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AN IMPROVED SYNTHESIS OF SUBSTITUTED 1,3,4-THIADIAZOLES

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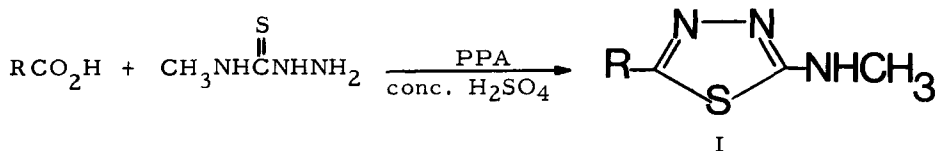
AN IMPROVED SYNTHESIS OF SUBSTITUTED

1,3,4-THIADIAZOLES

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The synthesis of 2-amino- and 2-alkylamino-5-substituted-1,3,4-thiadiazoles is well documented.¹⁻⁶ The present paper describes an improved procedure for the one-step preparation of 2-methylamino-5-alkyl-1,3,4-thiadiazoles,⁷⁻⁹ which affords the desired products in higher purity than previously reported.¹⁰



a) R = C₂H₅ (93%); b) R = (CH₃)₂CH (97%); c) R = (CH₃)₃C (93%)

The reaction of suitable carboxylic acids and 4-methylthiosemicarbazide in the presence of three parts of polyphosphoric acid and one part (w/w) of conc. sulfuric acid gave I which can be reacted without further purification with alkyl isocyanates leading to the corresponding urea. Lower yields are obtained if either conc. sulfuric acid or polyphosphoric

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acid is employed alone in the reaction. This procedure has been scaled up with good reproducibility.

EXPERIMENTAL

All mps were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained in CDCl_3 on an Varian HA 60 spectrometer using TMS as internal standard. Mass spectra were obtained on a CEC 110 mass spectrometer.

General Procedure. - 4-Methylthiosemicarbazide (21 g., 0.2 mole) was added to a solution of polyphosphoric acid and conc. sulfuric acid (72 g., 3:1 by weight) maintained at 10-15° with an ice-water bath. Propionic acid (14.8 g., 0.2 mole) was then added while the temperature was kept between 10-15°. After the addition, the reaction mixture was allowed to warm up to 30° and it was then heated to 100-105° for 3 hrs. Water (50 ml) and toluene (50 ml) were added and the pH of the reaction mixture was adjusted to 7 with conc. ammonium hydroxide. The toluene layer was azeotropically dried and toluene was removed under vacuum to give 27 g., (93.5%) of Ia, mp. 84-87°.

Nmr: δ 1.30 (t, 3, CH_3), 2.92 (q, 2, CH_2), 3.00 (s, 3, N- CH_3); M^+ 143.

Anal. Calcd for $\text{C}_5\text{H}_9\text{N}_3\text{S}$: C, 41.93; H, 6.33

Found: C, 41.67; H, 6.09

Ib, liquid; nmr: δ 1.35 (d, 6, CH_3), 3.20 (m, 1, C-H), 3.00 (s, 3, N- CH_3); M^+ 157.

Anal. Calcd for $\text{C}_6\text{H}_{11}\text{N}_3\text{S}$: C, 45.83; H, 7.05

Found: C, 45.50; H, 7.00

SUBSTITUTED 1,3,4-THIADIAZOLES

Ic, mp. 80-82°; nmr: δ 1.38 (s, 9, CH₃), 300 (s, 3, N-CH₃);
M⁺. 171.

Anal. Calcd for C₇H₁₃N₃S: C, 49.09; H, 7.65.

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7. The impetus for our work came from the unpublished works
of Dr. T. Thibault, Lilly Research Laboratories, Greenfield,
Indiana, who discovered that the reaction of 4-methyl-
thiosemicarbazide and pivalic acid gave 73% yield of 2-
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