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# Direct Synthesis of Trisubstituted Isothiazole 1,1-Dioxides. Regioselective Substitution Reactions at C-3 and C-4

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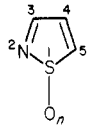
A direct synthesis of trisubstituted mononuclear isothiazole 1,1-dioxides (isothiazole sulfones) has been achieved. Regioselective nucleophilic substitutions of 3,4-dichloro- and 4-chloro-3-ethoxy-5-(ethoxycarbonyl)isothiazole 1,1-dioxide with alcohol, amines, and *N*-(trimethylsilyl)amines at the C-3 and C-4 positions were elucidated. The crystal structure of 3-ethoxy-4-amino-5-(ethoxycarbonyl)isothiazole 1,1-dioxide was determined to characterize the ring system and establish regioselectivity of ammonolysis. The $^{13}C$ spectra of several isothiazole sulfones have been obtained and the chemical shifts assigned and correlated with calculated CNDO/2 charge densities.

Despite extensive studies of isothiazole chemistry,[1] very little is known about the corresponding 1-oxide (**1a**) and

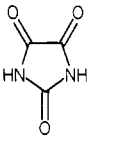


**1a**, $n = 1$
**b**, $n = 2$

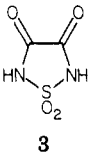
1,1-dioxide (**1b**) derivatives. Successful S-nuclear oxidations have been performed on some isothiazolin-3-ones,[2] and there are fragmentary reports on the S-oxidation of 3-amino-5-phenylisothiazole[3a] and of 3-morpholino-5-phenylisothiazole.[3b] The failure to investigate these ring systems is due to the lack of synthetic methods for preparing mononuclear isothiazole *S*-oxides by ring-forming reactions. The goal in this work was to devise a general synthesis for substituted isothiazole 1,1-dioxides and to evaluate the chemical properties of the ring system.

## Results and Discussion

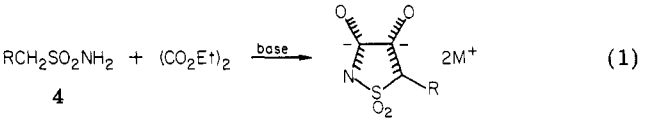
The synthetic strategy employed involved the condensation of a substituted methanesulfonamide with diethyl oxalate (eq 1).[4] A similar approach had been utilized in



**2**



**3**



**4**

(1)

**5a**, R = $CO_2Et$; M = Na
**b**, R = $CO_2Et$; M = H
**c**, R = H, M = Na or Li

(1) (a) Wooldridge, K. R. H. *Adv. Heterocycl. Chem.* **1972**, *14*, 1. (b) Slack, R.; Wooldridge, K. R. H. *Ibid* **1965**, *4*, 107. (c) Kurzer, F. "Organic Compounds of Sulphur, Selenium, and Tellurium"; The Chemical Society: London, 1977, Vol. 4, pp 339–355. (d) Kurzer, F. *Ibid.* 1973; Vol. 2, pp 556–586. (e) Kurzer, F. *Ibid.* 1970; Vol. 1, pp 369–377.

(2) (a) Lewis, S. N.; Miller, G. A.; Hausman, M; Szamborski, E. C. *J. Heterocycl. Chem.* **1971**, *8*, 591. (b) Kamiya, T.; Teraji, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *J. Am. Chem. Soc.* **1975**, *97*, 5020.

(3) (a) Walsh, R. J. A.; Wooldridge, K. R. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1247. (b) Bruno, A.; Purrello, G. *Gazz. Chim. Ital.* **1966**, *96*, 1009.

(4) An alternative, two-step approach resulting in 5-arylisothiazole 1,1-dioxides was devised independently in these laboratories: Cochran, D. W.; Cragoe, E. J., Jr.; Rooney, C. S.; Williams, H. W. R.; Ziegler, C., manuscript in preparation.

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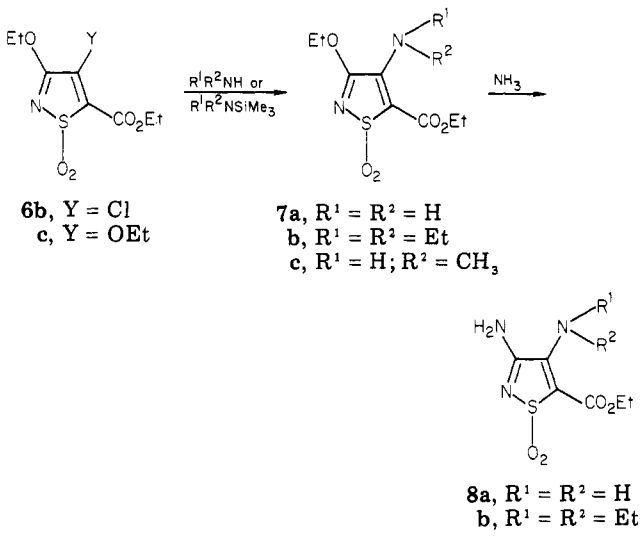
Scheme I



**6b**, Y = Cl
**c**, Y = OEt

**7a**, $R^1 = R^2 = H$
**b**, $R^1 = R^2 = Et$
**c**, $R^1 = H; R^2 = CH_3$

**8a**, $R^1 = R^2 = H$
**b**, $R^1 = R^2 = Et$

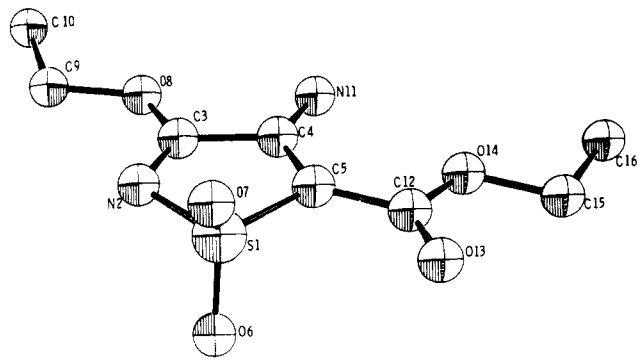


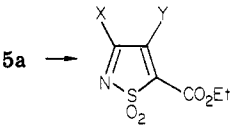
**Figure 1.** Computer-generated perspective drawing of **7a** with hydrogens omitted.

the syntheses of parabanic acid (**2**)[5] and 3,4-disubstituted-1,2,5-thiadiazole 1,1-dioxides (**3**).[6]

When R in **4** was ethoxycarbonyl, carbanion formation occurred in preference to deprotonation of the sulfamoyl group to yield **5a**, where R = H; ring formation to give **5c** was not observed under a variety of conditions.[7]

Of the two reported syntheses of **4** (R = $CO_2Et$),[8] the method of LeBerre[8b] offered the more efficient route. The final step of that route, reaction of ammonia with ethyl (chlorosulfonyl)acetate in ether at 10 °C, was reported to afford (ethoxycarbonyl)methanesulfonamide in 70% yield. We found that **4** could be obtained more conveniently, and in quantitative yield, by simply treating a methylene chloride solution of ethyl (chlorosulfonyl)acetate with an equivalent of hexamethyldisilazane followed by a brief treatment of the concentrated reaction mixture with ethanol. Condensation of **4** (R = $CO_2Et$) with diethyl oxalate proceeded in excellent yield to give the disodium salt **5a**, characterized as a hemihydrate. The strongly acidic ($pK_{a_1}$ = 2.90, $pK_{a_2}$ = 3.35) conjugate diacid **5b** was isolated by cation-exchange-resin treatment of **5a**.[9]

In order to study the relative reactivity of positions 3 and 4, reproducible conditions for converting the disodium salt groups of **5a** into effective leaving groups X and Y were required (eq 2). Sequential reaction of **5a** with phosphorus

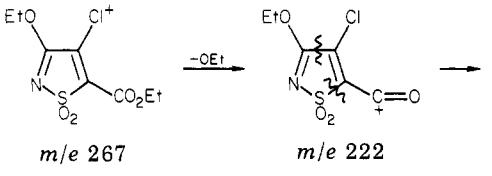


(2)

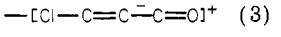
**6a**, X = Y = Cl
**b**, X = OEt; Y = Cl
**c**, X = Y = OEt

pentachloride and ethanol, according to Carmack's procedure,[6] afforded **6b**, but the yields were quite low and not reproducible. Initial results with thionyl chloride or oxalyl chloride, followed by an ethanol quench, were likewise disappointing, presumably by virtue of a sensitivity of **6a** and/or **6b** to excess hydrochloric acid generated in the reactions. Conditions were established for obtaining **6b** reproducibly, and in acceptable yield, by a pyridine-catalyzed oxalyl chloride chlorination of **5a** in refluxing toluene. The intermediate dichloro compound **6a** was not isolated but converted to **6b** in situ by treatment with silica gel saturated with ethanol. The presence of the silica gel was found to be necessary for consistent yields of **6b**, perhaps because of its ability to absorb much of the hydrochloric acid.

Treatment of **6b** with ethanol in the presence of an equivalent of triethylamine at 0 °C afforded the 3,4-diethoxy intermediate **6c** in 80% yield. Warming **6b** in excess ethanol without a base resulted in destruction of the isothiazole sulfone ring system as evidenced by NMR. The structure of **6b** was assigned unequivocally on the basis of its mass spectrum. Significant peaks containing chlorine at *m/e* 222 and 87 were rationalized according to the fragmentation shown in eq 3.



*m/e* 267 *m/e* 222



(3)

*m/e* 87

**Amine Displacement Reactions. Monoamines.** In experiments designed to effect monosubstitution at C-3 or C-4, silylated amines were used with the expectation that their reduced nucleophilicity would minimize random and bis-substitution. In addition to lessened nucleophilicity, the silylated amines offered the advantage of neutral reaction conditions, i.e., formation of $(CH_3)_3SiCl$ instead of HCl.

With either **6a** or **6b** it was found that ammonolysis or aminolysis occurred preferentially at C-4. This regioselectivity was not affected by the nature of the leaving groups (OEt or Cl) or by the nucleophile (silylated or unsilylated amine).

For example, **6b** and **6c** afforded the same ammonolysis product, **7a** (Scheme I), whose structure was determined by single-crystal X-ray analysis (Figure 1).[10]

(5) Murray, J. I. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 744.
(6) Wen, R. Y.; Komin, A. P.; Street, R. W.; Carmack, M. *J. Org. Chem.* **1975**, *40*, 2743.
(7) Conditions tried for forming and capturing the methanesulfonamide carbanion include: $CH_3SO_2NH_2$ + 3 equiv of base (NaH/DME/Δ or *n*-BuLi/HMPA/THF/Δ), trapping with $(CO_2Et)_2$; $CH_3SO_2NHSiMe_3$ + excess NaH/DME, trapping with $(CO_2Et)_2$; $CH_3SO_2NHCOCO_2Et$ + excess base (10 × NaH/DME/Δ or 2 equiv of *n*-BuLi/TMEDA/ether/25 °C).
(8) (a) Hinman, R. L.; Locatelli, L., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 5655. (b) LeBerre, A.; Etienne, A.; Desmazieres, B. *Bull. Soc. Chim. Fr.* **1975**, *3–4*, 807.
(9) The corresponding 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**3**), obtained by Carmack from the dipotassium salt, was reported to have ionization constants $pK_{a_1}$ = 2.20 and $pK_{a_2}$ = 5.55.[6]

Table I. $^{13}C$ Chemical Shifts[a] and Net Atomic Charges ($\times 10^3$)[b]

| | $^{13}C$ chemical shift | | | net atomic charge | | |
|---|---|---|---|---|---|---|
| compd | C-3 | C-4 | C-5 | C-3 | C-4 | C-5 |
| 7a | 159.9 | 146.5 | 101.6 | 307 | 191 | −179 |
| 8a | 156.9 | 148.7 | 101.4 | 281 | 190 | −177 |
| 8b | 158.4 | 149.3 | 118.0 | 273 | 183 | −135 |

[a] Chemical shifts in ppm from internal $Me_4Si$ solution in $Me_2SO$. [b] Calculated by using CNDO/2.

Use of silylated amines did preclude bis-substitution and, in the examples studied, displacement of the 3-OEt group could be accomplished only with unsilylated amines. In general, the most convenient and reproducible conditions for achieving monoamine substitution at C-4 were found to be reaction of either **6b** or **6c** with an excess of silylated amine in refluxing acetonitrile. Identical monosubstitution products (**7a** and **7b**) were obtained from both **6b** and **6c** with silylated and with unprotected amines as confirmed by $^{13}C$ NMR and mixed melting points.

**Diamines.** Ammonia and the alkylamines diethylamine and methylamine reacted first at C-4 to give the amines **7**. The bis-ammonolysis product **8a** was obtained upon reaction of **6c** with 2 equiv of ammonia. With the alkylamines, bis-substitution proceeded slowly even when excess amine was used. The diamine **8b** was prepared from **7b** and ammonia at 25 °C. Prolonged reflux of an acetonitrile solution of **7b** and hexamethyldisilazane gave no evidence of **8b** formation. A small amount of **8a** was observed in the reaction of **7b** with ammonia; apparently even a tertiary amine function at C-4 can serve as a leaving group.

Potentiometric titrations of the diamines **8a** and **8b** confirmed the anticipated weak acidity of these compounds ($pK_a$ 9.15 and 9.60, respectively, protons lost), thus corroborating other evidence[11] for the alicyclic, nonaromatic nature of the isothiazole sulfone ring system.

**$^{13}C$ NMR and CNDO/2 Calculations.** The chemical shift assignments were relatively straightforward. The ester carbonyl carbon at C-5 was the most downfield resonance, occurring in the range 160–165 ppm,[12] while the $OCH_2CH_3$ and $N(CH_2CH_3)_2$ carbons were within normal ranges. It was expected that C-5 should have the most upfield ring carbon resonance by analogy with a series of 5-aryl analogues[4] and based on CNDO/2 calculations (see Experimental Section). One of the two remaining ring carbons exhibited a narrow range (156–160 ppm), the other a wider range (141–153 ppm) of chemical shifts. The latter was assigned to C-4, for which substituents varied from Cl to OEt. C-3 substituents thus were assigned the 156–160 ppm range. These assignments are consistent with those made for the 5-aryl analogues[4] and correlated well with the results from the CNDO/2 calculations.

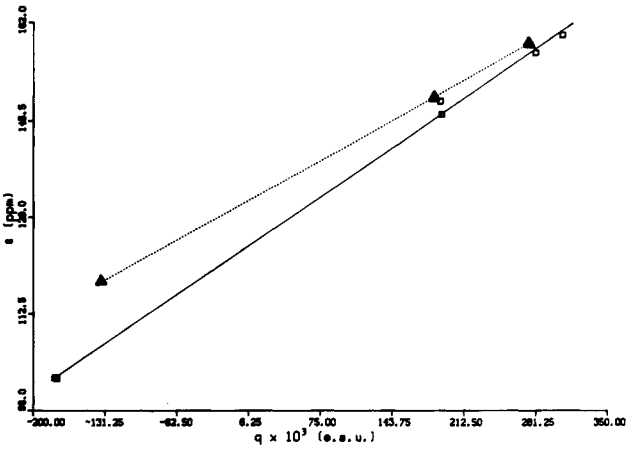



**Figure 2.** Correlations of $^{13}C$ chemical shifts and CNDO net atomic charges of 3,4-disubstituted-isothiazole 1,1-dioxides: (▲) **8b**; (□) **7a**, **8a**.

In contrast with reported data for the unoxidized isothiazoles, where correlations with $\pi$ charge densities were good and those with total calculated CNDO/2 charge densities were poor,[13] the correlation of chemical shifts with calculated total charge densities (Table I) in the 1,1-dioxide series was good. A better correlation was obtained for ring carbons from a single compound than for analogous carbons from different molecules. As shown in Figure 2, chemical shifts of **7a** and **8a** were correlated by one least-squares regression equation ($R^2 = 0.998$, $N = 6$) and those for the ring carbon atoms of **8b** by another ($R^2 = 1.000$, $N = 3$). These two different correlations suggest that the presence of a 4-NH function may alter the ring structure, perhaps through amino–imino tautomerism.

In summary, a practical synthesis of trisubstituted mononuclear isothiazole 1,1-dioxides has been developed. The regiochemistry of their nucleophilic substitution reactions has been elucidated, and spectroscopic and molecular orbital studies have helped to define some of the physical and chemical properties of this ring system.

## Experimental Section

Capillary melting points were determined on a Thomas-Hoover apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian EM-390 spectrometer, unless otherwise specified, and are expressed in parts per million from $Me_4Si$ as internal standard. $^{13}C$ NMR spectra were recorded on a Varian CFT-20 spectrometer with a 4000-Hz spectral window and 8K data points.

Thin-layer chromatography (TLC) was performed on silica gel (Analtech plates), and the components were visualized by UV light and $I_2$ vapor.

CNDO/2 calculations[14a] were performed with the aid of the Merck Modelling System[14b] using geometries for **7a** based on X-ray coordinates. Geometries for **8a** and **8b** were based on refined structures using the MOLBLD2 program.[14b]

**X-ray Structure Determination of 7a.** Crystals of **7a** formed from ethyl acetate solutions with symmetry $P2_1/n$. The cell constants determined from preliminary diffraction experiments were $a = 6.910$ (2) Å, $b = 13.833$ (5) Å, $c = 12.060$ (3) Å, and $\beta = 91.06$ (2)° for $Z = 4$ and a calculated density of 1.43 g/cm$^3$. All unique reflections with $2\theta \leq 114°$ were measured with Cu K$\alpha$ radiation ($\lambda$ 1.5418 Å) and a variable rate with scan technique on a four-circle diffractometer. Of the 1067 reflections measured, 1000 (94%) were observed ($I \geq 3\sigma I$) and corrected for Lorentz

(10) Johnson, C. K. "ORTEP-II, a Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations"; U. S. Atomic Energy Commission Report ORNL-3794 (2nd Rev. with Supplemental Instructions), 1970, Oak Ridge National Laboratory, Oak Ridge, TN. The heterocyclic ring of **7a** is planar with a maximum deviation of 0.015 Å from the least-squares plane for the five atoms. The observed torsional angle of 179° for C4–C5–C12–O13 and the shortened C5–C12 bond of 1.438 Å indicate that the carbonyl is conjugated with the C4–C5 double bond. The observed alternation of bond lengths of 1.280, 1.507, and 1.360 Å for N2–C3, C3–C4, and C4–C5 is structural evidence, which confirms the chemical evidence, for the alicyclic nature of **7a**. N11 is involved in two intermolecular hydrogen bonds in the crystal lattice: N–(H11a)O13, 2.84 Å; N11–(H11b)O6, 2.88 Å.

(11) $pK_a$ values for **5b**, susceptibility of **6** to nucleophilic attack at C-3 and C-4, X-ray spectral data of **7a**.

(12) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 295–303.

(13) Wasylishen, R. E.; Clem, T. R.; Becker, E. D. *Can. J. Chem.* **1975**, *53*, 596.

(14) (a) Pople, J. A.; Beveridge, D. L. "Appoximate Molecular Orbital Theory"; McGraw-Hill: New York, 1971. (b) Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. *Science (Washington, D.C.)* **1980**, *208*, 1425.

and polarization effects. Application of direct methods[15] gave initial positions for all of the non-hydrogen atoms. Refinements and Fourier difference maps allowed the selection of the hydrogen atoms. Full-matrix least-squares refinement minimizing $(F_o - F_c)^2$ with $w = (1/F_o)^2$ gave an unweighted $R$ value of 0.038.[16] The fractional coordinates and temperature parameters, bond distances and bond angles for **7a** can be found in Tables II, III, and IV, respectively (supplementary material).

**Ethyl *N*-(Methylsulfonyl)oxamate.**[7] A mixture of methanesulfonamide (4.4 g, 0.046 mol) and ethyl oxalyl chloride (6.3 g, 0.046 mol) was stirred at 100 °C for 1 h and then evaporated at 50 °C under aspirator pressure for 30 min. The thick oil that remained was crystallized from *n*-BuCl, and the solid was collected and washed with a 1:1 mixture of ether–*n*-BuCl. The crude oxamate, 7.75 g (86%), had mp 63–70 °C; an analytical sample was recrystallized from *n*-BuCl, mp 73.5–75 °C. $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (t, 3 H), 3.35 (s, 3 H), 4.40 (q, 2 H), 8.2–9.5 (br s, 1 H).

Anal. Calcd for $C_5N_9NO_5S$: C, 30.77; H, 4.65; N, 7.18. Found: C, 30.80; H, 4.63; N, 7.33.

**(Ethoxycarbonyl)methanesulfonamide (4, R = $CO_2Et$).** To a magnetically stirred solution of (ethoxycarbonyl)methanesulfonyl chloride[8b] (54.6 g, 0.29 mol) in 250 mL of $CH_2Cl_2$ under nitrogen at 0 °C was added dropwise hexamethyldisilazane (46.8 g, 0.29 mol). The resulting cloudy solution was allowed to warm to room temperature over 1 h and was then evaporated to dryness. The oil that remained was chilled in an ice bath and then carefully dissolved in EtOH. The EtOH solution was stirred at room temperature for 30 min and then concentrated in vacuo to an oil that crystallized on standing. The crude solid, 48.4 g (100%), that crystallized had mp 63–67 °C [lit.[8a] mp 66–68 °C; lit.[8b] mp 67–68 °C].

**Disodium Salt of 3,4-Dihydroxy-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (5a).** A sodium ethoxide solution was prepared from 7.6 g (0.33 g atom) of sodium spheres in 200 mL of absolute EtOH under nitrogen. To this solution at 25 °C was added a solution of 27.6 g (0.165 mol) of **4** (R = $CO_2Et$) in 200 mL of EtOH, followed by dropwise addition of diethyl oxalate (24.1 g, 0.165 mol) dissolved in 50 mL of EtOH. The resulting thick suspension was stirred mechanically at reflux for 18 h, cooled to 25 °C, and filtered, and the white solid was washed with 100 mL of EtOH. The disodium salt, 41.4 g (95%), was analyzed as a hemihydrate; mp 265–285 °C dec. The anhydrous salt could be obtained by drying at 110 °C (0.1 mmHg) over $P_2O_5$ for 24 h.

**5-(Ethoxycarbonyl)-4-hydroxy-3(2*H*)-isothiazolone 1,1-Dioxide (5b).** This compound was prepared from **5a** (3.0 g, 10.5 mmol) and the cation-exchange resin Bio-Rad AG50W-X8 (wet volume, 40 mL). Elution with water gave a strongly acidic eluent, which was lyophilized to afford a white solid. Crystallization of the latter from acetone–$CHCl_3$ gave 780 mg of **5b** (32%): mp 147–158 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.18 (t, 3 H), 4.06 (q, 2 H), 11.25 (s, 2 H); potentiometric titration in water with NaOH gave $pK_{a_1}$ 2.90 and $pK_{a_2}$ 3.35.

Anal. Calcd for $C_6H_7NO_6S$: C, 32.58; H, 3.19; N, 6.33. Found: C, 32.47; H, 3.30; N, 6.37.

**4-Chloro-3-ethoxy-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (6b).** Anhydrous **5a** (5.0 g, 18.9 mmol; dried at 100 °C (0.1 mmHg) over $P_2O_5$ for 24 h) was treated with 5.0 mL of freshly distilled oxalyl chloride and the mixture stirred very vigorously under a nitrogen atmosphere. Toluene (50 mL) containing 1 mL of dry pyridine was added, and the rapidly stirred mixure was heated by a stream of hot air until gas evolution commenced. The reaction was allowed to proceed exothermically until copious gas evolution had ceased, at which point heating was resumed and continued until no more $CO_2$ was given off. The mixture was concentrated in vacuo and the residue taken up in 100 mL of $CH_2Cl_2$. This solution was added to a stirred suspension of silica gel (70–230 mesh, 25 g, previously saturated with absolute EtOH, from which the EtOH had been decanted, and the silica gel then washed with 50 mL of $CH_2Cl_2$ and collected by filtration) in $CH_2Cl_2$, and the resulting suspension was stirred at room temperature for 1 h. Suction filtration through glass fiber paper afforded a clear solution, which was evaporated to dryness in vacuo. The residue, dissolved in $CHCl_3$, was percolated through a silica gel column and the product eluted with $CHCl_3$; 2.4 g (47%); mp 134–136 °C; MS, $m/e$ 267 ($M^+$), 222 ($M - OC_2H_5$), 135 ($M - OC_2H_5 - [ClC{\equiv}C{=}CO]^+$), 87 ($ClC{\equiv}C{=}CO^+$); $^1$H NMR ($CDCl_3$) $\delta$ 1.4 (t, 3 H), 1.52 (t, 3 H), 4.45 (q, 2 H), 4.65 (q, 2 H).

Anal. Calcd for $C_8H_{10}ClNO_5S$: C, 35.90; H, 3.77; N, 5.23. Found: C, 35.70; H, 3.84; N, 5.48.

Recrystallization of **6b** from EtOH yielded a product that was not identical with **6c** (vide infra) by TLC, $^1$H NMR, and $^{13}$C NMR. Although the material appeared homogeneous by TLC and had a mp of 78–80 °C, the proton NMR was not consistent with a 3:2 ratio of methyls to methylenes. The $^{13}$C NMR spectrum showed peaks at $\delta$ 172.8, 162.1, and 105.4 instead of those expected for **6c**.

**3,4-Diethoxy-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (6c).** Triethylamine (1.05 mL, 7.5 mmol) dissolved in 10 mL of $CH_2Cl_2$ was added dropwise at 0 °C to a stirred solution of 2.0 g (7.5 mmol) of compound **6b** and 2.5 mL of absolute EtOH in 10 mL of $CH_2Cl_2$. After 45 min, the solution was concentrated in vacuo to an oil which was chromatographed on silica gel. Elution with $CH_2Cl_2$ gave 1.6 g (80%) of pure product, mp 129–133 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.3–1.58 (m, 9 H), 4.3–4.88 (m, 6 H).

Anal. Calcd for $C_{10}H_{15}NO_6S$: C, 43.31; H, 5.45; N, 5.05. Found: C, 43.21; H, 5.60; N, 5.30.

**4-Amino-3-ethoxy-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (7a). Method A.** A mixture of the 4-chloro-3-ethoxy compound **6b** (5.2 g, 19.4 mmol) and hexamethyldisilazane (5.2 mL, 25 mmol) in 50 mL of dry MeCN was stirred at reflux under a nitrogen atmosphere for 5 h. Concentration in vacuo gave a thick paste which was chilled in an ice bath before dissolving in 25 mL of $CHCl_3$. The solution was stirred at 0 °C while a mixture of EtOH–$CHCl_3$ (5 mL:15 mL) was added dropwise. After stirring overnight at room temperature, the mixture was evaporated to a yellow solid which was collected and washed with a mixture of ether–EtOH. **7a**: 4.5 g (93%), mp 167–172 °C. An analytical sample was obtained by recrystallization from EtOAc; mp 172.5–173 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.27 (t, 3 H), 1.42 (t, 3 H), 4.29 (q, 2 H), 4.55 (q, 2 H), 7.98 (s, 1 H exchanged with $D_2O$), 8.68 (s, 1 H exchanged with $D_2O$).

Anal. Calcd for $C_8H_{12}N_2O_5S$: C, 38.71; H, 4.87; N, 11.28. Found: C, 38.76; H, 4.91; N, 11.40.

**Method B.** Compound **7a** was prepared from the 3,4-diethoxy compound **6c** (3.19 g, 11.5 mmol) and hexamethyldisilazane (3.2 mL, 15.1 mmol) in 35 mL of dry MeCN as described in method A above. The crude product, 2.14 g (74%), had mp 168–172 °C. A mixed melting point of this material with that of crude **7a** prepared by method A was undepressed (mp 169–172 °C). A TLC comparison (silica GF, 95:5 $CHCl_3$–EtOH) of products from methods A and B revealed them to be identical.

**Method C.** The 3,4-diethoxy compound **6c** (277 mg, 1 mmol) dissolved in 5 mL of dry THF was stirred in an ice bath while being treated with a solution of $NH_3$ in THF (2.2 mL, 0.465 M, 1 mmol). After 15 min at 0 °C there was no unreaceted **6c**. Evaporation of the reaction solution to dryness afforded a yellow solid which was collected and washed with ether; 190 mg (77%) of crude **7a**, mp 165–171 °C. NMR data and TLC comparisons of the products **7a** from methods A–C confirm them to be the same.

**4-(Diethylamino)-3-ethoxy-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (7b).** To a solution of **6b** (150 mg, 0.56 mmol) in 5 mL of $CH_2Cl_2$ stirred under a nitrogen atmosphere in an ice bath was added diethylamine (0.116 mL, 1.12 mmol). TLC (silica GF, 95:5 $CHCl_3$–EtOH) indicated the reaction was complete after 1 h at 0 °C. Evaporation to dryness left **7b** as a crystalline solid (155 mg, 91%), mp 123.5–125 °C.

Recrystallization from EtOAc provided the analytical sample as yellow needles, mp 124–125 °C. Compound **7b** was also prepared from **6b** and *N*-(trimethylsilyl)diethylamine (Pierce Chemical Co., 88% yield), from **6c** and *N*-(trimethylsilyl)diethylamine (88% yield), and from **6c** and diethylamine (68% yield) according to the procedures of methods A–C, respectively, described for **7a**; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.05–1.5 (m, 12 H), 3.65

(15) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.; Woolfson, M. M., "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; Universities of York, England, and Louvain, Belgium, 1978.

(16) Stewart, J. M.; Kruger, G. J.; Ammon, H. L.; Dickinson, C.; Hall, S. R. "The X-Ray System, Version of June, 1972"; TR-192, 1972, University of Maryland, College Park, MD.

(q, 4 H, $N(CH_2CH_3)_2$), 4.22 (q, 2 H), 4.48 (q, 2 H).

Anal. Calcd for $C_{12}H_{20}N_2O_5S$: C, 47.35; H, 6.62; N, 9.21. Found: C, 47.26; H, 6.63; N, 9.20.

**3-Ethoxy-5-(ethoxycarbonyl)-4-(methylamino)isothiazole 1,1-Dioxide (7c).** To a solution of compound **6b** (1.61 g, 6.0 mmol) in 10 mL of $CH_2Cl_2$ was added dropwise a solution of methylamine in THF (5.77 mL, 2.6 M, 15 mmol) at such a rate that the temperature remained at 30–35 °C. After stirring for 30 min, the mixture was filtered and the filtrate concentrated in vacuo. Chromatography of the residue on Merck silica gel, eluting with $CH_2Cl_2$, gave 110 mg (7%) of recovered **6b**. Elution with 1% EtOH, followed by 2%, and then 5% EtOH in $CH_2Cl_2$ gave 930 mg (59%) of crude 7c. Recrystallization from EtOAc gave analytically pure material, mp 183–185 °C; $^1H$ NMR (Varian T-60, $CDCl_3$) $\delta$ 1.38 (t, 3 H), 1.5 (t, 3 H), 3.35 (d, 3 H), 4.40 (q, 2 H), 4.70 (q, 2 H), 7.95 (br s, 1 H).

Anal. Calcd for $C_9H_{14}N_2O_5S$: C, 41.21; H, 5.38; N, 10.68. Found: C, 40.91; H, 5.41; N, 10.67.

**3,4-Diamino-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (8a).** The 3,4-diethoxy compound **6c** (1.0 g, 3.6 mmol) dissolved in 60 mL of dry THF was stirred in an ice bath while a solution containing $NH_3$ in THF (7.7 mL, 0.465 M, 3.6 mmol) was added. A TLC (silica GF, 95:5 $CHCl_3$–EtOH) inspection of the reaction solution after 30 min at 0 °C showed that all of **6c** had reacted to give compound **7a**, with a trace of a second, more polar product. Addition of a second equivalent (7.7 mL, 0.465 M, 3.6 mmol) of $NH_3$ resulted in formation of a white precipitate after 30 min at ambient temperature. TLC showed the reaction mixture to contain only the lower $R_f$ material seen previously as a minor spot. The white solid was collected by filtration and washed with ether to give **8a**, 560 mg (71%), mp 259–265 °C dec. This material analyzed correctly without further purification. $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.27 (t, 3 H), 4.25 (q, 2 H), 8.20 (br s, 4 H exchanged with $D_2O$). A potentiometric titration in 30% aqueous EtOH with NaOH gave $pK_a$ = 9.60 (proton lost).

Anal. Calcd for $C_6H_9N_3O_4S$: C, 32.88; H, 4.14; N, 19.17. Found: C, 32.99; H, 4.25; N, 19.01.

**3-Amino-4-(diethylamino)-5-(ethoxycarbonyl)isothiazole 1,1-Dioxide (8b).** To a solution of compound **7b** (300 mg, 1 mmol) in 10 mL of dry THF was added $NH_3$ in THF (4.3 mL, 0.465 M, 2 mmol). The solution was stirred at room temperature overnight. TLC (silica GF, 9:1 $CHCl_3$–EtOH) revealed two products at $R_f$ 0.48 (major) and $R_f$ 0.30 (minor). Evaporation of the solvent followed by trituration with absolute EtOH gave 180 mg (65%) of a yellow solid that contained the two components indicated previously. The minor component, at $R_f$ 0.30, was shown to have the same $R_f$ and was not separable from a mixture with the 3,4-diamino compound **8a**. Flash chromatography of the crude solid (Merck silica gel, 230–400 mesh), eluting with a 9:1 $CHCl_3$–EtOH mixture, afforded TLC pure **8b** (140 mg). Recrystallization from THF-ether gave analytically pure material, mp 175–177 °C dec; $^1H$ NMR ($CDCl_3$) $\delta$ 1.1–1.45 (m, 9 H), 3.48 (q, 4 H), 4.37 (q, 2 H), 6.70 (br s, 2 H). A potentiometric titration in water with NaOH gave $pK_a$ = 9.15 (proton lost).

Anal. Calcd for $C_{10}H_{17}N_3O_4S$: C, 43.62; H, 6.22; N, 15.26. Found: C, 43.78; H, 6.54; N, 15.20.

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**Registry No.** 4 (R = $CO_2Et$), 55897-04-6; **5a**, 84538-31-8; **5b**, 84538-32-9; **6b**, 84538-33-0; **6c**, 84538-34-1; **7a**, 84538-35-2; **7b**, 84538-36-3; **7c**, 84538-37-4; **8a**, 84538-38-5; **8b**, 84538-39-6; ethyl oxalyl chloride, 4755-77-5; ethyl *N*-(methylsulfonyl)oxamate, 84538-30-7; (ethoxycarbonyl)methanesulfonyl chloride, 55896-93-0; methanesulfonamide, 3144-09-0; diethyl oxalate, 95-92-1.

**Supplementary Material Available:** Tables II–IV containing atomic coordinates, thermal parameters, bond lengths and bond angles (3 pages). Ordering information is given on any current masthead page.

# Preparation of 4-Substituted Arsabenzenes[1]

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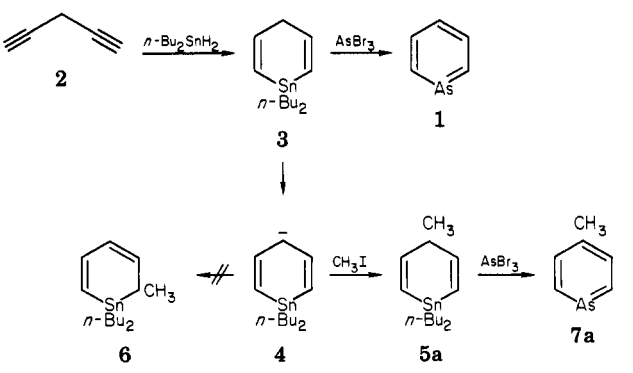
Alkylation of lithium 1,1-dibutylstannacyclohexadienide with primary alkyl halides gives the corresponding 4-alkyl-1,1-dibutylstannacyclohexa-2,5-dienes, which on treatment with arsenic tribromide afford 4-substituted arsabenzenes.

In 1971 we reported the synthesis of the new heteroaromatic arsabenzene.[2] Work in the past decade has indicated that arsabenzene is electronically, structurally, and chemically very similar to carbocyclic aromatics.[3] Thus, it is not unreasonable to hope that suitable derivatives of arsabenzene might display some of the biological activity of the corresponding carbocyclic aromatics. In order to explore this possibility, we sought to prepare arsabenzenes substituted with manipulatively useful functional groups. We now report on a general synthesis of 4-substituted arsabenzenes and its application to the preparation of arsabenzene analogues of $\beta$-phenethylamines.

Scheme I




Arsabenzene (1) itself is easily prepared by a two-step synthesis.[2] 1,4-Pentadiyne (2) may be hydrostannated with

(1) Based in part on the Ph.D. Thesis of S. T. A.-O., The University of Michigan, 1982.

(2) Ashe, A. J., III. *J. Am. Chem. Soc.* **1971**, *93*, 3293.

(3) For reviews of the chemistry of arsabenzene, see: (a) Märkl, G. *Phosphorus Sulfur* **1977**, *3*, 77. (b) Jongsma, C.; Bickelhaupt, F. *Top. NonBenzenoid Aromat. Chem.* **1977**, *2*, 139. (c) Jutzi, P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 232. (d) Ashe, A. J., III. *Acc. Chem. Res.* **1978**, *11*, 153. (e) Tzschach, A.; Heinicke, J. "Arsenheterocyclen"; VEB Deutscher Verlag für Grundstoffindustrie: Leipzig, 1978; pp 124–130, 135–138. (f) Ashe, A. J., III. *Top. Curr. Chem.* **1982**, *105*, 125.

0022-3263/83/1948-0767$01.50/0 