

HYDROXYLATION OF ALKYL GROUPS ON THE PYRAZINE RING

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Abstract --- Treatment of THF solutions of 2,5-dialkylpyrazine 1-oxides with oxygen in the presence of bases gave the corresponding 2-hydroxypyrazine 1-oxides and dimers. On the other hand, when 2-chloro-3,6-dialkylpyrazine 1-oxides and 3,6-dialkyl-2-hydroxypyrazine 1-oxides were treated under the same conditions, hydroxylation occurred successfully at the α -position of the side chain.

Among the naturally occurring hydroxypyrazines and 2-hydroxypyrazine 1-oxides as mold metabolites,¹ the one carrying a hydroxyl group on the side chain, especially a tertiary hydroxyl group on the α -carbon of the side chain, are of interest synthetically. Sugiyama *et al.* reported the synthesis of mutaaspergillilic acid by a cyclisation of 4-methoxy-2-(3-hydroxy-3-methyl-2-oxobutylamino)valero-hydroxamic acid in poor yield.² Although we have already achieved the syntheses of neohydroxyaspergillilic acid (6c) and deoxyneo- β -hydroxyaspergillilic acid starting from leucine anhydride,^{3,4} the introduction of a tertiary hydroxyl group to the α -carbon of side chains on the pyrazine ring has not been perfected as of yet. It is the purpose of this report to describe a simple method of introduction of a hydroxyl group in the side chain and the synthesis of d,l-neohydroxyaspergillilic acid (6c).

In a similar manner to the work on a base-catalysed hydroxylation of the carbon adjacent to a carbonyl group,⁵ dry oxygen was continuously circulated in a THF solution of 2,5-diisopropylpyrazine 1-oxide⁶ (1a) in the presence of various bases at low temperatures (0 and -78 °C), and the results are shown in Table I. The use of lithium diisopropylamide (LDA) gave the products, 3,6-diisopropyl-2-hydroxypyrazine 1-oxide⁷ (2a) and a dimer (3a), in the best yields. The structure of the dimer (3a) was determined on the basis of PMR spectral data. Namely, the spectrum

Thus, 2-chloro-3,6-diisopropylpyrazine 1-oxide⁷ (4a) was treated at -78°C with oxygen in the presence of LDA and the hydroxylated products (5a and 6a) were successfully obtained. An alkaline hydrolysis of 5a led to give 6a in almost quantitative yields. For determining the structure, 5a was subjected to the de-chlorination reaction⁹ and the structure of the product (7a) was elucidated by the comparison of the PMR spectrum with that of 1a. The methine proton signal of 1a in the lower field disappeared in the presence of 7a.⁸ This evidence supports that the hydroxylation occurred on the alkyl group adjacent to the N-O group.

Although 4a was subjected to the reaction at 0°C , any desired products were not detected.

The two other 2-chloropyrazine 1-oxides (4b¹⁰ and 4c⁷) were also treated similarly to the reaction of 4a to yield two products, respectively. However, the reaction of 4b at 0°C resulted in formation of the resinous products. The conversion of 5b and 5c to 6b and 6c, respectively, was also achieved efficiently.

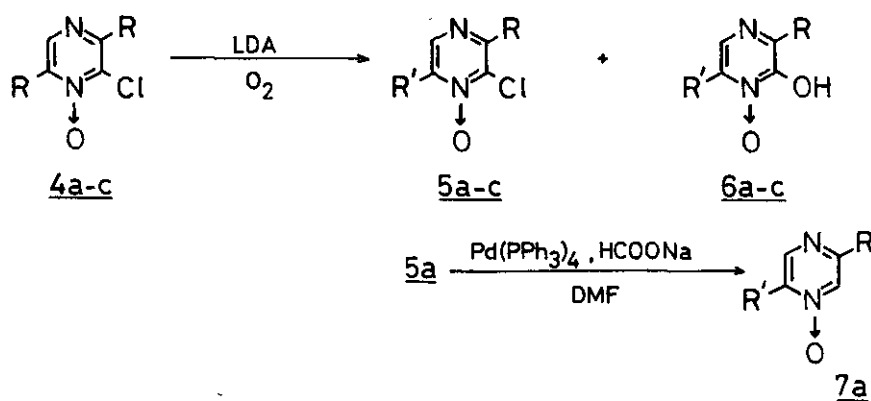


Table II

R	R'	yield(%)			
		-78°C		0°C	
		5	6	5	6
a: $(\text{CH}_3)_2\text{CH}-$	$(\text{CH}_3)_2\text{C(OH)}-$	30.4	25.2	0	0
b: $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{CH}-$	$\text{CH}_3\text{CH}_2(\text{CH}_3)\text{C(OH)}-$	42.5	25.4	0	0
c: $(\text{CH}_3)_2\text{CHCH}_2-$	$(\text{CH}_3)_2\text{CHCH(OH)}-$	23.0	31.0	15.0	8.1

Although 3,6-dialkyl-2-hydroxypyrazine 1-oxides (2a-c) were also subjected to the α -hydroxylation reaction, only 2c gave the desired product in satisfactory yield (Table III). The separation of the products from the starting materials was made by the reported method,¹¹ in which the chloroform solution of the reaction mixture was extracted with 0.1 or 0.005 M sodium bicarbonate to isolate the products.

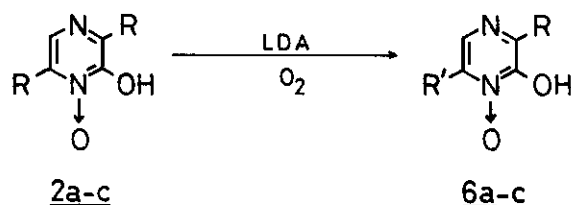


Table III		yield(%)	
R	R'	-78°C	0°C
a : (CH ₃) ₂ CH-	(CH ₃) ₂ C(OH)-	14.6	recovered
b : CH ₃ CH ₂ (CH ₃)CH-	CH ₃ CH ₂ (CH ₃)C(OH)-	recovered	recovered
c : (CH ₃) ₂ CHCH ₂ -	(CH ₃) ₂ CHCH(OH)-	42.9	40.2

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- 10 Compound 4b was prepared from 2-chloro-3,6-di-*sec*-butylpyrazine (R. A. Baxter and F. S. Spring, J. Chem. Soc., 1179 (1947)) by the reported manner.⁸
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