INTRODUCTION OF THE METHYL GROUP INTO THE PYRAZINE RING

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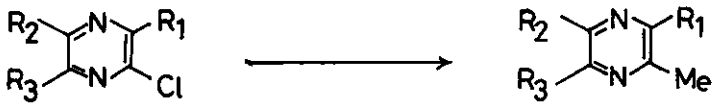
Abstract —— By the coupling reaction of mono- and dichloropyrazines with trimethylaluminum in the presence of a palladium catalyst, the corresponding mono- and dimethylpyrazines were prepared in excellent yields.

Recent investigations have established the utility of palladium catalysts in the diazine chemistry. The palladium catalyzed cross-coupling reaction enabled the introduction of alkenyl and alkynyl groups into the diazines, such as pyrimidines and pyridazines[1]. It is also known that the nickel phosphine complexes catalyze the coupling reaction of chloropyrimidines with the Grignard reagents[2]. The pyrazine chemistry has received likewise the benefits from palladium catalysts. Namely, in the presence of palladium catalysts, chloropyrazines undergo the coupling reaction with ethylenic and acetylenic compounds and potassium cyanide[3]. The present work constitutes a continuation of our investigation on the coupling reaction of chloropyrazines and deals with the introduction of the methyl group as a C_1 unit into the pyrazine ring, using trimethylaluminum in the presence of a palladium catalyst.

Although chloropyrazines were heated under reflux with trimethylaluminum in dry dioxane, the coupling reaction failed and the starting chloropyrazines were entirely recovered. However, the addition of tetrakis(triphenylphosphine)palladium accomplished the coupling reaction. Namely, a solution of a chloropyrazine, trimethylaluminum (a 15% hexane solution), and the palladium catalyst in dry dioxane under argon stream was refluxed for 2 h. After cooling, the reaction mixture was diluted with water. The product was extracted with methylene chloride and then purified by chromatography on a silica gel column. The yields are satisfactory as shown in Table 1.

Table 1. Reaction of 2-Chloropyrazines with Trimethylaluminum



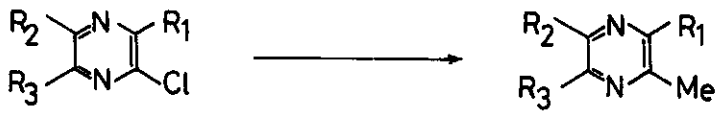
1a-g 2a-g

	Substrate R_1	R_2	R_3		Product R_1	R_2	R_3	mp or bp (lit. mp or bp, °C or °C/torr)	Yield (%)
1a[4]	Me	H	Me	2a	Me	H	Me	bp 90/50 (lit.[10] bp 171-172)	64
1b[5]	Et	H	Et	2b	Et	H	Et	bp 83/10	88
1c[6]	i-Pr	H	i-Pr	2c	i-Pr	H	i-Pr	bp 90-91/8	92
1d[7]	i-Bu	H	i-Bu	2d	i-Bu	H	i-Bu	bp 99-100/3	97
1e[8,9]	H	Ph	Ph	2e	H	Ph	Ph	mp 88-89 (lit.[11] mp 86-87)	88
1f[9]	Ph	Ph	H	2f	Ph	Ph	H	mp 90.5-91.5	95
1g[9]	Ph	H	Ph	2g	Ph	H	Ph	mp 91-92 (lit.[12] mp 88-89)	96

The coupling reaction of some dichloropyrazines (3a-f) with trimethylaluminum was also achieved under almost the same conditions as above. Among the dichloropyrazines adopted, 2,3-dichloro-5,6-diphenylpyrazine (3e) gave merely a monomethyl derivative, 2-chloro-5,6-diphenyl-3-methylpyrazine (4e), under reflux for 4 h. Although crystalline substances were obtained from 3e by being heated longer, the structure of these substances was not made clear. Heating of 2,6-dichloro-3,5-diphenylpyrazine (3f) for 4 h resulted in giving a mixture of mono- and dimethyl derivatives. The aimed dimethylpyrazine (4f) was barely obtained after heating for 12 h. Thus, tetrasubstituted pyrazines were prepared in almost all cases without difficulty by this coupling reaction.

As mentioned above, trimethylaluminum was found to be a useful reagent for methylation of pyrazines. These results may suggest that other trialkylaluminums may also be utilizable for alkylation of pyrazines and for preparation of the pyrazinic flavors[20].

Table 2. Reaction of Dichloropyrazines with Trimethylaluminum



3a-f 4a-f

	Substrate R_1	R_2	R_3		Product R_1	R_2	R_3	mp or bp (lit. mp or bp, °C or °C/torr)	Yield (%)
3a[4]	Me	Cl	Me	4a	Me	Me	Me	mp 83-84 (lit.[16] mp 84-86)	90
3b[13]	Et	Cl	Et	4b	Et	Me	Et	bp 82/7 (lit.[17] bp 81/7.6)	93
3c[6]	i-Pr	Cl	i-Pr	4c	i-Pr	Me	i-Pr	mp 40-41 (lit.[18] mp 41-44)	87
3d[7]	i-Bu	Cl	i-Bu	4d	i-Bu	Me	i-Bu	bp 118/4 (lit.[19] bp 110-112/12)	93
3e[14]	Cl	Ph	Ph	4e	Cl	Ph	Ph	mp 139-140 (lit.[8] mp 136-137)	93
3f[15]	Ph	Ph	Cl	4f	Ph	Ph	Me	mp 92-93	93[a]

a: Refluxed for 12 h.

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 Chloropyrazines (1a-g and 3a-f) with Trimethylaluminum --- A mixture of a chloropyrazine (1a-g and 3a-f; 6 mmol), trimethylaluminum (2 ml of 15% hexane solution, 4 mmol for 1a-g and 4 ml of the solution, 8 mmol for 3a-f), and tetrakis(triphenylphosphine)palladium (348 mg, 0.3 mmol) in dry dioxane (20 ml) was refluxed for 2 h (in the case of 1a-g) or 4 h (in the case of 3a-f) under argon stream, diluted with water (20 ml), and then extracted with methylene chloride. The extract was dried with Na_2SO_4 and the solvent was removed by distillation. The residue was purified by chromatography on silica gel (5 g) eluting with a mixture of hexane and methylene chloride (10:1) and the following distillation or recrystallization.

3,6-Diethyl-2-methylpyrazine (2b): colorless oil; MS: m/e 150 (M^+); UV: λ_{max}^{EtOH} 278 (log ε = 3.96), 300 (3.42, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.28 (6H, t, J = 7 Hz, 2 x $CH_2\underline{CH}_3$), 2.52 (3H, s, CH_3), 2.75 (2H, t, J = 7 Hz, $\underline{CH}_2CH_3$), 2.83 (2H, t, J = 7 Hz, $\underline{CH}_2CH_3$), 8.16 (1H, s, pyrazine H) ppm; Anal. Calcd. for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.76; H, 9.46; N, 18.57.

3,6-Diisopropyl-2-methylpyrazine (2c): colorless oil; MS: m/e 178 (M^+); UV: λ_{max}^{EtOH} 278 (log ε = 3.72), 3.07 (2.95, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.25 (6H, d, J = 7 Hz, $CH(\underline{CH}_3)_2$), 1.28 (6H, d, J = 7 Hz, $CH(\underline{CH}_3)_2$), 2.37 (3H, s, CH_3), 2.66-3.47 (2H, m, 2 x $\underline{CH}(CH_3)_2$), 8.03 (1H, s, pyrazine H) ppm; Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.84; H, 10.01; N, 15.75.

3,6-Diisobutyl-2-methylpyrazine (2d): colorless oil; MS: m/e 206 (M^+); UV: λ_{max}^{EtOH} 278 (log ε = 3.79), 300 (3.25, s) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.89 (6H, d, J = 7 Hz, $CH_2CH(\underline{CH}_3)_2$), 0.93 (6H, d, J = 7 Hz, $CH_2CH(\underline{CH}_3)_2$), 2.12 (2H, m, 2 x $CH_2\underline{CH}(CH_3)_2$), 2.52 (3H, s, CH_3), 2.56 (2H, d, J = 7 Hz, $\underline{CH}_2CH(CH_3)_2$), 2.64 (2H, d, J = 7 Hz, $\underline{CH}_2CH(CH_3)_2$), 8.10 (1H, s, pyrazine H) ppm; Anal. Calcd. for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found: C, 75.45; H, 10.77; N, 13.50.

3,5-Diphenyl-2-methylpyrazine (2f): colorless prisms (hexane); MS: m/e 246 (M^+), 245 (M^+-H); UV: λ_{max}^{EtOH} 235 (log ε = 4.26), 254 (4.20, s), 317 (4.05) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.60 (3H, s, CH_3), 7.27-7.70 (8H, m, benzene H), 7.87-8.07 (2H, m, benzene H), 8.77 (1H, s, pyrazine H) ppm; Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.04; H, 5.76; N, 11.38.

2,6-Dimethyl-3,5-diphenylpyrazine (4f): colorless needles (hexane); MS: m/e 260 (M^+), 259 (M^+-H); UV: λ_{max}^{EtOH} 213 (log ε = 4.01), 231 (4.06), 294 (3.91), 310 (3.90) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.62 (6H, s, 2 x CH_3), 7.27-7.67 (10H, m, benzene H) ppm; Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.20; H, 6.21; N, 10.71.

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Received, 4th June, 1984