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Synthesis of Sulfones from Organozinc Reagents, DABSO, and Alkyl Halides

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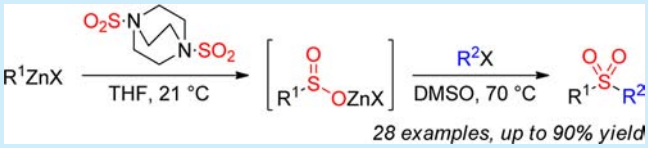
Supporting Information

ABSTRACT: Organozinc reagents react with the SO_2 surrogate DABSO, and the resulting zinc sulfinate salts are alkylated in situ to afford sulfones. This transformation has a broad scope and is compatible with a wide range of structural motifs of medicinal chemistry relevance including nitrile, secondary carbamates, and nitrogen-containing heterocycles.



Sulfones constitute a diverse structural class associated with important applications. In organic synthesis, such molecules are intermediates in the Julia olefination[1a−c] and Ramberg−Bäcklund rearrangement,[1c−f] two transformations routinely used to construct olefins. Furthermore, as demonstrated by the antimigraine medicine eletriptan (Relpax, **1**),[2] sulfones are found in numerous medicines and drug candidates under development for the treatment of a host of diseases impacting human health worldwide (Figure 1).[3]

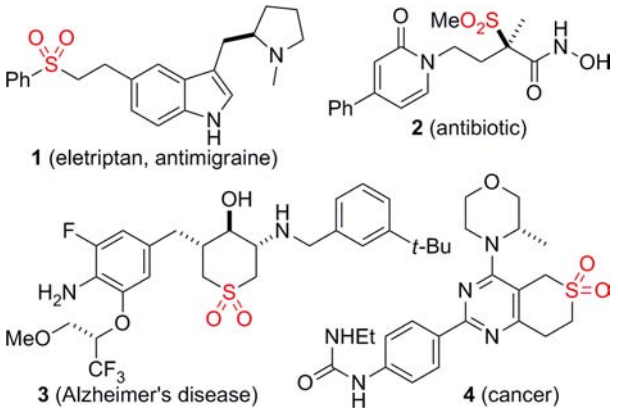
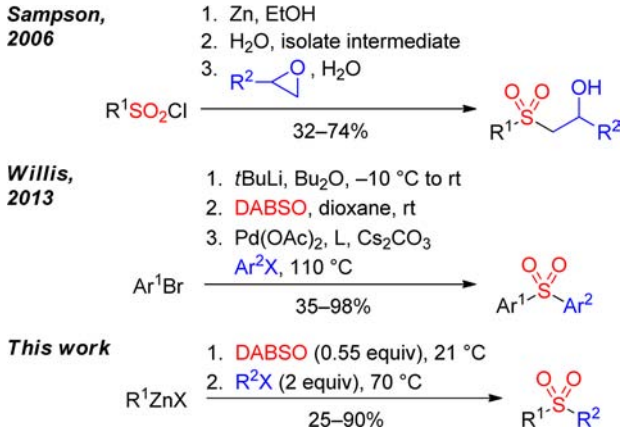


Figure 1. Biologically active sulfones.

Sulfones are prepared by a variety of methods. Thiol building blocks are typically employed, and the desired oxidation state is subsequently achieved via redox chemistry[3a,c−e] using protocols often lacking practicality. Because speed to establish structure−activity relationships (SAR) is critical in medicinal chemistry programs, we sought to facilitate access to this chemotype by developing a method that would be conducive to rapid analogue generation. Such a reaction would need to be operationally simple, mild (for functional group tolerance), and of broad scope while using readily available and easily handled reactants. Although the use of sulfinate salts addresses this goal,[4] these intermediates have been underutilized in medicinal chemistry due to the limited practicality associated with their current synthesis (synthesis of precursors,[4b,h,i] harsh conditions,[4a,f,g] side reactions,[5] the propensity of their conjugate acids to disproportionate,[6] and the use of SO_2, a toxic gas).

Recent publications from Willis[7] highlighted the discovery of the reagent DABSO ($DABCO{\cdot}2SO_2$) as a surrogate for SO_2 and its application to sulfonamide, *N*-aminosulfonamide, sulfamide, and sulfone synthesis. We envisioned that sulfones could be advantageously obtained in a one pot reaction of organozinc reagents, DABSO, and alkyl halides (Scheme 1). Organozinc reagents are (1) available commercially or are mildly prepared (vs sulfonyl chlorides[4b,i]), (2) they do not necessarily require prefunctionalization, and (3) their decreased reactivity (vs organolithium and Grignard reagents[4a,f,g,7b]) was expected to increase functional group tolerance, decrease side reactions during sulfinylation, and improve operational

Scheme 1. Sulfone Synthesis via Sulfinate Salts



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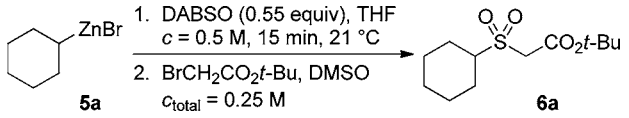
simplicity for potential parallel chemical synthesis applications. To the best of our knowledge, the addition of organozinc reagents to SO_2 has not been described.[8]

Initial experiments were designed to establish standard conditions for this transformation. Cyclohexylzinc bromide (**5a**) was selected as an unfunctionalized, commercially available organozinc reagent. We quickly determined that good yields were achieved when sulfinylation was conducted in the presence of only 0.55 equiv of DABSO for 15 min at room temperature (21 °C). Although colder temperatures or shorter reaction times seemed feasible, we found further optimization to be unnecessary. In situ alkylation of the resulting zinc sulfinate intermediate[9] was probed with *tert*-butyl bromoacetate, a reagent in which we had particular interest for one of our programs and which we observed to afford purely *S*-alkylated

Table 1. Optimization of Zinc Sulfinate Alkylation



5a **6a**

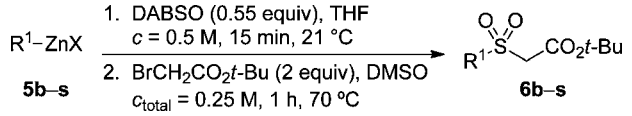
entry	alkylation conditions	yield[a] (%)
1	$BrCH_2CO_2$-*t*-Bu (1.1 equiv), 70 °C, 1 h	46
2	$BrCH_2CO_2$-*t*-Bu (1.1 equiv), 21 °C, 17 h	59
3	$BrCH_2CO_2$-*t*-Bu (2 equiv), 70 °C, 1 h	78
4	$BrCH_2CO_2$-*t*-Bu (2 equiv), 21 °C, 17 h	81
5[b]	$BrCH_2CO_2$-*t*-Bu (2 equiv), 70 °C, 1 h	<5

[a]Yields are for products isolated after chromatography. [b]DMSO was *not* added.

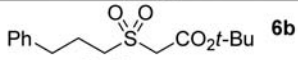
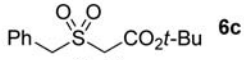
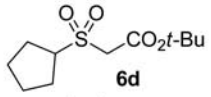
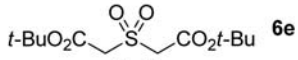
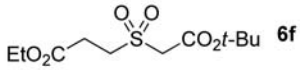
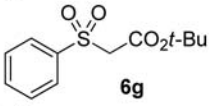
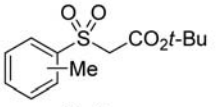
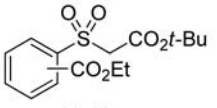
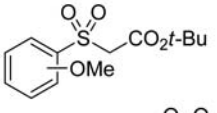
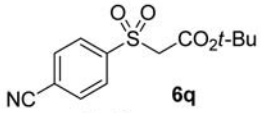
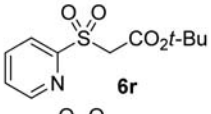
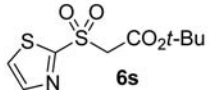
products[10] (Table 1). Although alkylation was accomplished in a moderate yield at 21 °C with as little as 1.1 equiv of alkylating agent (entries 1 and 2), we observed significant improvements by employing 2 equiv of alkylating agent at either 70 °C for 1 h (entry 3) or at 21 °C overnight (entry 4). Addition of DMSO as a cosolvent was required to effect alkylation (entry 5), likely to solubilize the intermediate zinc sulfinate (many of which are insoluble in THF). Although alkyl halides are known to undergo Kornblum oxidation[11] in DMSO at elevated temperatures, we did not observe detrimental effects on the intended reaction.[12] Thus, we selected the 1 h, 70 °C reaction using 2 equiv of alkylating reagent as our standard conditions.

With optimized reaction conditions in hand, we investigated the reactivity of a series of commercially available organozinc reagents (Table 2). Using *tert*-butyl bromoacetate as the alkylating agent, we obtained good yields of the corresponding sulfone products from primary (entries 1–2) and cyclic secondary (entry 4) alkylzinc reagents. Reformatsky-type reagents (entries 5–6) afforded sulfone products in modest yields. A range of arylzinc reagents also reacted under the standard conditions to afford the desired sulfones (entries 7–17). The highest yields were obtained when electron-withdrawing substituents (entries 11–13 and 17) were present in the organozinc reagent; electron-neutral (entries 8–10) and electron-rich (entries 14–16) substrates afforded products in lower yields (31–44%). Using the reaction to sulfone **6n** (entry 14) as an example, anisole was observed to account for greater than 80% of the remaining mass balance.[13] Ortho substitution (entries 10, 13, and 16) appeared to have little effect on the reaction. In addition, heterocyclic zinc reagents (entries 18 and 19) were competent substrates in this reaction. In all of the above cases, only *S*-alkylation was observed.

Table 2. Scope of the Reaction between DABSO and Organozinc Reagents



5b–s **6b–s**

entry	sulfone		yield[a]
1[b]		**6b**	84%
2			75%
3		**6c**	62%[c]
4		**6d**	70%
5[b]		**6e**	57–63%
6		**6f**	30–34%
7		**6g**	44%
8		*p*-Me (**6h**)	25–36%
9		*m*-Me (**6i**)	34%[d]
10		*o*-Me (**6j**)	44%[e]
11		*p*-CO_2Et (**6k**)	65%
12		*m*-CO_2Et (**6l**)	80%
13[b]		*o*-CO_2Et (**6m**)	85%[d]
14		*p*-OMe (**6n**)	38–56%
15		*m*-OMe (**6o**)	34%[e]
16		*o*-OMe (**6p**)	38%
17		**6q**	64%
18		**6r**	64%[d]
19		**6s**	58%

[a]Yields are for products isolated after chromatography. [b]The reaction was conducted under similar but nonstandard conditions. See the Supporting Information for details. [c]SO_2 gas was substituted for DABSO. Products estimated to be 90–95% pure. [d]Product estimated to be 90–95% pure. [e]Product estimated to be 80–85% pure.

As illustrated with compound **6c**, DABSO (entry 2) proved superior in a direct comparison to SO_2 gas (entry 3), leading to higher isolated yields (75% vs 62%).

With organozinc sulfinylation established, a range of additional alkyl halide electrophiles were selected to probe the scope of the in situ alkylation of the zinc sulfinate intermediates (Table 3). Suitable electrophiles included primary alkyl iodides (entries 1 and 2) and benzyl bromide (entry 3), producing sulfones **6t–v** in 68–89% yield. A secondary alkyl iodide (entry 4) returned sulfone **6w** in modest, yet useful, yield whereas the corresponding secondary alkyl bromide (entry 5) proved ineffective. As already demonstrated

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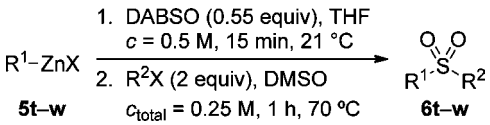
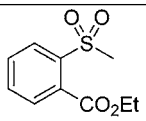
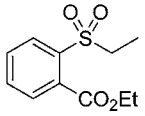
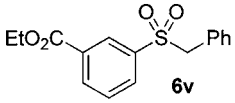
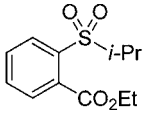
Table 3. Electrophile Scope in the Alkylation of Zinc Sulfinate Salts



entry	R^2X	sulfone	yield[a]
1	MeI	 **6t**	68%
2	EtI	 **6u**	71–75%
3	BnBr	 **6v**	89%[b]
4	*i*-PrI		36%[b]
5	*i*-PrBr	 **6w**	<2%

[a]Yields are for products isolated after chromatography. [b]Product estimated to be 90–95% pure.

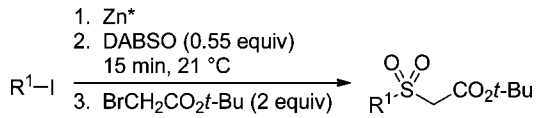
elsewhere, chloroacetonitriles[4c] and epoxides[4i] are also competent electrophiles in reactions with zinc sulfinate salts.

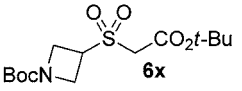
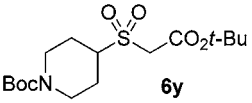
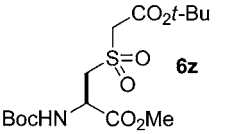
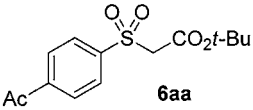
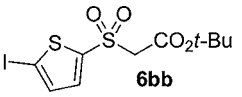
To expand the utility of this protocol beyond commercially available organozinc reagents and explore its potential for parallel medicinal chemistry applications, we investigated a series of tandem reactions converting alkyl and aryl iodides of medicinal chemistry relevance into sulfones (Table 4). Zinc insertion was accomplished according to standard procedures.[14] Sulfinylation in the presence of 0.55 equiv of DABSO and subsequent alkylation produced sulfones **6x–z** and **6bb** in 77–90% yield. Addition of DMSO was unnecessary when the reaction was conducted in a polar aprotic solvent. Yields were consistent with the results in Table 2, although a lower yield was observed in the case of **6aa**, where the highly sensitive acetophenone substrate (**5aa**) was used.

In contrast to methods employing organolithium and Grignard reagents,[4a,f,g,7b] the present method is notable for its functional group tolerance and operational simplicity. Halides, esters, nitriles, and even weakly acidic secondary carbamates can be incorporated into products with high yields, and sulfinylation is smooth at 21 °C. Of particular note, (1) ester homoenolates react productively, allowing a synthesis of β-sulfonyl esters (e.g., **6f**) complementary to the traditional 1,4-addition to an enone;[4a,g] (2) although obtained in low yield, product **6aa** would not be readily accessible by methods such as Mg/I exchange[15a] or electrophilic aromatic substitution;[15b] and (3) the compatibility of secondary carbamate functionality with organozinc reagents allows for the synthesis of unnatural amino acid derivatives (e.g., **6z**).

In conclusion, we have established the reaction between organozinc reagents, DABSO, and alkyl halides as an important route to mixed dialkyl and alkyl aryl sulfones. This method will prove useful in subsequent studies for transition-metal-mediated sulfone synthesis,[4c–e,7e] oxidative sulfonamide synthesis,[4f,7b] and C–C bond-forming reactions.[1]

Table 4. One-Pot Conversion of Alkyl and Aryl Halides to Sulfones



entry	sulfone	alkylation conditions	yield[a]
1[b]	 **6x**	DMSO, 21 °C, 17 h	81%[b]
2	 **6y**	DMSO, 21 °C, 17 h	79%[b]
3	 **6z**	DMF, 70 °C, 1 h	77%[c]
4[d]	 **6aa**	DMSO, 65 °C, 1 h	20%[c]
7	 **6bb**	DMSO, 70 °C, 1 h	90%[b]

[a]Yields are for products isolated after chromatography. [b]Calculated using a titrated[16] organozinc solution as the limiting reagent. [c]Calculated using the starting halide as the limiting reagent. [d]Sulfinylation was conducted with similar but nonstandard conditions. See the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **6a–bb**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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