ABSTRACT: Sulfonamides have played a defining role in the history of drug development and continue to be prevalent today. In particular, primary sulfonamides are common in marketed drugs. Here we describe the direct synthesis of these valuable compounds from organometallic reagents and a novel sulfinylamine reagent, t-BuONS O. A variety of (hetero)aryl and alkyl Grignard and organolithium reagents perform well in the reaction, providing primary sulfonamides in good to excellent yields in a convenient one-step process.
The classical synthesis of primary sulfonamides involves the reaction of activated sulfonyl electrophiles, usually sulfonyl chlorides, with ammonia, or an ammonia surrogate with a subsequent deprotection step (Scheme 1a). Although this approach is still widely used where the appropriate sulfonyl chloride is easily available, it has some notable drawbacks. Sulfonyl chlorides are moisture-sensitive and are not always available due to limitations in both functional group tolerance and available substitution patterns inherent in their synthesis via harshly acidic and oxidizing chlorosulfonation conditions.22 Furthermore, the handling of gaseous ammonia can be challenging, while the use of solid or liquid ammonia surrogates necessarily leads to losses in atom and step economy. For these reasons, the development of alternative methods for sulfonamide synthesis in general, and primary sulfonamide synthesis in particular, has received much attention in recent years.

Two recent papers have redefined the state of the art of sulfonamide synthesis. A copper-catalyzed direct synthesis of sulfonamides23 from the SO₂ surrogate DABSO,24 boronic sulfonamide synthesis. A copper-catalyzed direct synthesis of sulfonamides in particular, has received much attention in recent years. Sulfonyl chlorides are moisture-sensitive and are not always available due to limitations in both functional group tolerance and available substitution patterns inherent in their synthesis via harshly acidic and oxidizing chlorosulfonation conditions.22 Furthermore, the handling of gaseous ammonia can be challenging, while the use of solid or liquid ammonia surrogates necessarily leads to losses in atom and step economy. For these reasons, the development of alternative methods for sulfonamide synthesis in general, and primary sulfonamide synthesis in particular, has received much attention in recent years.

Two recent papers have redefined the state of the art of sulfonamide synthesis. A copper-catalyzed direct synthesis of sulfonamides from the SO₂ surrogate DABSO, boronic acids, and amines by our laboratory showed broad scope and functional group tolerance, but failed when ammonia was used. An elegant electrochemical synthesis of sulfonamides using thiols and amines from the Noël group25 did succeed in using ammonia (Scheme 1b). However, only one example was shown on a simple aryl scaffold, and electrochemistry has not yet been widely adopted in academic synthetic chemistry laboratories. The use of thiols as starting materials can also be problematic due to their malodorous nature and tendency to oxidize in air to form disulfides. Primary sulfonamides may also be prepared from sulfinate salts by reaction with an electrophilic nitrogen source such as O-mesitylenesulfonyl-hydroxylamine (MSH) or hydroxylamine-O-sulfonic acid (HOSA, Scheme 1c).26 This strategy is limited by the explosive risk of such reagents.27 Sulfinate salts can also undergo halogenation followed by the addition of an ammonia source.28 The low commercial availability of sulfinate salts is an issue, although new methods have further expanded access to these compounds, including by C–H activation (via thianthrenium salts and Pd catalysis)29 and using inexpensive nickel catalysts with DABSO and boronic acids.30 Useful oxidative syntheses of primary sulfonamides from thiols have also been developed,31 notably including a recent paper by Bull using iodobenzene diacetate and ammonium carbonate as an ammonia equivalent (Scheme 1d).32 Disadvantages of these methods include the use of thiols and lack of tolerance of some functional groups such as amines and thioethers to strong oxidants. Considering all these factors, a bespoke approach to primary sulfonamides starting from widely available alkyl and aryl halides would likely be welcomed by the synthetic community; the work reported in this Letter describes such an approach (Scheme 1e).

Our group has pioneered the use of sulfinylamine33 reagents \( \text{R(O)}\text{–N} = \text{S} = \text{O} \) for the preparation of synthetically and medicinally valuable high oxidation state sulfur compounds. Using organometallic nucleophiles generally derived from alkyl and aryl bromides, such as Grignard and organolithium reagents, we have designed one-pot syntheses of sulfonimida- mides, sulfinimines (precursors to sulfondiimines),35 and sulfoximines.36 During our investigation into the synthesis of sulfoximines we developed a new class of sulfonilamides, \( \text{N} = \text{S} = \text{O} \)-arylhydroxylamines, containing a cleavable N–O bond. When reacted with organometallic reagents at \( -78 \) °C, these compounds form highly electrophilic sulfinyl nitrenes; these reactive intermediates could then be reacted with a second carbon nucleophile, or amine, to give sulfoximines or sulfonimidamides, respectively. Our initial intention at the outset of this project was to develop a variant of this reaction which could be performed at noncryogenic temperatures. We therefore set out to design a reagent with a stronger N–O bond, reasoning that this would raise the barrier to N–O cleavage. We decided that replacing the aryl group on oxygen with an electron-releasing tert-butyl group would be optimal. The synthesis of this reagent, \( \text{N} = \text{S} = \text{O} \)-arylhydroxylamine (t-BuONSO, 1), was conveniently achieved in one step using commercially available \( \text{O} \)-tert-butylhydroxylamine hydrochloride, thionyl chloride, and triethylamine, with a simple distillation (under reduced pressure) delivering the pure reagent 1 (Scheme 2a). The reaction was scalable and could be performed on 200 mmol scale to afford 15 g of t-BuONSO, as a stable, colorless nonviscous liquid.38

When we reacted t-BuONSO 1 with the commercially available Grignard reagent 4-fluorophenylmagnesium bromide and morpholine, in sequence at \( -78 \) °C, our standard reaction conditions for the preparation of sulfonimidamides using our original BiPhONSO reagent, we were frustrated to observe only 10% of the sulfonimidamide product in the crude reaction mixture (Scheme 2b). Similar reactions using two organometallic reagents as nucleophiles did not result in appreciable sulfoximine formation. Curiously, precipitation of a white solid was observed in both reactions when deuterated chloroform was added to the crude sample after aqueous workup. The solid did, however, dissolve in deuterated acetone, and we were surprised to find the \( 1 \)H NMR spectra matched that of the primary sulfonamide 2a. Indeed, when the reaction was performed without the addition of a second nucleophile,
product 2a was isolated in 80% yield. In the event, changing the structure of the sulfonylamine reagent did not result in different conditions for our previous reaction, but instead enabled a new, unusual primary sulfonamide synthesis. Increases in temperature and equivalents of Grignard reagent resulted in lower yields, confirming −78 °C and 1 equiv of the organometallic reagent as optimal (Scheme 2c). Importantly, the reactions could also be performed on preparative scale. For example, a reaction using 1 mmol of t-BuONSO delivered sulfonamide 2a in 71% yield (862 mg). A reaction using 1.098 g of t-BuONSO (8.0 mmol) provided sulfonamide 2a in 62% yield.

We were curious to see if this new reaction would prove general. Varying the aryl organometallic nucleophile confirmed that para-, meta-, and ortho-methyl substituents were all tolerated, with a minor drop in yield for the bulky o-tolylmagnesium bromide (2d) (Scheme 3). Using aryl nucleophiles with electron-donating and -withdrawing aryl groups delivered primary sulfonamides in high yields. A basic, and oxidatively sensitive tertiary amine could also be incorporated in excellent yield (2j). Turning to more medicinally relevant basic nitrogen heterocycles, we were pleased to find that 2- and 3-pyridyl sulfonamides, as well as a fused imidazopyridine, could all be prepared in synthetically useful yields (2k−2n). Five-membered heterocycles were also amenable to the reaction, with organometallic nucleophiles containing 2-thienyl, 2-benzofuranyl, and even the highly base-sensitive 4-isoxazolyl moiety all giving the desired primary sulfonamides (2o−2q). Alkyl organomagnesiums proved to be competent nucleophiles; steric factors did not affect the reaction significantly, with phenethyl, benzyl, isopropyl, and tert-butyl Grignard reagents all delivering product in moderate to good yields (2r−2u). Cyclopropylmagnesium bromide gave a higher yield of 72% (2v), and allylmagnesium bromide delivered the potentially sensitive sulfonamide 2w in 50% yield. The final two examples demonstrate that medicinally relevant structures can be readily prepared, with substituted tetrahydroisoquinoline 2x, a motif exploited by UCB in their dopamine receptor program,40 and celecoxib (2y), both obtained in workable yields.

Preliminary mechanistic investigations have provided some insight into the mechanism of this unusual transformation, and our working model is shown in Scheme 4. Addition of the Grignard reagent to t-BuONSO 1 gives sulfonamide intermediate I, which then converts into sulfonimidate ester anion II, either via a sulfonyl nitrene intermediate36 or from a concerted N→S O-migration.41 An intramolecular proton transfer to the nitrogen atom proceeds to eliminate isobutene and give sulfonamide anion III, which is quenched upon workup to give the final sulfonamide product 2a. This proposal is supported by the lack of 18O incorporation when the reaction was quenched using 18O-labeled water at either −78 °C or room temperature, and by the observation of 1H NMR signals corresponding to isobutene in an aliquot of the crude reaction mixture (see Supporting Information for details).
These preliminary experiments are consistent with both oxygen atoms of the sulfonamide originating from the t-BuONSO reagent.

In summary, the development of the novel sulfinylamine reagent t-BuONSO 1 has led to a new synthesis of primary sulfonamides. Simply combining this method will range of medicinally relevant primary sulfonamides. We believe our gold bromide gives rapid and convenient access to a broad range of medicinally relevant primary sulfonamides. We believe this method will find use as a straightforward way to install polarity and dramatically alter the physicochemical properties of molecules, starting from common amyl and aryl halides.

**ACKNOWLEDGMENTS**

This work was supported by the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1).

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**Notes**

The authors declare no competing financial interest.
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