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An Expeditious Entry to Benzylic and Allylic Sulfones through Byproduct-Catalyzed Reaction of Alcohols with Sulfinyl Chlorides

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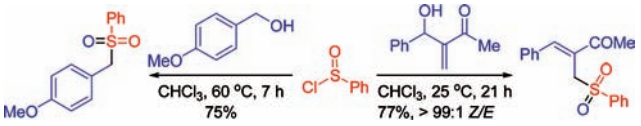
Received September 14, 2009

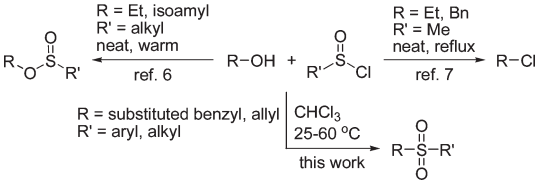


In the absence of external catalysts and additives, a broad range of benzylic and allylic alcohols react with various sulfinyl chlorides to afford structurally diversified benzylic and allylic sulfones in moderate to excellent yields, and importantly, a catalysis with byproduct HCl is involved in this new protocol for sulfone synthesis.

Benzylic and allylic sulfones serve as versatile building blocks for a number of important carbon−carbon bond-forming reactions owing to the useful reactivity of α-sulfonyl carbanions under various reaction conditions.[1] Moreover, they are the necessary constituents of some biologically important compounds that have potential for the treatment of Alzheimer's disease,[2] cancer, and abnormal cell proliferation diseases.[3] Therefore, much attention has been paid to the synthesis of benzylic and allylic sulfones, for which the general approaches include the oxidation of the corresponding sulfides and the coupling of sulfinate salts with benzylic and allylic carbon electrophiles.[4] Although several new methods have recently been reported to improve the synthesis of benzylic and allylic sulfones, they require expensive reagents/catalysts and/or harsh reaction conditions.[5]

As early as 1930, Braun and Weissbach disclosed the condensation reaction of alcohols with aliphatic sulfinyl chlorides to yield sulfinate esters without requiring external catalysts and additives (Scheme 1).[6] More than 20 years later, Douglass and Farah found, however, that alkyl chlorides rather than sulfinate esters were obtained as the major products when similar reaction mixtures were subjected to high temperatures.[7] Particularly, they noted that benzyl alcohol (1.6 equiv) and methanesulfinyl chloride were refluxed together to give benzyl chloride in 83% yield together with benzyl methyl sulfone in 8% yield. In the course of developing new reactions with carbocations,[8] we investigated the reaction of benzylic and allylic alcohols with sulfinyl chlorides and found, to our surprise, that milder reaction conditions could predominantly lead to the formation of benzylic and allylic sulfones (Scheme 1). Herein, we wish to describe the synthesis of benzylic and allylic sulfones from the corresponding alcohols and sulfinyl chlorides in the absence of external catalysts and additives, wherein byproduct HCl plays a vital role to accelerate the sulfone synthesis.

SCHEME 1. Reactions of Alcohols with Sulfinyl Chlorides in the Absence of External Catalysts and Additives



We investigated the possibility to obtain a benzylic sulfone from the corresponding alcohol and a sulfinyl chloride under milder reaction conditions relative to those reported by Douglass and Farah.[7,9] To our delight, the reaction of 4-methoxybenzyl alcohol (**1a**) with benzenesulfinyl chloride proceeded smoothly in chloroform at room temperature to afford 4-methoxybenzyl phenyl sulfone (**2a**) in 63% yield. Notably, 4-methoxybenzyl benzenesulfinate was not obtained at all, though 4-methoxybenzyl chloride was identified as a minor product, the molar ratio of which to sulfone **2a** was

(1) For reviews, see: (a) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: New York, 1993. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(2) Churcher, I.; Beher, D.; Best, J. D.; Castro, J. L.; Clarke, E. E.; Gentry, A.; Harrison, T.; Hitzel, L.; Kay, E.; Kerrad, S.; Lewis, H. D.; Morentin-Gutierrez, P.; Mortishire-Smith, R.; Oakley, P. J.; Reilly, M.; Shaw, D. E.; Shearman, M. S.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 280 and references therein.

(3) Neamati, N.; Kabalka, G. W.; Venkataiah, B.; Dayam, R. WO2007081966, **2007**.

(4) For a review, see: Solladie, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 133.

(5) For some recent examples, see: (a) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 172. (b) Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462. (c) Liu, C.-R.; Li, M.-B.; Cheng, D.-J.; Yang, C.-F.; Tian, S.-K. *Org. Lett.* **2009**, *11*, 2543. (d) Chandrasekhar, S.; Saritha, B.; Jagadeshwar, V.; Narsihmulu, C.; Vijay, D.; Sarma, G. D.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 2981. (e) Liao, M.; Duan, X.; Liang, Y. *Tetrahedron Lett.* **2005**, *46*, 3469. (f) Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441. (g) Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506. (h) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673.

(6) v. Braun, J.; Weissbach, K. *Ber.* **1930**, *63B*, 2836. The authors mentioned a warm reaction mixture but did not specify the temperature.

(7) Douglass, I. B.; Farah, B. S. *J. Org. Chem.* **1958**, *23*, 805.

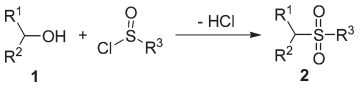
(8) (a) Liu, C.-R.; Li, M.-B.; Yang, C.-F.; Tian, S.-K. *Chem.—Eur. J.* **2009**, *15*, 793. (b) Li, H.-H.; Jin, Y.-H.; Wang, J.-Q.; Tian, S.-K. *Org. Biomol. Chem.* **2009**, *7*, 3219. (c) Li, H.-H.; Dong, D.-J.; Tian, S.-K. *Eur. J. Org. Chem.* **2008**, 3623. (d) Liu, C.-R.; Li, M.-B.; Yang, C.-F.; Tian, S.-K. *Chem. Commun.* **2008**, 1249.

(9) For the preparation of sulfinyl chlorides, see: (a) Whitesell, J. K.; Wong, M.-S. *J. Org. Chem.* **1991**, *56*, 4552. (b) Peyronneau, M.; Roques, N.; Mazières, S.; Roux, C. L. *Synlett* **2003**, 631.

DOI: 10.1021/jo901974h Published on Web 11/13/2009

determined to be 2:98 by ^{1}H NMR analysis of the reaction mixture. The yield for sulfone **2a** was further improved to 75% by heating the reaction mixture at 60 °C.[10] In addition, there was no need to exclude air and moisture for this reaction, and the yield for sulfone **2a** decreased significantly when chloroform was replaced with another common organic solvent such as 1,2-dichloroethane (57%), toluene (30%), ethyl acetate (43%), tetrahydrofuran (16%), dioxane (61%), acetonitrile (44%), or nitromethane (34%).

TABLE 1. Synthesis of Benzylic Sulfones[a]



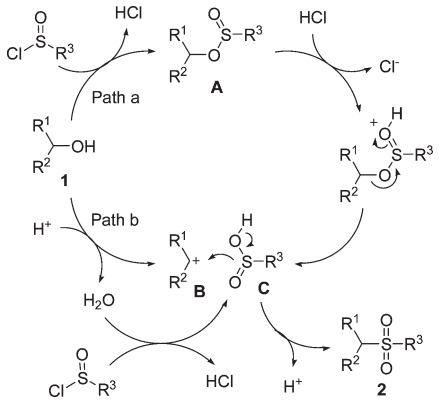
entry	1	R^1	R^2	R^3	2	temp (°C)	time (h)	yield (%)[b]
1	**1a**	MeO-	H	Ph	**2a**	60	7	75
2	**1b**	Me_2N-	H	Ph	**2b**	60	7	76
3	**1c**	HO-	Me	Ph	**2c**	60	9	61
4	**1d**	MeO-	Me	Ph	**2d**	25	4	96
5	**1e**	MeO-	Me, Me	Ph	**2e**	25	1	99
6	**1f**	Me-	Me	Ph	**2f**	60	9	74
7	**1g**	OH-	Me	Ph	**2g**	25	1	76
8	**1h**		Me	Ph	**2h**	60	4	76
9	**1i**		Me	Ph	**2i**	25	2	78
10	**1j**	R^1R^2CH =		Ph	**2j**	60	7	66
11	**1k**	Ph	Ph	Ph	**2k**	60	8	94
12	**1l**	MeO-	Ph	Ph	**2l**	25	2.5	99
13	**1m**	Cl-	Ph	Ph	**2m**	60	4	67
14	**1n**		Ph	Ph	**2n**	25	4	86
15	**1o**	Ph	Ph	Ph	**2o**	25	2	86
16	**1o**	Ph	Ph	Me-	**2ob**	25	1.5	71
17	**1o**	Ph	Ph	MeO-	**2oc**	25	1.5	81
18	**1o**	Ph	Ph	Cl-	**2od**	60	9	61
19	**1o**	Ph	Ph	Me	**2oe**	25	24	78
20[c]	**1p**	Ph	H	Ph	**2p**	60	6	0
21	**1q** = Ph_3COH			Ph	**2q**[d]	60	12	0

[a]Reaction conditions: alcohol **1** (0.25 mmol), sulfinyl chloride (0.30 mmol), chloroform (0.25 mL). [b]Isolated yield. [c]Benzyl benzenesulfinate was obtained in 65% yield. [d]**2q** = phenyl triphenylmethyl sulfone.

In the absence of external catalysts and additives, a broad range of benzylic alcohols reacted with aromatic and aliphatic sulfinyl chlorides in chloroform at room temperature or at 60 °C to give the corresponding benzylic sulfones in good to excellent yields (Table 1, entries 1−19). It should be noted

(10) This reaction was carried out on a 0.25-mmol scale, and the yield was improved to 87% when performing the reaction on a 10-mmol scale.

SCHEME 2. Proposed Reaction Pathways Involving a Catalysis with Byproduct HCl



that the present reaction conditions successfully avoided the sulfinylation reaction toward the electron-rich aromatic (or heteroaromatic) moieties of substrates such as alcohols **1a**−**e**, **1g**, **1i**, and **1l** (Table 1, entries 1−5, 7, 9, and 12).[11] To our delight, no isomerization occurred in the reaction with benzylic propargylic alcohol **1n**, the hydroxy group of which was simply substituted to afford sulfone **2n** in 86% yield (Table 1, entry 14). Nevertheless, the reaction of benzyl alcohol (**1p**) with benzenesulfinyl chloride in chloroform at 60 °C did not yield the corresponding sulfone but gave benzyl benzenesulfinate in 65% yield (Table 1, entry 20). Moreover, we did not obtain a sulfone product from the reaction with a tertiary alcohol such as triphenylmethanol (**1q**) under similar reaction conditions (Table 1, entry 21).

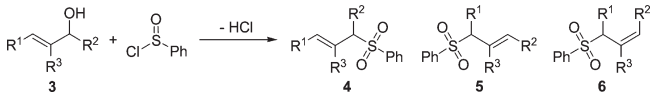
Optically active (*R*)-1-(4-methoxyphenyl)ethanol [(***R*)-1d**, > 99% ee] reacted with benzenesulfinyl chloride at room temperature for 4 h to give sulfone **2d** in nearly racemic form (6% ee). This result suggests that a carbocation intermediate is involved in the reaction. On the basis of the above experiments and the results reported in the literature, we propose the following reaction pathways to account for the formation of sulfones (Scheme 2). The condensation reaction of alcohol **1** with a sulfinyl chloride proceeds first to give sulfinate ester **A** and byproduct HCl,[6] and then the former is promoted by the latter to undergo carbon−oxygen bond cleavage. The resulting sulfinic acid **C** acts as a sulfur nucleophile to couple with carbocation **B** to yield sulfone **2** (Scheme 2, path a). The rearrangement of sulfinate esters to sulfones under acidic conditions was reported previously[12] and was further confirmed by the following experiment. Treatment of 4-methoxybenzyl benzenesulfinate with HCl (1.2 equiv) in chloroform at 60 °C for 2 h resulted in the formation of sulfone **2a** in 92% yield. Alternatively, byproduct HCl promotes the conversion of alcohol **1** to carbocation **B**,[13] and the released water further decomposes the sulfinyl chloride to give sulfinic acid **C** (Scheme 2, Path b). This byproduct

(11) (a) Chasar, D. W.; Pratt, T. M. *Phosphorus, Sulfur, Silicon* **1978**, *5*, 35. (b) Chasar, D. W.; Pratt, T. M.; Shockcor, J. P. *Phosphorus, Sulfur, Silicon* **1980**, *8*, 183. (c) Chasar, D. W.; Hunt, D. J.; Lupyan, D. A. *Phosphorus, Sulfur, Silicon* **1981**, *12*, 55. (d) Jung, M. E.; Kim, C.; von dem Bussche, L. *J. Org. Chem.* **1994**, *59*, 3248.

(12) Wragg, A. H.; McFadyen, J. S.; Stevens, T. S. *J. Chem. Soc.* **1958**, 3603.

(13) At an early stage of the reaction, a significant portion of alcohol was converted to the corresponding ether that could serve as another source for carbocation **B** under acidic conditions. For a relevant study, see ref [8c].

TABLE 2. Synthesis of Allylic Sulfones[a]



entry	alcohol **3**		product **4**		product **5** or **6**		**4**/**5**[b]	temp (°C)	time (h)	yield (%)[c]	*E*/*Z*[b]
1		**3a**		**4a**				60	8	63	
2[d]		**3b**		**4b**				75	12	60	> 99:1
3		**3c**, X = H		**4c**		**5c**	49:51	25	3	84[e]	> 99:1 (> 99:1)[f]
4		**3d**, X = OMe		**4d**		**5d**	33:67	25	1	86[e]	> 99:1 (> 99:1)[f]
5		**3e**, X = Cl		**4e**		**5e**	94:6	60	4	69[e]	> 99:1
6		**3f**		**4c**		**5c**	48:52	25	23	95[e]	> 99:1 (> 99:1)[f]
7		**3g**		**4g**				60	1	61	
8		**3h**, X = H				**6h**		25	21	77	< 1:99
9		**3i**, X = Cl				**6i**		25	48	62	< 1:99
10		**3j**, X = Cl				**6j**		25	18	49	< 1:99
11		**3k**, X = Me				**6k**		25	24	61	< 1:99
12		**3l**				**6l**		25	30	72	< 1:99
13		**3m**				**6m**		25	34	53	< 1:99

[a]Reaction conditions: alcohol **3** (0.25 mmol), PhSOCl (0.30 mmol), chloroform (0.25 mL). [b]Determined by ^{1}H NMR analysis. [c]Isolated yield. [d]1,2-Dichloroethane was used as the solvent. [e]Total yield of isomers **4** and **5**. [f]The *E*/*Z* ratios of allylic sulfones **5c,d** are shown in parentheses.

catalysis was substantially supported by the following experiments.[14] While alcohol **1a** could react with benzenesulfinic acid in chloroform at 60 °C for 7 h to give sulfone **2a** in 46% yield, the addition of HCl (1.2 equiv) increased the yield to 58%. The removal of byproduct HCl with an organic base, such as pyridine or triethylamine, from the reaction of benzylic alcohols with sulfinyl chlorides has been reported to result in the formation of the corresponding sulfinate esters rather than sulfones.[15] Moreover, the use of molecular sieves (4 Å) to sequester byproduct HCl in the reaction of alcohol **1l** with benzenesulfinyl chloride decreased the yield for the formation of sulfone **2l** from 99% to 18%.[16]

The sulfone synthesis catalyzed by byproduct HCl was successfully extended to a wide variety of acyclic and cyclic allylic alcohols (Table 2). Although the hydroxy group of primary allylic alcohol **3b** was simply substituted in the presence of benzenesulfinyl chloride to give allylic sulfone **4b** as a single product (Table 2, entry 2), a 49:51 mixture of allylic sulfones **4c** and **5c** was obtained from the reaction with secondary allylic alcohol **3c**, wherein an allylic rearrangement took place in addition to a simple hydroxy substitution (Table 2, entry 3). While the replacement of the phenyl group of allylic alcohol **3c** with a 4-methoxyphenyl group favored an allylic rearrangement (Table 2, entry 4), similar replacement with a 4-chlorophenyl group predominantly led to a simple hydroxy substitution with a regioselectivity of 94:6 (Table 2, entry 5). Interestingly, the reaction with secondary allylic alcohol **3f**, a regioisomer of allylic alcohol **3c**, furnished a mixture of allylic sulfones **4c** (an allylic rearrangement product) and **5c** (a hydroxy substitution product) in nearly the same ratio as that for the reaction with alcohol **3c** (Table 2, entry 6 versus entry 3). It should be noted that both allylic sulfones **4** and **5** were obtained in all cases with exclusive *E* selectivity (Table 2, entries 2−6).

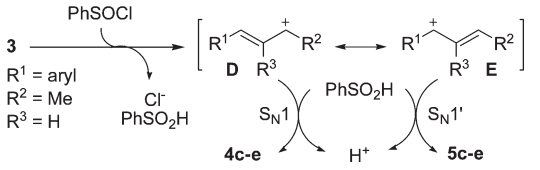
The product distribution can be accounted for by the relative steric demands of the R^1 and R^2 groups in allylic alcohol **3** and the relative stability of the two major resonance structures, **D** and **E**, of an allylic carbocation intermediate generated from alcohol **3** during the reaction (Scheme 3). While a phenyl group is superior to a methyl group in stabilizing an allylic carbocation, the former exhibits a steric demand larger than that of the latter toward the nucleophilic attack of a sufinic acid. The balance of these two factors allows the reaction with either allylic alcohol **3c** or its regioisomer **3f** to afford a nearly 1:1 mixture of an S_N 1-type hydroxy substitution product and an S_N1'-type allylic rearrangement product. When the phenyl group of allylic

(14) For some recent examples of the acidic byproduct co-catalyzed reactions, see: (a) Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2007**, *9*, 4931. (b) Yang, B.-L.; Tian, S.-K. *Eur. J. Org. Chem.* **2007**, 4646. (c) Song, Q.-Y.; Yang, B.-L.; Tian, S.-K. *J. Org. Chem.* **2007**, *72*, 5407.

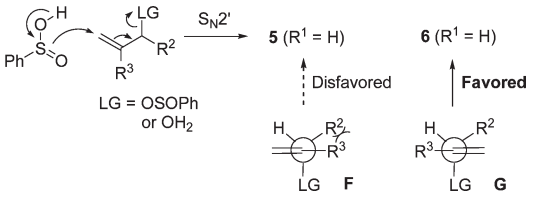
(15) (a) Braverman, S.; Steiner, S. *Isr. J. Chem.* **1967**, *5*, 267. (b) Coulomb, J.; Certal, V.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 633. (c) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.

(16) For an example, see: Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, *16*, 3979.

SCHEME 3. Proposed Reaction Pathways for the Formation of Allylic Sulfones 4c−e and 5c−e

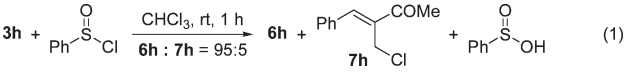


SCHEME 4. Proposed S_N2'-Type Process for the Formation of Allylic Sulfone 6 (R^1 = H)



alcohol **3c** bears an electron-donating group, the resulting larger energetic gap between resonance structures **D** and **E** shifts the balance to favor an S_N1'-type allylic rearrangement. Otherwise, an S_N1-type hydroxy substitution is favored when the phenyl group of alcohol **3c** bears an electron-withdrawing group.

To our great delight, only allylic rearrangement products were obtained from the reaction with allylic alcohols bearing activated terminal carbon−carbon double bonds. The reaction of 2-acetylallylic alcohols with benzenesulfinyl chloride proceeded smoothly at room temperature to afford a range of trisubstituted allyl sulfones with exclusive *Z* selectivity (Table 2, entries 8−13).[17] The exquisite regioselectivity and stereoselectivity suggest a reaction pathway different from the aforementioned ones involving carbocations that should be disfavored by the presence of acyl groups. To gain insight to the mechanism, we carried out ^{1}H NMR analysis of the reaction mixture of alcohol **3h** with benzenesulfinyl chloride and observed the formation of benzenesulfinic acid and (*Z*)-trisubstituted allyl chloride **7h**, the molar ratio of which to sulfone **6h** was determined to be 5:95 when the reaction proceeded at room temperature for 1 h (eq 1).[18] Notably, treatment of allylic chloride **7h** with benzenesulfinic acid in chloroform at room temperature for 24 h could afford sulfone **6h** in 33% yield, which is, however, significantly lower than that for the reaction of alcohol **3h** with benzenesulfinyl chloride (77%, Table 2, entry 8). Thus, we propose that the reaction involves an S_N2'-type process that is allowed to take place by the activation of a terminal carbon−carbon double bond with the acetyl group and by the activation of a hydroxy group with a sulfinyl group or a proton (*vide supra*) and the *Z* selectivity for the formation of trisubstituted allyl sulfones originates from the attack of benzenesulfinic acid to reactive conformation **G**, which is energetically favored relative to reactive conformation **F** by relieving allylic 1,2-strain (Scheme 4).[5a,c,19,20] Similarly, the attack of a chloride anion to reactive conformation **G** accounts for the exclusive *Z* selectivity for the formation of a trisubstituted allyl chloride as a minor product.



In summary, we have developed a convenient synthesis of benzylic and allylic sulfones through the reaction of alcohols with sulfinyl chlorides. In the absence of external catalysts and additives, a broad range of benzylic alcohols react with various sulfinyl chlorides to afford structurally diversified benzylic sulfones in good to excellent yields. Notably, byproduct HCl can accelerate the sulfone synthesis by catalyzing the formation of carbocation intermediates from the corresponding alcohols. This byproduct-catalyzed sulfone synthesis has further been extended to a wide variety of acyclic and cyclic allylic alcohols, and importantly, exquisite regioselectivity and stereoselectivity has been achieved from an S_N2'-type reaction with 2-acylallylic alcohols, which provides a convenient access to trisubstituted allyl sulfones with exclusive *Z* selectivity.

Experimental Section

General Procedure for the Synthesis of Benzylic and Allylic Sulfones. To a solution of a benzylic or allylic alcohol (0.25 mmol) in chloroform (0.25 mL) at room temperature was added a sulfinyl chloride (0.30 mmol). The resulting mixture was stirred at the temperature specified in Table 1 or 2 until no further transformation was detected by TLC analysis and was then purified directly by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (20:1 to 5:1), to give a benzylic or allylic sulfone.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China and the Chinese Academy of Sciences.

Supporting Information Available: General information, detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For reviews of such highly functionalized alcohols, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(18) Benzenesulfinic acid could also be generated through the decomposition of benzenesulfinyl chloride with moisture.

(19) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223.

(20) Our results are inconsistent with the [2,3]-sigmatropic rearrangement of an allylic sulfinate, which should favor the formation of allylic sulfone **5** (R^1 = H) rather than its stereoisomer **6** (R^1 = H). For the rearrangement of allylic sulfinates to yield allylic sulfones, see: (a) Knight, D. J.; Whitham, G. H.; Williams, J. G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2149. (b) Braverman, S. *Int. J. Sulfur Chem. C* **1971**, 149. (c) Braverman S. In *The Chemistry of Sulfinic Acids, Esters and Their Derivatives*; Patai, S., Ed.; John Wiley and Sons: New York, 1990; pp. 297.