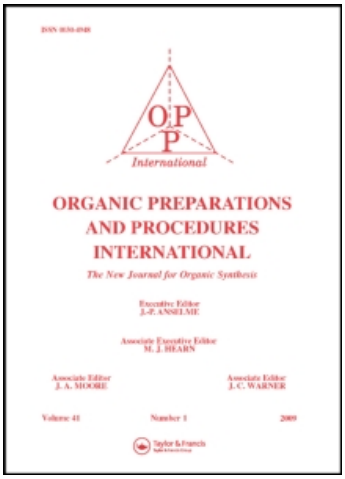

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SYNTHESIS OF 3-(CARBOXYMETHYL)BENZOTHIAZOLINE-2-THIONE

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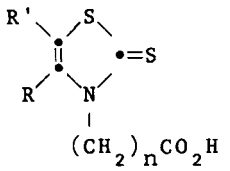
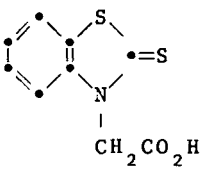
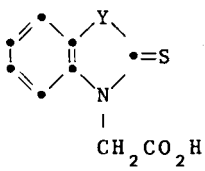
Synthesis of N-substituted carboxylic acid derivatives of thiazoline-2-thione I traditionally involves either the condensation of amino acids, carbon disulfide and an appropriate α-halomethyl carbonyl compound[1] or the Michael addition of the corresponding 2-thiazolethiol to a properly activated double bond (I, n = 2).[2]



I



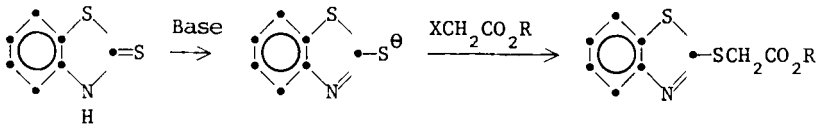
II



III

These reactions, though appearing quite general, are limited in that they are not applicable to the synthesis of II and related compounds such as III (Y = NR or O), wherein R' and R are part of an aromatic system. Other approaches to II using benzothiazoline-2-thione IV as a starting material in a nucleophilic reaction have not been successful owing to the well-known ambident nature of the anion of IV, which affords the S-substitution almost exclusively under a variety

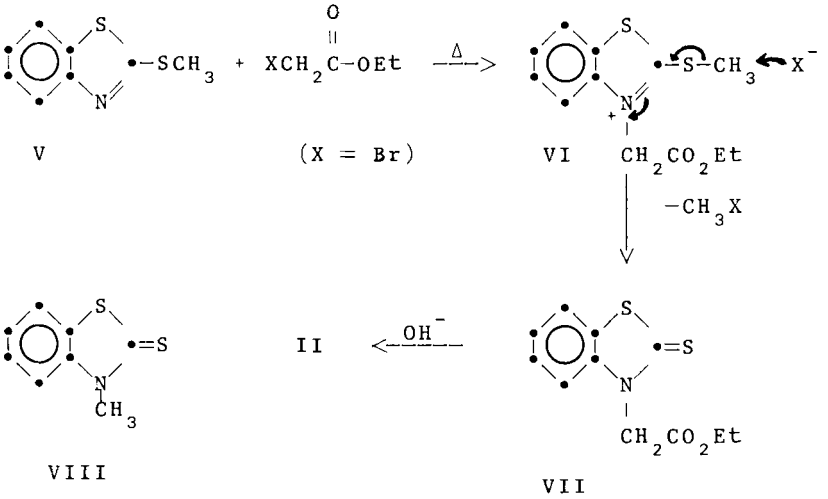
of reaction conditions.[3]



IV

Our successful solution to this interesting synthetic problem has come by our undertaking a rather different approach, as depicted in Scheme I, using 2-(methylthio)benzothiazole (V) as our starting material.

Scheme I



V VI VII VIII II

The major by-product of these reactions is 3-(methyl)-benzothiazoline-2-thione (VIII) (which can be readily separated from II by treatment with base), presumably resulting from the competing reaction of CH_3X and V. In attempts to minimize the formation of this by-product and thus to increase the yield of the desired thione II, the following conclusions have been drawn from our experiments:

1. The reaction is best conducted "neat," in the absence of solvents. Polar solvents, such as DMSO or HMPA, tend to promote other side reactions, whereas nonpolar solvents, such as o-dichlorobenzene or xylene, decrease the rate of alkylation of V.

2. The optimum temperature range is 140°-150° and the reaction is usually completed within a few hours as evidenced by the gradual subsiding of the effervescence (CH_3Br) from the reaction mixture.

3. In choosing the proper halogenated ethyl acetates, the order Br > I > Cl is recommended. Ethyl iodoacetate afforded more 2-(methyl)benzothiazoline-2-thione than ethyl bromoacetate, presumably because the CH_3I (bp 41-43°) generated during the dealkylation step of VI is more electrophilic and less volatile than CH_3Br (bp 4°). In the case of ethyl chloroacetate (X = Cl), its poor alkylating ability renders the formation of the key quarternary salt VI extremely slow even at reaction temperatures above 160°. As a result, mostly starting V is recovered under these conditions.

EXPERIMENTAL[4]

3-(Carbethoxymethyl)benzothiazoline-2-thione (VII). - A mixture of 100 g (0.56 moles) of 2-(methylthio)benzothiazole (Eastman Chemical 4008) and 100 g (0.6 moles) of ethyl bromoacetate was heated with stirring in an oil bath at 140-145° for 2 hr or until the evolution of methyl bromide had practically ceased. On cooling, the partially solidified, brown reaction product was extracted with a liberal amount

of hot hexanes (~3 l.) containing ca. 200 ml of benzene. The combined extracts crystallized on cooling to give 35 g of a first crop and 44 g of a second crop (obtained on concentrating the mother liquor) of VII (a total of 56% yield). An analytical sample of VII was obtained by recrystallization from hexanes (bp. 68-72°), mp. 100-100.5°; $\lambda_{max}^{CHCl_3}$ (uv) 245, 330 nm; nmr ($CDCl_3$/TMS): δ1.26 (t, $\underline{CH_3}CH_2O$-, 3), 4.23 (q, $CH_3\underline{CH_2}O$-, 2) 5.2 (s, -N-$\underline{CH_2}CO_2$-, 2) and 7.35 (m, Ar$\underline{H}$, 4) ppm.

Anal. Calcd for $C_{11}H_{11}NO_2S_2$: C, 52.2, H, 4.4; N, 5.5; S, 25.3. Found: C, 51.8; H, 4.7; N, 5.3; S, 25.8.

3-(Carboxymethyl)benzothiazoline-2-thione (II). - A mixture of 100 g (0.56 moles) of 2-(methylthio)benzothiazole (V) and 100 g (0.6 moles) of ethyl bromoacetate was heated in an oil bath (150-155°) with vigorous stirring for 1.5 hr. TLC (silica gel, eluted with EtOAc: ØH = 1:5 v/v) assay revealed only 3-(carbethoxymethyl)benzothiazoline-2-thione (VII) and 3-(methyl)benzothiazoline-2-thione (VIII) in the reaction mixture. Without purification, the crude product was saponified by refluxing on a steam bath for 2.5 hr with 52 g NaOH in the presence of 200 ml H_2O and 50 ml EtOH. The ice-cooled, brown, oily suspension was diluted with water and extracted with ether twice to remove the neutral by-product. The alkaline solution was acidified by pouring into 150 ml conc. HCl and ice. The precipitated yellow solid was collected, washed thoroughly with water, and recrystallized from ethanol and water giving 72 g of crude II in 57% yield based on V. Further purification was achieved by repeated

recrystallization from dichloroethane, to afford 45 g (36%) pure II, mp. 192-193°; $\lambda_{max}^{CHCl_3}$ (uv) 328 nm; nmr (DMSO-d_6/TMS): δ 5.13 (s, -N-$\underline{CH_2}$-CO_2, 2), 6.0 (s, -$CO_2\underline{H}$, 1), and 7.3 (m, Ar$\underline{H}$, 4).

Anal. Calcd for $C_9H_7NO_2S_2$: C, 48.0; H, 3.1; N, 6.2; S, 28.4. Found: C, 47.6; H, 3.4; N, 6.1; S, 28.3.

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2. W. J. Humphlett, ibid., 5, 387 (1968).
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4. Mps were uncorrected; nmr spectra were recorded on a Varian T-60 spectrometer using TMS as internal standard; uv spectra were obtained on a Perkin-Elmer 202 spectrophotometer. Elemental analyses were done by the Analytical Sciences Division of the Kodak Research Laboratories.

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