A New and Efficient Synthesis of α-Bromoalkyl Perfluoroalkyl Ketones via Opening of Epoxides

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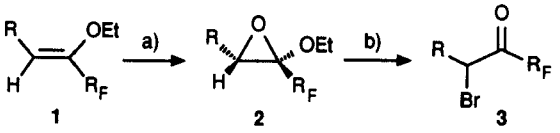
Regioselective ring opening of various substituted perfluoroepoxy ethers was achieved with magnesium bromide, leading to new α-bromofluoroalkyl ketones in good yields.

In our general interest for a versatile preparation of α-functionalized fluoroalkyl ketones, we have investigated a new preparation of α-bromotrifluoromethyl ketones extended to α-bromoperfluoroalkyl ketones. Until recent years, synthesis of α-bromotrifluoromethyl ketones required drastic conditions.[1] We have recently described[2] a method of preparation under mild conditions by bromination of silylated trifluoromethyl enol ethers. However this method was limited to trifluoromethyl ketones due to the lack of commercially available silylated synthons. We report here another valuable strategy to such compounds which extends the scope of the reaction to any R_F.

We have already shown[3] that, unlike R_F olefins,[4] trifluoromethyl enol ethers are reactive towards epoxidation. First, this reaction has been extended to fluoroalkylated enol ethers **1**, readily available by a Wittig reaction from ethyl perfluoroalkanoates.[5]

All enol ethers **1**, in the presence of *meta*-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature provided, after 48 hours of reaction, the corresponding epoxides **2** in very good yields (Table 1) (90%).

Their opening by magnesium bromide ($MgBr_2$) has been investigated. Epoxides **2** readily reacted with 10 equivalents of $MgBr_2$, in refluxing anhydrous THF. The course of the reaction was followed by GC analysis. The reaction provided in all but three cases (d,k,l) α-bromoperfluoroalkyl ketones **3** in moderate to good yields (see Table 2). The nucleophilic attack of bromide anion is regiospecific; no product from the attack at the carbon bearing the R_F group was isolated. The success of the reaction seems to be dependent on steric hindrance and electronic factors. However the balance between these two factors could not be unambiguously determined. In particular, the failure of the reaction performed with **2d** (Table 2, entry 4) was surprising and could not be explained. Only the presence of both a bulky R and a long R_F chain clearly inhibits the reaction (Table 2, entry 11 and 12). In other cases, reaction rate decreases with the length of the R_F chain, but yields are not affected.



Conditions: a) mCPBA, CH_2Cl_2, 20°C, 48h, (90%); b) $MgBr_2$, THF, 70°C.

1-3	R	R_F	1-3	R	R_F
a	$Ph(CH_2)_2$-	CF_3	g	c-C_6H_{11}-CH_2-	CF_3
b	$Ph(CH_2)_2$-	C_2F_5	h	c-C_6H_{11}-CH_2-	C_2F_5
c	$Ph(CH_2)_2$-	C_3F_7	i	c-C_6H_{11}-CH_2-	C_3F_7
d	Ph-	CF_3	j	c-C_6H_{11}-	CF_3
e	Ph-	C_2F_5	k	c-C_6H_{11}-	C_2F_5
f	Ph-	C_3F_7	l	c-C_6H_{11}-	C_3F_7

The easy access to R_F epoxy ethers and their regioselective opening shows the synthetic use of these new fluorinated synthons. The present procedure has no alternative and provides a simple access to α-bromoperfluoroalkyl ketones which are themselves useful precursors for a variety of other α-functionalized ketones. Reactivity of such bromo ketones towards substitution and elimination reactions are in progress.

Table 1. NMR Data of Epoxy Ethers **2**

Compounds[a]	^{19}F NMR[b] ($CDCl_3/CFCl_3$) δ	^{13}C NMR[c] ($CDCl_3$/TMS) δ, J_{C-F} (Hz)	^{1}H NMR[c] ($CDCl_3$/TMS) δ_{HC-C}, J (Hz)
2a	−76.6 (CF_3)	122 (q, J = 282, CF_3), 81.7 (q, J = 40, C–CF_3)	3.2 (t, J = 6.1)
2b	−83.3 (CF_3), −125, −126.6 (CF_2)	121.5 (qt, ^1J = 265, ^2J = 35, CF_3), 111.2 (tq, ^1J = 297, ^2J = 37, CF_2), 82 (t, J = 24, C–C_2F_5)	3.2 (t, J = 6)
2c	−81 (CF_3), −122, −123 (CF_2), −127 (CF_2–C_2F_5)	114–126 (m, C_3F_7), 81.8 (t, J = 29.1, C–C_3F_7)	3.2 (t, J = 6)
2d	−77 (CF_3)	122 (q, J = 282, CF_3), 82 (q, J = 40, C–CF_3)	4.25 (s)
2e	−83 (CF_3), −124.5, −125.5 (CF_2)	124.5 (qt, ^1J = 265, ^2J = 35, CF_3), 112.2 (tq, ^1J = 298, ^2J = 37.2, CF_2), 82.5 (t, J = 25, C–C_2F_5)	4.2 (s)
2f	−81.6 (CF_3), −122, −123 (CF_2), −126.3 (CF_2–C_2F_5)	107–118 (m, C_3F_7), 82.9 (t, J = 30, C–C_3F_7)	4.2 (s)
2g	−77.3 (CF_3)	121.8 (q, J = 282, CF_3), 82 (q, J = 38, C–CF_3)	3.3 (t, J = 5.6)
2h	−83 (CF_3), −126.6, −127.6, (CF_2)	118.6 (qt, ^1J = 286, ^2J = 35, CF_3), 111.3 (tq, ^1J = 262, ^2J = 37.4, CF_2), 81.4 (t, J = 29, C–C_2F_5)	3.2 (t, J = 5.5)
2i	−81.6 (CF_3), −123.3, −124.3 (CF_2), −127.6 (CF_2–C_2F_5)	113.6–118.4 (m, C_3F_7), 81.5 (t, J = 29, C–C_3F_7)	3.2 (t, J = 5.1)
2j	−77.4 (CF_3)	123 (q, J = 282, CF_3), 82 (q, J = 38, C–CF_3)	2.9 (d, J = 8.6)
2k	−83 (CF_3), −125.6, −127 (CF_2)	118.8 (qt, ^1J = 286, ^2J = 35.4, CF_3), 111.5 (tq, ^1J = 260, ^2J = 37, CF_2), 81.5 (t, J = 28, C–C_2F_5)	2.8 (d, J = 8.6)
2l	−81.6 (CF_3), −122.7, −124.5 (CF_2), −125 (CF_2–C_2F_5)	112.9–117.7 (m, C_3F_7), 81.8 (t, J = 28, C–C_3F_7)	2.85 (d, J = 8.6)

[a] Satisfactory microanalyses obtained: C ± 0.21, H ± 0.14.
[b] Obtained on a Varian EM 360 L (60 MHz) spectrometer.
[c] Obtained on a Bruker AC 200 spectrometer.

Table 2. Preparation of Bromo Ketones **3** from Epoxy Ethers **2**

Entry	Epoxy Ether **2**	Product[a]	Reaction Time (h)	Yield[b] (%)
1	**2a**	**3a**	1	85
2	**2b**	**3b**	16	68
3	**2c**	**3c**	72	66
4	**2d**	unidentified	2	–
5	**2e**	**3e**	1	60
6	**2f**	**3f**	4	70
7	**2g**	**3g**	2	50
8	**2i**	**3h**	4	76
9	**2h**	**3i**	4	70
10	**2j**	**3j**	16	80
11	**2k**	**2k**	–	–
12	**2l**	**2l**	–	–

[a] Satisfactory HRMS obtained.
[b] Yield of isolated product **3**.

Synthesis of Epoxy Ethers: Preparation of 2a; Typical Procedure: Enol ether **1a** (2.0 g, 8.19 mmol) was dissolved in CH_2Cl_2 (10 mL) in a three-necked flask. The flask was cooled in an ice bath and MCPBA 70% (2.45 g, 1.2 equiv) in CH_2Cl_2 (15 mL) was added dropwise. After the addition, the solution was stirred at r.t. for about 48 h (the reaction was monitored by GC). After washing with an aq sat. $NaHCO_3$ solution (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on silica gel (eluent: pentane/Et_2O: 95/5) to give 1.95 g (91%) of epoxy ether **2a**.

Synthesis of Bromo Ketones: Preparation of 3a; Typical Procedure: $MgBr_2$ (purchased from Aldrich Chemical Co, 2 g, 10 equiv) was dissolved in refluxing freshly distilled THF (8 mL) in a dried and argon flushed three-necked flask. A solution of epoxide (0.2 g, 0.77 mmol) in THF (5 mL) was added dropwise. The course of the reaction was monitored by GC. After the complete reaction (see Table 1), the flask was cooled and the reaction mixture was smoothly hydrolyzed (5 mL) and extracted with Et_2O (3 × 10 mL); the combined extracts were washed with an aq sat. NaCl solution (25 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil which was purified by chromatography on silica gel (eluent: pentane/Et_2O: 9/1) to give 0.19 g (85%) of bromo ketone **3a**. (Table 3).

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Table 3. Analytical Data of Bromo Ketones **3**

Compounds	IR[a] ν_{CO} (cm^{-1})	^{19}F NMR ($CDCl_3/CFCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$/TMS) δ, J_{C-F} (Hz)	^{1}H NMR ($CDCl_3$/TMS) $\delta_{\underline{CH}Br}$, J (Hz)
3a	1750	−75.6 (CF_3)	42.7 (CHBr), 115.2 (q, J = 292, CF_3), 185.2 (q, J = 35.6, CO)	4.5 (t, J = 6.6)
3b	1740	−83 (CF_3), −121, −121.6 (CF_2)	42.7 (CHBr), 106.8 (tq, ^1J = 269, ^2J = 38.4, CF_2), 117.5 (qt, ^1J = 287, ^2J = 34, CF_3), 187.9 (t, J = 27, CO)	4.6 (t, J = 7)
3c	1740	−81.6 (CF_3), −118.3, −119.5 (CF_2), −127 ($COCF_2$)	43 (CHBr), 110.3 (tt, ^1J = 269, ^2J = 32, CF_2CO), 117.3 (qt, ^1J = 288, ^2J = 33, CF_3), 188 (t, J = 26, CO)	4.6 (t, J = 7.1)
3e	1750	−82.3 (CF_3), −120.6 (CF_2)	46 (CHBr), 107 (tq, ^1J = 269, ^2J = 38, CF_2), 117.5 (qt, ^1J = 287, ^2J = 33.5, CF_3), 185.9 (t, J = 27, CO)	5.8 (s)
3f	1750	−81 (CF_3), −118.3 (CF_2), −126.3 ($COCF_2$)	46 (CHBr), 108–132 (m, C_3F_7), 185.9 (t, J = 25, CO)	5.8 (s)
3g	1750	−75.6 (CF_3)	41.5 (CHBr), 115.3 (q, J = 293, CF_3), 185.5 (q, J = 36, CO)	4.85 (t, J = 7.5)
3h	1740	−82.3 (CF_3), −121, −121.6 (CF_2)	41.5 (CHBr), 106.8 (tq, ^1J = 267, ^2J = 38, CF_2), 117.6 (qt, ^1J = 287, ^2J = 34, CF_3), 188 (t, J = 26, CO)	4.8 (t, J = 6.7)
3i	1740	−81 (CF_3), −118, −119.3 (CF_2), −127 ($COCF_2$)	41.8 (CHBr), 105–128 (m, C_3F_7), 188 (t, J = 27, CO)	4.7 (t, J = 7.7)
3j	1750	−76.6 (CF_3)	50.1 (CHBr), 115.2 (q, J = 292, CF_3), 185 (q, J = 35.5, CO)	4.3 (d, J = 7.5)

[a] Recorded on a Perkin-Elmer 1420 Infrared spectrophotometer.

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