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Benzothiazole Sulfinate: A Sulfinic Acid Transfer Reagent under Oxidation-Free Conditions

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Abstract

Sulfinic acids are commonly encountered intermediates found in natural product synthesis and medicinal chemistry. However, because of high reactivity, instability, and harsh reaction conditions, they are difficult to synthesize. Herein we have developed an oxidation-free method to produce sulfinic acids and sulfinate salts using 2-sulfinyl benzothiazole (BTS). We have also demonstrated the synthetic usefulness by developing one-pot syntheses of sulfones and sulfonamides.

Graphical Abstract

Sulfinic acids and their salts are common intermediates in organic synthesis. They can be converted to sulfones,^{1–5} sulfonamides,^{5–7} and sulfonyl fluorides,^{3,8} which are found in natural products,⁹ pharmaceuticals,^{10–13} and materials^{14,15} and used for bioconjugation.^{16,17} Classically, sulfinic acids are synthesized via oxidation of thiols using H₂O₂ or by the reduction of sulfonyl chlorides (Scheme 1A).¹⁸ However, these methods have many drawbacks, including harsh conditions and generally poor yields due to the many byproducts that can be produced from the various oxidation states of sulfur. In addition, sulfinic acids are inherently unstable, decomposing via over/underoxidation, elimination, and reactivity toward electrophiles.^{19,20} Therefore, they are often synthesized freshly or generated in situ, further complicating synthetic pathways. These drawbacks have led to a focus on new

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Notes

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Supporting Information

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Detailed synthetic procedures and characterization data (PDF)

methods to produce sulfinic acids for the preparation of sulfones, sulfonamides, and sulfonyl fluorides. For example, organolithium, Grignard, and palladium reagents can react with sulfur dioxide gas^{21,22} or sulfur dioxide surrogates such as Na₂SO₃,²³ K₂S₂O₅,²⁴ or DABSO^{6,25–27} to form sulfinic acid salts in situ. (Scheme 1B).²⁸ Furthermore, coupling of ronalite³ or sodium 3-methoxy-3-oxopropene-1-sulfinate (SMOPS)²⁹ with alkyl halides in the presence of a base to produce sulfinic acid salts has also been reported. Although useful, many of the above reactions still suffer from some problems. Reactions of carbanions with SO₂ gas require dangerous and reactive reagents under an inert atmosphere. Reactions of ronalite and SMOPS with alkyl halides produce unstable and unisolatable intermediates, often resulting in poor yields.

Recently, our group discovered methyl sulfone-substituted benzothiazoles (MSBTs) as specific thiol blocking reagents.³⁰ This was extended further into use in our “tag-switch” assay for identifying protein S-persulfidation, a hydrogen sulfide-mediated post-translational modification.³¹ While optimizing the chemistry for our tag-switch technique, we discovered a unique benzothiazole sulfinate salt, 2-sulfinyl benzothiazole (BTS), which can slowly decompose under acidic conditions to release sulfur dioxide.³² BTS was thus identified as a water-soluble and slow-releasing SO₂ donor that can induce vasorelaxation in isolated rat aorta. Because of the unique chemistry of 2-substituted benzothiazoles, we decided to further investigate BTS’s utility in organic synthesis. Herein we describe a new method for the synthesis of sulfinic acids under mild conditions (Scheme 1C). This method also provides a unique protecting group for sulfinic acids. We further extended this method to synthesize sulfones and sulfonamides in one pot.

We envisaged that BTS would be able to react as a nucleophile with alkyl halides to produce sulfones analogous to MSBT. These sulfones are unique as they can easily be reacted with thiols via S_NAr reaction or reduced by NaBH₄.^{30,33} Cleavage releases a benzothiazole derivative plus a sulfinate, thus transferring the sulfinate from BTS to the alkyl halide with no oxidation or inert atmosphere required. Another advantage of this method is that the benzothiazole moiety acts as a protecting group for the sulfinic acid, providing a common intermediate for functionalization to a sulfone, sulfonamide, or sulfonyl fluoride. It should be noted that the reaction between BTS and an alkyl halide also provides a one-step, oxidation-free method to produce modified Julia sulfones.

To begin, a model reaction was used to optimize the conditions for benzothiazolation (Table 1). We attempted to find a suitable solvent system for both BTS and alkyl halides. Acetonitrile, DMSO, and water were all considered as suitable solvents, but DMF gave the best yields as well as good solubility of BTS (data not shown). First, we used BTS as the limiting reagent and obtained a good yield of 90% (entry 1). However, this decreased as the equivalence of BnBr was lowered (entry 2). Understanding the electrophile to be more important in terms of sulfonyl transfer, we found that by increasing the equivalence of BTS to 4 we could achieve quantitative conversion to the benzothiazole sulfone (entry 6). Attempts to speed up the reaction by elevating the temperature to over 50°C decreased the yield because of the decomposition of BTS to benzothiazole via the release of SO₂.

Next, we tested the scope of potential electrophiles with which BTS can react (Table 2). We found most alkyl halides to have very high yields of sulfone formation. Primary halides proved very facile with no byproduct except for trace amounts of benzothiazole (entries 1–6). We also found the reaction to be practical in the presence of alkenes (entries 3 and 5), ketones (entry 6), esters (entry 8), and secondary benzylic positions with almost no loss of efficiency (entry 7). The secondary α -carbon of an ester also provided a good yield. Reactions between sulfinate salts and secondary halides in poor yields have been reported, but they proceed under high temperature almost exclusively,³⁴ which BTS is unable to withstand.

Having established the protocol for sulfone transfer, we turned our attention to the removal of benzothiazole. We first considered cleavage via sodium hydrosulfide (NaHS), as we have demonstrated thiols to be good nucleophiles for benzothiazole sulfones.³⁰ NaHS gave the isolated sodium sulfinate in good yield (75%) after 24 h (Table 3, entry 1). Benzyl mercaptan (in the presence of Na₂CO₃) also gave an excellent yield after 18 h (entry 2). Sodium hydroxide was shown to be effective for the cleavage of the benzothiazole, but it took even longer (30 h; entry 3). We then turned our attention to NaBH₄, and it gave excellent yields as well as the shortest reaction time. Therefore, we set out to isolate the sulfinate salts produced by the reduction to prove our concept. The reduction proceeded without complication for all of the substrates tested (entries 4–7). Primary benzyl and alkyl substrates reacted in near-quantitative yields (entries 4 and 6). The secondary substrate was also isolated in excellent yield (entry 7).

To demonstrate the usefulness of BTS, we decided to explore the one-pot formation of unsymmetrical sulfones. We found that 1 h of incubation of the benzothiazole sulfones with NaBH₄ in ethanol was efficient to produce the sulfinate salts, but solubility was lacking for the electrophiles. We then found that a 1:1 mixture of ethanol and THF could provide sufficient solubility for both reactants as well as NaBH₄. After 1 h, 1.5 equiv of an electrophile was added, and the mixture was brought to 80 °C and stirred for 12 h. The reaction proceeded in excellent yield for all primary electrophiles (Table 4). Methyl sulfones gave quantitative yields (entries 1 and 2), but the yields were somewhat diminished for pentene substrates (entries 3–5). The benzyl position also gave good yields for both primary and secondary substrates (entries 6 and 7). Overall, this method provides a streamlined approach for producing unsymmetrical sulfones in good yields over three steps.

We next turned our attention to the formation of sulfonamides. Most methods for sulfonamide synthesis proceed through oxidation of thiols or sulfinic acids to sulfonyl chloride or bromide. Therefore, we believed that our new method could provide a simple way to access these sulfur oxidation states efficiently in one pot. We explored several methods of oxidation, finally settling on modifying a previously reported procedure using *m*CPBA as an oxidant in the presence of tetrabutylammonium bromide (TBAB) while using diisopropylethylamine (DIPEA) as a base.⁷ Ethanol and THF were again found to be a suitable solvent system. Overall, this led to modest yields for both primary and secondary amines (Table 5). Benzylamine, cyclohexylamine, and butylamine gave yields of 28–52% (entries 1–3), which were comparable to those of other synthetic strategies for sulfonamidation.³ Secondary amines such as pyrrolidine and morpholine afforded similar

yields (~50%; entries 4 and 5). However, aniline gave no reaction, most likely because of the lack of nucleophilicity of aromatic amines.

In conclusion, we have developed a novel method for the generation of sulfinate salts in two steps under mild, oxidation-free conditions. Utilizing this new method, we were able to synthesize sulfones and sulfonamides in modest to excellent yields in one pot. We believe BTS to be a useful reagent in synthetic chemistry as a protecting group of sulfinic acids that can be removed under mild conditions, providing late-stage functionality to a host of substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A) Traditional Methods

B) Recent Advances

C) This Work:

Scheme 1.

Syntheses of Sulfinic Acids, Sulfones, and Sulfonamides

Table 1

Optimization of the Reaction between BTS and Alkyl Halides

entry	equiv of BTS	equiv of BnBr	time (h)	yield (%)
1	1.0	2.0	1	90
2	1.0	1.0	4	73
3	2.0	1.0	overnight	66
4	3.0	1.0	overnight	85
5	4.0	1.0	1.5	79
6	4.0	1.0	overnight	99

Table 2

Scope of Electrophiles

$$\text{R-X} \xrightarrow[\text{DMF, rt}]{\text{BTS (4 equiv)}} \text{Product}$$

The product is a benzothiazole derivative with a sulfonamide group:

entry	electrophile	product	yield (%)
1		1	99
2		2	95
3		3	99
4		4	95
5		5	97
6		6	91
7		7	98
8		8	95

Table 3

Benzothiazole Removal Conditions

entry	reductant	time (h)	product	yield (%)
1	NaHS	24	10	75
2	BnSH/Na ₂ CO ₃	18	10	91
3	NaOH	30	10	89
4	NaBH ₄	1	10	98
5	NaBH ₄	1	11	98
6	NaBH ₄	1	12	95
7	NaBH ₄	1	13	75

Table 4

One-Pot Trans-Sulfonation from Benzothiazole Sulfones

entry	benzothiazole	R ¹ -X	prod	yield (%)
1	R = PhCH ₂ (1)	CH ₃ I	14	99
2	R = PhCH ₂ CH ₂ (2)	CH ₃ I	15	99
3	R = PhCH ₂ (1)		16	73
4	R = PhCH ₂ CH ₂ (2)		17	79
5	R = PhCH ₂ (1)		18	94
6	R = PhCH ₂ CH ₂ (2)		19	92
7	R = PhCH ₂ (1)		20	70

Table 5

One-Pot Sulfonamidation of Benzothiazole Sulfones

Entry	amine	prod	yield (%)
1		23	52
2		24	28
3		25	42
4		26	50
5		27	48
6		28	N/R