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Fluorinated enol ethers bearing chiral arylsulphinyl groups

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Abstract

A synthesis of 2-alkoxy-2-fluoroalkyl-1-(*p*-tolylsulphinyl)ethenes **4** with good regioselectivity from γ-fluorosubstituted β-ketosulphoxides **3** is described

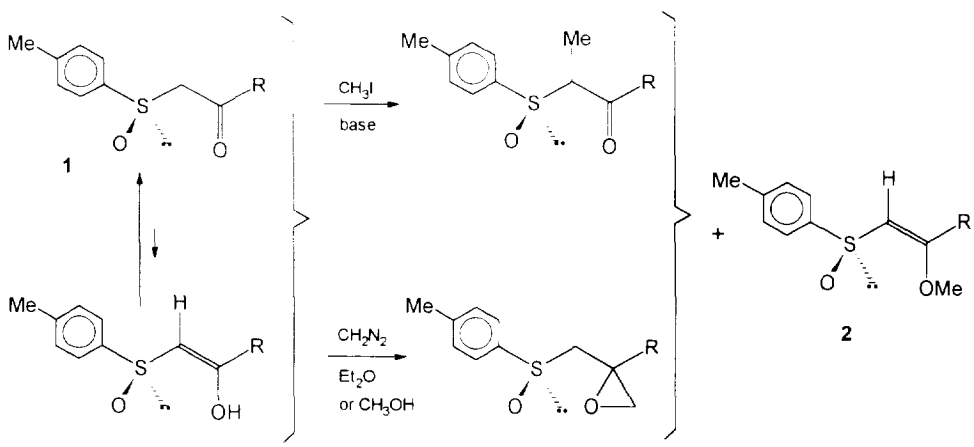
Keywords: Fluorinated enol ethers; Synthesis; Alkoxyfluoroalkyl(*p*-tolylsulphinyl)ethenes; NMR spectroscopy; Regioselectivity

1. Introduction

Because of the equilibrium occurring in solution between the keto and enol forms, each showing quite distinct chemical properties, enolizable ketones generally give rise to mixtures of products when involved in reactions. In contrast, enol-ethers, -acetates, -phosphonates and -silyl derivatives, in which the enolic form has been blocked by a substituent on oxygen, occupy a central position in modern organic chemistry [1]. They have been used in [2+2], [4+2] or dipolar [3+2] cycloaddition reaction processes which greatly increase the molecular complexity. Generally, these reactions are highly selective and therefore constitute an efficient synthetic way to build complex molecules [2]. Quite recently we have extended our interests to include the use of cycloaddition reactions for the construction of selectively fluorinated chiral and optically pure molecules [3]. In this paper we report a synthetic entry to enol ethers bearing fluorinated substituents and the arylsulphinyl chiral auxiliary group we needed to explore the potential of cycloaddition reaction in the synthesis of chiral fluoroorganic compounds.

Only low yields of methyl enol ethers **2** along with *C*-alkylated products have been obtained by methyl iodide alkylation of lithium, sodium or potassium derivatives of β-ketosulphoxides **1** [4]. We have already shown that variable amounts of the methyl enol ethers **2**, along with oxiranes, are formed by reacting diazomethane with the same ketones. Perfluoroalkyl or aryl γ-substituents as well as the use of aprotic dipolar solvents favour the formation of enol ethers [5].

It is well known that α-fluoroketones, because of the highly electronegative fluorine atoms, show an enhanced Lewis acid



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character of the carbonyl group, so that hydrates, hemiketals and ammonia adducts can be easily isolated. Furthermore, the hydroxy groups of the adducts are acidic and potentially capable of alkylation. Hemiketals of α-fluorinated ketones react with alkyl sulphates in the presence of a base to give ketals, and unsymmetrical ketals can be obtained in pure form by that route [6]. In contrast, γ-substituted β-ketosulphoxides are not easily transformed into the corresponding ketals under the same reaction conditions [7].

2. Results and discussion

We have now found conditions which allow the transformation of γ-fluoro-substituted β-ketosulphoxides **3** into the corresponding methyl enol ethers **4** in reasonable yield and with high regioselectivity in many cases.

β-Ketosulphoxides **3** were treated at room temperature in an appropriate solvent with an alkyl sulphate in the presence of potassium carbonate. After the time listed in Table 1, enol ethers **4** could be obtained by flash chromatography, either in the pure *Z* form or as *Z*/*E* mixtures (see Table 1). The *Z* or *E* isomer ratio was established either by comparison with authentic samples [5b], or on the basis of the chemical shift of ^{19}F signals which generally appear more downfield in the *E* isomer than in the *Z* isomer [5b].

Compound **4a** was obtained in highest yield and with good regioselectivity with DMF as the reaction solvent; therefore this solvent was mainly used for the other substrates studied. In all cases, some quantities (10%–20%) of the starting β-ketosulphoxides **3** were recovered. A general, unambiguous trend in the influence of the substituents on the *Z*/*E* ratio of the enol ethers **4** obtained was not clearly detectable. However, it should be noted that, in the absence of a carbon chain on the sulphinyl α-carbon, polyhalogenation generally favours the *Z*-isomer.

Table 1
Preparation of fluorinated enol ethers **4**

Compound	Solvent	Reaction time (h)	Yield [a] (%)	*Z*/*E* ratio
4a	DMF	1	54	83:17
	THF	1	42	84:16
	$CHCl_3$	1	40	77:23
4b	DMF	1	40	100:0
4c	DMF	0.5	35	100:0
4d	DMF	1.5	40	100:0
4e [b]	DMF	1	51	81:19
4f	DMF	0.8	21	100:0
4g	benzene/MeOH	8	42	56:44
4h	Et_2O/EtOH	9	41	58:42
4i	DMF	0.5	55	89:11
4l	DMF	2	52	86:14
4m	n-pentane/MeOH	5	68	18:82 [c]

[a] Isolated yields.
[b] S_S isomers.
[c] *Z* and *E* products were ca. 55:45 and 65:35 mixtures, respectively, of ($1R$, R_S) and ($1S$, R_S) diastereomers, not assigned.

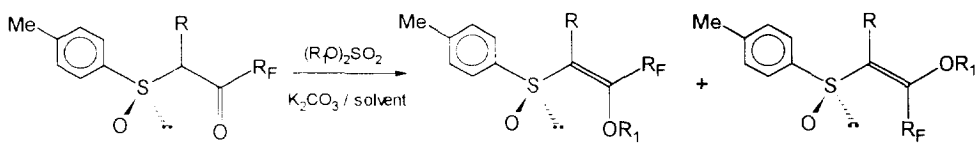
3. Experimental details

^1H and ^{19}F spectra were recorded on a Bruker AC-250 spectrometer, using TMS as internal standard or with reference to C_6F_6.

The β-ketosulphoxides **3a–d** [5b], **3e** [8], **3g,h** [9], **3l** [4] and **3m** [10] were prepared as described in the literature. Compounds **4a–d** had been described previously [5b].

3.1. Preparation of the β-ketosulphoxides 3f and 3i

A solution of (*R*)-methyl-*p*-tolylsulphoxide or (*R*)-n-butyl-*p*-tolylsulphoxide (20 mmol) in dry THF (12 ml) was added dropwise to a stirred solution of LDA [24 mmol, pre-



3 (*Z*) 4 (*E*)

a R = H, R_F = CHF_2, R_1 = Me
b R = H, R_F = CF_2Cl, R_1 = Me
c R = H, R_F = CF_3, R_1 = Me
d R = H, R_F = CF_2CF_3, R_1 = Me
e (S_S) R = H, R_F = CH_2F, R_1 = Me
f R = H, R_F = CF_2Br, R_1 = Me
g R = $-(CH_2)_2-CH=CH_2$, R_F = CF_2Cl, R_1 = Me
h R = $-(CH_2)_2-CH=CH_2$, R_F = CF_2Cl, R_1 = Et
i R = $-(CH_2)_2-CH_3$, R_F = CF_3, R_1 = Me
l R = $-CH_2-CH=CH_2$, R_F = CH_2F, R_1 = Me
m R = $-(CH_2)_2-CH=CH_2$, R_F = CHClF, R_1 = Me

pared from diisopropylamine (3.47 ml) and a 1.6 N solution of butyllithium in n-hexane (15 ml)] at −70 °C under nitrogen. After 3 min, a solution of ethyl bromodifluoroacetate or ethyl trifluoroacetate (24 mmol), respectively, in THF (10 ml) was added at −70 °C and stirring was continued for 5 min. The reaction mixture was quenched by adding a saturated aqueous solution of ammonium chloride (200 ml). The pH value was adjusted to ca. 3 with 2 N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate (3×150 ml). The organic layer was washed with aqueous NaCl and dried over sodium sulphate. Evaporation and flash chromatography of the residue with a mixture of n-hexane/ethyl acetate 70:30 as eluant gave compounds **3f** and **3i**, respectively.

Compound **3f** (as a ca. 8:2 mixture of ketonic and hydrate form): yield, 93%; m.p. 103–105 °C (from diethyl ether n-hexane). ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H); 3.09, 3.15, 4.06, 4.29 (d, 2H, due to hydrate and ketonic forms); 3.96, 6.88 (br s, 2H); 7.3–7.6 (m, 4H) ppm. α_D^{20} (0.6, $CHCl_3$) = +208°.

Compound **3i** [as a 50:50 mixture of (3*R*, R_S) and (3*S*, R_S) diastereoisomers, and a ca. 8:2 mixture of hydrate and ketonic form]: Yield, 78%. ^{1}H NMR ($CDCl_3$) δ: 0.9–1.0 (overl., 3H); 1.2–1.4 (m, 2H); 1.3 (br s, 2H); 1.9–2.3 (m, 2H); 2.47 (s, 3H); 4.1–4.3 (m, 1H); 7.2–7.5 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −80.4, −80.6 (s, 3F, hydrate form); −84.1, −84,2 (s, 3F, ketonic form) ppm.

3.2. General procedure for the preparation of the fluorinated enol ethers 4

To a solution of the β-ketosulphoxide **3** (0.4 mmol) in the indicated solvent (Table 1) (3 ml), dimethyl or diethyl sulphate (0.6 mmol) and potassium carbonate (0.4 mmol) were added. After stirring at room temperature for the time given in Table 1, water (10 ml) was added and the mixture was extracted with diethyl ether (3×5 ml). The organic layer was dried over sodium sulphate and the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column with n-hexane/ethyl acetate mixtures as eluant to give products **4**.

Compound **4e** (S_S isomer): *Z* isomer: ^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H); 4.04 (s, 3H); 4.62 (dd, 1H, $J_{(H,H)}$ = 13, $J_{(H,F)}$ = 47 Hz); 4.92 (dd, 1H, $J_{(H,F)}$ = 47 Hz); 5.67 (d, 1H, $J_{(H,F)}$ = 1.5 Hz); 7.25–7.60 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −220.3 (t, 1F, $J_{(H,F)}$ = 47 Hz) ppm.

Compound **4f**: *Z* isomer: ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H); 4.26 (s, 3H); 6.13 (s, 1H); 7.3–7.6 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −54.4 (d, 1F, $J_{(F,F)}$ = 170 Hz); −55.3 (d, 1F) ppm.

Compound **4g**: *Z*/*E* = 56:44. ^{1}H NMR ($CDCl_3$) δ: 1.7–2.6 (*E*+*Z*) (m, 4H); 2.40+2.42 (*E*+*Z*) (s, 3H); [3.84 (*E*) + 3.95 (*Z*)] (s, 3H); 4.8–5.0 (*E*+*Z*) (m, 2H); 5.5–5.8 (*E*+*Z*) (m, 1H); 7.2–7.6 (*E*+*Z*) (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: [−43.28 (*E*) + (−52.32) (*Z*)] (d, 1F, $J_{(F,F)}$ = 168 Hz); [−51.49 (*E*) + (−55.24) (*Z*)] (d, 1F) ppm.

Compound **4h**: *Z* isomer: ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, *J* = 7 Hz); 1.7–1.9 (m, 2H); 2.3–2.6 (m, 2H); 2.40 (s, 3H); 4.1–4.3 (m, 2H); 4.9–5.0 (m, 2H); 5.6–5.8 (m, 1H); 7.3–7.6 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −51.67 (d, 1F, $J_{(F,F)}$ = 168 Hz); −55.42 (d, 1F) ppm. *E* isomer: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, 3H, *J* = 7 Hz); 1.7–1.9 (m, 2H); 2.1–2.3 (m, 2H); 2.47 (s, 3H); 4.0–4.2 (m, 2H); 4.8–5.0 (m, 2H); 5.6–5.8 (m, 1H); 7.2–7.6 (m, 4HP) ppm. ^{19}F NMR ($CDCl_3$) δ: −43.2 (d, 1F, $J_{(F,F)}$ = 168 Hz); −51.5 (d, 1F) ppm.

Compound **4i**: *Z* isomer: ^{1}H NMR ($CDCl_3$) δ: 0.83 (t, 3H, *J* = 7 Hz); 1.3–1.5 (m, 2H); 2.1–2.3 (m, 2H); 2.38 (s, 3H); 3.87 (s, 3H); 7.2–7.6 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −64.8 (s, 3F) ppm.

Compound **4l**: *Z* isomer: ^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H); 2.8–3.0 (m, 2H); 3.87 (s, 3H); 4.7–4.8 (m, 2H); 5.2–5.4 (m, 1H); 5.42 (dd, 1H, $J_{(H,H)}$ = 12, $J_{(H,F)}$ = 47 Hz); 5.73 (dd, 1H, $J_{(H,F)}$ = 47 Hz); 7.2–7.5 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −211.3 (t, 1F, $J_{(H,F)}$ = 47 Hz) ppm.

Compound **4m**: *Z* isomer [as a ca. 55:45 mixture of (1*R*, R_S) and (1*S*, R_S) diastereoisomers, not assigned]: ^{1}H NMR ($CDCl_3$) δ: 1.8–2.1 (m, 2H); 2.2–2.6 (m, 2H); 2.40 (s, 3H); 3.9–4.1 (overl. 3H); 4.7–5.1 (m, 2H); 5.5–5.8 (m, 1H); 8.75 (d, 1H, $J_{(H,F)}$ = 47 Hz); 7.2–7.6 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −134.8, −140.9 (d, 1F, $J_{(H,F)}$ = 47 Hz) ppm. *E* isomer [as a ca. 65:35 mixture of (1*R*, R_S) and (1*S*, R_S) diastereoisomers, not assigned]: ^{1}H NMR ($CDCl_3$) δ: 1.9–2.1 (m, 2H); 2.2–2.4 (m, 2H); 2.41 (s, 3H); 3.98, 4.04 (d, 1H, $J_{(H,F)}$ = 2.5 Hz); 4.7–4.9 (m, 2H); 5.5–5.7 (m, 1H); 7.2–7.5 (m, 4H); 7.73, 7.75 (d, 1H, $J_{(H,F)}$ = 47 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −133.3, −136.2 (d, 1F, $J_{(H,F)}$ = 47 Hz) ppm.

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