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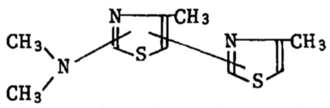
ONE STEP SYNTHESIS OF 5,2'-BITHIAZOLE DERIVATIVES: REACTION OF N,N-DIMETHYL-2,4-DITHIOBIURET WITH α-HALOKETONES

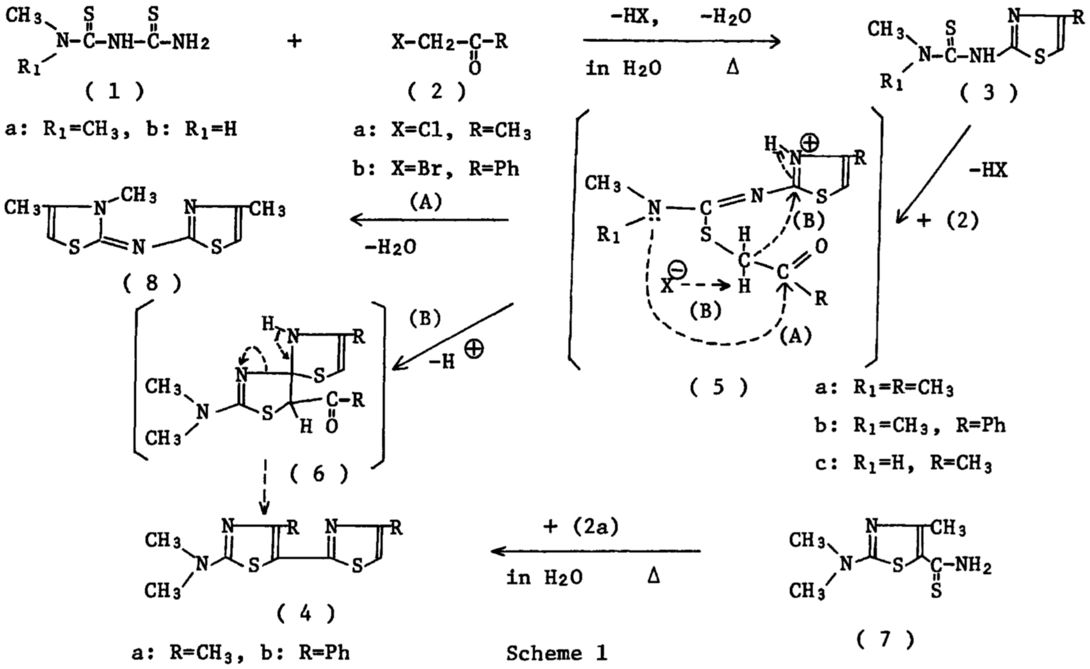
Yuichi YAMAMOTO, Reiko YODA, and Kyoko SEKINE
Organic Synthesis Laboratory, Kyoritsu College of Pharmacy,
Shibakōen, Minato-ku, Tokyo 105

Thermal reaction of N,N-dimethyl-2,4-dithiobiuret (1a) with monochloroacetone (2a) in aqueous solution gave 4-methyl-2-(N,N-dimethylthiocarbamoyl)aminothiazole (3a) and 5,2'-bithiazole derivative, 4-methyl-2-dimethylamino-5-(4'-methylthiazol-2'-yl)thiazole (4a). Reaction of (1a) and phenacyl bromide (2b) gave 2-dimethylamino-4-phenyl-5-(4'-phenylthiazol-2'-yl)thiazole (4b) alone in one step and in a good yield.

Thermal reaction of N,N-dimethyl-2,4-dithiobiuret (1a) with an equivalent of α-haloketone, $X\text{-}CH_2\text{-}\underset{O}{\underset{\|}{C}}\text{-}R$ (2a: X=Cl, R=CH_3), in aqueous solution gave 4-methyl-2-(N,N-dimethylthiocarbamoyl)aminothiazole (3a) and structurally unknown substance as pale yellow crystals (4a-HCl) (from 2-PrOH), mp 196-198° in equal amounts (yield, 90%). Neutralization of (4a-HCl) with $NaHCO_3$ solution gave a free base (4a), mp 85-86° (from hexane). The free base (4a) showed no absorption in the region beyond 3100 cm^{-1} and no absorption for $\nu_{C=O}$ in the region of 1700-1600 cm^{-1} in its IR spectrum (KBr). (4a); Found C, 50.03; H, 5.32; N, 17.54; S, 26.82%; mol wt (MS, M^+), 239. Calcd for $C_{10}H_{13}N_3S_2$; C, 50.18; H, 5.47; N, 17.56; S, 26.79%; mol wt 239.363. The free base (4a) was also obtained in 90% yield by the reaction of (3a) and (2a). In the NMR spectrum ($CDCl_3$) of (4a) a signal at δ 3.13 (3H, s) indicated the presence of $\frac{CH_3}{CH_3}\!\!>\!N\text{-}$, a doublet at δ 2.42 (3H, J=1.0 Hz) was due to the signal for 4-<u>CH_3</u> which undergoes a long-range coupling with 5-<u>H</u> in the thiazole ring appearing at δ 6.72 (1H, d, J=1.0 Hz), and a singlet at δ 2.50 (3H, s) corresponded to the <u>CH_3</u> in the thiazole ring. These data suggest the following bithiazole structure for (4a).



In order to establish unequivocally the bithiazole structure 4-methyl-2-dimethylamino-5-(4'-methylthiazol-2'-yl)thiazole (4a) was synthesized independently by the condensation of (2a) with 4-methyl-2-dimethylamino-5-thiocarbamoylthiazole (7), as shown in Scheme 1. IR and NMR spectral data of this compound agreed with those of the above-mentioned pale yellow crystals. Therefore, the structure of (4a) was finally established as 5,2'-bithiazole structure,



Scheme 1

4-methyl-2-dimethylamino-5-(4'-methylthiazol-2'-yl)thiazole. The similar reaction of (1a) and (2b) gave only orange yellow precipitates (4b) in 90% yield and (3b) was not obtained. The IR spectrum of (4b) showed no absorption of $\nu_{C=O}$ in the region of 1700 - 1600 cm^{-1}. (4b); mp 184-186° (from EtOH), Found C, 66.17; H, 4.57; N, 11.71; S, 17.82%; mol wt (MS, M^+), 363. Calcd for $C_{20}H_{17}N_3S_2$; C, 66.08; H, 4.71; N, 11.56; S, 17.64%; mol wt, 363.505. However, reaction of (1a) and (2b) in dioxane at room temperature gave (3b), mp 76-78° (from 2-PrOH) in 80% yield. The elemental analysis and mass spectral data gave a molecular formula of $C_{12}H_{13}N_3S_2$ for 2-(N,N-dimethylthiocarbamoyl)amino-4-phenylthiazole (3b).

In a previous paper,$^{1)}$ we reported that the reaction of N-methyl-2,4-dithiobiuret (1b) and (2a) gave 2-(4-methylthiazol-2-yl)imino-3,4-dimethyl-4-thiazoline (8) <u>via</u> route (A), in which a nucleophilic attack of the amide-nitrogen to the carbonyl-carbon in an intermediate (5c) is included. In contrast, (5a) and (5b) may be produced by the condensation <u>via</u> route (B), in which an active methylene in the intermediate (5a,b) attacks on a carbon at 2-position of the thiazole ring. Recently, Le Count <u>et al</u>.$^{2)}$ proved by X-ray analysis the formation of a trisubstituted thiazole by the reaction of N,N-dialkyl-N'-(5-chloropyridin-2-yl)thiourea and (2b), and proposed the reaction mechanism passing through the spiro intermediate (corresponding to 6). The reaction from (5) to (4) may be explained by a similar reaction mechanism. This is the first time that the 5,2'-bithiazole derivatives (4a,b) are obtained from (1a) in one step in a high yield, while the known bithiazole synthesis had required several steps with a poor total yield.

References

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2) D. J. Le Count and J. A. J. Jarvis, J. Chem. Soc., Chem. Comm., 282 (1977).

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