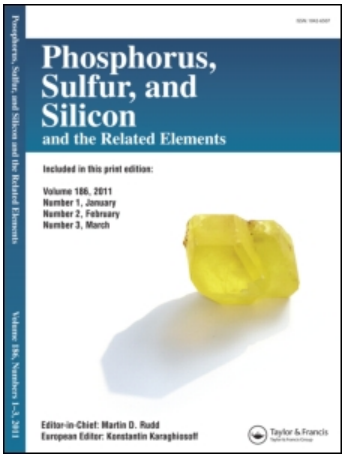

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ONE-POT AND SIMPLE REACTION FOR THE SYNTHESIS OF ALKYL *p*-TOLUENESULFINATE ESTERS UNDER SOLID-PHASE CONDITIONS

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A manipulatively one-pot and rapid method for the synthesis of alkyl *p*-toluenesulfinate esters **1** from *p*-toluenesulfinic acid, supported thionyl chloride on silica gel and aliphatic alcohols in solid phase conditions is described.

Keywords: Sulfinate esters; *p*-Toluenesulfinic acid; Thionyl chloride; Solid-phase conditions; Silica gel; Chiral synthesis

INTRODUCTION

The reaction of the organometallic reagent with a diastereomerically pure sulfinate ester of menthol continues to be the method most often employed for the preparation of optically active sulfoxides,[1] despite recent advancement in the asymmetric oxidation of sulfides to sulfoxides[2]. The requisite sulfinate esters are generally prepared from the corresponding sulfinic acids either directly[3] or via the sulfinyl chlorides[4]. Alternatively, the sulfinyl chloride may be directly prepared from a more available precursor, the disulfide, by reaction with chlorine[5] or sulfuryl chloride in the presence of acetic acid.[6] The most commonly used methods are the reaction of sulfinyl chlorides with alcohols[7] and sodium sulfinates with chlorocarbonates in alcohols.[8] Other methods including alkylation of sulfinic acids also

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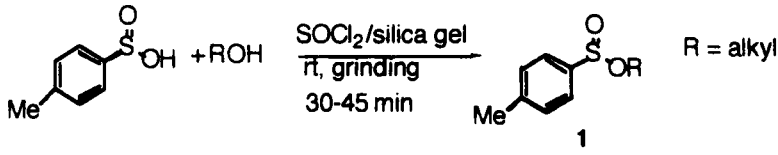
known[9–11], a useful one-step synthesis of alkyl *t*-alkansulfinates was reported.[12]

Heterogeneous reaction that are facilitated by supported reagents on various solid inorganic surfaces have received attention in recent years[13-15] The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity. We now wish to report a convenient one-step method for the preparation of sulfinate esters, starting from supported thionyl chloride on silica gel (33 %) with sulfinic acid and aliphatic alcohols under solvent-free conditions. This method would be widely applicable as general method for synthesis of alkyl sulfinate esters. In continuation of our ongoing program to develop environmentally benign methods using solid supports,[16] we now wish to report an extremely convenient one-step synthesis of sulfinate ester **1** from *p*-toluenesulfinic acid, supported thionyl chloride on silica gel and aliphatic alcohols under solid phase conditions (Scheme 1).

Results and Discussion

The process in its entirety involves a simple mixing of *p*-toluenesulfinic acid, supported thionyl chloride on silica gel (33 %) and aliphatic alcohols in a mortar and grinding the mixture for the time specified in the Table at room temperature. In our best of knowledge this methodology for preparation of chiral sulfinate esters in solid phase conditions has not been reported in literature. This method does not require additional step and excess of thionyl chloride for preparation of sulfinyl chlorides, which are thermally unstable and sensitive to moisture during the reaction, work-up and evaporation of excess thionyl chloride. This method also does not need any catalysts which can be relatively expensive and can cause problems during purification.[9–11]



1

SCHEME 1

The compounds **1** have been identified by ^{1}H NMR analysis. Because of the low reactivity of aromatic alcohols only aliphatic alcohols could be converted into the desired products, the results of these efforts are presented in table I. The desired product was usually isolated in good to excellent yield, and excellent diastereoselectivity (Table I).

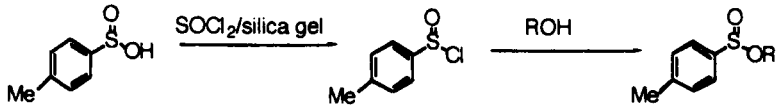
TABLE I Preparation of p-Toluenesulfinate Esters **2**

Entry	*R*	*Reaction Time (min)*	*Yield (%)*
1	CH_3	30	85
2	CH_3CH_2	40	95
3	$CH_3(CH_2)_2$	40	75
4	$CH_3(CH_2)_3$	40	70
5	$CH_3CH(CH_3)CH_2$	40	75
6	$CH_3(CH_2)_2CH(CH_3)$	40	78
7	cyclohexyl	45	60
8	$C_6H_5CH_2$	35	85
9	$C_6H_5CH_2CH_2$	40	79
10	l-menthyl	45	95
11	$ClCH_2CH_2$	40	75
12	$CH_3(CH_2)_6CH_2$	40	68
13	$CH_3CH_2CH(CH_3)$	40	70
14	$(CH_3)_2CH$	35	75

The diastereoselectivity of product formation when we used l-menthol, as determined by ^{1}H NMR analysis on the crude reaction products, was 90:10 (Table I, entry 10); the major diastereomer proved to have a negative sign. Literature precedent suggests that this compound has (S) configuration at sulfur.[17]

We believe that the effect of silica gel is to absorb the thionyl chloride on its surface. The supported thionyl chloride then reacts with sulfinic acid to produce sulfinyl chloride. The alcohol then reacts with sulfinyl chloride to produce alkanesulfinates, the probably mechanism is shown in Scheme 2.

In order to evaluate the effect of silica gel in this reaction, several experiments were demonstrated. As shown in Table II, when *p*-toluenesulfinic acid with thionyl chloride and ethanol was used in the absence of silica



SCHEME 2

gel, the *p*-toluenesulfinic acid was converted to the corresponding ester in 10 % yield after 60 min grinding in a mortar at room temperature (Table II, entry 2). The reaction of supported thionyl chloride on silica gel in dichloromethane (2 h, reflux) was unsuccessful and the *p*-toluenesulfinic acid remained unchanged (entry 3). The reaction of *p*-toluenesulfinic acid and ethanol in the presence of silica gel without thionyl chloride was unsuccessful and the yield of corresponding *p*-toluenesulfinic ester after 80 min grinding in a mortar at 70°C was only 10 % (entry 4). Similarly when we used thionyl chloride without silica gel for 40 min the condensation proceeded in 25 % yield (entry 5). Only in the case of reaction of supported thionyl chloride on silica gel with *p*-toluenesulfinic acid and ethanol *p*-toluenesulfinic ester produced in excellent yield (entry 1).

TABLE II Preparation of Ethyl p-Toluenesulfinate Ester

Entry	*Catalyst*	*Temp (°C)*	*Time (min)*	*Solvent*	*Sulfinate Ester[a] (%)*
1	silica gel	rt.	40	none	95
2	none	rt.	60	none	10
3	silica gel	40	120	CH_2Cl_2	0
4	silica gel	70	80	none	10[b]
5	none	rt.	40	none	25

a. Evaluated by TLC ((silica gel using a mixture of ethyl acetate and hexane as eluent (90:10)) analysis.
b. Without thionyl chloride.

In conclusion a simple and one-pot method for synthesis of p-toluenesulfinate ester has been developed. The discovery of the method promises to find widespread application in the preparation of chiral sulfinate esters. This method should allow a more rapid and complete screening of sulfur substituent effects in chiral sulfoxide chemistry than has previously

been possible. This methodology is superior from point of view of yield, short reaction time and the easier work-up to the reported methods.

Experimental

General

All products were identified by spectroscopy data (IR, NMR, mass and CHN analysis). All mps. were taken on a Gallenkamp melting apparatus and are uncorrected. Elemental analysis was performed by Research Institute of Petroleum Industry, Tehran, I.R. Iran. ^{1}H NMR spectra were recorded on a Varian EM-390 NMR Spectrometer operating at 90 MHz. The spectra were measured in $CDCl_3$ unless otherwise stated, relative to TMS (0.00 ppm). Optical rotations were recorded with a JASCO, DIP-370, Digital Polarimeter. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Supported thionyl chloride (33 %) on silica gel was prepared from mixing thionyl chloride (13 mmol, 1.5 g), silica gel (3 g) in a mortar and grinding the mixture for one min. The mixture can be kept in a sealed tube in freezer for week without loosing its activity.

General Procedure

A mortar was charged with 33% supported thionyl chloride on silica gel (0.45 g, 1.3 mmol thionyl chloride on 0.90 g silica gel), *p*-toluenesulfinic acid (0.16 g, 1 mmol), and the mixture was ground with a pestle for 1 min, then alcohol (1 mmol) was added to the mixture. The reaction mixture was ground for the time specified in table I. When TLC ((silica gel using a mixture of ethyl acetate and hexane as eluent (90:10)) showed no remaining *p*-toluenesulfinic acid, the reaction mixture was poured into a mixture of ether (20 ml) and H_2O (5 ml). The ethereal layer was washed with saturated $NaHCO_3$ (15 ml), dried ($CaCl_2$), and evaporated to dryness using a rotary evaporator to give pure product.

Methyl p-toluenesulfinate 2a

(0.14 g, 0.85, 85 %) oil bp 110–112°C/16 mm Hg (lit., [18]129–100 °C/16 mm Hg); 1128 cm^{-1} (S=O); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.60 (d, J=8 Hz, 2 H), 3.60 (s, 3 H, Me), 2.46 (s, 3 H, Me). MS (CI) m/z 170 (60, M^+). Anal calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; S, 18.83 %. Found: C, 56.30; H, 6.10; S 18.80 %.

Ethyl p-toluenesulfinate 2b

(0.17 g, 0.95, 95 %) oil bp 139–140°C/16 mm Hg (lit., [19]92°C/2.0 mm Hg); 1128 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.40 (d, J=8 Hz, 2 H), 4.40–4.00 (m, 1 H), 3.90–3.50 (m, 1 H), 2.60 (s, 3 H, Me), 1.30 (t, J=6 Hz, 3 H). MS (CI) m/z 184 (64, M^+). Anal calcd for $C_9H_{12}O_2S$: C, 58.68; H, 6.57; S, 17.37 %. Found: C, 58.60; H, 6.60; S 17.30 %.

N-Propyl p-toluenesulfinate 2c

(0.15 g, 0.75, 75 %) oil bp 146–147°C/16 mm Hg; 1130 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.50 (d, J=8 Hz, 2 H), 4.40–4.00 (m, 1 H), 4.20–3.80 (m, 1 H), 3.70–3.30 (m, 1 H), 2.50 (s, 3 H, Me), 1.80–1.40 (m, 2 H), 1.00 (t, J=6 Hz, 3 H). MS (CI) m/z 198 (55, M^+). Anal calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12; S, 16.17 %. Found: C, 60.60; H, 7.30; S 16.20 %.

N-Butyl p-toluenesulfinate 2d

(0.15 g, 0.70, 70 %) oil bp 110–111°C/8 mm Hg (lit., [19]104°C/1.5 mm Hg); 1132 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8 Hz, 2 H), 7.25 (d, J=8 Hz, 2 H), 4.20–3.80 (m, 1 H), 3.60–3.30 (m, 1 H), 2.55 (s, 3 H, Me), 1.70–1.1 (m, 4 H), 0.80 (t, J=6 Hz, 3 H). MS (CI) m/z 212 (52, M^+). Anal calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10 %. Found: C, 62.20; H, 7.50; S 15.10 %.

Iso-Butyl p-toluenesulfinate 2e

(0.17 g, 0.75, 75 %) oil bp 114–116°C/10 mm Hg; 1132 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.30 (d, J=8 Hz, 2 H), 4.00–3.80 (dd, J=4.5, 6.8 Hz, 1 H), 3.50–3.10 (dd, 4.5, 6.8 Hz, 1 H), 2.55 (s, 3 H, Me), 2.20–1.7 (m, 1 H), 1.00 (d, J=9 Hz, 6 H). MS (CI) m/z 212 (52, M^+). Anal calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10 %. Found: C, 62.20; H, 7.50; S 15.10 %.

Sec-Pentyl p-toluenesulfinate 2f

(0.17 g, 0.78, 78 %) oil bp 112–115°C/10 mm Hg; 1128 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.45 (d, J=8 Hz, 2 H), 4.70–3.80 (m, 1 H), 3.60–3.30 (m, 1 H), 2.55 (s, 3 H, Me), 1.70–1.1 (m, 4 H), 0.80 (t,

J=6 Hz, 3 H). MS (CI) m/z 226 (52, M^+). Anal calcd for $C_{12}H_{18}O_2S$: C, 63.28; H, 8.02; S, 14.16 %. Found: C, 63.20; H, 8.20; S 14.10 %.

Cyclohexyl p-toluene sulfinate 2g

(0.13 g, 0.60, 68 %), as a solid; mp 73°C 1130 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.50 (d, J=8 Hz, 2 H), 4.50–4.20 (m, 1 H), 2.50 (s, 3 H, Me), 2.10–1.20 (m, 7 H), 1.90–1.40 (m, 10 H). MS (CI) m/z 238 (60, M^+). Anal calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S. 13.45 %. Found: C, 65.30; H, 7.50; S 13.30 %.

Benzyl p-toluene sulfinate 2h

(0.20 g, 0.85, 85 %) oil bp 181–183°C/10 mm Hg (lit., [19]161°C/2.5 mm Hg); 1132 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.50–7.20 (m, 7 H), 4.70 (AB q, J=13.8 Hz, 2 H), 2.55 (s, 3 H, Me), 1.70–1.1 (m, 4 H), 0.80 (t, J=6 Hz, 3 H). MS (CI) m/z 246 (80, M^+), 91 (100). Anal calcd for $C_{14}H_{14}O_2S$: C, 68.27; H, 5.73; S, 13.02 %. Found: C, 68.30; H, 5.80; S 13.10 %.

2-Phenyl p-toluene sulfinate 2i

(0.20 g, 0.79, 79 %) oil bp 195–197°C/10 mm Hg; 1132 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.60 (d, J=8 Hz, 2 H), 7.40–7.10 (m, 7 H), 4.40–4.00 (m, 1 H), 3.90–3.50 (m, 1 H), 2.80 (t, J=9 Hz, 2 H), 2.40 (s, 3 H, Me). MS (CI) m/z 260 (70, M^+), 91 (100). Anal calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19; S, 12.31 %. Found: C, 69.10; H, 6.30; S 12.20 %.

1-Menthyl p-toluene sulfinate 2j

(0.28 g, 0.95, 95 %), as a solid; mp 105–106°C 1132 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8 Hz, 2 H), 7.45 (d, J=8 Hz, 2 H), 4.18 (m, 0.90 H, major diastereomer), 4.13 (m, 0.10 H, minor diastereomer), 2.22 (s, 2.70 H, Me, major diastereomer), 2.16 (s, 0.30 H, Me, minor diastereomer), 1.70–0.70 (m, 18 H). Recrystalization from acetone afforded pure (S)-(menthyl *p*-toluenesulfinate (0.20 g, 70 %); mp 103–105 °C (lit., [17]mp 103 105°C); $[\alpha]^{25}_D$ –200.7 (*c* 1.5, acetone) (lit., [15]$[\alpha]^{25}_D$ -200.3 (*c* 1.23, acetone).

2-Chloro ethyl p-toluene sulfinate 2k

(0.16 g, 0.75, 75 %), as a solid mp 59–61°C, 1132 cm^{-1}(S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.44 (d, J=8 Hz, 2 H), 4.30 (m, 1 H), 3.80

(m, 3 H), 2.50 (s, 3 H, Me. MS (CI) m/z 218 (80, M^+). Anal calcd for $C_9H_{11}ClO_2S$: C, 49.43; H, 5.07; S, 14.66 %. Found: C, 49.30; H, 5.20; S 14.50 %.

N-Octyl p-toluene sulfinate 21

(0.20 g, 0.75, 75 %), oil bp 168–170°C/10 mm Hg (lit., [19]152 °C/2.0 mm Hg); 1139 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.25 (d, J=8 Hz, 2 H), 4.00 (m, 1 H), 3.60 (m, 3 H), 2.55 (s, 3 H, Me, 1.50 (m, 4 H), 0.80 (t, 3 H). MS (CI) m/z 268 (52, M^+). Anal calcd for $C_{15}H_{24}O_2S$: C, 67.13; H, 9.02; S, 11.92 %. Found: C, 67.00; H, 9.20; S 11.70 %.

Sec-Butyl p-toluene sulfinate 2m

(0.15 g, 0.70, 70 %) oil bp 104–106°C/15 mm Hg; 1130 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.40 (d, J=8 Hz, 2 H), 4.50 (m, 1 H), 2.50 (s, 3 H, Me), 1.5–0.7 (m, 8 H). MS (CI) m/z 212 (59, M^+). Anal calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10 %. Found: C, 62.10; H, 7.80; S 15.20 %.

Iso-Proyl p-toluene sulfinate 2n

(0.15 g, 0.75, 75 %) oil bp 100–102°C/2 mm Hg; 1133 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8 Hz, 2 H), 7.40 (d, J=8 Hz, 2 H), 4.70 (m, 1 H), 2.50 (s, 3 H, Me), 2.20 (d, J=6.8 Hz, 3 H), 2.00 (d, J=6.8 Hz, 3 H). MS (CI) m/z 198 (50, M^+). Anal calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.60; S, 15.10 %. Found: C, 62.10; H, 7.80; S 15.20 %.

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