# DABSO-Based, Three-Component, One-Pot Sulfone Synthesis

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ⓢ *Supporting Information*
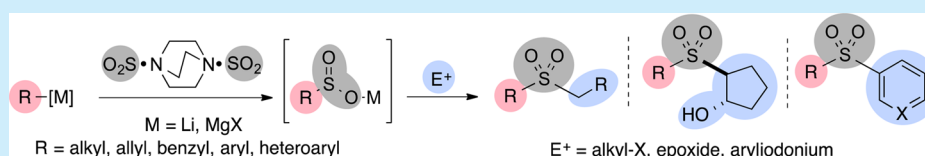
ABSTRACT: The addition of Grignard reagents or organolithium reagents to the SO$_2$-surrogate DABSO generates a diverse set of metal sulfinates, suitable for direct conversion to sulfone products. The metal sulfinates can be trapped in situ with a wide range of *C*-electrophiles, including alkyl, allyl, and benzyl halides, epoxides, and (hetero)aryliodoniums.

The importance of the sulfonyl unit (−SO$_2$−) is apparent from its ubiquity in medicinal chemistry and agrochemical targets.[1] Sulfones are an important subclass of these compounds and are found in a variety of biologically active molecules. For example, they have been shown to display antibacterial, anti-HIV, and antifungicidal activity (Figure 1).[2,3]
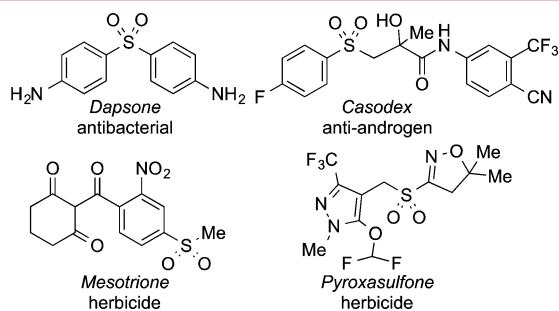

Figure 1. Representative biologically active sulfones.

From a synthetic perspective, sulfones are also versatile intermediates[4] and are implicit in such classic transformations as the Ramberg−Backlund reaction[5] and the Julia olefination.[6]

As a result of their widespread use, efficient and robust approaches toward the synthesis of sulfones are in high demand. The most common method of forming sulfones is a two-pot protocol from the corresponding sulfide,[7] which usually requires thiol substrates and oxidative conditions. The availability of alkenyl- and heterocyclic thiols is poor, and the use of oxidative conditions imposes limitations on the functional groups that can be tolerated. Reactions of sodium sulfinates with electrophiles[8] and in metal-catalyzed processes[9] have also been applied in sulfone synthesis. However, the very limited commercial availability of the sodium salts, and their alternative preparation from the corresponding sulfonyl chlorides, restricts their applicability.[10] Metal sulfinates can also be formed by treating an organometallic reagent with sulfur dioxide gas,[11] but this protocol is particularly unattractive due to the difficulties in handling a toxic gaseous reagent.[12] We therefore sought to develop a one-pot process capable of delivering a diverse array of sulfones via sulfur dioxide incorporation but employing an amine−SO$_2$ complex in place of SO$_2$ gas. The complex formed between DABCO and sulfur dioxide, DABSO, was first employed by us in a novel palladium-catalyzed aminosulfonylation reaction[13] and subsequently in a streamlined version of Barrett's sulfonamide synthesis.[14] The use of such reagents not only eradicates the hazards associated with the gaseous reagent but also allows for the measured delivery of sulfur dioxide in reaction systems. Consequently, the generation of metal sulfinates from organometallic reagents and DABSO was identified as a potentially efficient and versatile route into sulfone synthesis. This could be achieved by exploiting the nucleophilicity of the sulfinate intermediates with subsequent in situ trapping with a host of different electrophiles (Scheme 1).[15]

Scheme 1. Three-Component Sulfone Synthesis Combining an Organometallic Reagent, DABSO, and an Electrophile
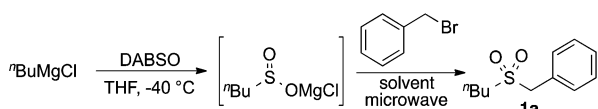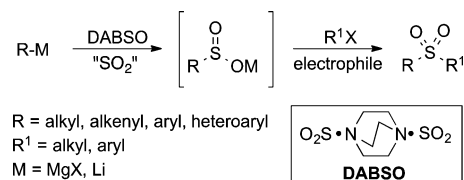

We began our studies by exploring the electrophilic trapping of alkylmagnesium sulfinates, employing benzyl bromide as the electrophile (Table 1). With the in situ formation of the *n*-butylmagnesium sulfinate from the corresponding Grignard

Table 1. Initial Screening and Optimization of Conditions for S-Alkylation of DABSO-Generated Magnesium Sulfinates[a]

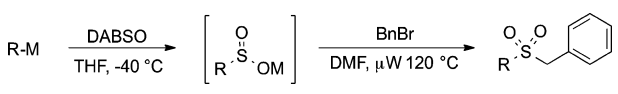| entry	solvent	temp (°C)	time (h)	yield (%)
1	THF	120	1	49
2	THF	120	2	55
3	THF/H₂O	120	2	58
4	THF/DMF	120	2	68
5	DMF	120	2	80
6	DMF	120	3	85
7	DMF	150	3	86
8	DMF	70[b]	16	78
9	DMF	120[b]	16	81
10	EtOH	120	3	68
11	DMA	120	3	72

[a]Reaction conditions: nBuMgCl (1 equiv), DABSO (1 equiv), THF, −40 °C then benzyl bromide (3 equiv), solvent, and heat using microwave. [b]Conventional heating.

reagent and DABSO, it was found that maintaining THF as the solvent in combination with microwave heating in the second step could deliver the desired S-alkylated product (**1a**) in a moderate 55% yield (entries 1 and 2). This was improved when moving to more polar solvents (entries 3−9), with the exception of water as a cosolvent which resulted in a significant amount of benzyl alcohol formation, and the product was isolated in only 58% yield (entry 3). The optimal set of conditions for sulfinate alkylation was identified as microwave heating at 120 °C in DMF for 3 h (entry 6). Employing a higher reaction temperature (entry 7) or normal overnight heating (entry 8) failed to deliver any improvement in sulfone yield. O-Alkylation, leading to the sulfinic acid ester products, was not observed in any examples.[8b]

With an optimal set of conditions in hand, we then explored the range of Grignard and organolithium reagents that were compatible with this system (Table 2). We were pleased to find that a range of alkyl-, allyl-, alkenyl-, aryl-, and hetero-arylmagnesium and -lithium reagents, generated using a variety of methods, delivered the desired metal sulfinates and that these could be efficiently alkylated in situ. For lower reactivity sulfinates, generated from electron poor aryl- or alkenyl organometallics, improved yields were obtained from the use of increased reaction times and/or benzyl bromide equivalents (see entries 6 and 9, for example). An attractive feature of the system was that heteroaromatic compounds such as benzo-thiazole and N-methylindole that are capable of undergoing direct deprotonation with butyllithium can serve as simple substrates yielding useful functionalized sulfone products (entries 17 and 19). For example, benzothiazol-2-yl sulfones serve as substrates in the modified Julia olefination reactions where alkenes can be generated in a single step.[16] From the data obtained there were no clear trends as to whether organomagnesium or organolithium reagents were more effective; the ease of preparation of the individual organometallic was most often the determining factor in selecting the type of reagent employed.

In order to demonstrate the versatility of this system, a range of electrophilic coupling partners were next evaluated, with initial studies concentrating on the use of additional alkyl

Table 2. Organometallic Substrate Scope for the One-Pot Preparation of Benzyl Sulfones[a]

entry	R-[M]	yield	entry	R-[M]	yield
1	Me⏜⏜MgCl	85%	11	MeO-C₆H₄-MgCl	85%
2	Me⏜⏜Li	87%	12[d]	Cl-C₆H₄-MgBr	67%
3	cyclopentyl-MgBr	86%	13[d,e]	Me₃Si-C₆H₄-Li	71%
4	Me₃C-MgCl	83%	14[d,e]	C₆D₅-Li	71%
5[b]	adamantyl-MgBr	75%	15[d,f]	MeO₂C-C₆H₄-MgCl	46%
6	⏝MgCl	70%	16[d,e]	(dioxolane)-C₆H₄-Li	61%
7[c]	⏝⏝MgBr	73%	17	thienyl-Li	83%
8	Bn-MgBr	70%	18[d,g]	benzothiazol-2-yl-Li	56%
9	(2-OMe-C₆H₄)-MgCl	79%	19[d,e,h]	N-TIPS-pyrrolyl-Li	58%
10[d]	(3-OMe-C₆H₄)-MgBr	70%	20[d,g]	N-Me-indol-2-yl-Li	73%

[a]Reaction conditions: organometallic (1 equiv, commercial reagent unless stated), DABSO (1 equiv), THF, −40 °C then benzyl bromide (3−5 equiv), DMF, 120 °C using microwave heating, 3 h. [b]RMgX generated from the corresponding bromide and Mg. [c]Using 5 equiv of BnBr and microwave heating for 5 h. [d]Using 5 equiv of BnBr. [e]RLi generated from the corresponding bromide and nBuLi or tBuLi. [f]RMgX generated from the corresponding iodide and iPrMgCl. [g]RLi generated via deprotonation with nBuLi or tBuLi. [h]The N−H pyrrole product was isolated.

halides (Table 3). As anticipated, alternative benzylic halides resulted in efficient trapping with the preparation of the corresponding sulfones in good yields (entries 1 and 2). Allylic (entries 3 and 4) as well as α-bromocarbonyl-derived (entry 5) electrophiles were also effective. The use of alkyl bromide electrophiles resulted in a reduction in sulfone yield (30−40%). However, this could be simply overcome by employing alkyl iodides, as demonstrated by the use of iodopropane to deliver the corresponding dialkyl sulfone in 74% yield (entry 6).

Table 3. Extending the Substrate Scope for the in Situ Electrophilic Trapping of Metal Sulfinates with Alternative Alkyl Halides[a]

entry	R¹-X	yield
1	(4-OMe benzyl chloride)	71%
2	(4-F benzyl bromide)	82%
3	(allyl bromide)	87%
4	(cinnamyl bromide)	94%
5	(phenacyl bromide)	90%
6[b]	(1-iodopropane)	74%

[a]Reaction conditions: [n]BuMgCl (1 equiv), DABSO (1 equiv), THF, −40 °C then electrophile (3 equiv), DMF, 120 °C using microwave heating, 3 h. [b]5 equiv of Pr-I.

Recent work from Manolikakes has shown that aryl hypervalent iodine reagents can be successfully employed as electrophiles in combination with metal sulfinates to yield diaryl sulfones.[17] To extend the profile of the compatible electrophiles in our system, an examination of iodonium salts as electrophilic aromatic counterparts was conducted (Scheme 2). Aryliodonium

Scheme 2. Symmetrical and Unsymmetrical Iodonium Salts as Electrophiles in a One-Pot Reaction with Magnesium Sulfinates
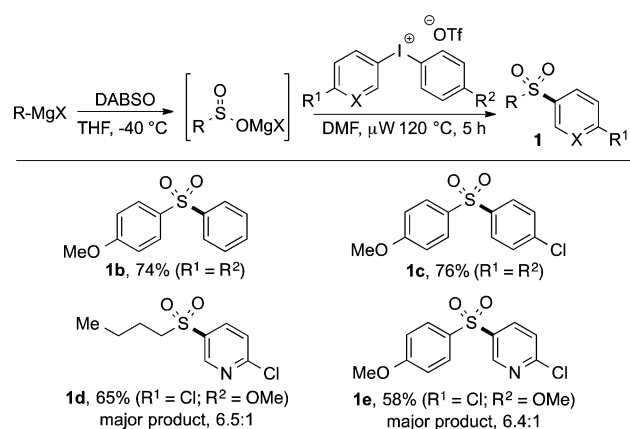

salts were successfully employed, affording unsymmetrical alkyl aryl and diaryl sulfones (**1b**, **1c**). Of particular note is the formation of pyridyl sulfones using the unsymmetrical aryl-heteroaryl iodonium triflates. Electronically distinguishing the two aromatic groups by using the p-methoxyphenyl- and 2-chloropyridyl constituents allowed heteroaryl group transfer to be favored, with the corresponding pyridyl sulfones formed

in good yield and with reasonable selectivity (**1d**, **1e**). These are the first examples of heteroaryl sulfones being prepared from the corresponding iodonium salts. Replacing the p-methoxyphenyl ring with a sterically encumbering mesityl group, or a dimethyluracil group,[18] had a detrimental impact on both yield and selectivity.

In order to access β-hydroxy sulfone products, we next turned our attention to the use of epoxides as electrophiles. Sodium sulfinates have been shown to effectively ring-open epoxides; however, the scope of such systems is significantly limited, with phenyl- and p-tolylsulfonyl being the major examples.[19] We therefore aimed to exploit the versatile formation of metal sulfinates using DABSO in the synthesis of a diverse set of β-hydroxy sulfones (Scheme 3). On initial

Scheme 3. Extending the Substrate Scope for the in Situ Electrophilic Trapping of Metal Sulfinates with Epoxides
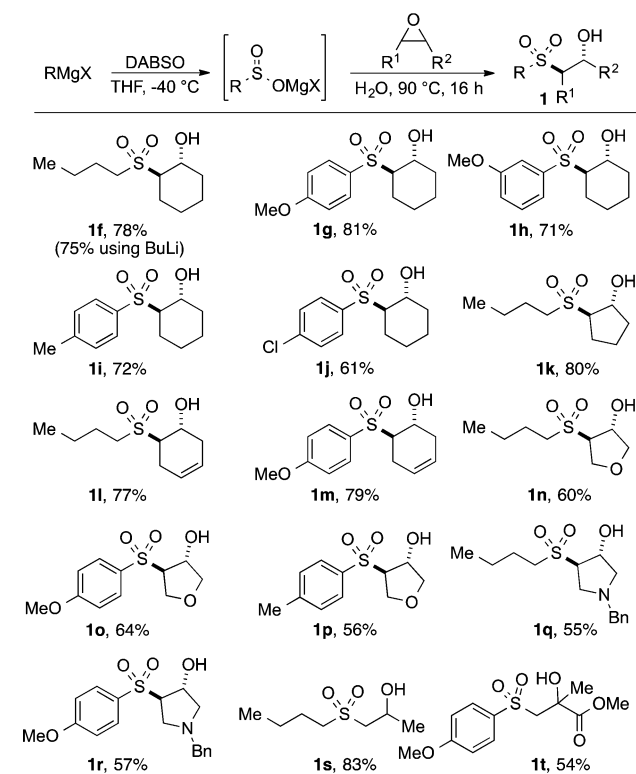
examination of the in situ reaction of the n-butylmagnesium sulfinate with cyclohexene oxide, it was found that the original set of conditions was not applicable, with negligible conversion in DMF observed. However, on switching to aqueous conditions productivity was improved significantly. It is generally considered that such a polar, protic solvent is integral for coordination to the epoxide oxygen, activating it toward nucleophilic attack.[19b] We found that with the use of 5 equivalents of the epoxide and heating at 90 °C in water, the anti-diastereomer of the desired β-hydroxy sulfone (**1f**) could be formed in 78% yield. Employing the corresponding organolithium reagent afforded a comparable result (75%). Using these optimized reaction conditions we set out to evaluate the range of hydroxy sulfones that could be accessed using this method (Scheme 3). Pleasingly, alkyl- and arylmagnesium sulfinates performed well in this system (**1f−i**). Again, electron-rich aryl sulfinates were the more effective nucleophiles, although electron-withdrawing groups were also shown to be compatible (**1j**). Several cyclic

epoxides could undergo ring-opening, with cyclopentane, cyclohexene, and the *N*- and *O*-heterocyclic substrates providing additional diversity (**1k,l,n,q**). Acyclic epoxides could also be employed (**1s**), and by using the ester-derived epoxide methyl 2-methylglycidate we were able to demonstrate the utility of this system with the generated sulfone (**1t**) providing the carbon backbone present in the antiandrogenic agent bicalutamide (Casodex, Figure 1) which is used in the treatment of prostate cancer.

In conclusion, we have developed a simple, versatile one-pot sulfone synthesis based on the in situ electrophilic trapping of metal sulfinates generated from organometallic reagents and DABSO. By employing a wide range of both organometallic substrates and electrophiles a broad class of sulfones can be synthesized in moderate to excellent yields using this method.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full characterization for all compounds. 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.

■ ACKNOWLEDGMENTS

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