α-Halosulfonamides. Synthesis and Base-Induced Reactions

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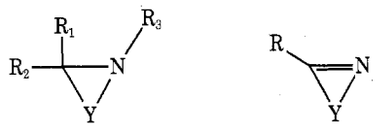
The syntheses of α-halosulfonamides by two methods are described. Base-induced reactions of α-halosulfonamides resulted in dimerization (**8a**), elimination–dimerization (**8g$_2$**), or cyclization (**8g**, **8h$_2$**).

Although no three-membered ring with two heteroatoms had been prepared before 1950, isolable compounds incorporating two nitrogens (diazirines, diaziridines),[1] or both nitrogen and oxygen (oxaziranes)[1,2] are known to date. Recently, the syntheses of three-membered ring systems comprised solely of heteroatoms (oxadiaziridines and thiadiaziridine 1,1-dioxides)[3] have been reported. However, nothing is known about such systems comprised of sulfur, nitrogen, and carbon (**1** and **2**).



1 **2**

a, Y = S
b, Y = SO_2

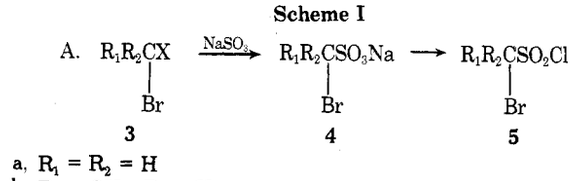
Three-membered heterocycles have been prepared by a variety of cyclization reactions.[4] α-Halosulfonamides would appear to be the most convenient and promising precursors for the synthesis of either the α-sultam or α-sultem (azathiirane dioxide **1b** and azathiirene **2b**, respectively).

The objective of this study was the synthesis of α-halosulfonamides (**8**) and the investigation of possible cyclization reactions leading to **1b**, **2b**, or degradation products.

Results and Discussion

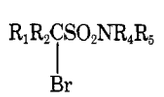
α-Halosulfonamides have been synthesized in two ways as shown in Scheme I.

Scheme I



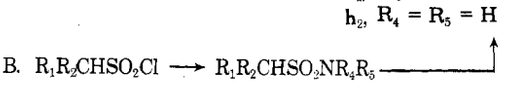
3 **4** **5**

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; R_2 = *tert*-butyl
d, $R_1 = H$; R_2 = *tert*-butyl; X = I
e, $R_1 = H$; $R_2 = p$-NO_2Ph
f, $R_1R_2 = -(CH_2)_5-$



8

a$_1$, R_4 = *tert*-butyl; $R_5 = H$
a$_2$, R_4 = *n*-propyl; $R_5 = H$
a$_3$, R_4 = cyclohexyl; $R_5 = H$
a$_4$, $R_4 = R_5 = CH_3$
a$_5$, $R_4R_5 = -(CH_2)_5-$
b, R_4 = *tert*-butyl; $R_5 = H$
g$_1$, R_4 = *tert*-butyl; $R_5 = H$
g$_2$, R_4 = *tert*-butyl; R_5 = Cl
h$_1$, R_4 = *tert*-butyl; $R_5 = H$
h$_2$, $R_4 = R_5 = H$



6 **7**

g, R_1 = Ph; $R_2 = H$
h, R_1 = Ph; R_2 = Br

Method A involves the Strecker reaction[5] of an alkyl halide with sulfite anion. This method was useful for the conversion of **3a** and **3b** to **4a** and **4b**[6] (X = Br). However, the more hindered *gem*-dihalides **3c–f** and **3h** were not converted to the α-halosulfonates even on treatment with sodium sulfite in refluxing aqueous ethanol or aqueous ethylene glycol. Use of this method with **3g** gave benzaldehyde as the main product. Thus it seems this type of reaction (**3** → **4**) is successful only if $R_1 = H$ and $R_2 = H$ or a linear alkyl group.[5b]

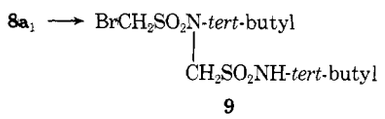
The selective α-halogenations of method B were achieved through radical-type reactions. *N*-Bromosuccinimide and molecular bromine were successfully applied for the benzylic brominations leading to the benzylsulfonamides **8g** and **8h**. In contrast to the easy α-halogenations of carbonyl compounds, α-halogenations of sulfonyl compounds are not facile using conventional ionic halogenation agents.[7] Such halogenations have been effected by reaction of a sulfonyl carbanion (prepared from the reaction of the parent sulfone with a strong base) with a source of X^+.[8] This method, however, was reported to be unsuccessful in some cases,[7] unless a very unusual source of X^+ (bromomethylmalonylacetonide) was applied. Primary or secondary sulfonamides would be expected to afford *N*-halo rather than *C*-halo products by this method.

The *N*-halosulfonamide **8g$_2$** was prepared from **7g** (R_4 = *tert*-butyl, R_5 = H) with *tert*-butyl hypochlorite.

The effects of bases on α-halosulfones, α,α-dihalosulfones, and α,α′-dihalosulfones have been studied extensively,[9-13] both mechanistically and synthetically. Two studies on the effect of alkali on α-chloromethanesulfonamides[12a,14] suggest the Ramberg–Bäcklund mechanism[12a] to be operative in these cases.

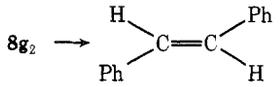
The intermediacy of episulfones and their vinylogs (thiirene dioxides) in the Ramberg–Bäcklund reaction of α-halosulfones and α,α-dichlorosulfones, respectively, has been established.[10-13] Furthermore, stable thiadiazirine 1,1-dioxides[3b] and thiirene dioxide[6a] were recently isolated by the treatment of substituted *N*-chlorosulfonylureas and α,α-dibromobenzyl sulfone, respectively, with bases. Therefore, the three-membered heterorings **1b** and **2b** might be accessible through the treatment of α-halosulfonamides **8a**, **8g**, and **8h** with a base.

Reaction of **8a$_1$** with metallic sodium in ether solution or with potassium *tert*-butoxide in ether or tetrahydrofuran afforded the dimer **9**. Compound **8a$_1$** was chosen as a representative of the α-bromoalkylsulfonamide series.



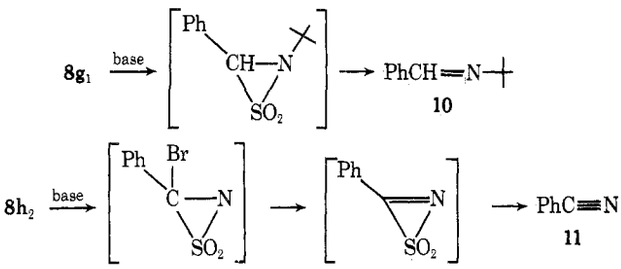
9

Treatment of the *N*-chloro compound **8g$_2$** with triethylamine in methylene chloride or with potassium *tert*-butoxide in ether gave **7g** (R_4 = *tert*-butyl; R_5 = H). Use of Baumgarten's procedure[15] for *in situ* generation of **8g$_2$** gave *trans*-stilbene.



Reaction of $8g_2$ with *n*-butyllithium followed by molecular bromine also gave *trans*-stilbene.

The α-halobenzylic sulfonamides $8g_1$ and $8h_2$ in the presence of thiethylamine in benzene or potassium *tert*-butoxide in ether gave products suggesting the intermediacy of an α-sultam.



Both episulfones and thiirene dioxides readily lose sulfur dioxide under Ramberg–Bäcklund reaction conditions.[9-13] Therefore **1b** and **2b** (the sulfo analogs of the α-lactam system[15,16] and the aza analogs of the thiirene dioxides, respectively) could behave similarly under comparable conditions.

The structures of the minor products from the reaction of $8h_2$ have not yet been established. In contrast to the isolated products from the rearrangement of the analogous α-halosulfones,[11,13] they were shown not to be derivatives of sulfonic acids.

The fact that $8g_2$ required hours whereas $8a_1$ required days for reaction with potassium *tert*-butoxide probably reflects the relative ease of displacement of benzyl bromine compared to alkyl bromine in α-bromosulfonamides.

Experimental Section

Melting points were obtained on a Reichert micro heating stage. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nmr spectra were obtained on a Varian T-60 and are reported in parts per million downfield from TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as internal standards. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6. Microanalyses were performed by S. M. Nagy, Belmont, Mass., and Galbraith Laboratories Inc., Knoxville, Tenn.

α-Bromosulfonyl Chlorides. α-Bromosulfonates were prepared according to a known procedure[6a] and treated with excess phosphorus pentachloride to obtain the sulfonyl chlorides.

Sulfonamides. General Procedure. A solution of the sulfonyl chloride (**5**, **6**, 0.05 mol) in 50 ml of methylene chloride was dropped into a solution of the amine (0.2 mol) in 200 ml of methylene chloride with stirring at 0°. The mixture was stirred at 0° for 2 hr and at 25° for 1 hr. The solution was washed with water, 5% hydrochloric acid, water, 10% sodium bicarbonate, and water. The organic layer was dried and evaporated. In most cases the sulfonamide obtained was pure enough for further synthetic use. Otherwise it was recrystallized from 90% ethanol. The following sulfonamides were obtained: *N-tert*-butyl-α-bromomethanesulfonamide ($8a_1$), 72%, mp 65–67°; *N*-propyl-α-bromomethanesulfonamide ($8a_2$), 48%, mp 31.5–33.5°; *N*-cyclohexyl-α-bromomethanesulfonamide ($8a_3$), 70%, mp 68–70°; *N,N*-dimethyl-α-bromomethanesulfonamide ($8a_4$) (the amines used were dimethylamine hydrochloride and triethylamine), 46%, mp 94–96°; *N,N*-cyclopentyl-α-bromomethanesulfonamide ($8a_5$), 63%, mp 100–102°; *N-tert*-butyl-α-bromoethanesulfonamide (**8b**), 77%, mp 103.5–105.5°; *N-tert*-butyl-α-toluenesulfonamide (**7g**), 94%, mp 107.5–109.5°.

α-Bromination of Sulfonamides. *N-tert*-Butyl-α-bromo-α-toluenesulfonamide ($8g_1$) and *N-tert*-Butyl-α,α-dibromo-α-toluenesulfonamide ($8h_1$). A suspension of **7g** (2.273 g, 10 mmol) and *N*-bromosuccinimide (3.56 g, 20 mmol) was refluxed with stirring in 150 ml of carbon tetrachloride under a nitrogen atmosphere for 18 hr with irradiation by a sun lamp (Westinghouse, 275 W). The reaction mixture was cooled and filtered and the solvent was evaporated to give a brown, viscous oil. The oil was dissolved in ether and the solution was washed with water, dried, and evaporated. The residue was chromatographed on SilicAR cc-7 (100–200 mesh) with benzene to give $8h_1$ (0.76 g, 20%) and $8g_1$ (1.27 g, 41%). Recrystallization from chloroform–pentane gave $8g_1$, mp 101–102°, and $8h_1$, mp 138.5–141°.

α,α-Dibromo-α-toluenesulfonamide ($8h_2$). Bromine (17.6 g, 0.10 mol) was added to a suspension of α-toluenesulfonamide[17] (6.85 g, 40 mmol) in 300 ml of carbon tetrachloride. The solution was refluxed for 28 hr under a sun lamp (Westinghouse, 275 W). Filtration of the cooled reaction mixture gave a solid, which was recrystallized from chloroform to give 9.2 g (70%) of $8h_2$, mp 168–170°.

***N*-Chloro-*N-tert*-butyl-α-toluenesulfonamide ($8g_2$).** *tert*-Butyl hypochlorite (3.0 g, 27 mmol) was added dropwise to a solution of **7g** in 50 ml methylene chloride (5.68 g, 25 mmol) over 30 min. The solution was stirred for 16 hr and evaporated to give $8g_2$, 95%, mp 52–55.5°.

Base-Induced Reactions. Dimerization. A solution of $8a_1$ (1.28 g, 5.67 mmol) in 25 ml of ether was added to a suspension of sodium (0.138 g, 5.67 mmol) in 15 ml of ether. The mixture was stirred at 25° for 3 days under nitrogen. The solution was evaporated and the residue was taken up in water and chloroform. The solution was acidified with 1 *N* hydrochloric acid and the organic layer was dried and evaporated to give 0.87 g of an oil. Spectral analysis showed the oil to be a mixture of $8a_1$ and the dimer **9**. The dimer was isolated and recrystallized from hexane–ethyl acetate to give 0.11 g (10%), mp 124–125.5°.

Treatment of $8a_1$ with potassium *tert*-butoxide in ether for 1 week gave 14% of the dimer **9**.

***trans*-Stilbene.** The method of Baumgarten[15] was used to generate $8g_2$ from **7g** (2.27 g, 10 mmol). Unreacted α-toluenesulfonamide (60%) and *trans*-stilbene (40%) were isolated. *trans*-Stilbene was identified by comparison with an authentic sample.

Base-Induced "Cyclizations." A. With Triethylamine. A solution of $8g_1$ (308 mg, 1.007 mmol) and triethylamine (102 mg, 1.008 mmol) in 6.5 ml of benzene was refluxed with stirring for 42 hr. The reaction mixture was cooled and filtered. The precipitate of triethylammonium hydrobromide (70.8% recovery) was washed with benzene, and the washings were combined with the filtrate. Removal of benzene *in vacuo* gave a yellow-brown oil which was shown by ir and nmr to consist of unreacted $8g_1$ and the Schiff base **10**. Nmr integration showed the yield of **14** to be 78.7%. The mixture was separated by chromatography on SilicAR cc-7, using either benzene or methylene chloride as eluent.

The Schiff base **10** was found to be identical with an authentic sample. No other products were observed.

B. With Potassium *tert*-Butoxide. To a stirred solution of $8g_1$ (300 mg, 0.98 mmol) in 20 ml of ethyl ether under nitrogen was added in one portion 110 mg (0.98 mmol) of potassium *tert*-butoxide (MSA sublimed). The temperature of the reaction mixture was kept at −12 ± 3° for 2 hr. Centrifugation of the reaction mixture gave a white precipitate of KBr, which was washed with ether, and the washings were combined with the main portion of the decanted etheral solution. Removal of ether *in vacuo* gave a solid shown to be a mixture of $8g_1$ and **10**. Nmr integration showed the yield of **10** to be 65.1%. The remainder was starting material. No other products were observed and **10** could be separated from $8g_1$ by chromatography as described previously.

Reactions of $8h_2$ with triethylamine or potassium *tert*-butoxide were carried out as described above. Benzonitrile (62%) was isolated and found to be identical with an authentic sample.

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Registry No.—**5a**, 10099-08-8; **5b**, 14403-02-2; **6g**, 1939-99-7; **6h**, 51270-34-9; **7g**, 51270-35-0; $8a_1$, 51270-36-1; $8a_2$, 51270-37-2; $8a_3$, 51270-38-3; $8a_4$, 51270-39-4; $8a_5$, 51270-40-7; **8b**, 51270-41-8; $8g_1$, 51270-42-9; $8g_2$, 51270-43-0; $8h_1$, 51270-44-1; $8h_2$, 51270-45-2; **9**, 51270-46-3; *tert*-butylamine, 75-64-9; propylamine, 107-10-8; cyclohexylamine, 108-91-8; dimethylamine hydrochloride, 506-59-2; piperidine, 110-89-4; *N*-bromosuccinimide, 128-08-5; *tert*-butyl hypochlorite, 507-40-4.

Supplementary Material Available. Spectral and analytical data for compounds 8 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155

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References and Notes

(1) E. Schmitz, "Dreiringe mit Zwei Heteroatomen," Springer-Verlag New York, New York, N. Y., 1967.
(2) W. D. Emons in "Heterocyclic Compounds with Three and Four Membered Rings," A. Weissberger, Ed., Interscience, New York, N. Y., 1964.
(3) (a) F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970); (b) J. W. Timberlake and M. L. Hodges, *J. Amer. Chem. Soc.*, **95**, 634 (1973).
(4) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968.
(5) (a) S. Zuffanti, *J. Amer. Chem. Soc.*, **62**, 1044 (1940); (b) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965.
(6) (a) L. A. Carpino, L. V. McAdams, R. H. Rynbrandt, and J. W. Spiewak, *J. Amer. Chem. Soc.*, **93**, 476 (1971); (b) W. E. Truce, D. J. Abraham, and P. Son, *J. Org. Chem.*, **32**, 990 (1967).
(7) J. P. Marino and D. P. Hesson, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972.
(8) (a) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969); (b) W. E. Truce and L. W. Christensen, *Tetrahedron*, **25**, 181 (1969); (c) W. E. Truce, T. C. Klingler, J. E. Paar, H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969).
(9) L. Ramberg and B. Bäcklund, *Ark. Kemi, Mineral. Geol.*, **13A**, 1 (1940); *Chem. Abstr.*, **34**, 4725 (1940).
(10) N. P. Neurieter and F. G. Bordwell, *J. Amer. Chem. Soc.*, **85**, 1209 (1963).
(11) L. A. Paquette and L. S. Wittenbrook, *J. Amer. Chem. Soc.*, **89**, 4483 (1967).
(12) (a) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5187 (1951); (b) L. A. Paquette, *ibid.*, **86**, 4085 (1964); (c) *ibid.*, **86**, 489 (1964).
(13) L. A. Paquette, L. S. Wittenbrook, and V. V. Kane, *J. Amer. Chem. Soc.*, **89**, 4487 (1967).
(14) T. B. Johnson and I. B. Douglas, *J. Amer. Chem. Soc.*, **63**, 1571 (1941).
(15) H. Baumgarten, *J. Amer. Chem. Soc.*, **84**, 4975 (1962).
(16) J. C. Sheehan and I. Lengyel, *J. Amer. Chem. Soc.*, **86**, 1356 (1964).
(17) S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

2-Amino-2-thiazoline. VII.[1] Unequivocal Structure Assignment of the Products of the Reaction of 2-Amino-2-thiazoline and Its Analogs with Carbethoxy Isothiocyanate

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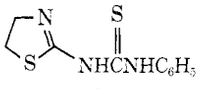
The reaction of 2-amino-2-thiazoline (**1**) with carbethoxy isothiocyanate (**3**) was found to give 2,3,6,7-tetrahydro-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (**5**), the structure of which was confirmed by an X-ray crystallographic study. The reaction of **3** with 2-amino-5,6-dihydro-4*H*-1,3-thiazine (**15**), with 2-amino-4,4-dimethyl-2-thiazoline (**17**), and with 2-amino-2-selenazoline (**20**) also gave the analogous heterobicycles, 2,3,7,8-tetrahydro-4*H*,6*H*-thiazino[3,2-*a*]-*s*-triazin-2-one-4-thione (**16**), 2,3,6,7-tetrahydro-6,6-dimethyl-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (**19**), and 2,3,6,7-tetrahydro-4*H*-selenazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (**21**), respectively. The product **19** showed magnetic nonequivalence of the two methyl groups. Treatment of **5** with diazomethane gave two products, the result of both S- and N-methylation.

The differing nucleophilic character of the exocyclic and endocyclic nitrogen atoms of 2-amino-2-thiazoline (**1**) has been the subject of many studies. Reactions at the exocyclic nitrogen atom have been noted with nitrous acid,[2] acyl chlorides,[3] and cyanate ion,[4] whereas reactions with the endocyclic nitrogen have been reported in alkylations[2,5] and sulfonylations.[6] The condensation of **1** and isothiocyanates has been surrounded by some controversy. Fromm and Kapeller-Adler[7] reported that the reaction of **1** with phenyl isothiocyanate gave the product resulting from attack on the ring nitrogen when conducted at low temperature, but the exocyclic thiourea product at higher temperature. Klayman and coworkers,[8] who were able to isolate only a single monoadduct regardless of conditions, demonstrated by chemical and physicochemical means that the exocyclic nitrogen atom of **1** reacted with phenyl isothiocyanate, giving 1-(2-thiazolinyl)-3-phenyl-2-thiourea (**2**). Their work was confirmed by an X-ray crystallographic study.[9]



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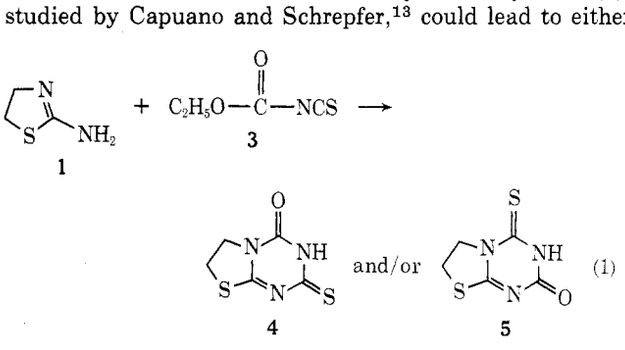
Carbethoxy isothiocyanate (**3**) is a useful reagent for the preparation of heterocyclic compounds through its reaction with amidines,[10] thiopseudoureas,[10] pseudoureas,[10] guanidines,[10] 2-aminopyridines,[11] 3-aminopyridazines,[12] 3-aminopyrazole,[13] 2-aminooxazoline,[13] 3-amino-1,2,4-triazoles,[13-15] 2-aminothiazoles,[16-18] enamines,[19] 2-amino-2-cyanoacetamide,[20] and 2-aminoacetonitrile.[21]

The reaction of **1** with carbethoxy isothiocyanate (**3**), studied by Capuano and Schrepfer,[13] could lead to either



1 **3** **4** **5**

(1)

or both of two possible products, **4** and **5** (eq 1). In fact, a single isomer is produced in the reaction, one to which Capuano and Schrepfer[13] assigned structure **4**; however, these workers presented no evidence for their structure assignment. The later work of Nagano, *et al.*,[16-18] indicated that 2-aminothiazole reacts with **3** to give, among other products, a heterobicycle resulting from attack of **3** on the endocyclic aromatic nitrogen atom. Extending the analogy to the case of **1**, the endocyclic attack could be favored, and structure **4**, proposed by the previous workers,[13] would thus be incorrect.

The present investigation was consequently undertaken to differentiate unequivocally between structures **4** and **5**,