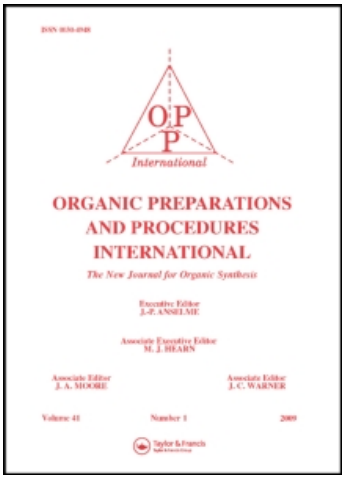

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A SYNTHESIS OF FUSED PYRIMIDINES

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A SYNTHESIS OF FUSED PYRIMIDINES

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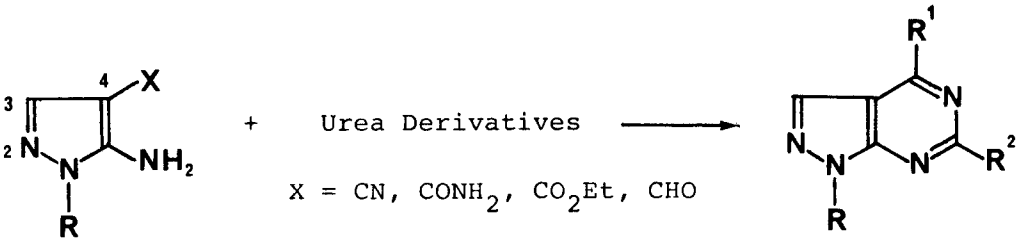
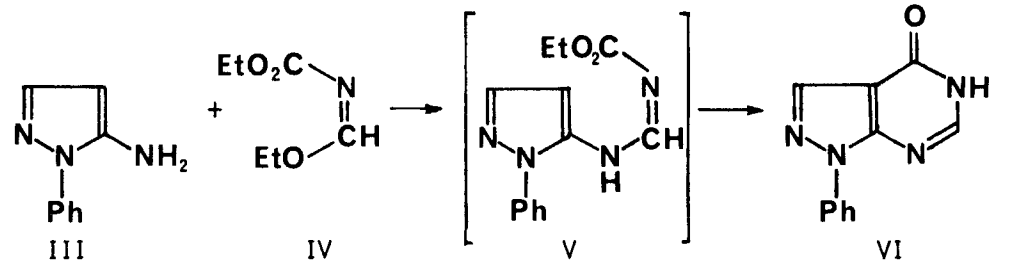
Many of the reported synthetic methods for the preparation of pyrazolo(3,4-d)pyrimidines start with a 5-aminopyrazole with an electron-withdrawing reactive substituent at position 4 (I). Condensation of these 5-aminopyrazoles with appropriate reactants such as ureas or suitable analogues leads to the desired heterocycle (II).[1] An important member of this class of compounds, pyrazole(3,4-d)pyrimidin-4(5H)-one (or its hydroxy tautomer, allopurinol, an isostere of 6-hydroxypurine or hypoxanthine) is a good inhibitor of xanthine oxidase[2] and has been in clinical use under the brand name, "Zyloprim", a drug for the relief of gout.[3] Several derivatives of it have been prepared and shown to exhibit xanthine oxadase inhibitory properties.[4]



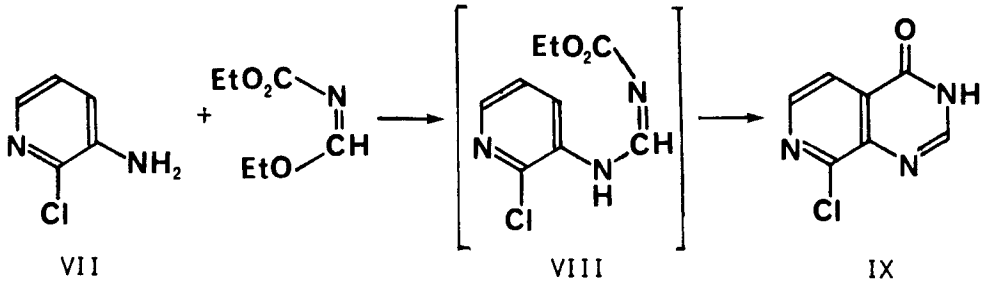
I II

We now describe an alternate synthesis of a pyrazolo(3,4-d)pyrimidine using a 5-aminopyrazole with no reactive substituent at position 4. 5-Amino-1-phenylpyrazole (III) was condensed with ethoxymethyleneurethane (IV, obtained from urethane and triethylorthoformate),[5] to give an intermediate V. The intermediate underwent smooth cyclization at elevated temp (250°) affording high yields of the desired product, 1-phenylpyrazolo(3,4-d)pyrimidin-4(5H)-one (VI).



III IV V VI

The synthesis of another fused heterocycle, 8-chloropyrido(3,4-d)pyrimidin-4(3H)-one (IX), was achieved by reaction of 3-amino-2-chloropyridine (VII) with IV. The intermediate (VIII) underwent smooth thermal cyclization at 250° to give



VII VIII IX

product IX in good yield. Some pyrido(3,4-d)pyrimidin-4(3H)-ones are reported to have analgesic and anti-inflammatory activity.[7]

General Procedure.- A mixture of equimolar quantities of the aminoheterocycle (0.01 m) and IV (0.01 m) was heated in an oil bath at 130-135° for 2.5 hrs under vacuo (aspirator suction). The viscous mass after trituration with pet. ether (bp. 40-60°) gave a crude residue which was heated for 30 min. in diphenyl ether (10 ml) at 250° under N_2. The reaction mixture, when cooled and triturated with pet. ether, gave a brown product which was crystallized from ethanol (Norite) to yield colorless needles. 1-Phenylpyrazolo(3,4-d)pyrimidin-4(5H)-one (VI), yield 85% mp. 297-299°; lit.[6] 299°. 8-Chloropyrido(3,4-d)pyrimidin-4(3H)-one (IX), yield 62% mp. 259-260°.

IR (Nujol): 5.85 μ(C=O); 6.20 μ(C=N).

Anal. Calcd. for $C_7H_4N_3OCl$: C, 46.30; H, 2.21; N, 23.14

Found: C, 46.21; H, 2.56; N, 22.84%

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ANHYDRIDE ACYLATION REACTIONS OF 2,4-DINITROPHENYLHYDRAZINE

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A convenient high yield preparation of 1-acyl-2-phenylhydrazines under mild conditions was recently described,[1] and we now report on the formation of the related 1-acyl-2-(2,4-dinitro)phenylhydrazines and comment on the substantive differences observed in synthesis and physical and spectral properties. Although some members of this class of carboxylic acid derivatives are known, general methods for their inexpensive preparation on useful scale from the anhydrides, as well as certain details of their characterization, have been neglected.[2-5]

In sharp contrast to the unsubstituted parent compound, 2,4-dinitrophenylhydrazine required a polar solvent and reflux temperature in order to undergo acylation with anhydrides. Thus 2,4-dinitrophenylhydrazine (18.5 mmoles) as a heterogeneous mixture in boiling 95% ethanol (40 ml) reacted smoothly