

# DABCO-Bis(sulfur dioxide), DABSO, as a Convenient Source of Sulfur Dioxide for Organic Synthesis: Utility in Sulfonamide and Sulfamide Preparation

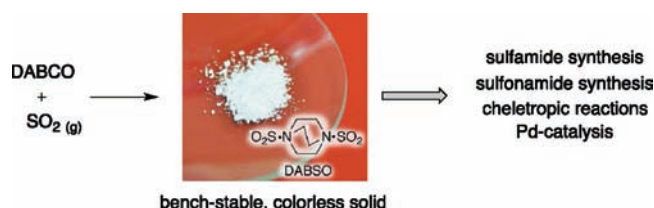
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## ABSTRACT



The charge-transfer complex generated from the combination of DABCO and sulfur dioxide, DABSO, is a bench-stable colorless solid suitable for use in organic synthesis as a replacement for gaseous sulfur dioxide. The complex can be combined with Grignard reagents to form sulfonates, which can then be converted in situ to a series of sulfonamides. Alternatively, reaction with anilines and iodine leads to the formation of a series of sulfamides. Cheletropic addition between DABSO and 2,3-dimethylbutadiene provides the corresponding sulfolene.

Sulfur dioxide has a long history as a reagent for organic synthesis.<sup>1</sup> It is known to take part in a number of distinct pericyclic processes, including cheletropic additions to dienes, hetero-Diels–Alder reactions, and ene processes.<sup>2</sup> Sulfur dioxide is also exploited in the synthesis of aromatic sulfonyl chlorides,<sup>3</sup> in copolymerization with alkenes<sup>4</sup> and in alkene isomerization reactions.<sup>5</sup> In addition, the electrophilic nature of sulfur dioxide has seen it utilized in the synthesis of sulfonates, and related sulfones, from combination with nucleophilic organometallic species such as

Grignard reagents and organolithiums.<sup>6</sup> More recently, it has found application in multicomponent systems, leading to the synthesis of complex polyfunctionalized molecules.<sup>7</sup> Despite this varied reactivity profile, and the corresponding range of compounds that can be prepared, the number of applications of these reactions in synthesis is arguably lower than would be expected. One reason for this is presumably the difficulties associated with the handling and use of a toxic gaseous reagent.<sup>8</sup> In this Letter we demonstrate the utility of DABCO-bis(sulfur dioxide), which we have abbreviated to DABSO, as a bench-stable solid reagent that can function as a sulfur dioxide equivalent in a number of processes.

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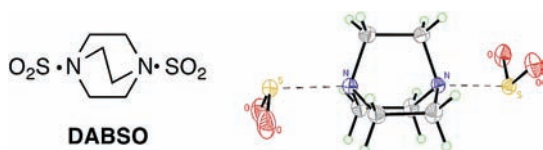
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The combination of sulfur dioxide and an amine can lead to the formation of charge transfer complexes; examples have been known since the early twentieth century, and during the mid-1900s they received attention from a structure and bonding perspective.<sup>9</sup> Olah has exploited tertiary amine-SO<sub>2</sub> complexes as dehydrating agents.<sup>10</sup> However, further applications to organic synthesis have been very limited.<sup>11</sup> Given the known stability of a number of amine-SO<sub>2</sub> complexes we were interested in whether a simple complex of this type could be exploited as an SO<sub>2</sub> equivalent and ideally replace the gaseous reagent in a number of transformations. The known DABCO·(SO<sub>2</sub>)<sub>2</sub> complex,<sup>12</sup> DABSO, is conveniently prepared in quantitative yield from the direct combination of DABCO and SO<sub>2</sub> and is a crystalline bench-stable colorless solid.<sup>13</sup> Single crystal X-ray analysis confirmed the structure was in agreement with related examples (Figure 1).<sup>14</sup>



**Figure 1.** X-ray crystal structure of DABCO-*bis*(sulfur dioxide) adduct, DABSO, with thermal ellipsoids shown at 50% probability; N...S distances are 2.0958(14) and 2.1732(15) Å.

Although we have recently demonstrated the utility of DABSO in a palladium-catalyzed aminosulfonylation process<sup>15</sup> – an unprecedented transformation using gaseous SO<sub>2</sub> – we wanted to explore DABSO in reactions for which the use of SO<sub>2</sub> has already been established. In 2003,

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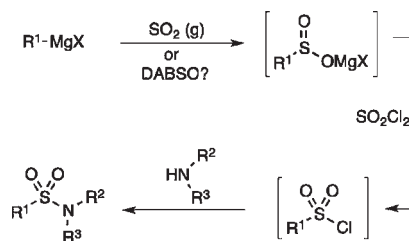
(13) For DABCO-AlMe<sub>3</sub> (DABAL) used as a stable version of AlMe<sub>3</sub>, see: Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, 4, 2322.

(14) Low temperature, single crystal diffraction data were collected on using a Nonius Kappa CCD diffractometer; data were reduced using DENZO-SMN/SCALEPACK [Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, 276, 307], solved using SIR92 [Altomare, A.; Casciarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1994**, 27, 435] and refined within the CRYSTALS suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, 36, 1487. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, 43, 1100]. Full refinement details are given in the Supporting Information (CIF); Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 840119) and can be obtained via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

(15) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, 132, 16372.

Barrett reported the one-pot preparation of sulfonamides from the combination of aryl Grignard reagents and sulfur dioxide gas, followed by treatment with sulfonyl chloride and an appropriate amine.<sup>16</sup> The basic process is shown in Scheme 1. Given the wide occurrence of sulfonamide functional groups in a range of bioactive compounds this transformation seemed an ideal candidate to investigate with an SO<sub>2</sub> equivalent.

**Scheme 1.** One-Pot Preparation of Sulfonamides



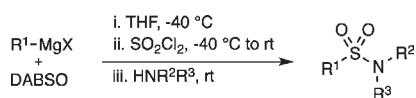
Pleasingly, we found that treatment of a THF suspension of DABSO with *p*-tolyl magnesium bromide at –40 °C, followed by addition of sulfonyl chloride and then after warming to room temperature, morpholine, provided the expected sulfonamide in 67% yield (Table 1, entry 1). Table 1 documents the scope of the process: Entries 1–6 demonstrate that variation of the amine component is readily achieved, including primary, secondary, and allylic examples. The use of a hydrazine nucleophile was less successful, with the *N*-aminomorpholine-derived sulfonamide being obtained in only 26% yield (entry 7). As well as aryl Grignard reagents (entries 8–10), it was also possible to employ benzyl (entry 11), allyl (entry 12), alkyl (entry 13), and heteroaryl examples (entry 14). In all cases the yields of the sulfonamide products were good (50–80%) and are comparable with the reactions reported using the gaseous reagent. The original report includes no examples of the use of primary amines or of alkenyl or alkyl Grignard reagents.<sup>16</sup>

Gaseous SO<sub>2</sub> has also been applied to sulfamide preparation: In 2006, Rudkevich demonstrated that treatment of anilines with SO<sub>2</sub> gas, iodine, and pyridine provided the corresponding diarylsulfamides.<sup>17,18</sup> The authors noted the need to employ ~100 equiv of SO<sub>2</sub>. We found that DABSO could be used as an effective replacement for the gaseous reagent in this protocol. For example, *N,N'*-diphenylsulfamide was prepared in 63% yield using a combination of DABSO, aniline, and iodine (Table 2, entry 1). It should be noted that only 2 equiv of DABSO, relative to aniline, were employed. Table 2 charts the scope of the reaction and demonstrates the effective preparation of a variety of diarylsulfamides.

(16) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, 68, 8274.

(17) Leontiev, A. V.; Rasika Dias, H. V.; Rudkevich, D. M. *Chem. Commun.* **2006**, 2887.

(18) The authors noted that SO<sub>2</sub> in combination with NET<sub>3</sub> in MeCN was also an effective reagent combination.

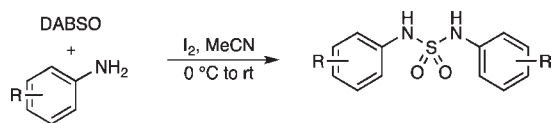
**Table 1.** Scope of the One-Pot Preparation of Sulfonamides Using DABSO<sup>a</sup>

entry	sulfonamide	yield <sup>b</sup>	entry	sulfonamide	yield <sup>b</sup>
1		67%	8		66%
2		80%	9		74%
3		81%	10		75%
4		50%	11		80%
5		60%	12		64%
6		60%	13		55%
7		26%	14		55%

<sup>a</sup> Reaction conditions: Grignard reagent (1.0 equiv), DABSO (2.5 equiv), THF, -40 °C, 1 h, then sulfonyl chloride (1.0 equiv), warm to rt, then amine (10 equiv). <sup>b</sup> Isolated yields.

As a final demonstration of the utility of DABSO we explored the chelotropic addition with 2,3-dimethyl-butadiene. Simply heating DABSO with an excess of the diene at 120 °C in a pressure tube delivered an 80% yield of the sulfolene product (**1**, Scheme 2).

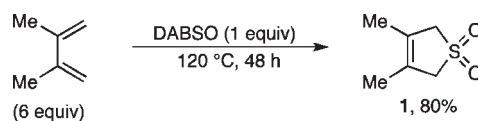
In conclusion, we have demonstrated that DABCO-bis(sulfur dioxide), DABSO, can be used as an effective replacement for gaseous sulfur dioxide in a number of established processes, leading to the synthesis of sulfona-

**Table 2.** Sulfamide Preparation Using DABSO<sup>a</sup>

entry	aniline	yield <sup>b</sup>	entry	aniline	yield <sup>b</sup>
1		63%	4		65%
2		73%	5		51%
3		60%	6		52%

<sup>a</sup> Reaction conditions: aniline (1.0 equiv), DABSO (2.0 equiv), I<sub>2</sub> (1.5 equiv), CH<sub>3</sub>CN, 0 °C to rt, 15 h. <sup>b</sup> Isolated yields.

mides, sulfamides, and sulfolenes. The reagent is a bench-stable colorless solid that should find wide application in synthesis; further applications are being developed in our laboratory.

**Scheme 2.** Chelotropic Addition of DABSO to 2,3-dimethyl-butadiene

**Acknowledgment.** We thank the EPSRC and Xunta de Galicia PGIDIT-INCITE and FSE (Angeles Alvariño contract and Estadias grants: 2009/188 and 2010/163 to C.G.R.) for their support of this study. We also thank Mr. Edward Emmett (University of Oxford) for preparation of the DABSO reagent.

**Supporting Information Available.** Experimental procedures and full characterization for all compounds (including X-ray data). This material is available free of charge via the Internet at <http://pubs.acs.org>.