Thioammonium Ions. Azasulfenylation Reactions

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Sulfenylating agents used in organic synthesis include sulfenyl halides (RSX, X = halogen) and, to some extent, thiosulfonium ions[1] ($RSSR_2^+$). Surprisingly, the corresponding thioammonium ions ($RSNR_3^+$) are virtually unknown.[2] We describe here results of a study on the incidence of (alkylthio)ammonium ions and their efficacy as azasulfenylating agents. We also describe mechanistic details of an interesting displacement reaction that converts 1,2 adducts of thiosulfonium ions and alkenes to the corresponding thioammonium adducts.

In principle, thioammonium ions are accessible by sulfenylation of amines (eq 1a) and by alkylation of sulfenamides (eq 1b).

$$RSX \xrightarrow{NR_3} \underset{\mathbf{2}}{RSNR_3^+X^-} \quad (1a)$$

$$RSNR_2 \xrightarrow{RX} \underset{\mathbf{2}}{RSNR_3^+X^-} \quad (1b)$$

Attempts to sulfenylate tertiary amines with dimethyl(methylthio)sulfonium fluoroborate (**1**) in nitromethane led not to thioammonium ions (**2**) but the hydrolytic products thereof (eq 2).

$$\underset{\mathbf{1}}{4MeSSMe_2^+} + 4R_3N \xrightarrow{MeNO_2} \underset{\mathbf{2}}{4[MeSNR_3^+]} + 4Me_2S \xrightarrow{2H_2O}$$

R_3 = Me_3, Et_3, Me_2(allyl), $(CH)_5$

$$4R_3NH^+ + \underset{\mathbf{3}}{MeSO_2SMe} + MeSSMe + 4Me_2S \quad (2)$$

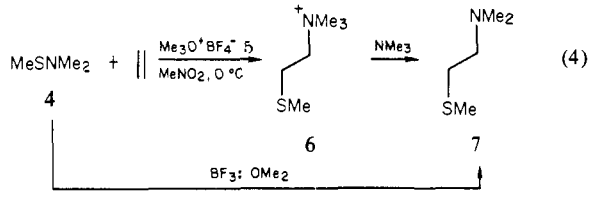
In the absence of amine, hydrolysis of **1** was very slow.[3] In the presence of amine, hydrolysis was instantaneous and quantitative, even through water was not intentionally added as a reagent. Suppression of hydrolysis by careful exclusion of air, moisture, and even solvent gave only mixtures of trialkyl- and tetraalkylammonium salts and mono- and polysulfides.[4] If, then, thioammonium ions are formed, they must rapidly dissociate to the observed products.

Alkylation of *N,N*-dimethylmethanesulfenamide (**4**) with alkyl iodides resulted in S–N cleavage and the products of eq 3. These

$$\underset{\mathbf{4}}{MeSNMe_2} + RI \xrightarrow{CHCl_3} \underset{\mathbf{2}}{[MeSN^+(R)Me_2^+I^-]} \xrightarrow{RI}$$

$$Me_2NR_2^+ + {}^1/_2MeSSMe + I_2 \quad (3)$$

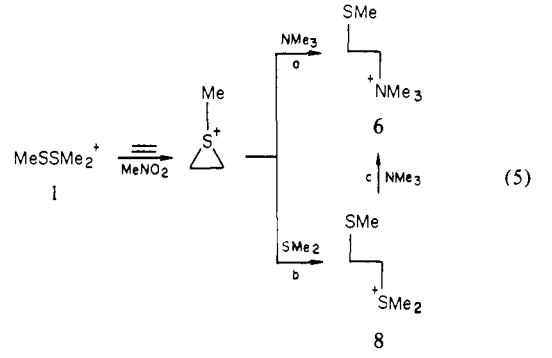
are products anticipated from thioammonium ions and iodide, but methylation with trimethyloxonium fluoroborate **5** (in $MeNO_2$, $CHCl_3$, or CH_2Cl_2) similarly led to ammonium salts (Me_3NH^+ and Me_4N^+) and polysulfides.[5,6] Again, these reactions suggest that (alkylthio)ammonium ions, if formed, decompose almost at once.[8] Therefore we tried to intercept the ions by trapping experiments with alkenes. In fact, a mixture of **4** with a 2-fold excess of alkene in $CHCl_3$ gave, upon addition of **5**, moderate yields of 1-trimethylamino-2-methylthio adduct **6** by anti addition (see Table I and eq 4).[10] The salt adduct **6** was demethylated



(4)

to neutral adduct **7** with excess trimethylamine. The *same* adduct **7** was produced by BF_3-catalyzed azasulfenylation of the alkene with **4**.[7]

No doubt then, (alkylthio)ammonium ions are produced transiently on alkylation of sulfenamides, and they do effect azasulfenylation of alkenes. However, evidence for the intervention of thioammonium ions in eq 2 was less conclusive because trapping experiments with alkenes, which indeed gave adducts **6** in low yields, do not distinguish direct azasulfenylation by **2** from sulfenylation by **1** followed by capture of episulfonium intermediates with amine (eq 5a). In fact, when the thiosulfenylation adducts



(5)

8 (eq 5b) were treated with excess amine *in a separate step*, good yields of 1-ammonio-2-methylthio adducts **6** were obtained (eq 5c and Table I).[12] The reaction has generality. Thus, five- and six-ring thiosulfonium ions **9**[13] gave cyclic adducts with alkenes, and these adducts cleaved to give acyclic ammonium salts on treatment with excess trimethylamine (see Table I). Also, the nucleophile can be varied. Thus, adducts **8** gave solvolysis products in water and methanol.

The mechanism of reaction 5c is interesting. Nucleophilic attack at carbon by either S_N1 or S_N2 mechanisms can be excluded because *displacement occurs with complete retention of configuration* and, with adducts from **9**, is selective for the α carbon (not α') in the sequence C_α'–S(Me)$^+$–C_α–C_β–S regardless of the degree of substitution. A possible mechanism is an elimination–addition sequence initiated by nucleophilic attack at sulfur (eq 6). Thioammonium ions so formed could subsequently add to the alkene. Another possibility requires that episulfonium ions, formed

(1) (a) Kline, M. L.; Beutow, N.; Kim, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1904. (b) Kim, J. K.; Caserio, M. C. *Tetrahedron Lett.* **1981**, 4159. (c) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (d) Anderson, S. A.; Kim, J. K.; Caserio, M. C. *J. Org. Chem.* **1978**, *43*, 4822.

(2) For a report on an (arylthio)ammonium salt see: Wevers, J. H.; Kloosterziel; H. *J. Chem. Soc., Chem. Commun.* **1975**, 413.

(3) In the absence of amine, **1** is stable in nitromethane for days at room temperature or below.

(4) The related reaction of **1** with dimethylamine gave the sulfenamide **4**.

(5) See also: Heimer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 3012.

(6) Alkylation of **4** and *N,N*-dimethylbenzenesulfenamide with allyl chloride or bromide also gave ammonium salts **8**, both (dimethylallyl)- and (dimethyldiallyl)ammonium salts. Methylthiolation of **4** with **1** gave ammonium salts and S–N cleavage.

(7) The active reagent is presumably $MeSN(Me)_2^+BF_3^-$: Burg, A. B.; Woodrow, H. W. *J. Am. Chem. Soc.* **1954**, *76*, 219.

(8) We also observed that the decomposition of sulfenamides $RSNR_2$ is acid catalyzed. The plethora of products reported in the preparation of **4** (ref 9) is due to the presence of proton sources that give thioammonium ions which subsequently dissociate.

(9) Armitage, D. A.; Clark, M. J. *J. Chem. Soc. C* **1971**, 2840. Knunyants, I. L.; Rozhkov, I. N.; Kuleshova, N. D. *Izv. Akak. Nauk. SSSR, Ser. Khim.* **1971**, *11*, 2499.

(10) Stereochemistry and regiochemistry was established spectroscopically and by alternate reactions. Products of anti addition of CH_3SCl to cyclopentene and tetrahydropyran (ref 11) were converted to **6** on treatment with $AgBF_4$ followed by trimethylamine.

(11) Baldwin, M. J., Brown, R. K. *Can. J. Chem.* **1968**, *46*, 1093.

(12) For imaginative exploitation of the synthetic potential of this reaction see: Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 000,000. Trost, B. M.; Shibata, T.; Martin, S. *Ibid.* **1982**, *104*, 000.

(13) Thiosulfonium salts **9** were prepared (85%) by methylation of 1,2-dithiane (ref 14) and 1,2-dithiolane.

(14) Hester, N. E.; Helmkamp, G. K.; Alford, G. L. *Int. J. Sulfur Chem. A* **1971**, *1*, 65. Hester, N. E.; Helmkamp, G. K. *J. Org. Chem.* **1973**, *38*, 461.

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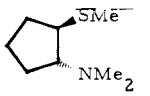
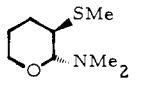
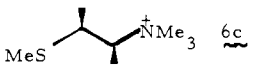
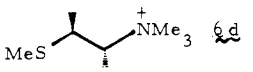
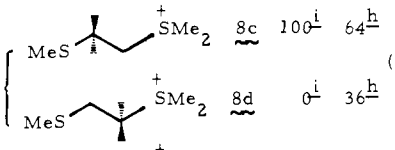
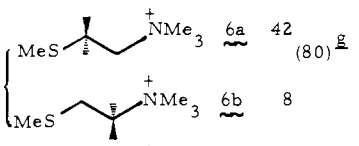
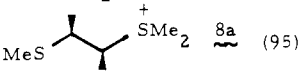
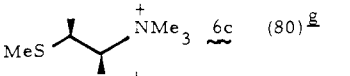
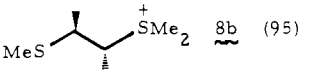
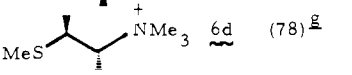
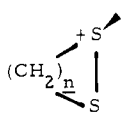
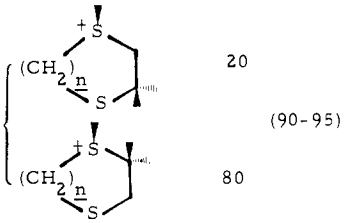
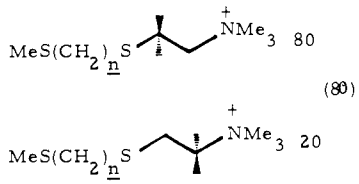
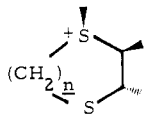
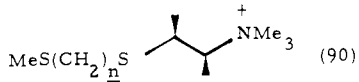
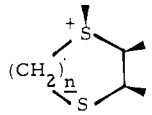
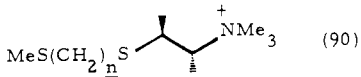
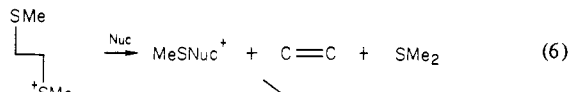
Table I. Methanesulfenyl Adducts of Alkenes

$$RSX + C{=}C \xrightarrow[MeNO_2,\ 0\ ^\circ C]{E} RS{-}C{-}C{-}X \xrightarrow[rt]{NMe_3} RS{-}C{-}C{-}NMe_3^+$$

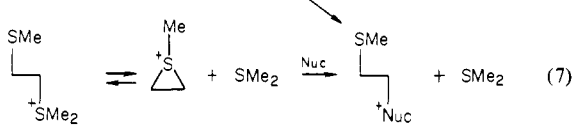
RSX	alkene	E	RS–C–C–X (yield)[j]	RS–C–C–NMe_3^+ (yield)
$MeSNMe_2$	cyclopentene	Me_3O^+ [a,f]	 (60)[b] (50)[c]	
		BF_3, OMe_2 [d]	(75)[e]	
	tetrahydropyran	Me_3O^+	 (60)[b] (27)[c]	
		BF_3, OMe_2 [d]	(61)[e]	
	cis-2-butene	Me_3O^+	 6c	
	trans-2-butene	Me_3O^+	 6d	
$MeSSMe_2^+$ [a]	2-methylpropene		 8c 100[i] 64[h]; 8d 0[i] 36[h] (90)	 6a 42; 6b 8 (80)[g]
	cis-2-butene		 8a (95)	 6c (80)[g]
	trans-2-butene		 8b (95)	 6d (78)[g]
 n = 3, 4 9	2-methylpropene		 20; 80 (90-95)	 80; 20 (80)
	cis-2-butene		 (94-98)	 (90)
	trans-2-butene		 (96-98)	 (90)

[a] Counterion was BF_4^-. [b] Isolated as the trimethylammonium salt. [c] Yield after demethylation of salt with Me_3N in $MeNO_2$ at room temperature. [d] In $CHCl_3$. [e] Isolated yield after distillation. [f] Solvent was $MeNO_2$ or 1:1 mixture of $CHCl_3/MeNO_2$. [g] Demethylation of the sulfonium adducts 8 was competitive with formation of ammonium adducts in the case of *cis*- and *trans*-2-butene and 3-methylpropene in $MeNO_2$. [h] Thermodynamic product ratio. [i] Kinetic product ratio. [j] Structure assigned on basis of ^1H and ^{13}C NMR spectrometry. Relative configuration at chiral carbons was thereby assigned but configuration at chiral sulfur is unspecified.

reversibly from the adducts **8**, are trapped by external nucleophiles (eq 5 and 7).[15]



(6)



(7)

(15) For reviews on episulfonium ions see: (a) Schmid, G. H. *Top. Sulfur Chem.* **1977**, *3*, 101. (b) Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282.

Experimental facts pertinent to the mechanisms in question follow. Solutions of sulfonium adducts **8a–d** (see Table I) in CD_3NO_2 underwent *rapid* sulfide exchange with dimethyl-d_6 sulfide (90% equilibrated in 3 min at room temperature). In the case of **8c**, which is the kinetic product of addition of **1** to 2-methylpropene, rearrangement occurred to give a 2:1 mixture of regioisomers **8c**/**8d** within 4–6 h at room temperature in CD_3NO_2. Not only was the rate of sulfide exchange in **8c**/**8d** *faster* than the rate of rearrangement **8c** ⇄ **8d** but the latter was *independent* of added sulfide. This result excludes eq 6 as a possible route for rearrangement and exchange because both should show the same dependence on sulfide.

Moreover, attempts to trap sulfenyl intermediates $MeSNuc^+$ were negative. Thus, **8a** with $(CD_3)_2S$ and excess *trans*-2-butene resulted in rapid sulfide exchange but *no* **8b**. Similarly, **8b** and $(CD_3)_2S$ with excess *cis*-2-butene gave sulfide exchange but no **8a**. Also, if thioammonium ions were intermediates in amine

Table II. S_N Reactions of Methanesulfenyl Adducts of 2-Methylpropene

	reactants[a]			products		
						
X	(%)	(%)	Nuc	(%)	(%)	yield, %
Cl	10a (4)	10b (96)[b]	Me_3N[c]	6a (85)	6b (15)	90
Cl	10a (4)	10b (96)	$AgBF_4$; Me_3N[d]	6a (78)	6b (22)	34
SMe_2^+	8c (64)	8d (36)[b]	Me_3N	6a (82)	6b (18)	60[e]
Cl	10a (4)	10b (96)	Me_2NH[c]	11a (81)	11b (19)	88
Cl	10a (4)	10b (96)	$AgBF_4$; Me_2NH[d]	11a (80)	11b (20)	37
SMe_2^+	8c (64)	8d (36)	Me_2NH	11a (81)	11b (19)	80[f]
Cl	10a (4)	10b (96)	H_2O[g]	12a (3)	12b (97)	>90
SMe_2^+	8c (64)	8d (36)	H_2O[g]		12b (100)	>90

[a] 25 °C in $MeNO_2$. [b] Equilibrium composition. [c] Four days at room temperature. [d] $AgBF_4$ was added to chloride in $MeNO_2$ at 0 °C; the nucleophile was added to the supernatant at 25 °C. [e] Competitive demethylation gave Me_4N^+ (37%). [f] Demethylation gave Me_3NH^+ (14%). [g] With or without $NaHCO_3$, or K_2CO_3, or with $MeNO_2$ as cosolvent.

displacements, considerable fragmentation to Me_3NH^+ and Me_4N^+ may be expected—but none was found.

The overall results strongly suggest that, in solution, the sulfonium adducts **8** dissociate *reversibly* to episulfonium ions (eq 7), which accounts for the observed rearrangements, sulfide exchange, and the displacement reactions.[16] This being so, episulfonium ions generated by authenticated routes should react with external nucleophiles to give product mixtures similar to those obtained in the present experiments. Accordingly, methanesulfenyl chloride adducts of 2-methylpropene, **10a** and **10b**, were prepared and converted to the corresponding azasulfenyl adducts **6** by way of episulfonium ions.[17] As can be seen from Table II, the same adducts in essentially the same distribution were obtained from both the chlorides **10** and the sulfonium salts **8** despite the disparity in the initial composition of regioisomers, whether or not silver fluoroborate was employed to preform the episulfonium ions. The same result was obtained with other nucleophiles (Me_2NH and H_2O).

Although the reality of episulfonium ions has been questioned under some reaction conditions,[15b] we conclude that, in the reactions described herein, episulfonium ions are formed rapidly and reversibly from sulfenyl adducts of the type RS–C–C–X, where X = Cl and SR_2^+. We further suggest that the synthetically useful sulfenylation reactions of alkenes described by Trost and Shibata[12] proceed by a similar route—that is, by the initial rapid addition of **1** to the alkene followed by a slower nucleophilic displacement by way of episulfonium ions.

Acknowledgment. We gratefully acknowledge support of this work by Grant No. GM27319 awarded by the Institute for General Medical Sciences, DHEW.

Registry No. 1 BF_4^-, 5797-67-7; 4, 33696-21-8; **6a** BF_4^-, 81206-91-9; **6b** BF_4^-, 81206-93-1; **6c** BF_4^-, 81206-95-3; **6d** BF_4^-, 81206-97-5; **8a** BF_4^-, 81206-99-7; **8b** BF_4^-, 81207-00-3; **8c** BF_4^-, 81207-02-5; **8d** BF_4^-, 81207-04-7; **9** (n = 3) BF_4^-, 81207-06-9; **9** (n = 4) BF_4^-, 81207-07-0; **10a**, 19826-04-1; **10b**, 13012-55-0; **11a**, 81207-08-1; **11b**, 81207-09-2; **12a**, 27874-69-7; **12b**, 33657-46-4; *trans*-(2-methylthiocyclohex-1-yl)-trimethylammonium BF_4^-, 81207-11-6; *trans*-2-methylthio-1-dimethylaminocyclohexane, 81207-12-7; *trans*-(3-methylthiotetrahydropyran-2-yl)trimethylammonium BF_4^-, 81207-14-9; *trans*-3-methylthio-2-dimethylaminotetrahydropyran, 81207-15-0; 1,3,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-17-2; 1,2,2-trimethyl-1,4-dithiepanium BF_4^-, 81207-19-4; 1,3,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-21-8; 1,2,2-trimethyl-1,4-dithiocanium BF_4^-, 81219-00-3; *trans*-1,2,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-23-0; *cis*-1,2,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-25-2; *trans*-1,2,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-27-4; *cis*-1,2,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-29-6; (2,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-31-0; (1,1-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-33-2; (2,2-dimethyl-2-(4-methylthiobutyl)ethyl)trimethylammonium BF_4^-, 81207-35-4; (1,1-dimethyl-2-(4-methylthiobutyl)-ethyl)trimethylammonium BF_4^-, 81207-37-6; (*R*,R**)-(1,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-39-8; (*R*,S**)-(1,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-41-2; (*R*,R**)-(1,2-dimethyl-2-(4-methylthiobutyl)ethyl)-trimethylammonium BF_4^-, 81207-43-4; (*R*,S**)-(1,2-dimethyl-2-(4-methylthiobutyl)ethyl)trimethylammonium BF_4^-, 81207-45-6; cyclopentene, 142-29-0; 3,4-dihydro-2*H*-pyran, 110-87-2; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 2-methylpropene, 115-11-7.

(16) It is worth noting that the sulfonium salt produced by methylation of 1,4-dithiane is stable to NMe_3—reflecting difficulty in forming an episulfonium ion by internal displacement.

(17) (a) Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2075. (b) Lucchini, V.; Modena, G.; Zaupa, T.; Capozzi, G. *J. Org. Chem.* **1982**, *47*, 590.

A New β-Lactam Synthesis

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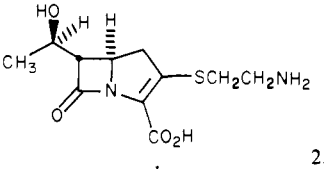
Interest in natural and semisynthetic β-lactam structures has recently surged with the discovery of thienamycin (**1**), an unusually



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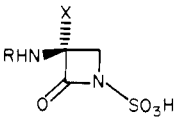

2, X = OCH_3
R = γ-D-glutamyl-D-alanyl

potent carbapenem antibiotic,[1] and the monobactams (e.g., sulfazecin (**2**), a family of monocyclic 2-azetidinone-*N*-sulfonic acids found in bacteria.[2,3] These substances possess reactive β-lactam linkages and exhibit promising antibiotic activity against both Gram-positive and Gram-negative organisms.[3,4] In this communication we disclose the oxidative cyclization of β,γ-unsaturated amidosulfamoyl esters and related structures to N-sulfonylated halo β-lactams which can be dehalogenated to afford structural

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