A Facile One-Pot Synthesis of 1-Acyl and 1-α-Hydroxyalkylvinyl *p*-Tolyl (*S*)-Sulfoxides

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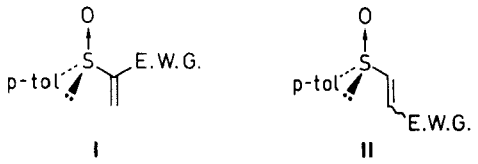
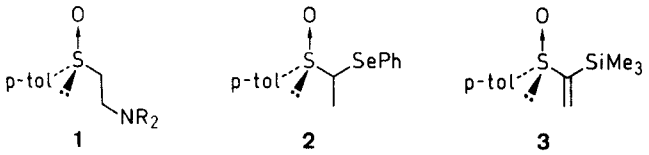
A novel chiral intermediate, 2-ethoxyethyl *p*-tolyl sulfoxide (**4**), permits access in one step to optically active α-methylene-β-oxo sulfoxides, which are very useful dienophiles.

Stereoselective reactions using chiral sulfoxides have provided useful new methods for synthetic organic chemistry.[1] In particular, the asymmetric Diels–Alder reaction using optically active *p*-tolylsulfinylethenes[2] **I** and **II** bearing an "additional" electron-withdrawing group in the α- or β-position, has recently received increased attention.



I **II**

The sulfoxides **II** are usually prepared by the Wittig–Horner procedure upon treatment of carbonyl compounds with the anion of dimethyl (*R*)-*p*-tolylsulfinylmethyl phopshonate.[3] We have previously reported[4] optically active α-methylene β-oxo sulfoxides **6** (type **I**), which were prepared from the amino sulfoxides **1**.

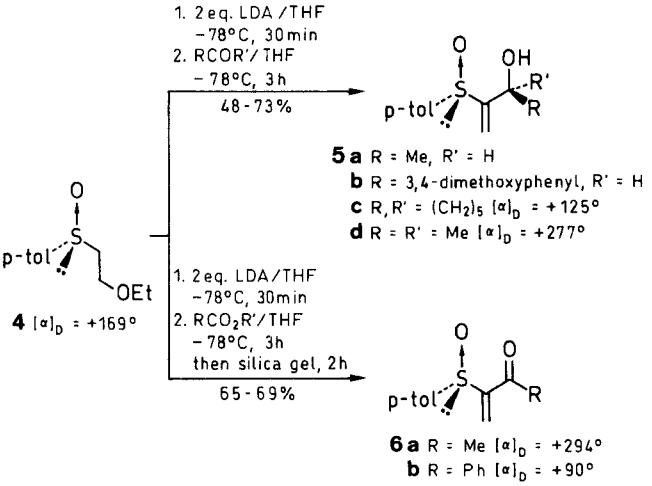


1 **2** **3**

However, although protection by an amino group of the unsaturated bond in (*R*)-vinyl *p*-tolyl sulfoxide permitted easy anion formation in the α position of the sulfoxide function, this procedure is long and limited in scope.[5]

Also, Koizumi et al.[6] and Yan et al.[7] utilized, respectively, selenylated **2** and silylated **3** precursors which suffered the same drawbacks as previously, namely that several steps are involved.

We report here a very quick synthesis of compounds **I**, in one step from 2-ethoxyethyl *p*-tolyl sulfoxide (**4**) which is readily prepared in high yield from (*R*)-*p*-tolyl vinyl sulfoxide by addition of sodium ethoxide (1 equiv) in excess ethanol. Thus, when the anion of **4**, generated in



situ by the action of 2 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, reacted with various aldehydes or ketones, the corresponding allylic alcohols **5** were obtained directly. Loss of ethoxy group took place in the reaction medium.

Furthermore, while esters did not react with the anion of amino sulfoxide **1**, treatment of compound **4** with LDA (2 equiv, THF, −78 °C) followed by addition of $MeCO_2Et$

or $PhCO_2Me$ resulted directly in the formation of carbonyl derivatives **6** [1-acylvinyl *p*-tolyl (*R*)-sulfoxides] after silica gel chromatographic purification of the crude product. We noted that passage through silica gel was necessary to include elimination of the ethoxy group.[8]

Introduction of electron-withdrawing groups (acyl groups) into the α-position of vinyl sulfoxides is easy and constitutes a convenient access to compounds of type **I**.

2-Ethoxyethyl *p*-Tolyl (*R*)-Sulfoxide (4):
NaOEt (2.04 g, 30 mmol) in EtOH (30 mL) was slowly added to *p*-tolyl vinyl sulfoxide (3.32 g, 20 mmol) in EtOH (10 mL) at r.t. during 15 min. The mixture was maintained at this temperature for 2 h. After evaporation of the solvent, water (30 mL) was added. The mixture was extracted with Et_2O (3 × 50 mL), washed with sat. NaCl (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (eluent: hexane/Et_2O) affording **4** in 92% yield; $[\alpha]_D^{20}$ + 169° (*c* = 1.7, EtOH).

Anal: calc. for $C_{11}H_{16}O_2S$: C, 62.22; H, 7.59; O, 15.1; S, 15.07: found: C, 62.38; H, 7.75; O, 15.75; S, 14.53.

MS: *m/z* (relative intensity) = 212 (1.65, M^+), 197 (2.20), 151 (14.49), 140 (33.96), 92 (38.77), 45 (100).

^1H NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3 H, *J* = 7.5 Hz, Me), 2.42 (s, 3 H, MeAr), 3.00 (t, 2 H, *J* = 6 Hz, CH_2S), 3.55 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.70 to 4.05 (m, 2 H, CH_2O), 7.55 (2 d, 4 H_{arom}).

α-Hydroxyalkylvinyl *p*-Tolyl Sulfoxides 5; General Procedure:
To a solution 2-ethoxyethyl *p*-tolyl sulfoxide **(4)** (14 mmol) in THF (30 mL) was slowly added to a solution of LDA (28 mmol, 2 equiv) in THF at − 78 °C under argon. 30 min after the end of the addition, a solution of aldehyde or ketone (14 mmol) was slowly added at − 78 °C and the mixture was maintained at this temperature for 3 h, then a solution of sat. NH_4Cl was added (50 mL). The mixture was diluted with Et_2O (50 mL) and the organic layer was washed with sat. NaCl (30 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (hexane/Et_2O, 7:3 as eluent) to give unsaturated sulfoxides **5**.

(+)-(S)-3(p-Tolylsulfinyl)-3-buten-2-ol **(5a)**:
Yield 48% (mixture of two diastereoisomers 40:60 as determined by ^1H NMR and GC).

IR (film): *v* = 3369, 1594, 1045 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.08–1.28 (2 d, 3 H, *J* = 6 Hz, Me), 2.35 (s, 3 H, Me-Ar), 4.0–4.60 (m, 2 H, CHOH), 6.0–6.12 (m, 2 H, H_2C=), 7.35 and 7.65 (2 d, 4 H, H_{arom}).

(+)-(S)-1-(3',4'-Dimethoxyphenyl)-2-(p-tolylsulfinyl)-2-propen-1-ol **(5b)**:
Yield 73% (mixture of two diastereoisomers 42:58 determined by ^1H NMR).

HRMS: *m/z* calc.: 332.10822; found: 332.1084.

IR (film): *v* = 3323, 1596, 1025 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, MeAr), 3.73 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 4.67 (m, 1 H, OH), 5.0 and 5.15 (2 m, 1 H, CHO), 5.47 to 6.15 (m, 2 H, H_2C=), 6.75 and 7.50 (2 m, 7 H, H_{arom}).

(+)-(S)-1-[1-(p-tolylsulfinyl)ethenyl]cyclohexan-1-ol **(5c)**:
Yield 58%; mp 105 °C; $[\alpha]_D^{20}$ + 126° (*c* = 0.59, acetone), [Lit.[4] $[\alpha]_D^{20}$ + 125° (*c* = 0.59, acetone)], ee > 95%.[9]

IR (KBr): *v* = 3376, 3057, 1583, 1032 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.35 to 1.80 (m, 10 H, $[CH_2]_5$), 2.45 (s, 3 H, MeAr), 5.93 and 6.20 (2 d, 2 H, *J* = 2.5 Hz, H_2C=), 7.45 and 7.80 (2 d, 4 H, H_{arom}).

(+)-(S)-2-Methyl-3-(p-tolylsulfinyl)-3-buten-2-ol **(5d)**:
Yield 68%; $[\alpha]_D^{20}$ + 277° (*c* = 0.72, acetone).

HRMS: *m/z*, calc.: 224.08709; found: 224.0882.

IR (Nujol): *v* = 3336, 1596, 1032 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, Me), 1.40 (s, 3 H, Me), 2.40 (s, 3 H, MeAr), 5.78 and 6.02 (2 d, 2 H, *J* = 1.5, H_2C=), 7.30 and 7.60 (2 d, 4 H, H_{arom}).

α-Acyl-α,β-unsaturated p-Tolyl Sulfoxides 6; General Procedure:
The crude product obtained using the same procedure as above with LDA (2 equiv), 2-ethoxyethyl *p*-tolyl sulfoxide **(4)** (1 equiv) and ester (1.2 equiv) was stirred with silica gel (2 h) before chromatography.

(+)-(S)-3-(p-Tolylsulfinyl)-3-buten-2-one **(6a)**:
Yield 69%; mp 46–47 °C; $[\alpha]_D^{20}$ + 294° (*c* = 0.72, acetone [Lit.[4] $[\alpha]_D^{20}$ + 298° (*c* = 0.64, acetone)]; ee > 95%.[9]

IR (Nujol): *v* = 1676, 1580, 1050 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, Me), 6.75 and 6.95 (2 d, 2 H, *J* = 1.5 Hz, H_2C=); 7.50–7.95 (m, 5 H, H_{arom}).

(+)-(S)-1-Phenyl-2-(p-tolylsulfinyl)-2-propen-1-one **(6b)**:
Yield 65%; $[\alpha]_D^{20}$ + 90° (*c* = 0.8, acetone) [Lit.[4] $[\alpha]_D^{20}$ + 92° (*c* = 0.74, acetone)].

IR (Nujol): *v* = 1650, 1597, 1055 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, MeAr), 6.40 and 6.90 (2 s, 2 H, H_2C=), 7.35–7.80 (m, 10 H, H_{arom}).

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(4) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1986**, 2603.
(5) Four steps are required: anion formation followed by action of aldehydes or ketones, Hofmann's elimination and oxidation of allylic alcohol. Furthermore esters do not react.
(6) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Tetrahedron Lett.* **1985**, 6205.
(7) Cheng, H.C.; Yan, T.H. *Tetrahedron Lett.* **1990**, 673.
(8) The same result is obtained by stirring the crude product with SiO_2 (10 equiv) in hexane/Et_2O (1:1).
(9) The ^1H NMR spectrum of **5c** and **6a** after the addition of the chiral shift reagent, Eu(hfc)$_3$, did not detect the enantiomer.