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A Convenient and Mild Procedure for the Synthesis of Alkyl *p*-Toluenesulfinates under Solvent-Free Conditions Using Microwave Irradiation

Abdol R. Hajipour*, Shadpour E. Mallakpour and Aboulfazl Afrousheh
College of Chemistry, Isfahan University of Technology, Isfahan, Iran.

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Abstract: The reactions of aliphatic alcohols with *p*-toluenesulfinic acid are accelerated by microwave irradiation under solvent-free conditions in the presence of silica gel to afford a high yielding synthesis of *p*-toluenesulfinate esters.

In contrast with the case of carboxylic acids, sulfinic acids cannot be converted to their esters by the reaction with alcohols in the presence of acid catalysts, since they readily undergo disproportionation to yield thiosulfonates and sulfonic acids under acid conditions. [1] Sulfinate esters of various types have been previously prepared by a number of methods. A useful, one-step synthesis consists of the oxidation of thiols or disulfides with lead(IV) acetate in an appropriate alcohol. [2,3] The most commonly used methods are the reactions of sulfinyl chlorides with alcohols [4] and sodium sulfinates with chlorocarbonates in alcohols. [5] Other methods including alkylation of sulfinic acids are also known. [6-8] Recently, a useful one-step synthesis of alkyl t-alkanesulfinates was reported. [9]

In recent years, organic reactions on solid supports [10] and those that are assisted by microwaves, [11] especially under solvent-free conditions, [12] have attracted attention. 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 sulfinic acids on silica gel and aliphatic alcohols using microwave irradiation. This method would be widely applicable as a general synthesis of alkyl sulfinates. In general we have found that the sulfinate esters were formed in good to high yield following less than 90 seconds of irradiation in a domestic microwave.

RESULTS AND DISCUSSION

This method consists of a one-step synthesis involving the reaction of supported *p*-toluenesulfinic acid (1) on silica gel [13] with an appropriate alcohol (Scheme 1). The process involves a simple mixing of supported *p*-toluenesulfinic acid (1) on silica gel and alcohol in a

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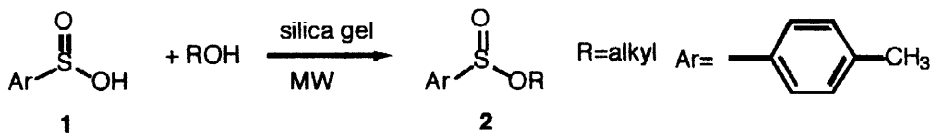
mortar, followed by grinding the mixture for 1 min and subsequent irradiation in a microwave oven for the time specified in Table 1. This method does not require sulfinyl chlorides, which are thermally unstable and sensitive to moisture, and also does not need any catalysts which can be relatively expensive and can cause problems during purification. [1] The yields of the reactions are good (60-95 %) and the reaction times are exceedingly short (30-90 seconds). To the best of our knowledge this technique for the preparation of sulfinate esters is completely novel and has not been reported in the literature. The compounds (2) were characterised by ^{1}H NMR analysis. Because of the low reactivity of aromatic alcohols, only aliphatic alcohols could be converted into the desired products.

Scheme 1



1 2

Table 1: Preparation of *p*-Toluenesulfinate Esters (2).

Entry	R	Reaction Time, sec	Solvent	Yield %	Power (W)
1	CH_3	40	none	65	900
2	CH_3CH_2	50	none	87	900
3	$CH_3(CH_2)_2$	60	none	60	900
4	$CH_3(CH_2)_3$	30	none	90	900
5	$CH_3CH(CH_3)CH_2$	30	none	95	900
6	$CH_3(CH_2)_2CH(CH_3)$	60	none	68	900
7	cyclohexyl	60	none	70	900
8	$C_6H_5CH_2$	70	none	75	900
9	$C_6H_5CH_2CH_2$	90	none	70	900
10	L-menthyl	60	none	86	900

The diastereoselectivity of product formation when we used l-menthol, as determined by ^{1}H NMR analysis on the crude reaction products, was 85:15 (Table 1, entry 10); the major diastereomer proved to have a negative sign of rotation. Literature precedent [14] suggests that this compound has (S) configuration at sulfur.

In order to evaluate the synergy between dry media and microwave irradiation in this reaction, several experiments were tried. As shown in Table 2, the reaction of *p*-toluenesulfinic acid and isobutyl alcohol without irradiation was unsuccessful and the *p*-toluenesulfinic acid remain unchanged after 60 min grinding in a mortar (entry 2). When silica gel was used as a catalyst in a dichloromethane solution (2 h, reflux), the corresponding sulfinic ester was obtained in 10 % yield (entry 4). The reaction of *p*-toluenesulfinic acid and isobutyl alcohol in the presence of silica gel without irradiation was unsuccessful and the yield of corresponding *p*-toluenesulfinic ester after 30 min. grinding in a mortar at 70 °C was only 10 % (entry 3).

Similarly when we used irradiation without silica gel for 6 min. the condensation proceeded in 20 % yield (entry 5). Only in the case of dry media coupled with microwave irradiation, taking advantage of the synergy between the two methodologies was the *p*-toluenesulfinic ester produced in excellent yield (entry 1).

Table 2. Preparation of Isobutyl *p*-Toluene Sulfinate Ester Under Different Conditions.

Entry	Catalyst	Temp (°C) or MW power (W)	Time (min.)	Solvent	Sulfinate Ester[a] (%)
1	silica gel	900 W	1.5	none	95
2	silica gel	r.t.	60	none	0
3	silica gel	70 °C	30	none	10
4	silica gel	100 °C	120	water	13
5	none	800 W	6	none	20

a) Evaluated by TLC analysis

In conclusion, the discovery of this novel method promises to find widespread application in the preparation of chiral sulfinate esters for which the corresponding sulfinyl chlorides are thermally unstable and sensitive to moisture. This methodology does not need any catalysts which can be relatively expensive and can cause problems during purification. This technique 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 the point of view of yield, diastereoselectivity, lower reaction time and the easier work-up to the reported methods. [1]

Experimental

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 the 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, or a Varian Unity 250 Fourier Transform NMR Spectrometer operating at 250 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. Irradiation was carried out in a domestic microwave oven (Samsung 2450 MHz, 900 Watts), for an optimised time and power. The temperature of the reaction, which was determined by thermometer after turning off the microwave, reached 80-90 °C.

General procedure:

A mortar was charged with the alcohol (1 mmol), *p*-toluenesulfinic acid (1 mmol, 0.16 g), and silica gel [13] (0.3 g). The reaction mixture was ground with a pestle in the mortar for 1 min, then the mortar was covered with a watch glass, placed in a microwave oven and irradiated for the time specified in Table 1. When TLC 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 $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness using a rotary evaporator to give the pure product.

Methyl *p*-toluenesulfinate 2a.

(0.11g, 0.65 mmol, 65 %) oil bp 110-112 °C/16 mm Hg (lit., [6] 129-130 °C/16mm Hg); IR(KBr): 2940, 2880, 1600, 1460, 1128 (S= O), 960, 730 cm^{-1}; ^1H 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, 56.40; H, 6.00; S, 18.80 %.

Ethyl *p*-toluenesulfinate 2b.

(0.16g, 0.87 mmol, 87 %) oil bp 139-140 °C/16 mm Hg (lit., [16] 92 °C/2.0 mm Hg);IR(KBr): 2940, 2880, 1600, 1460, 1128 (S= O), 960, 730 cm^{-1}; ^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), 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, 6.50; S, 17.40 %.

***n*-Propyl *p*-toluenesulfinate 2c.**

(0.12g, 0.60 mmol, 60 %), oil bp 146-147 °C/16mm Hg; IR(KBr): 2940, 2880, 1600, 1460, 1130 (S= O), 965, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.50 (d, J=8 Hz, 2 H), 4.20-3.80 (m, 1 H), 3.70-3.30 (m, 1 H), 2.50 (s, 3 H), 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, 60.50; H, 7.20; S, 16.20 %.

***n*-Butyl *p*-toluenesulfinate 2d.**

(0.19g, 0.90 mmol, 90 %) oil bp 110-111 °C/8 mm Hg (lit., [16] 104 °C/1.5 mm Hg); IR(KBr): 2940, 2880, 1600, 1460, 1132 (S= O), 960, 736 cm^{-1}; ^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), 1.70-1.10 (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.**

(0.20g, 0.95 mmol, 95 %), oil bp 114-116 °C/10 mm Hg; IR(KBr): 2940, 2880, 1600, 1460, 1132 (S= O), 960, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8 Hz, 2 H), 7.50 (d, J=8 Hz, 2 H), 4.00-3.70 (dd, J=4,5, 6.8 Hz, 1 H), 3.50-3.10 (dd, J=4.5, 6.8 Hz, 1 H), 2.50 (s, 3 H), 2.20-1.70 (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.**

(0.15 g, 0.68 mmol, 68 %), oil bp 112-115 °C/10 mm Hg; IR(KBr): 2940, 2880, 1600, 1460, 1128 (S= O), 965, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (d, J=8 Hz, 2 H), 7.45 (d, J=8 Hz, 2 H), 4.70-4.30 (m, 1 H), 2.50 (s, 3 H), 1.70-1.10 (m. 7 H), 0.80 (t, J=9 Hz, 3 H). MS (CI) m/z 226

(50, M^+). Anal calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.16 %. Found: C, 63.60; H, 8.10; S, 14.20 %.

Cyclohexyl *p*-toluenesulfinate 2g.

(0.15 g, 0.68 mmol, 68 %), as a solid; mp 73 °C IR(KBr): 2940, 2880, 1600, 1460, 1130 (S= O), 965, 746 cm^{-1}; ^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), 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, 65.40; H, 7.70; S, 13.40 %.

Benzyl *p*-toluenesulfinate 2h.

(0.18 g, 0.75 mmol, 75 %), oil bp 181-183 °C/10 mm Hg (lit., [16] 161 °C/2.5 mm Hg); IR(KBr): 2940, 2880, 1600, 1460, 1132 (S= O), 965, 746 cm^{-1}; ^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), 2.50 (s, 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 ethyl *p*-toluenesulfinate 2i.

(0.18 g, 0.70 mmol, 70 %), oil bp 197-140 °C/12 mm Hg; IR(KBr): 2940, 2880, 1600, 1460, 1132 (S= O), 965, 746 cm^{-1}; ^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). 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, 6.20; S, 12.30 %.

Menthyl *p*-toluenesulfinate 2j.

(0.25 g 0.86 mmol, 86 %) as a solid, mp 105-106 °C; ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8 Hz, 2 H), 7.45 (d, J=8 Hz, 2 H), 4.18 (m, 0.85 H, major diastereomer), 4.13 (m, 0.15 H, minor diastereomer), 2.22 (s, 2.55 H, Me, major diastereomer), 2.16 (s, 0.45 H, Me, minor diastereomer), 0.70-2.30 (m, 18 H). Recrystalization from acetone afforded pure (S)-(-)menthyl *p*-toluenesulfinate (0.17g, 60 %): mp 103-105 °C (lit.,[15] mp 103 -105 °C); $[\alpha]^{25}_D$ -200.7 (*c* 1.5, acetone) (lit., [15] $[\alpha]^{25}_D$ -200.3 (*c* 1.23, acetone).

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