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Mild α-fluorination of enantiomerically pure β-ketosulfoxides by F-TEDA-BF_4

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Abstract

A wide range of α-sodium derivatives of chiral and enantiomerically pure β-ketosulfoxides have been regioselectively fluorinated with the 'F^+' fluorinating agent F-TEDA-BF_4 without affecting the sulfinyl stereogenic center. α-Monofluoro-β-ketosulfoxides produced in this reaction can undergo further fluorination providing the corresponding α,α-difluoro derivatives, easily transformed by deacylation into enantiomerically pure (*S*)-difluoromethyl-*p*-tolylsulfoxide. © 1997 Elsevier Science S.A.

Keywords: Fluorination; Chiral sulfoxides; F-TEDA-BF_4

1. Introduction

The worldwide market of single enantiomer forms of chiral drugs will grow constantly in future years at the expense of racemic versions [1]. The same is true for several classes of fluorine containing biologically active compounds. Therefore there is a surge of interest in new synthetic routes to chiral and enantiomerically pure (e.p.) selectively fluorinated organic compounds [2]. We have developed new synthetic routes to a number of e.p. fluorinated molecules starting from γ-fluorosubstituted-β-ketosulfoxides, easily obtained in optically pure form by acylation of α-lithiated sulfoxides with α-fluorosubstituted esters [3].

A number of reports dealing with fluorination of activated or inactivated ketones or ketone enolates, enol acetates, trimethylsilyl enolethers and enamines appears in the literature [4]. For sulfoxides it is well known that fluorination by DAST, the most commonly used fluorinating agent, produces the corresponding α-fluoro-sulfides through a Pummerer-type reaction [5]. Subsequent oxidation of the α-fluorosulfides to the corresponding sulfoxides followed by sulfinic acid elimination represent the final stages of a well established and useful entry to terminal fluoro-olefines [6]. In this paper we report that F-TEDA-BF_4, a stable and easy to handle fluorinating reagent introduced by Banks [7], belonging to the 'F^+' delivery class, reacts with preformed α-sodium β-ketosulfoxides providing the corresponding α-fluoro derivatives and preserving the sulfinyl chiral auxiliary [8].

2. Results and discussion

Treatment of the e.p. β-ketosulfoxides **1** [3] with an equimolar amount of NaH in dry THF at 0 °C, followed by addition of one equivalent of F-TEDA-BF_4 at room temperature afforded, in reasonable yields, thermodynamic mixtures of the diastereoisomeric α-monofluorinated β-ketosulfoxides **2** (see Scheme 1 and Table 1).

In most cases small amounts of α,α-difluorinated products **3** formed. These compounds should arise from NaH deprotonation of the monofluorinated products **2**, to provide the corresponding α-sodium derivatives, still reactive toward F-TEDA-BF_4. Traces of difluoromethyl *p*-tolylsulfoxide (*S*)-**4** formed by deacylation of the difluorinated products **3**, probably occurred during work-up and flash chromatography (FC) of the raw fluorination mixtures. We assessed the origin of difluoromethyl *p*-tolylsulfoxide (*S*)-**4** by submitting the monofluoro derivative **2b** to the fluorination protocol (Scheme 2). As expected, (*S*)-**4** was obtained in almost quantitative yield after purification of the crude mixture.

The α-fluorination of **1** by F-TEDA-BF_4 did not take place without preliminary treatment with NaH. In that case only

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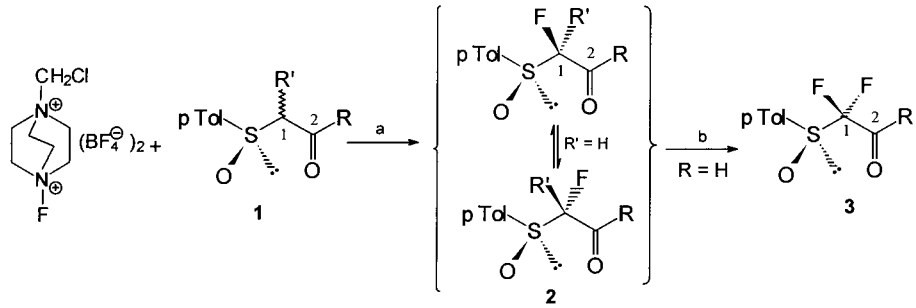


Scheme 1. F-TEDA-BF_4 promoted α-fluorination of e.p. β-ketosulfoxides: (a) NaH, THF, 0 °C to room temperature; (b) F-TEDA-BF_4, room temperature. **a** $R' \equiv H$, $R \equiv CH_3$; **b** $R' \equiv H$, $R \equiv Ph$; **c** $R' \equiv H$, r ≡ *o*-pyridyl; **d** $R' \equiv H$, r ≡ *p*-pyridyl; **e** $R' \equiv CH_3$, $R \equiv Ph$; **f** $R' \equiv H$, $R \equiv CH_2F$; **g** $R' \equiv H$, $R \equiv CHF_2$; **h** $R' \equiv H$, $R \equiv CF_3$; **i** $R' \equiv H$, $R \equiv CF_2Cl$; **j** $R' \equiv H$, $R \equiv CF{=}CH{-}Ph$.

Table 1
F-TEDA-BF_4 promoted α-fluorination of e.p. β-ketosulfoxides

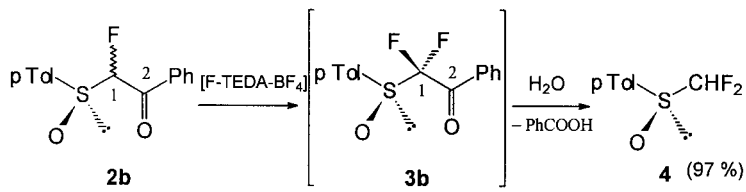
Ketone	Reaction time (h)	Yield of **2**[a] (%)	Yield of **3** (%)	Conversion (%)
1a[b]	48	60	trace	60
1b[b,d]	15	23	20	48
1c[b]	1	82	trace	84
1d[c]	1	52	17	73
1e[c,e]	0.5	67	/	71
1f[c]	5	23	27	90
1g[c]	12	19	41	70
1h[c]	1.5	27	38	not determined
1i[c]	12	33	32	not determined
1j[b]	2	70	15	87

[a]Thermodynamic mixture of diastereoisomers.
[b]Yields and conversion calculated on isolated product.
[c]Yields and conversion determined by ^1H and ^{19}F NMR analysis of the crude reaction mixture.
[d]5% of difluoromethyl *p*-tolyl-sulfoxide was recovered by FC.
[e]Two non-epimerizable diastereoisomers were obtained in a 63:37 ratio.

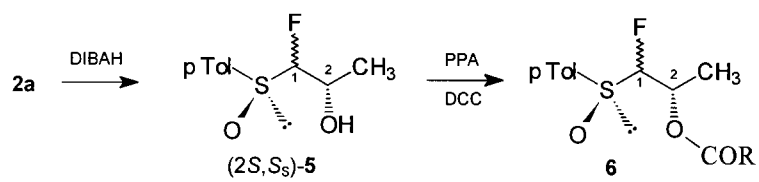
oxidation to the corresponding sulfones occurs, though at slow rate. It is worth noting that β-ketosulfoxides bearing an alkyl (**1a**), an aryl (**1b,1e**), a heteroaromatic (**1c,1d**), and even a fluoroalkyl (**1f**–**1i**) or fluoroalkenyl group (**1j**) have been successfully submitted to the reaction, providing interesting e.p. molecules, the latter having more than one selectively fluorinated site.

The enantiomeric purity of the fluorination products was confirmed by reduction of a mixture of C-1 epimers of the monofluoro ketone **2a** with DIBAH, and subsequent esterification of the carbinols **5** with both enantiomers of α-phenylpropionic acid. The reduction occurs with excellent diastereoselection and 75% overall yield. The preferential formation of a C-1 epimer of **5**, starting from an almost equimolar mixture of **2a**, can be explained as follows. The single epimers **2a** are reduced at different rates; since epimerization immediately occurs at C-1, in order to establish the thermodynamic equilibrium mixture, one diastereoisomer of **5** is produced in large excess. By NMR analysis of the esters **6** only the two expected C-1 epimers **6** were detected in the mixture, confirming the stereochemical homogeneity of the sulfinyl group. By this method it has also been possible to assign (*S*) stereochemistry to the C-2 of the carbinols **5**, as shown in Scheme 3 (see Section 3 for details) [9].

In summary we have described an unprecedented mild fluorination of the activated C–H moiety of chiral and optically pure β-ketosulfoxides, which does not affect the sulfinyl stereocenter. The reaction applies to a wide range of β-ketosulfoxides. The reactivity and the exploitation of the e.p. α-fluorinated sulfoxides **2**–**4** in the synthesis of fluoro-organic target molecules are currently under investigation.



Scheme 2. α-Fluorination of α-fluoro-α-sulfinylacetophenone **2b**.



Scheme 3. Reduction and esterification of α-fluoro-α-sulfinylacetone **2a**. PPA ≡ α-phenylpropionic acid; $R \equiv CH(CH_3)Ph$.

3. Experimental details

General. The instrumentation and general experimental and analytical procedures were recently described in detail [10]. Starting β-ketosulfoxides **1** were prepared according to the literature [3].

Fluorination (*procedure A*). A THF solution (50 ml) of β-ketosulfoxide **1** (1 mmol) was added to an oil-free suspension of NaH (1 mmol) in THF (5.0 ml) under N_2 at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. A solution of F-TEDA-BF_4 (1 mmol) in DMF (2.0 ml) was added. After the appropriate time (see Table 1), the mixture was poured into diethyl ether, washed with aqueous 5% H_2SO_4 (10 ml) and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and the solvent removed at reduced pressure. Procedure A was used for compounds **1a** and **1f**–**1j**.

Fluorination (*procedure B*). The differences with respect to Procedure A are as follows: F-TEDA-BF_4 (1 equivalent) was added neat (solid). A saturated aqueous ammonium chloride solution was used instead of 5% H_2SO_4. Procedure B was used for compounds **1b**–**1e**.

Purification by flash chromatography (FC) on silica gel, using mixtures of *n*-hexane/ethyl acetate as eluent, afforded the pure fluorinated products **2** (we could not separate the C-1 epimers) and **3**. Mixtures of **2** and **3** were obtained by FC from compounds **1d**–**1i**.

Selected ^{1}H and ^{19}F NMR data of **2** and **3** are given in Table 2.

Difluoromethyl-*p*-tolylsulfoxide (*S*)-**4**. R_f 0.22 in *n*-hexane:AcOEt = 9:1; $[\alpha]_D^{20} + 143.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.62 and 7.42 (m, 4H, Ar<u>H</u>), 6.03 (t, 1H, $J = 55.5$ Hz, C*H*F_2), 2.46 (br s, 3H, C<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$) δ −120.57 (d, $J = 55.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 143.8, 133.7, 130.3, 125.6, 121.0 (t, $J = 289.4$ Hz), 21.6.

3.1. Reduction of *2a* with DIBAH

To a 0.1 M solution of compound **2a** (1 mmol) in THF at −78 °C, a solution of DIBAH in THF (1 M, 1.1 mmol) was added dropwise. After 30 min, the mixture was diluted with saturated aqueous NH_4Cl, extracted with AcOEt and the organic phases dried over Na_2SO_4. Purification by flash chromatography on silica gel (45:55 mixture *n*-hexane:AcOEt) afforded the pure product 1-fluoro-1[(4-methyl)sulfinyl]-propan-2-ol **5** (R_f 0.35 in *n*-hexane:AcOEt = 1:1) in 75% yield as a mixture of C-1 epimers in 6:1 ratio.

Major epimer. ^{1}H NMR ($CDCl_3$) δ 7.7–7.2 (m, 4H, Ar<u>H</u>), 4.83 (dd, $J = 46.7$ and 8.1 Hz, 1H, C<u>H</u>F), 4.28 (m, 1H, C<u>H</u>OH), 3.75 (br signal, 1H, O<u>H</u>), 2.45 (br s, 3H, ArC<u>H</u>$_3$), 1.36 (dd, $J = 6.3$ and 2.4 Hz, 3H, C<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$), δ −193.10 (ddq, $J = 46.7$, 4.5 and 2.4 Hz).

Minor epimer. ^{1}H NMR ($CDCl_3$) δ 7.7–7.2 (m, 4H, Ar<u>H</u>), 4.68 (dd, $J = 47.4$ and 1.5 Hz, 1H, C<u>H</u>F), 4.28 (m, 1H, C<u>H</u>OH), 3.35 (br signal, 1H, O<u>H</u>), 2.45 (br s, 3H, ArC<u>H</u>$_3$),

Table 2
Selected ^{1}H and ^{19}F NMR data of products **2** and **3** in $CDCl_3$[a,b]

Compound	Signal (δ)	**a**(R ≡ CH_3)	**b**(R ≡ Ph)	**c**(R ≡ *o*-Py)	**d**(R ≡ *p*-Py)	**f**(R ≡ CH_2F)	**g**(R ≡ CHF_2)	**h**(R ≡ CF_3)	**i**(R ≡ CF_2Cl)	**j**(R ≡ CF=CHPh)
2 (two epimers)	H-1	5.53; 5.37	6.12; 6.27	7.27; 7.13	6.07; 6.08	5.69; 5.64	4.92; 5.00	4.95; 5.08	5.06; 5.20	6.16; 6.07
	F-1	−190.52; −193.89	−187.15; −188.91	−202.99; −203.22	−186.25; −189.27	−198.82; −204.49	−190.17; −205.04	−188.02; −203.00	−187.32; −201.32	−191.77; −193.07
	$^2J_{HF}$	51.0; 49.0	48.6; 50.0	51.5; 51.8	52.5; 48.5	49.5; 48.0	47.5; 47.5	47.9; 47.4	48.5; 48.0	49.2; 48.0
3	F_2-1	−110.72; −114.50	−103.32; −106.68	−108.90; −111.40	−103.49; −107.51	−113.60; −121.41	−113.04; −120.93	−112.64; −120.31	−111.69; −117.85	−104.49; −108.38
	$^1J_{HF}$	229.0	238.5	224.5	242.0	225.04	224.0	222.5	216.0	238.5

[a] In compound **2e** ^{19}F resonates at −156.88 ppm.
[b] The remaining ^{1}H and ^{19}F NMR signals of compounds **2** and **3** showed the expected chemical shifts and usual patterns.

1.39 (dd, $J=6.5$ and 1.0 Hz, 3H, C$\underline{H}_3$); ^{19}F NMR ($CDCl_3$) δ −196.63 (ddq, $J=47.4$, 25.0 and 1.0 Hz).

3.2. Esterification of **5** with (R)- and (S)-α-phenylpropionic acid

To a solution of the alcohol (1 mmol), acid (1.1 mmol) and DCC (1.1 mmol) in dichloromethane (5 ml) at 0 °C, 4-(*N*,*N*-dimethylamino)-pyridine (0.1 mmol) was added. After 10 min the solvent was removed under reduced pressure and the crude product was purified by FC (80:20 *n*-hexane:AcOEt) affording the esters **6**.

3.2.1. With (R)-phenylpropionic acid

Major product **6**. R_f 0.35 in *n*-hexane:AcOEt = 80:20; $[\alpha]_D^{20}$ +98.67 (c 0.2, $CHCl_3$); $[\alpha]_{365}^{20}$ +472.80 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 9H, ArH), 5.26 (ddq, $J=14.5$, 5.4 and 6.6 Hz, 1H, OCH), 4.89 (dd, $J=48.0$ and 5.4 Hz, 1H, CHF), 3.73 (q, $J=7.1$ Hz, 1H, CHMe), 2.44 (br s, 3H, ArC$\underline{H}_3$), 1.51 (d, $J=7.1$ Hz, 3H, C$\underline{H}_3$CPh), 1.28 (dd, $J=6.6$ and 2.0 Hz, 3H, C$\underline{H}_3$CO); ^{19}F NMR ($CDCl_3$) δ −200.83 (ddq, $J=48.0$, 14.5 and 2.0 Hz).

Minor product **6**. R_f 0.30 in *n*-hexane:AcOEt = 80:20; $[\alpha]_D^{20}$ +151.65 (c 0.1, $CHCl_3$); $[\alpha]_{365}^{20}$ +731.9 (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.65–7.20 (m, 9H, ArH), 5.54 (ddq, $J=26.5$, 6.6 and 2.4 Hz, 1H, OCH), 4.67 (dd, $J=47.2$ and 2.4 Hz, 1H, CHF), 3.84 (q, $J=7.2$ Hz, 1H, CHMe), 2.44 (br s, 3H, ArC$\underline{H}_3$), 1.58 (d, $J=7.2$ Hz, 3H, C$\underline{H}_3$CPh), 1.32 (dd, $J=6.6$ and 1.2 Hz, 3H, C$\underline{H}_3$CO); ^{19}F NMR ($CDCl_3$) δ −193.62 (ddq, $J=47.2$, 26.5 and 1.2 Hz).

3.2.2. With (S)-phenylpropionic acid

Major product **6**. R_f 0.38 in *n*-hexane:AcOEt = 80:20; $[\alpha]_D^{20}$ +109.3 (c 0.9, $CHCl_3$); $[\alpha]_{365}^{20}$ +560.6 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 9H, ArH), 5.29 (ddq, $J=13.5$, 5.8 and 6.6 Hz, 1H, OCH), 4.73 (dd, $J=48.0$ and 5.8 Hz, 1H, CHF), 3.74 (q, $J=7.1$ Hz, 1H, CHMe), 2.42 (br s, 3H, ArC$\underline{H}_3$), 1.52 (d, $J=7.1$ Hz, 3H, C$\underline{H}_3$CPh), 1.38 (dd, $J=6.6$ and 2.0 Hz, 3H, C$\underline{H}_3$CO); ^{19}F NMR ($CDCl_3$) δ −201.63 (ddq, $J=48.0$, 13.5 and 2.0 Hz).

Minor product **6**. R_f 0.30 in *n*-hexane:AcOEt = 80:20; $[\alpha]_D^{20}$ +53.70 (c 0.4, $CHCl_3$); $[\alpha]_{365}^{20}$ +276.46 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 9H, ArH), 5.54 (ddq, $J=27.4$, 6.7 and 2.2 Hz, 1H, OCH), 4.59 (dd, $J=47.3$ and 2.2 Hz, 1H, CHF), 3.82 (q, $J=7.1$ Hz, 1H, CHMe), 2.42 (br s, 3H, ArC$\underline{H}_3$), 1.57 (d, $J=7.1$ Hz, 3H, C$\underline{H}_3$CPh), 1.41 (dd, $J=6.6$ and 1.0 Hz, 3H, C$\underline{H}_3$CO); ^{19}F NMR ($CDCl_3$) δ −193.54 (ddq, $J=47.3$, 27.4 and 1.0 Hz).

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