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A mild, efficient method for the synthesis of aromatic and aliphatic sulfonamides

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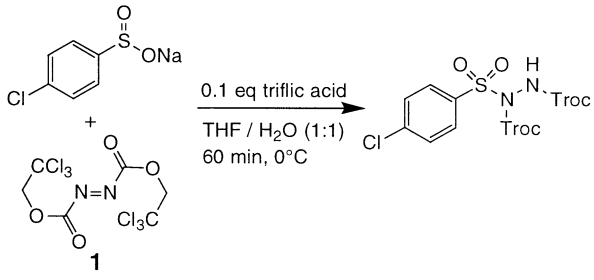
Abstract—A two-step method was developed for the synthesis of aromatic and aliphatic sulfonamides from the corresponding sulfinates using bis(2,2,2-trichloroethyl)azodicarboxylate as the electrophilic nitrogen source. The intermediate sulfonylhydrazides were obtained in very good yields and were cleaved under reductive conditions to deliver the desired sulfonamides. A variety of substituents in the aromatic ring are well tolerated as well as heterocycles. © 2002 Published by Elsevier Science Ltd.

Sulfonamides are widely used as antibacterial agents in the pharmaceutical industry. Traditional synthesis of unsubstituted sulfonamides involve nucleophilic attack by ammonia on a sulfonyl halide.[1] Although this method is efficient, the formation of the sulfonyl chloride is not always possible. Alternatively, arylsulfonyl azides can be reduced to give arylsulfonamides.[2] However, the synthesis of sulfonamide using an electrophilic nitrogen source is not that common. To our knowledge, only one communication has appeared in the literature using hydroxylamine-*O*-sulfonic acid as an electrophile.[3] This reagent is water-soluble and sparingly soluble in organic solvents, resulting in a major drawback for hydrophobic compounds. As an extension to this work and our interest in developing new routes for the formation of sulfonamides, we wish to report a new mild and efficient synthesis for such compounds.

Bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD, **1**) has been used extensively as an electrophilic source of nitrogen in the formation of aromatic amines and phenylhydrazines.[4] We envisaged that we could couple sulfinic acids with azodicarboxylate and then reduce the resulting hydrazide intermediate to provide access to a variety of sulfonamides in a two-step sequence.

We began our study with the commercially available 4-chlorobenzenesulfinic acid sodium salt. Treatment with 1 equiv. of BTCEAD and a catalytic amount of triflic acid gave the corresponding hydrazide in 57% yield after 60 min at 0°C in a THF/H_2O mixture (Scheme 1).[5]



Scheme 1. Synthesis of sulfonylhydrazides from 4-chlorobenzenesulfinate and BTCEAD (**1**).

A variety of reaction conditions were then tested to optimize the yields of sulfonylhydrazides. Efficiency of the hydrazide formation was unaffected by the removal of triflic acid. Using Lewis acids, sodium bicarbonate or others additives did not affect the yields.[6] We observe also that many organic solvents like THF, ether, dioxane and DME were well tolerated for this reaction.[7]

The stoichiometry of **1** was also investigated and 3 equiv. proved to be the best compromise, affording the hydrazide in 87% isolated yield in a shortened 30 min reaction time at 0°C (Method A).[8] Further attempts to lengthen the reaction time or raise the temperature of the reaction only led to reduced yields. A control experiment was performed to test the stability of **1** alone in the THF/H_2O mixture. Surprisingly, the azo-

Keywords: sulfonamides; azodicarboxylate; sulfinate; sulfonylhydrazide; reductive cleavage.

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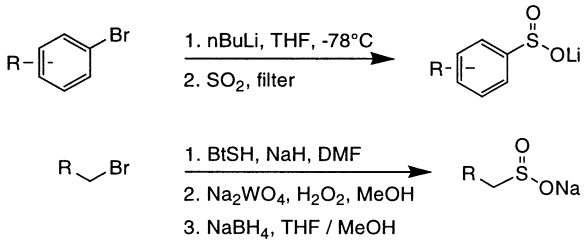
dicarboxylate significantly decomposes upon stirring at 0°C after only a few minutes under these conditions. This finding prompted us to consider a new set of reaction conditions that will remove water from the reaction as well as decrease the amount of **1** required. After many optimization experiments, we found that TFA (1.1 equiv.) with BTCEAD (1.05 equiv.) in THF or DMF at 0°C afforded the corresponding sulfonylhydrazide in excellent yields (Method B). The use of TFA presumably allows the sulfinic acid salt to be protonated and thus improve its solubility in organic solvents.

Since few sulfinic acid salts are commercially available, we have prepared them using two methods (Scheme 2). First, the reaction of organolithium or Grignard reagents with sulfur dioxide affords the sulfinate salt in good yields after addition of hexanes and a simple filtration. If more sensitive substrates are used, an alternative method consists of displacing a halide with the anion of benzothiazoyl. Oxidation of the resulting thioether to the sulfone using sodium tungstate and hydrogen peroxide followed by sodium borohydride cleavage affords the sulfinate salt in excellent yields.

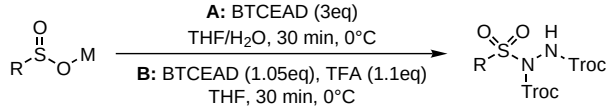


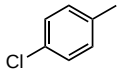
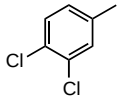
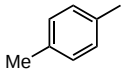
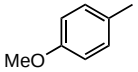
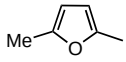
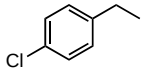
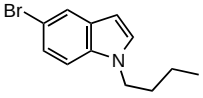
Scheme 2. Preparation of aromatic and aliphatic sulfinic acid salts.

The optimized methods (A or B) were then used for the formation of various hydrazides (Table 1). The reaction proceeded smoothly for aryl sulfinates with an electron withdrawing or electronically neutral substituent. Method A afforded moderate to good yields of the hydrazide in a mild fashion. Alternatively, method B gave excellent yields for nearly all the substrates tested, although the use of TFA can potentially be problematic for acid sensitive substrates.

We also subjected aliphatic sulfinates to our standard conditions, and we were pleased to isolate 58 and 89% of the butyl sulfonylhydrazide (Table 1, entry 7) using methods A and B, respectively. Benzylic sulfinate was obtained by a modified literature procedure and converted to the sulfonylhydrazide in 85% yield using method B.[9] We also decided to investigate the preparation of an indole sulfonylhydrazide that could be problematic to synthesize using conventional method as described earlier (entry 8). The substrate was made using commercially available 4-bromoindole in a four steps sequence.[10] The 4-bromoindolesulfonylhydrazide was then obtained in 81% yield using method B. This example illustrates well the utility of the present method.

Table 1. Synthesis of sulfonylhydrazide



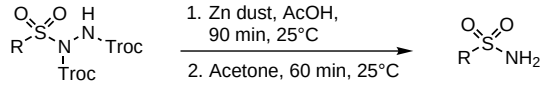
Entry	R	M	Yield (%) [a] A	B
1		Na	93	99
2		Na	87	97
3		Na	61	92
4		Li	36[b]	74
5		Li	46[b]	99[c]
6		Na	--	85
7		Li	58	89
8		Na	--	81

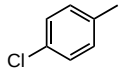
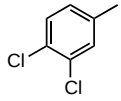
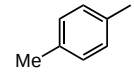
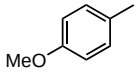
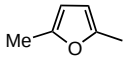
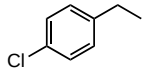
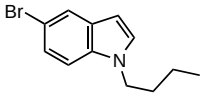
[a] Isolated yield of analytically pure (^{1}H,^{13}C and HRMS) sulfonylhydrazide.
[b] Required purification by reverse phase HPLC.
[c] Product contains 20% of mono cleaved Troc.

We next turned our attention to reduce the sulfonylhydrazides using zinc in acetic acid, but none of the desired sulfonamides was obtained. However, a literature example suggested the addition of acetone after the treatment with zinc and acetic acid.[11] When we implemented these conditions, we obtained the desired sulfonamide in 59% yield. Increasing the amount of acetone used did not affect the yield, but we were able to increase the yield to 73% by doubling the reaction time with zinc. Nevertheless, further increases in the reaction time of either step only resulted in diminished yields. The optimized reaction conditions were then used to cleave the sulfonylhydrazides (Table 2).

With our aromatic substrates, the reaction provided high yields and purity of the sulfonamides after a simple work-up. The one exception to this case was 2-methylfuranyl (Table 2, entry 5) where a mixture of the sulfonamide and the corresponding hydrazone was obtained.[12] When we subjected the butyl and the indole hydrazide (Table 2, entries 7 and 8) to the same condi-

Table 2. Deprotection of sulfonylhydrazides to sulfonamides



Entry	R	Yield (%) [a]
1		80
2		86
3		88
4		99
5		87[b]
6		95
7		82[c]
8		94

[a] Isolated yield of analytically pure (^{1}H, ^{13}C and HRMS) sulfonamide.

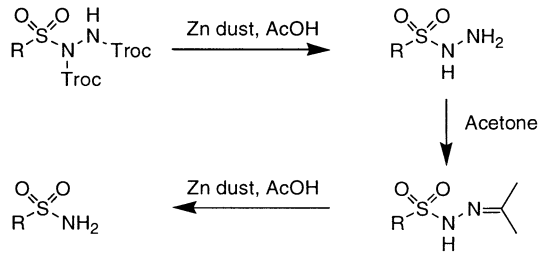
[b] Product contains 10% of the intermediate sulfonylhydrazone.

[c] Water extraction was avoided due to aqueous solubility.

tions, we were pleased to isolate the corresponding aliphatic sulfonamides in 82 and 94% yields, respectively.

Mechanistically, we expect the cleavage of the hydrazide to proceed via a hydrazone intermediate. To test this hypothesis, benenesulfonylhydrazone was synthesized from the corresponding hydrazine. When we subjected this hydrazone to our cleavage conditions, the desired sulfonamide was obtained. Together with spectroscopic data, these results give support for the formation of a hydrazone intermediate in the Zn-mediated cleavage reaction (Scheme 3).

In summary, using aromatic and aliphatic sulfinates, we have developed a mild, two-step method for the formation of the corresponding sulfonamides utilizing BTCEAD as our electrophilic source of nitrogen. Further investigations are under way to extend the scope of this method.



Scheme 3. Proposed mechanism for the cleavage of hydrazide.

Experimental

All compounds gave satisfactory spectral and analytical data.

Typical procedure for hydrazide formation: bis(2,2,2-trichloroethyl) 1-[(4-chlorophenyl)sulfonyl]hydrazine-1,2-dicarboxylate

Method A: BTCEAD (575 mg, 1.51 mmol) was added to a solution of 4-chlorobenzenesulfinic acid sodium salt (100 mg, 0.50 mmol) in a 1:1 THF/H_2O mixture (2.60 mL) at 0°C. The yellow suspension was stirred at 0°C for 30 min and quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted three times with EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (15% EtOAc in hexane) provided the titled hydrazide as a white solid (260 mg, 93%).

Method B: BTCEAD (400 mg, 1.05 mmol) was added to a solution of 4-chlorobenzenesulfinate (200 mg, 1.00 mmol) in 5 mL of anh. THF at 0°C. TFA (85 μL, 1.10 mmol) was then added and the reaction was stirred for 30 min followed by the previous workup. The hydrazide was isolated as a white solid (555 mg, 99%). ^{1}H NMR: (500 MHz, acetone-d_6) δ 10.30 (1H, br s), 8.14 (2H, d, J=8.8 Hz), 7.72 (2H, d, J=8.8 Hz), 4.97 (2H, s), 4.92 (2H, s). ^{13}C NMR: (125 MHz, acetone-d_6) δ 206.2 (2C), 154.7, 150.8, 141.3, 137.2, 131.9, 130.0, 95.8, 94.8, 76.6, 75.5. HRMS calcd for $C_{12}H_9Cl_7N_2O_6S$ (M+K)$^+$: 592.7637. Found: 592.7638. Anal. calcd for $C_{12}H_9Cl_7N_2O_6S$: C, 25.86; H, 1.63; N, 5.03; found: C, 26.05; H, 1.55; N, 5.02%.

Typical procedure for sulfonamide formation: 4-chlorobenzenesulfonamide

Zn dust (309 mg) was added to a solution of the previous hydrazide (103 mg, 0.18 mmol) in AcOH (2 mL) at rt. The suspension was stirred for 1 h prior to dropwise addition of acetone (1 mL). The mixture was stirred for an additional 1 h and CH_2Cl_2 was then added, sonicated 1 min and filtered over a pad of celite. The organic solution was washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give a white solid (25 mg, 80%). ^{1}H, ^{13}C NMR and MS were identical to that of an authentic commercially available sample.

Acknowledgements

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3. Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 1031–1032.
4. (a) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett*. **1993**, *34*, 2441–2444; (b) Mitchell, H.; Leblanc, Y. *J. Org. Chem*. **1994**, 682–687; (c) Leblanc, Y.; Boudreault, N. *J. Org. Chem*. **1995**, 4268–4271; (d) Dufresne, C.; Leblanc, Y.; Berthelette, C.; McCooeye, C. *Synth. Commun*. **1997**, *27*, 3613–3624.
5. Troc: 2,2,2-trichloroethoxycarbonyl (CCl_3-CH_2-COO-).
6. $MgBr_2$-Et_2O, BF_3-Et_2O and $NaHCO_3$ gave 53, 51 and 55% isolated yields, respectively.
7. THF, ether, dioxane and DME gave similar yields.
8. Reaction progress was monitored using time-lapsed IR spectroscopy (React IR).
9. Adapted from (a) Ueno, Y.; Kojima, A.; Okawara, M. *Chem. Lett*. **1984**, 2125–2128; (b) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett*. **2001**, *42*, 5149–5153.
10. Alkylation of the indole was made with 1,3-dibromopropane followed by benzothiolate displacement, oxidation to the corresponding sulfone and formation of the sulfinate by cleavage using sodium borohydride as described in the second part of Scheme 2.
11. Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett*. **1989**, *30*, 2889–2892.
12. Identity of the hydrazone was confirmed by ^1H NMR and MS.