)_2PO{\cdot}C(CH_3)FCO{\cdot}OC_2H_5$ (**41**) (nc), (HRMS, Found: $(M+NH_4)^+$ 274.1220; $C_9H_{22}FNO_5P$ requires 274.1220); δ_H=1.3 (9H, m), 1.8 (3H, dd, J_{HF}=23.4, J_{HP}=15.1), 4.2 (6H, m); δ_F=−172 (dq, $^2J_{FP}$=83.3, $^3J_{HF}$=23.4); δ_P=13.4 (d, $^2J_{FP}$=83.3); δ_C=(100 MHz) 13.7 (s, $COOCH_2CH_3$), 16.1 (s, OCH_2CH_3), 19.9 (d, $^2J_{CF}$=21.8 CH_3CF), 62.1 (s, $COOCH_2CH_3$), 64.0 (dd, $^2J_{CP}$=19.1, $^4J_{CF}$=6.5 OCH_2CH_3), 92.7 (dd, $^1J_{CF}$, $^1J_{CP}$=165 and 193, CF), 167.6 (dd, $^2J_{CF}$=22.5, $^2J_{CP}$=4.9 CO); *m/z* (CI^+, NH_3) 274 ($(M+NH_4)^+$, 100%).

Fluorination of tetraisopropyl methylenediphosphonate (**37**). (SiO_2/Ethyl acetate) Tetraisopropyl fluoromethylenediphosphonate, $\{((CH_3)_2CH)_2PO{\cdot}\}_2CHF$ (**42**) (nc), (HRMS, Found: $(M+NH_4)^+$ 380.1767; $C_{13}H_{33}FNO_6P_2$ requires 380.1767); δ_H=1.37 (12H, d, J_{HH}=6.2), 1.38 (12H, d, J_{HH}=6.2), 4.8 (5H, m); δ_F=−227 (dt, J_{HF}=46, $^2J_{FP}$=64); δ_P=9.7 (d, $^2J_{FP}$=64); δ_C=(100 MHz) 23.6 (m, CH_3), 24.1 (d, $^3J_{CP}$=11.9, CH_3), 72.7 (d, $^2J_{CF}$=37.8, $CH(CH_3)$), 84.3 (dt, $^1J_{CF}$=191.5, $^1J_{CP}$ 158, CFH); *m/z* (CI^+, NH_3) 380 ($(M+NH_4)^+$, 24%). Tetraisopropyl difluoromethylenediphosphonate, $\{((CH_3)_2CH)_2PO{\cdot}\}_2CF_2$ (**43**) (nc), (HRMS, Found: $(M+NH_4)^+$ 398.1673; $C_{13}H_{32}F_2NO_6P_2$ requires 398.1673); δ_H=1.44 (3H, d, J_{HH}=6.2), 1.46 (3H, d, J_{HH}=6.2), 4.97 (1H, m); δ_P=2.3 (t, $^2J_{FP}$=87); δ_F=−123 (t, $^2J_{FP}$=87); δ_C=(100 MHz) 23.5 (s, CH_3), 24.1 (s, CH_3), 74.6 (s, $CH(CH_3)$), 115.5 (tt, $^1J_{CF}$=278.8, $^1J_{CP}$=189.6, CF_2); *m/z* (CI^+, NH_3) 398 ($(M+NH_4)^+$, 39%).

Fluorination of ethyl methanesulphonylacetate (**38**). (SiO_2/DCM) Ethyl methanesulphonyl fluoroacetate, $CH_3SO_2CHFCO{\cdot}OC_2H_5$ (**44**) (nc), (Found: C, 32.3; H, 4.7; $C_5H_9FO_4S$ requires C, 32.6; H, 4.9%); δ_H=1.42 (3H, t, J_{HH}=6.0), 3.1 (3H, d, J_{HF}=2.2), 4.42 (2H, q, J_{HH}=7.0), 5.6 (1H, d, J_{HF}=47.4); δ_F=−184 (dq, J_{HF}=47.3, $^4J_{HF}$=2.2); δ_C=(50 MHz) 13.7 (s, CH_2CH_3), 37.4 (s, SCH_3), 63.6 (s, CH_2), 96.5 (d, $^1J_{CF}$ CHF), 161.2 (d, CO, $^2J_{CF}$=23.1); *m/z* (CI^+, NH_3) 202 ($(M+NH_4)^+$, 35%). Ethyl methanesulphonyl difluoroacetate, $CH_3SO_2CF_2CO.OC_2H_5$ (**45**), (not pure) δ_F=−111 (s); δ_H=1.38 (3H, t, J_{HH}=7.1), 3.13 (3H, s), 4.55 (2H, q, J_{HH}=7.1); *m/z* (CI^+, NH_3) 220 ($(M+NH_4)^+$, 3%), 203 (M+1, 2), 63 (100).

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