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Synthetic Methods

A Sulfur Monoxide Surrogate Designed for the Synthesis of Sulfoxides and Sulfinamides**

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Abstract: Sulfur monoxide (SO) is a highly reactive species that cannot be isolated in bulk. However, SO can play a pivotal role as a fundamental building block in organic synthesis. Reported herein is the design and application of a sulfinylhydrazine reagent as an easily prepared sulfur monoxide surrogate. We show facile thermal SO transfer from this reagent to dienes where a reaction using a mechanistic probe suggests the generation of singlet SO. Combined with Grignard reagents and appropriate carbon or nitrogen electrophiles, the reagent serves as an effective "SO" donor to enable the one-pot, three-component synthesis of sulfoxides and sulfinamides.

Despite its relevance in astrochemistry[1] and synthetic chemistry,[2] sulfur monoxide (SO) has been scarcely explored because of its exceptionally reactive nature. SO rapidly disproportionates to SO_2 and elemental sulfur under ambient conditions[3] and escapes bulk isolation for (in)organic applications. As a result, a number of molecular precursors for SO generation have been developed including episulfoxides (e.g., **A**[4] and **B**[5]), trisulfide-2-oxide **C**,[6] vicinal disulfoxide **D**,[7] bridged bicyclic sulfoxide **E**,[8] phosphine complex **F**,[9] and sulfinylhydrazine **G**[10] (Figure 1). However, synthetic uses of these sulfur monoxide surrogates have been limited to SO transfer reactions to organic traps (e.g., dienes) and metal complexes.

Sulfoxides[11] and sulfinamides[12] are venerable S^{IV} functionalities found in ligands for transition metal catalysis,[13] organocatalysts,[14] and chiral auxiliaries.[15] Also, these S^{IV} functional groups are linchpin intermediates to prepare S^{VI} motifs such as sulfoximines[16] and sulfonimidamides[17] for medicinal and agrochemical sciences. Synthetic strategies based on sulfinylative three-component coupling[18] can provide modular and rapid preparation of a large number of sulfoxide and sulfinamide building blocks for these applications. In this paper, we present the development of sulfinylhydrazine **1** as a readily prepared, storable sulfur monoxide surrogate. In addition to thermal SO transfer to dienes, we show the synthetic utility of reagent **1** as an "SO" building block in a one-pot, three-component assembly of sulfoxides and sulfinamides.

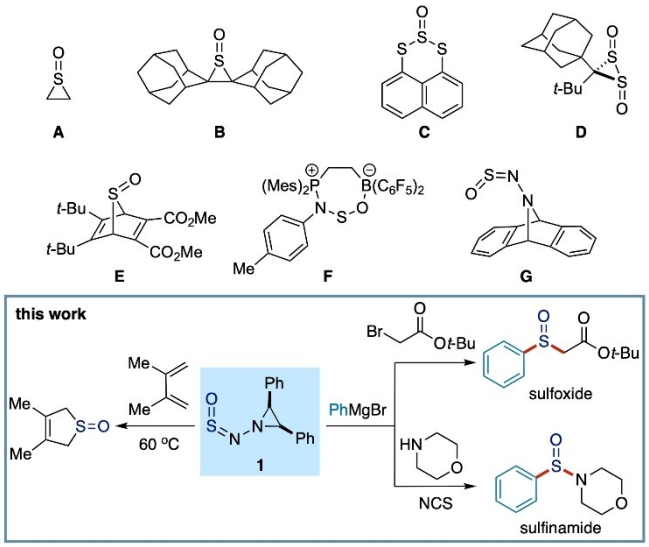

Figure 1. Sulfur monoxide surrogates. Selected examples of previously reported compounds (**A**–**G**) and our sulfinylhydrazine **1** presented in this work.

Sulfinylamines have recently gained a revival of interest in organic synthesis[19] for the efficient construction of medicinally relevant S^{VI} functionalities including sulfoximines[20] and sulfonimidamides.[21] These syntheses often involve the initial formation of anionic sulfinamide intermediates resulting from the addition of nucleophiles to the electrophilic sulfur of a sulfinylamine. We surmised that a designed sulfinylamine, namely, sulfinylhydrazine **1** would form anionic sulfinamide **H** upon the Grignard reaction, followed by facile decomposition of **H** into sulfenate anion **I**, stilbene, and nitrogen (Scheme 1a). As we and others have shown previously, sulfenate anions are versatile intermediates to forge sulfoxides[22] and sulfinamides.[23] Thus, we envisioned a one-pot, three-component synthesis of these S^{IV} motifs exploiting sulfinylhydrazine **1**, Grignard reagents, and suitable carbon or nitrogen electrophiles.

We began our studies by preparing sulfinylhydrazine **1** in three steps from commercial starting materials (Scheme 1b). Oxidative cyclization of *N*-aminophthalimide (**2**) and *cis*-

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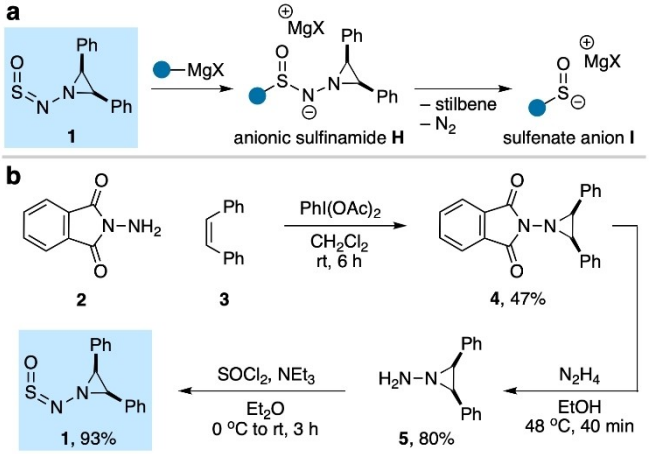
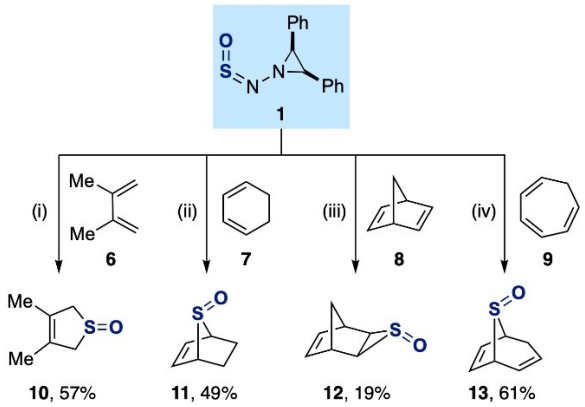


Scheme 1. Design and synthesis of sulfinylhydrazine **1**. (**a**) Our initial mechanistic working hypothesis for the formation of sulfenate anion **I** via anionic sulfinamide **H**. (**b**) Preparation of reagent **1**.



Scheme 2. Thermal SO transfer from sulfinylhydrazine **1**. (i) **6** (neat), 60 °C, 17 h. (ii) **7**, benzene, 60 °C, 2 h. (iii) **8**, benzene, 60 °C, 2 h. (iv) **9**, benzene, rt, 17 h. Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

stilbene (**3**) formed aziridine **4**,[24] which was subjected to hydrazinolysis to reveal *N*-aminoaziridine **5**. Note that *N*-aziridinylimines derived from compound **5** or its related *N*-aminoaziridine structures have been used for the Eschenmoser fragmentation,[25] the Shapiro reaction,[26] and radical cyclization.[27] The reaction of **5** with thionyl chloride in the presence of triethylamine gave our target compound **1**. Sulfinylhydrazine **1** is stable in the freezer (−20 °C) for at least one month (see Supporting Information). On the other hand, reagent **1** is unstable in solution; for example, more than 50 % decomposition was observed within one hour in $CDCl_3$ or THF-d_8 at room temperature.

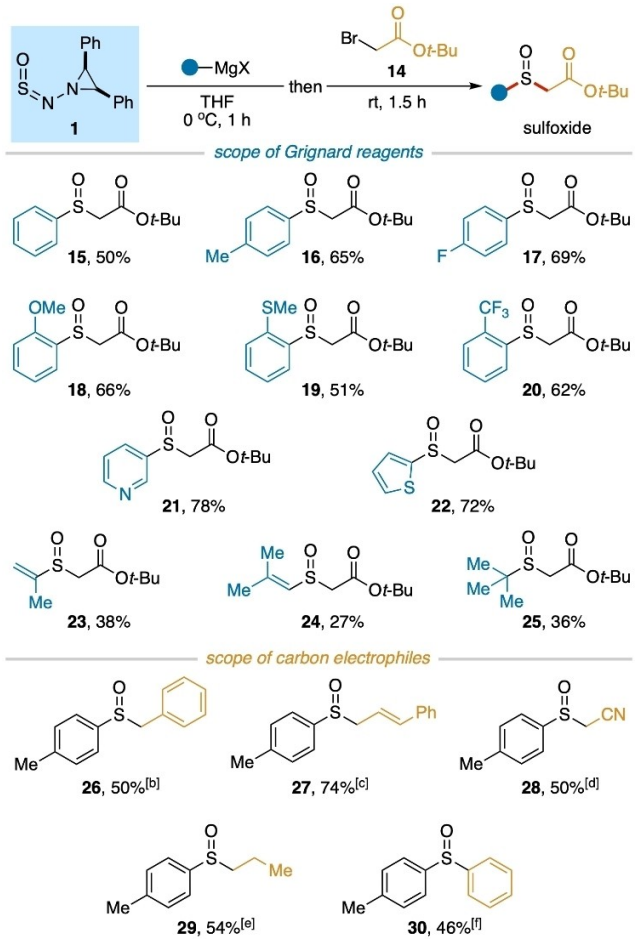
With reagent **1** in hand, we first explored thermal SO transfer to dienes: 2,3-dimethyl-1,3-butadiene (**6**), 1,3-cyclohexadiene (**7**), and norbornadiene (**8**). The reaction was facile, as indicated by immediate gas evolution from the reaction mixture upon heating to 60 °C. Capture of SO with the excess dienes was successful, forming cyclic unsaturated sulfoxides **10**–**12** (Scheme 2). We also carried out a trapping experiment with cycloheptatriene (**9**), as **9** is a known mechanistic probe to distinguish between triplet and singlet SO.[6b] This attempt resulted in the production of bridged bicyclic sulfoxide **13** with no detectable formation of 7,7′-dicycloheptatriene (a dimer of **9**), suggesting that sulfinylhydrazine **1** thermally releases singlet SO.

To date, only two examples have been reported as practical sulfur monoxide surrogates for generation of singlet SO. The first example **E**, reported by Nakayama and co-workers, is only generated in situ through the Diels–Alder reaction and cannot be isolated.[8] The Cummins group developed sulfinylhydrazine **G** as the other precursor of singlet SO.[10] The preparation of **G** requires six steps from commercial chemicals where one of the steps involves the use of an explosive reagent and a tedious purification procedure,[28] thus presenting a challenge in the large-scale preparation of **G**. When SO is released, both **E** and **G** produce byproducts that cannot be recycled. Our reagent **1**, on the other hand, was synthesized in a shorter route (three steps, one chromatographic purification) and *cis*-stilbene can be recycled. These features render reagent **1** an exceptionally convenient source of singlet SO.

Next, we sought to use reagent **1** for a one-pot, three-component assembly of sulfoxides (Table 1). We examined this reaction using phenylmagnesium bromide and *tert*-butyl bromoacetate (**14**) as model coupling fragments. After optimization (see Supporting Information), we obtained sulfoxide **15** in 50 % yield, which was readily separated from *cis*-stilbene, a byproduct derived from **1**, using column chromatography. This coupling platform applied to other aryl Grignard reagents with various substituents to provide sulfoxides **16**–**20**. Importantly, heterocyclic Grignard reagents proved to be viable, as exemplified by the synthesis of 3-pyridyl and 2-thienyl sulfoxides **21** and **22**. Although this three-component coupling system succeeded in yielding alkenyl and *tert*-butyl sulfoxides **23**–**25**, we failed to synthesize the sulfoxides derived from primary- and secondary alkyl Grignard reagents (e.g., methyl, *n*-butyl, and isopropyl). An examination of carbon electrophiles revealed that activated alkyl bromides, primary alkyl iodides, and hypervalent iodine reagents are competent substrates to provide the corresponding sulfoxides **26**–**30**. Secondary alkyl iodides (e.g., 2-iodopropane), however, turned out to be poor substrates, forming the sulfoxides in low yields (< 10 %). In addition, we could not detect the formation of the target sulfoxides when non-activated primary alkyl bromides (e.g., 1-bromobutane) were employed.

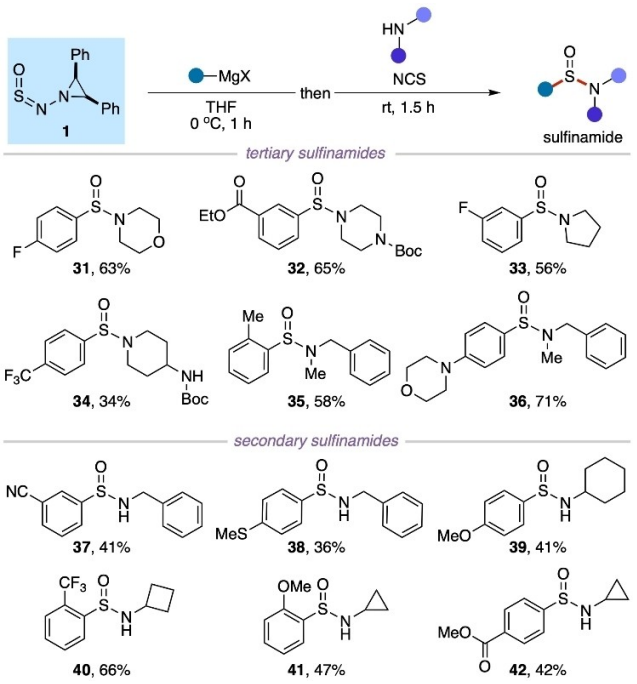
We also explored the one-pot, three-component synthesis of sulfinamides (Table 2). We employed our previously developed oxidative amination protocol with commercially available amines and *N*-chlorosuccinimide (NCS).[23b] Using this procedure, a variety of secondary amines including morpholine, piperazine, pyrrolidine, and piperidine, as well as *N*-benzylmethylamine were coupled to give tertiary sulfinamides (**31**–**36**). The coupling of primary amines, such as benzyl, cyclohexyl, cyclobutyl, and cyclopropyl amines, was equally effective in affording secondary sulfinamides **37**–**42**.

Table 1: Scope of one-pot, three-component synthesis of sulfoxides using sulfinylhydrazine **1**.[a]

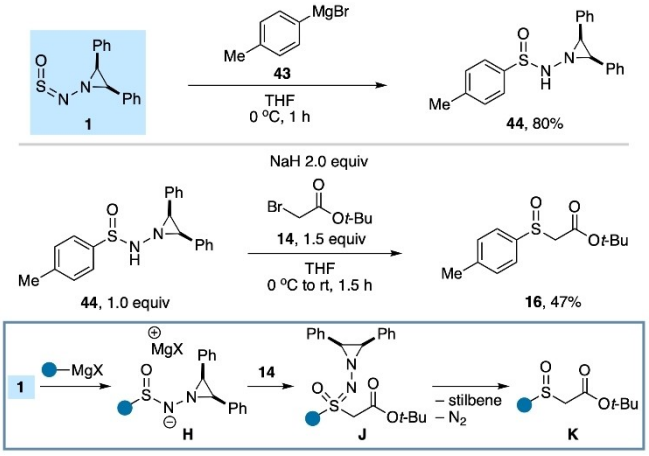


[a] Isolated yields are shown. Typical reaction conditions: sulfinylhydrazine **1** (0.20 mmol, 1.0 equiv), Grignard reagent (1.1 equiv), THF, 0 °C, 1 h, then alkyl bromide **14** (1.5 equiv), room temperature, 1.5 h. [b] With benzyl bromide. [c] With cinnamylbromide. [d] With bromoacetonitrile. [e] With 1-iodopropane. [f] With diphenyliodonium triflate.

Table 2: Scope of one-pot, three-component assembly of sulfinamides using reagent **1**.[a]



[a] Isolated yields are shown. Typical reaction conditions: sulfinylhydrazine **1** (0.20 mmol, 1.0 equiv), Grignard reagent (1.1 equiv), THF, 0 °C, 1 h, then amine (3.0 equiv), NCS (1.1 equiv), room temperature, 1.5 h.



Scheme 3. Proposed reaction mechanism.

Unfortunately, we failed to synthesize primary sulfinamides using reagent **1** as the SO donor; neither a combination of ammonia (as a solution in THF) and NCS nor O-(diphenylphosphinyl)hydroxylamine (DPPH) yielded desired primary sulfinamides, even though our previous studies revealed DPPH was a reagent of choice to transfer the NH_2 group to sulfenate anion **I**.[23b] The unsuccessful attempts to access primary sulfinamides triggered us to question the validity of our initially formulated mechanistic working hypothesis that involves sulfenate anion **I** (Scheme 1a).

To gain insight into a reaction mechanism for the formation of sulfoxides using **1**, we first monitored an intermediate formed upon the Grignard reaction (with reagent **43**) without adding an electrophile and found the clean formation of sulfinamide **44** in 80 % yield (Scheme 3). This observation suggests that anionic sulfinamide **H** (Scheme 1a) is stable under the reaction conditions and resistant to undergo degradation into sulfenate anion **I**. Next, the isolated sulfinamide **44** was deprotonated with NaH in the presence of alkyl bromide **14**, resulting in the formation of **16** in 47 % yield. These experimental data support a mechanism of sulfoxide synthesis that involves the S-alkylation of anionic sulfinamide **H** with an electrophile to form sulfoximine **J**.[29] This species would likely undergo instantaneous decomposition to sulfoxide **K**, stilbene, and nitrogen. Related degradation of sulfoximines into sulfoxides through extrusion of nitrogen was reported previously.[30]

Sulfur monoxide (SO) as a building block for the synthesis of S^{IV} functionalities has been little explored. In this paper, we present a sulfinylhydrazine reagent as an easily prepared, synthetically useful sulfur monoxide surrogate. In addition to thermal SO transfer to dienes, we demonstrate the synthetic utility of the reagent as an "SO" unit donor in the one-pot, three-component synthesis of sulfoxides and sulfinamides. The synthetic accessibility, stability, and multifaceted applications of the sulfur monoxide surrogate reported herein will be advantageous in a variety of scientific disciplines including synthetic and medicinal chemistry for efficient and modular preparation of S^{IV} functionalities as well as astrochemistry to investigate the role of SO.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Grignard Reaction · One-Pot Synthesis · Sulfoxides · Sulfur Monoxide · Synthetic Methods

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