One-Pot Synthesis of Aryl Sulfones from Alcohols

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Abstract: A one-pot synthesis of aryl sulfones from primary alcohols is described. Alcohols were treated with N-bromosuccinimide and triphenylphosphine, followed by addition of sodium arenesulfinate with a catalytic amount of tetrabutylammonium iodide to afford the aryl sulfones in good to high yields.

Key words: sulfones, alcohols, sulfinates, one-pot synthesis

Alkyl aryl sulfones have been widely used as useful intermediates in organic synthesis.1 In particular, allylic aryl sulfones are versatile agents for carbon-carbon bond forming reactions. They can act as regio-defined allylic nucleophiles,2 allylic electrophiles,3 non-stabilized nucleophiles4 and radical species5 under appropriate reaction conditions. Their versatility stems from the ability of the sulfone group to stabilize an adjacent carbocation, the leaving group ability of the arylsulfonl group, and the presence of π-electrons.

Among the many preparative methods available, aryl sulfones are commonly prepared either by substitution reaction of alkyl halides with alkali-metal salts of arenesulfonlates6 or by oxidation of alkyl aryl sulfides.7 For allylic derivatives, palladium-catalyzed substitution of allylic acetates (or other derivatives) with metal arenesulfonlates has been developed. These substrates (halides, sulfides, acetates) can be easily prepared from alcohols, but their isolation is necessary before sulfonylation. From an economical and ecological point of view, one-pot reactions have attracted considerable attention in recent years. Since alcohols are readily available, more stable, and less toxic than the corresponding alkyl halides or sulfides, in general, a direct one-pot synthesis procedure of sulfones from alcohols would be convenient. To our knowledge, a few reports10a,b,c exist for the direct sulfonylation of alcohols. However, substrates of all the methods are limited to allylic alcohols and the reaction examples are few (only one10a or two10b). One of the methods requires acidic conditions.10c Therefore, it would be difficult to apply these sulfonylations to non-activated alcohols and/or acid-labile alcohols.

We wish to report a convenient one-pot synthesis of alky aryl sulfones from primary alcohols using N-bromosuccinimide, triphenylphosphine, and sodium arenesulfonlates under mild reaction conditions.

In the course of our synthetic studies on sphingolipids, we required 2(E)-dodecenyl phenyl sulfone in sufficient quantities.11 We prepared the sulfone from 2(E)-dodecen-1-ol (1a) in two steps: (1) preparation of 2-dodecenyl chloride by treatment with methanesulfonyl chloride and triethylamine in dichloromethane followed by addition of lithium chloride and DMF;12 (2) displacement of the chloride with benzenesulfinate in DMF at 50 °C for 5 hours. The overall yield of the sulfone 2a was satisfactory (83%), but purification of the intermediate, 2-dodecenyl chloride, was necessary. Then, we tried a one-pot synthesis of the sulfone by adding sodium benzenesulfinate to a solution of the intermediate mesylate. After optimization of the reaction conditions, sulfone 2a was obtained in 70% yield from 1a using THF as the solvent and tetrabutylammonium iodide as the catalyst.13 However, the yield was lower than that of the former two-pot process and 2-dodecenyl benzenesulfinate was always formed (7–12%).

Since sulfinate anion is an ambident nucleophile, both S-alkylation product (sulfone) and O-alkylation product (sulfinate ester) can be formed. Meek and Fowler reported14 that reaction of sodium p-toluenesulfinate with hard alkylation agents such as dimethyl sulfate gave methyl tolenesulfinate mainly (>50%), whereas reaction with methyl iodide, a soft alkylation agent, gave methyl tolyl sulfone predominantly (>90%).

These results prompted us to investigate a halide-mediated approach to sulfones, which involves (a) activation of alcohols with a halogenating agent and a trivalent phosphorous compound,15 followed by (b) displacement of the reactive intermediates by sodium arenesulfinate. Similar halide-mediated approaches have been already used for the one-pot syntheses of azides,16 nitriles,17 amines,18 and thiols19 from alcohols. We chose N-bromosuccinimide as the halogen source in view of its reactivity, ease of handling, and the atom economy for halogen. The results are summarized in Table 1 (Scheme 1). Thus treatment of 2-dodecenol (1a) with N-bromosuccinimide (1.3 equiv) and triphenylphosphine (1.4 equiv) in acetonitrile at 0 °C immediately gave the bromide20 (monitored by TLC). Without isolation, the bromide was treated with sodium benzenesulfinate (2.0 equiv) and tetrabutylammonium iodide (0.1 equiv) at 0 °C. The mixture was stirred at 50 °C for 5 hours to yield phenyl sulfone 2a11 in 84% yield (entry 1) along with a small amount of dodecenyl benzenesulfinate (ca. 3% yield). In the absence of
tetrabutylammonium iodide (entry 2), longer reaction time was necessary. When the reaction was carried out in toluene instead of acetonitrile, the yield of 2a slightly decreased (entry 3) and the sulfinate increased (6% yield). In THF, the reaction was completed in 2 hours at 50 °C (entry 4) to afford 2a in a similar yield to entry 1.

Readily available sodium benzenesulfinate hydrated crystals can replace the anhydrous salt without lowering the yield (entry 5).

Next, other allylic and benzylic alcohols were examined. Sulfonylation of 2(Z)-hexen-1-ol (1b) in acetonitrile or in THF gave 2(Z)-hexyl phenyl sulfone (2b)\textsuperscript{16} without isomerization of the double bond. The yield of 2b from the reaction in THF (entry 7) was higher than that in acetonitrile (entry 6). The following sulfonylations were carried out in THF. 1-Hexen-3-ol (1c), a secondary allylic alcohol, gave a mixture of the isomeric sulfones in 71% yield (entry 8). The \textsuperscript{1}H NMR analysis indicated that the mixture consisted of three isomers: the rearranged 2(E)-hexen-1-yl phenyl sulfone, its 2(Z)-isomer 2b, and 1-hexen-3-yl phenyl sulfone (2e)\textsuperscript{25} in 93% yield. In this case, geranyl bromide, a presumed intermediate,\textsuperscript{25} was so reactive that the reaction was carried out in DMF instead of THF, the yield of 2e was obtained in 76% yield (Table 2, entry 1, Scheme 2) with consumption of dodecyl bromide. Since the reaction was carried out in DMF instead of THF, the sulfinate ester increased (6%) and the sulfinate ester increased (6%). When the reaction was carried out in THF (entry 7) was higher than that in acetonitrile (entry 6). The following sulfonylations were carried out in THF. 1-Hexen-3-ol (1c), a secondary allylic alcohol, gave a mixture of the isomeric sulfones in 71% yield (entry 8). The \textsuperscript{1}H NMR analysis indicated that the mixture consisted of three isomers: the rearranged 2(E)-hexen-1-yl phenyl sulfone, its 2(Z)-isomer 2b, and 1-hexen-3-yl phenyl sulfone (2e)\textsuperscript{25} in 93% yield. In this case, geranyl bromide, a presumed intermediate,\textsuperscript{25} was so reactive that the reaction proceeded smoothly at room temperature. A sensitive allylic alcohol 1f, bearing an acetal group was also transformed to the sulfone 2f\textsuperscript{1} in high yield. Benzyl- (1g) and furfuryl- (1i) alcohols were efficiently converted to the corresponding phenyl sulfones 2g\textsuperscript{22} and 2i\textsuperscript{23}, respectively.

\textit{p}-Chlorobenzyl alcohol (1h) was similarly activated and treated with sodium \textit{p}-toluenesulfinate tetrahydrate to give \textit{p}-chlorobenzyl \textit{p}-tolyl sulfone (2h)\textsuperscript{22} in 86% yield.

We then extended the sulfone synthesis to non-activated alcohols. 1-Dodecanol (1j) was treated as above in THF at reflux for 16 hours to give dodecyl phenyl sulfone (2j)\textsuperscript{24} in 45% yield along with dodecyl bromide (53%). When the reaction was carried out in DMF instead of THF, the sulfone 2j was obtained in 76% yield (Table 2, entry 1, Scheme 2) with consumption of dodecyl bromide. Since sodium benzenesulfinate is soluble in DMF, tetrabutylammonium iodide can be replaced by the inexpensive sodium iodide, which would accelerate the reaction by Br–I exchange. The results for non-activated alcohols are summarized in Table 2. Phenethyl alcohol (1k), 2-propyn-1-ol (1l), and 4-penten-1-ol (1m) were converted to the corresponding aryl sulfones 2k\textsuperscript{25} 2l\textsuperscript{26} and 2m\textsuperscript{27} in good yields, respectively. To examine the scope of the procedure, this sulfonylation was applied to alcohols bearing a functional group such as ether 1n, ester 1o, and nitrile 1p. These groups proved to be compatible under the reaction conditions to afford the corresponding sulfones 2n\textsuperscript{27} 2o\textsuperscript{28} and 2p\textsuperscript{29} in most cases. The yields of the sulfones from non-activated alcohols were slightly lower than those of allylic sulfones.

Next, other allylic and benzylic alcohols were examined. Sulfonylation of 2(Z)-hexen-1-ol (1b) in acetonitrile or in THF gave 2(Z)-hexyl phenyl sulfone (2b)\textsuperscript{16} without isomerization of the double bond. The yield of 2b from the reaction in THF (entry 7) was higher than that in acetonitrile (entry 6). The following sulfonylations were carried out in THF. 1-Hexen-3-ol (1c), a secondary allylic alcohol, gave a mixture of the isomeric sulfones in 71% yield (entry 8). The \textsuperscript{1}H NMR analysis indicated that the mixture consisted of three isomers: the rearranged 2(E)-hexen-1-yl phenyl sulfone, its 2(Z)-isomer 2b, and 1-hexen-3-yl phenyl sulfone (2e)\textsuperscript{25} in 93% yield. In this case, geranyl bromide, a presumed intermediate,\textsuperscript{25} was so reactive that the reaction proceeded smoothly at room temperature. A sensitive allylic alcohol 1f, bearing an acetal group was also transformed to the sulfone 2f\textsuperscript{1} in high yield. Benzyl- (1g) and furfuryl- (1i) alcohols were efficiently converted to the corresponding phenyl sulfones 2g\textsuperscript{22} and 2i\textsuperscript{23}, respectively.

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R-OH | NBS (1.3 eq.) | Ph3P (1.4 eq.) | ArSO2Na (2 eq.) | Bu4N.I (0.1 eq.) | Conditions | R-SO2
------ | ------------ | -------------- | -------------- | -------------- | ---------- | -------
1a-j  | ⋯           | ⋯              | ⋯              | ⋯               | ⋯         | 2a-j

Scheme 1

Table 1 Preparation of Allylic and Benzylic Sulfones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-</th>
<th>Conditions (Solvent')</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-C8H17OH</td>
<td>50 °C, 5 h (CH3CN)</td>
<td>2a</td>
</tr>
<tr>
<td>2</td>
<td>la</td>
<td>50 °C, 10 h (CH3CN)</td>
<td>2a</td>
</tr>
<tr>
<td>3</td>
<td>la</td>
<td>55 °C, 5 h (toluene)</td>
<td>2a</td>
</tr>
<tr>
<td>4</td>
<td>la</td>
<td>50 °C, 2 h</td>
<td>2a</td>
</tr>
<tr>
<td>5</td>
<td>la</td>
<td>50 °C, 2 h (toluene)</td>
<td>2a</td>
</tr>
<tr>
<td>6</td>
<td>la</td>
<td>55 °C, 5 h (CH3CN)</td>
<td>2b</td>
</tr>
<tr>
<td>7</td>
<td>lb</td>
<td>50 °C, 6 h</td>
<td>2b</td>
</tr>
<tr>
<td>8</td>
<td>n-C8H17H</td>
<td>55 °C, 24 h (mix)</td>
<td>2d</td>
</tr>
<tr>
<td>9</td>
<td>le</td>
<td>55 °C, 5 h</td>
<td>2d</td>
</tr>
<tr>
<td>10</td>
<td>le</td>
<td>r.t., 5 h</td>
<td>2e</td>
</tr>
<tr>
<td>11</td>
<td>le</td>
<td>r.t., 20 h</td>
<td>2f</td>
</tr>
<tr>
<td>12</td>
<td>If</td>
<td>50 °C, 4 h</td>
<td>2g</td>
</tr>
<tr>
<td>13</td>
<td>lg</td>
<td>50 °C, 2 h</td>
<td>2h</td>
</tr>
<tr>
<td>14</td>
<td>lh</td>
<td>r.t., 20 h</td>
<td>2i</td>
</tr>
<tr>
<td>15</td>
<td>li</td>
<td>reflux, 16 h</td>
<td>2j</td>
</tr>
</tbody>
</table>

a THF was used as solvent unless otherwise noted.
b Isolated yield.
c Bu4NI not added.
d PhSO2Na:2H2O used.
e See text.
f TsNa:4H2O used.
g Dodecyl bromide obtained in 53% yield.
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mass spectrometer. TLC and column chromatography were performed on Merck pre-coated silica gel 60F254 plates and silica gel (Wako gel C-200 or C-300), respectively. On TLC, the aryl sulfones could be detected by UV 254 nm absorption; they had slightly higher Rf values than the parent alcohols (eluent: hexane–EtOAc mixture). The arenesulfinate esters, if formed, showed higher Rf values and stronger UV absorption than the corresponding aryl sulfones.

Aryl Sulfones (2a–p): General procedure

To a stirred soln of alcohol (1.0 mmol) and Ph3P (1.4–1.6 mmol) in THF (5 mL) at –20 °C (or in DMF at 0 °C for non-activated alcohols) under Ar was added NBS (1.3–1.6 mmol) in small portions over 15 min. The mixture was stirred for 30 min from –10 °C to 0 °C (or at r.t. for non-activated alcohols). To this soln was added a mixture of ArSO2Na (2.0 mmol) and Bu4NI (0.1 mmol) (or NaI, 0.1 mmol) in 3 portions over 10 min. The mixture was stirred under the conditions shown in the Tables, and then diluted with EtOAc (10 mL) and 3% aq Na2S2O3 (10 mL). The layers were separated and the aq phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were successively washed with H2O and brine, and then dried over Na2SO4. After filtration and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (hexane–EtOAc) to afford the aryl sulfone.

The residue from organic extracts contained mainly aryl sulfone and triphenylphosphine oxide (Ph3PO). For sulfones 2a–e, 2j, and 2m, most of Ph3PO could be removed before chromatography. To the residue was added (hexane–EtOAc, 9:1), and insoluble solid (Ph3PO) was filtered off and washed with the same solvent. Sulfones 2g, 2h, and 2o are highly crystalline solids. In these cases, the residue was dissolved in CH2Cl2, and purified by chromatography eluting with (hexane–EtOAc–CH2Cl2, 3:1:1).

All the sulfones 2a–p (except secondary sulfone 2e) are known compounds, and their physical and spectroscopic data are consistent with those reported in the references quoted in the main text (e.g. 2a, 2d). However, the optical rotation of 2f is inconsistent, with the reported value and some sulfones 2k, 2l, 2o have not been fully characterized in the literature. Their data are shown below.

(4S)-2,2-Dimethyl-4-[(E)-3-phenylsulfonylprop-1-ene]-1,3-dioxolane (2f)

[optod]25D +33.7 (c 1.30, CHCl3) [Lit.21 [α]20D +13.2 (c 1.03, CHCl3)]. Spectral data were in good agreement with those reported.21

Phenethyl p-TolyI Sulfone (2k)

Colorless solid, mp 75–76 °C (Lit.22 mp 73.0–73.5 °C).

1H NMR: δ = 2.36 (s, 3 H), 2.93 (m, 2 H), 3.25 (m, 2 H), 7.01 (m, 2 H), 7.14 (m, 3 H), 7.27 (d, 2 H, J = 8.1 Hz), 7.72 (d, 2 H, J = 8.1 Hz).

13C NMR: δ = 21.5, 28.7, 57.5, 126.7, 128.0 (2 C), 128.2 (2 C), 128.7 (2 C), 129.9 (2 C), 135.9, 137.4, 144.7.

HRMS (CI): m/z calcd for C19H17O2S (M + H)+: 261.0879; found: 261.0913.

3-Phenylsulfonyl-1-propanyl (2l)

Colorless solid, mp 93–94 °C (Lit.23 mp 93 °C).

1H NMR: δ = 2.36 (t, 1 H, J = 2.7 Hz), 3.96 (m, 2 H, J = 2.7 Hz), 7.59 (m, 2 H), 7.70 (m, 1 H), 7.99 (m, 2 H).

13C NMR: δ = 48.3, 71.5, 76.2, 128.8 (2 C), 129.1 (2 C), 134.3, 137.6.

2-(Phenylsulfonyl)ethyl Benzoate (2o)

Colorless solid, mp 127–129 °C (Lit.25 mp 125 °C).

\[ \delta = 3.61 (t, 2 H, J = 6.0 Hz), 4.67 (t, 2 H, J = 6.0 Hz), 7.35 (m, 2 H), 7.51 (m, 3 H), 7.58 (m, 1 H), 7.72 (m, 2 H), 7.94 (m, 2 H). \]

\[ \delta = 55.2, 58.2, 128.0 (2 C), 128.3 (2 C), 128.9, 129.4 (2 C), 129.6 (2 C), 133.3, 133.8, 139.4, 165.7. \]


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(13) To increase the solubility of arenesulfinate salts in common organic solvents, phase transfer catalysts such as Bu4NI are often employed; see: (a) Wildeman, J.; van Leusen, A. M. Synthesis 1979, 733. (b) Crandall, J. K.; Pradat, C. J. Org. Chem. 1985, 50, 1327.


(19) Bandgar, B. P.; Sadavarte, V. S. Synlett 2000, 908.

(20) In refs. 18 and 19, the authors assumed that the intermediate alkoxyphosphonium bromides directly reacted with a nucleophile to give the final products. In our cases, however, rapid formation of alkyl bromides and triphenylphosphine oxide was observed by TLC and NMR analysis before addition of ArSO2Na, see: Bose, A. K.; Lal, B. Tetrahedron Lett. 1973, 9397.


