REACTION OF CHLOROPYRAZINE N-OXIDES WITH TRIMETHYLALUMINUM

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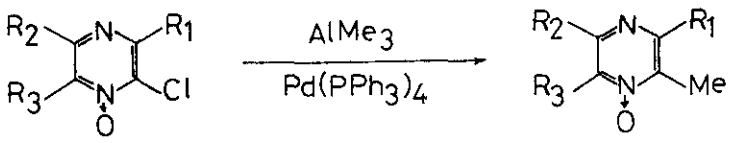
Abstract —— some 2-chloropyrazine 1- and 4-oxides were submitted to the coupling reaction with trimethylaluminum in the presence of a palladium catalyst. The corresponding 2-methylpyrazine 1- and 4-oxides were obtained in excellent yields.

Palladium catalysts play an important role in C-substitution of the pyrazine ring[1]. In the previous paper, we described that a methyl group can be satisfactorily introduced into pyrazine ring, by the coupling reaction of chloropyrazines with trimethylaluminum in the presence of a palladium catalyst[2]. The object of this paper is to describe the application of this reaction system to chloropyrazine N-oxides, such as 2-chloropyrazine 1- and 4-oxides.

Table 1. Reaction of 2-Chloropyrazinel-Oxides with Trimethylaluminum

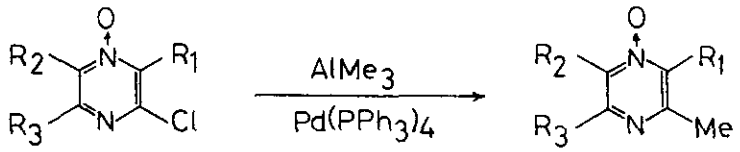


1a-e 2a-e

	Substrate R_1	R_2	R_3	Product	Yield (%)
1a[3]	Me	H	Me	2a	79
1b[4]	Et	H	Et	2b	82
1c[4]	i-Pr	H	i-Pr	2c	96
1d[5]	i-Bu	H	i-Bu	2d	90
1e[4]	H	Ph	Ph	2e	76

Under similar conditions as reported[2], a solution of a chloropyrazine monoxide, trimethylaluminum and tetrakis(triphenylphosphine)palladium in dry dioxane was refluxed under argon stream. The solvent was removed by distillation in vacuo and then the product was extracted with hexane. In all cases, the N-oxide groups were not affected, and all the aimed coupling products were obtained in good yields, as illustrated in Table 1 and 2.

Table 2. Reaction of 2-Chloropyrazine 4-Oxides with Trimethylaluminum



3a-e 4a-e

	Substrate R_1	R_2	R_3	Product	Yield (%)
3a[6]	Me	H	Me	4a	82
3b[7]	Et	H	Et	4b	84
3c[8]	i-Pr	H	i-Pr	4c	86
3d[9]	i-Bu	H	i-Bu	4d	82
3e[10]	H	Ph	Ph	4e	89

The structure elucidation of the products was made on the basis of the mass and ^{1}H-NMR spectral data. The mass spectra of all the products indicated the corresponding molecular ion peaks. The proton signals of newly introduced methyl groups of 2-methylpyrazine 1-oxides appeared in the region between 2.47 and 2.53 ppm. On the other hand, the ones of 2-methylpyrazine 4-oxides were observed in the region between 2.53 and 2.60 ppm. As already known, the signal of the methyl group adjacent to the N-oxide group in 2,5-dimethylpyrazine 1-oxide appears in a higher field than the one of the other methyl group[11]. The present ^{1}H-NMR data are coincident with the reported ones[11].

When trialkylpyrazines are oxidized with percarboxylic acids, such as peracetic and permaleic acids, the formation of two kinds of the monoxides is observed[12]. It is difficult to separate these monoxides from each other, even by column chromatography. The present work enabled the individual preparation of two kinds of trialkylpyrazine monoxides.

Conclusively, the evidence thus obtained indicates that trimethylaluminum is a convenient reagent for preparation of 2-methylpyrazine 1- and 4-oxides. The methylation of other heterocyclic compounds is now in progress and will be reported later.

EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data: ^{1}H-NMR: Varian EM-360 and EM-390; IR spectra: Shimadzu IR-400; UV spectra: Hitachi Model 557; MS: Hitachi M-80 spectrometer.

General Procedure for the Reaction of 2-Chloropyrazine 1- and 4-Oxides with Trimethylaluminum --- A mixture of a 2-chloropyrazine N-oxide (6 mmol), trimethylaluminum (2 ml of a 15% hexane solution, 4 mmol), and tetrakis(triphenylphosphine)-palladium (348 mg, 0.3 mmol) in dry dioxane (20 ml) was gently refluxed for 2 h under argon stream, and concentrated to dryness in vacuo. The resulting solid or oil was triturated with water (20 ml), and then extracted with hexane (20 ml x 3). After the solution had been dried over Na_2SO_4, the solvent was removed by distillation to give the product.

2,3,6-Trimethylpyrazine 1-Oxide (2a)[13]: colorless needles (from hexane); mp 68-69°C; MS: m/e 138 (M^+), 121 (M^+-OH); UV: λ_{max}^{EtOH} 226 (log ε = 3.94), 265 (3.94), 294.5-296.5 (3.54) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 8.17 (s, 1H, pyrazine H) ppm.

2,3,6-Trimethylpyrazine 1-Oxide Picrate: yellow needles (from EtOH); mp 179-180°C (darkening); Anal. Calcd. for $C_{13}H_{13}N_5O_8$: C, 42.51; H, 3.57; N, 19.07. Found: C, 42.54; H, 3.54; N, 19.10.

3,6-Diethyl-2-methylpyrazine 1-Oxide (2b): colorless oil; bp 76°C/1 torr; MS: m/e 166 (M^+), 149 (M^+-OH); UV: λ_{max}^{EtOH} 223.5 (log ε = 4.13), 265.5 (3.09), 293 (3.42, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.28 (t, J = 7.5 Hz, 3H, $CH_2\underline{CH}_3$), 1.31 (t, J = 7.5 Hz, 3H, $CH_2\underline{CH}_3$), 2.50 (s, 3H, CH_3), 2.84 (q, J = 7.5 Hz, 2H, $\underline{CH}_2CH_3$), 2.86 (q, J = 7.5 Hz, 2H, $\underline{CH}_2CH_3$), 8.18 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.78; H, 8.47; N, 16.55.

3,6-Diisopropyl-2-methylpyrazine 1-Oxide (2c): colorless oil; bp 96-97°C/1 torr; MS: m/e 194 (M^+), 177 (M^+-OH); UV: λ_{max}^{EtOH} 225 (log ε = 4.15), 266 (4.01), 292 (3.56, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.28 (d, J = 7 Hz, 6H, $CH(\underline{CH}_3)_2$), 1.31 (d, J = 7 Hz, 6H, $CH(\underline{CH}_3)_2$), 2.50 (s, 3H, CH_3), 3.22 (m, J = 7 Hz, 1H, $\underline{CH}(CH_3)_2$), 3.60 (m,

J = 7 Hz, 1H, C<u>H</u>$(CH_3)_2$), 8.07 (s, 1H, pyrazine H) ppm; <u>Anal</u>. Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.22; H, 9.45; N, 14.19.

3,6-Diisobutyl-2-methylpyrazine 1-Oxide (2d): colorless oil; bp 109°C/2 torr; MS: m/e 222 (M^+), 205 (M^+-OH); UV: λ_{max}^{EtOH} 225 (log ε = 4.27), 266.5 (3.98), 291.5-293.5 (3.55) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.95 (d, J = 7 Hz, 12H, 2 x $CH_2CH(C\underline{H}_3)_2$), 1.83-2.38 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.47 (s, 3H, CH_3), 2.68 (d, J = 7 Hz, 4H, 2 x $C\underline{H}_2CH(CH_3)_2$), 8.16 (s, 1H, pyrazine H) ppm; <u>Anal</u>. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.34; H, 10.03; N, 12.54.

2,3-Diphenyl-6-methylpyrazine 1-Oxide (2e): colorless needles (from MeOH); mp 161-162°C; MS: m/e 262 (M^+), 261 (M^+-H), 245 (M^+-OH); UV: λ_{max}^{EtOH} 222 (log ε = 4.32), 260 (4.41), 322 (3.59) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.53 (s, 3H, CH_3), 7.30 (s, 4H, benzene H), 7.37 (s, 6H, benzene H), 8.60 (s, 1H, pyrazine H) ppm; <u>Anal</u>. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.85; H, 5.37; N, 10.61.

2,3,6-Trimethylpyrazine 4-Oxide (4a)[13]: colorless needles (from hexane); mp 62-63°C; MS: m/e 138 (M^+), 121 (M^+-OH); UV: λ_{max}^{EtOH} 225 (log ε = 3.83), 264 (3.81), 292-294 (3.33, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.42 (s, 6H, 2 x CH_3), 2.53 (s, 3H, CH_3), 7.89 (s, 1H, pyrazine H) ppm.

2,3,6-Trimethylpyrazine 4-Oxide Picrate: yellow needles (from EtOH); mp 175-176°C (darkening); <u>Anal</u>. Calcd. for $C_{13}H_{13}N_5O_8$: C, 42.51; H, 3.57; N, 19.07. Found: C, 42.34; H, 3.51; N, 18.98.

3,6-Diethyl-2-methylpyrazine 4-Oxide (4b): colorless oil; bp 112°C/4 torr; MS: m/e 166 (M^+), 149 (M^+-OH); UV: λ_{max}^{EtOH} 225 (log ε = 4.27), 267.5 (4.11), 296 (3.68, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.20 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.26 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.53 (s, 3H, CH_3), 2.68 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.94 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 7.87 (s, 1H, pyrazine H) ppm; <u>Anal</u>. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.76; H, 8.55; N, 16.91.

3,6-Diisopropyl-2-methylpyrazine 4-Oxide (4c): colorless prisms (from MeOH-H_2O); mp 56-57°C; MS: m/e 194 (M^+), 177 (M^+-OH); UV: λ_{max}^{EtOH} 226 (log ε = 4.19), 284.5 (3.96), 297 (3.57, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.26 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.42 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.56 (s, 3H, CH_3), 2.63-3.15 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.30-3.85 (m, J = 7 Hz, 1H, C<u>H</u>$(CH_3)_2$), 7.81 (s, 1H, pyrazine H) ppm; <u>Anal</u>. Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.12. Found: C, 68.26; H, 9.51; N, 14.23.

3,6-Diisobutyl-2-methylpyrazine 4-Oxide (4d): colorless needles (from MeOH-H_2O); mp 49-50°C; MS: m/e 222 (M^+), 205 (M^+-OH); UV: λ_{max}^{EtOH} 228 (log ε = 4.13), 269.5 (3.89), 292.5-298.5 (3.48) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.93 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.97 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.78-2.42 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.50 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.53 (s, 3H, CH_3), 2.80 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.25; H, 10.00; N, 12.60.

2,3-Diphenyl-6-methylpyrazine 4-Oxide (4e): colorless needles (from MeOH); mp 158-159°C; MS: 262 (M^+), 261 (M^+-H), 245 (M^+-OH); UV: λ_{max}^{EtOH} 222 (log ε = 4.30), 261 (4.40), 325 (3.68) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.60 (s, 3H, CH_3), 7.33 (s, 5H, benzene H), 7.42 (s, 5H, benzene H), 8.10 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.65; H, 5.39; N, 10.60.

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13 Since this substance is hygroscopic and sublimable, the picrate was submitted to an elemental analysis.

Received, 20th September, 1984