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SPECIFIC EFFECTS OF ACETIC ACID ON THE REACTION OF 2,4-DIMETHYLPYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE

Yoshinori Kitaoka*
Research Reactor Institute of Kyoto University, Noda, Kumatori-cho, Sennan-gun
Osaka, Japan
Shigeru Oae
Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun
Ibaragi-ken, Japan

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The reaction mechanisms of tertiary amine oxides with acid anhydrides have been studied by several different groups.[1-4] We also studied the mechanisms of 2- and 4-methylpyridine N-oxides with acetic anhydride using oxygen-18 as a tracer.[5-7] Recently, Cohen and Deets[8] trapped picolyl cations in the reactions of 2- and 4-picoline N-oxides with acetic anhydride and favored an ion pair mechanism. However,there are still some ambiguities about the bond breakage of the intermediate.

As acyloxy group rearranges to a side chain at the position of conjugation with the ring nitrogen of pyridine, 2,4-dimethylpyridine N-oxide(I) which has two reactive methyl groups is an interesting compound. Comparing with results obtained previously in the reactions of 2- and 4-methylpyridine N-oxides, we tried to elucidate stereochemical effects on the reaction of I with acetic anhydride and found specific effects of acetic acid. I was reacted with acetic anhydride under various conditions. After removal of volatile products and reagents, the resulting ester mixture was separated by glcp.[9] In the order emerged from the column, each peak was identified by IR spectra to be 3-acetoxy-2,4-dimethylpyridine(II), 5-acetoxy-2,4-dimethylpyridine(III), 4-acetoxymethyl-2-methylpyridine(IV) and 2-acetoxymethyl-4-methylpyridine(V), respectively.

The experimental conditions and results are shown in Table 1. Xylene, the change of the ratio of I to acetic anhydride or the addition of DPPH did not give the result so different from that of Exp. No.1. However, an addition of acetic acid increased dramatically the ratio of IV to II or the other esters. The relative yields of IV in Exp. No. 1,2,3,5,8 and 9 were plotted against the molar ratios of I to acetic acid and the following equation was obtained graphycally.

$$Y = \frac{1}{0.217} \log C - 0.714$$

where Y is the relative yield of IV and C the molar ratio of I to acetic acid.

TABLE I. THE REACTION OF 2,4-DIMETHYLPYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE.

Exp. No.	Reagents (g) I	Ac_2O	AcOH	Xylene (DPPH)	$\frac{[AcOH] + [AcO^-]^*}{[I]}$	Products (Peak Ratio) II	III	IV	V
1	3.0	3.8	-	-	1.0	1	1.4	0.67	3.4
2	3.0	3.8	2.3	-	2.56	1	2.5	2.9	5.1
3	3.0	3.8	13.0	-	9.89	1	2.0	4.9	4.3
4	3.0	3.8	-	13.0	-	1	2.7	0.33	4.7
5	3.0	3.8	20.0	-	14.6	1	1.7	6.1	3.3
6	3.0	3.8	13.0	(0.50)	-	1	1.4	6.2	4.6
7	3.0	7.6	-	-	-	1	1.7	0.53	4.3
8	3.0	3.8	50.0	-	35.1	1	1.7	7.8	3.0
9	3.0	3.8	100.0	-	69.3	1	1.8	8.8	4.3

*Acetate anions of pyridinium salt. Separation conditions: Column, PEG 4000, 3(Dia.)x1500mm+Silicon DC 550, 3(Dia.)x3750mm, Column Temp., 190°C, Carrier gas, He, 12.5ml/min, Retention time, II(23.5min), III(28.5min), IV(33.0min), V(37.0min).

TABLE II. OXYGEN-18 DISTRIBUTION IN THE ESTERS.

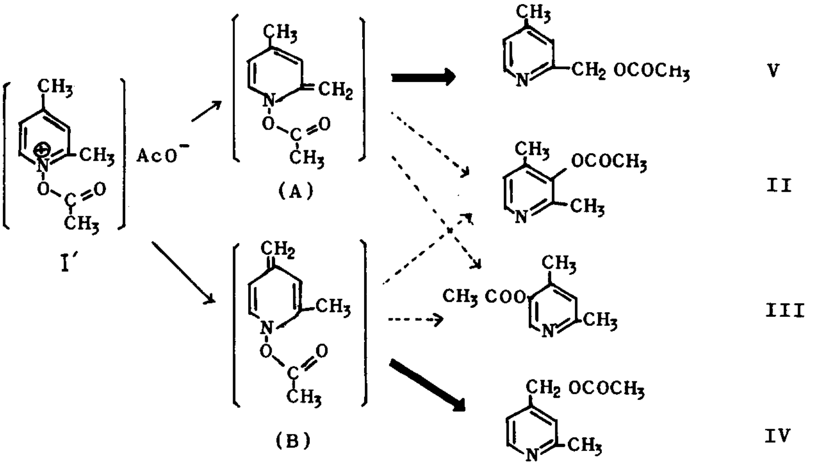
Ester	Retention Time(min)	Purity (%)	Atom % ^{18}O* Obs.	Corr.	Theoretical Inter.**	Intra.	Inter. (%)
II+III	20	-	0.541	-	0.794	0.518	8.3
IV	30	75.0	0.607	0.627	0.794	0.518	39.5
V	35	78.5	0.557	0.533	0.794	0.518	5.4

*IV and V contaminated each other. Then, these values were corrected for purity. ** It was assumed that all oxygen atoms were scrambled. Natural abundance of oxygen-18 was 0.204 atom % ^{18}O. Separation conditions: Column, PEG 4000, 3(Dia.)x2000mm + Silicon DC 550, 3(Dia.)x2000mm, Column temp., 185°C, Carrier gas, H_2, 40ml/min.

In order to see the oxygen distributions in the esters, I(5.0g, 0.040mole, 0.204 atom % ^{18}O) was reacted with ^{18}O-labeled acetic anhydride(5.0g, 0.049mole, 0.633 atom % ^{18}O) under the presence of ^{18}O-labeled acetic acid(15.0g, 0.25mole, 0.889 atom % ^{18}O), which was added to get an appreciable amount of IV. The results are shown in Table II with the ratios of an intermolecular to intramolecular process which were calculated on the basis of the results of the contents of oxygen-18 in the corresponding esters.

It is generally accepted that the first step of the reaction of I with acetic anhydride is the formation of the pyridinium salt(I'). When the basicity of the reagent is strong, the following deprotonation process does not take place easily.[11,12] In the case of pyridine[13] or 3-methylpyridine N-oxide[14], acetate anions attack only the ring carbon of the corresponding pyridinium salt yielding the ring-substituted compounds. On the other hand, it is suggested that the reaction of 2- or 4-methylpyridine with acetic anhydride proceeds through anhydrobase and that the deprotonation step is the rate-determining in the rearrangement of acyloxy group to the side chain.[7,8]

When we shed a light on the reaction mechanism of I with acetic anhydride, two anhydrobases(A and B) are considered depending upon the position of removal of a proton. Anhydrobase A similar to that of 2-methylpyridine N-oxide gives mainly V with small amount of II and III. From our results, we can safely say that the process through A to the final products (V,II and III) is essentially intramolecular. Oxygen-18 analyses of esters show that the intramolecular process is about 95% even under the presence of acetic acid.



On the other hand, anhydrobase B is similar to that of 4-methylpyridine N-oxide. If this is the case, the yield of the products formed through B should be affected by the environments. As the rearrangement between IV and V was not observed in the control experiment, IV should be formed directly through B.

Under the reaction conditions of oxygen-18 shown in Table II, IV were formed by 40 % intermolecularly. The ratio of intermolecular process increased with increasing number of acetic acid. This observation is in a good agreement with those of our previous[5-7] and Cohen's recent[8] results obtained in the 4-methylpyridine N-oxide. Although we did not yet clearly elucidate at what step acetic acid molecules or anions play an important role, the increase of the number of the acid in the neighbor of I′ seems to favor the formation of the anhydrobase B over A. Furthermore, the fact that the increase of the relative yield of IV was proportional to the logarithmic number of the acetic acid means that only the acetic acids which occupy the site favorable to the formation of IV can be effective and very limited. The similar effect of acetic acid on the position para to the ring nitrogen was observed in the reaction of 2,4,6-trimethylpyridine N-oxide with acetic anhydride, too. The details on the mechanism are under study.

REFERENCES

1. V.Boekelheid and D.L.Harrington, Chem. and Ind., 1428 (1955).
2. V.J.Traynelis and R.F.Martello, J. Am. Chem. Soc., 80, 6590 (1958).
3. T.Cohen and J.H.Fager, ibid, 87, 5701 (1965).
4. T.Koenig, ibid, 88, 4045 (1966).
5. a) S.Oae, T.Kitao and Y.Kitaoka, ibid, 84, 3359 (1962). b) ibid, 84, 3362 (1962).
6. S.Oae, Y.Kitaoka and T.Kitao, Tetrahedron, 20, 2685 (1964).
7. S.Oae, S.Tamagaki, T.Negoro and S.Kozuka, ibid, 26, 4051 (1970).
8. T.Cohen and L.Deets, J. Am. Chem. Soc., 94, 932 (1972).
9. S.Furukawa, Pharm. Bull., Tokyo, 3, 413 (1955). He did not isolate four esters but he identified three alcoholic substances as picrates from the alkaline hydrolysis products of the ester mixture.
10. P.W.Ford and J.M.Swan, Aust. J. Chem., 18, 867 (1965).
11. J.F.Vozza, J. Org. Chem., 27, 3856 (1962).
12. V.Traynelis, Sr.A.I.Gallagher and R.F.Martello, ibid, 26, 4365 (1961).
13. a) J.H.Markgraf, H.B.Brown, Jr.S.C.Mohr and R.G.Peterson, J. Am. Chem. Soc., 85, 958 (1963). b) S.Oae and S.Kozuka, Tetrahedron, 21, 1971 (1965).
14. S.Oae and S.Kozuka, ibid, 20, 2671 (1964).