One-Pot Synthesis of Sulfonamides and Sulfonyl Azides from Thiols using Chloramine-T

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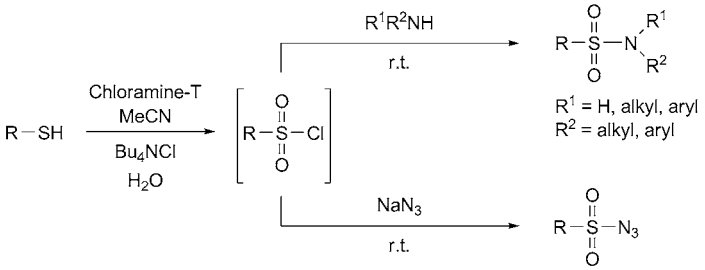
A convenient synthesis of sulfonamides and sulfonyl azides from thiols is described. *In situ* preparation of sulfonyl chlorides from thiols was accomplished by oxidation with chloramine-T (= *N*-chlorotosylamide = *N*-chloro-4-methylbenzenesulfonamide), tetrabutylammonium chloride (Bu_4NCl), and H_2O. The sulfonyl chlorides were then further allowed to react with excess amine or NaN_3 in the same pot.

Introduction. – Frequently, sulfonamides are formed from a sulfonyl chloride, and a primary or secondary amine. 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 [1]. 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 [2]. Recently, the direct oxidative conversions of thiols to sulfonamides using various catalysts were reported [3].

The most practical method for preparing sulfonyl azides involves the reaction of sulfonyl chlorides with azides [4]. The reaction requires the availability of sulfonyl chlorides, which are troublesome to prepare and handle. Generally, sulfonyl chlorides are prepared by treating sulfonic acids with chlorinating agents such as $SOCl_2$ [5], $POCl_3$ [6], PCl_5 [7], triphosgene [8], and cyanuric chloride [9]. A convenient one-pot synthesis of sulfonyl azides from sulfonic acids was reported by *Kim* and *Jang* [10].

Results and Discussion. – Herein, as part of our ongoing study on the application of *N*-halogen reagents in organic synthesis [11], we present the direct convenient one-pot synthesis of sulfonamides and sulfonyl azides from thiols using chloramine-T (= *N*-chlorotosylamide = *N*-chloro-4-methylbenzenesulfonamide) under mild conditions (*Scheme 1*).

Scheme 1



Initially, we surmised that it might be possible to generate controlled amounts of Cl_2 in nonprotic organic solvents by mixing a tetraalkylammonium chloride with chloramine-T. Indeed, we found that treatment of Bu_4NCl (3 equiv.) and H_2O (2.5 equiv.) with chloramine-T (3 equiv.) in MeCN (20 min, room temperature) provided a light yellow solution as a good oxidizing and chlorinating system to afford phenylmethanesulfonyl chloride from phenylmethanethiol under mild conditions. Based on this result, we studied the use of this system for the *in situ* preparation of sulfonyl chlorides from thiols to synthesize sulfonamides in one pot. Subsequent addition of a primary or secondary amine afforded the desired sulfonamide. To optimize the reaction conditions, the reaction of phenylmethanethiol and benzylamine in MeCN at room temperature was selected as model. Repeating the reaction of phenylmethanethiol (1 equiv.) and Bu_4NCl (4 equiv.), H_2O (2.5 equiv.) with chloramine-T (3 equiv.) in MeCN (20 min, room temperature), followed by addition of benzylamine (4 equiv., 20 min), provided the corresponding sulfonamide in 98% yield.

Encouraged by our initial studies, we then investigated the generality and versatility of this procedure by using a series of structurally different thiols and amines (commercially available) under these optimized conditions. A combinatorial library (parallel format) of sulfonamides was prepared in good-to-high yields. The results are compiled in *Table 1*. Arenethiols carrying either electron-donating or electron-withdrawing substituents reacted smoothly to give the corresponding sulfonamides with equal efficiency. Also, areneamines appeared to be insensitive to substitution. Primary and secondary alkenamines and also NH_3 undergo this reaction with equal efficiency. Butane-1-thiol (*Table 1*, *Entry 9*) also was oxidized efficiently.

The present system was further examined for the synthesis of sulfonyl azides from thiols in excellent yield. The results are collected in *Table 2* (*Entries 1–8*). We developed a one-pot process for preparing sulfonyl azides from thiols with chloramine-T, Bu_4NCl, and H_2O. The reaction offers convenience, efficiency, and generality for the preparation of sulfonyl azides from various thiols. Employing less toxic reagents render this process attractive from the standpoint of environmental protection.

A plausible mechanism for this transformation is presented in *Scheme 2*. Molecular Cl_2 generated from chloramine-T and Bu_4NCl effects the oxidative chlorination. It is assumed that the thiol can be chlorinated in the presence of Cl_2. Therefore, the mechanism proceeds through hydroxylation of thiol, leading to the formation of sulfenic acid **I**, which gives the corresponding symmetric disulfide **II**. Then, the successive oxidation of both S-atoms of the disulfide by HOCl affords the intermediate

Table 1. *Synthesis of Various Sulfonamides* ($R–SO_2–NR^1R^2$) *from Thiols* (R–SH) *and Amines* (R^1R^2NH)

Entry	R	R^1	R^2	Time [min]	Yield [%]
1	$PhCH_2$	$PhCH_2$	H	40	98
2	$PhCH_2$	cyclopentyl	H	0.7	98
3	$PhCH_2$	4-Me–C_6H_4–CH_2	H	1.2	98
4	Naphthalen-2-yl	$PhCH_2$	H	2	90
5	Naphthalen-2-yl	cyclopentyl	H	1.5	92
6	Naphthalen-2-yl	$PhCH_2$	$PhCH_2$	2	90
7	4-MeO–C_6H_4	4-Me–C_6H_4–CH_2	H	2	94
8	Pyridin-2-yl	–$CH_2CH_2OCH_2CH_2$–		2	90
9	Bu	4-Me–C_6H_4–CH_2	H	1.5	90
10	Ph	Ph	H	1	98
11	4-Me–C_6H_4	2-Cl–C_6H_4	H	1	96
12	Ph	4-Me–C_6H_4	H	1.2	90
13	4-Br–C_6H_4	Cyclohexyl	H	1	98
14	$PhCH_2$	H	H	1	96
15	4-MeO–C_6H_4	H	H	1	90
16	Ph	Et	Et	1	98

Table 2. *Synthesis of Various Sulfonyl Azides*[a]) *from Thiols*

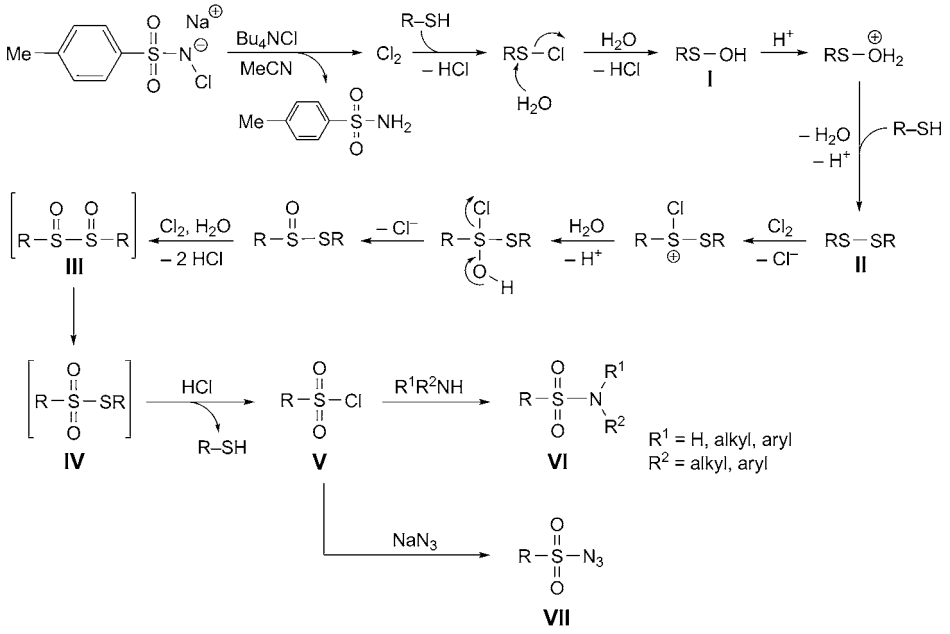
Entry	Sulfonyl azide	Time [min]	Yield [%]	Ref.
1	$PhCH_2–SO_2–N_3$	45	98	[10]
2	$Ph–SO_2–N_3$	60	98	[10]
3	4-Me–C_6H_4–$SO_2–N_3$	45	98	[10]
4	4-MeO–C_6H_4–$SO_2–N_3$	60	92	[10]
5	4-Cl—C_6H_4–$SO_2–N_3$	45	95	[10]
6	4-NO_2–C_6H_4–$SO_2–N_3$	90	88	[3a]
7	(Naphthalene-1-yl)–$SO_2–N_3$	45	90	[10]
8	Et–$SO_2–N_3$	70	85	[10]

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

III that undergoes rapid isomerization to the thiosulfonate **IV**, which can easily furnish sulfonyl chloride **V**. Then, **V** reacts with with amine or azide to form the corresponding sulfonamides **VI** or sulfonyl azides **VII**, respectively.

In conclusion, we have developed a mild, one-pot procedure for the preparation of alkene- and arenesulfonamides from thiols in the presence of primary and secondary amines by using readily available chloramine-T in MeCN. Also, we have developed a one-pot process for preparing sulfonyl azides from thiols under these conditions in the presence of NaN_3. The advantages are excellent yields, the inexpensiveness and availability 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. Therefore, we assume that this methodology would open new possibilities for medicinal chemistry and material sciences and could be an important contribution to the existing procedures.

Scheme 2



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Experimental Part

General. Chemicals were obtained from *Merck* and *Fluka*. M.p.: *Stuart SMP3* apparatus; uncorrected. IR Spectra: *Shimadzu-435-U-04* spectrophotometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker* FT NMR spectrometer, at 200 and 50 MHz in $CDCl_3$, δ in ppm rel. to Me_4Si as internal reference, *J* in Hz. MS: *MAT 8200 Finnigan* high-resolution mass spectrometer; *m*/*z*.

General Procedure for the Conversion of Thiols to Sulfonamides. To a stirred mixture of thiol (1 mmol), Bu_4NCl (4 mmol), and H_2O (2.5 mmol) in MeCN (10 ml) at 0°, chloramine-T (3 equiv.) was added as a solid in portions over 1–2 min. After 30 min, the amine (1 mmol) was added to the mixture over 1–2 min. The resulting mixture was stirred at r.t. until TLC showed complete disappearance of starting material (*Table 1*). The mixture was filtered and rinsed twice with MeCN (10 ml). The filtrate was evaporated, and the corresponding pure sulfonamide was obtained as a crystalline solid. Recrystallization from EtOH/H_2O afforded anal. pure product.

General Procedure for the Conversion of Thiols to Sulfonyl Azides. To a stirred mixture of thiol (1 mmol), Bu_4NCl (4 mmol), and H_2O (2.5 mmol) in MeCN (5 ml) at 0°, chloramine-T (3 equiv.) was added as solid in portions over 1–2 min. After 30 min, NaN_3 (2.2 mmol) was added to the mixture over 1–2 min. The resulting mixture was stirred at r.t. for 3 h. The mixture was diluted with CH_2Cl_2 (15 ml) and washed with H_2O (5 ml). The org. layer was dried ($MgSO_4$). After filtration, the solvent was removed, and the residue was purified by column chromatography (CC; SiO_2; hexane/AcOEt 20:1) to give the corresponding sulfonyl azide in good-to-excellent yield.

Data for Selected Compounds. N-*Benzyl-1-phenylmethanesulfonamide* (*Entry 1*, *Table 1*): IR: 1138, 1310 (SO_2), 3287 (NH). ^{1}H-NMR: 4.13 (*s*, 2 H); 4.21 (*s*, 2 H); 7.25–7.38 (*m*, 10 H). ^{13}C-NMR: 47.6; 59.3; 128.0; 128.1; 128.5; 128.8; 129.1; 130.6; 133.3; 136.8. MS: 261, 256, 239, 196, 182, 120, 106, 91, 77, 65. Anal. calc. for $C_{14}H_{15}NO_2S$: C 64.34, H 5.79, N 5.36; found: C 64.65, H 5.70, N 5.18.

N,N-*Dibenzylnaphthalene-2-sulfonamide* (*Entry 6*, *Table 1*): IR: 1157, 1329 (SO_2). ^{1}H-NMR: 4.38 (*s*, 4 H); 7.09–7.66 (*m*, 10 H); 7.78–7.98 (*m*, 6 H); 8.39 (*s*, 1 H). ^{13}C-NMR: 50.5; 123.4; 127.6; 128.3; 128.6; 128.7; 129.0; 129.3; 131.3; 132.5; 134.8. MS: 387, 318, 296, 254, 196, 159, 127, 115, 91, 77, 65, 43. Anal. calc. for $C_{24}H_{21}NO_2S$: C 74.39, H 5.46, N 3.61; found: C 74.22, H 5.60, N 3.65.

4-Methoxy-N-*(4-methoxybenzyl)benzenesulfonamide* (*Entry 7*, *Table 1*): IR: 1154, 1325 (SO_2), 3280 (NH). ^{1}H-NMR: 3.79 (*s*, 3 H); 3.91 (*s*, 3 H); 4.08 (*s*, 2 H); 6.82–7.52 (*m*, 8 H); 7.82 (*s*, 1 H). ^{13}C-NMR: 46.8; 55.3; 55.6; 114.1; 114.3; 128.4; 129.3; 129.3; 131.6; 159.4; 163.0. Anal. calc. for $C_{15}H_{17}NO_4S$: C 58.61, H 5.57, N 4.56; found: C 58.76, H 5.56, N 4.81.

N-*(2-Chlorophenyl)-4-methylbenzenesulfonamide* (*Entry 11*, *Table 1*): IR: 1108, 1373 (SO_2), 3258 (NH). ^{1}H-NMR: 2.36 (*s*, 3 H); 6.95–7.06 (*m*, 2 H); 7.15–7.22 (*m*, 4 H); 7.60–7.62 (*m*, 3 H). ^{13}C-NMR: 22.5; 122.8; 125.5; 126.3; 127.9; 128.3; 129.8; 130.2; 133.9; 136.3; 144.8.

4-Bromo-N-*cyclohexylbenzenesulfonamide* (*Entry 13*, *Table 1*): IR: 1155, 1386 (SO_2), 3242 (NH). ^{1}H-NMR: 1.20–1.43 (*m*, 5 H); 1.54–1.79 (*m*, 5 H); 3.22–3.54 (*m*, 1 H); 4.98 (*d*, $J = 7$, NH); 7.72 (*d*, $J =$ 6.8, 2 H); 7.81 (*d*, $J = 6.8$, 2 H). ^{13}C-NMR: 24.8; 25.32; 33.8; 52.7; 127.3; 128.6; 132.3; 140.6.

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