

Indium-mediated Coupling Reaction of Sulfonyl Chlorides with Alkyl Bromides in Water. A Facile Synthesis of Sulfones†

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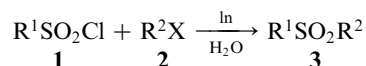
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Indium-mediated coupling of alkyl bromides with aromatic sulfonyl chlorides gives the corresponding sulfones in aqueous media with moderate to good yields.

Recently, metal-mediated organic reactions in aqueous media have attracted considerable interest in organic synthesis.¹ Such reactions in aqueous media offer a number of advantages over conventional organometallic reactions in organic solvents. There is the practical convenience, possible environmentally friendliness and no need to use anhydrous organic solvents.² As for the metal used, in addition to zinc and tin, indium has been found by Chan and co-workers³ to be the metal of choice. Indium is considered to be more effective than zinc and tin since the reaction requires no activation, and produces only few side reactions. It has been reported that coupling of allyl halides with carbonyl compounds could be mediated by indium in aqueous media.⁴ So far, the carbonyl component in the indium-mediated coupling reaction in aqueous media has been confined to aldehydes and ketones. Carboxylate esters and even carboxylic acids show remarkable stability under the reaction conditions.

Organosulfones are important intermediates in organic synthesis.⁵ Sulfones are generally prepared either by oxidation of the corresponding sulfides and sulfoxides or by a displacement reaction of sodium arenosulfonates with appropriate alkyl halides. A drawback of the former method is that the foul smelling thiols are the basic starting materials and other functional groups such as carbon-carbon double bonds are involved in the reaction during the oxidation, while the sulfinate method requires rather long reaction times, anhydrous conditions and usually results only in moderate yields of sulfones.⁶ As a consequence, a number of modifications of the latter method have been reported. For example, the reaction can be

performed more efficiently by alkylation of tetrabutylammonium salts of sulfinic acids.⁷ However, this procedure requires the additional step of preparing the sulfinate salts. Recently, we have reported zinc-mediated C–S coupling reactions in dry diethyl ether for the preparation of sulfones, but the substrates are limited.⁸ Herein we report a facile synthesis of sulfones by using indium-mediated coupling reactions of aromatic sulfonyl chlorides with alkyl bromides in aqueous media at 0 °C. The results are listed in Table 1.



It is clear from Table 1 that aromatic sulfonyl chlorides react with active alkyl halides such as allyl bromide, benzyl bromide, 2-bromoacetophenone, ethyl bromoacetate, cinnamyl bromide and 2,4-dibromoacetophenone to give the corresponding products in moderate to good yields. Unfortunately, ethanesulfonyl chloride gives too little product to be isolated (entry **p**) because it hydrolyses easily to form the sulfonic acid in water. Interestingly, the addition of aprotic solvents, such as THF, slows the reaction (entries **b** and **c**). Moreover, when R²X was a less active alkyl halide such as the fluoride or chloride, no product was isolated, even at longer reaction times (entry **o**).

In summary, the present work provides a new and facile method for the preparation of sulfones through an indium-mediated reaction of aromatic sulfonyl chlorides with suitable alkyl bromides in aqueous media. The notable advantages of this methodology are mild conditions, short

Table 1 Synthesis of sulfones

Entry	R ¹	R ² X	Reaction conditions			Yield (%) ^a
			Solvent	t/h	T/°C	
a	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ Br	A	4	0	67
b	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ Br	B	7	0	63
c	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ Br	C	36	25	45
d	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅ CH=CHCH ₂ Br	A	5	0	63
e	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅ COCH ₂ Br	A	4	0	80
f	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -BrC ₆ H ₄ COCH ₂ Br	A	4	0	82
g	<i>p</i> -CH ₃ C ₆ H ₄	C ₂ H ₅ O ₂ CCH ₂ Br	A	5	0	57
h	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂ Br	A	4	0	84
i	C ₆ H ₅	CH ₂ =CHCH ₂ Br	A	5	0	64
j	C ₆ H ₅	C ₆ H ₅ CH=CHCH ₂ Br	A	4	0	61
k	C ₆ H ₅	C ₆ H ₅ COCH ₂ Br	A	4	0	78
l	C ₆ H ₅	<i>p</i> -BrC ₆ H ₄ COCH ₂ Br	A	5	0	80
m	C ₆ H ₅	C ₂ H ₅ O ₂ CCH ₂ Br	A	5	0	55
n	C ₆ H ₅	C ₆ H ₅ CH ₂ Br	A	4	0	80
o	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ Cl	A	16	25	—
p	C ₂ H ₅	CH ₂ =CHCH ₂ Br	A	3	0	—

^aIsolated yield. A = water, B = THF–water (1:1), C = THF(anhydrous).

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

reaction times, simple operation, higher yields and no polluting solvents. It is a new application of metallic indium in the synthesis of organic sulfur compounds.

Experimental

Melting points were uncorrected. ^1H NMR spectra were recorded on a JEOL PMX 60 SI instrument in CDCl_3 using SiMe_4 as internal standard, IR spectra on a Perkin-Elmer 683 spectrophotometer.

Metallic indium and other chemicals were from commercial sources and used without purification.

General Procedure for the Synthesis of Sulfoxes.—Aromatic sulfonyl chloride (1.0 mmol) and indium (1.5 mmol, small grains cut from a bar of indium metal) were added to water (3 ml) and then the appropriate alkyl bromide (1.5 mmol) was added. The mixture was stirred at 0°C for the time indicated in Table 1. The product was extracted with ether (20 ml \times 2), and the extract washed with brine. After being dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure and the pure sulfoxide was separated from the residue through preparative TLC (silica gel) with cyclohexane–ethyl acetate as eluent.

3a: mp $51\text{--}52^\circ\text{C}$ (lit.,⁷ $50\text{--}52^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3058, 1598, 1335, 1290 and 1150 cm^{-1} ; ^1H NMR δ 2.42 (3 H, s), 3.69 (2 H, d, $J = 6.4$ Hz), 5.31–6.03 (3 H, m) and 7.21–7.88 (4 H, m).

3d: mp $116\text{--}118^\circ\text{C}$ (lit.,⁹ $116\text{--}118^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3083, 1595, 1330, 1280 and 1145 cm^{-1} ; ^1H NMR δ 2.40 (3 H, s), 4.21 (2 H, d, $J = 6.3$), 6.15–6.52 (1 H, m), 6.68 (1 H, d, $J = 15.8$ Hz) and 7.05–7.88 (9 H, m).

3e: mp $109\text{--}110^\circ\text{C}$ (lit.,⁷ $108\text{--}109.5^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3105, 1680, 1334, 1220 and 1139 cm^{-1} ; ^1H NMR δ 2.41 (3 H, s), 4.73 (2 H, s) and 7.23–8.03 (9 H, m).

3f: mp $146\text{--}147^\circ\text{C}$ (lit.,¹⁰ $145\text{--}147^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3093, 1690, 1320, 1280 and 1135 cm^{-1} ; ^1H NMR δ 2.42 (3 H, s), 4.69 (2 H, s) and 7.20–8.00 (8 H, m).

3g: mp $34\text{--}35^\circ\text{C}$ (lit.,¹¹ $34\text{--}35^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3090, 1750, 1600, 1330, 1280 and 1140 cm^{-1} ; ^1H NMR δ 1.18 (3 H, t), 2.42 (3 H, s), 3.95–4.60 (4 H, m) and 7.25–7.90 (4 H, m).

3h: mp $144\text{--}145^\circ\text{C}$ (lit.,¹¹ $143\text{--}145^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3080, 1580, 1325, 1280 and 1140 cm^{-1} ; ^1H NMR δ 2.38 (3 H, s), 4.28 (2 H, s) and 7.00–7.60 (9 H, m).

3i: Oil (lit.¹²); IR (film, $\tilde{\nu}_{\text{max}}$) 3090, 1600, 1325 and 1150 cm^{-1} ; ^1H NMR δ 3.62 (2 H, d, $J = 6.4$ Hz), 5.20–6.08 (3 H, m) and 7.19–7.90 (5 H, m).

3j: mp $109\text{--}110^\circ\text{C}$ (lit.,¹³ 110°C); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3115, 1590, 1340 and 1135 cm^{-1} ; ^1H NMR δ 4.22 (2 H, d, $J = 5.0$), 6.20–6.58 (1 H, m), 6.68 (1 H, d, $J = 16.4$ Hz) and 7.05–7.88 (10 H, m).

3k: mp $94\text{--}95^\circ\text{C}$ (lit.,¹⁴ $93\text{--}95^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3100, 1690, 1340 and 1150 cm^{-1} ; ^1H NMR δ 4.72 (2 H, s) and 7.30–8.10 (10 H, m).

3l: mp $138\text{--}140^\circ\text{C}$ (lit.,¹⁵ $138.5\text{--}139.5^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3100, 1700, 1340 and 1145 cm^{-1} ; ^1H NMR δ 4.72 (2 H, s) and 7.23–8.00 (9 H, m).

3m: mp $40\text{--}42^\circ\text{C}$ (lit.,¹⁶ $42\text{--}43^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3080, 1750, 1600, 1330, 1280 and 1150 cm^{-1} ; ^1H NMR δ 1.15 (3 H, t), 3.90–4.48 (4 H, m) and 7.20–7.95 (5 H, m).

3n: mp $146\text{--}147^\circ\text{C}$ (lit.,¹⁷ $146\text{--}146.5^\circ\text{C}$); IR (KBr, $\tilde{\nu}_{\text{max}}$) 3065, 1595, 1320 and 1150 cm^{-1} ; ^1H NMR δ 4.25 (2 H, s) and 7.10–8.10 (10 H, m).

Received, 28th May 1998; Accepted, 3rd June 1998

Paper E/8/03996H

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