HYDROXYLATION OF ALKYL GROUPS ON THE PYRAZINE RING

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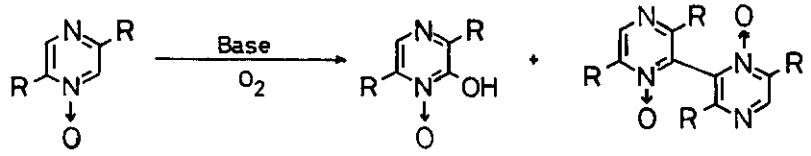
Abstract --- Treatment of THF solutions of 2,5-dialkylpyrazine 1-oxides with oxygen in the presence of bases gave the corresponding 2-hydroxypyrazine 1-oxides and dimers. On the other hand, when 2-chloro-3,6-dialkylpyrazine 1-oxides and 3,6-dialkyl-2-hydroxypyrazine 1-oxides were treated under the same 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 mutaaspergillic acid by a cyclisation of 4-methoxy-2-(3-hydroxy-3-methyl-2-oxobutylamino)valerohydroxamic acid in poor yield.[2] Although we have already achieved the syntheses of neohydroxyaspergillic acid (6c) and deoxyneo-β-hydroxyaspergillic 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-neohydroxyaspergillic 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-oxide[6] (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-oxide[7] (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

of the starting material (1a) indicates two singlets (8.20 and 8.55 ppm) owing to the ring protons,[6] while the one in the higher field disappears in the spectrum of the dimer (3a).

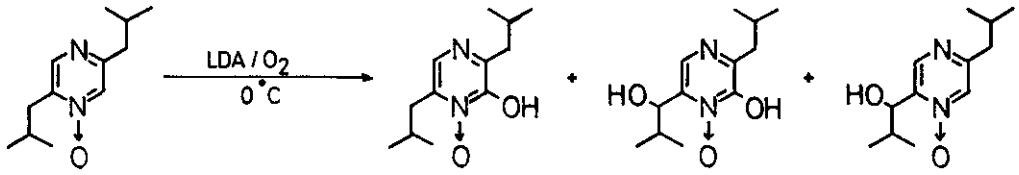
On the basis of the results obtained above, LDA was adopted as base for the other experiments. The reactions of 2,5-di-sec-butylpyrazine 1-oxide[8] (1b) and 2,5-diisobutylpyrazine 1-oxide[6] (1c) were carried out at 0 and -78 °C. Except the reaction of 1c at 0 °C, two products, the hydroxamic acids (2b and 2c[7]) and the dimers (3b and 3c), were obtained, as shown in Table I. Interestingly, the hydroxylation of 1c took place in the side chain at 0 °C, giving rise to 6c and 2-(α-hydroxyisobutyl)-5-isobutylpyrazine 1-oxide (7c), in addition to 2c.



1a-c 2a-c 3a-c

Table I

R	Base	yield(%) -78 °C 2	-78 °C 3	0 °C 2	0 °C 3
a : $(CH_3)_2CH$-,	t-BuOK	-	-	0	0
	n-BuLi	12.5	12.3	9.0	8.4
	LDA	16.2	17.6	26.6	19.4
b : $CH_3CH_2(CH_3)CH$-,	LDA	11.0	23.7	9.0	12.4
c : $(CH_3)_2CHCH_2$-,	LDA	18.2	20.0	9.0	0



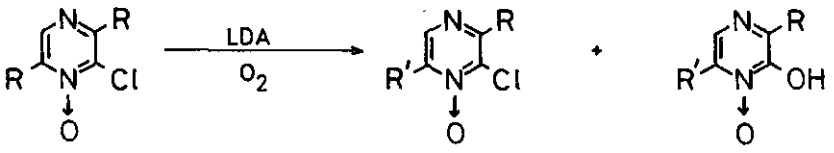
1c 2c 6c 7c

These results would suggest that the C-6 of 1a and 1b, adjacent to the N-O group, is more reactive than the α-position of the side chain and that the oxidation may occur at the side chain, when the C-6 is blocked with any groups.

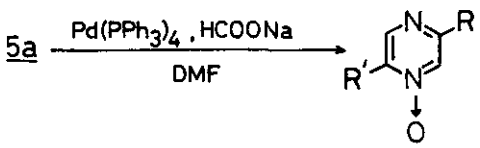
Thus, 2-chloro-3,6-diisopropylpyrazine 1-oxide[7] (4a) was treated at -78 °C with oxygen in the presence of LDA and the hydroxylated products (5a and 6a) were successfully obtained. An alkaline hydrolysis of 5a led to give 6a in almost quantitative yields. For determining the structure, 5a was subjected to the dechlorination reaction[9] 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 (4b[10] and 4c[7]) 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.



4a-c 5a-c 6a-c

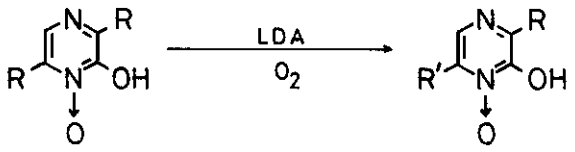


7a

Table II

		yield(%)			
		-78°C		0°C	
R	R'	5	6	5	6
a: $(CH_3)_2CH$-,	$(CH_3)_2C(OH)$-	30.4	25.2	0	0
b: $CH_3CH_2(CH_3)CH$-,	$CH_3CH_2(CH_3)C(OH)$-	42.5	25.4	0	0
c: $(CH_3)_2CHCH_2$-,	$(CH_3)_2CHCH(OH)$-	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.



2a-c 6a-c

Table III

R	R′	yield (%) -78°C	yield (%) 0°C
a : $(CH_3)_2CH$-,	$(CH_3)_2C(OH)$-	14.6	recovered
b : $CH_3CH_2(CH_3)CH$-,	$CH_3CH_2(CH_3)C(OH)$-	recovered	recovered
c : $(CH_3)_2CHCH_2$-,	$(CH_3)_2CHCH(OH)$-	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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