A Simple Method for the Preparation of *N*-Sulfonylsulfilimines from Sulfides†

Andreas L. Marzinzik‡ and K. Barry Sharpless*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037

sharples@scripps.edu

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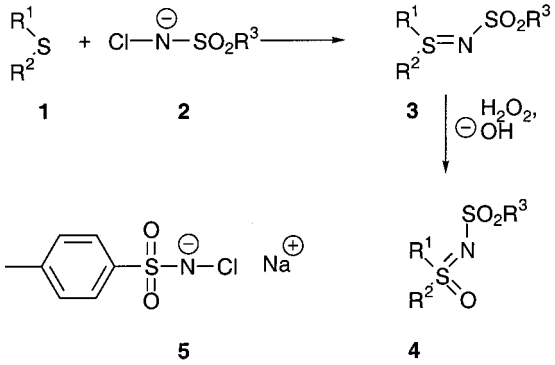
While excellent methods exist for the oxidation of sulfides to sulfoxides $R^1R^2S \rightarrow R^1R^2SO$, the aza-version of this atom transfer redox process, i.e., $R^1R^2S \rightarrow R^1R^2S{=}N{-}SO_2R^3$, has been less reliable. In sulfilimine synthesis, sulfoxide has been an inevitable byproduct in all cases to date, and the yields of sulfilimine have varied widely. A nearly ideal procedure for the sulfide to sulfonyl sulfilimine transformation is described. Almost quantitative yields are achieved from a diverse set of sulfides and a broad range of the readily available sulfonyl nitrenoid sources known as chloramine salts (R^3SO_2NClNa), essentially by simply stirring them together in acetonitrile.

Introduction

While excellent methods exist for the oxidation of sulfides to sulfoxides,[1] $R^1R^2S \rightarrow R^1R^2SO$, the aza-version of this atom transfer redox process, i.e., $R^1R^2S \rightarrow R^1R^2S{=}N{-}SO_2R^3$, is not yet as reliable.[2] Of course, the latter transformation is made more complex by nitrogen's extra valence, but this same feature also provides a nexus for structural enrichment not available with the oxygen analogue. Interest in sulfilimines and the derived sulfoximines is growing rapidly thanks to their use in organic synthesis[3] and applications based on their inherent biological activities.[4] Three research groups have been largely responsible for pioneering and developing the sulfilimine field.[5] Emerging from their efforts is the best general method for the synthesis of sulfilimines **3** and thence the related sulfoximines **4** (Scheme 1).

By far the most common *N*-haloamide salt (**2**) used in these oxidations is Chloramine-T (**5**). Among the various procedures, the best results are reported when R^3 is arenesulfonyl, as in **5**, and when dry solvent and anhydrous samples of the chloramine salts are used to curtail sulfoxide formation. In any case, to the best of our knowledge, the sulfoxide has been an inevitable byproduct in all procedures reported to date, and the yields of sulfilimine have varied widely (10−90%).[6] It is in this light and, not without trepidation given the seemingly "trivial" basis for the advance (i.e., use of CH_3CN as solvent), that we report a dramatically improved process for the sulfide → sulfilimine (**1** → **3**) conversion.

Scheme 1



Discussion

Upon first encountering the facility with which sulfonyl sulfilimines are produced upon exposure of sulfides to salts **2** in pure acetonitrile, we assumed this simple fact was known. However, the closest report we have found was by Taylor et al. in 1997.[7] These authors described using salts **2** in pure acetonitrile solvent but always with "catalytic" amounts of CuOTf present. However, we find that the presence of the CuOTf is highly deleterious to the reaction, as evident from the reported yields and product mixtures, and which we confirmed in several control experiments following the described procedures.[8]

We find that with a slight excess of the *N*-chlorosulfonamide salt (1.2 equiv, $R^3SO_2N{-}ClNa$), the reactions proceed readily to completion. Product isolation is easy. CH_2Cl_2 is simply added to the heterogeneous reaction mixture, and an excess of the chloramine salt **2** joins the NaCl precipitate, whereupon both are removed by filtration. Virtually pure product remains after concentration

† Dedicated to Carl R. Johnson for for his pioneering work on the fascinating and important chemistry of sulfilimines.

‡ Novartis Pharma AG, CH-4002 Basel, Switzerland.

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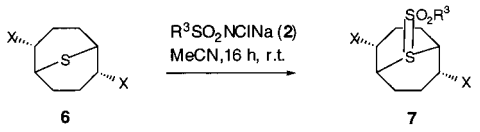
Table 1. Reaction of 9-Thiabicyclo[3.3.1]nonanes (6) with Sodium *N*-Chlorosulfonamides

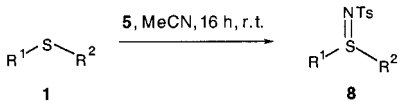


6 **7**

entry	X	R^3	compd	yield, %[a]	mp (°C)
1	Cl	Ph	**7a**	86	67
2	H	Ph	**7b**	95	118
3	Cl	2-$O_2NC_6H_4$	**7c**	93	230
4	Cl	Me	**7d**	99	223
5	Cl	4-Me-C_6H_4	**7e**	97	183
6	OH	4-Me-C_6H_4	**7f**	98	130
7	N_3	4-Me-C_6H_4	**7g**	92	162

[a] Isolated yields of pure products after recrystallization.

Table 2. Reaction of Acyclic Sulfides with Chloramine-T Trihydrate



1 **8**

entry	R^1	R^2	compd	yield, %[a]	mp °C [°C][b]
1	Me	4-$CH_3C_6H_4$	**8a**	98	115−117 [121−122[11]]
2	Me	*t*-Bu	**8b**	98	85−86 [89−90[9]]
3	Ph	Bn	**8c**	95	142 [146−147[12]]
4	Et	CH_2CH_2OH	**8d**	70	85 [85−86[5a]]
5	Bn	Bn	**8e**	76	185 [190−191[5a]]
6	Ph	Ph	**8f**	86	108 [110−111[5a]]
7	Me	4-$O_2NC_6H_4$	**8g**	99	150 [not reported[15b]]

[a] Isolated yields of pure products after crystallization. [b] Measured/literature.

of the filtrate. The attractiveness of this route to sulfilimines is further enhanced by its lack of sensitivity to water. Thus, off the shelf reactants and solvents gave excellent results in reactions performed open to the atmosphere.

Sulfilimines are first mentioned in a 1917 report on the reaction of mustard gas with Chloramine-T.[9] Coincidentally, we also encountered this improved sulfilimine synthesis in studies on mustard derivatives. Table 1shows the yields of sulfilimines derived from some 2,6-substituted 9-thiabicyclo[3.3.1]nonanes (**6**) with several chloramine salts (2-NsNClNa and CH_3SO_2NClNa are not commercially available; they were prepared by published procedures).[10] Interestingly, although 2,6-dichloro-9-thiabicyclo[3.3.1]nonane (**6a**) is a reactive mustard electrophile (in fact, all of the other bicyclic precursors **6b**−**g** arise in mustard-enabled substitution processes from **6a**), only traces of products resulting from $TsNCl^-$ substitution could be detected, indicating that sulfilimine formation is a fast process and that, after sulfilimine formation, anchimeric assistance by the sulfur is shut down.

Entry 4, in which the simplest alkyl analogue **7d** is obtained in excellent yield and purity by the standard procedure, suggests that this new process will not be limited to arenesulfonamides. Functional groups such as aliphatic secondary alcohols and azides do not interfere with the reaction. Thus, the diol **7f** and diazide **7g** were formed free of any side product (entries 6 and 7).

The preliminary results suggest that this method for preparing *N*-sulfonylsulfilimines is the best available to date. For example, three of the monomethyl sulfides in Table 2 (entries 1, 2, and 7) furnished products in ≥98% yield. Reaction of benzyl phenyl sulfide provided the corresponding sulfilimine **8c** in 95% yield. Tosylimination of sulfides bearing functional groups on the β-carbon often gives low yields in the traditional procedures.[11−13] Utilizing the new method, ethyl 2-hydroxyethyl sulfide gave the corresponding sulfilimine **8d** in 70% yield. With dibenzyl sulfide (entry 5), sulfoxide side product was detected by LC/MS. However, sulfonyl sulfilimines tend to be crystalline, and a single recrystallization in this case gave pure **8e** in 76% yield. Diaryl sulfides are reported to require phase-transfer catalysts for achieving complete conversion.[14] In fact, reaction of diphenyl sulfide in acetonitrile with **5** at rt for 16 h led to only 20% conversion. However, nearly complete conversion to *S,S*-diphenyl-*N*-tosylsulfilimine (**8f**) was observed under otherwise identical conditions when a few drops of AcOH were added at the start. Unfortunately, this also caused some sulfoxide to form. We then found that sulfoxide formation could be almost completely suppressed by heating at reflux for 2 h (entry 6) without acid catalyst. Use of 20% excess of the chloramine salt **2** (i.e., 1.2 equiv) ensures more rapid completion of the reaction (generally ca. 1 h at rt for dialkyl and alkyl aryl sulfides). With only 1 equiv of **2**, incomplete conversion even after 24 h was noted. Among all the sulfide substrates tried, only di-*tert*-butyl sulfide did not produce the corresponding sulfilimine.

Most of the mechanisms proposed to date[15] involve an $RR'S-Cl^+$ intermediate which accounts for the formation of sulfoxides as byproducts when water is present. In any case, the published mechanistic rationales are not always in accord with the experimental data,[16] especially regarding the observed diastereoselectivity in relevant cases. Under the present conditions, i.e., acetonitrile as solvent, no sulfoxide was detected even when water was intentionally added to the reaction mixture. The synthesis of compound **8a** was performed in 5, 10, and 15% water/acetonitrile mixtures. No sulfoxide formation was observed, which also explains why this procedure gives equally good results when chloramine salts **2** are used in either their anhydrous form or as hydrates. Thus, the only concern about the degree of hydration of salts **2** is the uncertainty it engenders in stoichiometry calculations. The latter concern is not serious since the 20% excess of salt **2** used should cover most conceivable hydration scenarios.

In a 1986 study on the diastereoselectivity of sulfilimine formation from sulfide **9** using **5** in methanol ("traditional procedure") the authors observed an *anti*-

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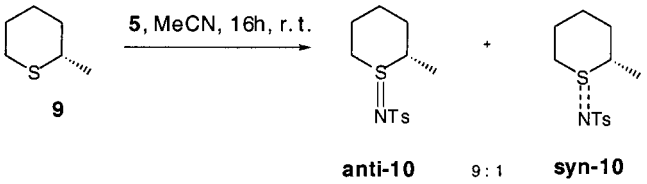
Scheme 2



10 and *syn*-**10** in a 9:1 ratio, whereas when *t*-BuOCl and $TsNH^-$ were used, *syn*-**10** was noted as the major isomer.[17] With the expectation that the new process would give the same stereochemistry as the "traditional procedure", 2-methylthiane (**9**) was treated with **5** in acetonitrile for 16 h and yielded a 9:1 mixture of *anti*- and *syn*-**10** in 75% yield. The complete absence of sulfoxide byproducts in this system, taken together with the anti-stereochemistry established by Kucsman et al.[17] are the key facts constraining mechanistic proposals for this transformation. The absence of sulfoxides and the observed anti preference are both consistent with the direct transfer of TsN to the least-hindered face of the sulfide in the rate-determining step. The simplest way to account for this is to propose direct nucleophilic attack by the sulfide at nitrogen, perhaps aided by prior formation of an adduct with acetonitrile.

In summary, a nearly ideal procedure for the sulfide to sulfonyl sulfilimine transformation has been deveoped. Almost quantitative yields are achieved from a diverse set of sulfides and a broad range of the readily available sulfonyl nitrenoid sources known as chloramine salts (R^3SO_2NClNa), essentially by simply stirring them together in acetonitrile.

Experimental Section

General Procedure for the Preparation of Sulfilimines from Sulfides As Exemplified for the Preparation of 7e on a 120 mmol Scale. To a magnetically stirred solution of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane (**6a**) (25 g, 0.12 mol) in 475 mL of CH_3CN (Fisher, A21−20, UN1648) was added Chloramine-T trihydrate (40 g, 0.14 mol). The reaction was stirred for 16h at rt and then quenched by addition of 800 mL of CH_2Cl_2; Et_2O or EtOAc can also be used. After NaCl and the excess of the sodium salt **2** were removed by filtration, the solvent was evaporated. The resulting solid product was recrystallized from hot 2-butanone to give sulfilimine **7e** (42.5 g, 97%) as a white solid, mp 183 °C.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane-*N*-phenylsulfonylsulfilimine (7a): yield after recrystallization from $AcOH/H_2O$: 699 mg (86%), white crystals, mp 67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.94 (m, 1H), 2.18 (m, 4H), 2.43 (m, 1H), 2.75 (m, 2H), 3.23 (s, 2H), 4.40 (m, 1H), 5.13 (m, 1H), 7.45 (m, 3H), 7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.56, 22,39, 30.39, 49.09, 51.59, 52.62, 55.53, 126.06, 128.91, 131.70; HRMS (FAB^+) calcd for $C_{14}H_{17}Cl_2NO_2S_2Na^+$ ($M + Na^+$): 387.9975, found: 387.9986.

9-Thiabicyclo[3.3.1]nonane-N-phenylsulfonysulfilimine (7b): yield after recrystallization from $AcOH/H_2O$, mp 118 °C: 739 mg (95%), white crystals; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (m, 4H), 2.00 (m, 2H), 2.15 (m, 4H), 2.83 (m, 2H), 2.98 s, 2H), 7.42 (m, 3H), 7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.76, 20.18, 29.75, 46.13, 126.14, 128.62, 131.06; HRMS (FAB^+) calcd for $C_{14}H_{19}NO_2S_2Na^+$ ($M + Na^+$): 320.0755, found: 320.0752.

2,6-Dichloro-9-thiabycyclo[3.3.1]nonane-*N*-(2-nitrophenyl)sulfonylsulfilimine (7c): yield after recrystallization from $AcOH/H_2O$: 953 mg (93%), white crystals, mp 230 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (m, 6H), 2.44 (m, 1H), 2.75 (m, 1H), 3.41 (s, 2H), 4.50 (m, 1H), 5.07 (m, 1H), 7.61 (m, 2H), 8.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.86, 22.42, 30.06, 30.39, 49.53, 51.94, 52.91, 55.59, 123.85, 130.43, 132.05, 132.58; HRMS (FAB^+) calcd for $C_{14}H_{16}Cl_2N_2NaO_4S_2Na^+$ ($M + Na^+$): 432.9826, found: 432.9818.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane-*N*-methylsulfonylsulfilimine (7d): yield after recrystallization from hot 2-butanone: 750 mg (99%) of white crystals, mp 223 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01 (m, 1H), 2.22 (m, 4H), 2.47 (m, 1H), 2.78 (m, 2H), 2.96 (s, 3H), 3.35 (s, 2H), 4.47 (m, 1H), 5.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.52, 22.39, 30.09, 30.37, 42.76, 49.55, 52.10, 52.70, 55.57; HRMS (FAB^+) calcd for $C_9H_{15}Cl_2NO_2S_2Na^+$ ($M + Na^+$): 325.9819, found: 325.9812

2,6-Dihydroxy-9-thiabycyclo[3.3.1]nonane-*N*-(4-methylphenyl)sulfonylsulfilimine (7f): yield after recrystallization from H_2O/iPrOH (9/1): 840 mg (98%) of white crystals, mp 130 °C; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.70 (m, 1H), 1.81 (m, 3H), 2.16 (m, 4H), 2.28 (m, 1H), 2.36 (s, 3H), 2.87 (s, 1H), 2.99 (s, 1H), 3.97 (m, 1H), 4.43 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.08, 19.36, 28.42, 47.75, 51.07, 62.37, 68.65, 126.04, 129.60, 140.46, 142.33; HRMS (FAB^+) calcd for $C_{15}H_{21}NO_4S_2$ ($M + H^+$): 344.0990, found: 344.0995.

2,6-Diazido-9-thiabycyclo[3.3.1]nonane-*N*-(4-methylphenyl)sulfonylsulfilimine (7 g): yield after recrystallization from $AcOH/H_2O$: 904 mg (92%) of white crystals, mp 162 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80 (m, 5H), 2.25 (m, 1H), 2.46 (s, 2H), 2.50 (m, 1H), 2.75 (m, 1H), 4.03 (m, 1H), 4.70 (m, 1H), 7.28 (d, J = 8.4, 2H), 7.79 (d, J = 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.18, 20.94, 21.00, 25.52, 25.75, 46,57, 48.82, 53.34, 59.05, 126.05, 129.50, 141.04, 142.27; HRMS (FAB^+) calcd for $C_{15}H_{19}N_7O_2S_2$ ($M + H^+$): 394.1120, found: 394.1134.All other compounds (i.e., those in Table 2) have been described before. Their identity has been established by comparing their melting points and ^1H NMR spectra with the published data. Melting points are given in Table 2.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **7a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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