

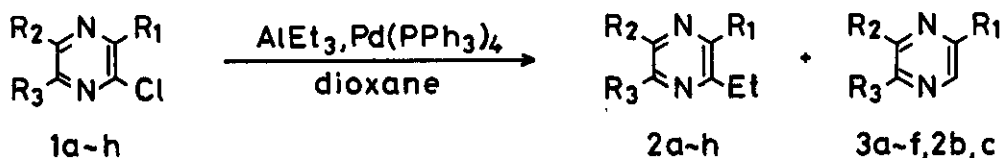
ETHYLATION OF PYRAZINES USING ALKYLMETALS, SUCH AS TRIETHYL-
ALUMINUM, DIETHYLZINC, AND TRIETHYLBORANE

Akihiro Ohta*, Masakatsu Ohta, Yoshiaki Igarashi, Kaemi Saeki,
Kayo Yuasa, and Tomoko Mori
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract — Triethylaluminum, diethylzinc and triethylborane were used for the ethylation of pyrazines. Among these reagents, triethylborane gave the best results.

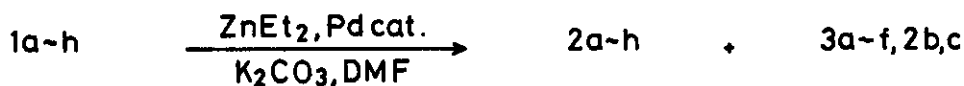
Recently, we reported that trimethylaluminum is a convenient reagent for cross-coupling methylation of chloropyrazines^{1,2}. Namely, the methylation occurred with good yields in the presence of palladium catalysts. We have further studied the alkylation of pyrazines using other alkylmetals and found that diethylzinc and triethylborane have also the ability to introduce the ethyl group into the pyrazine ring. In this report, the comparison of the ethylation ability among triethylaluminum, diethylzinc, and triethylborane will be presented. Under the same conditions as previously reported, several chloropyrazines were heated with triethylaluminum³ in dioxane in the presence of tetrakis(triphenylphosphine)palladium. Although the desired products were obtained in moderate to good yields (Table 1), the formation of dechlorinated products was also observed in all cases. The products were purified by preparative HPLC. Next, the ethylation of pyrazines using diethylzinc⁴ was performed. 2-Chloro-3,6-diisobutylpyrazine (1c)⁵ was treated with diethylzinc under various conditions and the optimum condition (reflux in DMF, tetrakis(triphenylphosphine)palladium as catalyst and potassium carbonate as base) was chosen. The results of the reaction of several chloropyrazines are shown in Table 2, and in all cases, the formation of dechlorinated products was unavoidable. In the case of chlorophenyl-

Table 1. Reaction of Chloropyrazines with Triethylaluminum



Substrates				Products						
	R ₁	R ₂	R ₃	R ₁	R ₂	R ₃	Yield (%)		Yield (%)	
1a ⁹	Me	H	Me	Me	H	Me	2a ¹³	23	3a ⁹	49
1b ¹⁰	i-Pr	H	i-Pr	i-Pr	H	i-Pr	2b	60	3b ¹⁵	13
1c ⁵	i-Bu	H	i-Bu	i-Bu	H	i-Bu	2c	63	3c ¹⁶	16
1d ¹¹	H	Ph	Ph	H	Ph	Ph	2d	51	3d ¹¹	47
1e ¹²	Ph	Ph	H	Ph	Ph	H	2e	59	3e ¹²	17
1f ⁹	Et	Cl	Et	Et	Et	Et	2f	32	3f	26
1g ¹⁰	i-Pr	Cl	i-Pr	i-Pr	Et	i-Pr	2g	25	2b	28
1h ⁵	i-Bu	Cl	i-Bu	i-Bu	Et	i-Bu	2h ¹⁴	39	2c	34

Table 2. Reaction of Chloropyrazines with Diethylzinc



Substrates	catalysts	Products			
			Yield (%)		Yield (%)
1a ⁹	A	2a ¹³	25	3a ⁹	49
1b ¹⁰	A	2b	26	3b ¹⁵	50
1c ⁵	A	2c	37	3c ¹⁶	54
1d ¹¹	A	2d	39	3d ¹¹	22
1d ¹¹	B	2d	66	3d ¹¹	19
1e ¹²	B	2e	43	3e ¹²	32
1f ⁹	A	2f	5	3f	8
1g ¹⁰	A	2g	5	2b	20
1h ⁵	A	2h ¹⁴	27	2c	27

A: Pd(PPh₃)₄

B: Pd(PPh₃)₂Cl₂

pyrazines, bis(triphenylphosphine)palladium dichloride gave better results than tetrakis(triphenylphosphine)palladium.

The reaction of chloropyrazines with triethylborane⁶ was next studied. As a result of examination of reaction conditions, the same condition used for diethylzinc was chosen. In the case of chlorophenylpyrazines, bis(triphenylphosphine)palladium dichloride gave the same results as tetrakis(triphenylphosphine)palladium. As shown in Table 3, the desired products were obtained with better results than in the reaction using two other reagents described and the yields of the dechlorinated products decreased.

Table 3. Reaction of Chloropyrazines with Triethylborane

Substrates	$\xrightarrow[\text{K}_2\text{CO}_3, \text{DMF}]{\text{BEt}_3, \text{Pd}(\text{PPh}_3)_4}$		2a-h		3a-f, 2b,c	
			Yield (%)		Yield (%)	
1a ⁹		2a ¹³	74	3a ⁹	5	
1b ¹⁰		2b	89	3b ¹⁵	—	
1c ⁵		2c	92	3c ¹⁶	2	
1d ¹¹		2d	91	3d ¹¹	4	
1e ¹²		2e	91	3e ¹²	6	
1f ⁹		2f	48	3f	22	
1g ¹⁰		2g	79	2b	1	
1h ⁵		2h ¹⁴	44	2c	18	

The ethylation reactions of 2-chloro-3,6-diisobutylpyrazine 1- (4)⁷ and 4-oxides (5)⁵ using the three reagents were performed under the same conditions as described for chloropyrazines. All the reactions proceeded without deoxygenation and the desired pyrazine N-oxides were obtained in satisfactory yields. Among three reagents, triethylborane gave the best results.

In all the ethylation reactions, the formation of dechlorinated products was observed. We believe that a metal hydride⁸, which was produced by thermolysis, contributed to the dechlorination.

Table 4.

Reaction of 2-Chloro-3,6-diisobutylpyrazine 1- and 4-Oxides with Ethylmetals

Substrates	AlEt ₃ Yield (%)	ZnEt ₂ Yield (%)	BEt ₃ Yield (%)
1-Oxide (4)	37 (38) ¹⁷	50 (3) ¹⁷	56 (31) ¹⁷
4-Oxide (5)	70 (9) ¹⁷	19 (46) ¹⁷	84 (6) ¹⁷

(): dechlorinated products

As stated above, three available ethylmetals can be used for ethylation of pyrazines. Among the three reagents, however, triethylborane was found to be the most useful with regard to the yields of the desired products and the less desired dechlorinated products.

EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data: Ms: Hitachi M-80 spectrometer; ¹H-Nmr (CDCl₃/TMS): Varian EM-390. The HPLC was carried out with a UVILOG ALPC-100 (Oyo-Bunko Kiki Co., Ltd., Tokyo) as a pump, a UVILOG 5 IIIA as a detector, and Kiesel Gel 60 (Merck AG., Darmstadt) as a packing material.

General Procedure for the Reaction of Chloropyrazines with Diethylzinc and

Triethylborane --- To a mixture of a chloropyrazine (2 mmol), a palladium catalyst (0.02-0.1 mmol) and K₂CO₃ (3 mmol) in dry DMF (5 ml), an alkylmetal (2 mmol) was added and the mixture was refluxed for 1-12 h under an argon atmosphere. For the reaction of a dichloropyrazine, 4 molar equivalents of alkylmetals were used. After cooling, the reaction mixture was filtered by suction. The filtrate was diluted with water (ca. 50 ml) and extracted with Et₂O to give a product, which was purified by preparative HPLC (column; 20 cm x 20 mm, pressure; 0.7 kg/cm², solvent; hexane-ACOEt).

2-Ethyl-3,6-diisopropylpyrazine (2b): colorless oil; bp 90-95°C/10 torr; ms: m/z 192 (M⁺), 177 (M⁺-CH₃); ¹H-nmr: δ 1.24 (d, J = 6.6 Hz, 6H, CH₂(CH₃)₂), 1.25 (t, J = 7.5 Hz, 3H, CH₂CH₃), 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.84 (q, J = 7.5 Hz, 2H, CH₂CH₃), 2.87-3.40 (m, J = 6.6 Hz, 2H, 2 x CH(CH₃)₂), 8.27 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₁₂H₂₀N₂: C, 74.95; H, 10.48; N, 14.57. Found: C, 74.75; H, 10.62; N, 14.38.

2-Ethyl-3,6-diisobutylpyrazine (2c): colorless oil; bp 105-110°C/5 torr; ms: m/z 220 (M⁺), 178 (M⁺-CH₂=CHCH₃); ¹H-nmr: δ 0.89 (d, J = 6.6 Hz, 6H, CH₂CH(CH₃)₂).

0.90 (d, $J = 6.6$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.23 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.83-2.37 (m, 2H, $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.58 (d, $J = 6.6$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.65 (d, $J = 6.6$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.81 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 8.15 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.08; H, 11.25; N, 12.55.

2-Ethyl-5,6-diphenylpyrazine (2d): colorless needles (from hexane); mp 101-102°C; ms: m/z 260 (M^+), 103 ($\text{C}_6\text{H}_5\text{CN}^+$); $^1\text{H-nmr}$: δ 1.40 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 2.93 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 7.19-7.50 (m, 10H, benzene H), 8.47 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.89; H, 6.26; N, 10.67.

2-Ethyl-3,5-diphenylpyrazine (2e): colorless needles (from hexane); mp 86-87°C; ms: m/z 260 (M^+), 103 ($\text{C}_6\text{H}_5\text{CN}^+$); $^1\text{H-nmr}$: δ 1.26 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 2.91 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 7.01-7.73 (m, 8H, benzene H), 7.90-8.17 (m, 2H, benzene H), 9.00 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.89; H, 6.08; N, 10.76.

2,3,5,6-Tetraethylpyrazine (2f): colorless oil; bp 85-90°C/5 torr; ms: m/z 192 (M^+), 177 (M^+-CH_3); $^1\text{H-nmr}$: δ 1.27 (t, $J = 7.5$ Hz, 12H, $4 \times \text{CH}_2\text{CH}_3$), 2.77 (q, $J = 7.5$ Hz, 8H, $4 \times \text{CH}_2\text{CH}_3$) ppm; Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_2$: C, 74.95; H, 10.48; N, 14.57. Found: C, 74.64; H, 10.63; N, 14.50.

2,5-Diethyl-3,6-diisopropylpyrazine (2g): colorless oil; bp 90-100°C/5 torr; ms: m/z 220 (M^+), 205 (M^+-CH_3); $^1\text{H-nmr}$: δ 1.20 (d, $J = 6.6$ Hz, 12H, $2 \times \text{CH}(\text{CH}_3)_2$), 1.22 (t, $J = 7.5$ Hz, 6H, $2 \times \text{CH}_2\text{CH}_3$), 2.77 (q, $J = 7.5$ Hz, 4H, $2 \times \text{CH}_2\text{CH}_3$), 3.17 (m, $J = 6.6$ Hz, 2H, $2 \times \text{CH}(\text{CH}_3)_2$) ppm; Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.35; H, 11.03; N, 12.66.

2,3,6-Triethylpyrazine (3f): colorless oil; bp 80-85°C/5 torr; ms: m/z 164 (M^+), 149 (M^+-CH_3); $^1\text{H-nmr}$: δ 1.33 (t, $J = 7.5$ Hz, 9H, $3 \times \text{CH}_2\text{CH}_3$), 2.65-2.95 (m, $J = 7.5$ Hz, 6H, $3 \times \text{CH}_2\text{CH}_3$), 8.21 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.85; H, 9.84; N, 16.80.

2-Ethyl-3,6-diisobutylpyrazine 1-Oxide (4): colorless oil; bp 138-145°C/4 torr; ms: m/z 236 (M^+), 219 (M^+-OH); $^1\text{H-nmr}$: δ 0.93 (d, $J = 6.6$ Hz, 12H, $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.14 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 2.14 (m, 2H, $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.57 (d, $J = 6.6$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.61 (d, $J = 6.6$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.88 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 8.07 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.25; H, 10.20; N, 11.80.

2-Ethyl-3,6-diisobutylpyrazine 4-Oxide (5): colorless oil; bp 140-147°C/4 torr;

ms: m/z 236 (M⁺), 219 (M⁺-OH); ¹H-nmr: δ 0.93 (d, J = 6.6 Hz, 6H, CH₂CH(CH₃)₂), 0.96 (d, J = 6.6 Hz, 6H, CH₂CH(CH₃)₂), 1.27 (t, J = 7.5 Hz, 3H, CH₂CH₃), 2.16 (m, 2H, 2 x CH₂CH(CH₃)₂), 2.50 (d, J = 7.5 Hz, 2H, CH₂CH(CH₃)₂), 2.80 (m, J = 7.5 Hz, 4H, CH₂CH(CH₃)₂ and CH₂CH₃), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₁₄H₂₄N₂O: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.22; H, 10.23; N, 11.93.

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Received, 19th May, 1987