COUPLING REACTION OF CHLOROPYRAZINES AND THEIR N-OXIDES WITH TETRAPHENYLTIN

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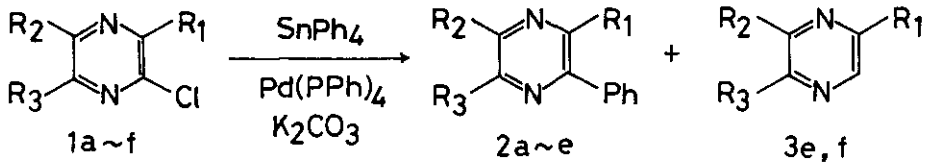
Abstract —— By the coupling reaction of monochloropyrazines, dichloropyrazines, 2-chloropyrazine 1-oxides, and 2-chloropyrazine 4-oxides with tetraphenyltin, the corresponding phenylpyrazines were prepared in satisfactory yields.

While the preparation of phenylpyrazines has been performed mainly by cyclization reaction[1-4], the only example involving a substitution is the phenylation using phenyllithium[5]. In the preceding papers[6,7], we described that trimethylaluminum exhibits special ability for methylation of pyrazines and pyrazine N-oxides by coupling reaction, and that tetrakis(triphenylphosphine)palladium is an effective catalyst for this reaction. In a continuation of these works, the present investigation was undertaken to find a convenient method for phenylation of pyrazines, and it will be now described that tetraphenyltin[8] answers our purpose. In the presence of tetrakis(triphenylphosphine)palladium, 2-chloro-3,6-diisobutylpyrazine[9] was heated under reflux with tetraphenyltin in dry dioxane, namely, under similar conditions as reported[6,7]. However, the reaction resulted in recovering the starting material. When dioxane was replaced by dry N,N-dimethylformamide (DMF), and potassium carbonate was added to the reaction mixture, the desired product was obtained in 44% yields under heating at 100°C and in 75% yields under reflux. Thus, 2-chloro-3,6-dialkylpyrazines were allowed to react with tetraphenyltin in the presence of the palladium catalyst in DMF under reflux, the corresponding phenylpyrazines were obtained in good yields, as illustrated in Table 1. In the case of the reaction of 2-chloro-diphenylpyrazines, dechlorination

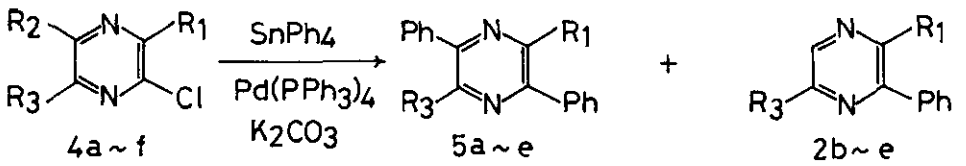
was observed concurrently. When a chloropyrazine was heated with the palladium catalyst and potassium carbonate in DMF, that is, without tetraphenyltin, the corresponding dechlorinated compound was yielded in ca. 20% yields. The solvent, DMF, would take part in dechlorination.

Table 1. Reaction of Monochloropyrazines with Tetraphenyltin



	Substrate R_1	R_2	R_3	Product	Yield (%)	Product	Yield (%)
1a[10]	Me	H	Me	2a[5]	75	-	
1b[10]	Et	H	Et	2b	78	-	
1c[11]	i-Pr	H	i-Pr	2c	81	-	
1d[9]	i-Bu	H	i-Bu	2d	75	-	
1e[12]	H	Ph	Ph	2e[13]	49	3e[12]	33
1f[3]	Ph	Ph	H	2e[13]	48	3f[3]	35

Table 2. Reaction of Dichloropyrazines with Tetraphenyltin

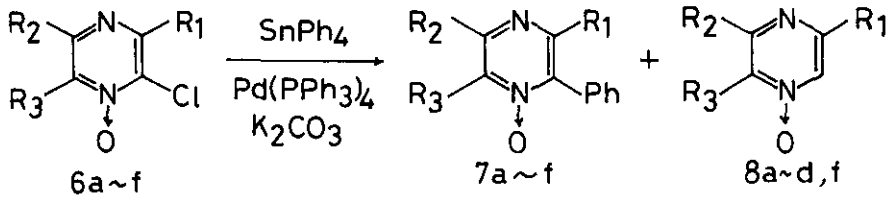


	Substrate R_1	R_2	R_3	Product R_1	R_3	Yield (%)	Product R_1	R_3	Yield (%)
4a[10]	Me	Cl	Me	5a[14] Me	Me	54	-		
4b[10]	Et	Cl	Et	5b[14] Et	Et	45	2b Et	Et	38
4c[11]	i-Pr	Cl	i-Pr	5c i-Pr	i-Pr	10	2c i-Pr	i-Pr	41
4d[9]	i-Bu	Cl	i-Bu	5d i-Bu	i-Bu	86	2d i-Bu	i-Bu	7
4e[12]	Cl	Ph	Ph	5e[14] Ph	Ph	25	2e[13] Ph	Ph	60
4f[3]	Ph	Ph	Cl	$5e_{14}$ Ph	Ph	16	2e[13] Ph	Ph	30

The coupling reaction of dichloropyrazines and 2-chloropyrazine 1- and 4-oxides with tetraphenyltin was also accomplished under the same conditions as mentioned

above, and the results are summarized in Table 2, 3 and 4. Although the dechlorinated compounds were formed in all cases, the N-oxide group was not affected by the reagent and the desired products were obtained in satisfactory yields.

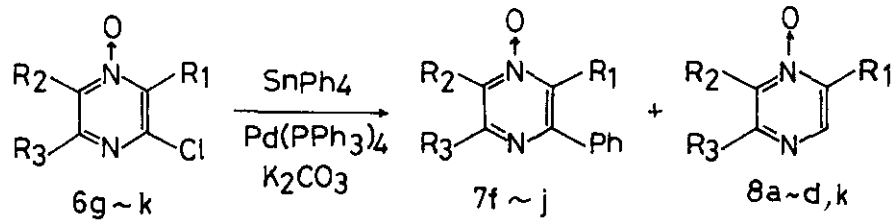
Table 3. Reaction of 2-Chloropyrazine 1-Oxides with Tetraphenyltin



6a~f 7a~f 8a~d,f

	Substrate R_1	R_2	R_3	Product	Yield (%)	Product	Yield (%)
6a[15]	Me	H	Me	7a	40	8a[17]	15
6b[11]	Et	H	Et	7b	56	8b[10]	7
6c[11]	i-Pr	H	i-Pr	7c	47	8c[18]	40
6d[16]	i-Bu	H	i-Bu	7d	38	8d[18]	11
6e[11]	H	Ph	Ph	7e	42	2e[13]	48
6f[3]	Ph	Ph	H	7f	26	8f[3]	38

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



6g~k 7f~j 8a~d,k

	Substrate R_1	R_2	R_3	Product	Yield (%)	Product	Yield (%)
6g[19]	Me	H	Me	7g	74	8a[17]	4
6h[10]	Et	H	Et	7h	63	8b[10]	37
6i[18]	i-Pr	H	i-Pr	7i	45	8c[18]	29
6j[9]	i-Bu	H	i-Bu	7j	62	8d[18]	7
6k[12]	H	Ph	Ph	7f	56	8k[12]	20

Among the results represented in Table 3 and 4, the yields of the products from the 4-oxides were recognized to be better on an average than the ones from the 1-oxides. The oxidation of the pyrazines, 2a-e, with permaleic acid led to give 7f-j, respectively[20]. Therefore, the reaction of 2-chloropyrazine 1-oxides, 6a-e, for the preparation of 7a-e seems to be of use.

The data presented in this paper support that tetraphenyltin is a useful reagent for phenylation of pyrazines. Further investigation on the phenylation of other aromatic rings is now in progress.

EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data: ^{1}H-NMR ($CDCl_3$/TMS): Varian EM-390; UV spectra (in EtOH): Hitachi Model 557; MS: Hitachi M-80 spectrometer.

General Procedure for the Coupling Reaction of Chloropyrazines with Tetraphenyltin — A mixture of a chloropyrazine (1 mmol), $Pd(PPh_3)_4$, K_2CO_3, and $SnPh_4$ in DMF (5 ml) was refluxed under an argon atmosphere. The solvent was removed by distillation in vacuo. The residue was triturated with water (ca. 1 ml) and extracted with Et_2O to give a dark brown solid, which was purified by column chromatography on Wakogel C-200 (10 g), eluting with hexane containing increasing amounts of AcOEt.

Table 5. Reaction Conditions of the Coupling Reaction

Substrate	Reaction Time (h)	Catalyst (mol.eq.)	$SnPh_4$ (mol.eq.)	K_2CO_3 (mol.eq.)
Monochloropyrazines (1a-f)	1	0.05	0.5	1.5
Dichloropyrazines (4a-f)	3	0.1	1	3
2-Chloropyrazine 1-Oxides (6a-f)	6	0.05	0.5	1.5
2-Chloropyrazine 4-Oxides (6g-k)	1	0.05	0.5	1.5

3,6-Diethyl-2-phenylpyrazine (2b): colorless oil; bp 86-90°C/2 torr; MS: m/z 212 (M^+), 211 (M^+-H); UV: λ_{max} 211 (log ε = 3.94), 227 (3.90), 285 (3.97) nm; ^{1}H-NMR: δ 1.10 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$), 1.20 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$), 2.77 (q, J = 7 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 7.33-7.53 (m, 5H, benzene H), 8.30 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.47; H, 7.75; N, 13.11.

3,6-Diisopropyl-2-phenylpyrazine (2c): colorless oil; bp 115-117°C/2 torr; MS: m/z 240 (M^+), 239 (M^+-H); UV: λ_{max} 227 (log ε = 4.04), 284 (4.11) nm; ^{1}H-NMR: δ 1.20 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.30 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 3.08 (m, J = 6 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.27 (m, J = 6 Hz, 1H, $C\underline{H}(CH_3)_2$), 7.33-7.60 (m, 5H, benzene H), 8.45 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.23; H, 8.48; N, 11.57.

3,6-Diisobutyl-2-phenylpyrazine (2d): colorless oil; bp 130-140°C/5 torr; MS: m/z 268 (M^+), 267 (M^+-H), 226 ($M^+-CH_3CH{=}CH_2$); UV: λ_{max} 222 (log ε = 3.92, shoulder), 286 (4.00), 305 (3.65, shoulder) nm; ^{1}H-NMR: δ 0.75 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.92 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.85-2.35 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.68 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.73 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.30-7.70 (m, 5H, benzene H), 8.37 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.78; H, 9.15; N, 10.57.

3,6-Diisopropyl-2,5-diphenylpyrazine (5c): colorless needles (from hexane); mp 189-190°C; MS: m/z 316 (M^+), 315 (M^+-H); UV: λ_{max} 244 (log ε = 4.02), 293 (4.04) nm; ^{1}H-NMR: δ 1.23 (d, J = 6 Hz, 12H, 2 x $CH(C\underline{H}_3)_2$), 3.32 (m, J = 6 Hz, 2H, 2 x $C\underline{H}(CH_3)_2$), 7.17-7.67 (m, 10H, benzene H) ppm; Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.39; H, 7.68; N, 8.76.

3,6-Diisobutyl-2,5-diphenylpyrazine (5d): colorless needles (from MeOH-H_2O); mp 100-101°C; MS: m/z 344 (M^+), 343 (M^+-H), 302 ($M^+-CH_3CH{=}CH_2$); UV: λ_{max} 248 (log ε = 3.99), 297 (4.01), 310 (3.93, shoulder) nm; ^{1}H-NMR: δ 0.80 (d, J = 7 Hz, 12H, 2 x $CH_2CH(C\underline{H}_3)_2$), 2.17 (m, J = 7 Hz, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.83 (d, J = 7 Hz, 4H, 2 x $C\underline{H}_2CH(CH_3)_2$), 7.27-7.63 (m, 10H, benzene H) ppm; Anal. Calcd. for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.96; H, 8.29; N, 8.11.

3,6-Dimethyl-2-phenylpyrazine 1-Oxide (7a): colorless prisms (from hexane); mp 86-87°C; MS: m/z 200 (M^+), 199 (M^+-H), 183 (M^+-OH); UV: λ_{max} 225 (log ε = 4.28), 265 (4.01), 305 (3.65) nm; ^{1}H-NMR: δ 2.32 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.27-7.57 (m, 5H, benzene H), 8.33 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.18; H, 6.01; N, 13.76.

3,6-Diethyl-2-phenylpyrazine 1-Oxide (7b): colorless needles (from hexane); mp 75-76°C; MS: m/z 228 (M^+), 211 (M^+-OH); UV: λ_{max} 227.5 (log ε = 4.22), 269 (3.92), 302 (3.57, shoulder) nm; ^{1}H-NMR: δ 1.13 (t, J = 7,5 Hz, 3H, $CH_2C\underline{H}_3$), 1.30 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 2.55 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.85 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 7.22-7.62 (m, 5H, benzene H), 8.33 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.60; H, 7.14; N, 12.16.

3,6-Diisopropyl-2-phenylpyrazine 1-Oxide (7c): colorless needles (from hexane); mp 128-129°C; MS: m/z 256 (M^+), 239 (M^+-OH); UV: λ_{max} 218.5 (log ε = 4.24), 270 (3.91), 306 (3.49, shoulder) nm; ^{1}H-NMR: δ 1.13 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.30 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.80 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.57 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)_2$), 7.20-7.53 (m, 5H, benzene H), 8.38 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.90; H, 7.86; N, 10.92.

3,6-Diisobutyl-2-phenylpyrazine 1-Oxide (7d): colorless needles; mp 47-49°C; bp 145-150°C/3 torr; MS: m/z 284 (M^+), 267 (M^+-OH); UV: λ_{max} 229.5 (log ε = 4.32), 270.5 (4.00), 303 (3.64, shoulder) nm; ^{1}H-NMR: δ 0.77 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.95 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.90-2.42 (m, J = 7 Hz, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.42 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.68 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.22-7.57 (m, 5H, benzene H), 8.27 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.89; H, 8.64; N, 9.83.

2,5,6-Triphenylpyrazine 1-Oxide (7e): slightly yellow needles (from MeOH); mp 163-164°C; MS: m/z 324 (M^+), 323 (M^+-H), 308 (M^+-O), 307 (M^+-OH); UV: λ_{max} 270 (log ε = 4.26), 339 (3.52) nm; ^{1}H-NMR: δ 7.20-7.53 (m, 13H, benzene H), 7.83-7.97 (m, 2H, benzene H), 8.72 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.79; N, 8.64. Found: C, 81.23; H, 5.00; N, 8.57.

2,5,6-Triphenylpyrazine 4-Oxide (7f): slightly yellow needles (from hexane); mp 211-212°C; MS: m/z 324 (M^+), 323 (M^+-H), 308 (M^+-O), 307 (M^+-OH); UV: λ_{max} 271 (log ε = 4.19), 341 (3.44) nm; ^{1}H-NMR: δ 7.17-7.53 (m, 13H, benzene H), 7.97-8.10 (m, 2H, benzene H), 8.63 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.49; H, 4.98; N, 8.62.

3,6-Dimethyl-2-phenylpyrazine 4-Oxide (7g): colorless prisms (from hexane); mp 73-74°C; MS: m/z 200 (M^+), 183 (M^+-OH); UV: λ_{max} 224 (log ε = 4.29), 251 (4.24), 264 (4.13, shoulder), 311 (3.63) nm; ^{1}H-NMR: δ 2.43 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.32-7.53 (m, 5H, benzene H), 8.02 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.89; H, 6.04; N, 13.92.

3,6-Diethyl-2-phenylpyrazine 4-Oxide (7h): colorless prisms (from hexane); mp 46-47°C; MS: m/z 228 (M^+), 211 (M^+-OH); UV: λ_{max} 225 (log ε = 4.31), 249 (4.16), 266 (4.10), 307 (3.74) nm; ^{1}H-NMR: δ 1.23 (t, J = 6 Hz, 3H, $CH_2C\underline{H}_3$), 1.30 (t, J = 6 Hz, 3H, $CH_2C\underline{H}_3$), 2.37 (q, J = 6 Hz, 2H, $C\underline{H}_2CH_3$), 2.93 (q, J = 6 Hz, 2H, $C\underline{H}_2CH_3$), 7.47 (s, 5H, benzene H), 8.07 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.68; H, 7.13; N, 12.09.

3,6-Diisopropyl-2-phenylpyrazine 4-Oxide (7i): colorless needles (from hexane); mp 76-77°C; MS: m/z 256 (M^+), 239 (M^+-OH); UV: λ_{max} 227 (log ε = 4.40), 251 (4.15), 269 (4.12), 305 (3.78) nm; ^{1}H-NMR: δ 1.27 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.38 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 3.00 (m, J = 6 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.30 (m, J = 6 Hz, 1H, $C\underline{H}(CH_3)_2$), 7.43 (s, 5H, benzene H), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.13; H, 7.96; N, 10.91.

3,6-Diisobutyl-2-phenylpyrazine 4-Oxide (7j): colorless needles (from MeOH-H_2O); mp 68-69°C; MS: m/z 284 (M^+), 267 (M^+-OH); UV: λ_{max} 228 (log ε = 4.38), 250 (4.19, shoulder), 266 (4.14, shoulder), 312 (3.80) nm; ^{1}H-NMR: δ 0.68 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.92 (d, J = 7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.90-2.38 (m, J = 7 Hz, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.58 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.85 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.47 (s, 5H, benzene H), 8.03 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.00; H, 8.68; N, 9.92.

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