

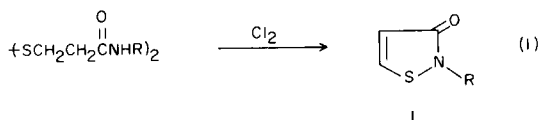
Isothiazoles V: 3-Methoxy and 3-Aminoisothiazoles

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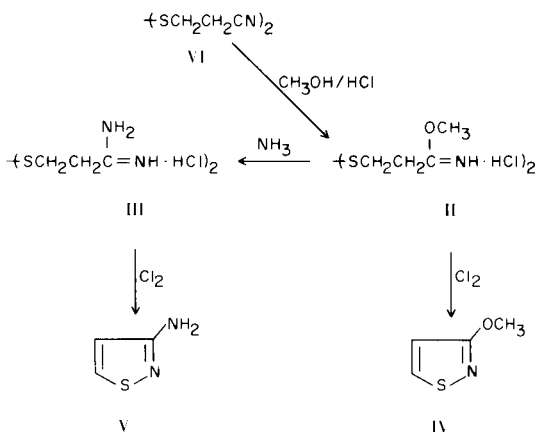
Received December 16, 1970 - Revised May 26, 1971

In a previous publication (1) the general synthesis of 4-isothiazolin-3-ones (I) by the chlorine induced cyclization (Eq. 1) of 3,3'-dithiodipropionamides was described. We wish to report the analogous transformation of the corresponding methyl imidate hydrochloride (II) and the amidine



hydrochloride (III) to 3-methoxyisothiazole (IV) and 3-aminoisothiazole (V) (2) respectively (Scheme I).

SCHEME I



The imidate (II) and amidine (III) were prepared from 3,3'-dithiodipropionitrile (VI) (3) by standard methods. The 3-methoxyisothiazole (IV) was isolated in good yield (58%) by distillation, while compound V was obtained in 26% yield as its perchlorate salt. Compounds IV and V were identified by elemental analysis and UV and NMR spectral data which were in complete agreement with the isothiazole structures.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus, and melting and boiling points are uncorrected. The uv absorption spectra were recorded on a Perkin Elmer Model 202 Ultraviolet-Visible Spectrophotometer; and NMR spectra were recorded on a Varian T-60 Spectrometer. Elemental analyses were performed by the analytical department of the Research Division of Rohm and Haas Company.

3-Methoxyisothiazole (IV).

To a solution of 43 g. (0.25 mole) of 3,3'-dithiodipropionitrile (3) (VI) and 80 g. (2.5 moles) of methanol in 250 ml. of ethylene dichloride at 0° was added 54.8 g. (1.5 moles) of anhydrous hydrogen chloride over one hour. The reaction solution was then stored at 10° for 72 hours, during which time a heavy white precipitate formed. This solid was filtered and dried under vacuum to yield 68 g. (88%) of white solid dimethyl 3,3'-dithiodipropionimidate dihydrochloride (II), m.p. 125-128° dec., which was used without further purification.

To a suspension of 61.8 g. (0.20 mole) of II in 650 ml. of ethyl acetate at 15-20° was added over one hour 44.7 g. (0.63 mole) of chlorine. After addition, the mixture was stirred an additional hour and then filtered. The white solid precipitate was dissolved in 100 ml. of water and neutralized with solid sodium bicarbonate. The resulting oil-water mixture was extracted with ether, and the extracts were dried over anhydrous magnesium sulfate and evaporated to an oil. Distillation, using an 8 in. Vigreux column, then gave 26.8 g. (58%) of IV: b.p. 147-150°; n_D^{24} 1.5173; uv max (methanol) 254 m μ (log ϵ 3.90); nmr (60 Mc in deuteriochloroform) δ 6.51 (d, $J_{4,5}$ = 5Hz, 4-H), 8.34 (d, $J_{4,5}$ = 5Hz, 5-H), 3.98 (s, CH₃).

Anal. Calcd. for C₄H₅NOS: C, 41.74; H, 4.35; N, 12.17; S, 27.83. Found: C, 41.77; H, 4.35; N, 11.95; S, 27.90.

3-Aminoisothiazole (V) (2).

To a mixture of freshly prepared II, 30.9 g. (0.10 mole), and 50 ml. of absolute ethanol was added 75 ml. of saturated ethanolic ammonia, keeping the temperature below 30°. After stirring for several hours the mixture was filtered, and the precipitate dried to give 19.8 g. (71%) of 3,3'-dithiodipropionamidine dihydrochloride (III), m.p. 182-192° dec., (Lit. (3) m.p. 182-183° dec.). This material was used without further purification.

To a suspension of III, 9.6 g. (25 mmoles), in 50 ml. of ethyl acetate was added at 0°, over one hour, 5.6 g. (78.8 mmoles) of chlorine gas. After addition the reaction was allowed to warm to room temperature, and a gummy material formed. The solvent was decanted from the gum, and ether was added to replace it.

The mixture was then neutralized with 5% aqueous sodium bicarbonate solution. The aqueous phase was extracted with ether, and the combined ether layers were dried over anhydrous magnesium sulfate. Evaporation of the ether gave 3.43 g. of impure V. This material was taken up in 15 ml. of glacial acetic acid, and 5 ml. of 70% perchloric acid was added. Dilution of the acetic acid solution with 200 ml. of ether gave a white precipitate which on filtration gave 2.6 g. (26%) of V perchlorate salt, m.p. 110-113°; uv max (methanol) 278 μ ($\log \epsilon$ 3.91), (water) 269 μ ($\log \epsilon$ 3.86); nmr (60 Mc in dimethylsulfoxide) δ 6.67 (d, $J_{4,5} = 5.5$ Hz, 4-H), 8.80 (d, $J_{4,5} = 5.5$ Hz 5-H), 7.77 (s, NH_3).

Anal. Calcd. for $\text{C}_3\text{H}_5\text{ClN}_2\text{O}_4\text{S}$: C, 17.96; H, 2.49; N, 13.92; S, 15.96; Cl, 17.71. Found: C, 18.20; H, 2.50; N, 13.91; S, 15.96; Cl, 17.70.

REFERENCES

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