Pergamon

Tetrahedron 54 (1998) 2867–2876

TETRAHEDRON

Alkylation and Decarboxylation of Ethyl 2-fluoro-3-oxobutanoate as a Route to Functionalised α-Fluoro-ketones

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Received 3 November 1997; revised 13 January 1998; accepted 15 January 1998

Abstract. Alkylation and decarboxylation of α-fluoro-β-ketoesters such as ethyl 2-fluoro-3-oxobutanoate offers a versatile route to a range of fluoro-ketoalkenes, demonstrating the synthetic utility of using α-fluoro-β-ketoesters as synthons for the preparation of synthetically more sophisticated selectively fluorinated systems.

Introduction

There is increasing interest and demand for selectively fluorinated molecules due to the profound changes in the physical, chemical and biological properties that can occur upon introduction of fluorine into an organic substrate. For example, selectively fluorinated substrates are playing an increasingly important role in the development of new pharmaceuticals and plant protection agents.[1]

Two approaches to the synthesis of selectively fluorinated compounds have been adopted. (1) Reaction of a fluorinating agent with a precursor results in functional group interconversion to give the target molecule directly (formation of carbon-fluorine bonds) and many reagents have been developed in an attempt to perform transformations in both high yield and high selectivity under mild conditions, with varying degrees of success.[2,3] (2) Synthesis of target molecules from smaller 'building blocks' that already contain fluorine (fluorinated synthons) is another approach (formation of carbon-carbon bonds),[4-7] providing that a range of fluorine containing synthons are readily available. Both methods are, therefore, mutually compatible.

The generality of using a fluorinated synthon approach to the preparation of selectively fluorinated compounds depends on developing methodology for the preparation of versatile fluorine containing building blocks and establishing their fundamental reaction chemistry. To be generally useful, a fluorinated synthon must be readily prepared, easily purified and synthetically versatile, and several approaches to the preparation of selectively fluorinated compounds using various fluorinated building blocks have been described.[7]

The carbonyl group is, of course, of fundamental importance in organic synthesis[8] since carbon-carbon bonds may be formed by either reaction directly with the carbonyl group (e.g. Grignard reagents, Wittig reactions, etc.) or by reaction with the corresponding enolates (e.g. alkylation, aldol condensations, etc.). Consequently, general routes to α-fluoro carbonyl derivatives have long been sought[9] in order to exploit the synthetic potential of such species. Although there has been extensive work directed to the preparation of various α-fluoro carbonyl and related fluoro β-dicarbonyl derivatives there has, nevertheless, been a lack of a general, simple, high-yielding synthetic procedure which may be readily scaled up. As a consequence, subsequent exploration of the chemistry of such fluorinated synthons has been hampered.

PII: S0040-4020(98)00040-4

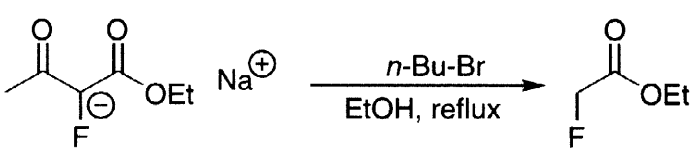
Recently, workers from these laboratories[10-12] reported high yielding routes to a range of fluorinated β-dicarbonyl systems using direct fluorination methodology which have been scaled-up to provide large quantities of these potentially useful substrates.[13] However, the chemistry of, for example, synthons such as 2-fluoro-ethylacetoacetate and related α-fluoro-β-ketoesters remains relatively undeveloped almost certainly due to a prior lack of a suitable synthetic route to these compounds and the literature contains only scattered examples of alkylation,[14] Michael addition,[15] use in the preparation of fluoroheterocyclic systems[16,17] and decarboxylation[18] reactions involving this class of fluorinated substrate. No detailed systematic studies of the reactions of, for example, α-fluoro-β-ketoesters have been carried out and, furthermore, a study of the reactions of α-fluorodicarbonyl compounds provides a useful probe for studying the influence of a fluorine atom upon the reactivity of such substrates. In the present paper, we describe alkylation and decarboxylation reactions of some α-fluoro-β-ketoesters as a method for the synthesis of potentially useful fluoro-ketoalkenes.

Results and Discussion

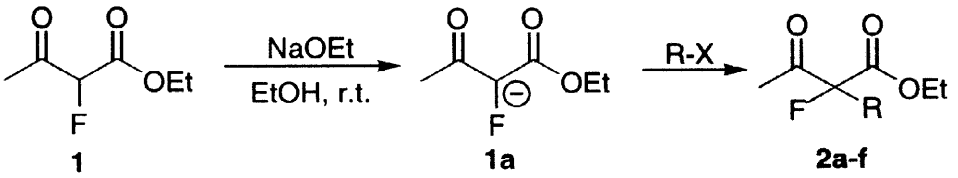
As previously described,[10] preparation of α-fluoro-β-ketoesters is achieved by passing an excess of fluorine, diluted to 10% mixture in nitrogen (v/v), through a solution of the ketoester in formic acid at 5°C, followed by work-up involving addition of the reaction mixture to water and extraction of the mono-fluorinated product into dichloromethane. Evaporation of the solvent leaves fluoro-ketoester in >98% purity by GC. Although some difluoro-ketoesters are produced as by-products in the fluorination reaction, the high volatility of these compounds enables their easy removal at the solvent evaporation stage of the work-up and, therefore, no further purification of the desired monofluoro-ketoester is required.

The carbanion species **1a** generated at room temperature by deprotonation of **1** using either sodium ethoxide/ethanol or sodium hydride/THF as the base/solvent system was trapped by a range of allyl, propargyl and benzyl bromides to give products **2a-f** in good yield (Table 1). ^{19}F nmr of the crude reaction mixture showed only the presence of reaction at the carbon site and no evidence for alkylation at oxygen was observed.

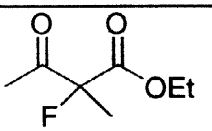
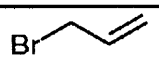
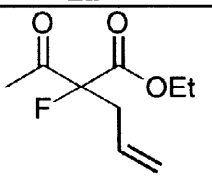
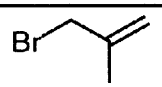
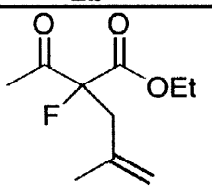
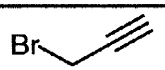
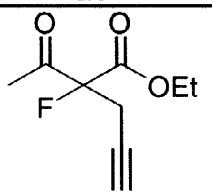
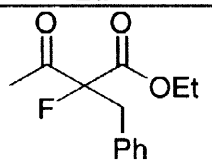
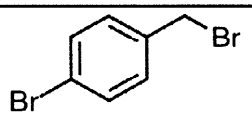
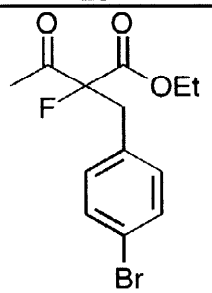
Methylation of carbanion **1a** by methyl iodide was also achieved at room temperature to give the methyl derivative **2a** (Table 1) in good yield. However, alkylation of carbanion **1a** using longer chain alkyl iodides such as *n*-butyl iodide is extremely slow at room temperature and not preparatively useful, consistent with increasing the steric hindrance to nucleophilic attack by the carbanion on the alkyl iodide substrates leading to reaction rate retardation. Furthermore, attempts to increase the rate of alkylation by heating a mixture of the carbanion **1a** in ethanol with *n*-bromobutane resulted in decomposition of the carbanion species **1a** and no alkylated products were observed. ^{19}F nmr analysis of the crude reaction mixture showed only one triplet at -230ppm ($J_{H,F}$ 47 Hz) corresponding to the presence of a CH_2F group, which is consistent with the data reported for 2-fluoroethylacetate.[19]



It is well known that when hydrogen attached to a carbon atom bearing negative charge that has sp_2 character (planar system) is replaced by fluorine, as in **1a**, then lone pair-electron pair repulsions (-Iπ) is maximised due to the geometry of the system and the stability of the carbanion decreases.[20] Thus, carbanion **1a** is less stable than the corresponding carbanion prepared from ethyl acetoacetate and this explains the decomposition of carbanion **1a** at temperatures higher than ambient.



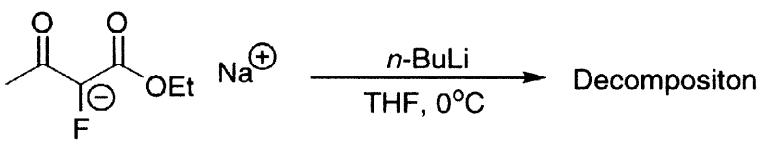
1 1a 2a-f

R-X	Product	Yield[a]
CH_3-I	 **2a**	68
	 **2b**	62
	 **2c**	64
	 **2d**	74
Ph-CH_2Br	 **2e**	65
	 **2f**	64

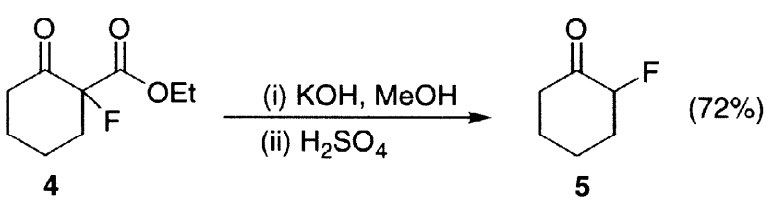
a) Isolated yield of pure compound

Stirring a solution of carbanion **1a** with dimethyl sulphate in THF overnight at room temperature gave, after the usual work-up, a mixture of at least 10 products as observed by ^{19}F nmr and GC/MS. Purification and identification of the components of the mixture was not achieved. Also, attempted methylation of **1a** by methyl tosylate gave no isolable products.

γ-Alkylation of β-ketoesters, involving generation and reaction of the appropriate dianions, has been widely exploited in organic synthesis. *n*-Butyl lithium was added to a solution of **1a** in THF at 0°C, following the method for generating dianions from ketoesters described in the literature.[21] Addition of allyl bromide, stirring overnight and work up gave a crude product that consisted of recovered allyl bromide and a large number of products (GC) resulting from the decomposition of the fluorinated starting material. The dianion is unstable presumably due to the factors already discussed above.



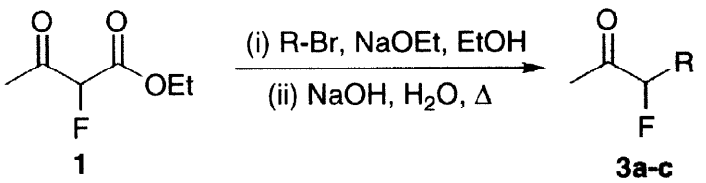
Decarboxylation of **2b** and **2e** proceeds smoothly upon heating with sodium hydroxide in ethanol to give potentially versatile fluoro-ketoalkenes **3a** and **3c** respectively in good yield (Table 2). However, alkylation and decarboxylation of ketoester **1** could be carried out in a one-pot process allowing very easy access to a range of functionalised α-fluorocarbonyl derivatives. The synthesis of **3b**, useful as a precursor to fluoro-terpenoid systems, has recently been reported using a multistep low yielding process.[22] Similarly, decarboxylation of **4** gives 2-fluorocyclohexanone **5**.



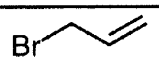
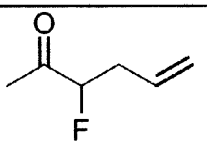
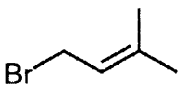
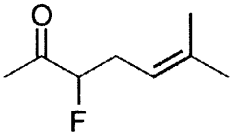
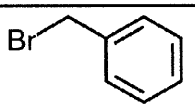
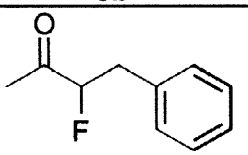
4 **5**

In summary, alkylation of carbanions generated from α-fluoro-ketoester **1** by reactive alkylating agents, such as allyl and benzyl bromides, is possible at room temperaure and subsequent decarboxylation of the alkylated products leads to a range of potentially useful fluoro-ketoalkenes. However, the synthetic utility of fluoro-ketoesters is limited by the instability of the corresponding anions and dianions at, or above, room temperature under the present conditions. This methodology demonstrates that the synthesis of many poly-functional selectively fluorinated substrates is possible by combining large scale direct fluorination processes with simple, high yielding, clean carbon-carbon bond forming reactions via carbanionic intermediates, using readily available bulk chemicals as start materials under extremely mild, convenient conditions. Consequently, the methodology described above is readily available for scale-up and further development of this building block approach for the preparation of selectively fluorinated molecules from fluoro-β-ketoesters is in progress.

Table 2. Preparation of Fluoroketones by alkylation/decarboxylation



1 3a-c

R-Br	Product	Yield
	 **3a**	67
	 **3b**	75
	 **3c**	77

Experimental

All start materials were either obtained commercially (Aldrich) or prepared by literature procedures and all solvents were dried before use. NMR spectra were recorded in deuteriochloroform on either a Varian Gemini 200, a Varian VXR 400S or a Bruker AC250 n.m.r. spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Coupling constants are given in Hz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fissons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer while elemental analyses were obtained on either a Perkin-Elmer 240 or a Carlo Erba Elemental Analyser. Melting points and boiling points were recorded at atmospheric pressure and are uncorrected. Column chromatography was performed using silica gel (Merck No. 9385) and silica plates (Merck) were used for TLC analysis.

Preparation of Ethyl-2-fluoro-3-oxobutanoate **1**

Ethyl acetoacetate (50.0g, 0.38mol) and formic acid (750ml) were placed in a fluorination vessel which was equipped with an overhead stirrer, a gas inlet and a gas outlet that led to a scrubbing tube packed with soda lime. The vessel was purged with dry nitrogen and cooled to 0°C by an external cryostat. A mixture of fluorine and nitrogen (10% F_2 : N_2 v/v) was passed through the stirred solution at a rate of *ca.* 250ml/min (approx. 70mmol F_2 per hour) for 16 hr (total amount of fluorine (*ca* 1.1mol). After the fluorine had been added, the reaction mixture was purged with nitrogen, poured into water (1000ml) and extracted with dichloromethane (3 x

200ml). The organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to leave ethyl-2-fluoro-3-oxobutanoate[10] **1** (35.2g, 62%)(>98% pure by GC); δ_H 1.34 (3H, t, J_{HH} 7.2, CH_2CH_3), 2.35 (3H, d, J_{HF} 4.0, CH_3CO), 4.32 (2H, q, J_{HH} 7.2, O-CH_2), 5.2 (1H, d, J_{HF} 49.3, CHF); δ_F -193.7 (d, J_{HF} 49.4); δ_C 15.8 (s, CH_3), 27.8 (s, CH_3CO), 64.5 (s, OCH_2), 93.3 (d, $^1J_{CF}$ 196.3, CF), 165.9 (d, $^2J_{CF}$ 23.6, CO-O), 200.7 (d, $^2J_{CF}$ 23.1, CO-CH_3); m/z (EI^+) 148 (M^+, 0.1%), 106 (4, M^+-CH_2CO), 78 (11), 43 (100, CH_3CO); the crude ethyl-2-fluoro-3-oxobutanoate **1** was used in the following reactions without any further purification.

Preparation of Ethyl 1-fluoro-2-oxocyclohexanecarboxylate **4**

By a similar procedure to that described above, ethyl 2-oxocyclohexanecarboxylate (8.5g, 50mmol), fluorine (*ca.* 120mmol) and formic acid (100ml) gave ethyl 1-fluoro-2-oxocyclohexanecarboxylate **4** (8.5g, 90%)(>95% pure by GC) as a colourless liquid; δ_H 1.20 (3H, t, J 7.1, CH_3), 1.6-2.6 (8H, m, ring H), 4.18 (2H, q, J 7.1, O-CH_2); δ_F - 161.02 (s); δ_C 15.9 (s, CH_3), 22.9 (s, ring CH_2), 28.4 (s, ring CH_2), 37.9 (d, $^2J_{CF}$ 21.5, CH_2-CHF), 41.6 (s, CH_2-CO), 64.2 (s, OCH_2), 98.2 (d, $^1J_{CF}$ 195.3, CF), 168.7 (d, $^2J_{CF}$ 24.6, CO-O), 203.7 (d, $^2J_{CF}$ 19.7, C=O); m/z (EI^+) 188 (M^+, 3%), 140 (12), 95 (10), 73 (15), 67 (40), 59 (40), 41 (73), 29 (100); as compared to the literature data;[10] the ethyl 1-fluoro-2-oxocyclohexanecarboxylate **4** was used in subsequent reactions without any further purification.

Alkylation of Ethyl-2-fluoro-3-oxobutanoate

General Procedure - use of sodium ethoxide as base

Ethyl-2-fluoro-3-oxobutanoate **1** and sodium ethoxide were added under nitrogen to dry ethanol and stirred at room temperature for one hour after which the alkyl bromide was added and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with dichloromethane. The organic extracts were dried and the solvent was evaporated under reduced pressure to leave the alkylated product which was further purified by column chromatography on silica gel.

Ethyl-2-fluoro-2-methyl-3-oxobutanoate **2a**

Ethyl-2-fluoro-3-oxobutanoate **1** (1.3g, 8.8mmol), methyl iodide (1.4g, 9.8mmol) and sodium ethoxide (0.7g, 10mmol) in ethanol (10ml) gave ethyl-2-fluoro-2-methyl-oxobutanoate **2a** (0.96g, 68%) as a colourless liquid; (Found: C, 51.2; H, 6.8. $C_7H_{11}FO_3$ requires: C, 51.8; H, 6.8%); δ_H (400MHz) 1.31 (3H, d, J 7.2, CH_2-C**H**$_3$), 1.69 (3H, d, $^3J_{HF}$ 22.4, CF-CH_3), 2.33 (3H, d, $^4J_{HF}$ 4.4, CH_3-C=O), 4.28 (2H, q, J 7.2, CH_2); δ_F (376MHz) -157.16 (qq, $^3J_{HF}$ 22.4, $^4J_{HF}$ 4.4); δ_C (100MHz) 14.0 (s, CH_2**C**H_3), 19.8 (d, $^2J_{CF}$ 22.9, CF-**C**H_3), 25.0 (s, **C**H_3-C=O), 62.6 (s, CH_2), 97.7 (d, $^1J_{CF}$ 193.4, CF), 166.9 (d, $^2J_{CF}$ 25.1, C=O-O), 202.3 (d, $^2J_{CF}$ 28.6, >C=O); m/z (EI^+) 120 (M^+-CH_2CO, 34%), 92 (21), 43 (100); as compared to the literature data.[10]

Ethyl-2-fluoro-2-(1-oxoethyl)-4-pentenoate **2b**

Ethyl-2-fluoro-3-oxobutanoate **1** (5.50g, 37mmol), allyl bromide (4.5g, 37mmol) and sodium ethoxide (2.5g, 37mmol) in ethanol (20ml) gave ethyl-2-fluoro-2-(1-oxoethyl)-4-pentenoate **2b** (4.3g, 62%) as a colourless liquid; R_F 0.61 (CH_2Cl_2); (Found: C, 57.3; H, 7.0. Calc. for $C_9H_{13}FO_3$: C, 57.4; H, 6.9%); δ_H (400MHz) 1.26 (3H, t, $^3J_{HH}$ 7.2, -CH_2-C**H**$_3$), 2.26 (3H, d, $^4J_{HF}$ 4.8, CH_3-CO), 2.81 (2H, m, **C**H_2-CH=),

4.23 (2H, m, -O-CH_2), 5.16 (2H, m, =CH_2), 5.68 (1H, m, -CH=); δ_F (235MHz) -166.70 (m); δ_C (100MHz) 13.9 (s, CH_3-CH_2), 25.8 (s, CH_3-CO), 38.0 (d, $^2J_{CF}$ 20.6, CH_2-CF), 62.5 (s, CH_2-O), 99.4 (d, $^1J_{CF}$ 198.3, CF), 120.8 (s, =CH_2), 129.1 (d, $^3J_{CF}$ 2.0, -CH=), 165.7 (d, $^2J_{CF}$ 25.5, CO-O), 201.6 (d, $^2J_{CF}$ 28.6, >C=O); m/z (EI^+) 146 (M^+-CH_2-CO, 65%), 118 (42), 73 (18), 43 (100).

Ethyl 2-fluoro-4-methyl-2-(1-oxoethyl)-4-pentenoate **2c**

Ethyl-2-fluoro-3-oxobutanoate **1** (1.3g, 8.8mmol), 3-bromo-2-methylpropene (1.35g, 10mmol) and sodium ethoxide (0.7g, 10mmol) in ethanol (10ml) gave ethyl 2-fluoro-4-methyl-2-(1-oxoethyl)-4-pentenoate **2c** (1.1g, 64%) as a colourless liquid; R_F 0.67 (CH_2Cl_2); (Found: C, 59.1; H, 7.5. Calc. for $C_{10}H_{15}FO_3$: C, 59.4; H, 7.4%); δ_H (400MHz) 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3), 1.78 (3H, s, =C-CH_3), 2.31 (3H, d, $^4J_{HF}$ 4.8, CH_3-C=O), 2.73 and 2.86 (1H, AB, J_{AB} 14.8, CF-CH_A), 2.79 and 2.92 (H, AB, J_{AB} 14.8, CF-CH_B), 4.26 (2H, m, O-CH_2), 4.82 (1H, m, =CH), 4.92 (1H, m, =C-H); δ_F (376MHz) -164.6 (m); δ_C (100MHz) 14.0 (s, CH_2CH_3), 23.8 (d, $^4J_{CF}$ 2.6, CH_3-C=), 25.9 (s, CH_3-C=O), 41.1 (d, $^2J_{CF}$ 20.2, CH_2-CF), 62.6 (s, OCH_2), 100.4 (d, $^1J_{CF}$ 199.8, CF), 116.2 (s, =CH_2), 138.5 (s, CH_3-C=), 165.9 (d, $^2J_{CF}$ 25.5, CO-O), 201.7 (d, $^2J_{CF}$ 28.9, C=O); m/z (EI^+) 160 (M^+-CH_2CO, 39%), 132 (38), 131 (16), 43 (100).

Ethyl 2-fluoro-2-(1-oxoethyl)-4-pentynoate **2d**

Ethyl-2-fluoro-3-oxobutanoate **1** (3.0g, 20mmol), propargyl bromide (2.4g, 20mmol) and sodium ethoxide (1.4g, 20mmol) gave ethyl 2-fluoro-2-(1-oxoethyl)4-pentynoate **2d** (2.8g, 74%) as a colourless liquid; R_F 0.71 (CH_2Cl_2); (Found: C, 57.7; H, 5.8. Calc. for $C_9H_{11}FO_3$: C, 58.0; H, 5.9%); δ_H (400MHz) 1.32 (3H, t, $^3J_{HH}$ 7.0, CH_3-CH_2), 2.11 (1H, t, $^4J_{HH}$ 2.7, C-H), 2.37 (3H, d, $^4J_{HF}$ 4.8, CH_3-CO), 3.02 (2H, dm, $^2J_{HH}$ 22.7, CH_2), 4.30 (2H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, CH_3-CH_2); δ_F (235MHz) -165.0 (m); δ_C (100MHz) 14.0 (s, CH_2-CH_3), 24.5 (d, $^2J_{CF}$ 21.7, CH_2-CF), 26.0 (s, CH_3-CO), 63.1 (s, O-CH_2), 72.2 (s, CH), 76.2 (s, -C=), 97.8 (d, $^1J_{CF}$ 201.7, C-F), 164.9 (d, $^2J_{CF}$ 24.9, -CO-O-), 201.0 (d, $^2J_{CF}$ 28.5, >C=O); m/z (EI^+) 144 (M^+ - CH_2-CO, 20%), 115 (8), 43 (100).

Ethyl 2-benzyl-2-fluoro-3-oxobutanoate **2e**

Ethyl-2-fluoro-3-oxobutanoate **1** (3.0g, 20mmol), benzyl bromide (3.4g, 20mmol) and sodium ethoxide (1.4g, 37mmol) gave ethyl 2-benzyl-2-fluoro-3-oxobutanoate **2e** (3.1g, 65%) as a colourless liquid; R_F 0.62 (CH_2Cl_2); (Found: C, 65.6; H, 6.3. Calc. for $C_{13}H_{15}FO_3$: C, 65.5; H, 6.3%); δ_H (400MHz) 1.23 (3H, t, J 7.2, CH_2CH_3), 2.11 (3H, d, $^4J_{HF}$ 4.8, CH_3CO), 3.39 (2H, dd, $^2J_{HH}$ 25.6, $^3J_{HF}$ 5.6, CH_2-CHF), 4.21 (2H, q, $^3J_{HH}$ 7.2, OCH_2), 7.15-7.3 (5H, m, Ar-H); δ_F (235MHz) -165.15 (m); δ_C (100MHz) 13.8 (s, CH_3-CH_2), 26.1 (s, CH_3-CO), 39.6 (d, $^2J_{CF}$ 20.6, CH_2-CF), 62.5 (s, CH_2-O), 99.9 (d, $^1J_{CF}$ 200.2, C-F), 127.4 (s, Ar-C4), 128.3 (s, Ar-C2), 130.2 (s, Ar-C3), 133.0 (s, Ar-C1), 165.6 (d, $^2J_{CF}$ 25.6, CO-O), 202.2 (d, $^2J_{CF}$ 29.4, >C=O); m/z (EI^+) 218 (M^+-HF, 32%), 196 (30), 195 (20), 91 (25), 43 (100).

Ethyl 2-fluoro-2-[(4-bromophenyl)methyl]-3-oxobutanoate **2f**

Ethyl-2-fluoro-3-oxobutanoate **1** (2.96g, 20mmol), 4-bromo-benzyl bromide (5.0g, 20mmol) and sodium ethoxide (1.36g, 20mmol) in ethanol (20ml) gave ethyl 2-fluoro-2-[(4-bromophenyl)methyl]-3-oxobutanoate **2f** (4.0g, 64%) as a colourless liquid; R_F 0.67 (CH_2Cl_2); (Found: C, 49.4; H, 4.5. Calc. for $C_{13}H_{14}BrFO_3$: C, 49.2; H, 4.4%); δ_H (400MHz) 1.25 (3H, t, $^3J_{HH}$ 7.2, CH_3CH_2), 2.16 (3H, d, $^4J_{HF}$ 5.2,

CH_3CO), 3.3-3.4 (2H, m, CH_2-CF), 4.22 (2H, q, $^3J_{HH}$ 7.2, CH_2-CH_3), 7.10 and 7.41 (4H, AX, J_{AX} 8.0, Ar-H); δ_F (235MHz) -164.85 (tq, $^3J_{HF}$ 25.6, $^4J_{HF}$ 4.9); δ_C (100MHz) 13.9 (s, CH_3), 26.2 (s, CH_3CO), 39.0 (d, $^2J_{CF}$ 20.2, CH_2-CF), 62.8 (s, OCH_2), 99.7 (d, $^1J_{CF}$ 200.2, CF), 121.6 (s, C-Br), 131.5 (s, Ar-C2), 132.1 (s, Ar-C3), 137.9 (s, Ar-C1), 165.4 (d, $^2J_{CF}$ 25.5, CO-O), 201.9 (d, $^2J_{CF}$ 29.1, CO); m/z (EI^+) 316 (M^+, 1.5%), 318 (M^+, 1.5%), 217 (12), 158 (27), 156 (26), 43 (100).

Attempted alkylation using n-bromobutane

Ethyl-2-fluoro-3-oxobutanoate **1** (3.0g, 20 mmol) and sodium ethoxide (1.4g, 20 mmol) were added under nitrogen to dry ethanol (20 ml) and stirred at room temperature for one hour after which n-bromobutane (2.8g. 20 mmol) was added and the reaction was heated to reflux for 5 h. ^{19}F nmr analysis of the crude reaction mixture showed that a sole product had been formed which was identified as 2-fluoro-ethylacetate; δ_F -230.3 (t, $^2J_{HF}$ 47, CH_2F) as compared to literature values.[19] Further purification was not attempted.

Decarboxylation Reactions

2-Fluoro-cyclohexanone **5**

Ethyl 1-fluoro-2-oxocyclohexanecarboxylate **4** (7.0g, 37mmol) was added to a solution of potassium hydroxide (2.7g, 48mmol) in methanol (60ml) and water (40ml). and left to stand at room temperature overnight. The aqueous layer was extracted by ethyl acetate. After methanol had been distilled from the aqueous layer under vacuum, dilute sulphuric acid was added until CO_2 evolution ceased. Extraction by dichloromethane (3 x 20ml), drying ($MgSO_4$) and evaporation gave crude *2-fluorocyclohexanone* **5** (3.1g, 72%); δ_F (235MHz) -188.74 (d, $^2J_{HF}$ 47.8); m/z (EI^+) 116 (M^+, 16%), 72 (12), 59 (24), 55 (100), 42 (66); as compared to literature data.[23,24]

Alkylation/Decarboxylation Reactions

General Procedure

Ethyl-2-fluoro-3-oxobutanoate **1** and sodium ethoxide were added under nitrogen to dry ethanol and stirred at room temperature for one hour after which the alkyl bromide was added and the reaction was stirred at room temperature overnight. Sodium hydroxide dissolved in water (15ml) was added to the mixture which was then heated at reflux temperature for 3 hours. Water (50ml) was added to the cooled solution which was then extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated at reduced pressure to leave the desired products which were further purified by column chromatography on silica gel using dichloromethane as eluant.

3-Fluoro-5-hexen-2-one ***3a***

Ethyl-2-fluoro-3-oxobutanoate **1** (5.50g, 37mmol), allyl bromide (4.5g, 37mmol) and sodium ethoxide (2.5g, 37mmol) followed by sodium hydroxide (1.8g, 45mmol) gave 3-fluoro-5-hexen-2-one[15] **3a** (2.9g, 67%) as a colourless liquid; δ_H (400MHz) 2.25 (3H, d, $^4J_{HF}$ 4.8, CH_3), 2.4-2.7 (2H, m, CH_2), 4.78 (1H, ddd, $^2J_{HF}$ 50.0, $^3J_{HH}$ 7.2, $^3J_{HH}$ 4.4, CFH), 5.18 (2H, m, $=CH_2$), 5.80 (1H, ddt, $^3J_{HH}$ 17.2, $^3J_{HH}$ 10.0, $^3J_{HH}$ 7.2, -CH=); δ_F (235MHz) -190.00 (m); δ_C (100MHz) 26.2 (s, CH_3), 36.1 (d, $^2J_{CF}$ 21.0, CH_2), 94.9 (d, $^1J_{CF}$ 186.2, CF), 119.3 (s, CH_2=), 131.0 (d, $^3J_{CF}$ 3.4, CH=), 207.6 (d, $^2J_{CF}$ 25.9, C=O); m/z (EI^+) 96 (M^+-HF, 17%), 81 (25), 53 (17), 43 (100), 39 (12).

3-Fluoro-6-methyl-hepten-2-one **3b**

Ethyl-2-fluoro-3-oxobutanoate **1** (3.0g, 20mmol), 2-methyl-4-bromo-but-2-ene (3.0g, 20mmol) and sodium ethoxide (1.4g, 20mmol) followed by sodium hydroxide (1.0g, 25mmol) gave 3-fluoro-6-methyl-hepten-2-one[22] **3b** (2.2g, 75%) as a colourless liquid; δ_H (400MHz) 1.62 (3H, s, CH_3), 1.73 (3H, s, CH_3), 2.24 (3H, d, $^4J_{HF}$ 4.8, CH_3-CO), 2.52 (2H, dt, $^2J_{HH}$ 26.0, $^3J_{HF}$ 6.0, CH_2), 4.73 (1H, ddd, $^2J_{HF}$ 49.6, $^3J_{HF}$ 6.0, $^3J_{HF}$ 5.4, CHF), 5.15 (1H, m, -CH=); δ_F (235MHz) -189.00 (m); δ_C (100MHz) 17.9 (s, CH_3), 25.8 (s, CH_3), 26.2 (s, CH_3-CO), 30.8 (d, $^2J_{CF}$ 21.0, CH_2), 95.6 (d, $^1J_{CF}$ 185.8, CF), 116.5 (d, $^3J_{CF}$ 3.4, -CH=), 136.3 (s, =C<), 208.1 (d, $^2J_{CF}$ 25.9, >C=O).

3-Fluoro-4-phenyl-2-butanone **3c**

Ethyl-2-fluoro-3-oxobutanoate **1** (3.0g, 20mmol), benzyl bromide (4.5g, 37mmol) and sodium ethoxide (1.4g, 20mmol) followed by sodium hydroxide (1.0g, 25mmol) gave 3-fluoro-4-phenyl-2-butanone[25] **3c** (2.6g, 77%) as a colourless liquid; R_F 0.79 (CH_2Cl_2); δ_H (400MHz) 2.11 (3H, d, J 5.2, CH_3), 3.2 (2H, m, CH_2), 4.91 (1H, ddd, $^2J_{HF}$ 49.6, $^3J_{HH}$ 7.6, $^3J_{HH}$ 4.0, CHF), 7.2-7.3 (5H, m, Ar-H); δ_F (235MHz) 186.6 (m); δ_C (100MHz) 26.4 (s, CH_3), 38.1 (d, $^2J_{CF}$ 20.2, CH_2), 95.9 (d, $^1J_{CF}$ 187.3, CF), 127.1 (s, Ar-C4), 128.6 (s, Ar-C2), 129.5 (s, Ar-C3), 133.7 (s, Ar-C1), 208.0 (d, $^2J_{CF}$ 26.3, >C=O); m/z (EI$^+$) 146 (M^+-HF, 58%), 145 (29). 131 (23), 103 (29), 91 (44), 77 (27), 43 (100).

Acknowledgements

We thank F2 Chemicals Ltd. (to GS, JH), the EPSRC/ROPA scheme (to J.F.S.V) and the Royal Society (University Research Fellowship to GS) for funding this work and Professor R.D. Chambers for helpful discussions.

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