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Direct Fluorination of 1,3-Dicarbonyl Compounds**†

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Abstract: In acid media, 1,3-diketones and 1,3-ketoesters can be fluorinated in high yield and often with high conversion mainly to the corresponding 2-fluoro- compounds. Diesters such as diethyl malonate do not react with fluorine under the same reaction conditions. The mechanism of these reactions has been investigated and while the identity of the electrophilic fluorinating species is uncertain, we believe that the essential features of the reaction pathway are understood.

Because of the growing importance of fluorinated organic compounds in biochemical systems[1,2], there is an existing and increasing demand for organic compounds containing one or two fluorine atoms. In recent years considerable effort has been devoted to finding ways of introducing fluorine into specific sites within small molecules to provide building blocks for the preparation of biologically active compounds which have more complex structures. In this context, the replacement of hydrogen at the 2-position in 1,3-diketones and 1,3-ketoesters by fluorine is one of the transformations that has aroused considerable interest.

This transformation has been carried out either by treating the parent compounds or their metal enolates with one of several "electrophilic fluorinating agents" that have been developed over the last fifteen years; for example, acetyl hypofluorite[3], perchloryl fluoride[4], xenon difluoride[5], lamellar $C_{19}XeF_6$[6], N-fluoro-pyridinium salts[7], N-fluorobis[(perfluoroalkyl)sulphonyl] imides[8], perfluoro-N-fluoropiperidine[9], the Selectfluor® Reagents[10] and caesium fluoroxysulphate[11].

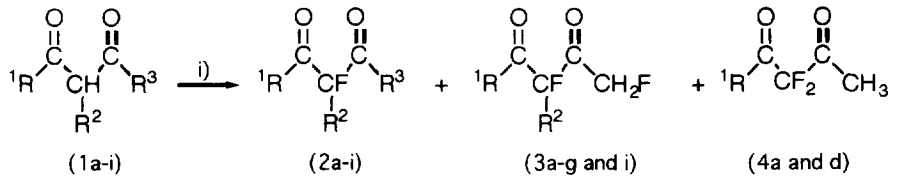
The only successful uses of elemental fluorine in the preparation of 2-fluoro-1,3-dicarbonyl compounds appear to have been by Purrington et. al.[12], who treated trimethyl silyl ethers of 1,3-ketoesters with fluorine at low temperature (-78 °C) and obtained the corresponding 2-fluoro-1,3-ketoesters in good yield, and by Adolph et. al. who fluorinated diethyl nitromalonate in aqueous sodium bicarbonate[13] and obtained diethyl fluoronitromalonate in high yield. We now wish to report that fluorine can be used directly to prepare 2-fluoro- 1,3-diketones and ketoesters.

Results and Discussion.

When fluorine, diluted with nitrogen, was passed through stirred solutions of 1,3-diketones and 1,3-ketoesters in formic acid at 10 -15 °C over two hours (Scheme 1), the results summarised in Table 1 were obtained.

† This paper is Part 2 in the series "Elemental Fluorine"

Scheme 1. Fluorination of 1,3-Dicarbonyl Compounds



i) 0.05mol fluorine (10% in nitrogen) /0.025mol substrate in 50ml formic acid/10-15 °C

Table 1. Reaction of elemental fluorine with 1,3-dicarbonyl compounds

1	R^1	R^2	R^3	2	3	4	Conversion,%
				Yield, %	Yield,%	Yield,%	
a	CH_3	H	CH_3	70	11	3	90
b	CH_3	CH_3	CH_3	76	9	-	90
c	CH_3	Cl	CH_3	65	7	-	85
d	OC_2H_5	H	CH_3	80	10	*ca.*1	60
e	OC_2H_5	CH_3	CH_3	85	5	-	25
f	OC_2H_5	Cl	CH_3	85	5	-	15
g	$-(CH_2)_4-$		CH_3	70	10	-	95
h	$-(CH_2)_4-$		OC_2H_5	90	-	-	90
i	$-O(CH_2)_2-$		CH_3	80	4	-	70

One of the most striking features of these reactions is the high yield and almost complete absence of tar formation despite being carried out at room temperature. At the end of the process, all of the monofluorinated products were essentially in their keto forms and, on work up, this remained so except in the case of 3-fluoro-2,4-pentanedione (**2a**). When the reaction product from the fluorination of 2,4-pentanedione (**1a**) was worked up but not distilled, the ^{19}F NMR spectrum showed the mono fluorinated product to comprise *ca.*15% of the previously unreported enol form (singlet at -173.7ppm) and furthermore, the enol content increased when the compound was vapourized. Thus, purification of the compound by preparative scale gas chromatography yielded a material containing *ca.* 35% enol, and when product from a large scale reaction was purified by fractionation under reduced pressure, the enol content of the distillate was *ca.* 95%. The re-formation of the keto tautomer was slow at room temperature but after about two months an equilibrium enol content of *ca.* 10% was reached. In formic acid however, ketonisation was very rapid and an equilibrium value of *ca.* 6% enol was soon attained. The rate of change in the concentrations of the enol and keto forms was measured by ^{19}F NMR spectrometry, and the first order rate constant for the ketonisation of 3-fluoro-2,4-pentanedione in formic acid was found to be 4.3×10^{-4} sec.$^{-1}$.

Mechanistic considerations.

Because each substrate was fluorinated under the same set of conditions, the amount of substrate converted into product over the 2 hour period may be regarded as a measure of its reactivity towards fluorine. Our findings are that, generally, 1,3-diketones are more reactive than the corresponding ketoesters, and diesters such as diethyl malonate fail to react. In the case of the 1,3-ketoesters, the observed relative reactivities are in the order ethyl 2-oxycyclohexane carboxylate (**1h**) > 2-acetyl butyrolactone (**1i**) > ethyl acetoacetate (**1d**) >> ethyl 2-methylacetoacetate (**1e**) > ethyl 2-chloro acetoacetate (**1f**) since the conversions into fluorinated products were >90%, 80%, 60%, 25% and 15% respectively. Following these observations, a series of competition reactions was carried out in which mixtures of pairs of keto esters were treated, over a period of 15 minutes, with *ca.*10% of the fluorine necessary for monofluorination. These experiments indicated the same order of reactivity as deduced above except for ethyl 2-chloroacetoacetate (**1f**) which appeared to have a similar reactivity to that of ethyl acetoacetate (**1d**) (Table 2).

Table 2. Relative reactivity of 1,3-ketoesters from competition experiments

Compound	Relative Reactivity
Ethyl 2-oxycyclohexane carboxylate, **1h**	6.7
2-Acetyl butyrolactone, **1i**	1.5
Ethyl acetoacetate, **1d**	1.0
Ethyl 2-chloro acetoacetate, **1f**	1.0
Ethyl 2-methylacetoacetate, **1e**	0.35

To help explain this apparent anomaly, tautomerisation of the substrates was examined in more detail since reaction of other halogens with ketones is known to proceed by attack of the halogen on the enol tautomer[16]. The enol content of substrates **1d - 1f** in formic acid was measured by analysing their ^{1}H NMR spectra. It was established that the enol contents of ethyl acetoacetate (**1d**) and ethyl 2 -methylacetoacetate (**1e**) were less than 5% but that the enol content of ethyl-2-chloroacetoacatate (**1f**) was *ca.*15%. Also, the rate of enolisation of these same substrates and **1h** in formic acid was measured by monitoring, by ^{1}H NMR, the rate at which the signal associated with the a CH diminished due to H/D exchange when the substrate was dissolved in a large excess of perdeuterioformic acid. The results of these exchange experiments showed the expected 1st order nature of the enolisation and the rate constants are presented in Table 3.

Table 3. Observed first order rate constants (k_1) and half lives for enolisation of 1,3-Ketoesters in perdeuterioformic acid

Substrate in D_2-formic acid at 20 °C	k_1 (sec^{-1})	Ketone enolisation half life
Ethyl 2-cyclohexanecarboxylate, **1h**	1.8×10^{-2}	-
Ethylacetoacetate, **1d**	2.6×10^{-4}	45 minutes
Ethyl 2-methylacetoacetate, **1e**	6.8×10^{-5}	*ca* 3 hours
Ethyl 2-chloroacetoacetate, **1f**	1.0×10^{-5}	*ca* 18 hours

Assuming that the kinetic isotope effect can be ignored, and that the generated hydrogen fluoride has little effect, it can be concluded that over the course of the reaction (2 hours) all of the ethyl 2-cyclohexylcarboxylate (**1h**) and most of the ethyl acetoacetate (**1d**) (essentially existing in keto form) have time to convert to the reactive enol form and react[14], less than half of the ethyl 2-methylacetoacetate (**1e**) (essentially existing in keto form) has time to enolise (25% starting material converted during fluorination reaction), and very little of the ethyl 2-chloroacetoacetate (**1f**) has time to convert to its reactive enol tautomer. The half-life of ethyl 2-chloroacetoacetate suggests that the 15% of this compound which is converted into product (Table 1) is in reality all produced from the enol component present at the beginning of the reaction. Indeed, when the fluorination of ethyl 2-chloroacetoacetate was monitored, *all* the product, **2f**, was formed in the first 15 minutes with scarcely any more being produced over the remaining reaction time.

Difluorination of 1,3-Dicarbonyls.

Previous work on the fluorination of 1,3-dicarbonyl compounds has shown that the structure of the difluorinated product obtained from 2,4-pentanedione depends upon the identity of the fluorinating agent. Thus the use of xenon difluoride[5] and N-fluorobis [(trifluoromethyl)sulphonyl]imide[8] yield the 3,3-difluoro- compound whereas caesium fluoroxysulphate[11] yields the 1,3- isomer. Furthermore, the introduction of a second fluorine atom appears to be no more difficult than the introduction of the first with these reagents. By contrast, in our reactions, difluorination occurs to only a small extent and reaction of fluorine with the monofluorinated compounds is much slower than reaction with the parent dicarbonyl. In substrates where there is a substituent in the 2- position, the second fluorine attacks the methyl (where present) adjacent to the carbonyl. In the cases of 2,4-pentanedione (**1a**) and ethyl acetoacetate (**1d**), where there are two potential sites for the second fluorine to attack, *i.e.* (-COCHFCO-) and (-$COCH_3$), it is interesting to note that more of the product is formed arising from attack on the terminal methyl group than by attack the carbon which already has a fluorine attached. This might suggest that the enol -$CHFC(OH)=CH_2$, A, is formed more rapidly than enol -$CF=C(OH)CH_3$, B, although this would be in sharp contrast to the enolisation of the parent substrates where the evidence points to -$CH=C(OH)CH_3$ being formed much more rapidly than -$CH_2C(OH)=CH_2$.

To assess the relative rates of the two potential enolisations, a sample of 3-fluoro-2,4-pentanedione was dissolved in perdeuterioformic acid and the rates at which intensities in the ^1H NMR spectrum due to -C*H*FCO- and -$COCH_2$*H* diminished were measured[15]. While it was found that the 3-hydrogen exchanged very slowly ($k_1 = 3x10^{-5}$ sec^{-1}), those of the methyl groups exchanged too slowly to be measured.

Thus the relative abundance of **3a** and **4a** in the reaction product is the opposite to what we might have anticipated from a consideration of the relative rates of enolisation. This implies that the two isomers are produced by different mechanisms. To understand the fluorination process better, a large excess of fluorine was passed through a solution of 2,4-pentanedione in formic acid (1.5 times scale of previously discussed reactions) and the abundance of the products, **2a**, **3a** and **4a**, was monitored throughout by ^{19}F NMR. The change in the concentration of **2a**, **3a**, and **4a** measured against an internal standard (α,α,α-trifluoromethylbenzene) with time is illustrated in Figures 1 and 2.

Figure 1. ^{19}F nmr integral due to 3-fluoro-2,4-pentanedione, **2a**, during fluorination

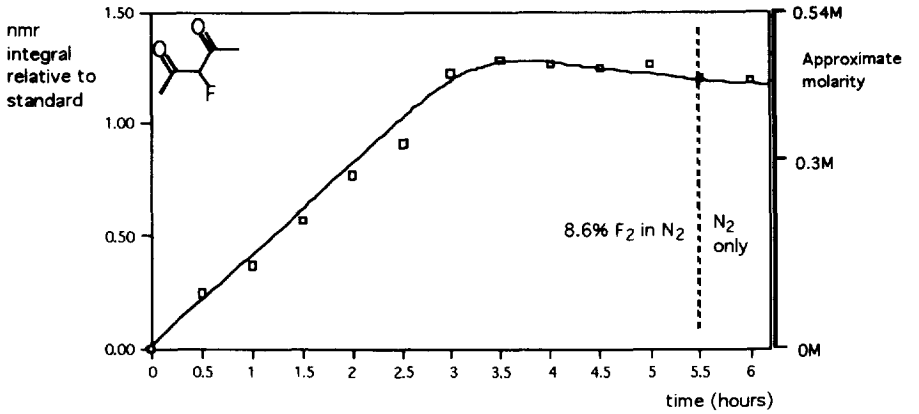
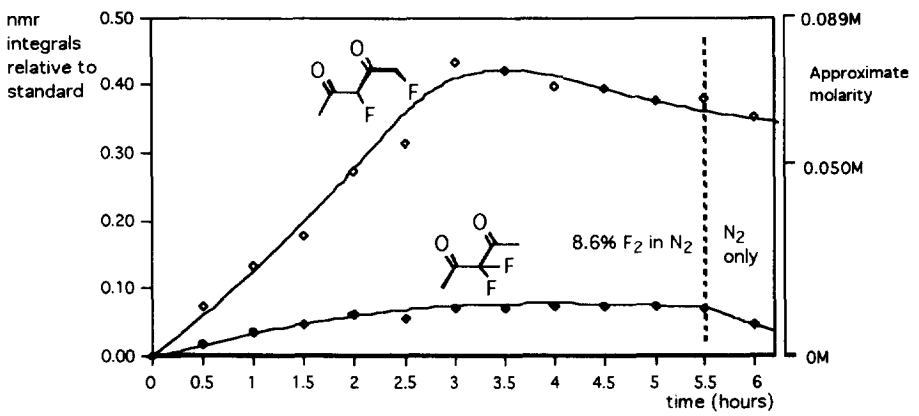
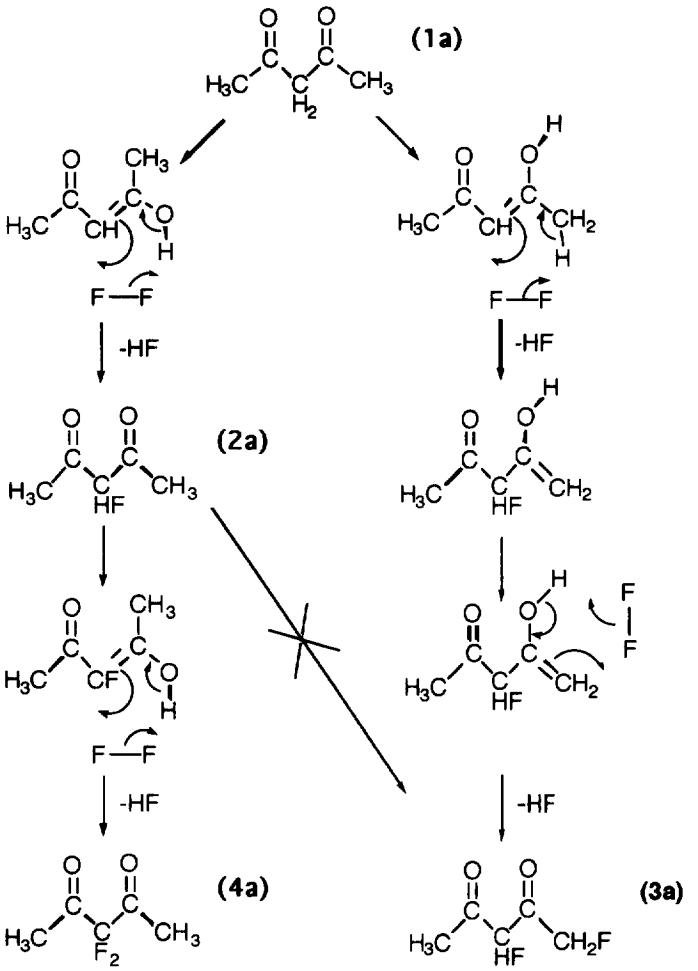


Figure 2. ^{19}F nmr integral due to 1,3- and 3,3-difluoro-2,4-pentanedione, **3a** and **4a** respectively during fluorination



From these it can be seen that all three compounds were formed from the *beginning* of the fluorination process. Initially, the monofluorinated product, **2a**, was the most rapidly formed compound but after about 3 hours (when all the starting material had reacted), a maximum was reached and then its concentration slowly declined. Interestingly, the concentration of the 1,3- difluorinated compound, **3a**, the second most rapidly generated product, reached a maximum at the same time, suggesting that this compound is not formed from **2a**[17]. The concentration of the 3,3-difluorinated compound, **4a**, reached a maximum and then remained essentially constant because its formation was also offset by evaporative loss in the gas stream. The graphs in Figures 1 and 2 also make it clear that difluorination is a very much slower process than monofluorination. These conclusions were confirmed when **2a**, purified by reduced pressure distillation, was fluorinated in formic acid and **4a** was the only difluorinated product. Therefore, while **4a** is produced by an analogous mechanism to that for the formation of **2a**, **3a** is probably formed by a mechanism akin to that suggested for the formation of 2,6-dichloro-4-*tert*-butyl cyclohexanone during the chlorination of 4-*tert*-butyl cyclohexanone[18] under acid conditions (Scheme 2).

Scheme 2. Proposed mechanism for the direct fluorination of 2,4-pentanedione.



Experimental.

NMR spectra were recorded on a Bruker AC250 spectrometer operating at 250 MHz for hydrogen or 235 MHz for fluorine with tetramethyl silane and fluorotrichloromethane as internal references. Unless stated otherwise, the spectra were recorded in $CDCl_3$. Except where stated otherwise, mass spectra were measured on a Fisons Trio 1000 mass spectrometer in the electron impact mode coupled to a Hewlett Packard 5890 II gas chromatograph fitted with a coated silicone elastomer column (25m. ; 0.2mm. i.d.). Accurate mass measurements were determined using a VG analytical 7070E mass spectrometer.

Fluorination reactions - General Procedure. Reactions were carried out under the conditions outlined in Scheme 1. The reaction vessel, constructed from FEP, was purged with nitrogen and cooled externally so that the internal temperature was maintained in the range stated (10-15 °C). A metered flow

of 50% fluorine in nitrogen, v/v, was diluted further with nitrogen to 10%, v/v, before being passed into a stirred solution of the substrate in formic acid. When reaction was complete, the vessel was purged with nitrogen before the product was worked up by pouring the reaction mixture into water, extracting with dichloromethane and removing the solvent from the dried extracts. The ^{19}F NMR spectrum of the reaction product was measured before it was poured into water to obtain the ratio of mono- to di-fluorinated products in case recovered material was not representative of the reaction product. Yields and conversions were calculated by analysis (GC and NMR) of the weighed recovered material. Pure samples of the main reaction products were obtained by GLC (10% SE30 on Chromosorb) but there was insufficient of the difluorinated products for them to be isolated. Most of the main products of these reactions have been made by other workers and so were identified by their NMR spectra, with confirmation from ms. Minor products were identified by NMR and GC/MS. Reactants were used as received.

Reaction of 2,4-Pentanedione (1a) with Fluorine. $CH_3COCHFCOCH_3$, (**2a**), (see lit. [5]) δ_H, 2.18 (m, enol CH_3), 2.31 (m, keto CH_3), 5.25 (d, J_{HF} = 50.0Hz, CHF); δ_F (keto), -192.0 (dm, J_{HF} = 49.2Hz) (enol), -173.7 (s). m/z (Found: 118.0419. Calc. for $C_5H_7FO_2$: 118.0430). *$CH_3COCHFCOCH_2F$, (3a)*, δ_F, -204.0 (d, J_{HF} = 42.4Hz), -236.6 (td, J_{HF} = 46.2Hz, J 2.8); m/z 136(M^+) 103(M-CH_2F) 43(CH_3O). $CH_3COCF_2COCH_3$, (**4a**), (see lit.[8a]) δ_F, -115.4 (s); m/z 136(M^+) 94(M-CH_2CO) 43(CH_3O).

Reaction of 3-Methyl-2,4-Pentanedione (1b) with Fluorine. $CH_3COC(CH_3)FCOCH_3$, (**2b**), (see lit. [8a]) δ_H, 1.62 (d, J_{HF} = 22Hz, CFC$\underline{H}_3$), 2.28 (s, CH_3), 2.30 (s, CH_3); δ_F, -158.0 (q, J_{HF} = 22Hz); m/z 133(M+1) 90(M-CH_2CO) 43(CH_3CO). *$CH_3COC(CH_3)FCOCH_2F$ (3b)*, δ_F, -166.1 (q, J_{HF} = 23Hz, 1F), -235.3 (t, J_{HF} = 46.5Hz, 1F); m/z 150(M^+), 61(CH_2FCO), 43(CH_3CO).

Reaction of 3-Chloro-2,4-Pentanedione (1c) with Fluorine. $CH_3COCClFCOCH_3$, (**2c**), (see lit.[8b]) δ_H, 2.44(d, J_{HF} = 2.5Hz, CH_3); δ_F, -126.2 (septet, J_{HF} = 2.6Hz); m/z 152(M^+), 117 (M-Cl), 110(M-$COCH_2$). *$CH_3COCClFCOCH_2F$, (3c)*, δ_F, -129.3 (m, 1F), -233.8 (td, J = 46.4Hz, J = 4.1Hz, 1F).

Reaction of Ethyl acetoacetate (1d) with Fluorine. $CH_3COCHFCOOC_2H_5$, (**2d**), (see lit.[8a,12]) δ_H, 1.34(t, J_{HH} = 7.2Hz $CH_2C\underline{H}_3$) 2.35(d, J_{HH} = 4.0Hz $COC\underline{H}_3$) 4.32(q, J_{HH} = 7.1Hz $OC\underline{H}_2$) 5.2(d, J_{HF} = 49.3Hz C$\underline{H}$F) δ_F, -193.7 (dq, J_{HF} = 49.4Hz); m/z 148(M^+) 106(M-CH_2CO) 43(CH_3CO). *$CH_2FCOCHFCOOC_2H_5$, (3d)*, δ_F, -204.5 (d, J_{HF} = 43Hz, 1F), -235.8(t, J_{HF} = 45.3Hz, 1F). $CH_3COCF_2COOC_2H_5$, (**4d**), (see lit[7b,8a]) δ_F, -114.7 (s).

Reaction of Ethyl 2-Methylacetoacetate (1e) with Fluorine. $CH_3COC(CH_3)FCOOC_2H_5$, (**2e**), (see lit.[8a]) δ_H, 1.31(t, J = 7.1Hz, C$\underline{H}_3CH_2$), 1.69(d, J = 22.2Hz, C$\underline{H}_3$CF), 2.33(d, J = 4.6Hz, $COC\underline{H}_3$), 4.28(q, J = 7.1Hz, C$\underline{H}_2$); δ_F, -157.7 (qq, $^2J_{HF}$ = 22.1Hz, ^5J = 4.5Hz); m/z 163(M^++1) 120(M-CH_2CO) 92($FCO_2C_2H_5$) 43($COCH_3$). *$CH_2FCOC(CH_3)FCOOC_2H_5$, (3e)*, δ_F, -166.6 (qm, J_{HF} = 23.2Hz, 1F), -236.7 (td, J = 46.7Hz, J = 3.7Hz, 1F).

Reaction of Ethyl 2-Chloroacetoacetate (1f) with Fluorine. $CH_3COCClFCOOC_2H_5$, (**2f**), (see lit.[8b])δ_H, 1.36(t, J_{HH} = 7.1Hz, C$\underline{H}_3CH_2$), 2.46(d, J_{HF} = 2.6Hz, C$\underline{H}_3CO$), 4.39(q, J_{HH} = 7.3Hz, $CH_3C\underline{H}_2$), δ_F, -123.5 (broad m); m/z 183(M+1) 43(CH_3CO). *$CH_2FCOCClFCOOC_2H_5$, (3f)*, δ_F, -127.6(s, 1F), -234.7(td, J_{HF} = 46.3Hz, J = 1.9Hz, 1F).

Reaction of 2-Acetylcyclohexanone (1g) with Fluorine. 2-Acety-2-fluorocyclohexanone, (**2g**), (see lit.[3]) δ_F, -157.8; m/z 158(M^+), 116(M^+-$COCH_2$) 43(CH_3CO). 2-(Fluoroacetyl)-2-

fluorocyclohexanone, (**3g**), (see lit.[3]) δ_F, -169(m, 1F), -236.9(td, J_{HF} = 46.8Hz, J = 7.3Hz, 1F); m/z 176(M^+) 134(M-CH_2CO) 43(CH_3CO).

Reaction of Ethyl 2-Cyclohexanone carboxylate (1h) with Fluorine. Ethyl 2-fluoro-2-cyclohexanone carboxylate (**2h**), δ_H, 1.33(t, J = 7.1Hz, $CH_2\underline{CH_3}$) 1.93(m, 4H) 2.1-2.8 (complex overlapping multiplet 4H) 4.30(q, J = 7.1Hz $\underline{CH_2}CH_3$) δ_F, -161.2 (t, J_{HF} = 16.4Hz); m/z 188(M^+).

Reaction of 2-Acetyl butyrolactone (1i) with Fluorine. *2-Fluoro-2-acetyl butyrolactone (2i),* δ_H, 2.47(d, J_{HF} = 5.0Hz, 3H), 2.55(m, 1H), 2.87(m, 1H), 4.5(m, 2H), δ_F, -163.4(ddqd, J = 11.8, 11.8, 4.9, and 1.5Hz). m/z Found (Chemical ionisation): 147.0442. $C_6H_8FO_3$ requires 147.0457). *2-Fluoro-2-(fluoroacetyl) butyrolactone (3i),* δ_F, -173.8 (m, 1F), -237.9(td, J = 46.3Hz, J = 6.8Hz, 1F).

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