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Direct conversion of thiols and disulfides into sulfonamides

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ABSTRACT

The H_2O_2–$ZrCl_4$ reagent system is used as a new and efficient reagent for the conversion of thiols and disulfides into sulfonamides. The protocol offers several advantages such as excellent yields of products and extremely fast reactions at room temperature. The reagent system is very easy to handle and is environmentally safe and economical.

1. Introduction

Sulfonamides have long been the subject of pharmaceutical interest as a result of their potent biological activities.[1] A large number of pharmaceutically active compounds contain arylsulfonamide motifs,[2] which are employed in the prevention and treatment of bacterial infections, diabetes mellitus, oedema, hypertension, and gout. Some have proved to be useful as herbicides[3] and plaguicides.[4] Sulfonamide derivatives of azo dyes have been reported to improve light-stability and fibre fixation.[5]

There are various synthetic methods available for the preparation of sulfonamides.[6] The most common involve nucleophilic attack by ammonia or primary or secondary amines on sulfonyl chlorides in the presence of a base. Although this method is efficient, it requires the availability of sulfonyl chlorides.

Recently, we found that the H_2O_2–$ZrCl_4$ system can be used for the conversion of thiols into sulfonyl chlorides,[7] which are important synthetic precursors.[8] As an extension to this work and in continuation of our interest in developing new routes for the formation of sulfonamides,[9] we report a new, mild and efficient synthesis of such compounds via the reaction of amines with thiols in the presence of H_2O_2–$ZrCl_4$ in acetonitrile at room temperature (Scheme 1). To the best of our knowledge such a sulfonamide preparation has not been described in the literature.

Zirconium tetrachloride ($ZrCl_4$) is a promising, mild and selective reagent. Due to its low toxicity, low cost, ease of handling and high activity, the application of $ZrCl_4$ in organic synthesis is of interest.[10,11] However, there are no examples of the use of $ZrCl_4$ as a promoter for the synthesis of sulfonamides.

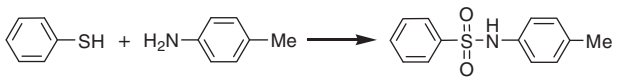
Hydrogen peroxide (H_2O_2) is an attractive and inexpensive oxidant widely used in laboratory and industrial synthesis.[12] The choice of the organic solvent was of particular importance. Acetonitrile and 1,4-dioxane were suitable, giving rise to relatively fast reaction rates at room temperature.

Scheme 1. Synthesis of sulfonamides from thiols.

To optimize the reaction conditions, thiophenol and 4-methylaniline were used as model substrates. The best result was achieved by carrying out using a 3:1:1:1 mole ratio of H_2O_2, $ZrCl_4$, thiophenol and 4-methylaniline in the presence of pyridine (0.5 mL) at 25 °C for 2 min with acetonitrile as solvent (Table 1).

This method was then applied to a variety of commercially available thiols and amines. As can be seen from the results in Table 2, aryl thiols possessing either electron-donating or electron-withdrawing substituents reacted very well to give the corresponding sulfonamides. Furthermore 2-naphthyl thiol and

Table 1
Optimization of the reaction conditions[a]



Entry	$ZrCl_4$ (mmol)	30% H_2O_2 (mmol)	Yield%[b]
1	0.5	4	40
2	0.7	4	57
3	0.8	4	80
4	1	2	70
5	1	3	98
6	1	4	98

[a] Reaction conditions: thiophenol (1 mmol), 4-methylaniline (1 mmol), pyridine (0.5 mL) as base, 2 min, 25 °C.
[b] Isolated yield.

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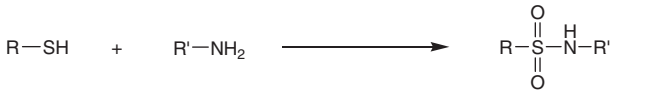
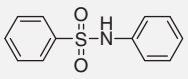
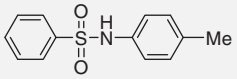
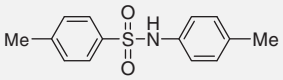
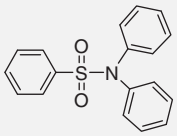
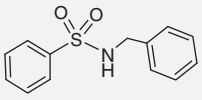
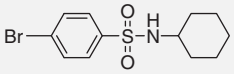
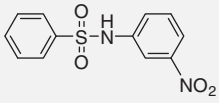
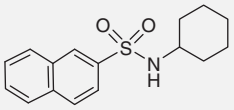
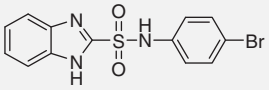
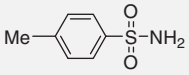
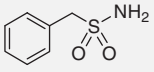
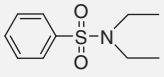
Table 2
Formation of sulfonamides from various thiols and amines[a]



Entry	Sulfonamide	Time (min)	Yield[b] (%)	Ref.
1		2	98	15
2		2	98	15
3		2	97	15
4		3	96	16
5		2	99	17
6		3	96	–
7		3	97	–
8		2	96	–
9		3	91	9
10		2	99	18a
11		3	99	18b
12		3	97	18c

[a] The purified products were characterized by mp and ^{1}H and ^{13}C NMR spectroscopy.
[b] Yield refers to pure isolated product.

benzyl thiol afforded the corresponding sulfonamides in excellent yields (Table 2, entries 8 and 11). Benzimidazole-2-sulfonyl chloride is unstable at room temperature and rapidly decomposes to 2-chlorobenzimidazole and 2-hydroxybenzimidazole,[6a] whereas the reaction of 2-mercaptobenzimidazole with 4-bromoaniline, contrary to our expectation, gave an excellent yield of product (Table 2, entry 9). It is noteworthy that this rapid reaction permits formation of the corresponding heterocyclic sulfonamide.

Aromatic amines possessing either electron-donating or electron-withdrawing substituents reacted efficiently and gave excellent yields. Also, aryl amines appeared to be insensitive to substitution. Ammonia and primary and secondary alkyl amines gave excellent yields of sulfonamides. Interestingly, this method proved to be very useful even for sterically hindered amines such as diphenylamine and diethylamine, the corresponding sulfonamides were obtained in 96% and 97% yields, respectively (Table 2, entries 4 and 12). The mechanism for the reaction was studied by NMR and sulfonyl chloride was confirmed as the reaction intermediate.

Disulfides are important compounds possessing unique and diverse chemistry in the synthetic and biochemical areas.[13] The disulfide bond is strong, the typical bond dissociation energy being 60 kcal/mol. Being about 40% weaker than C–C and C–H bonds, the disulfide bond is thus often the 'weak link' in many molecules. Furthermore, reflecting the polarizability of divalent sulfur, the S–S bond is susceptible to scission by polar reagents, both electrophiles and especially nucleophiles.[14]

In a recent Letter,[7] we demonstrated the intermediacy of disulfides in the oxidative chlorination of thiols using H_2O_2–$ZrCl_4$. Therefore, the reactions were repeated with various symmetric disulfides (Scheme 2). The optimum conditions required 30% H_2O_2 (2 mmol), $ZrCl_4$ (1 mmol), disulfide (1 mmol), amine (2 mmol) and pyridine (0.5 mL) in acetonitrile at room temperature.

The generality and scope of the reaction were investigated and a series of sulfonamides having different steric and electronic properties were synthesized (Table 3). The sulfonamides were obtained in excellent yields and with high purity.

In conclusion, a simple and convenient method for the synthesis of sulfonamides utilizing H_2O_2–$ZrCl_4$ has been established. The protocol offers several advantages such as excellent yields of products and extremely fast reactions at room temperature. Most importantly, the reagent system is very easy to handle, environmentally safe and economical. Further investigations into the scope and synthetic applications of this reaction are currently under investigation in our laboratory.

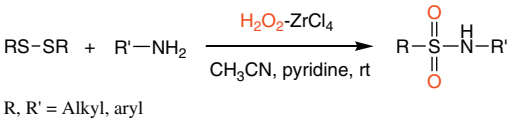
2. General procedure for the synthesis of sulfonamides

A mixture of thiol (1 mmol), H_2O_2 (30%, 3 mmol, 0.3 mL) and $ZrCl_4$ (1 mmol, 0.233 g) was stirred in CH_3CN at 25 °C for the appropriate period of time. After consumption of the thiol as indicated by TLC, a solution of amine (1 mmol) in pyridine (0.5 mL) was added. The resulting mixture was stirred at room temperature until TLC showed complete disappearance of substrates. The mixture was acidified with 2 N HCl and extracted with EtOAc (4 × 5 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. The filtrate was evaporated and the corresponding sulfonamide was obtained as a crystalline solid. Recrystallization from a mixture of EtOH and H_2O gave the analytically pure product. An identical procedure was employed using disulfide (1 mmol), amine (2 mmol), 30% H_2O_2 (2 mmol, 0.2 mL) and $ZrCl_4$ (1 mmol, 0.233 g) for the conversion of disulfides into sulfonamides.

The known compounds were characterized easily by comparison with authentic samples (^{1}H NMR, ^{13}C NMR, mp). Spectral and analytical data for new compounds follow.

2.1. *N*-Cyclohexyl-4-bromobenzenesulfonamide (Table 2, entry 6)

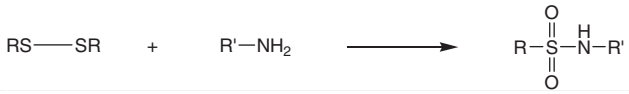
Mp = 100 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (m, 5H), 1.53–1.74 (m, 5H), 3.10 (m, 1H), 4.96 (d, 1H, J = 7.5 Hz, NH), 7.63 (d, 2H, J = 8 Hz), 7.75 (d, 2H, J = 8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6, 25.0, 33.8, 52.7, 127.3, 128.5, 132.3, 140.6. Anal. Calcd for $C_{12}H_{16}NSO_2Br$: C, 45.28; H, 5.03; N, 4.40; S, 10.06. Found: C, 45.25; H, 5.01; N, 4.23; S, 9.77.

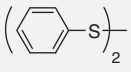
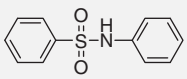
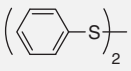
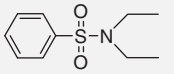
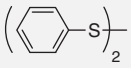
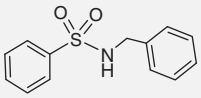
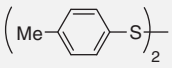
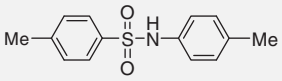
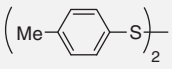
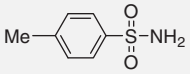
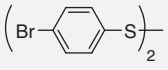
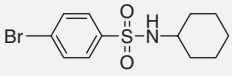
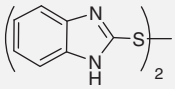
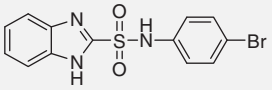
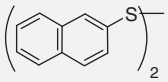
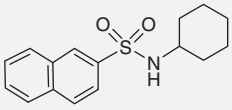
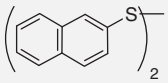
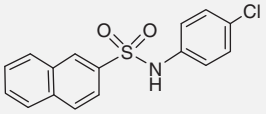
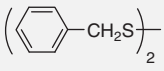
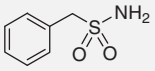


R, R' = Alkyl, aryl

Scheme 2. Synthesis of sulfonamides from disulfides.

Table 3
Formation of sulfonamides from various disulfides and amines[a]



Entry	Disulfide	Sulfonamide	Time (min)	Yield[b] (%)
1			2	97
2			2	95
3			1	99
4			2	97
5			1	98
6			2	98
7			2	92
8			2	96
9			2	95
10			1	99

[a] The purified products were characterized by mp and ^1H and ^{13}C NMR spectroscopy.
[b] Yield refers to pure isolated product.

2.2. *N*-3-(Nitrophenyl)benzenesulfonamide (Table 2, entry 7)

Mp = 134 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.43–7.63 (m, 6H), 7.84–7.86 (m, 1H), 7.87–7.79 (m, 1H), 7.93–7.97 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 114.8, 119.4, 125.9, 126.8, 129.0, 129.9, 133.3, 137.4, 137.9, 148.3. Anal. Calcd for $C_{12}H_{10}N_2SO_4$: C, 51.80; H, 3.59; N, 10.07; S, 11.51. Found: C, 51.45; H, 3.63; N, 10.06; S, 11.13.

2.3. *N*-Cyclohexyl-2-naphthalenesulfonamide (Table 2, entry 8)

Mp = 128–130 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.15–1.77 (m, 10H), 3.19 (m, 1H), 4.65 (br s, 1H, NH), 7.57–7.69 (m, 2H), 7.82–7.98 (m, 4H), 8.46 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.2, 33.7, 52.5, 122.7, 127.3, 128.0, 128.2, 129.0, 129.6, 129.7, 132.2, 134.4, 139.7. Anal. Calcd for $C_{16}H_{19}NSO_2$: C, 66.44; H, 6.57; N, 4.84; S, 11.07. Found: C, 66.17; H, 6.39; N, 4.56; S, 10.68.

2.4. *N*-4-Chlorophenyl-2-naphthalenesulfonamide (Table 3, entry 9)

Mp = 115 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.12 (d, 2H, J = 8.9 Hz), 7.25 (d, 2H, J = 8.9 Hz), 7.57–8.13 (m, 6H), 8.43 (d, 1H, J = 1.3 Hz), 10.56 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 122.0, 122.3, 128.2, 128.3, 128.5, 128.6, 129.5, 129.6, 129.7, 130.0, 132.0, 134.7, 136.6, 137.1. Anal. Calcd for $C_{16}H_{12}NSO_2Cl$: C, 60.48; H, 3.78; N, 4.41; S, 10.07. Found: C, 60.31; H, 3.87; N, 4.14; S, 9.88.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.056.

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