

ONE STEP SYNTHESIS OF 5,2'-BITHIAZOLE DERIVATIVES:

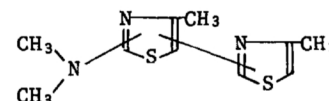
REACTION OF N,N-DIMETHYL-2,4-DITHIOBIURET WITH α -HALOKETONES

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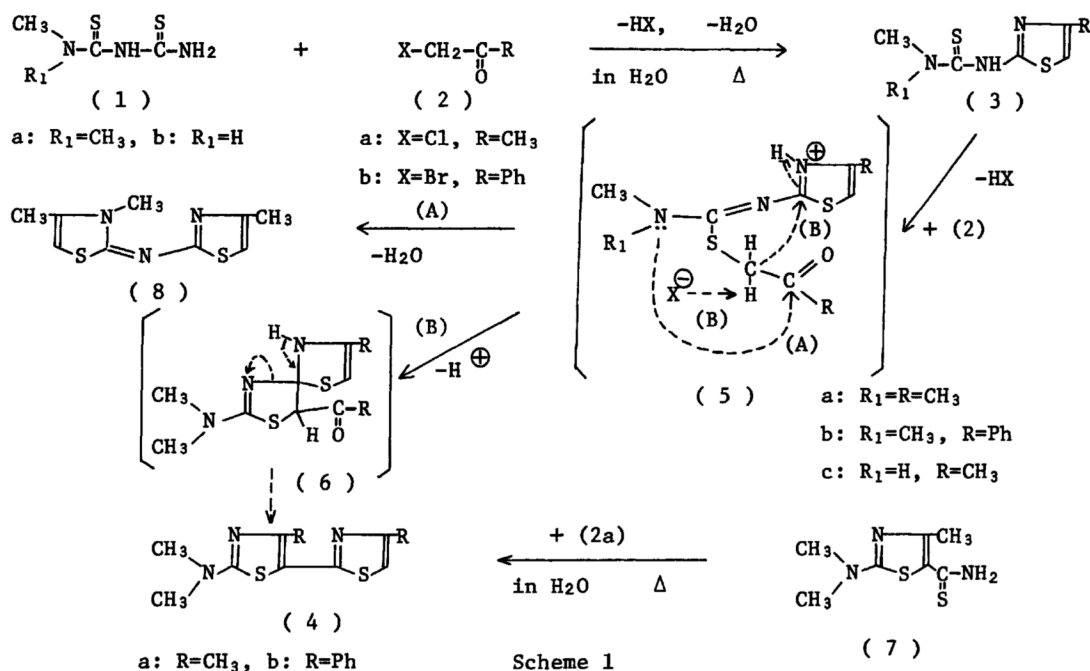
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Thermal reaction of N,N-dimethyl-2,4-dithiobiuret (1a) with monochloroacetone (2a) in aqueous solution gave 4-methyl-2-(N,N-dimethylthiocarbamoyl)aminothiazole (3a) and 5,2'-bithiazole derivative, 4-methyl-2-dimethylamino-5-(4'-methylthiazol-2'-yl)thiazole (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, $X-CH_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-R$ (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 $1700-1600\text{ cm}^{-1}$ 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 $\frac{CH_3}{CH_3}N-$, a doublet at δ 2.42 (3H, $J=1.0\text{ Hz}$) was due to the signal for 4- $\underline{CH_3}$ which undergoes a long-range coupling with 5- $\underline{H}$ in the thiazole ring appearing at δ 6.72 (1H, d, $J=1.0\text{ Hz}$), and a singlet at δ 2.50 (3H, s) corresponded to the $\underline{CH_3}$ 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,



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 $\nu_{\text{C=O}}$ in the region of $1700 - 1600 \text{ cm}^{-1}$. (4b); mp $184-186^\circ$ (from EtOH), Found C, 66.17; H, 4.57; N, 11.71; S, 17.82%; mol wt (MS, M^+), 363. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{S}_2$; 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 $76-78^\circ$ (from 2-PrOH) in 80% yield. The elemental analysis and mass spectral data gave a molecular formula of $\text{C}_{12}\text{H}_{13}\text{N}_3\text{S}_2$ 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) via 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 via 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 *et al.*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

- 1) Y. Yamamoto, H. Nakamura, and R. Yoda, *Kyoritsu Yakka Daigaku Kenkyu Nempo*, **15**, 31 (1970).
- 2) D. J. Le Count and J. A. J. Jarvis, *J. Chem. Soc., Chem. Comm.*, 282 (1977).

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