

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

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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*-toluenesulfonate esters. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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 Sulfonate 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 alcohols⁴ and sodium sulfonates 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*-alkanesulfonates was reported.⁹

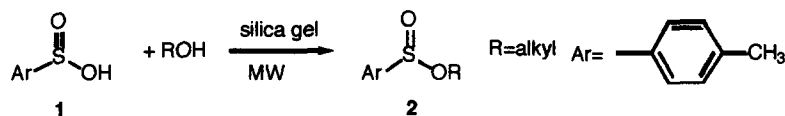
In recent years, organic reactions on solid supports¹⁰ and those that are assisted by microwaves,¹¹ especially under solvent-free conditions,¹² have attracted attention. The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity. We now wish to report a convenient one-step method for the preparation of sulfonate 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 sulfonates. In general we have found that the sulfonate 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 gel¹³ 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

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 sulfinic acid esters is completely novel and has not been reported in the literature. The compounds (2) were characterised by ¹H NMR analysis. Because of the low reactivity of aromatic alcohols, only aliphatic alcohols could be converted into the desired products.

Scheme 1

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

| Entry | R | Reaction Time, sec | Solvent | Yield % | Power (W) |
|-------|--|--------------------|---------|---------|-----------|
| 1 | CH ₃ | 40 | none | 65 | 900 |
| 2 | CH ₃ CH 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 ₃ CH(CH ₃)CH ₂ | 30 | none | 95 | 900 |
| 6 | CH ₃ (CH ₂) ₂ CH(CH ₃) | 60 | none | 68 | 900 |
| 7 | cyclohexyl | 60 | none | 70 | 900 |
| 8 | C ₆ H ₅ CH ₂ | 70 | none | 75 | 900 |
| 9 | C ₆ H ₅ CH ₂ CH 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 ¹H 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 precedent¹⁴ 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 Sulfinic Ester Under Different Conditions.

| Entry | Catalyst | Temp (°C) or MW power (W) | Time (min.) | Solvent | Sulfinic 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 sulfinic 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. ¹H 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 CDCl₃ 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 H₂O (5 ml). The ethereal layer was washed with saturated NaHCO₃, dried (MgSO₄), and evaporated to dryness using a rotary evaporator to give the pure product.

Methyl *p*-toluenesulfinate 2a.

(0.11 g, 0.65 mmol, 65 %) oil bp 110–112 °C/16 mm Hg (lit., ⁶ 129–130 °C/16 mm Hg); IR(KBr): 2940, 2880, 1600, 1460, 1128 (S=O), 960, 730 cm⁻¹; ¹H NMR (CDCl₃) 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 C₈H₁₀O₂S: C, 56.45; H, 5.92; S, 18.83 %. Found: C, 56.40; H, 6.00; S, 18.80 %.

Ethyl *p*-toluenesulfinate 2b.

(0.16 g, 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 (CDCl₃) 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 C₉H₁₂O₂S: C, 58.68; H, 6.57; S, 17.37 %. Found: C, 58.60; H, 6.50; S, 17.40 %.

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

(0.12 g, 0.60 mmol, 60 %), oil bp 146–147 °C/16 mm Hg; IR(KBr): 2940, 2880, 1600, 1460, 1130 (S=O), 965, 740 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₀H₁₄O₂S: C, 60.58; H, 7.12; S, 16.17 %. Found: C, 60.50; H, 7.20; S, 16.20 %.

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

(0.19 g, 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 (CDCl₃) 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 C₁₁H₁₆O₂S: C, 62.23; H, 7.60; S, 15.10 %. Found: C, 62.20; H, 7.50; S, 15.10 %.

***iso*-Butyl *p*-toluenesulfinate 2e.**

(0.20 g, 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 (CDCl₃) 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 C₁₁H₁₆O₂S: 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 (CDCl₃) 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 C₁₂H₁₈O₂S: 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 (CDCl₃) 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 C₁₃H₁₈O₂S: 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 (CDCl₃) 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 C₁₄H₁₄O₂S: 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 (CDCl₃) 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 C₁₅H₁₆O₂S: 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 (CDCl₃) 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). Recrystallization from acetone afforded pure (S)-(-)-menthyl *p*-toluenesulfinate (0.17g, 60 %): mp 103–105 °C (lit., ¹⁵ mp 103–105 °C); [α]_D²⁵ -200.7 (c 1.5, acetone) (lit., ¹⁵ [α]_D²⁵ -200.3 (c 1.23, acetone).

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