Tetrahedron Letters,Vol.23,No.46,pp 4759-4762,1982 0040-4039/82/464759-04$03.00/0
Printed in Great Britain

A NOVEL METHOD FOR THE SYNTHESIS OF 6,7-UNSUBSTITUTED PYRROLO[3,2-d]PYRIMIDINES

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Summary: The synthesis of 2,4-dimethoxypyrrolo[3,2-d]pyrimidine (4) is described. This facile, 3-step synthesis involves the bromination of 2,4-dimethoxy-6-methyl-5-nitropyrimidine (1), and the subsequent conversion of compound 1 into compound 4.

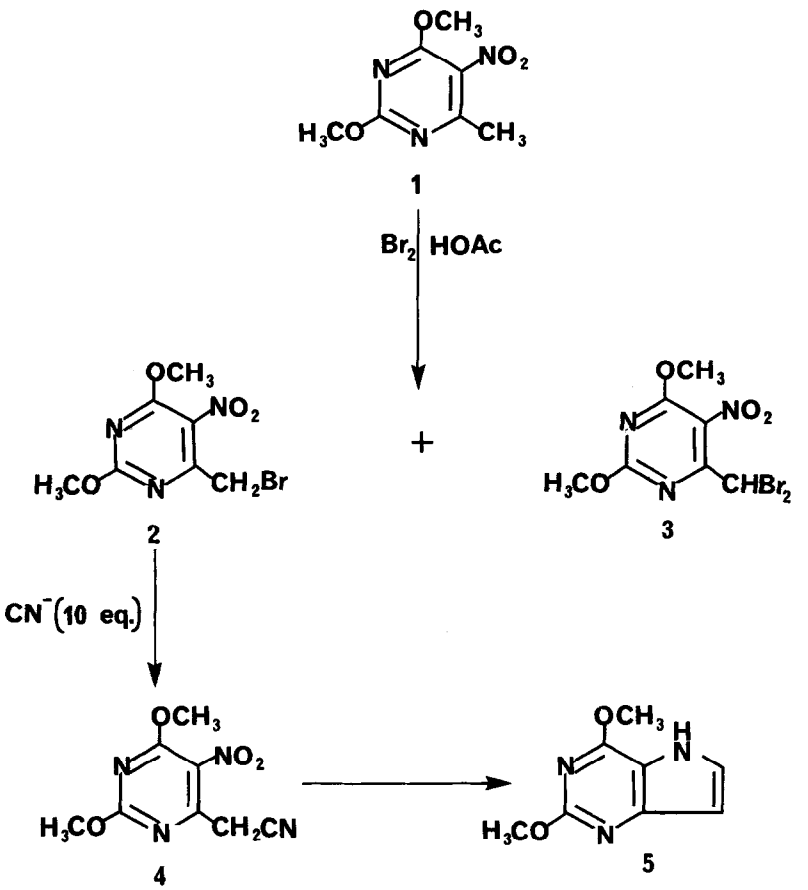
A number of recent reports[1-4] have appeared on the synthesis of the pyrrolo-[3,2-d]pyrimidine ring system. This interest has been renewed by the finding that 9-deazaadenosine {4-amino-7-(β-D-ribofuranosyl)pyrrolo[3,2-d]pyrimidine} has demonstrated significant *in vitro* and *in vivo* antitumor activity[5,6].

Traditionally, the synthesis[7,8] of pyrrolo[3,2-d]pyrimidines which are unsubstituted at the six and seven positions has only been accomplished by the pyrolytic (300 °C, copper powder) decarboxylation of the corresponding 6-carboxy-pyrrolo[3,2-d]pyrimidine. Several additional methods starting from substituted pyrimidines[7] have produced pyrrolo[3,2-d]pyrimidines, however, the products of these reactions always contained either an alkyl, aryl or ethoxycarbonyl substituent at the seven position. We now wish to report a facile, 3-step procedure for the synthesis of a novel 6,7-unsubstituted pyrrolo[3,2-d]pyrimidine (4).

The procedure we have developed is simple and avoids the above mentioned decarboxylation which is too harsh for compounds which might contain sensitive groups such as a carbohydrate moiety. The synthesis of 2,4-dimethoxypyrrolo-[3,2-d]pyrimidine (5) was accomplished starting from 2,4-dimethoxy-5-nitro-pyrimidine[9] (1). Bromination of 1 with bromine (1.0 eq.) in refluxing glacial acetic acid which contained sodium acetate (10 eq.) afforded a mixture of 4-bromomethyl-2,6-dimethoxy-5-nitropyrimidine (2, 43%, yellow oil) and the dibromomethyl derivative 3 (31%, m.p. 90-91 °C). After isolation by chromatography on

silica gel (CH_2Cl_2 used as the elution solvent), pure 2 was reacted with excess sodium cyanide (10 eq.) in aqueous ethanol at 0 °C to give the crystalline

REACTION SCHEME



4-cyanomethyl-2,6-dimethoxy-5-nitropyrimidine[10] (4, 55%, m.p. 75-77 °C). Compound 4 was then reductively ring closed by hydrogenation at 80 psig and 70 °C

over 10% palladium on carbon. This reductive annulation appeared to follow the same course as has been reported[11] previously for the synthesis of substituted indoles from o-nitro-α-cyanotoluenes. Thus, not only was the nitro group readily reduced to an amino group, but the cyano group was evidently also reduced to the corresponding imine which reacted with the ortho amino functionality to produce, after loss of ammonia, 2,4-dimethoxypyrrolo[3,2-d]pyrimidine[12] (5, 47%, 174-176 °C). The application of this facile synthesis of specific pyrrolo[3,2-d]-pyrimidines in the area of general heterocyclic chemistry as well as the synthesis of C-nucleoside is under further investigation in our laboratory.

Acknowledgement: This study was funded in part by funds from the National Institute of Health (Training Grant #5-T32-GM 07767) and the American Cancer Society (Grant CH-133).

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10) Mass spectral and ^{1}H-nmr data for compound 4: m/z 224 (M*); ^{1}H-nmr (60MHz, $CDCl_3$): δ 4.07 (2, singlet, $C\underline{H}_2CH$), 4.12 (6, 2 singlets, 2-OCH_3, 6-$O\underline{C}H_3$).

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12) Mass spectral and ^{1}H-nmr data for compound 5: m/z 179 (M*); ^{1}H-nmr (60 MHz, $CDCl_3$): δ 3.87, 4.03 (6, 2 singlets, 2-$OC\underline{H}_3$ and 4-$OC\underline{H}_3$), 6.37 (1, triplet, $\underline{H}$-7, $J_{7,6} = J_{7,5}$ = 3 Hz), 7.52 (1, triplet, $\underline{H}$-6, $J_{6,7} = J_{6,5}$ = 3 Hz), 11.73 (1, broad, D_2O exchangeable, 5-$\underline{H}$).

(Received in USA 19 July 1982)