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Alkylation of Magnesium Sulfinates: A Direct Transformation of Functionalized Aromatic/Heteroaromatic Halides into Sulfones

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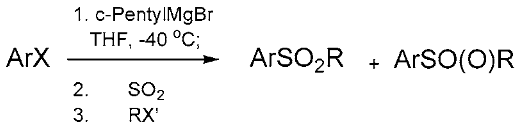
ABSTRACT

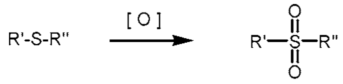


$$\mathrm{ArX}\xrightarrow[\text{2. } SO_2\quad \text{3. } RX']{\text{1. c-PentylMgBr, THF, -40 °C;}}\mathrm{ArSO_2R}+\mathrm{ArSO(O)R}$$

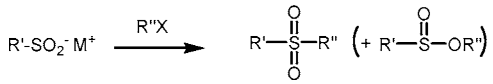
Ar = functionalized aromatic or heteroaromatic groups
X = I, Br
RX' = primary bromide or iodide, Michael acceptors

Sulfinate alkylation is one of the conventional methods for sulfone synthesis. The alkylation of magnesium sulfinates, which are easily accessible via reactions of organomagnesium intermediates with sulfur dioxide, provides a convenient route for sulfone preparation. In this communication, we report a preliminary study of the alkylation of arylmagnesium sulfinates. An application of this reaction to directly transform functionalized aromatic/heteroaromatic halides into sulfones is also described.

The sulfone functional group is frequently present in synthetic targets in medicinal chemistry research. The most common methods for sulfone preparation include the oxidation of sulfides and the alkylation of sulfinate salts (eqs 1 and 2).[1]



$$\mathrm{R'\text{-}S\text{-}R''}\xrightarrow{[\,O\,]}\mathrm{R'\text{-}S(=O)_2\text{-}R''}\qquad \text{Equation 1}$$



$$\mathrm{R'\text{-}SO_2^-\,M^+}\xrightarrow{R''X}\mathrm{R'\text{-}S(=O)_2\text{-}R''}\ \left(+\ \mathrm{R'\text{-}S(=O)\text{-}OR''}\right)\qquad \text{Equation 2}$$

During a recent SAR study, we desired a procedure to synthesize sulfone **4** from iodide **1** (Scheme 1). A conceptually simple procedure would be the alkylation of sulfinate **3**, which could be obtained by reaction of sulfur dioxide (SO_2) with the Grignard intermediate **2**. The intermediate **2** in turn can be generated from iodide **1** via magnesium−iodine exchange.[2] Given that the generation of Grignard intermediate **2** from iodide **1** had been established in our lab,[3] and that the reaction of SO_2 with Grignard reagents has been well documented,[4] the overall transformation outlined in Scheme 1 rested on the alkylation of the magnesium sulfinate **3** (step c, Scheme 1).

The literature precedents on the subject of sulfinate alkylation concern mostly sodium salts, with a few examples involving ammonium sulfinates.[5] Despite the easy accessibility of magnesium sulfinates, via reactions of Grignard

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[1] Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: 1993; Chapter 2.

[2] Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701−1703.

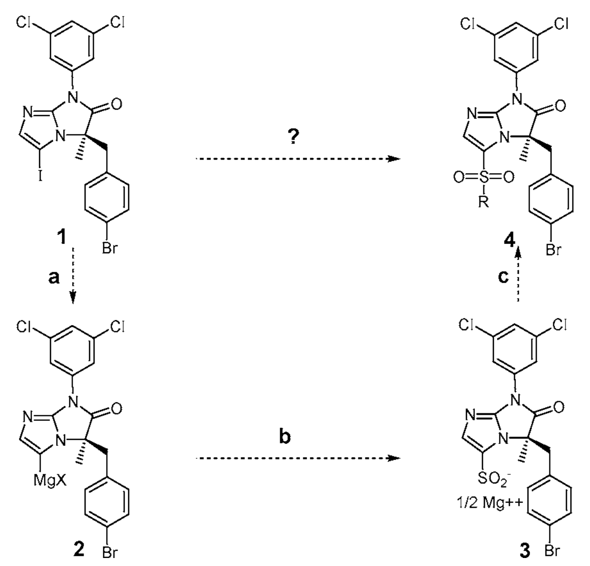
[3] Wu, J.-P.; Emeigh, J.; Gao, D. A.; Goldberg, D. R.; Kuzmich, D.; Miao, C.; Potocki, I.; Qian, K. C.; Sorcek, R. J.; Jeanfavre, D. D.; Kishimoto, K.; Mainolfi, E. A.; Nabozny, G., Jr.; Peng, C.; Reilly, P.; Rothlein, R.; Sellati, R. H.; Joseph, R.; Woska, J. R., Jr.; Chen, S.; Gunn, J. G.; O'Brien, D.; Norris, S. H.; Kelly, T. A. *J. Med. Chem*. **2004**, *47*, 5356−5366.

[4] March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: Hoboken, NJ, 1992; pp 613−614.

[5] For an example of the alkylation of an ammonium sulfinate, see: Manescalchi, F.; Orena, M.; Savoia, D. *Synthesis* **1979**, 445−446.

10.1021/ol0474554 CCC: $30.25

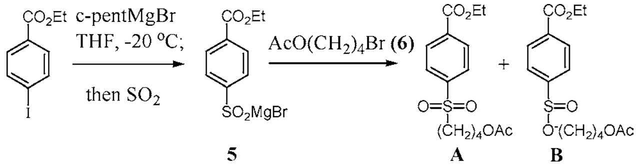
Scheme 1. Proposed Transformation of Iodide **1** into Sulfones **4**



intermediates with SO_2, for example, the alkylation of magnesium sulfinates remains largely unexplored. It is known that the alkylation of sodium or ammonium sulfinates usually generates both sulfones and sulfinate esters (the S- and O-alkylation products, respectively), with the sulfone/sulfinate ester ratio varying with reaction conditions and substrate.[6] Given the stronger coordinating property of magnesium ion compared to sodium or ammonium, we were concerned that the presence of a magnesium cation may affect the reactivity of the sulfinates and alter the product ratio. Additionally, the typical literature conditions for the alkylation of sodium/ammonium sulfinates may not be appropriate for magnesium sulfinates. These considerations prompted us to conduct a preliminary investigation of the basic experimental parameters using a model system.

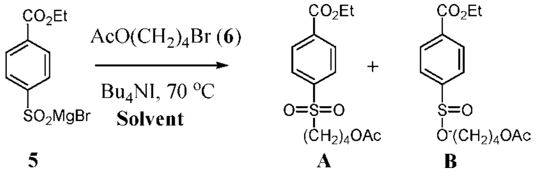
The substrates selected for the preliminary studies were magnesium sulfinate **5** and 4-bromobutyl acetate (**6**). Sulfinate **5** was generated from ethyl 4-iodobenzoate via magnesium−iodine exchange followed by reaction with SO_2 (Scheme 2).[7]

Scheme 2. Preparation of Sulfinate **5**



A screen of solvents was conducted first. Those examined include the nonpolar solvent toluene, the protic solvents ethanol and poly(ethylene glycol), and the polar aprotic solvents acetonitrile, DMF, and DMSO.[8] At room temperature, sulfinate **5** was unreactive toward bromide **6** in all of the solvents tested, even in the presence of tetrabutylammonium iodide.[9] At 70 °C, although reactions in toluene, ethanol, poly(ethylene glycol), and acetonitrile were not successful, the reactions in DMF and DMSO did produce sulfone **A**, albeit in low and variable yield (0 to ~60%, Table 1, entries 5 and 6).

Table 1. Solvents and Additive Effects



entry	solvent	base	yield (%)	**A**:**B**
1	$PhCH_3$		0	
2	EtOH		0	
3	CH_3CN		0	
4	PEG		0	
5	DMSO		0−60%	1:0
6	DMF		0−60%	1:0
7	DMF	Et_3N	60%	4:1
8	DMF	K_2CO_3	91%	3:1
9	DMSO	K_2CO_3	82%	3:1

It was subsequently observed that the pH[10] of magnesium sulfinate **5** had a significant influence on the alkylation yield: low pH values correlate with poor yields. This suggested that the residual acid (from SO_2) caused the decomposition of the sulfinate salt and that the addition of an acid scavenger may improve the yields. Thus, the reactions in DMF and DMSO were repeated in the presence of potassium carbonate or triethylamine. Under these conditions, sulfone **A** was formed in consistently high yields (Table 1, entries 7−9). Sulfinate ester **B** was also isolated, the **A**:**B** ratio being ~3−4 to 1.[11]

Next, the reactivity of alkylating reagents was examined. As shown in Table 2, primary alkyl bromides and iodides were good alkylating reagents (Table 2, entries 1−3). Secondary iodides were not suitable (Table 2, entries 5 and 6), although the more reactive secondary allylic bromides were effective (Table 2, entry 4). Under modified conditions, Michael acceptors were also good alkylating reagents. In acetonitrile and aqueous $NaHCO_3$ mixture, methyl propiolate

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[6] (a) Meek, J. S.; Fowler, J. S. *J. Org. Chem*. **1968**, *33*, 3422−3424. (b) Kielbasinski, P.; Zurawinski, R.; Drabowcz, J.; Mikolajczyk, M. *Tetrahedron* **1988**, *44*, 6687−6692.

[7] Sulfinate **5** thus prepared is stable and can be stored in a refrigerator for months without noticeable decomposition.

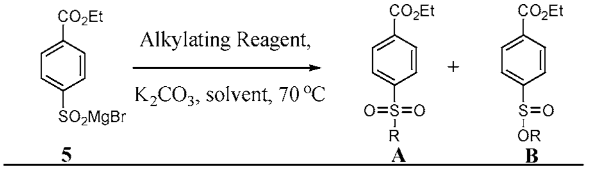
[8] These solvents are among the common solvents used for the alkylation of sodium or ammonium sulfinates. See refs 1, 5, and 6.

[9] Initially, a catalytic amount of tetrabutylammonium iodide (TBAI) was added to activate the alkylating reagent. It was later found that TBAI was not necessary when reactions were run at 70 °C; see Table 2, entries 1 and 3.

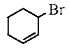
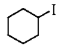
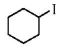
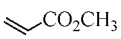
[10] Different batches of sulfinate **5** displayed different pH values (~1−5) in aqueous solution, reflecting the varying amounts of residual SO_2 in the samples.

[11] Product ratio **A**:**B** was determined by ^1H NMR integration. Compounds **A** and **B** can be separated by silica gel chromatography.

Table 2. Scope of Alkylating Reagents



5 **A** **B**

Entry	Alkylating Reagent	Solvent	Yield (%)[a]	A : B
1	$AcO(CH_2)_4Br$	DMF	94	4 : 1
2	$AcO(CH_2)_4I$	DMF	91	3 : 1
3	$AcO(CH_2)_4Br$/ 0.1eq Bu_4NI	DMF	91	3:1
4		DMF	65%	4:1
5		DMF	<5%	---
6		DMSO	<5%	---
7[b]	$\equiv$—CO_2CH_3	CH_3CN-aq.$NaHCO_3$	98% (*cis* : *trans* = 16 : 1)	1 : 0
8[b]		CH_3CN-aq.$NaHCO_3$	62%	1 : 0

[a] Combined yield of **A** + **B**. [b] Reaction was run at room temperature.

and methyl acrylate reacted with sulfinate **5** to generate sulfones exclusively in good yield (Table 2, entries 7 and 8).

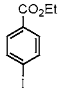
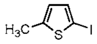
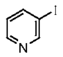
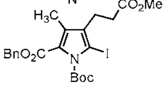
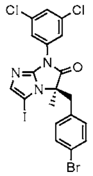
With optimized reaction conditions for the sulfone generation at hand, we proceeded to test the reaction on other functionalized substrates. In a typical experiment, an aromatic halide was treated with cyclopentylmagnesium bromide in THF at −20 °C for 30 min. Next, sulfur dioxide was passed through the mixture for 10 min. The mixture was then warmed to room temperature, stirred for 30 min, and concentrated. The residue was coevaporated twice with fresh THF to remove residual SO_2. The organomagnesium intermediate thus obtained was subsequently treated with 4-bromobutyl acetate and potassium carbonate in DMF at 70 °C overnight. Using this procedure, sulfones were obtained in good yields. Various amounts of sulfinate esters were also produced. Functional groups such as esters, imides, and aryl chlorides and bromides were tolerated. Functional groups sensitive to oxidation such as pyridine, pyrrole, and thiophene were also compatible (Table 3).[12]

To summarize, we have shown that the alkylation of magnesium sulfinates is a convenient method for sulfone preparation. The reaction requires a polar aprotic solvent such as DMF or DMSO. The use of an acid scavenger is essential to achieve reproducibly good yields. Active alkyl halides such as primary iodides/bromides and allylic halides are effective alkylating reagents, while simple secondary iodides are not suitable. Michael acceptors can be useful alkylating reagents under modified conditions.

We also described a practical protocol to directly transform aromatic/heteroaromatic halides into sulfones. This protocol involves a three-step one-pot procedure consisting of (1) generation of a Grignard reagents from the aromatic/heteroaromatic iodide via magnesium−halide exchange; (2) reaction of the Grignard reagent with SO_2 to produce the corresponding magnesium sulfinate; and (3) reaction of the sulfinate intermediate with an alkylating reagent. A variety of functional groups are tolerated.

Table 3. Transformation of Aromatic Halides into Sulfones

$$ArI \xrightarrow[\substack{2.\ SO_2 \\ 3.\ AcO(CH_2)_4Br \\ Bu_4NI,\ DMF}]{\substack{1.\ c\text{-}PentylMgBr \\ THF,\ -40\ ^{\circ}C;}} \underset{\mathbf{C}}{ArSO_2(CH_2)_4OAc} + \underset{\mathbf{D}}{ArSO(O)(CH_2)_4OAc}$$

Entry	Substrate	Yield (%)	C : D
1		91	3 : 1
2		94	4 : 1
3		60	3 : 1
4[a]		60	19 : 1
5		80	1:0

[a] Boc group was cleaved.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0474554

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[12] The fact that this protocol is compatible with oxidizable moieties may prove to be advantageous when substrates contain oxidation-sensitive groups that preclude the sulfide oxidation approach.