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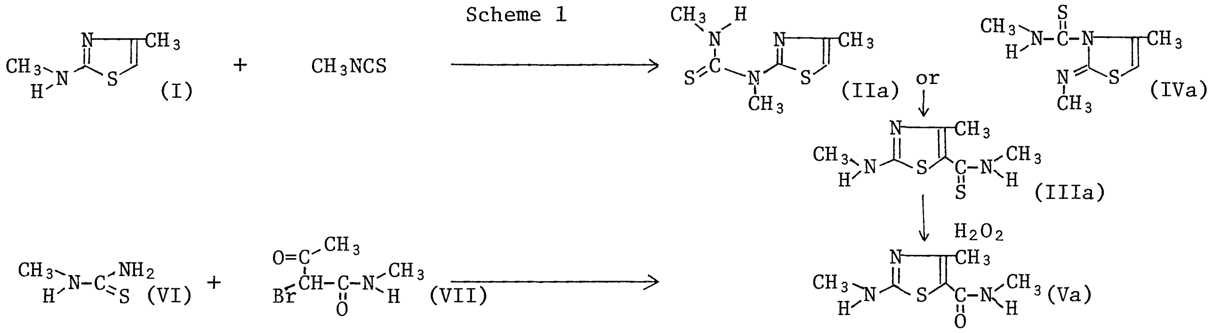
NEW SYNTHESIS OF 4-METHYL-2-METHYLAMINO-5-(N-METHYLTHIOCARBAMOYL)-THIAZOLE BY THERMAL ISOMERIZATION

Yuichi YAMAMOTO, Reiko YODA, and Chihiro TAMURA [1]
Organic Synthesis Laboratory, Kyoritsu College of Pharmacy,
Shiba Park, Minato-ku, Tokyo 105

A reaction of 4-methyl-2-methylaminothiazole (I) with methyl isothiocyanate gave 1,3-dimethyl-1-(4-methylthiazol-2-yl)thiourea (IIa), whose structure was established by an X-ray analysis. A thermal isomerization of (IIa) gave 4-methyl-2-methylamino-5-(N-methylthiocarbamoyl)thiazole (IIIa) in a good yield.

The reaction of 4-methyl-2-methylaminothiazole (I) with methyl isothiocyanate in toluene in the presence of pyridine gave the crystals of mp 56-57°C (IIa) having Rf value of 0.75 (2-propanol:ether, 1:1), λ_{max}(2-propanol) 260 (sh.), 291 nm (ε=19500) and yellow crystals of mp 249-250°C (IIIa) having Rf value of 0.53, λ_{max}(2-propanol) 294 (ε=6310), 340 nm (ε=11500).

Scheme 1



The elemental analysis and mass spectral data (MW 201) gave a molecular formula of $C_7H_{11}N_3S_2$ for both (IIa) and (IIIa), isomeric to each other. The thermal isomerization of (IIa) in pyridine gave (IIIa). As the spectral interpretation could not differentiate 1,3-dimethyl-1-(4-methylthiazol-2-yl)thiourea (IIa) and 4-methyl-2-methylimino-3-(N-methylthiocarbamoyl)-4-thiazoline (IVa), the structure of (IIa) was established by an X-ray analysis.

The NMR spectrum (d_6-DMSO) of (IIIa) showed signals at δ 2.29 (singlet, 3H, $=C-\underline{CH_3}$), 3.10 (doublet,3H, J=5.0 Hz, singlet after D_2O exchange, singlet after irradiation at 9.06, $-\underline{NH}$), 2.28 (doublet, 3H, J=5.0 Hz, singlet after D_2O exchange, singlet after irradiation at 7.86, $-\underline{NH}$), 9.06 (broad, 1H, disappeared after D_2O exchange, $-CH_3-\underline{NH}-$), and 7.86 δ (broad, 1H, disappeared after D_2O

exchange, CH_3-<u>NH</u>-). The structure of (IIIa) was estimated from the appearance of two doublets for <u>CH_3</u>NH and the absence of a singlet due to H at position 5.

The product obtained by the alkaline H_2O_2 treatment of (IIIa) was identified with the product, 4-methyl-2-methylamino-5-(N-methylcarbamoyl)thiazole (Va) from the reaction of (VI) and (VII), by the mixed mp, and from UV, Mass, and NMR spectral comparison.

Table I shows the result of monitoring of the thermal rearrangement of (IIa) to (IIIa), by measuring the absorption at 340 nm due to (IIIa) every 2.5 hr in a different solvent. This result suggests that an essential factor in the rearrangement is the presence of pyridine.

Table I

Solvent	Absorption at 340 nm[b]	Reflux time (hr)	IIIa Yield (%)
Cyclohexane	-	30	0
Toluene	-	30	0
Toluene-pyridine[a]	> 5 hr	10	80
Pyridine	> 5 hr	30	90

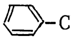
a) Ratio 2:1

b) Time required for the appearance of the absorption at 340 nm

Scheme 2

The thermal isomerization from (A) to (B) in pyridine shown in the Scheme 2 is summarized in Table II. The effect of substituents, R, R', and R", was traced by using TLC (ether:2-propanol, 1:1).

Table II

	R	R'	R"	Rearrangement
IIa	CH_3	CH_3	CH_3	+
IIb	CH_3	-CH_2	CH_3	+
IIc	CH_3		CH_3	+

	R	R'	R"	Rearrangement
IId	H	CH_3	H	-
IIe[2]	CH_3	CH_3	H	-
IIf	H	CH_3	CH_3	-

There was no rearrangement when R=H as in (IId) and (IIf). There was also no rearrangement when R=H as in (IId) and (IIf), while the rate of rearrangement was faster when R'=phenyl, as in (IIc), than for (IIa) and (IIb). Therefore, this rearrangement seems to take place when an electron donating group such as CH_3 is present at position 4 in the thiazole ring, with the exception of (IIf). The reaction mechanism including the roles of 4-CH_3 and of pyridine which is required for the rearrangement is currently under investigation in our laboratory.

Reference

1) Central Research Laboratories, Sankyo Co., Ltd. Hiromachi, Shinagawa-ku, Tokyo 141.

2) T. Noguchi, Y. Yasuda, S. Kanō, and T. Kato, Japan patent 20999 (1969).

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