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The synthesis of α-fluoroketones by 1,4-additions of mono-fluorinated enamines to Michael acceptors

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Abstract

Stork enamine reactions are explored with mono-fluorinated enamines derived from α-fluoroacetophenones and pyrrolidine. The resulting enamines react under mild conditions with Michael acceptors (acrylonitrile, methyl acrylate, methyl methacrylate, methyl vinyl ketone and cyclohexenone) to generate a variety of substituted α-fluoroketones.

Keywords: 1,4-Addition; α-Fluoroketones; Michael acceptors; Mono-fluorinated enamines

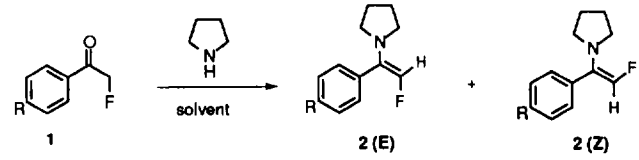
1. Introduction

Mono-, di- and tri-α-fluoroketones have attracted considerable interest in bioorganic and medicinal chemistry as potential transition state analogues for hydrolytic enzymes [1]. The electron-withdrawing effect of the fluorine atoms, α to the ketone, increases the susceptibility of the ketone to hydration and results in a stable tetrahedral hydrate. In some cases, this design strategy has led to potent inhibitors of hydrolytic enzymes, such as proteases [2], esterases [3] and phospholipases [4], all of which proceed through enzyme-bound tetrahedral transition states.

The reaction of electrophilic fluorinating agents with enolates [5,6] and silyl enol ethers [7], and the treatment of enolizable ketones with fluorine gas [8,9], offer direct methods for the introduction of the fluorine atom to generate α-fluoroketones. The reaction of electrophiles with α-fluorinated enolate anions [10] or azaenolates, generated after the deprotonation of imines of fluoroacetone [11], has met with some success. In addition, hydrogen fluoride-mediated isomerization of 2-fluoro-oxiranes [12] has been proven to be effective in generating α-fluoroketones, although it is restricted to appropriate systems. We were attracted by the possibility of carrying out Stork enamine-type Michael reactions [13] with appropriate α-fluoroenamines as this offered a neutral and potentially mild method for entry into α-fluoroketones. We therefore explored the reaction of α-fluoroacetophenones (**1**) with pyrrolidine to generate the corresponding fluorinated enamines (**2**) (Scheme 1), and now report the subsequent reactions of these enamines with a variety of Michael acceptors.

2. Results

The α-fluoroacetophenones (**1a–1d**) were prepared from the appropriate acid chlorides by reaction with diazomethane to generate the corresponding diazoketones. Treatment of the diazoketones with hydrogen fluoride in pyridine [14] allowed access to the requisite starting materials. This one-pot procedure gave a mixture of the α-chloroacetophenones and α-fluoroacetophenones, which were readily separated by chromatography. The α-fluoroacetophenones (**1**), when treated with pyrrolidine in a variety of solvents under reflux, generated a mixture of *E*- and *Z*-enamines (**2**) as shown in Scheme 1. The ratios were judged by ^{19}F nuclear magnetic resonance (NMR) of the reaction solutions and these results are collated in Table 1. In general, the conversion to enamine is high and the E/Z ratio is independent of the solvent (entries 1–3).



Scheme 1.

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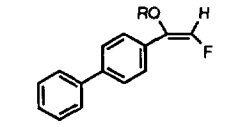
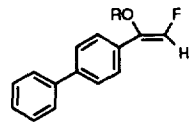
Table 1
E/Z ratios determined by ^{19}F NMR

Enamine	Substituent	Solvent	Conversion (%)	E/Z ratio
2a	H	Et_2O	100	1.22 : 1.0
2a	H	CCl_4	76	1.11 : 1.0
2a	H	Benzene	96	1.27 : 1.0
2b	NO_2	Benzene	70	1.65 : 1.0
2c	OMe	Benzene	69	1.45 : 1.0
2d	Br	Benzene	95	1.44 : 1.0



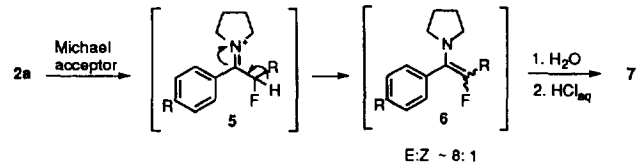
R = MOM 3(E) (-162.9 ppm)
R = TBDMS 4(E) (-164.7 ppm)



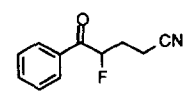
R = MOM 3(Z) (-154.0 ppm)
R = TBDMS 4(Z) (-157.2 ppm)

We did not purify and separate the enamine isomers as they were reaction intermediates and their relative ratios had no bearing on the product stereochemistry. The predominant enamine signals in all cases were at lower frequencies (between −166.3 and −173.0 ppm) in the ^{19}F NMR spectrum, and we tentatively assign these to the E isomers, consistent with the previous assignments of the E and Z isomers of structurally related methoxymethyl (MOM) and tert-butyldimethylsilyl (TBDMS) enol ether systems **3** and **4** [15,16], which are shown with their relative ^{19}F NMR assignments.

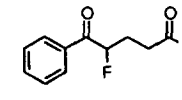
Treatment of the *E*-enamine–*Z*-enamine mixture (**2a**), derived from pyrrolidine and α-fluoroacetophenone (**1a**), with a variety of Michael acceptors was investigated. The consumption of the enamine, presumably via iminium (**5**) (Scheme 2), led to the generation of a new intermediate, alkylated enamines (**6a–6c**), after treatment with acrylonitrile, methyl vinyl ketone and methyl acrylate respectively. The accumulation of the enamines (**6a–6c**) was readily monitored by ^{19}F NMR of the reaction mixtures prior to aqueous acid work-up. There was a significant stereochemical bias (approximately 8 : 1) in favour of one of the geometrical isomers. These reaction intermediates were not isolated and separated and, on the basis of a correlation with **3** and **4**, we assign the major components to the *E*-enamine as they all exhibited ^{19}F NMR signals at lower frequencies (upfield) (−145.5 to −164.0 ppm) than the minor enamine signal.



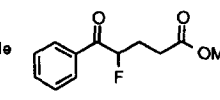
Scheme 2.



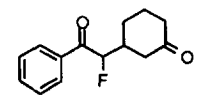
7a



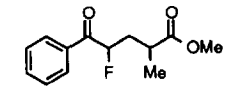
7b



7c



7d



7e

Aqueous work-up of the enamines (**6**) generated the respective α-fluoroketones (**7a–7c**) in moderate overall yields (48%–60%). The reaction of **2a** with cyclohexenone gave α-fluoroketone (**7d**) as a 2 : 3 mixture of diastereoisomers, and the reaction of **2a** with methyl methacrylate generated **7e** as a 1 : 1.13 mixture of diastereoisomers. The reaction with methyl methacrylate was significantly slower than that with methyl acrylate, with complete consumption of the enamine (**2a**) taking several days compared with several hours in the latter case (**7c**). Thus the methyl group of the methacrylate deactivates the double bond to nucleophilic attack. These Michael reactions emerge as good preparative methods for the generation of α-fluoroketones with pendant functional groups amenable to further elaboration. However, our attempts to broaden the scope of the methodology failed. Enamine **2a** did not react with methyl cinnamate under similar reaction conditions and reaction with methyl propiolate generated a complex mixture of unidentified products. We were also unable to alkylate **2a** with methyl iodide or allylbromide.

In summary, the enamines (**2**) of pyrrolidine and α-fluoroacetophenones undergo addition to a range of Michael acceptors under neutral conditions, and provide a mild method for the preparation of α-fluoroketones (**7a–7e**) with pendant functional groups.

3. Experimental details

All NMR spectra were recorded in solutions of $CDCl_3$ on a Varian Gemini 200 MHz (^1H at 199.9 MHz, ^{13}C at 50.29 MHz), Varian VXR 400S (^1H at 399.95 MHz, ^{13}C at 100.577 MHz) or Bruker AC250 (^{19}F at 235.42 MHz) instrument. ^1H and ^{13}C NMR chemical shifts are quoted in parts per million relative to tetramethylsilane (Me_4Si), ^{19}F chemical shifts are quoted relative to fluorotrichloromethane and *J* values are recorded in hertz. IR spectra were recorded on a Perkin–Elmer FT 1720X or 1600 spectrometer and mass spectra were obtained using a VG Analytical 7070E organic mass spectrometer operating at 70 eV. Chromatography was carried out using silica gel-60 (35 μm) (Fluka) or Sorbsil-C60-H (40–60 μm), and all solvents were distilled and dried before use.

3.1. General method for the preparation of α-fluoroacetophenones [14]

To a solution of pyridinium poly(hydrogen fluoride) (30 ml) at −15 °C was slowly added an ethereal solution of diazoacetophenone which was prepared in situ from benzoyl chloride (5.03 g, 35.8 mmol) and an excess of diazomethane. The reaction was allowed to warm to room temperature and was stirred for 4 h. The product was isolated by extraction into pentane (300 ml), and hydrogen fluoride was removed by treatment of the extract with anhydrous KF until neutral. The combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification over silica gel, eluting with CH_2Cl_2–petrol 40/60 (20 : 80), afforded the α-fluoroacetophenone.

3.1.1. α-Fluoroacetophenone [8]

Yield: 2.20 g (45%). ^{1}H NMR ($CDCl_3$) δ: 5.53 (d, J=46.8 Hz, 2H, CH_2F), 7.45–7.95 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 83.37 (d, J=182 Hz, CH_2F), 127.7, 128.2, 128.8, 133.5, 134.0, 193.3 (d, J=15.3 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −231.8 (t, J=46 Hz). IR ν_{max} (cm^{-1}): 3063, 2935, 1706, 1597. GC-MS (EI+): 138 (6.8%, M^+), 105 (100%, $M^+ - CH_2F$).

3.1.2. p-Nitro-α-fluoroacetophenone

Yield: 3.63 g (63%). Melting point (m.p.), 90–92 °C. ^{1}H NMR ($CDCl_3$) δ: 5.54 (d, J=46.7 Hz, 2H, CH_2F), 8.09 (d, J=8.9 Hz, 2H, Ar), 8.35 (d, J=8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 83.7 (d, J=184.7 Hz, CH_2F), 124.0, 129.2, 129.8, 138.1, 192.5 (d, J=8.48 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −229.83 (t, J=47.0 Hz). IR ν_{max} (cm^{-1}): 3111, 2937, 2111, 1709, 1598, 1524, 1345. m/z (EI+): 183 (0.65 M^+), 164 ($M^+ - HF$), 149 ($M^+ - CH_2F$). Analysis: $C_8H_6O_3NF$ requires: C, 52.47%; H, 3.30%; N, 7.65%; found: C, 52.12%; H, 3.27%; N, 7.43%.

3.1.3. p-Methoxy-α-fluoroacetophenone

Yield: 2.45 g (54%). M.p., 78–79 °C (78.5–79.4 °C [17]). ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H, OMe), 5.44 (d, J=47.0 Hz, 2H, CH_2F), 6.92 (d, J=8.9 Hz, 2H, Ar), 7.85 (d, J=8.9 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 56.0 (OMe), 83.9 (d, J=183.7 Hz, CH_2F), 114.6, 127.1, 130.7, 164.7, 192.6 (d, J=15.5 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −228.87 (t, J=46.8 Hz). IR ν_{max} (cm^{-1}): 3110, 2935, 1695, 1598. m/z (CI+): 169 (M^++1), 186 (M^++18); (EI+): 168 (M^+), 135 ($M^+ - CH_2F$). Analysis: $C_9H_9O_2F$ requires: C, 64.28%; H, 5.39%; found: C, 64.35%; H, 5.52%.

3.1.4. p-Bromo-α-fluoroacetophenone

Yield: 2.04 g (47%). M.p., 71–72 °C (70–72 °C [18]). ^{1}H NMR ($CDCl_3$) δ: 5.47 (d, J=46.9 Hz, 2H, CH_2F), 7.63 (d, J=8.6 Hz, 2H, Ar), 7.76 (d, J=8.6 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 83.5 (d, J=185.7 Hz, CH_2F), 129.3, 129.3, 132.2, 132.3, 192.6 (d, J=15.9 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −230.49 (t, J=46.1 Hz). IR ν_{max} (cm^{-1}): 3115, 2945, 1687, 1588. m/z (EI+): 216, 218 (M^+), 183, 185 ($M^+ - CH_2F$). Analysis: C_8H_6BrFO requires: C, 44.27%; H, 2.79%; found: C, 44.38%; H, 2.80%.

3.2. General procedure for the formation of Michael adducts (7a–7e)

Pyrrolidine (1.5 mmol) was added to a solution of α-fluoroacetophenone (1 mmol) in benzene over 4 Å molecular sieves (5 g). The solution was heated under reflux and the progress of the reaction was monitored by ^{19}F NMR. On consumption of the ketone, the appropriate Michael acceptor (10 mmol) was added and the solution was heated under reflux for 12 h. Water (10 ml) was added and the solution was heated for a further 1 h. After cooling, the reaction was filtered through celite and the product was extracted into diethyl ether. The ethereal extracts were combined and washed successively with dilute HCl (25 ml), $NaHCO_3$ (25 ml) and water (25 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification over silica gel, eluting with CH_2Cl_2–petrol 40/60, afforded the α-fluoroketones (**5a–5e**) as clear oils (45%–63%).

3.2.1. Adduct with acrylonitrile (7a)

Yield: 103 mg (55%). ^{1}H NMR ($CDCl_3$) δ: 2.30 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 5.74 (ddd, J=48.4 Hz, 8.9 Hz and 3.6 Hz, 1H, CHF), 7.49–7.98 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 13.0 (d, J=5.0 Hz, CH_2), 28.0 (d, J=21.8 Hz, CH_2), 90.7 (d, J=184.6 Hz, CHF), 118.4 (CN), 128.9, 129.0, 133.7, 134.4, 194.6 (d, J=20.1 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −190.95 (ddd, J=48.5 Hz and 28.97 Hz). IR ν_{max} (cm^{-1}): 3110, 2985, 2248, 1698, 1597. m/z (CI+): 191 (M^+ 9.5%), 209 (M^++18 100%). Analysis: $C_{11}H_{11}NOF$ requires; 192.082467; found: 192.082699.

3.2.2. Adduct with methyl vinyl ketone (7b)

Yield: 127 mg (52%). ^{1}H NMR ($CDCl_3$) δ: 2.13 (s, 3H, Me), 2.20 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 5.68 (ddd, J=49.6 Hz, 9.0 Hz and 3.6 Hz, 1H, CHF), 7.42–7.99 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 26.4 (d, J=21.3 Hz, CH_2), 29.9 (Me), 37.6 (d, J=3.4 Hz, CH_2), 91.7 (d, J=181.6 Hz, CHF), 128.6, 128.7, 128.7, 133.9, 195.9 (d, J=18.3 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −193.46 (ddd, J=50.0 Hz and 19.2 Hz). IR ν_{max} (cm^{-1}): 2923, 1710, 1702, 1597. m/z (CI+): 209 (M^++1 100%), 226 (M^++18 82.8%). Analysis: $C_{12}H_{14}O_2F$ requires: 209.09778; found: 209.09746.

3.2.3. Adduct with methyl acrylate (7c)

Yield: 137 mg (60%). ^{1}H NMR ($CDCl_3$) δ: 2.25 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 3.69 (s, 3H, Me), 5.75 (ddd, J=49.2 Hz, 9.2 Hz and 3.2 Hz, 1H, CHF), 7.45–8.01 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 27.6 (d, J=21.4 Hz, CH_2), 28.6 (d, J=3.4 Hz, CH_2), 51.8 (OMe), 91.8 (d, J=182.8 Hz, CHF), 128.8, 128.8, 128.8, 133.9, 173.0 (COOMe), 195.7 (d, J=18.7 Hz, CO). ^{19}F NMR ($CDCl_3$) δ: −193.02 (ddd, J=50.8 Hz and 19.2 Hz). IR ν_{max} (cm^{-1}): 2953,

1737, 1700, 1597. *m/z* (CI+): 225 ($M^+ + 1$ 100%), 242 ($M^+ + 18$ 72.4%). Analysis: $C_{12}H_{14}O_3F$ requires: 225.092697; found: 225.092700.

3.2.4. Adduct with 2-cyclohexen-1-one (7d)

Yield: 125 mg (48%). Product obtained was an inseparable mixture of diastereoisomers in a 62 : 38 ratio. IR ν_{max} (cm^{-1}): 3115, 2942, 1709, 1597. *m/z* (CI+): 235 ($M^+ + 1$ 19.3%), 252 ($M^+ + 18$ 100%). Analysis: $C_{14}H_{16}O_2F$ requires: 235.11343314; found: 235.113660. Major diastereoisomer (selected data): ^{1}H NMR ($CDCl_3$) δ: 5.53 (dd, J=48.8 Hz and 3.6 Hz, CHF); ^{13}C NMR ($CDCl_3$) δ: 95.6 (d, J=188.4 Hz, CHF), 195.4 (d, J=19.8 Hz, COCHF), 209.6 (CO); ^{19}F NMR ($CDCl_3$) δ: −199.27 (dd, J=48.5 and 24.1 Hz). Minor diastereoisomer (selected data): ^{1}H NMR ($CDCl_3$) δ: 5.42 (dd, J=48.6 Hz and 3.2 Hz, 1H, CHF); ^{13}C NMR ($CDCl_3$) δ: 95.54 (d, J=188.4 Hz, CHF), 195.46 (d, J=19.5 Hz, COCHF), 209.68 (CO); ^{19}F NMR ($CDCl_3$) δ: −199.6 (dd, J=48.5 Hz and 24.8 Hz).

3.2.5. Adduct with methyl methacrylate (7e)

Yield: 95 mg (40%). Product obtained was an inseparable mixture of diastereoisomers in a 52 : 48 ratio. IR ν_{max} (cm^{-1}): 3110, 2985, 1732, 1701, 1597. *m/z* (CI+): 239 ($M^+ + 1$ 100%), 256 ($M^+ + 18$ 78%). Analysis: $C_{13}H_{15}O_3F$ requires: 239.10834; found: 239.10839. Major diastereoisomer (selected data): ^{1}H NMR ($CDCl_3$) δ: 1.25 (d, J=7.2 Hz, 3H, Me), 3.67 (s, 3H, OMe), 5.65 (ddd, J=46.6 Hz, 9.0 Hz and 3.4 Hz, 1H, CHF); ^{13}C NMR ($CDCl_3$) δ: 91.6 (d, J=183.9 Hz, CHF), 175.9 (CO_2Me), 195.6 (d, J=17.9 Hz, COCHF); ^{19}F NMR ($CDCl_3$) δ: −189.19 (ddd, J=50.0 Hz, 33.9 Hz and 16.6 Hz). Minor diastereoisomer (selected data): ^{1}H NMR ($CDCl_3$) δ: 1.30 (dd, J=7.2 Hz and 0.8 Hz, 3H, Me), 3.75 (s, 3H, OMe), 5.77 (ddd, J=49.8 Hz, 10.8 Hz and 2.4 Hz, 1H, CHF); ^{13}C NMR ($CDCl_3$) δ: 91.3 (d, J=181.2 Hz, CHF), 176.2 (CO_2Me), 196.0 (d, J=19.4 Hz); ^{19}F NMR ($CDCl_3$) δ: −193.37 (ddd, J=50.0 Hz, 38.0 Hz and 15.1 Hz).

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