# ALKYLATION AND ARYLATION OF PYRAZINES BY ORGANOBORON COMPOUNDS

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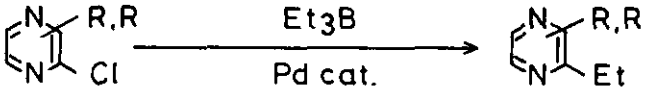
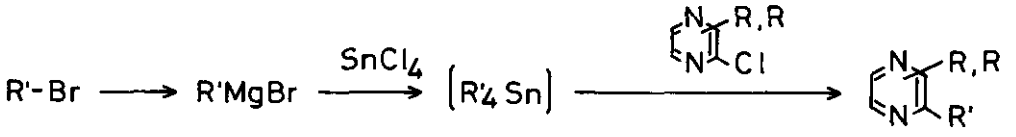
Abstract —— By palladium-catalyzed cross-coupling reactions of chloropyrazines with organoboron compounds prepared from Grignard reagents, various alkyl and aryl groups were successfully introduced into the pyrazine ring.

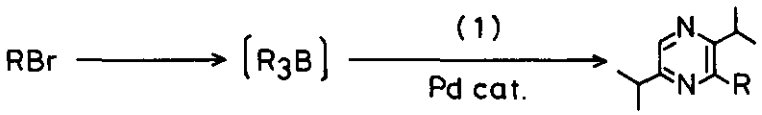
The reaction of organoborons with organic halides, such as aryl and allylic halides has been extensively studied to provide a new approach to the formation of carbon-carbon bonds[1]. Triethylboron was found to serve as a good reagent for the ethylation of pyrazines in our previous study[2]. The alkylation and arylation of pyrazines in a one pot reaction were also recently reported by us using organotin compounds prepared in situ from Grignard reagents[3]. Brown et al. found it possible to prepare organoboron compounds from Grignard reagents and boron trifluoride[4]. Making reference to their methods and results, we conducted the alkylation and arylation of pyrazines using organoboron compounds prepared from Grignard reagents. The results are presented in the following.



Two methods[5], Methods A and B as presented in Experimental section, were used for conducting the reactions. Although the reason was not evident, Method A was suited for pyrazine phenylation, while Method B for their alkylation. The results of the reactions of 2-chloro-3,6-diisopropylpyrazine (1)[6], 2-chloro-3,6-diisobutylpyrazine (2)[7] and 2-chloro-5,6-diphenylpyrazine (3)[8] with various organoborons are presented in Tables 1, 2 and 3. Satisfactory results for isopropylation could not be obtained in all cases, but the reactions were carried out successfully in others. On using organotin compounds, the results were somewhat better than those obtained in the present study.

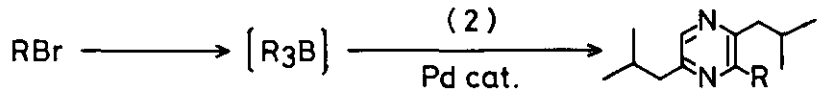
Table 1. Reactions of 2-Chloro-3,6-diisopropylpyrazine (1)[6] with Organoborons




| R | Yield (%) | |
|---|---|---|
| | Method A | Method B |
| Ph | 47[12] (32)[a] | 27[12] (9)[a] |
| n-$C_3H_7$ | 45 (15)[b] | 52 (23)[b] |
| n-$C_5H_{11}$ | 16[3] (21)[b] | 66[3] (4)[b] |
| n-$C_8H_{17}$ | 8[3] (28)[b] | 50[3] (21)[b] |

a: Starting Material b: 2,5-Diisopropylpyrazine[13]

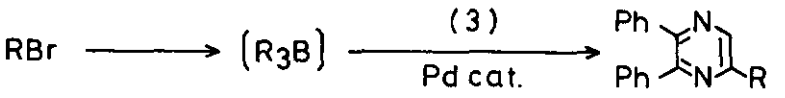
Table 2. Reactions of 2-Chloro-3,6-diisobutylpyrazine (2)[7] with Organoborons




| R | Method | Yield (%) |
|---|---|---|
| Ph | A | 48[12] (43)[a] |
| n-$C_3H_7$ | B | 54 (19)[b] |
| n-$C_5H_{11}$ | B | 44[3] (53)[b] |
| n-$C_8H_{17}$ | B | 39[3] (38)[b] |

a: Starting Material b: 2,5-Diisobutylpyrazine[14]

Table 3. Reactions of 2-Chloro-5,6-diphenylpyrazine (3)[8] with Organoborons

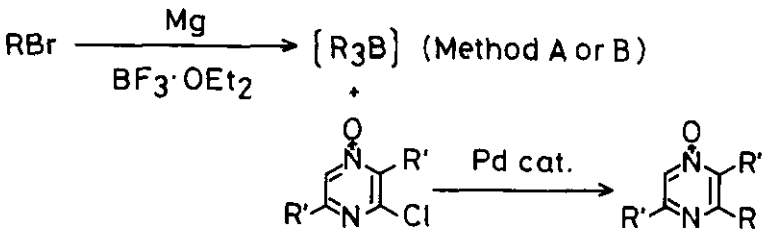



| R | Method | Yield (%) |
|---|---|---|
| Ph | A | 73[12] (16)[a] |
| n-$C_5H_{11}$ | B | 51[3] (37)[a] |
| n-$C_8H_{17}$ | B | 36[3] (36)[a] |

a: 2,3-Diphenylpyrazine[8]

Reactions of 2-chloro-3,6-diisopropylpyrazine 4-oxide (4)[9] and 2-chloro-3,6-diisobutylpyrazine 4-oxide (5)[7] with organoborons were carried out under the same conditions as above. Although the desired alkyl- and phenyl-pyrazines were obtained in both cases, yields from both compounds were not satisfactory. In the cases of 2-chloro-3,6-diisopropylpyrazine 1-oxide (6)[6] and 2-chloro-3,6-diisobutylpyrazine 1-oxide (7)[6], the phenylated products were obtained in nearly

Table 4. Reaction of 2-Chloro-3,6-diisopropylpyrazine 4-Oxide (4)[9] and 2-Chloro-3,6-diisobutylpyrazine 4-Oxide (5)[7] with Organoborons



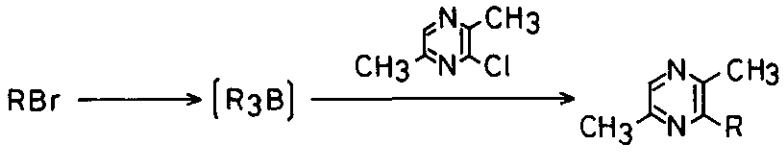

| R | Method | R' | Yield (%) |
|---|---|---|---|
| Ph | A | i-Pr | 14 (20)[a] |
| n-$C_5H_{11}$ | B | i-Pr | 47 (26)[a] |
| n-$C_8H_{17}$ | B | i-Pr | 41 (31)[a] |
| Ph | A | i-Bu | 19 (42)[b] |
| n-$C_5H_{11}$ | B | i-Bu | 41 (26)[a] |
| n-$C_8H_{17}$ | B | i-Bu | 46 (37)[a] |

a: Dechlorinated Product b: Deoxygenated Product

6-7% yield, respectively. As described above, products yields from 2-chloropyrazine N-oxides were inferior to those from reactions using organotin compounds.

Two ants pheromones, 2,5-dimethyl-3-isopentylpyrazine (8) and 2,5-dimethyl-3-(2-methylbutyl)pyrazine (9), were isolated from Rhytidoponera metallica[10]. These compounds were characterized by the reaction of 2,5-dimethylpyrazine (10)[11] with isopentyllithium and 2-methylbuthyllithium in 19 and 10% yields, respectively. Our Method B was applied to the synthesis of these pheromones (8 and 9) and both compounds were successfully synthesized by the coupling reactions of 2-chloro-3,6-dimethylpyrazine (11)[11] with the organoborons prepared from 1-bromo-3-methylbutane and 1-bromo-2-methylbutane via the corresponding Grignard reagents in 44 and 41% yields, respectively.

Table 5. Synthesis of Ants Pheromones




| R | product | Yield (%) |
|---|---|---|
| $CH_2CH_2CH(CH_3)_2$ | (8) | 44 |
| $CH(CH_3)CH_2CH(CH_3)_2$ | (9) | 41 |

In conclusion, it thus follows that organoborons prepared from Grignard compounds can be used for the alkylation and arylation of pyrazines. Although the yields are slightly less than those using organotin compounds, the reactions can be carried out quite easily and permit the alkylation and phenylation of pyrazines.

## EXPERIMENTAL

No correction was made for melting and boiling points. The following apparatus was used to obtain spectral data; ms: Hitachi M-80 spectrometer; $^1$H-nmr ($CDCl_3$/TMS): Varian EM-390 and Brucker AM-400. For liquid chromatography silca gel (230-400 mesh, Merck A. G.) was used as the packing material.

General Procedure for Conducting Alkylation and Arylation of Pyrazines and Pyrazine N-Oxides with Organoborons: Method A: To a mixture of Mg (146 mg, 6 mmol) and $BF_3 \cdot Et_2O$ (0.2 ml, 1.5 mmol) in absolute $Et_2O$ (5 ml), an alkyl bromide

or bromobenzene (ca. 7-8 mmol) was added accompanied by stirring. The reaction mixture started to reflux. After the reaction mixture had been allowed to stand for 3 h, the $Et_2O$ layer was poured into a mixture of a chloropyrazine (1 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), $K_2CO_3$ (691 mg, 5 mmol) and absolute DMF (5 ml) in a two-necked round bottomed flask through a gum seal with an injector. Refluxing was then carried out for 12 h under an argon atmosphere, followed by filtering the reaction mixture and removing the solvent by distillation in vacuo. The residue was triturated with water and extracted with $Et_2O$. The crude products were purified by medium pressure liquid chromatography using a hexane-AcOEt mixture as the developing solvent.

Method B: To a solution of Grignard reagent prepared from an alkyl or aryl bromide (ca. 7-8 mmol), Mg (146 mg, 6 mmol) and $Et_2O$ (5 ml), $BF_3 \cdot Et_2O$ (0.2 ml, 1.5 mmol) was added using ultrasonic apparatus (20 W, 30 KHz) in an argon stream. After the reaction mixture had been allowed to stand for 2 h, the $Et_2O$ layer was poured into a mixture of a chloropyrazine (1 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), $K_2CO_3$ (691 mg, 5 mmol) and DMF (5 ml) in a two-necked round bottomed flask through a gum cap with an injector. The reaction mixture was refluxed for 12 h under an argon stream and worked up as described above.

3,6-Diisopropyl-2-propylpyrazine: colorless oil, bp 40-42°C/0.4 torr; ms: m/z 206 ($M^+$), 178 ($M^+-CH_2=CH_2$); $^1$H-nmr: δ 0.97 (t, J = 7.5 Hz, 3H, $(CH_2)_2\underline{CH}_3$), 1.23 (d, J = 6.9 Hz, 6H, $CH(\underline{CH}_3)_2$), 1.26 (d, J = 6.9 Hz, 6H, $CH(\underline{CH}_3)_2$), 1.50-1.96 (m, 2H, $CH_2\underline{CH}_2CH_3$), 2.75 (t, J = 7.5 Hz, 2H, $\underline{CH}_2CH_2CH_3$), 2.75-3.40 (m, 2H, 2 x $\underline{CH}(CH_3)_2$), 8.19 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found: C, 75.72; H, 10.86; N, 13.54.

3,6-Diisobutyl-2-propylpyrazine: colorless oil; bp 65-67°C/0.06 torr; ms: m/z 234 ($M^+$), 192 ($M^+-CH_3CH=CH_2$); $^1$H-nmr: δ 0.84 (d, J = 6.6 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 0.85 (t, J = 6.9 Hz, 3H, $(CH_2)_2\underline{CH}_3$), 0.87 (d, J = 6.6 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 1.44-2.22 (m, 4H, $CH_2\underline{CH}_2CH_3$, 2 x $CH_2\underline{CH}(CH_3)_2$), 2.55 (t, J = 6.9 Hz, 2H, $\underline{CH}_2CH_2CH_3$), 2.63 (d, J = 6.6 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 2.73 (d, J = 6.6 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$, 8.05 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.95. Found: C, 76.87; H, 11.41; N, 11.76.

3,6-Diisobutyl-2-pentylpyrazine: colorless oil; 50-52°C/0.07 torr; ms: m/z 262 ($M^+$), 206 ($M^+-CH_3CH_2CH=CH_2$); $^1$H-nmr: δ 0.93 (d, J = 6.6 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 0.94 (t, J = 6.6 Hz, 3H, $(CH_2)_4\underline{CH}_3$), 0.97 (d, J = 6.6 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 1.20-1.47 (m, 4H, $CH_2CH_2(\underline{CH}_2)_2CH_3$), 1.53-2.39 (m, 4H, $CH_2\underline{CH}_2(CH_2)_2CH_3$, 2 x

$CH_2C\underline{H}(CH_3)_2$), 2.60 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.67 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.79 (t, J = 6.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 8.17 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{17}H_{30}N_2$: C, 77.80; H, 11.52; N, 10.68. Found: C, 77.61; H, 11.54; N, 10.41.

3,6-Diisobutyl-2-octylpyrazine: colorless oil; bp 102-104°C/0.06 torr; ms: m/z 304 ($M^+$), 206 ($M^+$-$CH_3(CH_2)_4CH{=}CH_2$); $^1$H-nmr: δ 0.88 (t, J = 7.0 Hz, 3H, $(CH_2)_7C\underline{H}_3$), 0.93 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.95 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.27-1.37 (m, 10H, $CH_2CH_2(C\underline{H}_2)_5CH_3$), 1.64-1.71 (m, 2H, $CH_2C\underline{H}_2(CH_2)_5CH_3$), 2.03-2.20 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.60 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.66 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.78 (t, J = 7.0 Hz, 2H, $C\underline{H}_2(CH_2)_6CH_3$), 8.14 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{20}H_{36}N_2$: C, 78.88; H, 11.92; N, 9.20. Found: C, 79.07; H, 12.04; N, 8.98.

3,6-Diisobutyl-2-pentylpyrazine 4-Oxide: colorless oil; bp 126-128°C/0.15 torr; ms: 278 ($M^+$), 261 ($M^+$-OH); $^1$H-nmr: δ 0.85 (t, J = 7.0 Hz, 3H, $(CH_2)_7C\underline{H}_3$), 0.90 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.94 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.20-1.43 (m, 4H, $CH_2CH_2(C\underline{H}_2)_2CH_3$), 1.52-1.83 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.92-2.38 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$) 2.47 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.70 (t, J = 6.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 2.78 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.82 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{17}H_{30}N_2O$: C, 73.38; H, 10.86; N, 10.06. Found: C, 73.11; H, 10.93; N, 10.02.

3,6-Diisobutyl-2-octylpyrazine 4-Oxide; colorless oil; bp 148-150°C/0.12 torr; ms: m/z 320 ($M^+$), 303 ($M^+$-OH); $^1$H-nmr: δ 0.88 (t, J = 7.0 Hz, 3H, $(CH_2)_7C\underline{H}_3$), 0.95 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.97 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.28-1.37 (m, 10H, $CH_2CH_2(C\underline{H}_2)_5CH_3$), 1.65-1.71 (m, 2H, $CH_2C\underline{H}_2(CH_2)_5CH_3$), 2.09-2.12 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.24-2.27 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.54 (t, J = 7.0 Hz, 2H, $C\underline{H}_2(CH_2)_6CH_3$), 2.80 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.81 (d, J = 6.6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.86 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C,74.71; H, 11.31; N, 8.69.

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