

THE KATADA REACTION: A STUDY OF EXPERIMENTAL CONDITIONS

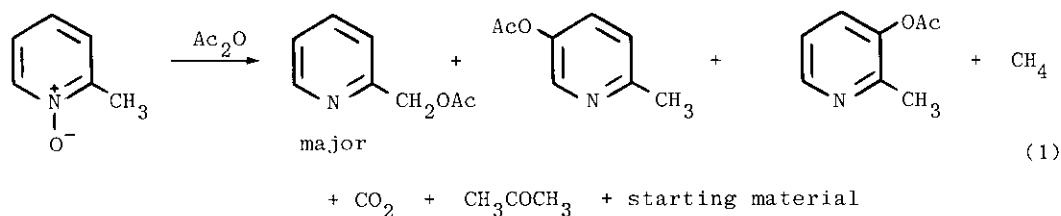
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Abstract -- Experimental conditions for the Katada reaction have been studied using 2-picoline N-oxide as a model substrate. Using a mixture of acetyl chloride and acetic anhydride, the reaction takes place rapidly at room temperature to give an excellent yield of 2-acetoxymethylpyridine.

Introduction

The Katada reaction is a well established and frequently used procedure in heterocyclic chemistry for the introduction of oxygen functionality at an alkyl group alpha to a ring nitrogen atom in a π -deficient heterocycle.¹ The mechanism of the overall transformation has been the subject of extensive investigation,¹ and some controversy, whereas by contrast there has been no systematic study of the optimum experimental conditions for the reaction. In most applications, a 2-alkyl substituted π -deficient heterocyclic N-oxide has simply been heated in the presence of acetic anhydride to give the desired 2-acetoxyalkyl substituted heterocycle - generally in good to excellent yield. It is now known, however, that in contradiction to the original reports,²⁻⁴ the Katada reaction of alkyl azines almost invariably gives mixtures of products, as outlined in equation (1) for the reaction of 2-picoline N-oxide with acetic anhydride, but little is known of the factors which control the product distribution.

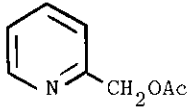
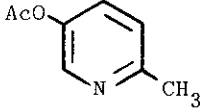
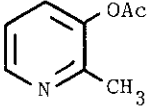


In recent studies we intended to use the Katada reaction in the synthesis of a natural product, but prior to its application undertook an examination of the effects of temperature, solvent, and the addition of both protic and Lewis acids and of acetyl chloride on the reaction of 2-picoline N-oxide with acetic anhydride. We now describe the results of these studies.

Discussion

Using the "classical" conditions - heating the N-oxide in acetic anhydride - the optimum temperature for the reaction was found to be 70°C as, at and above this temperature, the relative ratios of the products remained constant (Table I). On a preparative scale, addition of boron trifluoride etherate had no effect, while

TABLE I
The Effect of Temperature on the reaction of 2-Picoline N-oxide
with Acetic Anhydride^a

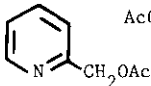
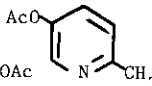
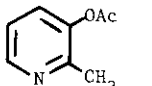
<u>Temp. °C</u>	<u>Time, min.</u>	<u>Yield, %^b</u>		
				
150	3	71.1	15.6	13.3
100	3	71.8	14.4	13.8
90	3	70.2	15.0	14.8
80	5	70.4	16.2	13.4
70	5	70.9	15.7	13.4
60	10 h	64.6	17.7	17.7

^a 2 equivalents of acetic anhydride were used. ^b glc yields are quoted

addition of sodium acetate led to a small decrease in the amount of the 2-acetoxymethyl product (Table II) relative to reaction with acetic anhydride at 70°C. The addition of a polar solvent, dimethylformamide, resulted in an increase in the rate of reaction and a change in product distribution. Use of a mixture of acetic anhydride and acetyl chloride not only produced a significant increase in the rate

TABLE II

Product Distribution Ratio (%) for the Reaction of 2-Picoline N-oxide with:

Reagent ^a	Temp. °C	Time	Yield, % ^b					
						Others		
Ac ₂ O	70	5 min	70.9	15.7	13.4	-	-	-
Ac ₂ O	60	10 h	64.6	17.7	17.7	-	-	-
Ac ₂ O/DMF 2 ml	60	3 h	59.3	18.5	18.5	3.6	-	-
Ac ₂ O/BF ₃ ·Et ₂ O ^c	60	10 h	71.0	15.0	14.0	-	-	-
Ac ₂ O/NaOAc ^d	100	3 min	65.9	17.7	16.4	-	-	-
Ac ₂ O/AcCl ^e	RT	2 sec	78.1	4.7	3.9	-	13.3	-
AcCl/DMF 1 ml ^f	RT	5 sec	-	-	-	-	26.0	74.0

^a 2 equivalents of Ac₂O were used. ^b glc yields are quoted. ^c 10 drops.

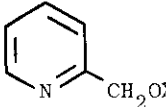
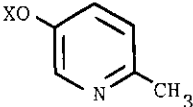
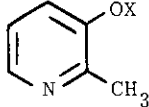
^d 1 equivalent. ^e 1 equivalent of acetyl chloride. ^f Excess of acetyl chloride was used.

of reaction, but led to the highest yield of 2-acetoxymethylpyridine, with the amounts of 3- and 5-acetoxy-2-methylpyridine formed being substantially decreased. This indicates that initial acetylation of the N-oxide may well be rate determining.

The above result with acetyl chloride partially corroborates Oae's⁵ statement: "the initial equilibrium reaction of acetylation is also quite important to control the overall rate of the reactions". However, as the product distribution ratio depends on the N-O bond cleavage and the subsequent recombination steps, it is possible that the acetyl chloride also has an effect on these steps; this could account for the lower yields of the 3- and 5-substituted products. The fourth product in the acetic anhydride/acetyl chloride reaction was not identified, but may well have been 2-chloromethylpyridine, as this compound was identified by Vozza⁶ as one of the three products formed during the reaction of 2-picoline N-oxide with acetyl chloride and acetic acid as solvent. Interestingly, in the present study the same product was also formed in the reaction of 2-picoline N-oxide with acetyl chloride and dimethylformamide as solvent.

Another interesting aspect of the present investigation is that the product distribution is affected to a significant extent by the nature of the anhydride used, although it is not at all obvious why this should be so. When acetic, propionic and *n*-butyric anhydrides were used, the yield of the corresponding 2-acyloxymethylpyridine increased from 71 to 88% (Table III). The amount of

TABLE III
Product Distribution Ratio (%) of the Reaction of 2-Picoline
N-Oxide with Anhydrides

<u>Anhydride</u> ^a	<u>Yield, %</u> ^{b,c}		
			
Acetic	71.1	15.6	13.3
Propionic	72.6	13.9	13.5
<i>n</i> -Butyric	88.4	11.6	-
Crotonic	77.6	16.4	5.9
Tiglic	82.7	17.3	-

^a The reaction was carried out at 150°C with 2 equivalents of anhydride.

^b ^c ^glc yields are quoted. $\text{X} = \begin{array}{c} \text{O} \\ \parallel \\ \text{-C-R} \end{array}$

5-acyloxy-2-methylpyridine formed in the reactions with anhydrides other than acetic anhydride did not differ to any significant extent to that obtained in the acetic anhydride reaction, but no 3-acyloxy-2-methylpyridine was detected in the reactions with *n*-butyric and tiglic anhydride. These results appear to indicate that there is a steric effect in the Katada reaction with respect to the anhydride used although, in terms of the commonly accepted mechanism(s), the origin remains obscure.

Conclusion

Use of a mixture of acetyl chloride and acetic anhydride allows the Katada reaction to be carried out rapidly at room temperature. Under these conditions the yield

of 2-acetoxymethylpyridine is better than with acetic anhydride alone and the amounts of 3- and 5-acetoxy-2-methylpyridine formed are substantially reduced.

EXPERIMENTAL

General procedure for the reaction of 2-picoline N-oxide with acid anhydrides

The acid anhydride (0.055 mol), together with additional reagents as outlined in Table II, was added to 2-picoline N-oxide (0.0275 mol) and the mixture allowed to react at the temperatures, and for the times summarised in Tables I-III. In most cases reaction was complete within a few minutes (glc). The excess anhydride and other volatile materials were removed by distillation under reduced pressure and the residue distilled under vacuum to give an oil which was analysed by glc on a Pye Unicam GCD Gas Chromatograph using a 2.1 m, 4 mm diameter OV-1 column. Pure samples of 2-acetoxymethylpyridine and of 3- and 5-acetoxy-2-methylpyridine were prepared by standard literature procedures.

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Received, 18th March, 1985