AROMATIC AMINE N-OXIDES IN SYNTHESES OF NUCLEOSIDES AND NUCLEOTIDES

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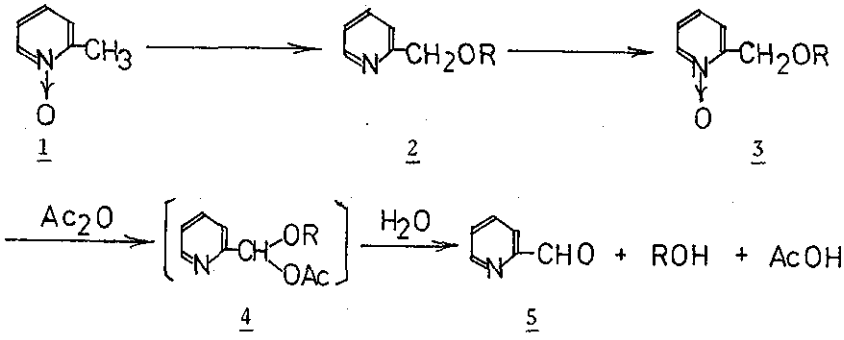
Kobayashi and Furukawa[1] showed that 2-picoline 1-oxide (1) was converted into 2-pyridylmethyl acetate (2, R=Ac) in acetic anhydride. Subsequently, Boekelheide and Linn,[2] reported a similar rearrangement of 2-pyridylmethyl acetate 1-oxide (3, R=Ac) into 2-formylpyridine (5) via the diacetate



1 2 3 4 5

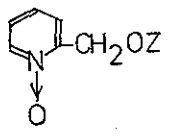
intermediate (4). We found[3] that the aldehyde (5) and alcohols were generated from 2-pyridylmethyl alkyl ether 1-oxides (3, R=alkyl) by way of the

(1) G. Kobayashi and S. Furukawa, Pharm. Bull. (Tokyo), 1, 347 (1953).
(2) V. Boekelheide and W. J. Linn, J. Amer. Chem. Soc., 76, 1286 (1954).
(3) Y. Mizuno, T. Endo, T. Miyaoka, and K. Ikeda, J. Org. Chem., 39, 1250 (1974).

hemiacetal acetates (4, R=alkyl). Similarly, thioethers (6)[4] or amines (or imines) (7)[5] were also converted into the aldehydes (5) and the corresponding thiols or amines (or imines) by way of *hemithioacetal acetates or hemiaminal* acetates under very mild conditions. 2-Picolyl 1-oxide (PO) was thus found to be useful as a readily removable protecting group of hydroxyl, thiol and amino (or imino) functions for the syntheses of otherwise rather inaccessible compounds.[3-5]

Scope of "PO"-Protection

The PO-protection has further been extended to cyano (8), acetamido (9), alkylthio (10), halogeno (11), and phosphate (12) group.



6 Z=SR
7 Z=NRR'
8 Z=CN
9 Z=SAc
10 Z=NHAc
11 Z=Cl
12 Z=PO_3^{2-}

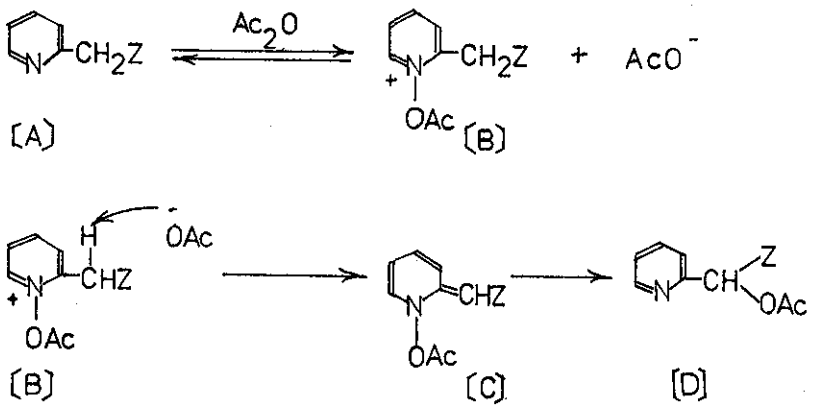
The mechanistic scheme of deblocking may be formulated in the following equations.[6-8]

(4) Y. Mizuno and K. Ikeda, Chem. Pharm. Bull. (Tokyo), 22, 2889 (1974).

(5) Y. Mizuno, W. Linn, and K. Tsuchida, J. Org. Chem., 37, 39 (1972).

(6) K. Ikeda, K. Tsuchida, T. Monma, and Y. Mizuno, J. Heterocyclic Chem., 11 321 (1974).

(7) a, V. J. Traynellis in "Mechanism of Molecular Migrations", vol. 2, B. S. Thyagarajan, Ed., Interscience Publishers, New York, 1969, p. 1; b, E. Ochiai, "Aromatic Amine Oxides", Elsevier Company, New York, 1967, p. 290.

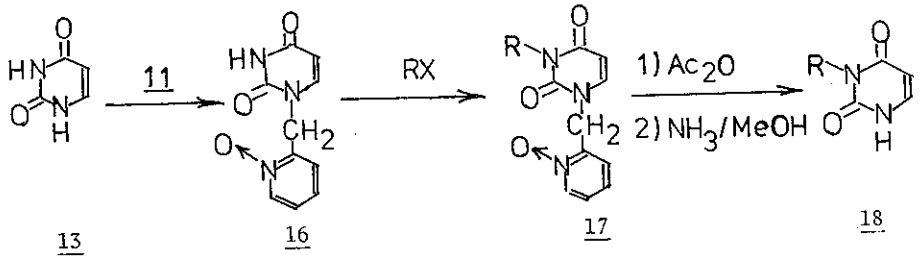


The rate of conversion from [A] to [D] was studied kinetically[6] and the process was found to follow the second order rate equation[6] with the proton abstraction step ([B]→[C]) being rate determining. We also found[6] that the ease with which the deblocking of the PO group is obtained depends on the proton abstraction by the acetate ion by kinetic studies of the reaction of some 2-picolyl 1-oxide derivatives (1, 3, 7-11) with acetic anhydride. The increasing order of the reaction rate was found to be 8 > 9 > 10 > 11 > 7 (X=NMe_2) > 3 (R=Ac) > 3 (R=Me) > 1. Formation of the aldehyde (5) and deprotected product (XH) from [D] occurs rapidly under mild basic or acidic conditions.

Introduction of PO Group into Substrates

PO group can be introduced readily to a ring nitrogen of nitrogenous heterocycles having a lactim-lactam system with 2-picolyl chloride 1-oxide (11) in

(8) S. Oae, S. Tamagaki, T. Negoro, K. Ogino, and S. Kozuka, Tetrahedron Lett., 917 (1968).



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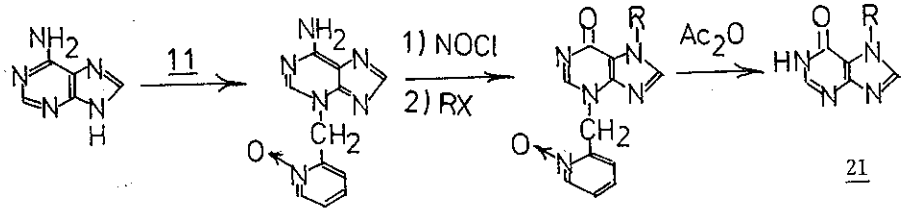

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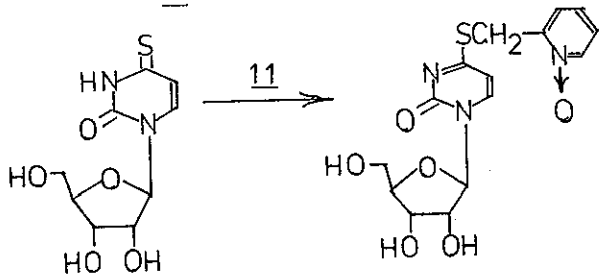

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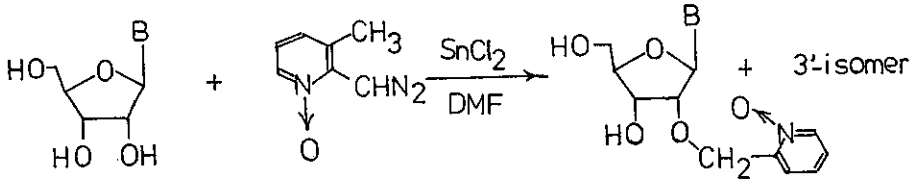

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in base.[4] A thiol group is also alkylated with this reagent (11) in base.[4] For the introduction of PO protection into one of the cis-glycol hydroxyls (viz., ribonucleosides), however, 1-oxido-3-methyl-2-pyridyldiazomethane (24) rather than 11 is the reagent of choice.[9] This novel diazoalkane (25) is useful for the preparation of 2'-O-PO-protected nucleosides (25). Diribonucleoside phosphates with natural linkage have been prepared from 25.[10] Also, 25 is useful for the PO protection of phosphate groups in nucleotides.[3]

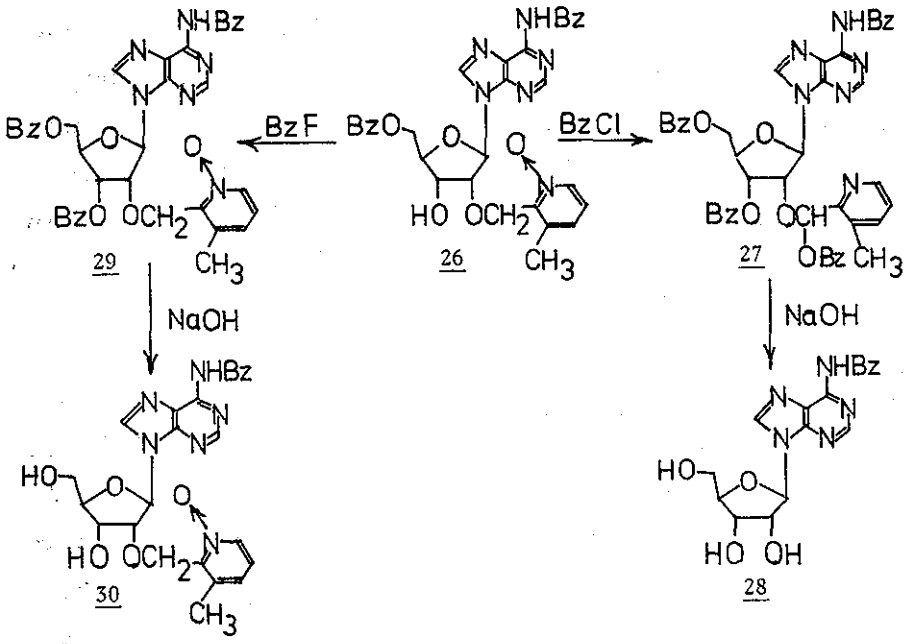
Deblocking and Controlled Acylation

In order to find optimal deblocking conditions, the introduction of 2-picolyl 1-oxide [A] with acyl anhydrides other than acetic anhydrides (viz., acyl halides) has been closely examined by NMR spectrometry.[11] It was found that equilibrium between [A] plus acyl halide (acyl X) and N-acyloxypicolinium salt $[B]X^-$ (or the stability of $[B]X^-$) is governed by the softness of counterion (X^-) as well as the sp^2-carbon nucleophilicity of the N-oxide oxygen atom. The N-acyloxypicolinium [B] is soft and forms a stable salt with soft base such as iodide or perchlorate, but they cannot form a stable salt with a very hard base such as fluoride. Thus, benzoyl chloride can be used for deblocking the PO-protection whereas benzoyl fluoride is suitable for benzoylation of PO-protected nucleosides without removing the PO group as shown below.

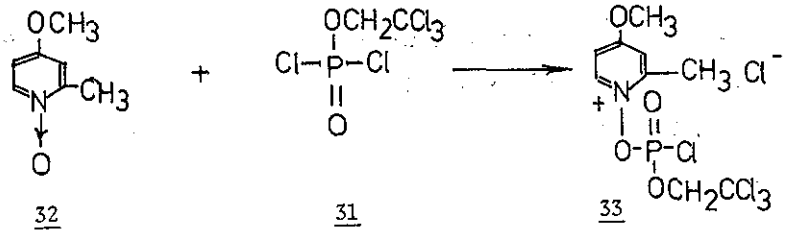
(9) a, Y. Mizuno and J. Kobayashi, J. Chem. Soc., Chem. Commun., 308 (1975); b, Y. Mizuno, T. Endo, and T. Nakamura, J. Org. Chem., 40, 1391 (1975).

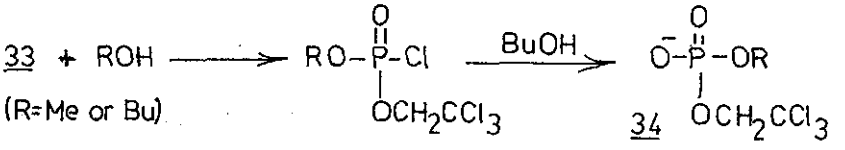
(10) Y. Mizuno, T. Endo, and K. Ikeda, J. Org. Chem., 40, 1385 (1975).

(11) Y. Mizuno and T. Endo, Paper in submission (JOC).



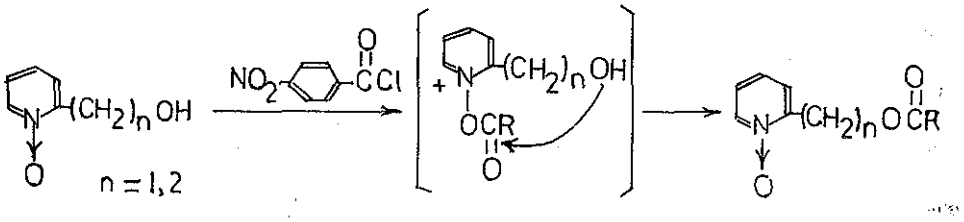
It was also found that whereas 2-picoline 1-oxide (1) did not react with 2,2,2-trichloroethyl phosphorodichloridate (31), 4-methoxy-2-picolyl acetate 1-oxide (32) reacted with 31 to give the corresponding picolinium salt (33). The latter (32) was found to be capable of phosphorylating alcohols (e.g., butyl alcohol) to give the corresponding 2,2,2-trichloroethyl alkyl phosphate (34).





Neighboring Group Participation of N-Oxide in Acylation

Competitice acylation of 2-(ω-hydroxyalkyl)pyridine 1-oxide and benzyl alcohol with p-nitrobenzoyl chloride in the presence of one equivalent of collidine exclusively afforded 2-(ω-p-nitrobenzoyloxyalkyl)pyridine 1-oxide. Benzyl p-nitrobenzoate could not be detected in the reaction mixture even with 30-fold excess of benzyl alcohol.[11]



Competitive phosphorylation of 2-hydroxymethyl-4-methoxypyridine 1-oxide (35) and n-butyl alcohol with 31 afforded 2,2,2-trichloroethyl 4-methoxy-2-picolyl phosphate (37) via 36.