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

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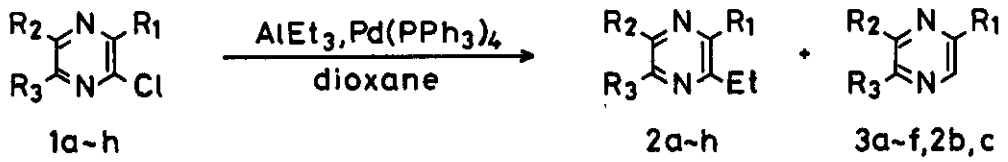
Abstract —— Triethylaluminum, diethylzinc and triethylborane were used for the ethylation of pyrazines. Among these reagents, triethylborane gave the best results.

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 triethylaluminum[3] 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 diethylzinc[4] 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-

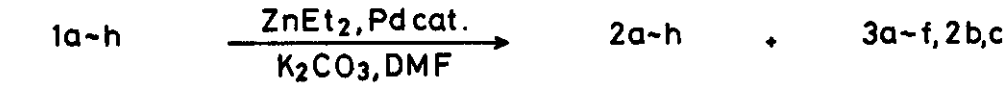
Table 1. Reaction of Chloropyrazines with Triethylaluminum



1a~h 2a~h 3a~f,2b,c

Substrates	R_1	R_2	R_3	Products	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



1a~h 2a~h 3a~f,2b,c

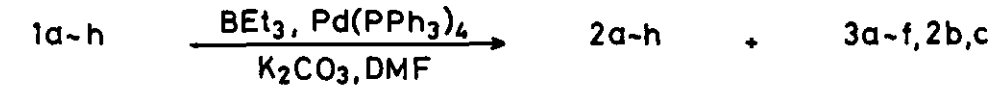
Substrates	catalysts	Products	Yield (%)		Yield (%)
1a [9]	A	2a [13]	25	3a [9]	49
1b [10]	A	2b	26	3b [15]	50
1c [5]	A	2c	37	3c [16]	54
1d [11]	A	2d	39	3d [11]	22
1d [11]	B	2d	66	3d [11]	19
1e [12]	B	2e	43	3e [12]	32
1f [9]	A	2f	5	3f	8
1g [10]	A	2g	5	2b	20
1h [5]	A	2h [14]	27	2c	27

A: $Pd(PPh_3)_4$ B: $Pd(PPh_3)_2Cl_2$

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

The reaction of chloropyrazines with triethylborane[6] 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	Products	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 hydride[8], 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; ^{1}H-Nmr ($CDCl_3$/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 K_2CO_3 (3 mmol) in dry DMF (5 ml), a 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 Et_2O to give a product, which was purified by preparative HPLC (column; 20 cm x 20 mm, pressure; 0.7 kg/cm^2, solvent; hexane-AcOEt).

2-Ethyl-3,6-diisopropylpyrazine (2b): colorless oil; bp 90-95°C/10 torr; ms: m/z 192 (M^+), 177 (M^+-CH_3); ^{1}H-nmr: δ 1.24 (d, J = 6.6 Hz, 6H, $CH_2(C\underline{H}_3)_2$), 1.25 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.27 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.84 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.87-3.40 (m, J = 6.6 Hz, 2H, 2 x $C\underline{H}(CH_3)_2$), 8.27 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{12}H_{20}N_2$: 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^+-CH_2=$CHCH_3$); ^{1}H-nmr: δ 0.89 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$),

0.90 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.23 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.83-2.37 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.58 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.65 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.81 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 8.15 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{24}N_2$: 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 ($C_6H_5CN^+$); ^{1}H-nmr: δ 1.40 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.93 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 7.19-7.50 (m, 10H, benzene H), 8.47 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{18}H_{16}N_2$: 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 ($C_6H_5CN^+$); ^{1}H-nmr: δ 1.26 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.91 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 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 $C_{18}H_{16}N_2$: 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}H-nmr: δ 1.27 (t, J = 7.5 Hz, 12H, 4 x $CH_2C\underline{H}_3$), 2.77 (q, J = 7.5 Hz, 8H, 4 x $C\underline{H}_2CH_3$) ppm; Anal. Calcd. for $C_{12}H_{20}N_2$: 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}H-nmr: δ 1.20 (d, J = 6.6 Hz, 12H, 2 x $CH(C\underline{H}_3)_2$), 1.22 (t, J = 7.5 Hz, 6H, 2 x $CH_2C\underline{H}_3$), 2.77 (q, J = 7.5 HZ, 4H, 2 x $C\underline{H}_2CH_3$), 3.17 (m, J = 6.6 Hz, 2H, 2 x $C\underline{H}(CH_3)_2$) ppm; Anal. Calcd. for $C_{14}H_{24}N_2$: 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}H-nmr: δ 1.33 (t, J = 7.5 Hz, 9H, 3 x $CH_2C\underline{H}_3$), 2.65-2.95 (m, J = 7.5 Hz, 6H, 3 x $C\underline{H}_2CH_3$), 8.21 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{10}H_{16}N_2$: 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}H-nmr: δ 0.93 (d, J = 6.6 Hz, 12H, 2 x $CH_2CH(C\underline{H}_3)_2$), 1.14 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.14 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.57 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.61 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.88 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 8.07 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{24}N_2O$: 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); ^{1}H-nmr: δ 0.93 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.96 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.27 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.16 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.50 (d, J = 7.5 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.80 (m, J = 7.5 Hz, 4H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_3$), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.22; H, 10.23; N, 11.93.

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