SYNTHESES OF PYRIMIDINYL KETONES

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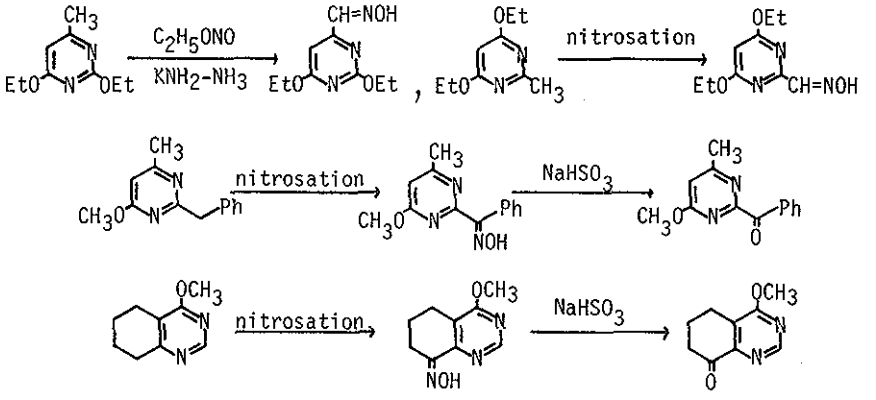
Synthesis of pyrimidine derivatives possessing an acyl group directly at the 2- and 4-positions from simple alkyl-(or phenyl)pyrimidines was described. In this connection, the relative reactivity of methyl groups attached to the mono- and di-azine rings was investigated.

There are not a great many pyrimidines with an acyl group directly at the 2- or 4-positions of the ring.[1] This may be owing to that the appropriate 1,3,5-triketones or acylamidines which are main starting materials of preparing pyrimidinyl ketones by the ring closure, are not easily accessible. In this paper we wish to report the synthesis of the titled compounds by converting simple alkyl(or phenyl)pyrimidines.

1) Nitrosation of 2,4-Dimethylpyrimidines

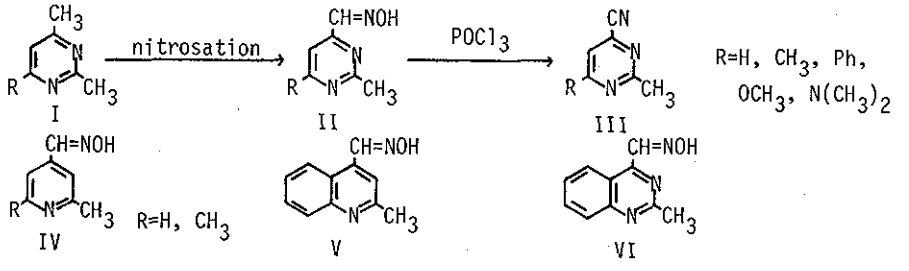
In 1964, Kato et al.[2] reported that an active methyl group on a pyridine ring was nitrosated with isoamyl nitrite in liq. NH_3 in the presence of KNH_2 to give 2- or 4-pyridinealdoximes. This reaction suggested the synthetic way from alkylpyrimidines to cyanopyrimidines and pyrimidinyl ketones. In fact the following results

were obtained.[3)]



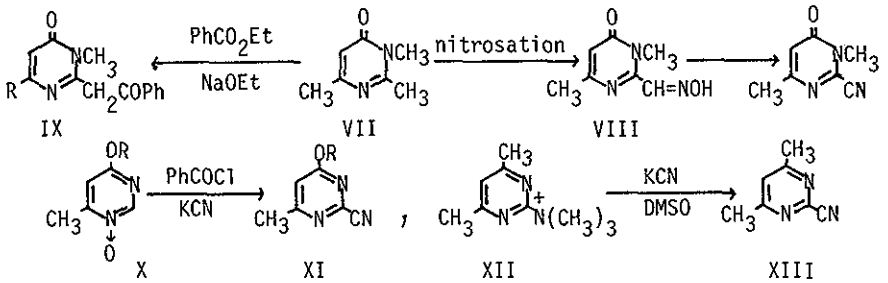
In the cases of pyrimidines containing two active methyl groups at the different positions, it was observed that the nitrosation under similar conditions occurred preferentially on the 4-methyl group without exception (I→II).[4)] The structures of the products (II) were determined after converting II into the corresponding cyano derivatives (III).

In order to examine the generality of this observation, the nitrosation of N-heteroaromatics such as 2,4-dimethyl-, 2,4,6-trimethyl-pyridine, 2,4-dimethylquinoline, and 2,4-dimethylquinazoline was investigated under identical conditions. In all the cases, the corresponding 4-aldoximes (IV, V, and VI) were obtained as sole product.



The following observations were consistent with the result of this selective nitrosation. Namely, i) benzoylation of these 2,4-dimethyl-N-heteroaromatics with ethyl benzoate under basic conditions afforded the 4-phenacyl derivatives preferentially, and ii) time dependent deformation of the NMR spectra of these 2,4-dimethyl-N-heteroaromatics in NaOD-D_2O-CD_3OD exhibited that the signal assignable to the 4-methyl group disappeared more rapidly than that to the 2-methyl group.[4)]

On the contrary, 2,3,6-trimethyl-4-pyrimidone (VII) was nitrosated to give 3,6-dimethyl-4-pyrimidone-2-aldoxime (VIII) whose structure was determined by the spectral measurements and the chemical reactions.[5)] The reverse reactivity of the methyl groups on VII might be explained by overlapping of electron withdrawing effects of the fixed C=N double bond and the amide carbonyl group.



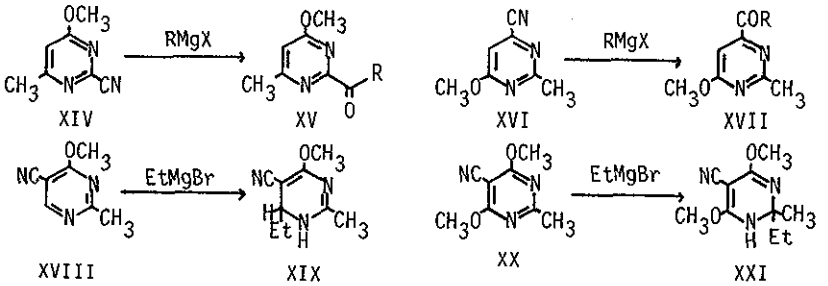
2) Synthesis of Pyrimidinecarbonitriles

On heating with $POCl_3$, 4-pyrimidinealdoximes (II) were readily dehydrated to the 4-cyano derivatives (IV) in a yield ranging from 65 to 95 %. Many alkylpyrimidines are so easily available that this method provides a facil synthetic way to 4-cyano pyrimidines. Although there is the disadvantage of this method over the preparation of 2-cyanopyrimidines, they are synthesized by the Reissert-

Henze reaction of pyrimidine N-oxides (X→XI)[6] or by replacement of a trimethyl ammonium group with cyanide ion in DMSO (XII→XIII).[7]

3) Reaction of Cyanopyrimidines with Grignard Reagents

The cyano groups at the 2- and 4-positions were characterized by replacement with alkoxide ion to give the corresponding alkoxyl derivatives.[8] This suggested undesirable formation of alkylpyrimidines through the Grignard reaction of pyrimidinecarbonitriles, however the reaction of these nitriles in usual manner gave rise to the carbonyl compounds (XIV→XV, XVI→XVII) in good yield. By comparison with XIV and XVI, the 5-cyano derivatives (XVIII, XX) reacted with ethylmagnesium bromide to afford the dihydro-compounds (XIX, XXI) instead of the pyrimidinyl ethyl ketones.[9] The spectral data of XIX and XXI are in good agreement with the assigned structure.

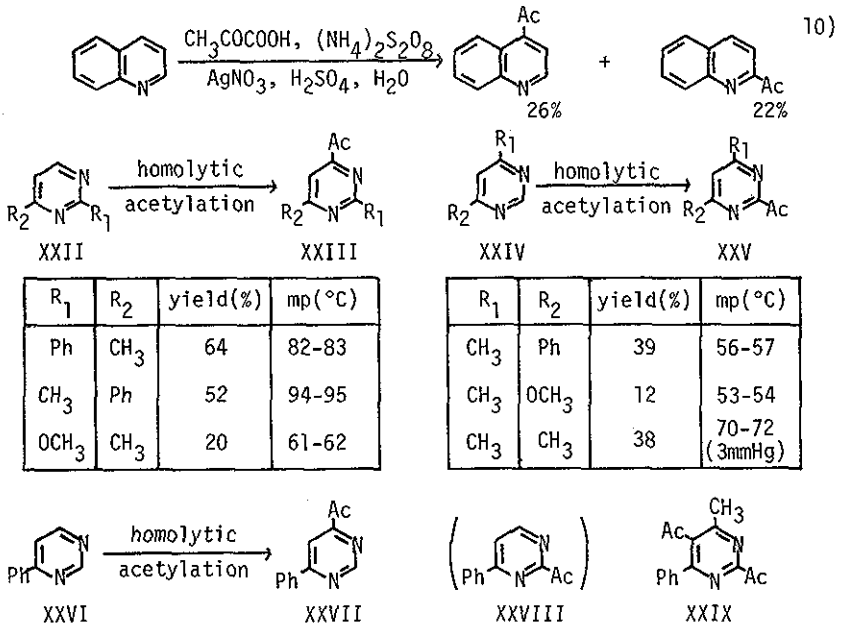


XIV XV XVI XVII XVIII XIX XX XXI

4) Homolytic Acetylation of Simple Pyrimidines

Recently, Minisci et al.[10] reported a nice C-acylation of N-heteroaromatics by means of homolytic reaction with α-keto acid, $(NH_4)_2S_2O_8$ and $AgNO_3$ in acidic media. One of the principal advantage of this reagents is a great specificity toward the α- and γ-positions of N-heteroaromatics. Thus, the pyrimidines possessing free 2- or 4-positions (XXII, XXIV) were allowed to react

with pyruvic acid under the Minisci's condition to give the acetylpyrimidines (XXIII, XXV) in a yield ranging from 12 to 64 %. By comparison with the case of quinoline, it was interesting that 4-phenylpyrimidine (XXVI) afforded 4-acetyl-6-phenylpyrimidine (XXVII). The formation of the 2-acetyl isomer (XXVIII) was not observed. An exceptional result was obtained in the case of 4-methyl-6-phenylpyrimidine giving 2,5-diacetyl-4-methyl-6-phenylpyrimidine (XXIX) as minor product (12 %).[11]



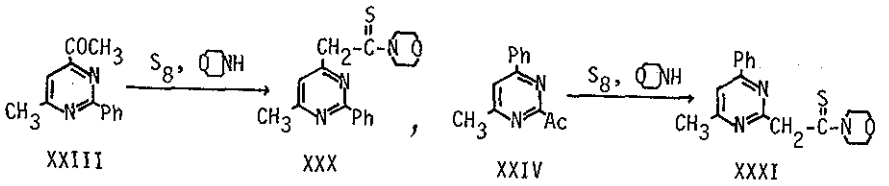
R_1	R_2	yield(%)	mp(°C)
Ph	CH_3	64	82-83
CH_3	Ph	52	94-95
OCH_3	CH_3	20	61-62

R_1	R_2	yield(%)	mp(°C)
CH_3	Ph	39	56-57
CH_3	OCH_3	12	53-54
CH_3	CH_3	38	70-72 (3mmHg)

5) Reactions of Pyrimidinyl Ketones

There are few reactions recorded for C-acylpyrimidines at present. Thus, the Willgerodt-Kindler reaction of XXIII and XXIV was investigated. The expected pyrimidinethioacetamides (XXX, XXXI) were obtained in reasonable yield. This finding suggested

the chemical properties of pyrimidinyl ketones being worthy of a further synthetic study.



XXIII XXX XXIV XXXI

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