Preparation of α-halo-*F*-2-ketones and *F*-2-ketones via fluorination of α,α-dihalo-*F*-2-ketones

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Abstract

Fluorination of α,α-dichloro-*F*-2-ketones with antimony pentafluoride provided excellent yields of α-chloro-*F*-2-ketones and *F*-2-ketones regioselectively. However, fluorination of α,α-dibromo-*F*-2-ketones with antimony pentafluoride gave a mixture of α-bromo-*F*-2-ketones and *F*-2-ketones.

Introduction

Fluorination of α-halogenated *F*-ketones with fluorinating reagents such as $SbF_3/SbCl_5$ or SbF_5 has been utilized as a method for the preparation of more highly fluorinated *F*-ketones. However, this method lacks regiospecificity and generality [1, 2]. Fluorination of α,α,α-trichloromethyl *F*-ketones [3] or 1-chloro-*F*-2-oxopentanesulfonyl fluoride [4, 5] with SbF_5 provided α-chloro-*F*-2-ketones or *F*-2-ketones regioselectively depending on the conditions, but the starting materials are not easily prepared. Alternatively, *F*-2-ketones can be prepared from the reaction of perfluoro-olefin oxides with $AlCl_3$ [3], CsF [6, 7] or SbF_5 [8]. These methods also lack regiospecificity and require severe reaction conditions. A recent report from our laboratory detailed a facile, general and high yield preparation of α,α-dihalo-*F*-2-ketones [9]. In this report, we address the regiospecific preparation of α-halo-*F*-2-ketones and *F*-2-ketones via fluorination of the α,α-dihalo-*F*-2-ketones.

Results and discussion

The fluorination of α,α-dihalo-*F*-2-ketones was carried out with several types of antimony fluorides. The reaction of α,α-dichloro-*F*-2-ketones with SbF_3 or $SbF_3/SbCl_5$ was carried out at reflux temperature for 15 h. However, the ^{19}F NMR spectrum of the reaction mixture showed only starting material. In the case of α,α-dibromo-*F*-2-ketones, only α-chlorinated ketones were observed in the ^{19}F NMR spectrum. This result indicates that $SbCl_5$ promotes a halogen-exchange reaction with α,α-dibromo-*F*-2-ketones. The fluorination of α,α-dihalo-*F*-2-ketones was successfully accomplished with the more reactive SbF_5 for the preparation of α-chloro-*F*-2-ketones and *F*-2-ketones, but α,α-dibromo-*F*-2-ketones could not be sequentially fluorinated by this method. Results of the reaction between 1,1-dibromo-*F*-2-pentanone and SbF_5 are summarized in Table 1 and indicate that *F*-2-ketones may be prepared by longer reaction times, but α-bromo-*F*-2-ketones could not be prepared selectively.

The reaction of 1,1-dichloro-*F*-2-pentanone with SbF_5 was also carried out under a variety of reaction conditions. The results of these reactions are summarized in Table 2. The reaction of 1 equiv. 1,1-dichloro-*F*-2-pentanone with 1 equiv. SbF_5 at 25 °C or 60 °C provides the best conditions for the regiospecific preparation of 1-chloro-*F*-2-pentanone. The reaction at 60 °C is faster than that at 25 °C. More vigorous reaction conditions are required for the preparation of *F*-2-pentanone. Thus, *F*-2-pentanone was prepared by the reaction of 1 equiv. 1,1-dichloro-*F*-2-pentanone with 3 equiv. SbF_5 at 60 °C for 12 h. These results indicate that the second fluorination of 1,1-dichloro-*F*-2-pentanone is much more

TABLE 1. Reaction of 1,1-dibromo-*F*-2-pentanone with SbF_5

$$\underset{\text{A}}{C_3F_7C(O)CFBr_2} \xrightarrow{SbF_5} \underset{\text{B}}{C_3F_7C(O)CF_2Br} + \underset{\text{C}}{C_3F_7C(O)CF_3}$$

[A]/SbF_5[a]	Temp. (°C)	Time (h)	A/B/C[b]
1:0.5	90	4	78:19:3
1:1.0	25	0.5	55:38:7
1:2.5	90	0.5	0:20:80

[a]Mole ratio.
[b]Normalization ratio of the three compounds.

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TABLE 2. Reaction of 1,1-dichloro-*F*-2-pentanone with SbF_5

$$C_3F_7C(O)CFCl_2 \xrightarrow{SbF_5} C_3F_7C(O)CF_2Cl + C_3F_7C(O)CF_3$$
D E F

[D]/SbF_5[a]	Temp. (°C)	Time (h)	D/E/F[b]
2:1	25	6	54:46:0
1:1	25	2	10:90:0
1:1	25	5	0:100:0
1:1	60	2	0:100:0
1:2	60	12	0:58:42
1:2	60	36	0:11:89
1:3	60	4	0:35:65
1:3	60	12	0:0:100

[a]Mole ratio.
[b]Normalization ratio of three compounds.

TABLE 3. Preparation of α-chloro-*F*-2-ketones and *F*-2-ketones

$$R_FC(O)CFCl_2 + nSbF_5 \xrightarrow{60\ ^\circ C} R_FC(O)CF_2X$$

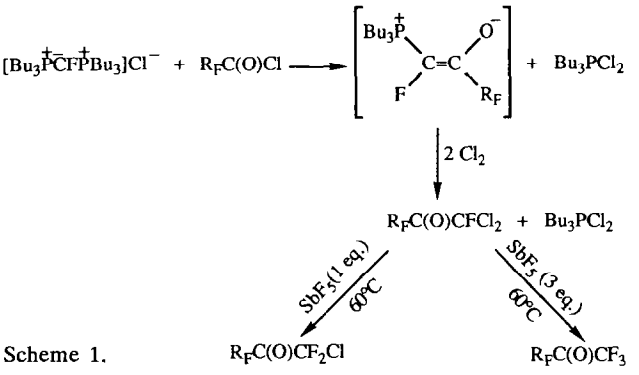
Entry	R_F	*n* (equiv.)	X	Yield[a] (%)
1	CF_3[b]	1	Cl	78
2	CF_2Cl	1	Cl	84
3	CF_3CF_2	1	Cl	82
4	$CF_3CF_2CF_2$	1	Cl	88
5	$CF_3(CF_2)_5CF_2$	1	Cl	88
6	CF_3CF_2[c,d]	3	F	80
7	$CF_3CF_2CF_2$	3	F	83
8	$CF_3(CF_2)_5CF_2$	3	F	85

[a]Isolated yield.
[b]The reaction was carried out at 45 °C for 5 h.
[c]The reaction was carried out at 45 °C for 60 h.
[d]The product contained 10% 1-chloro-*F*-2-butanone.

difficult than the initial fluorination of 1,1-dichloro-*F*-2-pentanone. This trend is similar to previous work on the fluorination of carbon–chlorine bonds which demonstrated that the reactivity decreases in the order $CCl_3 > CFCl_2 > CF_2Cl$ [10, 11].

The reaction of several 1,1-dichloro-*F*-2-ketones with SbF_5 was carried out under conditions selected from the study outlined in Table 2 ([ketone]/[SbF_5] = 1:1, 60 °C, 2 h) and ([ketone]/[SbF_5] = 1:3, 60 °C, 12 h). The results of these reactions are summarized in Table 3. Most products were easily isolated via distillation from the reaction mixture followed by a second distillation from an equal volume of conc. H_2SO_4.

In conclusion, α-chloro-*F*-2-ketones and *F*-2-ketones can be prepared selectively in high yields via the fluorination of α,α-dichloro-*F*-2-ketones with SbF_5. Selectivity is best controlled by the use of equal equivalents of ketone and SbF_5 for the preparation of α-chloro-*F*-2-ketones and excess SbF_5 for the preparation of *F*-2-ketones. Fluorination of α,α-dibromo-*F*-2-ketones did not provide α-bromo-*F*-2-ketones selectively. Thus, α-chloro-*F*-2-ketones and *F*-2-ketones can be easily prepared from *F*-acyl chlorides by a two-step sequence from commercially available precursors (Scheme 1).



Scheme 1.

Experimental

NMR spectra were recorded on a JEOL FX 90-Q multinuclear spectrometer. ^{19}F NMR spectra were obtained at an operating frequency of 84.26 MHz with $CFCl_3$ as an internal reference. IR spectra were obtained on a Beckman Acculab 8 grating IR spectrometer. Mass spectra were obtained on a Hewlett-Packard 5985 GC–MS system at 70 eV. GLPC analysis were performed on a Hewlett-Packard 5830A instrument with helium as the carrier gas. The column used was a 3% OV-101, 2 mm i.d.×6 ft. Boiling points were obtained during distillation using a partial immersion thermometer and are uncorrected.

General procedure

A 25 ml, one-neck round-bottom flask equipped with a septum, magnetic stir bar, Dry Ice/isopropyl alcohol condenser connected to a source of nitrogen was charged with the α,α-dichloro-*F*-2-ketone. Antimony pentafluoride was added dropwise at room temperature via a glass syringe. The reaction mixture was stirred at 60 °C for the desired period of time. When the reaction was complete (as determined by ^{19}F NMR spectroscopy), the mixture was distilled directly under reduced pressure or at atmospheric pressure. The distillate was redistilled by simple distillation (for liquid product) or trap-to-trap distillation (for gaseous product) to give the final product.

*Preparation of 1-chloro-*F*-propanone (1)*

Antimony pentafluoride (10.9 g, 50.3 mmol) was added dropwise to 1,1-dichloro-*F*-propanone (10.0 g, 50.3 mmol) according to the general procedure. The reaction mixture was stirred at 45 °C for 5 h. When the reaction was complete (as determined by ^{19}F NMR spectroscopy),

the volatiles were removed at 50 °C (bath temperature). Trap-to-trap distillation of the distillate at room temperature provided 7.15 g (78% yield) of 1-chloro-*F*-propanone (lit. value [12] b.p. 7–11 °C); the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1810 (w) (C=O); 1315 (w); 1250 (s); 1205 (s); 1030 (m); 900 (w); 730 (w). GC–MS *m/e* (relative intensity): 184 (1.7, M^+); 182 (5.2, M^+); 147 (77.7); 137 (4.3); 135 (13.4); 97 (27.9); 87 (28.7); 85 (87.1); 78 (12.9); 69 (100.0).

*Preparation of 1,3-dichloro-*F*-propanone (2)*

Antimony pentafluoride (9.55 g, 44.1 mmol) was added dropwise to 1,1,3-trichloro-*F*-propanone (9.5 g, 44.1 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 2 h. When the reaction was complete (as determined by ^{19}F NMR spectroscopy), the reaction mixture was distilled at 100 °C (bath temperature). Simple redistillation of the distillate from an equal volume of conc. H_2SO_4* provided 7.4 g (84% yield, 99% GLPC purity) of 1,3-dichloro-*F*-propanone: b.p. 44–45 °C (lit. value [1] b.p. 44 °C); the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1795 (s) (C=O); 1265 (s); 1190 (s); 1155 (s); 1065 (s); 990 (s); 875 (s); 810 (s); 690 (m). GC–MS *m/e* (relative intensity): 202 (0.4, M^+); 200 (2.1, M^+); 198 (3.3 M^+); 165 (12.7); 163 (40.0); 137 (6.1); 135 (19.1); 87 (32.6); 85 (100.0); 78 (10.5).

*The product was distilled from conc. H_2SO_4 to convert any hydrate formed in work-up to the anhydrous ketone.

*Preparation of 1-chloro-*F*-2-butanone (3)*

Antimony pentafluoride (4.94 g, 22.8 mmol) was added dropwise to 1,1-dichloro-*F*-2-butanone (5.67 g, 22.8 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 2 h. When the reaction was complete (as determined by ^{19}F NMR spectroscopy), the reaction mixture was distilled at 90 °C (bath temperature). Simple redistillation of the distillate from an equal volume of conc. H_2SO_4 provided 4.34 g (82% yield, 97% GLPC purity) of 1-chloro-*F*-2-butanone: b.p. 34–36 °C (lit. value [3] b.p. 32 °C); the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1790 (s) (C=O); 1340 (s); 1230 (s); 1180 (s); 1100 (s); 985 (s); 965 (m); 875 (s); 835 (s); 720 (s). GC–MS *m/e* (relative intensity): 234 (0.5, M^+); 232 (1.5, M^+); 197 (22.0); 147 (22.3); 119 (100.0); 97 (56.0); 87 (24.9); 85 (73.6); 69 (35.2).

*Preparation of 1-chloro-*F*-2-pentanone (4) (nc)*

Antimony pentafluoride (8.41 g, 38.8 mmol) was added dropwise to 1,1-dichloro-*F*-2-pentanone (11.6 g, 38.8 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 2 h. When the reaction was complete (as determined by ^{19}F NMR spectroscopy), the reaction mixture was distilled at 120 °C (bath temperature). Simple redistillation of the distillate from an equal volume of conc. H_2SO_4 provided 9.65 g (88% yield, 99% GLPC purity) of 1-chloro-*F*-2-pentanone: b.p. 58–60 °C; the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1790 (s) (C=O); 1350 (s); 1255–1205 (vs); 1170 (s); 1140 (s); 1030 (s); 960 (m); 915 (w); 855 (s); 800 (m); 715 (m). GC–MS *m/e* (relative in-

TABLE 4. ^{19}F NMR data for 1-chloro-*F*-2-ketones and *F*-2-ketones

Ketone	δ (ppm)						J (Hz)			
	a	b	c	d	e	f	ab	ac	bd	df
$CF_3C(O)CF_2Cl$ b a	−67.1	−73.6					7.3			
$CF_2ClC(O)CF_2Cl$ b a	−64.7	−64.7								
$CF_3CF_2C(O)CF_2Cl$ c b a	−66.7	−120.0	−82.5				9.8			
$CF_3CF_2CF_2C(O)CF_2Cl$ d c b a	−66.7	−117.3	−126.5	−81.2			9.8	4.9	9.8	
$CF_3CF_2CF_2(CF_2)_3CF_2C(O)CF_2Cl$ f e d c b a	−66.5	−116.4	(−122.0 to −123.4)		−126.9	−81.6				9.8
$CF_3CF_2C(O)CF_3$ c b a	−75.6	−122.5	−82.6				7.3			
$CF_3CF_2CF_2C(O)CF_3$ d c b a	−75.7	−119.7	−126.8	−81.4			9.8		9.8	
$CF_3CF_2CF_2(CF_2)_3CF_2C(O)CF_3$ f e d c b a	−75.5	−118,.9	(−122.4 to −123.4)		−126.9	−81.6				9.8

tensity): 247 (8.2, $M^+ - Cl$); 197 (16.9); 187 (4.4); 185 (13.9); 169 (98.9); 147 (12.2); 119 (22.6); 109 (11.3); 100 (35.4); 98 (48.9); 87 (34.1); 85 (97.3); 78 (19.2); 69 (100.0); 50 (28.9).

*Preparation of 1-chloro-*F*-2-nonanone (5) (nc)*

Antimony pentafluoride (1.77 g, 8.17 mmol) was added dropwise to 1,1-dichloro-*F*-2-nonanone (4.06 g, 8.14 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 2 h. When the reaction was complete (as determined by ^{19}F NMR spectroscopy), the reaction mixture was flash-distilled at 50 °C (bath temperature)/0.5 mmHg. Vacuum distillation of the distillate from an equal volume of conc. H_2SO_4 provided 3.45 g (88% yield, 99% GLPC purity) of 1-chloro-*F*-2-nonanone: b.p. 79–80 °C/80 mmHg; the ^{19}F NMR data are listed in Table 4. IR (neat) (cm^{-1}): 1790 (m) (C=O); 1360 (m); 1320 (m); 1250 (s); 1210 (s); 1150 (s); 1115 (m); 1060 (m); 990 (m); 900 (m). GC–MS *m/e* (relative intensity): 169 (26.0); 131 (56.2); 119 (48.3); 109 (10.5); 100 (43.3); 97 (41.6); 93 (11.1); 87 (31.3); 85 (100.0); 78 (15.3); 69 (87.8); 50 (11.2).

Preparation of F*-2-butanone (6)*

Antimony pentafluoride (7.97 g, 36.8 mmol) was added dropwise to 1,1-dichloro-*F*-2-butanone (3.05 g, 12.3 mmol) according to the general procedure. The reaction mixture was stirred at 45 °C for 60 h. The reaction mixture was distilled at 50 °C (bath temperature). Trap-to-trap distillation of the distillate at room temperature provided 2.13 g (80% yield, based on ketone) of *F*-2-butanone. ^{19}F NMR spectroscopy showed that this material was contaminated with 10% 1-chloro-*F*-2-butanone: lit. value [8] b.p. 0 °C; the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1790 (m) (C=O); 1315 (s); 1240 (s); 1205 (s); 1105 (m); 1000 (w); 920 (m); 895 (m); 730 (s). GC–MS *m/e* (relative intensity): 147 (1.4, $M^+ - CF_3$); 119 (16.7); 97 (39.0); 69 (100.0).

Preparation of F*-2-pentanone (7)*

Antimony pentafluoride (9.16 g, 42.3 mmol) was added dropwise to 1,1-dichloro-*F*-2-pentanone (4.21 g, 14.1 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was distilled at 80 °C (bath temperature). Trap-to-trap distillation of the distillate at 50 °C (bath temperature) provided 3.1 g (83% yield, based on ketone) of *F*-2-pentanone: lit. value [8] b.p. 27–28 °C; the ^{19}F NMR data are listed in Table 4. IR (gas) (cm^{-1}): 1805 (m) (C=O); 1365 (m); 1260 (s); 1205 (s); 1140 (m); 1025 (m); 875 (m); 720 (m). GC–MS *m/e* (relative intensity): 197 (0.9, $M^+ - CF_3$); 169 (12.0); 97 (38.6); 69 (100.0).

Preparation of F*-2-nonanone (8) (nc)*

Antimony pentafluoride (5.72 g, 26.4 mmol) was added dropwise to 1,1-dichloro-*F*-2-nonanone (4.39 g, 8.8 mmol) according to the general procedure. The reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was flash-distilled at 80 °C/3 mmHg. Simple redistillation of the distillate from an equal volume of conc. H_2SO_4 provided 3.5 g (85% yield, based on ketone, 98% GLPC purity) of *F*-2-nonanone; b.p. 118–120 °C; the ^{19}F NMR data are listed in Table 4. IR (neat) (cm^{-1}): 1800 (w) (C=O); 1250 (s); 1215 (s); 1155 (m); 1115 (w); 1030 (w); 950 (w). GC–MS *m/e* (relative intensity): 397 (0.3 $M^+ - CF_3$); 181 (15.3); 169 (55.3); 131 (94.5); 119 (72.1); 109 (12.9); 100 (49.2); 97 (95.0); 93 (15.9); 69 (100.0).

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