Thiazolo[3,2-*b*]-*s*-triazole

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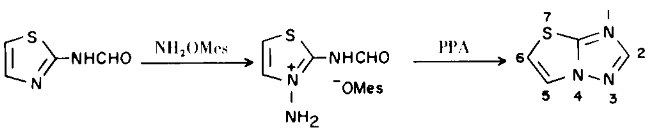
Received January 29, 1974

2-Formamidothiazole and *O*-mesitylenesulfonylhydroxylamine readily gave 3-amino-2-formamidothiazolium mesitylenesulfonate that with polyphosphoric acid gave thiazolo[3,2-*b*]-*s*-triazole. In its nmr spectrum, a long-range coupling of 1.4 Hz between H-2 and H-6 is observed.



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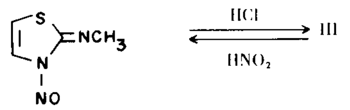

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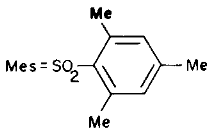
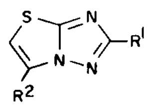
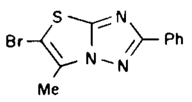




V, R¹ = H, R² = Me
VI, R¹ = Me, R² = H
VII, R¹ = R² = Me
VIII, R¹ = Ph, R² = H
IX, R¹ = Ph, R² = Me



X

Bicyclic fused 5-5 heteroaromatic ring systems with bridgehead nitrogen have been the subject of numerous investigations (1). Recently (2), we described a novel synthetic method for the thiazolo[3,2-*b*]-*s*-triazole ring system. We now wish to report a synthesis of the parent compound, thiazolo[3,2-*b*]-*s*-triazole (III), by an application of this method, and the spectral and chemical properties of III, in particular a long-range coupling between H-2 and H-6.

Compound III was prepared in 90% yield by dehydrocyclization with polyphosphoric acid of 3-amino-2-formamidothiazolium mesitylenesulfonate (II), which in turn was readily obtained by reaction of 2-formamidothiazole (I) with *O*-mesitylenesulfonylhydroxylamine (MSH) (3). The spectral data are consistent with the structure III: its uv spectrum (λ max (methanol) 242 nm and 247 sh) is similar to those observed with other thiazolo[3,2-*b*]-*s*-triazoles (2,4), its mass spectral fragmentation pattern follows the general ones reported for thiazolo[3,2-*b*]-*s*-triazoles (2,4), and the nmr spectrum shows H-2 at τ 1.89, H-5 at τ 2.22, and H-6 at τ 2.98. The chemical shift assignments are based on those derived from earlier studies (2,4).

Of particular interest in the nmr spectrum (Figure 1) is that H-6 forms a doublet of doublets (J = 4.3 and 1.4 Hz) by coupling with H-5 and small long-range coupling with H-2. This long-range coupling was confirmed not only by double resonance experiments, but also by substituent labeling. First, irradiation at the frequency of H-2 simplified the H-6 signal to a sharp doublet, and second, irradiation at the frequency of H-6 sharpened the broad signal of H-2. The small coupling was again observed in the nmr spectrum of 5-methylthiazolo[3,2-*b*]-*s*-triazole (V), which was synthesized from 2-amino-4-methylthiazole, but in that of the 2-methyl derivative (VI), no such coupling was observed. Analogous long-range coupling between protons separated by six bonds in an extended zig-zag path has been reported for bicyclic fused 5-6 heterocycles such as benzothiophene (5a,b), indole (5b), and indolizine (5c), and for bicyclic fused 5-5 systems such as thieno[3,2-*b*]pyrroles (6a), thieno[3,2-*b*]thiophene (6b), and pyrrolo[2,1-*b*]thiazolium perchlorate (6c).

In 1891, Näf reported that acid treatment of 2-(*N*-methylimino)-3-nitroso-2,3-dihydrothiazole (IV) affords compound III and nitrosation of III gives back IV (7). However, our compound was shown to be stable under nitrosation conditions (sodium nitrite in hydrochloric acid at 0°). Moreover, the reported melting point (darkens at 130° and melts at 210-220°) for the hydrochloride of

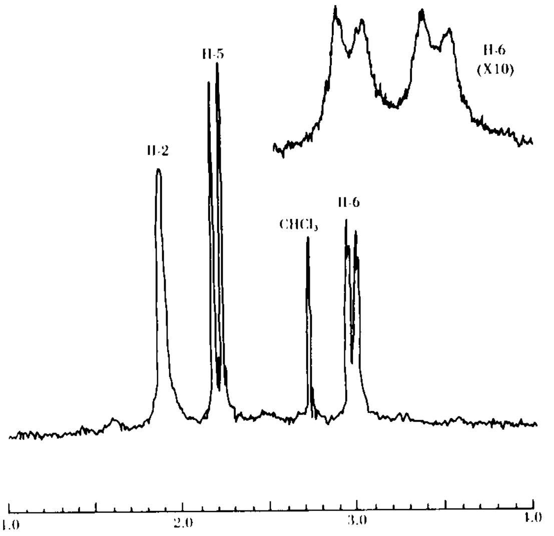


Figure 1. The 90 MHz nmr spectrum of thiazolo[3,2-*b*]-*s*-triazole (III) in the region τ 1.0-4.0 (solvent, deuteriochloroform).

Näf's compound is different from that of the hydrochloride of our compound (m.p. 226-227° in an open capillary) which does not change color until it melts but gradually sublimes during heating. This evidence indicates that the structural assignment of Näf's compound may be incorrect.

Finally, we have compared the chemical reactivities of III and some substituted thiazolo[3,2-*b*]-*s*-triazoles. It has been reported that 5-methyl (V) and 2,5-dimethyl (VII) derivatives are readily brominated at C-6 (8). In our hands, the 5-methyl-2-phenyl derivative (IX) was also found to be readily brominated by *N*-bromosuccinimide in refluxing chloroform within 1 hour. However, unsubstituted (III), and 2-methyl (VI) and 2-phenyl (VIII) derivatives failed to react with bromine under the conditions employed for bromination of V, VII, and IX, and the starting materials were recovered unchanged in all of these cases. These results suggest that thiazolo[3,2-*b*]-*s*-triazole (III) is resistant to electrophilic substitution but the introduction of a 5-methyl substituent greatly activates the C-6 position, presumably due to stabilization of the transition state through hyperconjugation.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on an Hitachi EPI G-2 spectrophotometer, uv spectra on an Hitachi 124 spectrophotometer, nmr spectra on Hitachi R-22 and R-20A spectrometers and mass spectra on an Hitachi RMU-6D mass spectrometer operating at 70 ev. Preparative thin layer chromatography was carried out on Merck Alumina PF_{254}. 2-Aminothiazole (I) and 4-methyl-2-aminothiazole were obtained commercially.

3-Amino-2-formamidothiazolium Mesitylenesulfonate (II).

To an ice-cooled solution of 2-formamidothiazole (I) (256 mg.) in methylene chloride (2 ml.) was added dropwise a solution of MSH (430 mg.) in methylene chloride (10 ml.). The reaction mixture was allowed to stand at room temperature for 10 minutes. After addition of ether, the solution was allowed to stand in a refrigerator. The precipitated crystals were collected and recrystallized from ethanol-ether to give white needles of II, m.p. 131-132°, yield, 480 mg. (70%).

Anal. Calcd. for $C_{13}H_{17}N_3O_4S_2$: C, 45.48; H, 4.99; N, 12.24. Found: C, 45.28; H, 4.95; N, 12.12.

Thiazolo[3,2-*b*]-*s*-triazole (III).

A mixture of II (250 mg.) and polyphosphoric acid (800 mg.) was heated at 100-110° for 1.5 hours. After cooling, the reaction mixture was poured into ice-water, made alkaline with 10% sodium hydroxide and extracted with chloroform. The dried extract was concentrated to give colorless crystals of III, which was recrystallized from ether-petroleum-ether, m.p. 98-100°, yield, 82 mg. (90%); ir (potassium chloride): cm^{-1} 1450 (s), 1390 (s), 1380 (s), and 1340 (s); uv λ max (methanol): 242 nm (log ε, 3.88) and 247 (sh) (3.73), mass spectrum m/e (rel. intensity): 125 (100), 98 (56), 71 (40), 58 (30), and 45 (77).

Anal. Calcd. for $C_4H_3N_3S$: C, 38.40; H, 2.42; N, 33.60. Found: C, 38.43; H, 2.57; N, 33.86.

The hydrochloride was obtained by passing dry hydrogen chloride into an ethereal solution of III, m.p. 226-227° (in an open capillary) (from ethanol-ether).

Anal. Calcd. for $C_4H_4ClN_3S$: C, 29.74; H, 2.50; N, 26.01. Found: C, 29.88; H, 2.53; N, 25.96.

2,3-Diamino-4-methylthiazolium Mesitylenesulfonate.

Using a similar procedure described for II, 2,3-diamino-4-methylthiazolium salt was obtained from 4-methyl-2-aminothiazole (342 mg.) and MSH (645 mg.). The precipitated crystals were recrystallized from ethanol-ether, m.p. 204-205°, yield, 643 mg. (65%).

Anal. Calcd. for $C_{13}H_{19}N_3O_3S_2$: C, 47.31; H, 5.82; N, 12.76. Found: C, 47.36; H, 5.80; N, 12.76.

5-Methylthiazolo[3,2-*b*]-*s*-triazole (V).

A solution of 2,3-diamino-4-methylthiazolium salt (500 mg.) in formic acid (4 ml.) was heated in a sealed tube (bath temperature 150-180°) for 2 hours. After evaporation of formic acid, the residue was treated with 10% sodium hydroxide and extracted with chloroform. The dried extract was concentrated and the residue was purified by preparative tlc using chloroform as solvent. The product was recrystallized from *n*-hexane, m.p. 70-71° [lit. m.p. 64-66° (9)], yield, 43 mg. (21%); ir (potassium chloride): cm^{-1} 3100 (w), 1460 (s), 1420 (w), 1400 (s), and 1350 (s); uv λ max (methanol): 244 nm (log ε, 3.94); mass spectrum (rel. intensity): 139 (100), 112 (73), 85 (12), 71 (54), 67 (95), and 45 (68); nmr (deuteriochloroform, 90 MHz): τ 1.87 (1H, bd, H-2), 3.39 (1H, m, H-6), and 7.45 (3H, d, J = 2 Hz, Me).

Anal. Calcd. for $C_5H_5N_3S$: C, 43.15; H, 3.62; N, 30.19. Found: C, 43.23; H, 3.75; N, 30.29.

6-Bromo-5-methyl-2-phenylthiazolo[3,2-*b*]-*s*-triazole (X).

Utilizing a procedure of Kano and Noguchi (8), a solution of 5-methyl-2-phenylthiazolo[3,2-*b*]-*s*-triazole (IX) (53 mg.) (2) and *N*-bromosuccinimide (90 mg.) in chloroform (2 ml.) was refluxed for half an hour. The solvent was removed and the residual solid was recrystallized from ethanol to give white needles of X, m.p.

155-156°, yield, 48 mg. (66%); ir (potassium chloride): cm^{-1} 1465 (s), 1430 (s), and 1320 (s); uv λ max (methanol): 224 (sh) nm (log ε, 3.69), 263 (sh) (4.16), 267 (4.16), 280 (sh) (4.14), and 287 (sh) (3.90); nmr (deuteriochloroform, 60 MHz): τ 1.75-2.62 (5H, m, phenyl), and 7.47 (3H, s, Me).

Anal. Calcd. for $C_{11}H_8BrN_3S$: C, 44.91; H, 2.74; N, 14.29. Found: C, 44.75; H, 2.84; N, 14.31.

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