PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS OF CHLOROPYRAZINES WITH AROMATIC HETEROCYCLES

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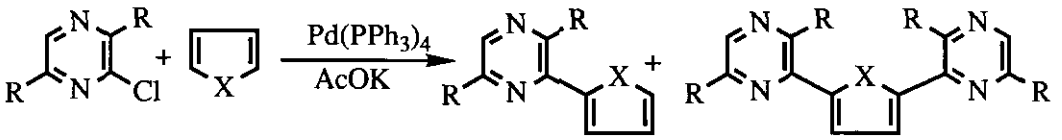
Abstract----In the presence of tetrakis(triphenylphosphine)palladium, chloropyrazines were treated with aromatic heterocycles such as furan, thiophene, pyrrole, *N*-substituted pyrroles, benzo[*b*]furan, benzo[*b*]thiophene, oxazole,thiazole, *N*-methylimidazoles, benz[*b*]oxazole and benzo[*b*]thiazole. The corresponding coupling products were obtained in moderate to good yields. The structures of the coupling products were determined.

Palladium-catalyzed cross-coupling reactions of aryl halides with organometallics, ethylenes or acetylenes proceeded easily and efficiently during carbon-carbon bond formation.[1] Some biaryls are important pharmaceutical agents,[2,3] but nowadays, they are of interest mainly from the standpoint of their physical properties in liquid crystals.[4] However, little is known in regard to the coupling reactions of aromatic heterocyclic halides with aromatic heterocycles. In previous papers, palladium-mediated cross-coupling reactions of 2-chloropyrazines with indoles,[5,6] ethylenes,[7] acetylenes,[8,9] and organometallics [10-12] were reported and in which the reactions of aryl bromides with π-sufficient aromatic heterocycles in the presence of Pd(0) catalyst were also discussed.[13] These coupling reactions proceeded regioselectively without conversion of aromatic heterocycles such as indoles, furan, thiophene, benzo[*b*]furan and benzo[*b*]thiophene to the corresponding organometallic reagents. In this study, we report the palladium-catalyzed cross-coupling reactions between 2-chloropyrazines and aromatic heterocycles.

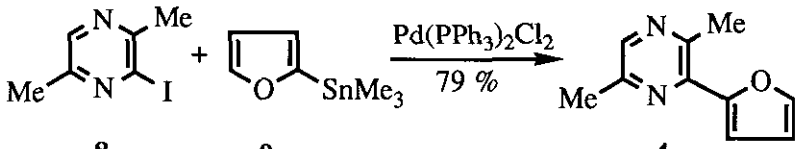
3,6-Dialkyl-2-chloropyrazines (**1a-c**) were reacted with π-sufficient aromatic heterocycles such as furan (**2**), thiophene (**3**), pyrroles (**11, 12** and **16**), benzo[*b*]furan (**22**) and benzo[*b*]thiophene (**23**) to give the corresponding coupling products in moderate to good yields (Schemes 1, 4, 5 and 7, Tables 1-4).

Scheme 1



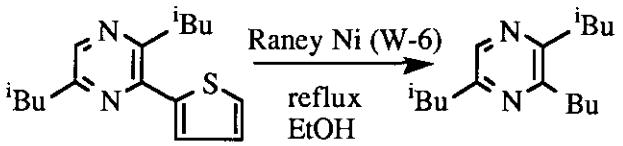
R = Me **1a** X = O **2** X = O **4a-c** X = O **5b,c**
Et **1b** S **3** S **6a-c** S **7c**
^{i}Bu **1c**

Scheme 2



8 **9** **4a**

Scheme 3



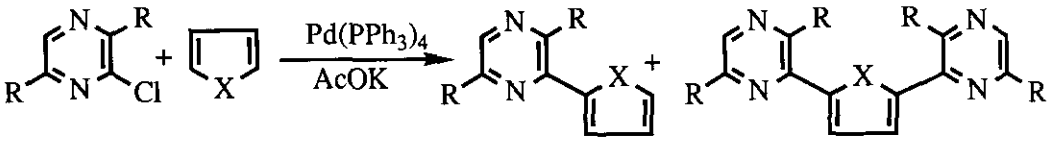
6c **10**

In the reactions of chloropyrazines with furan (**2**), thiophene (**3**) and pyrrole (**11**), disubstituted heterocycles (**5b, c, 7c** and **14 a-c**) were also obtained though in low yields. These coupling reactions occurred almost regioselectively. However, on using *N*-phenylsulfonylpyrrole (**16**) as the reaction substrate, a mixture of regioisomers (**17** and **18**) which could not be separated, was obtained. The ratio of **17** to **18** was determined by ^{1}H-nmr spectroscopy. The hydrolysis of a mixture of **17** and **18** with 5N aq. NaOH afforded **13** and **19**, which

could be separated by medium-pressure liquid chromatography. It is thus evident that the more bulky alkyl groups on the pyrazine ring favor the predominant production of 3-substituted pyrroles (See Table 3).

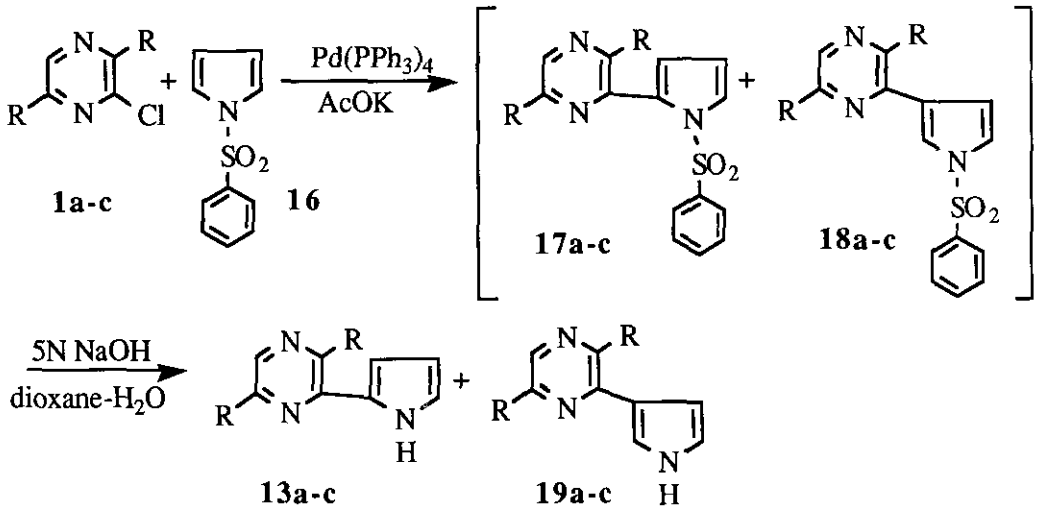
Structural determination of the coupling products was carried out as shown in the Schemes 2, 3, 6 and 8. Compounds (**4a**) and (**15a**) were identified based on specimens prepared *via* an alternative method.[14,15]

Scheme 4



1a-c X = NH **11** NMe **12** X = NH **13a-c** NMe **15a-c** X = NH **14a-c**

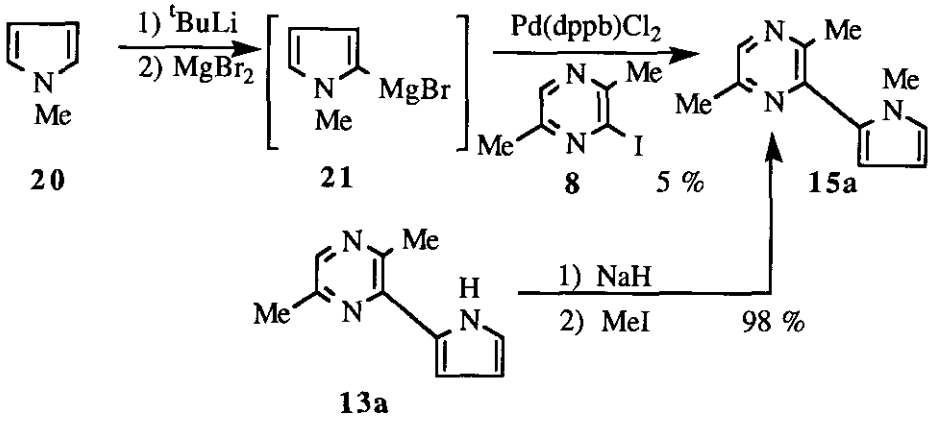
Scheme 5



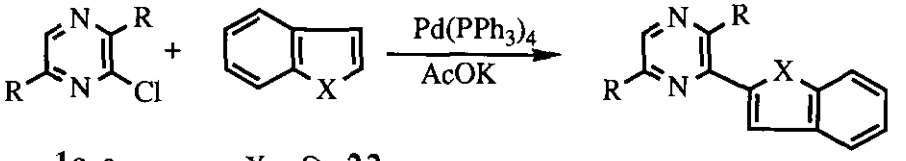
1a-c **16** **17a-c** **18a-c** **13a-c** **19a-c**

Compound (**13a**) was methylated to give **15a** in 98 % yield, thus showing **13a** to be a 2-substituted pyrrole. Since **6c** and **25a** were desulfurized using Raney Ni (W-6) in EtOH to give **10** and **26** in high yields, the structures of **6c** and **25a** were established deductively. In the 400 MHz ^{1}H-nmr spectra, the structure of **24** was determined based on observation of long range coupling between 3-H and 7-H.[16]

Scheme 6

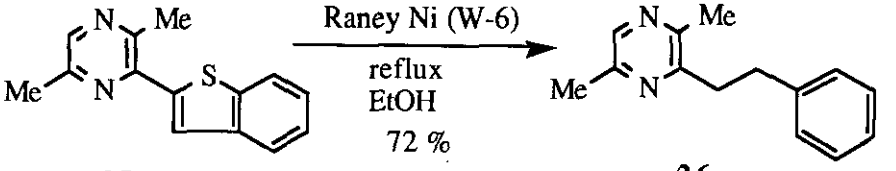


Scheme 7



1a-c

Scheme 8



25a 26

Table 1. Reactions of 2-Chloropyrazines (**1a-c**) with Furan (**2**) and Thiophene (**3**)

1	X	Product (Yield %)
1a	O	**4a** (75)
	S	**6a** (77)
1b	O	**4b** (63), **5b** (16)
	S	**6b** (70)
1c	O	**4c** (55), **5c** (22)
	S	**6c** (82), **7c** (9)

Table 2. Reactions of 2-Chloropyrazines (**1a-c**) with Pyrrole (**11**) and *N*-Methylpyrrole (**12**)

1	X	Product (Yield %)
1a	NH	**13a** (25), **14a** (14)
	NMe	**15a** (28)
1b	NH	**13b** (28), **14b** (27)
	NMe	**15b** (25)
1c	NH	**13c** (29), **14c** (25)
	NMe	**15c** (25)

Table 3. Reactions of 2-Chloropyrazines (**1a-c**) with *N*-Phenylsulfonylpyrrole (**16**)

1	Yield (%) of a mixture of 17 and 18	17:18*	13	19
1a	41	1:1	23	36
1b	40	2:3	29	59
1c	44	2:5	15	62

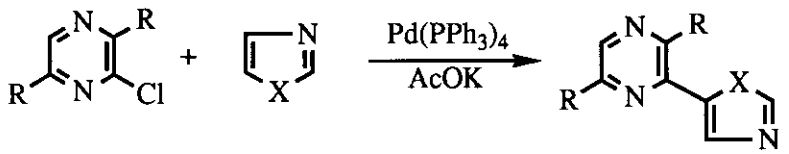
* Ratios were determined from ^{1}H-nmr spectral data.

Table 4. Reactions of 2-Chloropyrazines (**1a-c**) with Benzo[*b*]furan (**22**) and Benzo[*b*]thiophene (**23**)

1	X	Product (Yield %)
1a	O	**24a** (54)
	S	**25a** (81)
1b	O	**24b** (45)
	S	**25b** (71)
1c	O	**24c** (68)
	S	**25c** (72)

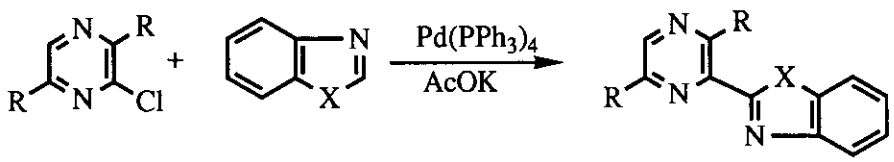
Examination was then made of the reactions of 3,6-dialkyl-2-chloropyrazines (**1a-c**) with azoles. In the presence of $Pd(PPh_3)_4$, azoles such as oxazole (**27**), thiazole (**28**), benz[*b*]oxazole (**31**), benzo[*b*]thiazole (**32**) and *N*-methylimidazoles (**35-38**) were treated with 3,6-dialkyl-2-chloropyrazines (**1a-c**) so that the corresponding coupling compounds were obtained in moderate to good yields (Schemes 9-11, Tables 5-7).

Scheme 9



1a-c X = O **27**, S **28** → X = O **29a-c**, S **30a-c**

Scheme 10



1a-c X = O **31**, S **32** → X = O **33a-c**, S **34a-c**

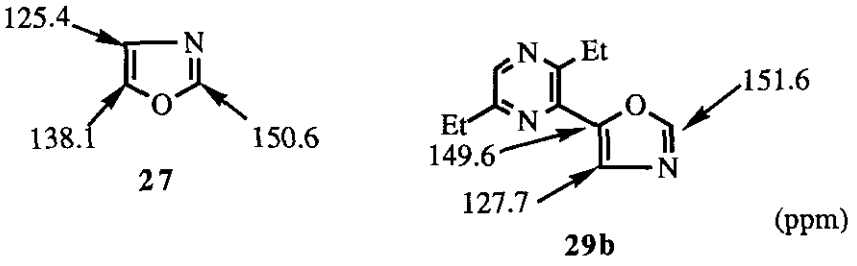
Table 5. Reactions of 2-Chloropyrazines (**1a-c**) with Oxazole (**27**) and Thiazole (**28**)

1	X	Product (Yield %)
1a	O	**29a** (72)
	S	**30a** (61)
1b	O	**29b** (80)
	S	**30b** (69)
1c	O	**29c** (68)
	S	**30c** (73)

Table 6. Reactions of 2-Chloropyrazines (**1a-c**) with Benz[*b*]oxazole (**31**) and Benzo[*b*]thiazole (**32**)

1	X	Product (Yield %)
1a	O	**33a** (52)
	S	**34a** (43)
1b	O	**33b** (65)
	S	**34b** (59)
1c	O	**33c** (83)
	S	**34c** (68)

Figure 1 ^{13}**C-Nmr Data of Oxazole (27) and 3,5-Diethyl-2-(5-oxazolyl)pyrazine (29b)**



Scheme 11

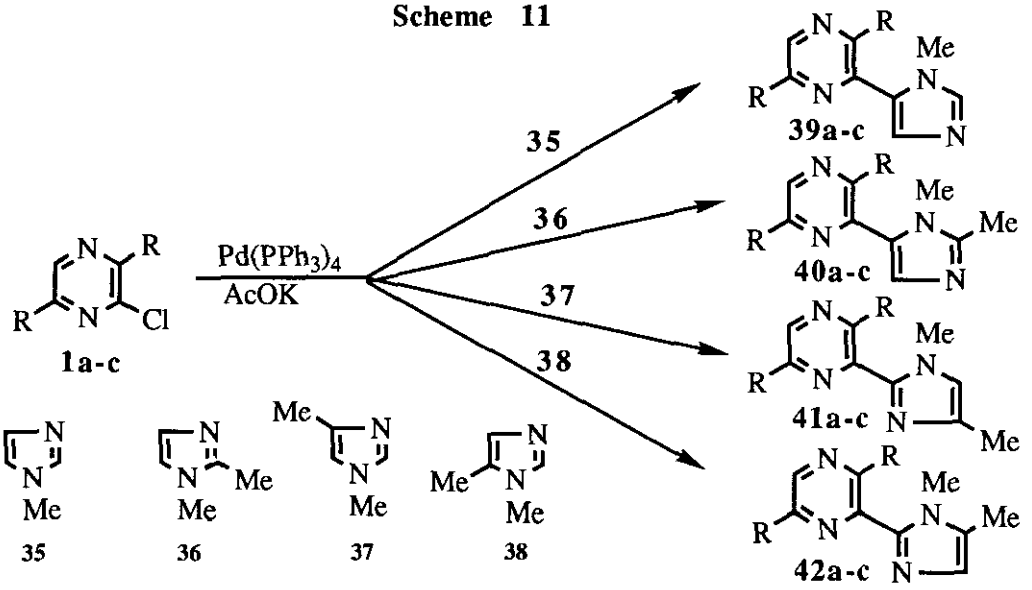
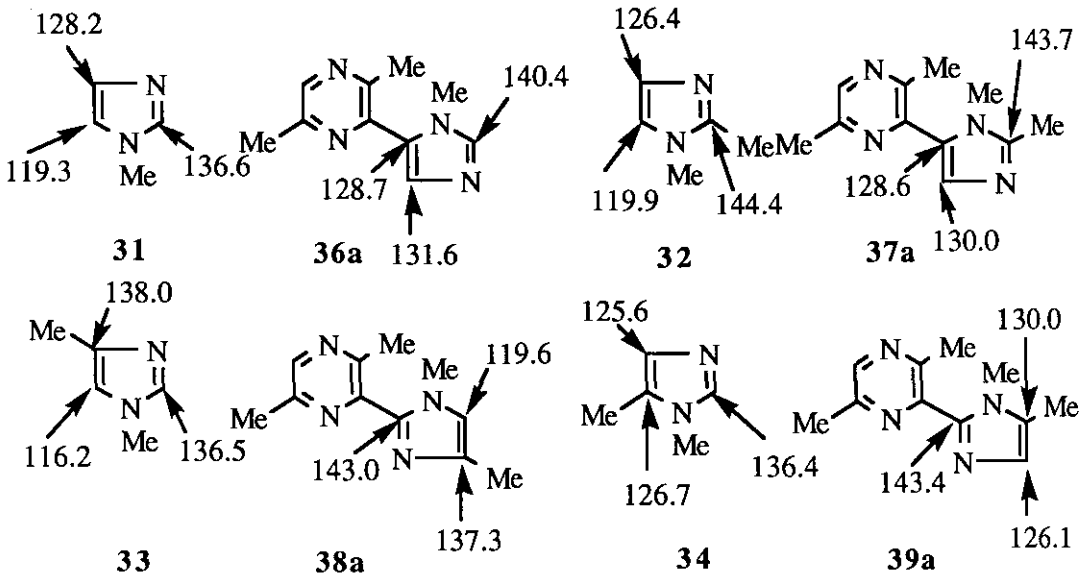


Table 7. Reactions of 2-Chloropyrazines (**1a-c**) with *N*-methylimidazoles (**35-38**)

1	*N*-Methylimidazole	Product (Yield %)
1a	**35**	**39a** (44)
	36	**40a** (62)
	37	**41a** (23)
	38	**42a** (32)
1b	**35**	**39b** (41)
	36	**40b** (83)
	37	**41b** (36)
	38	**42b** (43)
1c	**35**	**39c** (40)
	36	**40c** (77)
	37	**41c** (44)
	38	**42c** (39)

Figure 2 ^{13}C-Nmr Data of *N*-Methylimidazoles (35-38) and Their Coupling Products (39a-42a)



The structure of **29b** was established from ^{13}C-nmr spectral data (Figure 1). Assignment of the carbons of **29b** was made based on C-H COSY and HMBC spectral data. In the ^{13}C-nmr spectra of **29b**, the signal due to 5-C was found in a field lower than that due to 5-C in the unsubstituted oxazole ring.[18] It was thus considered that **29b** had been substituted at the 5-position. The structure of compounds (**30a-c**) was determined from 400 MHz ^{1}H-nmr spectral data. It was already known that the coupling between 4-H and 2- or 5-H in a thiazole ring was observed, but not between 2-H and 4-H.[17] In the ^{1}H-nmr spectra of compounds (**30a-c**), two singlets on the thiazole ring could be detected. Thus **30a-c** may possibly be 5-substituted thiazoles. Finally, the structural determination of **36a-39a** was made on the basis of ^{13}C-nmr spectral data (Figure 2). In all cases, chemical shifts due to the carbon joined to the pyrazine ring were observed in a field lower than that of the corresponding *N*-methylimidazoles (**31-34**).[19]

Table 8. Physical Properties and Analytical Data of Compounds

Compound	mp (°C) or bp* (°C/torr)	Molecular Formula	Anal. (Calcd); C,H,N (Found); C,H,N	Ms (m/z) (M^+)	^{1}H-Nmr** ($CDCl_3$, δ)
4a	95-100 / 3	$C_{10}H_{10}N_2O$	68.95 5.79 16.08 68.66 5.80 15.96	174	2.50 (3H, s), 2.70 (3H, s), 6.50 (1H, dd, J = 3.5 and 2.0 Hz), 6.95 (1H, dd, J = 3.5 and 1.0 Hz), 7.57 (1H, dd, J = 2.0 and 1.0 Hz), 8.13 (1H, s)
4b	115-120 / 3	$C_{12}H_{14}N_2O$	71.25 6.98 13.85 71.08 7.01 13.84	202	1.30 (6H, t, J = 7.0 Hz), 2.80 (2H, q, J = 7.0 Hz), 3.08 (2H, q, J = 7.0 Hz), 6.53 (1H, dd, J = 3.2 and 2.0 Hz), 7.03 (1H, dd, J = 3.2 and 0.8 Hz), 7.58 (1H, dd, J = 2.0 and 0.8 Hz), 8.27 (1H, s)
4c	138-143 / 2	$C_{16}H_{22}N_2O$	74.38 8.58 10.84 74.31 8.65 10.85	258	0.90 (6H, d, J = 7.5 Hz), 0.93 (6H, d, J = 7.5 Hz), 2.10 (2H, m), 2.62 (2H, d, J = 7.5 Hz), 2.97 (2H, d, J = 7.5 Hz), 6.48 (1H, dd, J = 3.8 and 2.0 Hz), 6.98 (1H, dd, J = 3.8 and 0.8 Hz), 7.53 (1H, dd, J = 2.0 and 0.8 Hz), 8.15 (1H, s)
5b	64-65 (MeOH-H_2O)	$C_{20}H_{24}N_4O$	71.40 7.19 16.60 71.57 7.18 16.78	336	1.35 (12H, t, J = 7.5 Hz), 2.85 (4H, q, J = 7.5 Hz), 3.22 (4H, q, J = 7.5 Hz), 7.25 (2H, s), 8.33 (2H, s)
5c	166 / 0.07	$C_{28}H_{40}N_4O$	74.96 8.99 12.49 75.21 9.15 12.66	448	0.95 (12H, d, J = 7.5 Hz), 0.97 (12H, d, J = 7.5 Hz), 2.17 (4H, m, J = 7.0 Hz), 2.67 (4H, d, J = 7.0 Hz), 3.07 (4H, d, J = 7.0 Hz), 7.12 (2H, s), 8.17 (2H, s)
6a	64-65 / 0.05	$C_{10}H_{10}N_2S$	63.12 5.30 14.72 63.27 5.31 14.72	190	2.47 (3H, s), 2.70 (3H, s), 7.07 (1H, dd, J = 6.0 and 3.8 Hz), 7.40 (1H, dd, J = 6.0 and 0.8 Hz), 7.48 (1H, dd, J = 3.8 and 0.8 Hz), 8.15 (1H, s)
6b	125-130 / 2	$C_{12}H_{14}N_2S$	66.01 6.47 12.83 65.80 6.45 12.76	218	1.30 (3H, t, J = 7.0 Hz), 1.32 (3H, t, J = 7.0 Hz), 2.80 (2H, q, J = 7.0 Hz), 3.05 (2H, q, J = 7.0 Hz), 7.12 (1H, dd, J = 5.3 and 3.8 Hz), 7.45 (1H, dd, J = 5.3 and 1.5 Hz), 7.50 (1H, dd, J = 3.8 and 1.5 Hz), 8.28 (1H, s)

6c	135-139 / 2	$C_{16}H_{22}N_2S$	70.02 70.16	8.08 8.07	10.21 10.21	274	0.92 (6H, d, J = 7.0 Hz), 0.93 (6H, d, J = 7.0 Hz), 2.17 (2H, m, J = 7.0 hz), 2.63 (2H, d, J = 7.0 Hz), 2.92 (2H, d, J = 7.0 Hz), 7.07 (1H, dd, J = 5.4 and 3.6 Hz), 7.38 (1H, dd, J = 5.4 and 0.8 Hz), 7.37 (1H, dd, J = 3.6 and 0.8 Hz), 8.17 (1H, s)
7c	54 (MeOH-H_2O)	$C_{28}H_{40}N_4S$	72.36 72.23	8.68 8.69	12.06 12.04	464	0.97 (24H, d, J = 7.0 Hz), 2.23 (4H, m, J = 7.0 Hz), 2.67 (4H, d, J = 7.0 Hz), 2.98 (4H, d, J = 7.0 Hz), 7.50 (2H, s), 8.22 (2H, s)
13a	48-50 (hexane)	$C_{10}H_{11}N_3$	69.34 69.37	6.40 6.38	24.26 24.48	173	2.50 (3H, s), 2.73 (3H, s), 6.43 (1H, m), 6.78 (1H, m), 7.03 (1H, m), 8.17 (1H, s), 10.00 (1H, br s)
13b	127-129 / 2	$C_{12}H_{15}N_3$	71.61 71.48	7.51 7.58	20.88 20.64	201	1.33 (3H, t, J = 7.0 Hz), 1.40 (3H, t, J = 7.0 Hz), 2.80 (2H, q, J = 7.0 Hz), 3.10 (2H, q, J = 7.0 Hz), 6.38 (1H, m), 6.80 (1H, m), 7.02 (1H, m), 8.22 (1H, s), 10.00 (1H, br s)
13c	135 / 0.3	$C_{16}H_{23}N_3$	74.66 74.93	9.01 9.06	16.33 16.32	257	0.97 (6H, d, J = 7.0 Hz), 1.00 (6H, d, J = 7.0 Hz), 2.27 (2H, m), 2.65 (2H, d, J = 7.0 Hz), 2.97 (2H, d, J = 7.0 Hz), 6.42 (1H, m), 6.77 (1H, m), 7.03 (1H, m), 8.17 (1H, s), 10.00 (1H, br s)
14a	184-186 (MeOH)	$C_{16}H_{17}N_5$	68.79 68.98	6.13 6.11	25.07 25.07	279	2.60 (6H, s), 2.78 (6H, s), 6.88 (2H, d, J = 3.0 Hz), 8.22 (2H, s), 11.27 (1H, br s)
14b	149-150 (MeOH)	$C_{20}H_{25}N_5$	71.61 71.43	7.51 7.43	20.88 20.90	335	1.43 (12H, t, J = 7.0 Hz), 2.88 (4H, q, J = 7.0 Hz), 3.13 (4H, q, J = 7.0 Hz), 6.88 (2H, d, J = 3Hz), 8.28 (2H, s), 11.17 (1H, br s)
14c	106-107 (MeOH)	$C_{28}H_{41}N_5$	75.12 74.96	9.23 9.42	15.65 15.37	447	1.02 (24H, d, J = 7.0 Hz), 2.32 (4H, m, J = 7.0 Hz), 2.72 (4H, d, J = 7.0 Hz), 3.00 (4H, d, J = 7.0 Hz), 6.87 (2H, d, J = 3.0 Hz), 8.23 (2H, s), 11.07 (1H, br s)
15a	104-105 (hexane)	$C_{11}H_{13}N_3$	70.56 70.67	7.00 7.02	22.44 22.47	187	2.53 (3H, s), 2.63 (3H, s), 3.73 (3H, s), 6.18 (1H, m), 6.42 (1H, m), 6.75 (1H, m), 8.20 (1H, s)

15b	98-101 / 2	$C_{13}H_{17}N_3$	72.52 72.25	7.96 7.97	19.52 19.23	215	1.27 (3H, t, J = 7.0 Hz), 1.33 (3H, t, J = 7.0 Hz), 2.82 (2H, q, J = 7.0 Hz), 2.93 (2H, q, J = 7.0 Hz), 3.68 (3H, s), 6.18 (1H, m), 6.35 (1H, m), 6.73 (1H, m), 8.25 (1H, s)
15c	123-126 / 1	$C_{17}H_{25}N_3$	75.23 75.48	9.28 9.52	15.48 15.31	271	0.83 (6H, d, J = 7.0 Hz), 0.98 (6H, d, J = 7.0 Hz), 2.17 (2H, m), 2.67 (2H, d, J = 7.0 Hz), 2.83 (2H, d, J = 7.0 Hz), 3.61 (3H, s), 6.20 (1H, m), 6.33 (1H, m), 6.73 (1H, m), 8.22 (1H, s)
19a	141-142 (cyclohexane)	$C_{10}H_{11}N_3$	69.34 69.29	6.40 6.39	24.26 24.00	173	2.50 (3H, s), 2.67 (3H, s), 6.75 (2H, m), 7.22 (1H, m), 8.08 (1H, s), 9.33 (1H, br s)
19b	103-104 (cyclohexane)	$C_{12}H_{15}N_3$	71.61 71.61	7.51 7.57	20.88 20.84	201	1.30 (6H, t, J = 7.0 Hz), 2.78 (2H, q, J = 7.0 Hz), 2.98 (2H, q, J = 7.0 Hz), 6.67 (1H, m), 6.78 (1H, m), 7.18 (1H, m), 8.13 (1H, s), 8.87 (1H, br s)
19c	126-130 / 0.02	$C_{16}H_{23}N_3$	74.66 74.73	9.01 9.04	16.33 16.56	257	0.90 (6H, d, J = 7.0 Hz), 0.95 (6H, d, J = 7.0 Hz), 2.17 (2H, m), 2.66 (2H, d, J = 7.0 hz), 2.92 (2H, d, J = 7.0 Hz), 6.72 (1H, m), 6.83 (1H, m), 7.23 (1H, m), 8.18 (1H, s), 9.10 (1H, br s)
24a	76-77 (^{i}PrOH)	$C_{14}H_{12}N_2O$	74.99 74.80	5.38 5.41	12.49 12.52	224	2.62 (3H, s), 2.89 (3H, s), 7.28 (1H, td, J = 7.2 and 0.9 Hz), 7.36 (1H, td, J = 7.2 and 1.3 Hz), 7.40 (1H, d, J = 7.7 Hz), 7.61 (1H, d, J = 8.2 Hz), 7.67 (1H, d, J = 7.7 Hz), 8.32 (1H, s)
24b	50-51 (^{i}PrOH)	$C_{16}H_{16}N_2O$	76.16 76.14	6.39 6.45	11.10 11.03	252	1.39 (6H, t, J = 7.5 Hz), 2.90 (2H, q, J = 7.6 Hz), 3.24 (2H, q, J = 7.5 Hz), 7.28 (1H, td, J = 7.3 and 0.9 Hz), 7.35 (1H, td, J = 8.2 and 1.3 Hz), 7.42 (1H, d, J = 0.9 Hz), 7.59 (1H, d, J = 8.2 Hz), 7.66 (1H, d, J = 7.6 Hz), 8.37 (1H, s)
24c	170-175 / 0.05	$C_{20}H_{24}N_2O$	77.88 77.82	7.84 7.89	9.08 9.07	308	0.97 (6H, d, J = 8.2 Hz), 0.99 (6H, d, J = 8.2 Hz), 2.18 (2H, m), 2.72 (2H, d, J = 7.2 Hz), 3.14 (2H d, J = 7.1 Hz), 7.28 (1H, td, J = 7.3 and 1.3 Hz), 7.35 (1H, td, J = 7.2 and 1.3 Hz), 7.43 (1H, d, J = 0.6

					Hz), 7.57 (1H, d, J = 8.1 Hz), 7.66 (1H, d, J = 7.6 Hz) 8.31 (1H, s)
25a	91-92 (EtOH)	$C_{14}H_{12}N_2S$	69.97 5.03 11.66 69.76 5.06 11.59	240	2.59 (3H, s), 2.88 (3H, s), 7.37 (2H, m), 7.76 (1H, s), 7.85 (2H, m), 8.27 (1H, s)
25b	46-48 (hexane)	$C_{16}H_{16}N_2S$	71.60 6.01 10.44 71.57 6.02 10.35	268	1.39 (3H, t, J = 7.6 Hz), 1.43 (3H, t, J = 7.5 Hz), 2.88 (2H, q, J = 7.6 Hz), 3.18 (2H, q, J = 7.5 Hz), 7.40 (2H, m), 7.73 (1H, s), 7.80 (2H, m), 8.33 (1H, s)
25c	166-170 / 0.05	$C_{20}H_{24}N_2S$	74.03 7.46 8.63 73.99 7.47 8.68	324	0.98 (6H, d, J = 7.1 Hz), 1.00 (6H, d, J = 6.6 Hz), 2.21 (1H, m), 2.31 (1H, m), 2.71 (2H, d, J = 7.1 Hz), 3.05 (2H, d, J = 7.1 Hz), 7.37 (2H, m), 7.69 (1H, s), 7.84 (2H, m), 8.28 (1H, s)
29a	103 (MeOH)	$C_9H_9N_3O$	61.70 5.18 23.99 61.67 5.21 23.95	175	2.60 (3H, s), 2.76 (3H, s), 7.66 (1H, s), 8.07 (1H, s), 8.32 (1H, s)
29b	95-100 / 0.05	$C_{11}H_{13}N_3O$	65.00 6.45 20.68 64.72 6.43 20.38	203	1.35 (3H, t, J = 7.5 Hz), 1.36 (3H, t, J = 7.6 Hz), 2.88 (2H, q, J = 7.6 Hz), 3.07 (2H, q, J = 7.5 Hz), 7.67 (1H, s), 8.05 (1H, s), 8.38 (1H, s)
29c	148 / 1	$C_{15}H_{21}N_3O$	69.46 8.16 16.21 69.18 8.16 16.07	259	0.95 (6H, d, J = 6.6 Hz), 0.96 (6H, d, J = 6.6 Hz), 2.12 (1H, m), 2.13 (1H, m), 2.69 (2H, d, J = 7.2 Hz), 2.94 (2H, d, J = 7.1 Hz), 7.65 (1H, s), 8.04 (1H, s), 8.31 (1H, s)
30a	110-115 / 0.06	$C_9H_9N_3S$	56.52 4.74 21.97 56.55 4.74 21.74	191	2.56 (3H, s), 2.79 (3H, s), 8.28 (1H, s), 8.31 (1H, s), 8.90 (1H, s)
30b	44 (hexane)	$C_{11}H_{13}N_3S$	60.24 5.98 19.16 60.25 5.89 18.97	219	1.35 (3H, d, J = 7.6 Hz), 1.39 (3H, d, J = 7.5 Hz), 2.85 (2H, q, J = 7.6 Hz), 3.08 (2H, q, J = 7.5 Hz), 8.28 (1H, s), 8.34 (1H, s), 8.89 (1H, s)
30c	38 (148 / 2)	$C_{15}H_{21}N_3S$	65.41 7.69 15.26 65.23 7.76 15.06	275	0.97 (12H, d, J = 6.6 Hz), 2.15 (1H, m), 2.23 (1H, m), 2.67 (2H, d, J = 7.2 Hz), 2.94 (2H, d, J = 7.2 Hz), 8.25 (1H, s), 8.28 (1H, s), 8.89 (1H, s)

33a	106-107 (MeOH)	$C_{13}H_{11}N_3O$	69.32 69.46	4.92 4.88	18.66 18.56	225	2.63 (3H, s), 3.01 (3H, s), 7.39 (2H, m), 7.66 (1H, m), 7.83 (1H, m), 8.46 (1H, s)
33b	120-121 (MeOH)	$C_{15}H_{15}N_3O$	71.12 71.17	5.97 5.93	16.59 16.63	253	1.41 (6H, t, J = 7.5 Hz), 2.98 (2H, q, J = 7.5 Hz), 3.47 (2H, q, J = 7.5 Hz), 7.44 (2H, m), 7.71 (1H, m), 7.89 (1H, m), 8.56 (1H, s)
33c	58-59 (MeOH)	$C_{19}H_{23}N_3O$	73.75 73.60	7.49 7.55	13.58 13.49	309	0.94 (6H, d, J = 6.9 Hz), 0.98 (6H, d, J = 6.9 Hz), 2.19 (2H, m), 2.78 (2H, d, J = 6.9 Hz), 3.32 (2H, d, J = 6.9 Hz), 7.36 (2H, m), 7.68 (1H, m), 7.85 (1H, m), 8.45 (1H, s)
34a	115-116 (MeOH)	$C_{13}H_{11}N_3S$	64.70 64.65	4.59 4.56	17.42 17.46	241	2.60 (3H, s), 3.10 (3H, s), 7.45 (2H, m), 7.93 (1H, m), 8.12 (1H, m), 8.39 (1H, s)
34b	106-107 (MeOH)	$C_{15}H_{15}N_3S$	66.88 66.84	5.61 5.49	15.60 15.67	269	1.37 (6H, t, J = 7.5 Hz), 2.86 (2H, q, J = 7.5 Hz), 3.57 (2H, q, J = 7.5 Hz), 7.41 (2H, m), 7.82 (1H, m), 8.08 (1H, m), 8.41 (1H, s)
34c	76 (MeOH)	$C_{19}H_{23}N_3S$	70.11 70.19	7.12 7.08	12.91 13.01	325	0.98 (12H, d, J = 6.6 Hz), 2.23 (2H, m), 2.70 (2H, d, J = 6.6 Hz), 3.45 (2H, d, J = 6.6 Hz), 7.42 (2H, m), 7.90 (1H, m), 8.06 (1H, m), 8.35 (1H, s)
39a	99-101 (cyclohexane)	$C_{10}H_{12}N_4$	63.81 63.76	6.43 6.36	29.77 29.80	188	2.47 (3H, s), 2.57 (3H, s), 3.70 (3H, s), 7.27 (1H, s), 7.50 (1H, s), 8.20 (1H, s)
39b	120-125 / 4	$C_{12}H_{16}N_4$	66.64 66.36	7.46 7.45	25.91 25.91	216	1.33 (3H, d, J = 7.0 Hz), 1.37 (3H, d, J = 7.0 Hz), 2.92 (2H, q, J = 7.0 Hz), 3.03 (2H, q, J = 7.0 Hz), 3.87 (3H, s), 7.48 (1H, s), 7.77 (1H, s), 8.53 (1H, s)
39c	145-150 / 2	$C_{16}H_{24}N_4$	70.55 70.49	8.88 8.95	20.57 20.56	272	0.83 (6H, d, J = 7.0 Hz), 0.93 (6H, d, J = 7.0 Hz), 2.10 (2H, m), 2.65 (2H, d, J = 7.0 Hz), 2.80 (2H, d, J = 7.0 Hz), 3.65 (3H, s), 7.20 (1H, s), 7.50 (1H, s), 8.20 (1H, s)
40a	115 / 0.07	$C_{11}H_{14}N_4$	65.32 65.04	6.98 7.00	27.70 27.46	202	2.43 (3H, s), 2.53 (3H, s), 2.60 (3H, s), 3.62 (3H, s), 7.17 (1H, s), 8.20 (1H, s)

40b	133 / 0.05	$C_{13}H_{18}N_4$	67.79 67.60	7.88 7.84	24.33 24.13	230	1.27 (3H, t, J = 7.5 Hz), 1.32 (3H, t, J = 7.5 Hz), 2.10 (3H, s), 2.82 (2H, q, J = 7.5 Hz), 2.92 (2H, q, J = 7.5 Hz), 3.60 (3H, s), 7.13 (1H, s), 8.28 (1H, s)
40c	130-135 / 0.06	$C_{17}H_{26}N_4$	71.29 71.12	9.15 9.13	19.56 19.41	286	0.82 (6H, d, J = 7.5 Hz), 0.92 (6H, d, J = 7.5 Hz), 2.08 (2H, m), 2.42 (3H, s), 2.63 (2H, d, J = 7.5 Hz), 2.77 (2H, J = 7.5 Hz), 3.50 (3H, s), 7.08 (1H, s), 8.25 (1H, s)
41a	79-80 (hexane)	$C_{11}H_{14}N_4$	65.32 65.57	6.98 6.99	27.70 27.51	202	2.25 (3H, s), 2.47 (3H, s), 2.68 (3H, s), 3.67 (3H, s), 6.68 (1H, s), 8.30 (1H, s)
41b	105 / 0.04	$C_{13}H_{18}N_4$	67.79 67.58	7.88 7.98	24.33 24.47	230	1.20 (3H, t, J = 7.5 Hz), 1.30 (3H, t, J = 7.5 Hz), 2.23 (3H, s), 2.80 (2H, q, J = 7.5 Hz), 3.08 (2H, q, J = 7.5 Hz), 3.67 (3H, s), 6.67 (1H, s), 8.32 (1H, s)
41c	105 / 0.02	$C_{17}H_{26}N_4$	71.29 71.43	9.15 9.15	19.56 19.82	286	0.82 (6H, d, J = 7.5 Hz), 0.93 (6H, d, J = 7.5 Hz), 2.15 (2H, m), 2.27 (3H, s), 2.67 (2H, d, J = 7.5 Hz), 3.05 (2H, d, J = 7.5 Hz), 3.67 (3H, s), 6.72 (1H, s), 8.32 (1H, s)
42a	61-62 (hexane)	$C_{11}H_{14}N_4$	65.32 65.23	6.98 6.80	27.70 27.85	202	2.27 (3H, s), 2.53 (3H, s), 2.73 (3H, s), 3.67 (3H, s), 6.95 (1H, s), 8.33 (1H, s)
42b	128-129 / 0.04	$C_{13}H_{18}N_4$	67.79 67.83	7.88 7.83	24.33 24.42	230	1.23 (3H, t, J = 7.5 Hz), 1.30 (3H, t, J = 7.5 Hz), 2.25 (3H, s), 2.82 (2H, q, J = 7.5 Hz), 3.10 (2H, q, J = 7.5 Hz), 3.60 (3H, s), 6.90 (1H, s), 8.33 (1H, s)
42c	139 / 0.04	$C_{17}H_{26}N_4$	71.29 71.18	9.15 9.12	19.56 19.28	286	0.75 (6H, d, J = 7.5 Hz), 0.90 (6H, d, J = 7.5 Hz), 2.00 (2H, m), 2.23 (3H, s), 2.62 (2H, d, J = 7.5 Hz), 2.98 (2H, d, J = 7.5 Hz), 3.53 (3H, s), 6.87 (1H, s), 8.28 (1H, s)

* Boiling points are the values determined in an oil bath.

** ^{1}H-Nmr spectral data of **4, 5, 6, 7, 13, 14, 15, 19, 33, 34** and **39-42** were obtained with the 90 MHz nmr spectrometer, and those of **24, 25, 29** and **30** were measured with the 400 MHz nmr spectrometer.

EXPERIMENTAL

No correction are made for melting or boiling points. ^{1}H-Nmr spectral data were obtained with a Varian EM-390 or a Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. ^{13}C-Nmr spectral data were obtained with a Brucker AM-400 in $CDCl_3$. Medium-pressure column chromatography was conducted using a UVILOG ALPC-100 as the pump, UVILOG 5IIIa as the UV detector (Oyo Bunko Kiki Ltd., Tokyo) and Kiesel gel 60 (Merck AG, Darmstadt) as the packing material. Mass spectral data were obtained with a Hitachi M-80 spectrometer.

General Procedure for Reactions of 3,6-Dialkyl-2-chloropyrazines (**1a-c**) with Aromatic Heterocycles

A mixture of a 2-chloro-3,6-dialkylpyrazine (**1a-c**) (2 mmol), an aromatic heterocycles (2.4 mmol),*a AcOK (294 mg, 3 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) in *N*,*N*-dimethylacetamide (5 ml) was refluxed for 6 h.*b*c The solvent was removed by distillation *in vacuo*. The residue thus obtained was triturated with H_2O (10 ml) and extracted with Et_2O (20 ml X 3). The Et_2O extract was dried with Na_2SO_4 and concentrated. The crude product was purified by medium-pressure liquid chromatography with appropriate solvents (ex. hexane-Et_2O, hexane-CH_2Cl_2, and hexane-AcOEt) to give the corresponding coupling product.

*a When furan (**2**) and thiophene (**3**) were used as a reaction substrate, excess quantity (1 ml) of these materials was required owing to their high volatility.

*b When pyrrole (**11**), *N*-phenylsulfonylpyrrole (**16**) and *N*-methylpyrazoles (**35-38**) were used, the reaction mixture was refluxed for 12 h.

*c In the case of furan (**2**), thiophene (**3**), oxazole (**27**) and thiazole (**28**), the reaction mixture was heated at 150 °C in a sealed tube.

Alternative Synthesis of Compound **4a**

To a THF solution (2 ml) of furan (136 mg, 2 mmol), 1.7 M ^{t}BuLi in pentane (1.5 ml, 2.6 mmol) was added at -78 °C under atmosphere of argon. The resulting mixture was stirred for 15 min, keeping the constant temperature. To the reaction mixture, $Pd(PPh_3)_2Cl_2$ (36 mg, 0.5 mmol) and compound **8**[20] (234 mg, 1 mmol) were added, followed by refluxing for 7 h. After the usual work-up, the residue was purified by medium-pressure column chromatography with a mixture of hexane and AcOEt (5:3) to afford **4a** as a colorless oil (137 mg, 79 %).

General Procedure for Desulfurization of **6c** and **25a**

A mixture of Raney Ni (W-6, 5 g), compound (**6c**) (516 mg, 2 mmol) and EtOH (50 ml) was refluxed for 8 h.

After the usual work-up, the residue was purified by medium-pressure liquid chromatography using a mixture of hexane and AcOEt (10:1) to give compound **10** (455 mg, 92 %).

2-Butyl-3,6-diisobutylpyrazine (**10**); colorless oil; bp 104-108 °C / 2 torr (oil bath temp.); ms: m/z 248 (M^+); ^{1}H-nmr: δ 0.90 (3H, m), 0.92 (6H, d, J = 7.0 Hz), 0.93 (6H, d, J = 7.0 Hz), 1.53 (4H, m), 2.10 (2H, m), 2.57 (2H, d, J = 7.0 Hz), 2.65 (2H, d, J = 7.0 Hz), 2.71 (2H, q, J = 7.0 Hz), 8.10 (1H, s) ppm; Anal. Calcd for $C_{16}H_{28}N_2$: C, 77.36; H, 11.36; N, 11.28. Found: C, 77.09; H, 11.25; N, 11.18.

3,6-Dimethyl-2-phenethylpyrazine (**26**); colorless oil; bp 120-125 °C / 1 torr (oil bath temp.); ms: m/z 212 (M^+); ^{1}H-nmr: δ 2.42 (3H, s), 2.51 (3H, s), 3.05 (4H, m), 7.20 (3H, m), 7.28 (2H, m), 8.17 (1H, s) ppm. Hrms Calcd for $C_{14}H_{16}N_2$: 212.131349. Observed:212.132169.

General Procedure for the Hydrolysis of a Mixture of Compound **17** and **18**

A solution of a mixture of **17** and **18** (1 mmol) in dioxane (2 ml)-MeOH (5 ml) and 5N aq. NaOH (4 ml) was stirred for 12 h at room temperature. The solvent was subsequently evaporated *in vacuo*. After the usual work-up, the residue was purified by medium-pressure column chromatography with CH_2Cl_2 to afford **13** and **19**.

Alternative Synthesis of **15a**

A mixture of compound **8**[20] (234 mg, 1 mmol), Pd(dppb)Cl_2 (12 mg, 0.02 mmol) in dry THF (5 ml) and *N*-methylpyrrolylmagnessium bromide **21** (2.5 mmol), prepared from *N*-methylpyrrole (202 mg, 2.5 mmol) in dry THF (5 ml), 1.7 M ^{t}BuLi in pentane (2 ml, 3.4 mmol) and $MgBr_2$ (60 mg, 2.6 mmol), was refluxed for 2 h. The reaction mixture was worked-up in the usual manner to give a crude product which was purified by medium-pressure liquid chromatography with a mixture of hexane and AcOEt (3:1) to give **15a** (9 mg, 5 %).

Methylation of **13a**

To a suspension of 60 % NaH (14.5 mg, 0.4 mmol) in dry THF (1 ml), a dry THF solution (1 ml) of **13a** (50 mg, 0.3 mmol) was added. The resulting mixture was stirred for 15 min at room temperature, followed by the addition of MeI (60 mg, 0.4 mmol) in dry THF (1 ml). The mixture was stirred for 1 h at room temperature. To the reaction mixture, H_2O (3 ml) was added carefully. After the usual work-up, the residue was purified by medium-pressure liquid chromatography with a mixture of hexane and AcOEt (2:1) to give **15a** (53 mg, 98 %).

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