Isothiazoles VII: *N*-Hydroxyalkylation and Mannich Reaction of 4-Isothiazolin-3-one

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Hydroxyalkylation and the synthesis of Mannich bases of 4-isothiazolin-3-one are described. Conversion of hydroxyalkyl to haloalkyl derivatives and the preparation of 2-arylcarbamoyloxymethyl-4-isothiazolin-3-ones are also reported.

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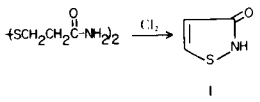
A previous publication (1) from this laboratory described a facile synthesis of 4-isothiazolin-3-ones (I) by the chlorination-cyclization of 3,3'-dithiodipropionamide. We now report several reactions of I to yield 2-hydroxyalkyl-4-isothiazolin-3-ones (II, IV, VII), various derivatives thereof,

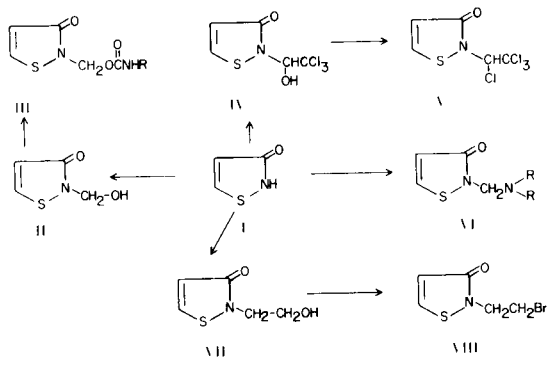


I

and representative Mannich bases VI, (Scheme I).

Hydroxymethylation of I with formaldehyde provided 2-hydroxymethyl-4-isothiazolin-3-one (II) in high yield. While stable in the solid state, in protonic solvents II reverted immediately to I as evidenced by nmr analysis in deuterium oxide. Treatment of II with arylisocyanates in benzene afforded exclusively 2-arylcarbamoyloxymethyl-4-isothiazolin-3-ones (III). However, alkylisocyanates under similar reaction conditions gave instead the respective 2-carbamoyl-4-isothiazolin-3-one derivatives (2).

Scheme I



Moreover, compound I reacted with chloral to afford the hydroxy derivative IV. Treatment of the alcohol IV with thionyl chloride provided the tetrachloroethyl derivative V.

Treatment of a methanolic solution of I with aqueous formaldehyde and various primary and secondary amines provided the Mannich bases VI. Similar products were also obtained from 2-hydroxymethyl-4-isothiazolin-3-one (II) and anilines. While compounds VI were stable in nonprotonic solvents, in water they reverted to I as shown by nmr analysis in deuterium oxide.

Compound I reacted under acidic conditions with ethylene oxide to give 2-(2-hydroxyethyl)-4-isothiazolin-3-one (VII). Compound VII and thionyl bromide provided 2-bromoethyl-4-isothiazolin-3-one (VIII). The alcohol VII reacted atypically and did not yield carbamates on treatment with various isocyanates.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were taken in mineral oil mulls on a Perkin Elmer Infracord, Model 137. Nmr spectra were recorded on a Varian T-60 Spectrometer. The multiplicity of the absorption is shown in brackets: s, singlet; d, doublet; m, multiplet. Elemental analyses were performed by the analytical department of the Research Division of the Rohm and Haas Company. The following experiments illustrate the general reaction procedures employed.

2-Hydroxymethyl-4-isothiazolin-3-one (II).

Method A.

To a mixture of 6.8 g. (0.068 mole) of 4-isothiazolin-3-one (I) (1), 5.7 g. (0.19 mole) of paraformaldehyde, 15 ml. of water, and 50 ml. of tetrahydrofuran was slowly added 2.8 g. (0.05 mole) of calcium oxide. The reaction slurry was stirred overnight and then acidified with formic acid. The solid residue was filtered off, and

the filtrate concentrated to near dryness. The thick, oily residue was taken up in 50 ml. of water, the latter was extracted twice with ether, and concentration of the aqueous solution gave 6.8 g. (76%) of II, m.p. 125-127° (chloroform); ir: 3.15 (OH), 6.20 (C=O) μ; nmr (DMSO-d_6): δ 4.98 (s, CH_2), 6.95 (d, $J_{4,5}$ = 6 Hz, H-4), 9.11 (d, $J_{5,4}$ = 6 Hz, H-5).

Anal. Calcd. for $C_4H_5NO_2S$: C, 36.64; H, 3.84; N, 10.67; S, 24.45. Found: C, 36.53; H, 3.80; N, 10.54; S, 24.75.

Method B.

To a solution of 5.0 g. (0.05 mole) of I in 10 ml. of methanol was slowly added 6.0 ml. (0.087 mole) of 38% aqueous formaldehyde solution. A slight temperature rise occurred, and after a few minutes a white precipitate formed. The latter was filtered off to give 4.1 g. (63%) of II.

2-(3,4-Dichlorophenylcarbamoyloxymethyl)-4-isothiazolin-3-one (III).

To a solution of 2.6 g. (0.02 mole) of II in 80 ml. of benzene was added 3.76 g. (0.02 mole) of 3,4-dichlorophenylisocyanate in 80 ml. of benzene. The reaction mixture was stirred at 50° for 20 hours, and filtration afforded 2.4 g. (38%) of III, m.p. 196-199° (ethanol); ir: 5.80, 6.00 (C=O's) μ; nmr (DMSO-d_6): δ 6.00 (s, CH_2), 6.49 (d, $J_{4,5}$ = 6 Hz, H-4), 8.81 (d, $J_{5,4}$ = 6 Hz, H-5), 7.72-7.99 (m, C_6H_3).

Anal. Calcd. for $C_{11}H_8Cl_2N_2O_3S$: C, 41.40; H, 2.53; N, 8.77; S, 10.04. Found: C, 41.41; H, 2.55; N, 8.78; S, 9.72.

2-(1-Hydroxy-2,2,2-trichloroethyl-4-isothiazolin-3

To a solution of 5.0 g. (0.05 mole) of I in 50 ml. of benzene was slowly added, over a period of 45 minutes, a solution of 7.8 g. (0.05 mole) of chloral in 15 ml. of benzene. A slight temperature rise occurred. The mixture was stirred for two hours at room temperature, and filtration yielded 11.2 g. (90%) of IV, m.p. 114-116° (benzene-ether); ir: 6.25 (C=O) μ.

Anal. Calcd. for $C_5H_4Cl_3NO_2S$: C, 24.15; H, 1.63; N, 5.63; S, 12.90. Found: C, 24.37; H, 1.90; N, 6.01; S, 12.58.

2-(1,2,2,2-Tetrachloroethyl)-4-isothiazolin-3-one (V).

A solution of 30 g. (0.121 mole) of IV in 300 ml. of thionyl chloride was heated at reflux for 2 hours. The reaction mixture was cooled and concentrated to give a red oily residue. Ether trituration of the oil gave a white solid which was filtered to yield 11.0 g. (35%) of V, m.p. 90-91°; ir: 6.15 (C=O) μ; nmr (DMSO-d_6): 6.98 (s, CH), 6.27 (d, $J_{4,5}$ = 6 Hz, H-4), 8.70 (d, $J_{5,4}$ = 6 Hz, H-5).

Anal. Calcd. for $C_5H_3Cl_4NOS$: C, 22.50; H, 1.13; N, 5.24; S, 12.01. Found: C, 22.17; H, 1.35; N, 5.05; S, 11.91.

2-(4-Chloroanilinomethyl)-4-isothiazolin-3-one (VI).

To a solution of 5.0 g. (0.05 mole) of I and 6.3 g. (0.05 mole) of 4-chloroaniline in 10 ml. of methanol was slowly added 6.0 ml. (0.06 mole) of a 38% aqueous formaldehyde solution. A slight temperature rise occurred and after a few minutes a white precipitate formed. The mixture was stirred for one and one-half hours, and filtration afforded 8.3 g. (69%) of VI, m.p. 93-95°; ir: 6.15 (C=O) μ.

Anal. Calcd. for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.63; S, 13.32. Found: C, 49.74; H, 3.81; N, 11.59; S, 13.28.

2-(2-Hydroxyethyl)-4-isothiazolin-3-one (VII).

A 500 ml. pressure apparatus was charged with 50 g. (0.5 mole) of I, 50 ml. of ethanol, and 25 drops of concentrated hydrochloric acid. The apparatus was thoroughly flushed with nitrogen and charged with 44 g. (1.0 mole) of gaseous ethylene oxide. The mixture was heated at 70° for 5 hours and allowed to stir at room temperature overnight. Chilling of the reaction mixture gave 43 g. (60%) of yellow solid VII, m.p. 109-111° (benzene-chloroform); ir: 6.25 (C=O) μ; nmr (DMSO-d_6): δ 4.00 (m, CH_2CH_2), 6.42 (d, $J_{4,5}$ = 6 Hz, H-4), 8.67 (d, $J_{5,4}$ = 6 Hz, H-5).

Anal. Calcd. for $C_5H_7NO_2S$: C, 41.37; H, 4.86; N, 9.64; S, 22.08. Found: C, 41.18; H, 4.91; N, 9.54; S, 12.80.

2-(2-Bromoethyl)-4-isothiazolin-3-one Hydrobromide (VIII HBr).

To a 1.0 g. (0.0069 mole) sample of VII was added dropwise with stirring 5 ml. (0.0065 mole) of thionyl bromide. A vigorous reaction occurred during the addition and subsided in a few minutes. The excess thionyl bromide was evaporated, and the residual deep red oil was dissolved in a small amount of methanol. A tan solid precipitated on dilution of the methanolic solution with ether. Filtration afforded 0.6 g. (30%) of VIII HBr; ir: 6.30 (C=O) μ; nmr (DMSO-d_6): δ 4.25 (m, NCH_2CH_2), 3.67 (m, NCH_2CH_2), 6.10 (d, $J_{4,5}$ = 6 Hz, H-4), 8.40 (d, $J_{5,4}$ = 6 Hz, H-5).

Anal. Calcd. for $C_5H_7Br_2NOS$: C, 20.78; H, 2.44; N, 4.84; S, 11.09. Found: C, 21.01; H, 2.69; N, 4.80; S, 11.31.

REFERENCES AND NOTES

(1) S. N. Lewis, G. A. Miller, M. Hausman and E. C. Szamborski, *J. Heterocyclic Chem.*, 8, 571 (1971).

(2) S. N. Lewis, G. A. Miller, E. C. Szamborski and M. Hausman, *ibid.*, 8, 587 (1971).