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Articles

Convenient One-Pot Synthesis of Sulfonamides from Thiols and Disulfides Using 1,3-Dichloro-5,5-dimethylhydantoin (DCH)

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A convenient synthesis of sulfonamides from thiols and disulfides is described. *In situ* preparation of sulfonyl chlorides from thiols is accomplished by oxidation with 1,3-dichloro-5,5-dimethylhydantoin (DCH) under *N*-benzyl-trimethylammonium chloride and water. The sulfonyl chlorides are then further allowed to react with excess amine in the same reaction vessel.

Key Words : 1,3-Dichloro-5,5-dimethylhydantoin, Sulfonyl chlorides, Sulfonamides

Introduction

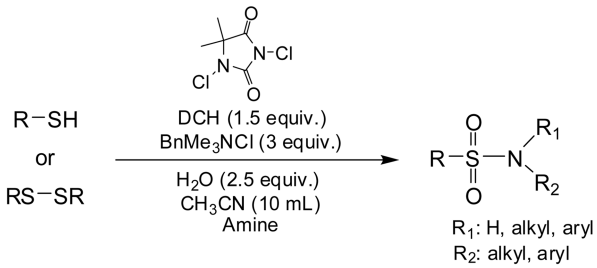
Sulfonamides, an important class of pharmaceutical compounds exhibit a wide spectrum of biological activities.[1] Over 30 drugs containing this functionality are in clinical use, including, antibacterials, diuretics, anticonvulsants, hypoglycemics and HIV protease inhibitors.[2] More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as Alzheimer's disease, arthritis and cancer.[3] Furthermore, sulfonamides were employed as herbicides,[4a] plaguicides,[4b] pesticides[4c] and surfactants.[4c,d]

Frequently, sulfonamides are formed from a sulfonyl chloride and a primary or secondary amines. In turn, sulfonyl chlorides can be prepared from the corresponding thiols using a number of methods, commonly by bubbling Cl_2 gas into aqueous acid or a biphasic mixture containing the thiol.[5-9] Although this methodology is relatively general, issues associated with the use of excess oxidant and/or aqueous acid have prompted the development of alternative methods.[10,11] We describe here an oxidation/substitution sequence that is mild and minimizes both the amount of oxidant required and the aqueous component. Recently, the direct oxidative conversion of thiols into sulfonamides with H_2O_2-$SOCl_2$ was reported by Bahrami and *et al.*[12]

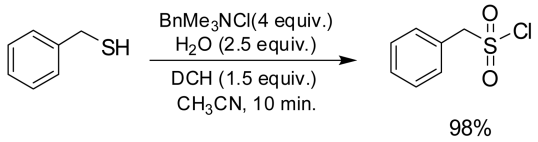
Results and Discussion

Herein, as part of our ongoing study on the application of *N*-halo reagents in organic synthesis,[13-17] we would like to present the direct convenient one-pot synthesis of sulfonamides from thiols and disulfides using 1,3-dichloro-5,5-dimethylhydantoin (DCH) under mild conditions (Scheme 1).

Initially, we surmised that it might be possible to generate controlled amounts of Cl_2 in nonprotic organic solvents by mixing a tetralkylammonium chloride salt with 1,3-dichloro-5,5-dimethylhydantoin (DCH). We were pleased to find that treatment of *N*-benzyl-trimethylammonium chloride ($BnMe_3NCl$) (3 equiv), H_2O (2.5 equiv) with DCH (1.5 equiv) in CH_3CN (10 min, rt) provided a light yellow solution as a good oxidize chlorinating system for the synthesis of benzylsolfunyl chlorides from benzyl thiol under mild conditions (Scheme 2).



Scheme 1. Synthesis of sulfonamides from thiols and disulfides.



Scheme 2. Synthesis of benzylsolfunyl chlorides from benzyl Thiol.

Based on this result, we tried to use this system to *in situ* preparation of sulfonyl chlorides from thiols to synthesis of sulfonamides in one-pot. Subsequent addition of a primary or secondary amine afforded the desired sulfonamide. To optimize the reaction conditions, the reaction of benzyl thiol and benzylamine was selected as model substrate in acetonitrile at room temperature. Repainting the reaction of benzyl thiol (1 equiv), $BnMe_3NCl$ (3 equiv), H_2O (2.5 equiv) with DCH (1.5 equiv) in CH_3CN (10 min, rt) and continual addition of benzylamine (4 equiv, 30 min) gave corresponding sulfonamide in 98% yield.

Table 1. Synthesis of Various Sulfonamides from Thiols and Amines

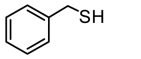
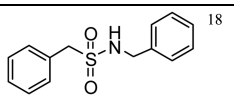
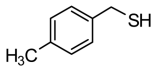
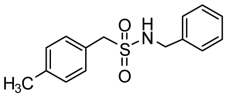
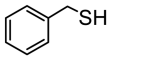
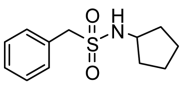
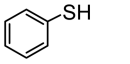
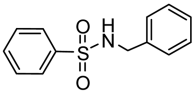
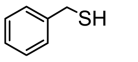
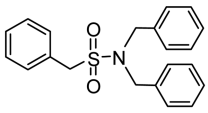
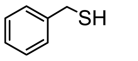
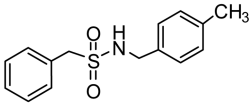
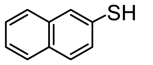
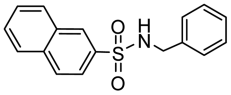
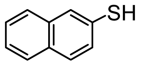
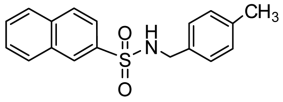
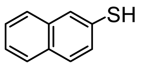
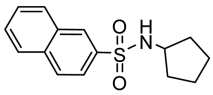
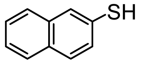
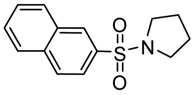
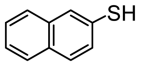
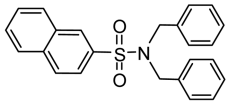
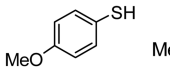
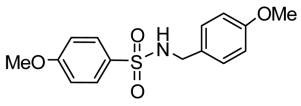
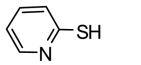
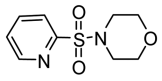
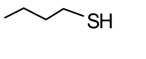
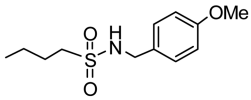
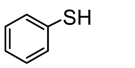
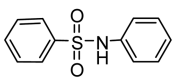
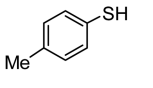
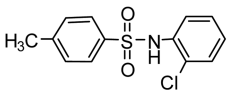
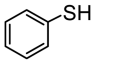
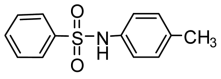
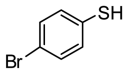
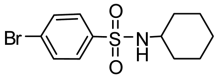
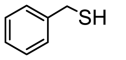
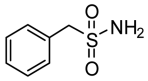
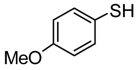
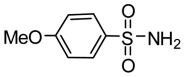
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2			96
3			98
4			96
5			98
6			98
7			92
8			95
9			96
10			92
11			96
12			94
13			80
14			90
15			90
16			96
17			90

Table 1. Continued

Entry	Thiol	Sulfonamide	Yield (%)
18			98
19			96
20			90
21			98

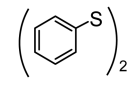
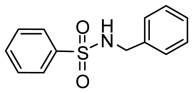
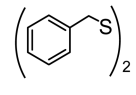
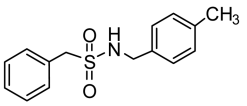
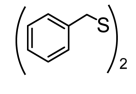
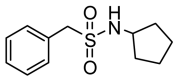
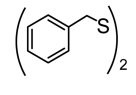
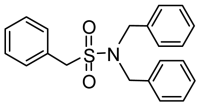
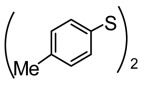
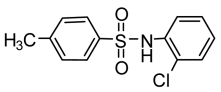
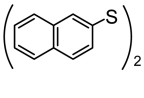
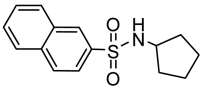
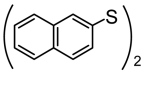
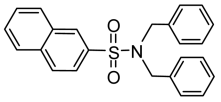
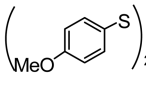
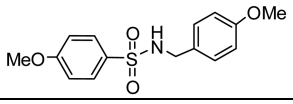
Encouraged by our initial studies, we then investigated the generality and versatility of this procedure using a series of structurally different thiols and amines (commercially available) under these optimized conditions. A combinatorial library (parallel format) of sulfonamides was smoothly prepared in good to high yields and the results are summarized in Table 1. Aryl thiols carrying either electron-donating or electron-withdrawing substituents reacted very well to give the corresponding sulfonamides with equal efficiency. Also, aryl amines appeared to be insensitive to substitution. Primary and secondary alkyl amines and also ammonia undergo this reaction with equal efficiency. 1-Butanethiol (Table 1, entry 14) also was oxidized efficiently.

An investigation into the mechanistic aspects of oxidative chlorination of thiols showed the corresponding disulfide is the main intermediate in this transformation. When the reaction of 4-methoxybenzyl thiol was carried out with 1: 0.15 molar ratios of thiol to DCH in the presence of $BnMe_3NCl$ (1.5 equiv), H_2O (1.5 equiv) in acetonitrile for 5 min, the desired disulfide was obtained as the major product.

In order to further verify the mediation of the disulfides in the oxidative chlorination of thiols, reactions were repeated with a range of symmetrical disulfides to obtain sulphonamides (Scheme 1). After optimizing the reaction in order to identify conditions that consistently produced excellent yields of sulphonamides, we found that the best reaction conditions required the presence of DCH (0.15 equiv), $BnMe_3NCl$ (1.5 equiv), H_2O (1.5 equiv) and disulfide (1 mmol) in acetonitrile at room temperature. The generality and the scope of the reaction were investigated and the results of the study are summarized in Table 2. As shown, all reactions resulted in the formation of the corresponding sulphonamides in excellent yields with high purity. This shows that successive oxidation of the sulfur atom, followed by S–S bond cleavage and subsequent chlorination, and occurs during the direct conversion of thiols into the corresponding sulfonyl chlorides and subsequently to sulphonamides.

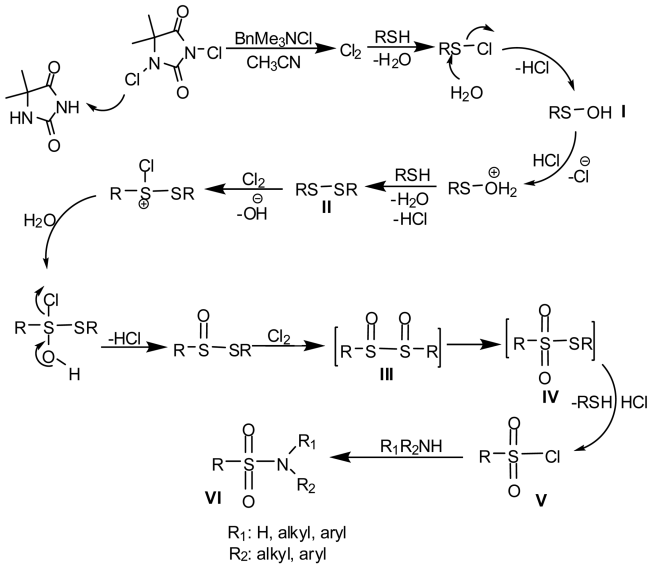
The possible mechanism for this transformation is shown in Scheme 3.[12] Molecular chlorine generated from DCH and $BnMe_3NCl$ effects the oxidative chlorination. It is accep-

Table 2. Synthesis of Sulfonamides from Disulfide

Entry	Disulfide	Sulfonamides	Yield (%)
1			96
2			98
3			98
4			98
5			98
6			98
7			98
8			96

[a]Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

table to assume that the thiol can chlorinate in the presence of chlorine. Therefore, the mechanism proceeds through hydroxylation of thiol leads to the formation of sulfenic acid (I), which gives the corresponding symmetric disulfide (II). Then the successive oxidation of both sulfur atoms of the disulfide molecule by chlorine produces the intermediate (III) that undergoes rapid isomerization to the thiosulfonate (IV), which can easily furnish sulfonyl chloride (V). Then, the sulfonyl chloride (V) reacts with amine o to form the corresponding sulfonamides (VI).



Scheme 3. The possible mechanism for this transformation.

Conclusion

In conclusion, we have developed a mild, one-pot synthetic method for the preparation of alkyl and aryl sulfonamides from thiols and disulfides in the presence of primary and secondary amine derivatives using 1,3-dichloro-5,5-dimethylhydantoin (DCH) in anhydrous acetonitrile. The advantages are excellent yields, the cheapness of the reagents, easy and clean workup, extremely fast reaction, high chemoselectivity, and operation at room temperature. No side reactions/products were observed during the course of the reaction, thus, we believe that the present methodology opens new possibilities for medicinal chemistry and material sciences and could be an important addition to the existing methodologies.

Experimental Section

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purifications unless otherwise stated. ^{1}H NMR spectra were recorded on a Jeol 200 MHz FT NMR spectrometer using TMS as internal standard and chemical shift are in d (ppm). Infrared (IR) was conducted on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

(i) General Procedures for the Conversion of Thiols to Sulfonamides. To a stirred mixture of thiol compond (1 mmol), $BnMe_3NCl$ (3 equiv), and water (2.5 mmol) in CH_3CN (10 mL) at 0 °C, DCH (1.5 equiv) was added as a solid in portions over 1-2 min. After 30 min, amine (4 mmol) was added to the mixture over 1-2 min. The resulting mixture was stirred at room temperature for 30 min. until TLC showed complete disappearance of starting material (Table 1). The mixture was filtered and rinsed twice with CH_3CN (10 mL). The filtrate was evaporated, and the corresponding pure sulfonamide was obtained as a crystalline solid. Recrystallization from a mixture of ethanol and water affords analytically pure product.

(ii) General Procedures for the Conversion of Disulfides to Sulfonamides. To a stirred mixture of thiol compond (1 mmol), $BnMe_3NCl$ (3 equiv), and water (2.5 mmol) in CH_3CN (10 mL) at 0 °C, DCH (1.5 equiv) was added as a solid in portions over 1-2 min. After 30 min, amine (4 mmol) was added to the mixture over 1-2 min. The resulting mixture was stirred at room temperature for 30 min. until TLC showed complete disappearance of starting material (Table 1). The mixture was filtered and rinsed twice with CH_3CN (10 mL). The filtrate was evaporated, and the corresponding pure sulfonamide was obtained as a crystalline solid. Recrystallization from a mixture of ethanol and water affords analytically pure product.

Analytical Data for Selected Compounds (Table 1).

Product (1): IR (KBr): ν_{max} 1138, 1310 cm^{-1} (SO_2), 3287 cm^{-1} (NH). ^1H NMR 200 MHz, $CDCl_3$): δ 4.13 (s, 2H), 4.21 (s, 2H), 7.25-7.38 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.6, 59.3, 128.0, 128.1, 128.5, 128.8, 129.1, 130.6, 133.3, 136.8. Mass (*m/z*): 261, 256, 239, 196, 182, 120, 106, 91, 77, 65.

Product (2): IR (KBr): ν_{max} 1134, 1309 cm^{-1} (SO_2), 3220 cm^{-1} (NH). ^1H NMR 200 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.17 (s, 2H), 4.28 (s, 2H), 7.20-7.58 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.3, 47.4, 59.8, 128.0, 128.1, 128.3, 128.6, 129.3, 130.6, 135.4 136.9. Mass (*m/z*): 276, 275, 260, 210, 184, 120, 105, 91, 77, 65, 41.

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