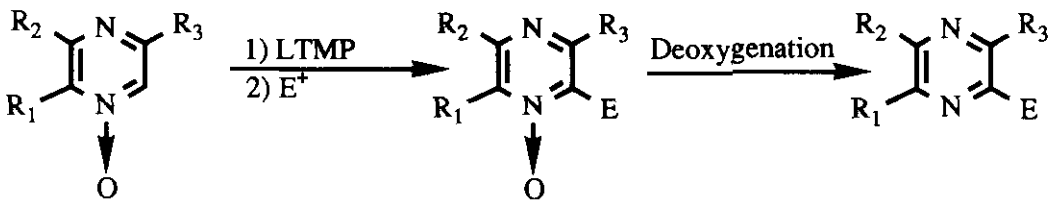
EFFICIENT ALKYLATION AND ACYLATION OF PYRAZINE 1-OXIDES

Yutaka Aoyagi, Atsushi Maeda, Masami Inoue, Mitsuhiro Shiraishi
Yuki Sakakibara, Yuko Fukui, and Akihiro Ohta*
Tokyo College of Pharmacy
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan
Kenzo Kajii and Yoshio Kodama
Pharmaceutical Research Center, Meiji Seika Kaisha, LTD.
760 Morooka-cho, Kohoku-ku, Yokohama 222, Japan

Abstract - Reactions of pyrazine 1-oxides with electrophiles in the presence of LTMP (lithium 2,2,6,6-tetramethylpiperidine) and TMEDA (N,N,N',N'-tetramethylethylenediamine) afforded 2-alkyl- and 2-acylpyrazine 1-oxides in good yields, and the products could be deoxygenated with PBr_3 and Raney Ni successfully.

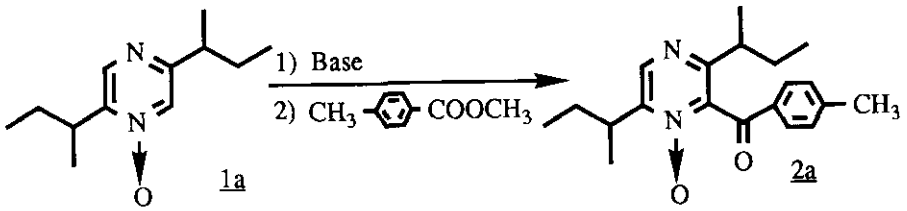
Diazines such as pyrazine are generally resistant to electrophilic substitution reactions, owing to their electron-deficiency. Little research has thus been reported on the introduction of acyl groups into the pyrazine ring. As for the alkylation of this ring, palladium-catalyzed cross-coupling reactions of chloropyrazines have been reported.[1] In 1967, Abramovitch reported treatment of pyridine 1-oxides with some electrophiles such as carbon dioxide and cyclohexanone in the presence of n-BuLi to give 2-carboxylated and 2-alkylated pyridine 1-oxides in poor yields, accompanied by the production of 2,6-disubstituted pyridine 1-oxides.[2]
The present paper deals with the efficient alkylation and acylation of pyrazine 1-oxides with some electrophiles in the presence of LTMP (lithium 2,2,6,6-tetramethylpiperidine) and TMEDA (N,N,N',N'-tetramethylethylenediamine), and deoxygenation of the products with PBr_3 or Raney Ni (Scheme 1).



Scheme 1

We investigated the reaction of 2,5-di-sec-butylpyrazine 1-oxide[3] (1a) with methyl p-toluate under various conditions (Table 1).

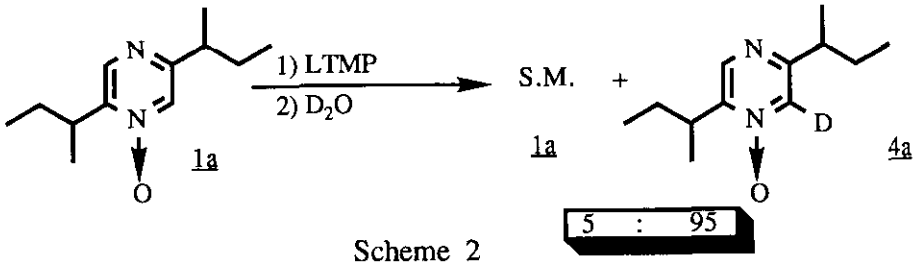
Table 1. Reaction of 2,5-di-sec-butylpyrazine 1-oxide with methyl p-toluate under various conditions



Entry	Base	Solvent	Additive	Temp.(°C)	Yield (%)
1	NaH	THF	none	reflux	--
2	n-BuLi	THF	none	-78	42
3	LDA	THF	none	-78	56
4	LDA	DME	none	-78	59
5	LTMP	THF	none	-78	62
6	LTMP	THF	HMPA	-78	68
7	LTMP	THF	TMEDA	-78	72
8	t-BuLi	THF	HMPA	-78	40

On using sodium hydride as a base, the starting material was recovered unchanged (Entry 1). The 6-proton of the pyrazine ring could be attracted efficiently by lithium bases to give the 6-p-toluoylpyrazine 1-oxide (2a) in moderate to good yields (Entries 2-8). The conditions of entry 7 was found to be most effective. When 1a was treated with deuterium oxide under this conditions, the pyrazine ring hydrogen adjacent to the N-oxide group was substituted by deuterium in 95% yield (Scheme 2). This was confirmed

on the basis of ^{1}H-nmr spectral data. Namely, in two pyrazine ring protons, the one that was observed in the higher field disappeared selectively.

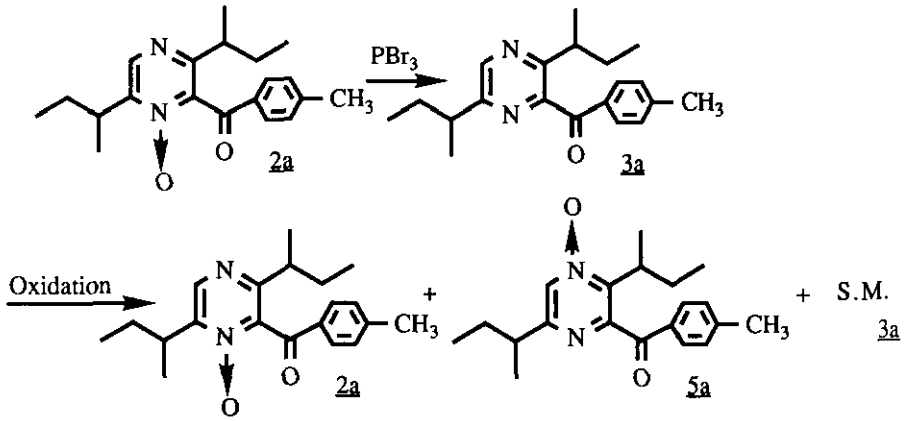


Scheme 2

To determine the structure of 2a, the following experiments were carried out:

1) deoxygenation of 2a to 3a and reoxidation of 3a (Table 2)
2) assignment of 2a using nmr (especially LSPD method)

Table 2. Deoxygenation of 2a and reoxidation of 3a



Reaction conditions	2a	5a	S.M.(3a)
mCPBA/reflux	8	30	60
PMA/reflux	18	32	41

Compound 2a was deoxygenated with PBr_3, followed by the reoxidation of compound 3a with either m-chloroperbenzoic acid (mCPBA) or permaleic acid (PMA) to afford a mixture of two monooxides (2a, 5a) and the starting material (3a) as shown in Table 2. In the molecule of 3a, N-4 in two

nitrogen atoms may be more oxidizable than N-1 by peracid, because of the less hindered steric environment of N-4. Compound 5a was actually obtained in better yield than 2a.

An attempt was made to assign the structure of 2a by nmr in the long-range selective proton decoupling (LSPD) method. Our previous paper[4] indicated the methine proton (Ha) of 2a to possibly be in a higher field than the methine proton (Hb) adjacent to 1-oxide. On irradiating the methine proton (Ha) at 2.52 ppm, a singlet-doublet signal due to C-2 was made changed into a singlet signal. A doublet-doublet signal arising from C-5 changed to a doublet by irradiation at 3.41 ppm (Figure 1). The structure of 2a is thus possibly assumed to be 3,6-di-sec-butyl-2-(p-toluoyl)pyrazine 1-oxide.

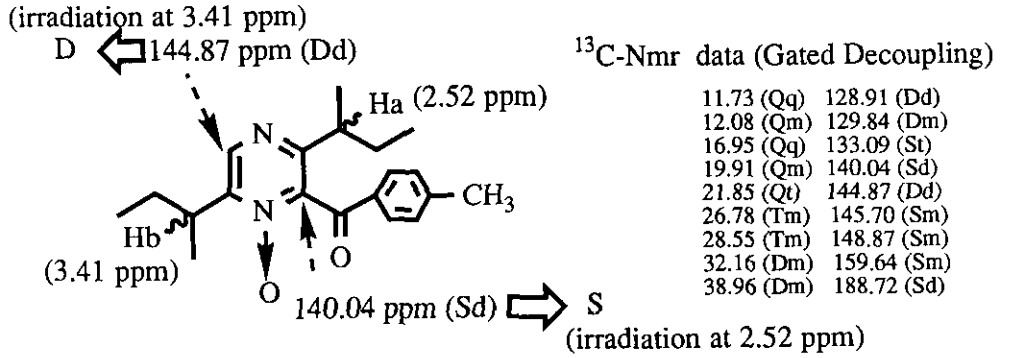


Figure 1 Assignment of compound 2a by the LSPD method

This assignment was also confirmed by X-Ray analysis of 2a as shown in Figure 2.

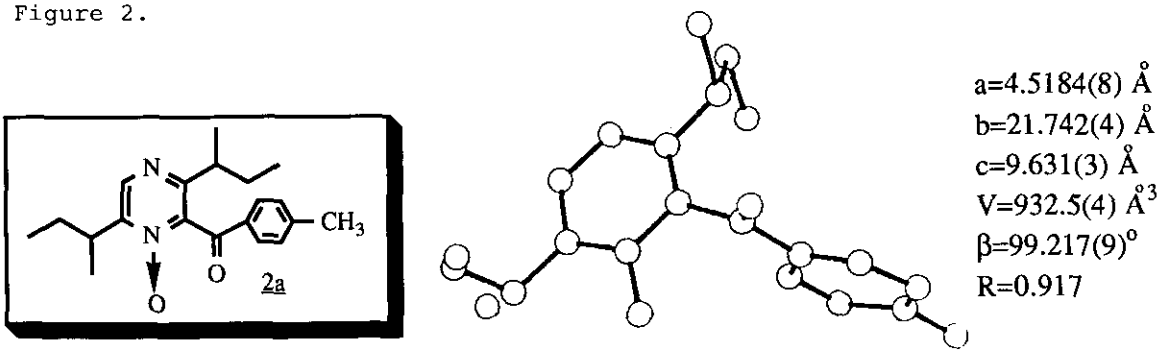
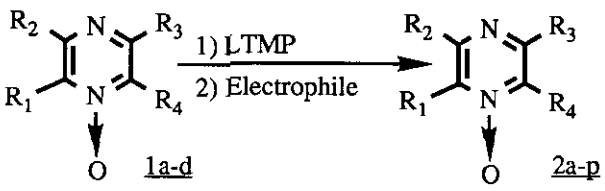


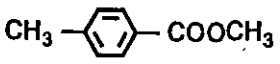
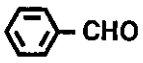
Figure 2 X-Ray diffraction of compound 2a

Based on the above results and the experiment using deuterium oxide, this reaction clearly occurs at the 6-position of the pyrazine 1-oxide.

Table 3. Reactions of pyrazine 1-oxides with electrophiles



1a: $R_1=R_3=sec\text{-}C_4H_9$, $R_2=R_4=H$ 1b[5]: $R_1=R_3=iso\text{-}C_4H_9$, $R_2=R_4=H$
1c[6]: $R_1=R_3=iso\text{-}C_3H_7$, $R_2=Cl$, $R_4=H$ 1d[7]: $R_1=R_2=Ph$, $R_3=R_4=H$

Substrate	electrophile	R_4	Product (%)
1a		p-toluoyl	2a (72)
1b		p-toluoyl	2b (30)
1c		p-toluoyl	2c (68)
1d		p-toluoyl	2d (40)
1a		p-toluoyl	2a (59)
1b		p-toluoyl	2b (58)
1c		p-toluoyl	2c (60)
1d		p-toluoyl	2d (40)
1a	CH_3CH_2CHO	α-hydroxypropyl	2e (74)
1b		α-hydroxypropyl	2f (57)
1c		α-hydroxypropyl	2g (62)
1d		α-hydroxypropyl	2h (47)
1a		α-hydroxybenzyl	2i (65)
1b		α-hydroxybenzyl	2j (65)
1c		α-hydroxybenzyl	2k (59)
1d		α-hydroxybenzyl	2l (55)
1a	DMF	formyl	2m (73)
1b		formyl	2n (17)
1c		formyl	2o (46)
1d		formyl	2p (15)
1a	$HCOOCH_3$	formyl	2m (82)
1b		formyl	2n (45)
1c		formyl	2o (71)
1d		formyl	2p (23)

Examination was subsequently made of the reactions of pyrazine 1-oxides (1a-d) with certain electrophiles such as ester, acyl halide, aldehyde and N,N-dimethylformamide (DMF)(Table 3). As expected, alkylation and acylation occurred in good yields. In the synthesis of formylpyrazine 1-oxides (2m-2p), methyl formate gave better results than DMF.

The deoxygenation of 2a, 2e, 2i, and 2m was examined (Table 4). The deoxygenation of pyrazine 1-oxides carrying p-toluoyl group (2a) and formyl group (2m) with PBr_3 gave the corresponding deoxygenated products in good yields, while no definite product was obtained from reactions of pyrazine 1-oxides carrying α-hydroxypropyl group (2e) and α-hydroxybenzyl group (2i). These latter pyrazine 1-oxides could be deoxygenated efficiently by H_2 over Raney Ni. Due to the instability of 2m, 2m was transformed to the 2,4-dinitrophenylhydrazone (2,4-DNP) and analysis was conducted for confirmation of the structure of the hydrazone.

Table 4. Deoxygenation of pyrazine 1-oxides

Substrate	Reagent	Yield %	(Recovery %)
2a	PBr_3	94	
2e	PBr_3	many products	
	H_2/Raney Ni	62	(26)
2i	PBr_3	many products	
	H_2/Raney Ni	54	(38)
2m	PBr_3	70	
	H_2/Raney Ni	many products	

The present findings are summarized as follows:

1) The alkylation and acylation of pyrazine 1-oxides mostly proceed in good yields.
2) Alkylated and acylated pyrazine 1-oxides can be deoxygenated efficiently with H_2 over Raney Ni or PBr_3. The synthesis of acylpyrazines *via* pyrazine 1-oxides is particularly useful, since, to date, it is the

first mean for the easy preparation of acylpyrazines.

EXPERIMENTAL

No correction was made for melting or biling points. ^{1}H-Nmr spectral data were obtained by a Varian EM-390, Gemini-300, or Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. ^{13}C-Nmr spectral data were measured in $CDCl_3$ with a Brucker AM-400. Medium-pressure column chromatography was conducted using a UVILOG 5III as the UV detector (Oyo Bunko Kiki Co.,LTD. Tokyo) and Kiesel gel 60 (Merk AG, Darmstadt) as the packing material. Other spectral data were obtained using the following instruments. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80b spectrometer. X-Ray diffraction data were obtained by Rigaku AFC-5R diffractometer with graphite monochromated Cu Kα radiation.

General Procedure for the Alkylation and Acylation of Pyrazine 1-Oxides (2a-2p)

To a dry THF solution (5 ml) of LTMP prepared from 2,2,6,6-tetramethylpiperidine (0.41 ml, 2.4 mmol) and 1.6M n-BuLi in hexane (1.38 ml, 2.2 mmol), a pyrazine 1-oxide (2 mmol) in dry THF (5 ml) was added at -78 °C under an atmosphere of argon. After 20 min of maintaining the temperature constant, TMEDA (0.37 ml, 2.4 mmol) was added to the mixture. The mixture was stirred for 20 min, and electrophile (2.2 mmol) in dry THF (5 ml) was added dropwise. After stirring at -78°C for 15 h and then 0°C for 2 h, 10% aq. NH_4Cl (10 ml) was added to the reaction mixture which was then diluted with ether (20 ml). The organic layer was separated, and the aquaous layer was extracted with ether (20 ml x 3), dried over Na_2SO_4 and concentrated. The residue was purified by medium-pressure liquid chromatography (hexane-AcOEt) to afford 2-alkyl- and 2-acylpyrazine 1-oxides.

3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine 1-oxide (2a): colorless prisms; mp 77-78°C (hexane); ms: m/z 326 (M^+); ^{1}H-nmr (400 MHz) : δ 0.76 (3H, br s, $CH(CH_3)CH_2\underline{CH}_3$), 0.96 (3H, t, J = 7.4 Hz, $CH(CH_3)CH_2\underline{CH}_3$), 1.20 (3H, d,

J = 5.0 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.32 (3H, dd, J = 7.0 Hz and 2.7 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.52-1.64 (2H, m, $CH(CH_3)C\underline{H}_2CH_3$), 1.78-1.89 (2H, m, $CH(CH_3)C\underline{H}_2CH_3$), 2.41 (3H, s, $C_6H_4C\underline{H}_3$), 2.52 (1H, m, J = 6.8 Hz, $C\underline{H}(CH_3)CH_2CH_3$), 3.41 (1H, m, J = 6.8 Hz, $C\underline{H}(CH_3)CH_2CH_3$), 7.27 (2H, d, J = 8.2 Hz, $C_6\underline{H}_4CH_3$), 7.67 (2H, d, J = 8.2Hz, $C_6\underline{H}_4CH_3$), 8.46 (1H, s, pyrazine H) ppm; ^{13}C-nmr (400 MHz): δ 11.68, 12.03, 16.91, 19.88, 21.80, 26.76, 28.54, 32.14, 38.93, 128.87, 129.79, 133.08, 140.00, 144.83, 145.60, 148.43, 159.59, 188.72 ppm; ir (KBr); 1670 cm^{-1}(C=O); Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.53. Found: C, 73.57; H, 8.11; N, 8.58.

3,6-Diisobutyl-2-(p-toluoyl)pyrazine 1-oxide (2b): colorless needles; mp 81-82°C (hexane); ms: m/z 326 (M^+); ^{1}H-nmr (90 MHz) : δ 0.87 (6H, d, J = 6 Hz, $CH_2CH(C\underline{H}_3)_2$), 1.00 (6H, d, J = 6 Hz, $CH_2CH(C\underline{H}_3)_2$), 1.90-2.40 (2H, m, $CH_2C\underline{H}(CH_3)_2$), 2.37 (3H, s, $C_6H_4C\underline{H}_3$), 2.50 (2H, d, J = 7.5 Hz, $C\underline{H}_2CH(CH_3)_2$), 2.73 (2H, d, J = 7.5 Hz, $C\underline{H}_2CH(CH_3)_2$), 7.27 (2H, d, J = 7.5 Hz, $C_6\underline{H}_4CH_3$), 7.67 (2H, d, J = 7.5 Hz, $C_6\underline{H}_4CH_3$), 8.43 (1H, s, pyrazine H) ppm; ir (KBr): 1670 cm^{-1} (C=O); Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; 8.53. Found: C, 73.62; H, 8.07; N, 8.56.

5-Chloro-3,6-diisopropyl-2-(p-toluoyl)pyrazine 1-oxide (2c): colorless needles; mp 136-137°C (hexane); CI-ms: m/z 333 (M^++1); ^{1}H-nmr (90 MHz) : δ 1.10 (6H, d, J = 6 Hz, $CH(C\underline{H}_3)_2$), 1.30 (6H, d, J = 6 Hz, $CH(C\underline{H}_3)_2$), 2.40 (3H, s, $C_6H_4C\underline{H}_3$), 2.53-2.93 (1H, m, $C\underline{H}(CH_3)_2$), 3.70-4.10 (1H, m, $C\underline{H}(CH_3)_2$), 7.25 (2H, d, J = 7.5 Hz, $C_6\underline{H}_4CH_3$), 7.63 (2H, d, J = 7.5 Hz, $C_6\underline{H}_4CH_3$) ppm; ir (KBr): 1670 cm^{-1} (C=O); Anal. Calcd for $C_{18}H_{21}N_2O_2Cl$: C, 64.95; H, 6.34; N, 8.41. Found: C, 65.07; H, 6.33; N, 8.46.

5,6-Diphenyl-2-(p-toluoyl)pyrazine 1-oxide (2d): colorless needles; mp 220-222°C (benzene); ms: m/z 366 (M^+); ^{1}H-nmr (90 MHz): δ 2.38 (3H, s, $C_6H_4C\underline{H}_3$), 7.10-7.47 (12H, m, $C_6\underline{H}_4CH_3$, benzene H), 7.80 (2H, d, J = 7.5 Hz, $C_6\underline{H}_4CH_3$), 8.62 (1H, s, pyrazine H) ppm; ir (KBr): 1660 cm^{-1} (C=O); Anal. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.45; H, 5.21; N, 7.63. Found: C, 78.50; H, 4.94; N, 7.79.

3,6-Di-sec-butyl-2-(α-hydroxypropyl)pyrazine 1-oxide (2e): colorless oil; bp 145-150°C/1 torr; ms: m/z 266 (M^+), 249 (M^+-OH); ^{1}H-nmr (90 MHz): δ

0.69-1.13 (9H, m, $CH(CH_3)CH_2C\underline{H}_3$, $CH(OH)CH_2C\underline{H}_3$), 1.19 (3H, d, J = 8 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.30 (3H, d, J = 8 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.40-2.23 (6H, m, $CH(CH_3)C\underline{H}_2CH_3$, $CH(OH)C\underline{H}_2CH_3$), 2.67-3.10 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 3.20-3.65 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 4.83 (1H, br s, $C\underline{H}(OH)CH_2CH_3$), 6.13 (1H, d, J = 11 Hz, $CH(O\underline{H})CH_2CH_3$), 8.33 (1H, s, pyrazine H) ppm; ir (neat): 3370 cm^{-1} (OH); Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.44; H, 9.99; N; 10.52.

3,6-Diisobutyl-2-(α-hydroxypropyl)pyrazine 1-oxide (2f): colorless oil; bp 120-125°C/2 torr; ms: m/z 266 (M^+), 249 (M^+-OH); ^{1}H-nmr (90 MHz): δ 0.86-1.03 (15H, m, $CH_2CH(C\underline{H}_3)_2$, $CH(OH)CH_2C\underline{H}_3$), 1.53-2.43 (4H, m, $CH_2C\underline{H}(CH_3)_2$, $CH(OH)C\underline{H}_2CH_3$), 2.47-2.77 (4H, m, $C\underline{H}_2CH(CH_3)_2$), 4.67-4.90 (1H,m, $C\underline{H}(OH)CH_2CH_3$), 5.90 (1H, br s, $CH(O\underline{H})CH_2CH_3$), 8.26 (1H, s, pyrazine H) ppm; ir (neat): 3390 cm^{-1} (OH); Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.42; H, 9.89; N. 10.44.

5-Chloro-3,6-diisopropyl-2-(α-hydroxypropyl)pyrazine 1-oxide (2g): colorless oil; bp 120-125°C/0.09 torr; ms: m/z 255 (M^+-OH); ^{1}H-nmr (90 MHz): δ 1.01 (3H, t, J = 7.5 Hz, $CH(OH)CH_2C\underline{H}_3$), 1.12-1.34 (12H, m, $CH(C\underline{H}_3)_2$), 1.60-2.35 (2H, m, $CH(OH)C\underline{H}_2CH_3$), 2.85-3.34 (1H, m, $C\underline{H}(CH_3)_2$), 3.65-4.10 (1H, m, $C\underline{H}(CH_3)_2$), 4.68-5.00 (1H, m, $C\underline{H}(OH)CH_2CH_3$), 5.34-5.70 (1H, br s, $CH(O\underline{H})CH_2CH_3$) ppm; ir (neat); 3370 cm^{-1} (OH); Anal. Calcd for $C_{13}H_{21}N_2O_2Cl$: C, 57.24; H, 7.76; N, 10.27. Found: C, 57.22; H, 7.83; N, 10.50.

5,6-Diphenyl-2-(α-hydroxypropyl)pyrazine 1-oxide (2h): colorless crystals; mp 134-136°C (cyclohexane); ms: m/z 289 (M^+-OH); ^{1}H-nmr (90 MHz): δ 1.08 (3H, t, J = 8 Hz, $CH(OH)CH_2C\underline{H}_3$), 1.87-2.15 (2H, m, $CH(OH)C\underline{H}_2CH_3$), 4.33-5.00 (2H, m, $C\underline{H}(O\underline{H})CH_2CH_3$), 7.12-7.42 (10H, m, benzene H), 8.51 (1H, s, pyrazine H) ppm; ir (KBr): 3360 cm^{-1} (OH); Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.59; H, 6.01; N, 9.02.

3,6-Di-sec-butyl-2-(α-hydroxybenzyl)pyrazine 1-oxide (2i): colorless oil; bp 210-212°C/1 torr; ms: m/z 297 (M^+-OH); ^{1}H-nmr (90 MHz): δ 0.60-0.98 (6H, m, $CH(CH_3)CH_2C\underline{H}_3$), 1.10-1.37 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.43-2.00 (4H, m, $CH(CH_3)C\underline{H}_2CH_3$), 2.83-3.17 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 3.18-3.53 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 6.13 (1H, m, $C\underline{H}(OH)C_6H_5$), 6.63 (1H, d, J = 12 Hz,

$CH(O\underline{H})C_6H_5$), 7.23 (5H, s, benzene H), 8.37 (1H, s, pyrazine H) ppm; ir (neat): 3380 cm^{-1} (OH); Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.46; H, 8.44; N, 9.05.

3,6-Diisobutyl-2-(α-hydroxybenzyl)pyrazine 1-oxide (2j): colorless needles; mp 93-94°C (hexane); ms: m/z 314 (M^+), 297 (M^+-OH); ^{1}H-nmr (90 MHz): δ 0.82-0.98 (12H, m, $CH_2CH(C\underline{H}_3)_2$), 2.08-2.15 (2H, m, $CH_2C\underline{H}(CH_3)_2$), 2.47-2.76 (4H, m, $C\underline{H}_2CH(CH_3)_2$), 6.01 (1H, br s, $C\underline{H}(OH)C_6H_5$), 6.43 (1H, br s, $CH(O\underline{H})C_6H_5$), 7.18-7.29 (5H, m, benzene H), 8.29 (1H, s, pyrazine H) ppm; ir (KBr): 3220 cm^{-1} (OH); Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.67; H, 8.39; N, 9.01.

5-Chloro-3,6-diisopropyl-2-(α-hydroxybenzyl)pyrazine 1-oxide (2k): colorless needles; mp 99-100°C (hexane); CI-ms: m/z 321 (M^++1), 303 (M^+-OH); ^{1}H-nmr (90 MHz): δ 1.23-1.38 (12H, m, $CH(C\underline{H}_3)_2$), 3.06-3.50 (1H, m, $C\underline{H}(CH_3)_2$), 3.70-4.10 (1H, m, $C\underline{H}(CH_3)_2$), 6.12 (2H, br s, $C\underline{H}(O\underline{H})C_6H_5$), 7.10-7.43 (5H, m, benzene H) ppm; ir (KBr): 3440 cm^{-1} (OH); Anal. Calcd for $C_{17}H_{21}N_2O_2Cl$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.81; H, 6.56; N, 8.75.

5,6-Diphenyl-2-(α-hydroxybenzyl)pyrazine 1-oxide (2l): pale yellow needles; mp 159-161°C (cyclohexane); CI-ms: m/z 355 (M^++1); ^{1}H-nmr (90 MHz): δ 5.16 (1H, br s, $C\underline{H}(OH)C_6H_5$), 6.09 (1H, br s, $CH(O\underline{H})C_6H_5$), 7.13-7.51 (15H, m, benzene H), 8.27 (1H, s, pyrazine H) ppm; ir (KBr): 3440 cm^{-1} (OH); Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 77.77; H, 5.21; N, 7.94.

3,6-Di-sec-butyl-2-formylpyrazine 1-oxide (2m): pale yellow oil; bp 150-155°C/3 torr; CI-ms: m/z 237 (M^++1); ^{1}H-nmr (90 MHz): δ 0.66-1.07 (6H, m, $CH(CH_3)CH_2C\underline{H}_3$), 1.07-1.40 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.41-2.00 (4H, m, $CH(CH_3)C\underline{H}_2CH_3$), 3.23-3.67 (2H, m, $C\underline{H}(CH_3)CH_2CH_3$), 8.47 (1H, s, pyrazine H), 10.93 (1H, s, CHO) ppm; ir (neat): 1750 cm^{-1} (C=O); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.13; H, 8.60; N, 11.84.

3,6-Di-isobutyl-2-formylpyrazine 1-oxide (2n): pale yellow oil; bp 130-135°C/2 torr; ms: m/z 236 (M^+); ^{1}H-nmr (90 MHz): δ 0.88 (6H, d, J = 6 Hz, $CH_2CH(C\underline{H}_3)_2$), 1.00 (6H, d, J = 6 Hz, $CH_2CH(C\underline{H}_3)_2$), 1.80-2.40 (2H, m, $CH_2C\underline{H}(CH_3)_2$), 2.65 (2H, d, J = 6 Hz, $C\underline{H}_2CH(CH_3)_2$), 2.87 (2H, d, J = 6 Hz,

$CH_2CH(CH_3)_2$), 8.37 (1H, s, pyrazine H), 11.10 (1H, s, CHO) ppm; ir (neat): 1720 cm^{-1} (C=O); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.80; H, 8.65; N, 11.61.

5-Chloro-3,6-diisopropyl-2-formylpyrazine 1-oxide (2o): colorless crystals; mp 69-70°C; bp 60-70°C/0.001 torr; ms: m/z 242 (M^+), 225 (M^+-OH); ^{1}H-nmr (90 MHz): δ 1.10-1.60 (12H, m, $CH(CH_3)_2$), 3.43-4.06 (2H, m, $CH(CH_3)_2$), 10.40 (1H, s, CHO) ppm; ir (neat): 1690 cm^{-1} (C=O); High-resolution ms Calcd for $C_{11}H_{12}N_2O_2Cl$ (M^+-OH): 225.0794. Found: 225.0823.

5,6-Diphenyl-2-formylpyrazine 1-oxide (2p): colorless needles; mp 246-248 °C (isopropyl ether); ms: m/z 276 (M^+), 259 (M^+-OH); ^{1}H-nmr (90MHz): δ 7.10-7.60 (10H, m, benzene H); 8.98 (1H, s, pyrazine H), 10.60 (1H, s, CHO) ppm; ir (KBr): 1680 cm^{-1} (C=O); High-resolution ms Calcd for $C_{17}H_{12}N_2O_2$ (M^+): 276.0898. Found: 276.0924.

Deoxygenation of 3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine 1-Oxide (2a)

A mixture of 2a (489 mg, 1.5 mmol) , PBr_3 (0.85 ml, 9 mmol), and AcOEt (6 ml) was refluxed for 1 h. The reaction mixture was poured into ice water and made alkaline with powdered K_2CO_3. After usual work-up, the residue was purified by medium pressure liquid chromatography (hexane:AcOEt = 19:1) to give 3a. (436 mg, 94%)

3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine (3a): colorless oil; bp 138-140 °C/2 torr; ms: m/z 310 (M^+); ^{1}H-nmr (90 MHz): δ 0.63-0.94 (6H, m, $CH(CH_3)CH_2CH_3$), 1.22 (3H, d, J = 8 Hz, $CH(CH_3)CH_2CH_3$), 1.30 (3H, d, J = 8 Hz, $CH(CH_3)CH_2CH_3$), 1.38-2.03 (4H, m, $CH(CH_3)CH_2CH_3$), 2.43 (3H, s, $C_6H_4CH_3$), 2.60-3.17 (2H, m, $CH(CH_3)CH_2CH_3$), 7.23 (2H, d, J = 7 Hz, $C_6H_4CH_3$), 7.71 (2H, d, J = 7 Hz, $C_6H_4CH_3$), 8.49 (1H, s, pyrazine H) ppm; ir (neat): 1670 cm^{-1} (C=O); Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.10; H, 8.59; N, 8.87.

Oxidation of 3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine (3a) with mCPBA

Compound (3a) (150 mg, 0.5 mmol) in $CHCl_3$ (10 ml) was treated with 85% mCPBA (142 mg, 0.7 mmol) with stirring at room temperature overnight and then refluxed for 8 h. The reaction mixture was washed with 5% aq. $NaHCO_3$ (10 ml) three times, dried over Na_2SO_4, and concentrated in vacuo. The

residue was purified by medium-pressure liquid chromatography (hexane-AcOEt = 9:1) to afford 2a (13 mg, 8%), 5a (48 mg, 30%), and 3a (90 mg, 60%).

3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine 4-oxide (5a): colorless oil; bp 150-160 °C/1 torr; CI-ms: m/z 327 (M^++1); ^{1}H-nmr (400 MHz): δ 0.75 (3H, t, J = 7.2 Hz, $CH(CH_3)CH_2C\underline{H}_3$), 0.88 (3H, t, J = 7.2 Hz, $CH(CH_3)CH_2C\underline{H}_3$), 1.25 (3H, d, J = 6.9 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.31 (3H, d, J = 6.9 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 1.55-2.04 (4H, m, $CH(CH_3)C\underline{H}_2CH_3$), 2.44 (3H, s, $C_6H_4C\underline{H}_3$), 2.69-2.74 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 3.02-3.07 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 7.29 (2H, d, J = 8.0 Hz, $C_6\underline{H}_4CH_3$), 7.72 (2H, d, J = 8.0 Hz, $C_6\underline{H}_4CH_3$), 8.03 (1H, s, pyrazine H) ppm; ir (neat): 1670 cm^{-1} (C=O); Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.38; H, 8.23; N, 8.53.

Oxidation of 3,6-Di-sec-butyl-2-(p-toluoyl)pyrazine (3a) with PMA

To a chloroform solution (10 ml) of PMA prepared from 88 mg (1.55 mmol) of 60% aq. H_2O_2 and 138 mg (1.41 mmol) of maleic anhydride, compound (3a) was added. The reaction mixture was refluxed for 2 h. After usual work-up, the residue was purified by medium-pressure liquid chromatography (hexane-AcOEt = 19:1) to give 2a (82 mg, 18%), 5a (147 mg, 32%), and 3a (180 mg, 41%).

Deoxygenation of 3,6-Di-sec-butyl-2-(α-hydroxypropyl)pyrazine 1-Oxide (2e) with Raney Ni

Compound (2e) (399 mg, 1.5 mmol) in MeOH (15 ml) was stirred under an atmosphere of H_2 in the presence of Raney Ni[8] (400 mg). After the adsorption of H_2 ceased, the catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by medium-pressure liquid chromatography (hexane-AcOEt=19:1) to give 3e (241 mg, 62%). The starting material was recoverd in 26% (104 mg) yield.

3,6-Di-sec-butyl-2-(α-hydroxypropyl)pyrazine (3e): colorless oil; bp 90 °C/0.07 torr; ms: m/z 250 (M^+), 234 (M^+-OH); ^{1}H-nmr (90 MHz): δ 0.77-1.07 (9H, m, $CH(CH_3)CH_2C\underline{H}_3$, $CH(OH)CH_2C\underline{H}_3$), 1.13-1.43 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.47-2.10 (6H, m, $CH(CH_3)C\underline{H}_2CH_3$, $CH(OH)C\underline{H}_2CH_3$), 2.63-3.03 (2H, m, $C\underline{H}(CH_3)CH_2CH_3$), 4.40 (1H, br s, $C\underline{H}(OH)CH_2CH_3$), 4.73-4.95 (1H, m, $CH(O\underline{H})CH_2CH_3$), 8.27 (1H, s, pyrazine H) ppm; ir (neat): 3450 cm^{-1} (C=O);

High-resolution ms Calcd for $C_{15}H_{26}N_2O$ (M^+): 250.2043. Found: 250.2023.

Deoxygenation of 3,6-Di-sec-butyl-2-(α-hydroxybenzyl)pyrazine 1-Oxide (2i) with Raney Ni

The reaction of 2i (628 mg, 2 mmol) with H_2 on Raney-Ni (600 mg) was carried out according to the method described above. (Yield 54%) The starting material was recovered in 38% yield.

3,6-Di-sec-butyl-2-(α-hydroxybenzyl)pyrazine (3i): colorless oil; bp 138-145°C/0.07 torr; ms: m/z 298 (M^+); ^{1}H-nmr (300 MHz): δ 0.69-1.00 (6H, m, $CH(CH_3)CH_2C\underline{H}_3$), 1.13-1.46 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.68-1.94 (4H, m, $CH(CH_3)C\underline{H}_2CH_3$), 2.76-2.80 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 2.82-2.95 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 5.76-5.90 (2H, m, $C\underline{H}(O\underline{H})C_6H_5$), 7.15-7.34 (5H, m, benzene H), 8.39 (1H, s, pyrazine H) ppm; ir (neat): 3420 cm^{-1} (OH); Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; 9.39. Found: C, 76.19; 8.71; N, 9.34.

Deoxygenation of 3,6-Di-sec-butyl-2-formylpyrazine 1-Oxide (2m) with PBr_3

The reaction of 2m (203 mg, 0.85 mmol) with PBr_3 (0.12 ml, 1.27 mmol) was carried out at room temperature. The reaction mixture was worked up according to the procedure for the preparation of compound (3a).

3,6-Di-sec-butyl-2-formylpyrazine (3m): colorless oil; bp 90-95°C/1 torr; ms: m/z 220 (M^+); ^{1}H-nmr (400 MHz): δ 0.78-0.88 (6H, m, $CH(CH_3)CH_2C\underline{H}_3$), 1.24-1.34 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.58-1.85 (4H, m, $CH(CH_3)C\underline{H}_2CH_3$), 2.91 (1H, m, J = 7.0 Hz, $C\underline{H}(CH_3)CH_2CH_3$), 3.93 (1H, m, J = 6.9 Hz, $C\underline{H}(CH_3)CH_2CH_3$), 8.52 (1H, s, pyrazine H), 10.17 (1H, s, CHO) ppm; ir (neat): 1715 cm^{-1} (C=O).

2,4-Dinitrophenylhydrazone derivative of compound (3m): pale yellow needles; mp 118-119°C (EtOH); ms: m/z 400 (M^+); ^{1}H-nmr (300 MHz): δ 0.90-0.97 (6H, m, $CH(CH_3)CH_2C\underline{H}_3$), 1.34-1.46 (6H, m, $CH(C\underline{H}_3)CH_2CH_3$), 1.72-2.01 (5H, m, $C\underline{H}(CH_3)C\underline{H}_2CH_3$), 3.35-3.42 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 7.27 (1H, s, $C\underline{H}NNH$), 7.93 (1H, s, pyrazine H), 8.25 (1H, d, J = 9.6 Hz, benzene 6-H), 8.39 (1H, m, benzene 5-H), 8.57 (1H, s, $CHNN\underline{H}$), 9.18 (1H, d, J = 2.7 Hz, benzene 3-H) ppm; ir (KBr): 3425 cm^{-1} (NH): Anal. Calcd for $C_{19}H_{24}N_6O_4$: C, 56.99; H, 6.04; N, 20.99. Found: C, 56.84; H, 6.04; N, 20.94.

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