Chem. Pharm. Bull.
34(4)1447—1458(1986)

Cross-Coupling Reaction of Chloropyrazines with Acetylenes

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(Received August 6, 1985)

Various chloropyrazines were subjected to cross-coupling reaction with acetylenes, such as phenylacetylene, 1-hexyne and propargyl alcohol, in the presence of palladium catalysts, to give the corresponding coupling products in good yields. It was found that tetrakis(triphenylphosphine)-palladium can catalyze the reaction of chloro-alkylpyrazines, and that a combination of bis-(triphenylphosphine)palladium dichloride and copper(I) iodide preferentially catalyzes the reaction of chloro-phenylpyrazines.

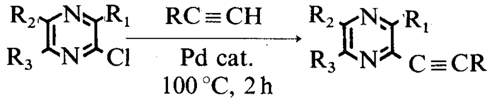
Keywords——cross-coupling reaction; chloropyrazine; acetylene; palladium catalyst

Palladium-catalyzed cross-coupling reactions are useful for the alkenylation and alkynylation of hetero-aromatic rings.1－4) We have recently reported that the reaction of chloropyrazines with potassium cyanide is facilitated by tetrakis(triphenylphosphine)palladium, giving cyanopyrazines in good yields,5) and that (*Z*)- and (*E*)-3,6-dimethyl-2-styrylpyrazines (**13** and **14**), isolated from the Argentine ant,6) can be readily synthesized from 2-chloro-3,6-dimethylpyrazine (**1a**)7) with the aid of a palladium catalyst.8) Methylation of pyrazines was also accomplished by using trimethylaluminum in the presence of the palladium catalyst.9) As a continuation of our work on reactions of pyrazines, this paper deals with the cross-coupling reactions of some chloropyrazines and chloropyrazine N-oxides with acetylenes, such as phenylacetylene, 1-hexyne, and propargyl alcohol, and presents full details of work previously described in a brief communication.8)

As a result of investigations on suitable reaction conditions, the coupling reaction of 2-chloro-3,6-dialkylpyrazines with phenylacetylene was achieved in the presence of tetrakis(triphenylphosphine)palladium and potassium acetate under heating at 100 °C for 2 h in *N*,*N*-dimethylformamide (DMF), to give the coupling products, as shown in Table I. However, this palladium catalyst was not effective for the phenylethynylation of 2-chloro-diphenylpyrazines. For instance, the reaction of 2-chloro-3,6-diphenylpyrazine (**1e**)10) under the same conditions as above yielded many products, which could not be separated from each other. Accordingly, a combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide was adopted for the reaction of 2-chloro-diphenylpyrazines, and the expected reaction occurred to afford the products in satisfactory yields. On the other hand, this combination gave the coupling product from 2-chloro-3,6-diisobutylpyrazine (**1d**)11) in only 10% yield. In conclusion, tetrakis(triphenylphosphine)palladium can catalyze the coupling reaction of 2-chloro-3,6-dialkylpyrazines, while the combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide preferentially catalyzes the reaction of 2-chloro-diphenylpyrazines, although the reason is not clear.

In the previous communication,8) we described the conversion of 3,6-dimethyl-2-phenylethynylpyrazine (**4a**) to (*Z*)- and (*E*)-3,6-dimethyl-2-styrylpyrazines (**13** and **14**), which have been isolated from the Argentine ant, *Iridomyrmex humilis*.6) In the present paper, the full details are presented. Namely, by the selective hydrogenation of **4a** with the Lindlar

Table I. Reaction of Monochloropyrazines with Acetylenes



1a—g

4a—g: R = C_6H_5
5a—g: R = C_4H_9
6a—g: R = CH_2OH

	Substrate R$_1$	R$_2$	R$_3$	Catalyst	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
1a[7]	CH_3	H	CH_3	A	**4a**	84	**5a**	76	**6a**	87
1b[17]	C_2H_5	H	C_2H_5	A	**4b**	78	**5b**	49	**6b**	65
1c[18]	iso-C_3H_7	H	iso-C_3H_7	A	**4c**	82	**5c**	65	**6c**	77
1d[11]	iso-C_4H_9	H	iso-C_4H_9	A	**4d**	84	**5d**	74	**6d**	61
1e[10]	C_6H_5	H	C_6H_5	B	**4e**	67	**5e**	91	**6e**	71
1f[19]	C_6H_5	C_6H_5	H	B	**4f**	67	**5f**	85	**6f**	86
1g[20]	H	C_6H_5	C_6H_5	B	**4g**	52	**5g**	96	**6g**	44

Catalyst A, $Pd(PPh_3)_4$; B, $Pd(PPh_3)_2Cl_2$–CuI.

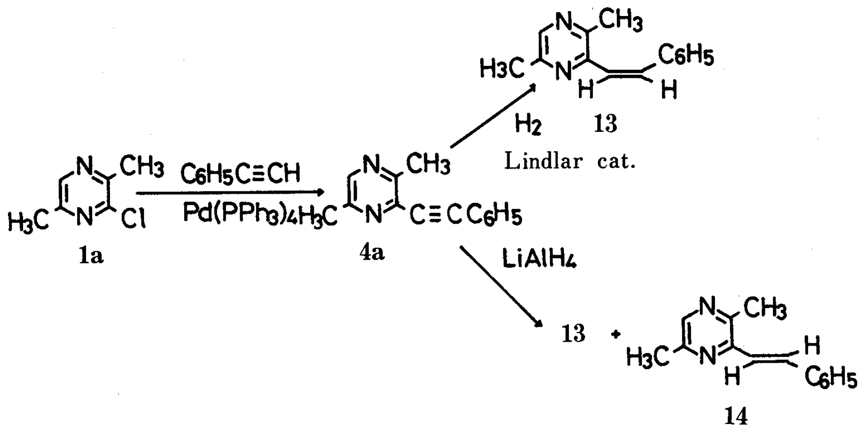


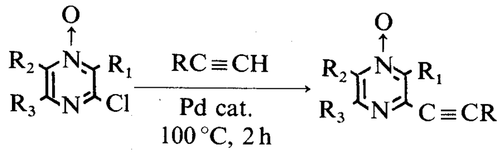
Chart 1

catalyst, **13** was obtained in quantitative yield. On the other hand, the reduction of **4a** with lithium aluminum hydride in refluxing tetrahydrofuran (THF)[12] gave a mixture of the (*Z*)- and (*E*)-forms, which were separated from each other by silica gel column chromatography. The spectral data of **13** and **14** were identical with those of the natural products.[6]

The coupling reaction of 2-chloro-3,6-dialkylpyrazines with 1-hexyne and propargyl alcohol was also successfully achieved under the same conditions as before. The combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide was also favorable for the reaction of 2-chloro-diphenylpyrazines.

Next, 2-chloropyrazine 1- and 4-oxides were subjected to the coupling reaction with acetylenes under the same conditions as before. Upon treatment of 2-chloro-3,6-dialkylpyrazine 4-oxides with phenylacetylene, 1-hexyne, and propargyl alcohol in the presence of tetrakis(triphenylphosphine)palladium, the expected products were obtained in good yields. The reactions of two 2-chloro-diphenylpyrazine 4-oxides, 2-chloro-3,6-diphenylpyrazine 4-oxide (**2e**)[10] and 2-chloro-5,6-diphenylpyrazine 4-oxide (**2g**),[13] were also achieved by using the combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide, except for the reaction of **2e** with propargyl alcohol. As the reaction of **2g**

Table II. Reaction of 2-Chloropyrazine 4-Oxides with Acetylenes

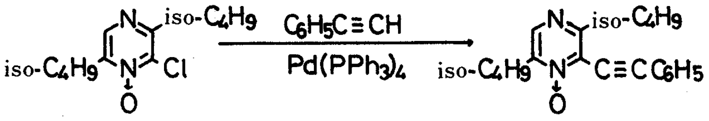


2a—**e**, **g**

7a—**e**, **g**: R = C_6H_5
8a—**e**, **g**: R = C_4H_9
9a—**e**, **g**: R = CH_2OH

	Substrate R$_1$	R$_2$	R$_3$	Catalyst	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
2a[21]	CH_3	H	CH_3	A	**7a**	74	**8a**	44	**9a**	73
2b[22]	C_2H_5	H	C_2H_5	A	**7b**	95	**8b**	72	**9b**	78
2c[23]	iso-C_3H_7	H	iso-C_3H_7	A	**7c**	89	**8c**	51	**9c**	85
2d[11]	iso-C_4H_9	H	iso-C_4H_9	A	**7d**	86	**8d**	72	**9d**	65
2e[10]	C_6H_5	H	C_6H_5	B	**7e**	66[a]	**8e**	82[a]	Recovery	
2g[13]	H	C_6H_5	C_6H_5	B	**7g**	39 77[b]	**8g**	66[a]	**9g**	25[a]

Catalyst A, $Pd(PPh_3)_4$; B, $Pd(PPh_3)_2Cl_2$–CuI. *a*) Heated for 3 h. *b*) Heated at 70 °C.



15 **16**

Chart 2

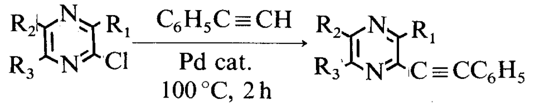
with phenylacetylene gave the best result at 70 °C, those with 1-hexyne and propargyl alcohol were carried out at the same temperature. In all cases, the N-oxide groups were not affected.

On the other hand, the reaction of 2-chloro-3,6-diisobutylpyrazine 1-oxide (**15**)[14] with phenylacetylene was troublesome. When the reaction mixture was heated at 100 °C for 2 h, the reaction gave a mixture of the starting material (80%) and the coupling compound (**16**) (10%). By extending the reaction time to 12 h, the yield of the product was elevated to 18%. However, under stronger conditions, at 130 °C for 2 h, the yields of the product and the starting material decreased to 8% and 65%, respectively. The reaction under reflux resulted in many spots on the thin layer chromatography plate. When the base was replaced by potassium carbonate, the situation was not improved. Efforts were made to find optimum conditions at 100 and 130 °C. However, the yield of the product did not exceed 11%.

No coupling product was obtained from 2-chloro-3,5-diphenylpyrazine 1-oxide[15] on reaction with three kinds of acetylenes, but the starting material was recovered in *ca.* 55% yield. Namely, 2-chloropyrazine 1-oxides reacted sluggishly in this system.

The cross-coupling reaction of 3,6-dialkyl-2,5-dichloropyrazines with phenylacetylene, 1-hexyne, and propargyl alcohol also gave the expected products. In order to find the optimum reaction conditions, 2,5-dichloro-3,6-diisobutylpyrazine (**3d**)[11] was treated with phenylacetylene under various conditions. In anticipation of the occurrence of mono-substitution, 1 equimolar phenylacetylene was employed at 100 °C. The result fell short of our expectation, and a mixture of 2-chloro-3,6-diisobutyl-5-phenylethynylpyrazine (**17**) (31%), 2,5-bis-(phenylethynyl)-3,6-diisobutylpyrazine (**10d**) (18%), and the starting material (**3d**) (43%)

TABLE III. Reaction of Dichloropyrazines with Phenylacetylene

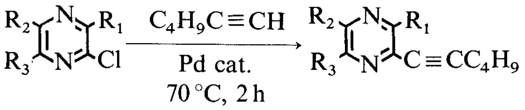


3a—g **10a—g**

	Substrate R₁	R₂	R₃	Catalyst		Product R₁	R₂	R₃	Yield (%)
3a[7]	CH_3	Cl	CH_3	A	**10a**	CH_3	$C_6H_5C\equiv C$	CH_3	71
3b[18]	C_2H_5	Cl	C_2H_5	A	**10b**	C_2H_5	$C_6H_5C\equiv C$	C_2H_5	61
3c[18]	iso-C_3H_7	Cl	iso-C_3H_7	A	**10c**	iso-C_3H_7	$C_6H_5C\equiv C$	iso-C_3H_7	90
3d[11]	iso-C_4H_9	Cl	iso-C_4H_9	A	**10d**	iso-C_4H_9	$C_6H_5C\equiv C$	iso-C_4H_9	80
3e[10]	C_6H_5	Cl	C_6H_5	B	**10e**	C_6H_5	$C_6H_5C\equiv C$	C_6H_5	42
3f[15]	C_6H_5	C_6H_5	Cl	B	**10f**	C_6H_5	C_6H_5	$C_6H_5C\equiv C$	40
3g[16]	Cl	C_6H_5	C_6H_5	B	**10g**	$C_6H_5C\equiv C$	C_6H_5	C_6H_5	46

Catalyst A, $Pd(PPh_3)_4$; B, $Pd(PPh_3)_2Cl_2$–CuI.

TABLE IV. Reaction of Dichloropyrazines with 1-Hexyne



3a—g **11a—g**

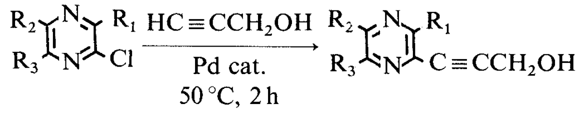
	Substrate R₁	R₂	R₃	Catalyst		Product R₁	R₂	R₃	Yield (%)
3a[7]	CH_3	Cl	CH_3	A	**11a**	CH_3	$C_4H_9C\equiv C$	CH_3	56
3b[18]	C_2H_5	Cl	C_2H_5	A	**11b**	C_2H_5	$C_4H_9C\equiv C$	C_2H_5	59
3c[18]	iso-C_3H_7	Cl	iso-C_3H_7	A	**11c**	iso-C_3H_7	$C_4H_9C\equiv C$	iso-C_3H_7	78
3d[11]	iso-C_4H_9	Cl	iso-C_4H_9	A	**11d**	iso-C_4H_9	$C_4H_9C\equiv C$	iso-C_4H_9	85
3e[10]	C_6H_5	Cl	C_6H_5	B	**11e**	C_6H_5	$C_4H_9C\equiv C$	C_6H_5	77
3f[15]	C_6H_5	C_6H_5	Cl	B	**11f**	C_6H_5	C_6H_5	$C_4H_9C\equiv C$	82
3g[16]	Cl	C_6H_5	C_6H_5	B	**11g**	$C_4H_9C\equiv C$	C_6H_5	C_6H_5	81

Catalyst A, $Pd(PPh_3)_4$; B, $Pd(PPh_3)_2Cl_2$–CuI.

was obtained. Accordingly, with the object of replacing two chlorine atoms, 2.4 equimolar phenylacetylene was used, and the expected product was obtained in satisfactory yields. Based on these results, 2.4 equimolar acetylenes were used in all cases; the results are shown in Tables III, IV, and V.

Among the reactions of dichloro-diphenylpyrazines, that with 1-hexyne was carried out at 70 °C and that with propargyl alcohol at 50 °C, because the formation of many products was observed at higher temperatures. In the case of the reactions of 2,5-dichloro-3,6-diphenylpyrazine (**3e**)[10] and 2,6-dichloro-3,5-diphenylpyrazine (**3f**)[15] with propargyl alcohol, the simultaneous formation of mono- and disubstitution product was always observed at 50 °C, even with 2.4 equimolar propargyl alcohol. On the other hand, in the case of 2,3-dichloro-5,6-diphenylpyrazine (**3g**),[16] only one chlorine atom was replaced by the acetylenic residue to give 3-(5-chloro-3,6-diphenylpyrazin-2-yl)propargyl alcohol (**12g′**) (87%) under the same conditions as in the other cases.

TABLE V. Reaction of Dichloropyrazines with Propargyl Alcohol



3a—g **12a—g**

	Substrate R$_1$	R$_2$	R$_3$	Catalyst		Product R$_1$	R$_2$	R$_3$	Yield (%)
3a[7]	CH_3	Cl	CH_3	A	**12a**	CH_3	$HOCH_2C{\equiv}C$	CH_3	74
3b[18]	C_2H_5	Cl	C_2H_5	A	**12b**	C_2H_5	$HOCH_2C{\equiv}C$	C_2H_5	74
3c[18]	iso-C_3H_7	Cl	iso-C_3H_7	A	**12c**	iso-C_3H_7	$HOCH_2C{\equiv}C$	iso-C_3H_7	61
3d[11]	iso-C_4H_9	Cl	iso-C_4H_9	A	**12d**	iso-C_4H_9	$HOCH_2C{\equiv}C$	iso-C_4H_9	72
3e[10]	C_6H_5	Cl	C_6H_5	B	**12e**	C_6H_5	$HOCH_2C{\equiv}C$	C_6H_5	42
					12e′	C_6H_5	Cl	C_6H_5	26 (22)[a]
3f[15]	C_6H_5	C_6H_5	Cl	B	**12f**	C_6H_5	C_6H_5	$HOCH_2C{\equiv}C$	21
					12f′	C_6H_5	C_6H_5	Cl	43 (19)[a]
3g[16]	Cl	C_6H_5	C_6H_5	B	**12g**	$HOCH_2C{\equiv}C$	C_6H_5	C_6H_5	—
					12g′	Cl	C_6H_5	C_6H_5	87 (10)[a]

Catalyst A, $Pd(PPh_3)_4$; B, $Pd(PPh_3)_2Cl_2$–CuI. *a*) The starting material.

Consequently, the cross-coupling reactions of chloropyrazines with several types of acetylenes using palladium catalysts proceeded in satisfactory yields. Although tetrakis(triphenylphosphine)palladium is effective in most cases, a combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide can also serve in some cases. A good choice of catalyst is important in this reaction system.

Experimental

All melting and boiling points are uncorrected. In the case of boiling points, the oil bath temperature was recorded. Infrared spectra (IR) were taken on a Shimadzu IR-400 spectrometer, and proton nuclear magnetic resonance spectra (^{1}H-NMR) on an Varian EM-390 instrument in $CDCl_3$, except in a few cases (**12a**—**e**, in DMSO-d_6), with tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 spectrometer. All reactions were carried out under an argon stream. For silica gel column chromatography, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Tokyo) was used.

a) General Procedure for Reaction of 2-Chloro-3,6-dialkylpyrazines and Their N-Oxides with Acetylenes——A mixture of a 2-chloro-3,6-dialkylpyrazine (2 mmol), an acetylenic compound (3 mmol), CH_3COOK (294 mg, 3 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in DMF (5 ml) was heated at 100 °C for 2 h. After removal of the solvent by distillation *in vacuo*, the residue was triturated with H_2O (20 ml) and extracted with Et_2O (15 ml × 3). The Et_2O layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using a mixture of hexane and AcOEt. In the case of the 4-oxides, 1 mmol of the substrate was reacted with the corresponding amounts of the reagents in the same way. The reaction of 2-chloro-3,6-diisobutylpyrazine 1-oxide (**15**) (242 mg, 1 mmol) with phenylacetylene (153 mg, 1.5 mmol) was achieved under the same conditions.

b) General Procedure for Reaction of 2-Chloro-diphenylpyrazines and Their 4-Oxides with Acetylenes——Catalytic amounts of $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) and CuI (10 mg, 0.05 mmol) were added to a solution of a 2-chloro-diphenylpyrazine or an N-oxide (1 mmol), an acetylenic compound (1.5 mmol), and CH_3COOK (147 mg, 1.5 mmol) in DMF (5 ml). The mixture was heated at 100 °C for 2 h and worked up as described before.

c) Hydrogenation of 3,6-Dimethyl-2-phenylethynylpyrazine (4a) with the Lindlar Catalyst——A hexane solution (20 ml) of **4a** (416 mg, 2 mmol) was stirred in a stream of hydrogen in the presence of the catalyst (30 mg). The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The resulting oil was then purified by distillation under reduced pressure to give **13** (408 mg, 97%).

(*Z*)-2,5-Dimethyl-3-styrylpyrazine (**13**): Colorless oil, bp 108—115 °C/3 Torr. High-resolution MS: Calcd for $C_{14}H_{14}N_2$: 210.1156. Obsd: 210.1148. MS *m/e*: 210 (M^+). ^{1}H-NMR δ: 2.26 (3H, s, CH_3), 2.46 (3H, s, CH_3), 6.62 (1H, d, $J=11$ Hz, $C\underline{H}=CH$), 6.86 (1H, d, $J=11$ Hz, $CH=C\underline{H}$), 6.69—7.40 (5H, m, benzene H), 8.21 (1H, s, pyrazine H).

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TABLE VI. Properties of Alkynylpyrazines

Compound	bp (°C/Torr) or mp (°C, recryst. from)	Formula	Analysis (%) Calcd (Found)			IR (C≡C) cm^{-1} (neat or KBr)	^{1}H-NMR (δ, ppm)
			C	H	N		
4a	130—134/1	$C_{14}H_{12}N_2$	80.74 (80.79	5.81 5.96	13.45 13.35)	2245	2.52 (3H, s), 2.71 (3H, s), 7.24—7.46 (3H, m), 7.46—7.70 (2H, m), 8.22 (1H, s)
4b	131—137/2	$C_{16}H_{16}N_2$	81.32 (81.22	6.83 6.79	11.86 11.88)	2240	1.33 (3H, t), 1.38 (3H, t), 2.88 (2H, q), 3.13 (2H, q), 7.38—8.00 (5H, m), 8.50 (1H, s)
4c	119—124/1	$C_{18}H_{20}N_2$	81.78 (81.68	7.63 7.54	10.60 10.58)	2220	1.33 (12H, d), 3.12 (1H, m), 3.70 (1H, m), 7.33—7.90 (5H, m), 8.47 (1H, s)
4d	138—142/1	$C_{20}H_{24}N_2$	82.14 (82.29	8.27 8.30	9.58 9.59)	2220	0.95 (6H, d), 1.00 (6H, d), 2.17 (2H, m), 2.67 (2H, d), 2.95 (2H, d), 7.20—7.80 (5H, m), 8.23 (1H, s)
4e	153—154, MeOH	$C_{24}H_{16}N_2$	86.72 (86.51	4.85 4.78	8.43 8.33)	2230	7.20—7.70 (11H, m), 7.90—8.33 (4H, m), 9.05 (1H, s)
4f	122—124, MeOH	$C_{24}H_{16}N_2$	86.72 (86.73	4.85 4.87	8.43 8.45)	2230	7.20—7.60 (11H, m), 8.00—8.24 (4H, m), 8.96 (1H, s)
4g	164—165, MeOH (173—175)[24)	$C_{24}H_{16}N_2$	86.72 (86.48	4.85 4.95	8.43 8.26)	2225	7.20—7.80 (15H, m), 8.80 (1H, s)
5a	83—86/1	$C_{12}H_{16}N_2$	76.55 (76.36	8.57 8.55	14.88 14.78)	2250	0.97 (3H, t), 1.63 (4H, m), 2.47 (3H, s), 2.53 (2H, t), 2.67 (3H, s), 8.45 (1H, s)
5b	94—99/1	$C_{14}H_{20}N_2$	77.73 (77.74	9.32 9.41	12.95 12.97)	2250	0.93 (3H, t), 1.30 (6H, t), 1.33—1.87 (4H, m), 2.50 (2H, t), 2.77 (2H, q), 2.98 (2H, q), 8.37 (1H, s)
5c	96—102/1	$C_{16}H_{24}N_2$	78.63 (78.67	9.90 10.00	11.46 11.64)	2230	0.97 (3H, t), 1.32 (6H, d), 1.33 (6H, d), 1.63 (4H, m), 2.53 (2H, t), 3.08 (1H, m), 3.57 (1H, m), 8.37 (1H, s)

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5d	107—114/1	$C_{18}H_{28}N_2$	79.36 (79.44	10.36 10.34	10.28 10.15)	2240	0.85—1.08 (3H, m), 0.93 (6H, d), 0.97 (6H, d), 1.60 (4H, m), 2.18 (2H, m), 2.53 (2H, t), 2.62 (2H, d), 2.83 (2H, d), 8.23 (1H, s)
5e	110—111, hexane	$C_{22}H_{20}N_2$	84.58 (84.39	6.45 6.45	8.97 8.97)	2250	0.93 (3H, t), 1.50 (4H, m), 2.46 (2H, t), 7.52 (6H, m), 8.12 (4H, m), 9.05 (1H, s)
5f	71—73, MeOH–H_2O	$C_{22}H_{20}N_2$	84.58 (84.59	6.45 6.48	8.97 8.99)	2240	0.90 (3H, t), 1.52 (4H, m), 2.47 (2H, t), 7.33—7.67 (6H, m), 8.00—8.33 (4H, m), 8.98 (1H, s)
5g	174—178/0.01	$C_{22}H_{20}N_2$	84.58 (84.80	6.45 6.51	8.97 8.96)	2250	0.96 (3H, t), 1.63 (4H, m), 2.53 (2H, t), 7.27—7.63 (10H, m), 8.70 (1H, s)
6a	86, hexane	$C_9H_{10}N_2O$	66.65 (66.43	6.22 6.11	17.27 17.10)	2240	2.50 (3H, s), 2.60 (3H, s), 3.63 (1H, t), 4.57 (2H, d), 8.22 (1H, s)
6b	140—143/2	$C_{11}H_{14}N_2O$	69.44 (69.46	7.42 7.44	14.73 14.73)	2250	1.30 (6H, t), 2.83 (2H, q), 3.00 (2H, q), 4.07 (1H, br s), 4.67 (2H, br s), 8.45 (1H, s)
6c	150—155/2	$C_{13}H_{18}N_2O$	71.52 (71.22	8.31 8.43	12.83 12.71)	2250	1.28 (6H, d), 1.32 (6H, d), 3.08 (1H, m), 3.43 (1H, br s), 3.53 (1H, m), 4.63 (2H, s), 8.42 (1H, s)
6d	154—156/2	$C_{15}H_{22}N_2O$	73.13 (73.05	9.00 9.04	11.37 11.34)	2230	0.97 (12H, d), 2.06 (2H, m), 2.63 (2H, d), 2.83 (2H, d), 2.50—3.00 (1H, br s), 4.60 (2H, br s), 8.42 (1H, s)
6e	118—119, cyclohexane	$C_{19}H_{14}N_2O$	79.70 (79.64	4.93 4.88	9.78 9.76)	2240	2.47—2.87 (1H, br s), 4.38 (2H, s), 7.20—7.57 (6H, m), 7.77—8.10 (4H, m), 8.90 (1H, s)
6f	127—129, MeOH	$C_{19}H_{14}N_2O$	79.70 (79.40	4.93 4.97	9.78 9.63)	2240	4.13 (1H, br s), 4.60 (2H, br s), 7.69 (6H, m), 8.30 (4H, m), 9.12 (1H, s)
6g	72—74, MeOH–H_2O	$C_{19}H_{14}N_2O$	79.70 (79.68	4.93 5.04	9.78 9.53)	2245	2.20 (1H, br s), 4.54 (2H, s), 7.20—7.57 (10H, m), 8.74 (1H, s)

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Table VII. Properties of Alkynylpyrazine N-Oxides

Compound	bp (°C/Torr) or mp (°C, recryst. from)	Formula	Analysis (%) Calcd (Found)			IR (C≡C) cm^{-1} (neat or KBr)	^{1}H-NMR (δ, ppm)
			C	H	N		
7a	139—140, iso-Pr_2O	$C_{14}H_{12}N_2O$	74.99 (75.21	5.38 5.45	12.49 12.49)	2220	2.50 (3H, s), 2.68 (3H, s), 7.33—7.83 (5H, m), 8.12 (1H, s)
7b	90—92, hexane	$C_{16}H_{16}N_2O$	76.16 (76.28	6.39 6.39	11.10 11.11)	2230	1.35 (6H, t), 2.78 (2H, q), 3.23 (2H, q), 7.40—7.92 (5H, m), 8.17 (1H, s)
7c	97—99, MeOH–H_2O	$C_{18}H_{20}N_2O$	77.11 (77.36	7.19 7.19	9.99 10.26)	2220	1.40 (6H, d), 1.60 (6H, d), 3.10 (1H, m), 4.27 (1H, m), 7.67—8.23 (5H, m), 8.42 (1H, s)
7d	125.5—126.5, hexane	$C_{20}H_{24}N_2O$	77.88 (77.89	7.84 7.92	9.08 8.86)	2230	0.93 (6H, d), 1.03 (6H, d), 2.23 (2H, m), 2.57 (2H, d), 3.05 (2H, d), 7.33—7.93 (5H, m), 8.05 (1H, s)
7e	207—208 (dec.), MeOH	$C_{24}H_{16}N_2O$	82.74 (82.83	4.63 4.61	8.04 8.06)	2240	7.37 (5H, s), 7.50—7.72 (6H, m), 7.72—7.93 (2H, m), 8.00—8.23 (2H, m), 8.70 (1H, s)
7g	180—182, MeOH	$C_{24}H_{16}N_2O$	82.74 (82.55	4.63 4.61	8.04 7.86)	2240	7.10—7.53 (13H, m), 7.53—7.77 (2H, m), 8.40 (1H, s)
8a	76.5, iso-Pr_2O	$C_{12}H_{16}N_2O$	70.56 (70.81	7.90 7.89	13.72 13.63)	2250	0.97 (3H, t), 1.62 (4H, m), 2.47 (3H, s), 2.53 (2H, t), 2.60 (3H, s), 8.08 (1H, s)
8b	130—135/1	$C_{14}H_{20}N_2O$	72.38 (72.08	8.68 8.68	12.06 11.96)	2250	0.95 (3H, t), 1.25 (3H, t), 1.28 (3H, t), 1.58 (4H, m), 2.53 (2H, t), 2.75 (2H, q), 3.12 (2H, q), 8.12 (1H, s)

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8c	115—117/0.1	$C_{16}H_{24}N_2O$	73.80 (73.72	9.29 9.13	10.76 10.48)	2245	0.97 (3H, t), 1.28 (6H, d), 1.47 (6H, d), 1.60 (4H, m), 2.53 (2H, t), 2.98 (1H, m), 4.02 (1H, m), 7.98 (1H, s)
8d	70—72, MeOH–H_2O	$C_{18}H_{28}N_2O$	74.95 (75.23	9.79 9.20	9.71 9.75)	2240	0.80—1.20 (3H, m), 0.92 (6H, d), 0.98 (6H, d), 1.62 (4H, m), 2.20 (2H, m), 2.48 (2H, t), 2.52 (2H, d), 2.97 (2H, d), 7.95 (1H, s)
8e	118—120, iso-Pr_2O	$C_{22}H_{20}N_2O$	80.46 (80.31	6.14 6.03	8.53 8.55)	2250	0.82 (3H, t), 1.32 (4H, m), 2.32 (2H, t), 7.45—7.82 (8H, m), 7.95—8.15 (2H, m), 8.68 (1H, s)
8g	75—76, hexane	$C_{22}H_{20}N_2O$	80.46 (80.32	6.14 6.21	8.53 8.46)	2240	0.94 (3H, t), 1.59 (4H, m), 2.49 (2H, t), 7.11—7.48 (10H, m), 8.31 (1H, s)
9a	180—181, AcOEt	$C_9H_{10}N_2O_2$	60.66 (60.46	5.66 5.63	15.72 15.60)	2230	2.45 (3H, s), 2.55 (3H, s), 3.22 (1H, br s), 4.53 (2H, d), 8.07 (1H, s)
9b	83—85, cyclohexane	$C_{11}H_{14}N_2O_2$	64.06 (64.16	6.84 6.65	13.58 13.32)	2250	1.23 (3H, t), 1.28 (3H, t), 2.73 (2H, q), 3.08 (2H, q), 4.60 (2H, s), 7.57 (1H, br s), 8.08 (1H, s)
9c	56—57, hexane	$C_{13}H_{18}N_2O_2$	66.64 (66.46	7.74 7.69	11.96 11.83)	2245	1.28 (6H, d), 1.45 (6H, d), 2.93 (1H, m), 3.47 (1H, br s), 3.92 (1H, m), 4.60 (2H, s), 7.98 (1H, s)
9d	105—106, iso-Pr_2O	$C_{15}H_{22}N_2O_2$	68.67 (68.40	8.45 8.49	10.68 10.45)	2250	0.95 (6H, d), 1.02 (6H, d), 1.97 (1H, br s), 2.18 (2H, m), 2.60 (2H, d), 3.00 (2H, d), 4.60 (2H, d), 8.00 (1H, s)
9g	129, hexane–AcOEt	$C_{19}H_{14}N_2O_2$	75.48 (75.23	4.67 4.68	9.27 9.19)	2230	3.67 (1H, br s), 4.47 (2H, s), 7.30 (5H, s), 7.38 (5H, s), 8.40 (1H, s)
16	130—131, hexane	$C_{20}H_{24}N_2O$	77.88 (77.76	7.84 7.76	9.08 8.98)	2250	0.93 (6H, d), 1.02 (6H, d), 2.22 (2H, m), 2.57 (2H, d), 3.03 (2H, d), 7.20—7.67 (5H, m), 7.88 (1H, s)

TABLE VIII. Properties of Dialkynylpyrazines

Compound	bp (°C/Torr) or mp (°C, recryst. from)	Formula	Analysis (%) Calcd (Found)			IR ($C\equiv C$) cm^{-1} (neat or KBr)	^{1}H-NMR (δ, ppm)
			C	H	N		
10a	174—175, hexane	$C_{22}H_{16}N_2$	85.69 (85.60	5.23 5.17	9.09 8.95)	2230	2.73 (6H, s), 7.30—7.83 (10H, m)
10b	177—178, cyclohexane	$C_{24}H_{20}N_2$	85.68 (85.41	5.99 6.00	8.33 8.20)	2220	1.42 (6H, t), 3.17 (4H, q), 7.40—8.00 (10H, m)
10c	219—222, Me_2CO	$C_{26}H_{24}N_2$	85.68 (85.59	6.64 6.75	7.69 7.88)	2230	1.53 (12H, d), 3.90 (2H, m), 7.13—8.03 (10H, m)
10d	150—153, cyclohexane	$C_{28}H_{28}N_2$	85.67 (85.69	7.19 7.36	7.14 7.37)	2220	1.00 (12H, d), 2.30 (2H, m), 2.93 (4H, d), 7.33—7.83 (10H, m)
10e	253—255, $CHCl_3$–MeOH	$C_{32}H_{20}N_2$	88.86 (88.67	4.66 4.64	6.48 6.42)	2240	7.33—7.77 (16H, m), 8.07—8.37 (4H, m)
10f	197—198, MeCN	$C_{32}H_{20}N_2$	88.86 (89.15	4.66 4.62	6.48 6.60)	2230	7.33—8.00 (16H, m), 8.25—8.67 (4H, m)
10g	192—194, MeCN	$C_{32}H_{20}N_2$	88.86 (88.68	4.66 4.62	6.48 6.54)	2225	7.27—8.17 (20H, m)
11a	51—52, MeOH	$C_{18}H_{24}N_2$	80.55 (80.46	9.01 9.05	10.44 10.33)	2230	0.92 (6H, t), 1.57 (8H, m), 2.47 (4H, t), 2.53 (6H, s)
11b	150—155/1	$C_{20}H_{28}N_2$	81.03 (80.80	9.52 9.56	9.45 9.33)	2250	0.93 (6H, t), 1.10 (6H, t), 1.57 (8H, m), 2.47 (4H, t), 2.90 (4H, q)
11c	59—61, MeOH–H_2O	$C_{22}H_{32}N_2$	81.43 (81.17	9.94 9.84	8.63 8.68)	2250	0.93 (6H, t), 1.27 (12H, d), 1.57 (8H, m), 2.48 (4H, t), 3.52 (2H, m)

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11d	56.5—57.5, MeOH–H_2O	$C_{24}H_{36}N_2$	81.76 (81.71	10.29 10.33	7.95 7.97)	2245	0.96 (12H, d), 0.98 (6H, t), 1.60 (8H, m), 2.22 (2H, m), 2.52 (4H, t), 2.82 (4H, d)
11e	105—107, hexane	$C_{28}H_{28}N_2$	85.67 (85.73	7.19 7.07	7.14 7.23)	2250	0.87 (6H, t), 1.47 (8H, m), 2.40 (4H, t), 7.40—7.67 (6H, m), 8.00—8.33 (4H, m)
11f	55.5, MeOH–H_2O	$C_{28}H_{28}N_2$	85.67 (85.42	7.19 7.14	7.14 7.00)	2250	0.90 (6H, t), 1.53 (8H, m), 2.44 (4H, t), 7.40—7.63 (6H, m), 8.07—8.38 (4H, m)
11g	80.5—81.5, hexane	$C_{28}H_{28}N_2$	85.67 (85.69	7.19 7.16	7.14 7.02)	2250	0.97 (6H, t), 1.66 (8H, m), 2.57 (4H, t), 7.20—7.60 (10H, m)
12a	254—256 (dec.), AcOEt	$C_{12}H_{12}N_2O_2$	66.65 (66.59	5.59 5.64	12.96 12.76)	2245	2.00 (6H, s), 4.13 (4H, d), 5.27 (2H, t)
12b	151—153, iso-Pr_2O	$C_{14}H_{16}N_2O_2$	68.83 (68.61	6.60 6.50	11.47 11.19)	2245	1.13 (6H, t), 2.70 (4H, t), 4.17 (4H, d), 5.30 (2H, t)
12c	199—201, iso-Pr_2O	$C_{16}H_{20}N_2O_2$	70.56 (70.54	7.40 7.40	10.29 10.21)	2245	1.13 (12H, d), 3.27 (2H, m), 4.20 (4H, d), 5.30 (2H, t)
12d	156—158, iso-Pr_2O	$C_{18}H_{24}N_2O_2$	71.97 (72.24	8.05 8.29	9.33 9.14)	2250	0.83 (12H, d), 1.97 (2H, m), 2.58 (4H, d), 4.17 (4H, d), 5.30 (2H, t)
12e′	155—157, cyclohexane	$C_{19}H_{13}ClN_2O$	71.14 (71.43	4.09 4.00	8.73 8.77)	2250	2.37 (1H, br s), 4.47 (2H, s), 7.47—7.73 (6H, m), 7.73—8.07 (2H, m), 8.07—8.30 (2H, m)
12e	221—222, cyclohexane	$C_{22}H_{16}N_2O_2$	77.63 (77.38	4.74 4.65	8.23 8.14)	2250	4.13 (4H, d), 5.30 (2H, t), 7.17—7.50 (6H, m), 7.67—7.97 (4H, m)
12f′	142—143, cyclohexane	$C_{19}H_{13}ClN_2O$	71.14 (71.16	4.09 4.14	8.73 8.71)	2250	2.33 (1H, br s), 4.47 (2H, s), 7.33—7.73 (6H, m), 7.83—8.33 (4H, m)
12f	210—211, $CHCl_3$	$C_{22}H_{16}N_2O_2$	77.63 (77.36	4.74 4.74	8.23 8.18)	2245	4.13 (4H, d), 5.27 (2H, t), 7.10—7.43 (6H, m), 7.67—8.00 (4H, m)
12g′	118—120, hexane	$C_{19}H_{13}ClN_2O$	71.14 (70.92	4.09 4.02	8.73 8.66)	2240	2.83 (1H, br s), 4.57 (2H, d), 7.20—7.67 (10H, m)

d) Reduction of 3,6-Dimethyl-2-phenylethynylpyrazine (4a) with Lithium Aluminum Hydride——A mixture of **4a** (280 mg, 1 mmol) and $LiAlH_4$ (74 mg, 2 mmol) in THF (5 ml) was refluxed for 4 h. The reaction mixture was usually worked up to yield a red-brown oil, which was chromatographed on silica gel (15 g) using hexane containing increasing amounts of AcOEt. The fractions eluted with a mixture of hexane and AcOEt (4 : 1) gave **13** (35 mg, 8%) and **14** (60 mg, 14%), successively.

(*E*)-3,6-Dimethyl-2-styrylpyrazine (**14**): Colorless oil, bp 117—122 °C/3 Torr. High-resolution MS: Calcd for $C_{14}H_{14}N_2$: 210.1156. Obsd: 210.1148. MS *m/e*: 210 (M^+). ^1H-NMR δ: 2.54 (3H, s, CH_3), 2.26 (3H, s, CH_3), 7.20 (1H, d, $J=16$ Hz, $C\underline{H}=CH$), 7.30—7.48 (3H, m, benzene H), 7.48—7.65 (2H, m, benzene H), 7.82 (1H, d, $J=16$ Hz, $CH=C\underline{H}$), 8.16 (1H, s, pyrazine H).

e) Reaction of 2,5-Dichloro-3,6-diisobutylpyrazine (3d) with Equimolar Phenylacetylene——A mixture of **3d** (540 mg, 2 mmol), phenylacetylene (196 mg, 2 mmol), CH_3COOK (294 mg, 3 mmol), and $Pd(PPh_3)_4$ (232 mg, 0.2 mmol) in DMF (10 ml) was heated at 100 °C for 2 h. The reaction mixture was worked up as described in the general procedure a). The resulting solid was chromatographed on silica gel (20 g), and elution with a mixture of hexane and AcOEt (50 : 1) gave the starting material (235 mg, 43%), 2-chloro-3,6-diisobutyl-5-phenylethynylpyrazine (**17**) (245 mg, 31%) and 2,5-bis(phenylethynyl)-3,6-diisobutylpyrazine (**10d**) (138 mg, 18%), successively.

2-Chloro-3,6-diisobutyl-5-phenylethynylpyrazine (**17**): Colorless needles (from $MeOH-H_2O$), mp 68 °C. *Anal.* Calcd for $C_{20}H_{23}ClN_2$: C, 73.48; H, 7.09; N, 8.57. Found: C, 73.21; H, 6.98; N, 8.51. ^1H-NMR δ: 0.98 (6H, d, $J=7$ Hz, $CH_2CH(C\underline{H}_3)_2$), 1.02 (6H, d, $J=7$ Hz, $CH_2CH(C\underline{H}_3)_2$), 2.33 (2H, m, $J=7$ Hz, $CH_2C\underline{H}(CH_3)_2$), 2.85 (2H, d, $J=7$ Hz, $C\underline{H}_2CH(CH_3)_2$), 2.93 (2H, d, $J=7$ Hz, $C\underline{H}_2CH(CH_3)_2$), 7.40—8.27 (5H, m, benzene H). IR (KBr) cm^{-1}: 2230 ($C\equiv C$).

f) Reaction of 3,6-Dialkyl-2,5-dichloropyrazines and Dichlorodiphenylpyrazines with 2.4 Equimolar Acetylenic Compounds——A mixture of a substrate (1 mmol), an acetylenic compound (2.4 mmol), CH_3COOK (235 mg, 2.4 mmol), and the catalyst, $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) or $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol)–CuI (20 mg, 0.1 mmol), in DMF (5 ml) was heated at 100 °C for 2 h and worked up as described under general procedure a).

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