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Simple Approach Towards the Synthesis of 5-Methyl-2-hydroxypyrazine Derivatives from Dipeptidyl Chloromethyl Ketones[1]

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Abstract: 5-Methyl-2-hydroxypyrazine derivatives were easily synthesized by short reflux of dipeptidyl chloromethyl ketone hydrochlorides in MeOH.

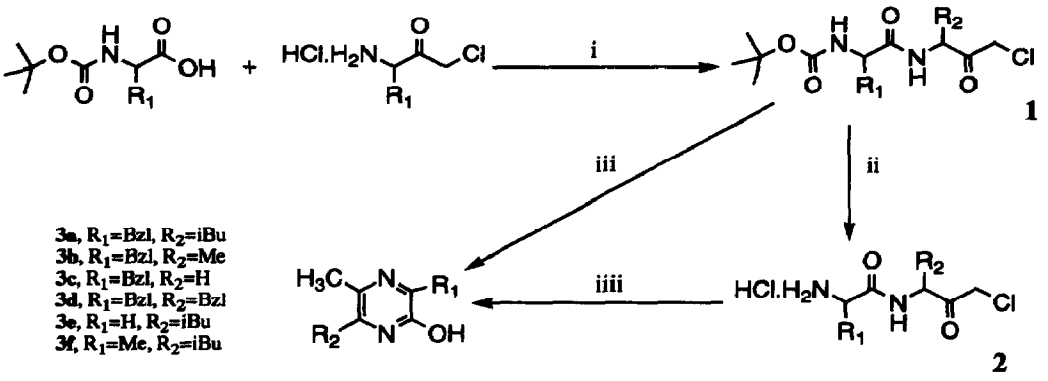
Hydroxypyrazine derivatives are key intermediates for preparing mold metabolites which exhibit antibiotic activities against gram-negative micro-organisms.[2] It is also well known that pyrazinols can be easily converted to the corresponding pyrazinethiols by 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent)[3]. Therefore, pyrazinol derivatives are useful intermediates for acyloxypyrazines[4] and acylthiopyrazines[5], which are convenient acylating agents for amines, alcohols and phenols.

Although pyrazinol derivatives were prepared by condensation of 1,2-dicarbonyl compounds with α-amino acid amides[6] or by hydrolysis of the corresponding methoxypyrazine derivatives,[4,7] which were prepared from the corresponding chloride[8,9] and sodium methoxide, the development of more convenient synthetic procedure of pyrazinol derivatives has been required. This paper deals with a simple and convenient synthesis of 5-methyl-2-hydroxypyrazine derivatives.

As shown in scheme 1, Boc-NH-CH(R_1)CONH-CH(R_2)-$COCH_2Cl$(1) was prepared by the coupling of Boc-NH-CH(R_1)-COOH and H_2N-CH(R_2)-$COCH_2Cl$[10] by mixed anhydride method[11], which coupling yields were more than 80%. This compound was converted to the corresponding 5-methyl-2-hydroxypyrazine derivative under the following conditions: 6N HCl, 110°C, 2h. Another route is as follows: After removal of Boc group by HCl/dioxane, HCl.H_2N-CH(R_1)-CONH-CH(R_2)-$COCH_2Cl$(2) in MeOH was refluxed for 2h to afford 5-methyl-3-R_1-6-R_2-2-hydroxypyrazine(3). The latter route afforded better yield as summarized in Table 1, because in the former route, the 5-methyl-2-hydroxypyrazine derivatives were decomposed during acid hydrolysis.[12]

Diastereoisomeric dipeptidyl chloromethyl ketone hydrochlorides, D-L, L-D, D-D, were converted to the corresponding pyrazinol derivatives in a similar yield to that of L-L compound, indicating that amino group of dipeptidyl chloromethyl ketones could attack the carbonyl group of the chloromethyl ketone moiety in every isomer.

Scheme 1



i $ClCOOCH_2CH(CH_3)_2$, Et_3N, THF.
ii 7.6N HCl/dioxane.
iii 6N HCl, reflux.
iiii MeOH, reflux.

Table 1 : 3-Benzyl-5,6-methyl -2-hydroxypyrazine formation under various conditions

Starting material	Condition*	(%)Yield
Boc-Phe-Ala-CH_2Cl	6N-HCl	29.3
	1N-HCl	31.0
	3N-HCl/MeOH	62.9
HCl.H-Phe-Ala-CH_2Cl	MeOH	65.3

* reflux for 2h

Boc-Phe-Leu-CH3 was also treated with 6N HCl at 110°C for 20h to afford phenylalanine residue in the yield of 75% and pyrazinol derivative was not obtained. Then, H-Phe-Leu-CH3.HCl in MeOH was refluxed for 2h to give the corresponding pyrazinol derivative in an yield of 65%. The difference in reactivity between chloromethyl ketone derivative and methyl ketone derivative might be explained as follows: 1) Electrophilicity of carbonyl group of chloromethyl ketone is higher than that of methyl ketone. 2) The formation of stable pyrazinol derivative from chloromethyl ketone derivative by leaving chloride anion is much easier than from methyl ketone derivative, in which pyrazinol derivative might be formed oxidatively in the presence of oxygen more slowly than from the corresponding chloromethyl ketone derivative.

Table 2 : Results for cyclization of dipeptidyl chloromethyl ketones

Products	(%)Yield[a]	m.p.(°C)
3a	70.0	133-5
3b	65.3	161-2
3c	65.0	189-90
3d	67.4	174-5
3e	90.6	128-30
3f	89.9	109-10

a, Isolated yield

Next, We examined the yields of other chloromethyl ketone derivatives. The conditions used were as follows. After removal of Boc group by HCl/dioxane, **2** in MeOH was refluxed for 2h. Table 2 shows the results of yield and m.p. of 5-methyl-2-hydroxypyrazine derivatives[13] from dipeptidyl chloromethyl ketones.

This novel method can afford pyrazinol derivatives substituted at the position 3 and 6(R1 and R2, Schem 1) with the desired alkyl groups. Thus, this simple and convenient synthetic procedure of pyrazinol derivatives from dipeptidyl chloromethyl ketones is a recommendable one.

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12. The rate of the decomposition of 5-methyl-2-hydroxypyrazine derivatives during acid hydrolysis(6N HCl, 110°C) as a function of time, was examined by HPLC. The peak corresponding to 5-methyl-2-hydroxypyrazine was disappeared after 48h.

13. All compounds gave satisfactory elemental analyses. ^{1}H-NMR spectra were measured with a Bruker AM400 spectrometer operating at a frequency of 400MHz and controlled by an Aspect3000 computer. Chemical shift values are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ-value). Mass spestra were determined on a Hitachi M-1000 mass spectrometer. Compound **3a**, ^{1}H-NMR($CDCl_3$) δ =13.3 (bs, 1H), 7.41-7.14 (m, 5H), 4.05 (s, 2H), 2.39 (d, 2H, *J*=7.6Hz), 2.26 (s, 3H), 2.06 (m, 1H), 0.97 (d, 6H, *J*=6.6Hz). m/z: 257 $(M+H)^+$. Compound **3b**, ^{1}H-NMR($CDCl_3$) δ =13.5 (bs, 1H), 7.40-7.12 (m, 5H), 4.07 (s, 2H), 2.24 (d, 3H, *J*=0.6Hz), 2.18 (s, 3H). m/z: 215 $(M+H)^+$. Compound **3c**, ^{1}H-NMR($CDCl_3$) δ =13.0 (bs, 1H), 7.40-7.16 (m, 5H), 6.88 (s, 1H), 4.11 (s, 2H), 2.27 (d, 2H, *J*=0.7Hz). m/z: 201 $(M+H)^+$. Compound **3d**, ^{1}H-NMR($CDCl_3$) δ =13.5 (bs, 1H), 7.40-7.16 (m, 10H), 3.99 (d, 4H, *J*=95.2Hz), 2.38 (s, 3H). m/z: 291 $(M+H)^+$.Compound **3e**, ^{1}H-NMR($CDCl_3$) δ =13.7 (bs, 1H), 8.04 (s, 1H), 2.32 (s, 3H), 2.05 (m, 1H), 1.00 (d, 6H, *J*=6.6Hz). m/z: 167 $(M+H)^+$.Compound **3f**, ^{1}H-NMR($CDCl_3$) δ =13.3 (bs, 1H), 2.44 (d, 2H, *J*=7.4Hz), 2.43 (s, 3H), 2.28 (s, 3H)2.03 (m, 1H), 0.98 (d, 6H, *J*=6.6Hz). m/z: 181 $(M+H)^+$.

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