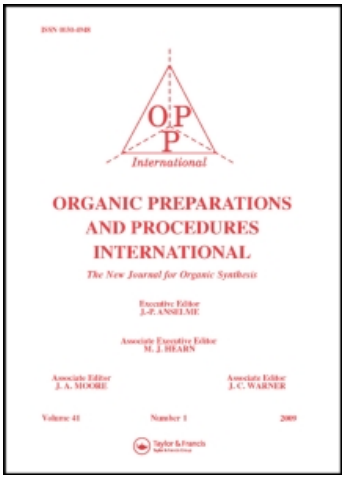

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A HIGHLY EFFICIENT SYNTHESIS OF 3,4,5-TRIBROMO-N,N,α-TRIMETHYLPYRAZOLE-1-ACETMIDE

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A HIGHLY EFFICIENT SYNTHESIS OF 3,4,5-TRIBROMO-N,N,α-TRIMETHYLPYRAZOLE-1-ACETAMIDE

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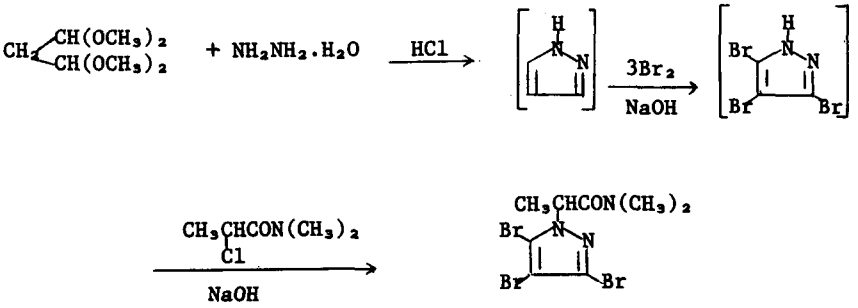
We have briefly reported the synthesis and biological activity of a number of tribromopyrazole derivatives.[1] One member of this group, 3,4,5-tribromo-N,N,α-trimethylpyrazole-1-acetamide (I), was required in large amounts. We now report a simple synthesis of this compound that does not require isolation of the intermediates, uses only water as a solvent, and furnishes the final product in an overall yield of 85% of better than 95% purity, without recrystallization.



(I)

The preparation of pyrazoles from 1,1,3,3-tetramethoxypropane and hydrazines in water has been shown by Copenhaven[2] to be a high yield reaction although pyrazole itself was isolated in only 50% yield. 3,4,5-Tribromopyrazole has been synthesized previously by Huttel[3] and by

Reimlinger.[4] Both methods require stepwise bromination of pyrazole using long periods of reflux, and isolation and purification of the di-and tribromopyrazoles; the yields ranged from 50 to 60%.

We have found that rapid bromination takes place at room temperature in the presence of excess sodium hydroxide to give a 90% yield of 3,4,5-tribromopyrazole which needs not be isolated.[5] The last step of the reaction sequence consists of the addition of another equivalent of sodium hydroxide and alkylation with 2-chloro-N,N-dimethylpropionamide[6] to give I in a yield of 85% based on hydrazine. This synthesis has been scaled up to furnish 250 kg of product in one run.

EXPERIMENTAL

To an ice cold solution of hydrazine hydrate (5 g, 0.1 mole) in water (5 ml) and ethanol (10 ml), conc. hydrochloric acid (12 g, 0.1 mole) was added dropwise with stirring followed by 1,1,3,3-tetramethoxypropane (16.4 g, 0.1 mole).[7] The reaction mixture was brought to reflux during 15 min and then heated for an additional 25 min. After cooling to 20°, a solution of sodium hydroxide (18.8 g, 0.47 mole) in water (110 ml) was added to the stirred reaction mixture, followed by dropwise addition of bromine (48 g ,0.3 mole) during 25 min; the internal temperature was kept between 28-33°. The reaction mixture was further stirred at room temperature for 20 min,[5] then a solution of sodium hydroxide (4.4 g, 0.11 mole) in water (50 ml) was added and the mixture heated under reflux for 10 min. To the hot solution, 2-chloro-N,N-dimethylpropionamide (14.85 g, 0.11 mole) was added during 5 min, then the mixture was heated for 45 min. Water (75 ml) was then added and the chilled solution was filtered to give a pale yellow precipitate 34.2 g (85%), mp 126-128° with satisfactory analysis.

SYNTHESIS OF 3,4,5-TRIBROMO-*N*,*N*,α-TRIMETHYLPYRAZOLE-1-ACETAMIDE

Recrystallization from benzene/hexane raised the mp to 131-132°,

NMR ($CDCl_3$): δ 1.68(d, 3H, CH_3), 2.91(s, 6H, $N(CH_3)_2$), 5.26(q, 1H, CH).

Anal. Calcd for $C_8H_{10}Br_3N_3O$: C, 23.79; H, 2.50; Br, 59.35; N, 10.40. Found: C, 23.64; H, 2.42; Br, 59.46; N, 10.52.

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4. H. Reimlinger, A. Noels, J. Jadot, and A. Van Overstraeten, Chem. Ber., 103, 1942 (1970).
5. At this point, if desired, acidification of the reaction mixture and filtration of the precipitate yields 27.3 g (90%) of 3,4,5-tribromopyrazole, mp 180-184° with satisfactory analysis.
6. Fr. Patent 1,426,086 (1966), J. Lehureau (Progil S.A.) Chem. Abstr., 65, 13619 b (1966). This was more conveniently prepared by heating under reflux a solution of 2-chloropropionic acid (1 mole) and thionyl chloride (1.1 mole) in benzene (400 ml) for 3 hr and adding dropwise the above mixture to a solution of dimethylamine (2.4 mole) in benzene (200 ml) at 5°. The mixture was heated under reflux for 1 hr, washed with ice water (80 ml) and the benzene solution, after concentration, provided an oil which gave upon distillation 115 g (85%) of 2-chloro-N,N-dimethylpropionamide, bp 98-99° (15 mm) identical in all respects with a sample obtained from Progil S.A.
7. Purchased from Kay-Fries Chemicals and distilled before use.

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