Synthesis of 2,4-Dimethylpyrazolo[1,5-*a*]-1,3,5-triazine

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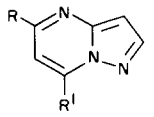
Sir:

We wish to report a new general synthesis of the pyrazolo[1,5-*a*]-1,3,5-triazine ring which allows ready introduction of different alkyl groups at positions 2 and 4. We have recently reported on the chemistry, 3′,5′-cAMP phosphodiesterase inhibitory activity, as well as the cardiovascular properties of various 5,7-dialkylpyrazolo-[1,5-*a*]pyrimidines (**1**) (1-3). In conjunction with these studies, we have investigated the synthesis of the closely related 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines (**2**).



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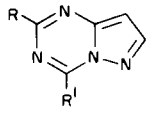

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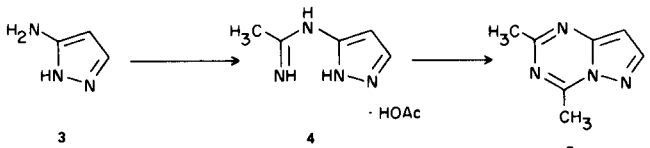
In a preliminary communication we describe the synthesis of certain 2,4,8-tri-substitutedpyrazolo[1,5-*a*]-1,3,5-triazines (4), however, these procedures do not yield the desired 2,4-dialkyl derivatives.

We now wish to report a facile process for the preparation of 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine. This process utilizes the readily available 3-aminopyrazole (**3**) (5) as a starting material. The reaction of **3** with ethyl acetimidate (6) afforded *N*-(pyrazol-3-yl)acetamidine (**4**) which was readily cyclized with triethyl orthoacetate to afford the desired 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (**5**).

A solution of 3-aminopyrazole (**3**) (6 g., 72.3 mmoles) and ethyl acetimidate (6.6 g., 75.9 mmoles) in acetonitrile (100 ml.) was stirred at room temperature while acetic acid (4.2 ml., 72.8 mmoles) was added dropwise. After the exothermic reaction had subsided, the resulting suspension was stirred at room temperature for an additional 6 hours. This produced 9.6 g. (72%) of the acetate salt of *N*-(pyrazol-3-yl)acetamidine (**4**) melting at 159-160°. Recrystallization from acetonitrile afforded an analytically pure sample that had a melting point of 159.5-160.5°, [ir (potassium bromide): 2610 (broad), 1655 cm^{-1}; m/e 124 (M^+), 107 (M-NH_3), 83 (3-aminopyrazole)].

Anal. Calcd. for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.62; H, 6.39; N, 30.59.



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A suspension of the acetate salt of *N*-(pyrazol-3-yl)-acetamidine (**4**) (2 g.) in triethyl orthoacetate (10 ml.) was heated at reflux until all the solid dissolved (*ca.*, 15 minutes). The excess solvent was then removed *in vacuo* and the resulting product (quantitative yield) was recrystallized from petroleum ether (30-60°) by cooling in a dry ice-acetone bath to afford an analytical sample of 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (**5**) that had a melting point of 49.5-50.5°; λ max (*p*H 1) ($\epsilon \times 10^3$) 205 nm (11.6), 238 nm (6.69); λ max (*p*H 11) 222 nm (26.6), 266 nm (3.05), 275 nm (sh); pmr (deuteriochloroform): δ 2.68 (s, 3), 2.94 (s, 3), 6.49 (d, J = 2 Hz, 1), 8.11 ppm (d, J = 2 Hz, 1); m/e 148 (M^+), 107 (M-CH_3CN).

Anal. Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.81. Found: C, 57.05; H, 5.31; N, 37.92.

This procedure should have utility in the preparation of symmetrically and unsymmetrically substituted 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines (**2**).

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