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FACILE SYNTHESIS OF DIARYLPYRAZINES USING SUZUKI COUPLING OF DICHLOROPYRAZINES WITH ARYL BORONIC ACIDS

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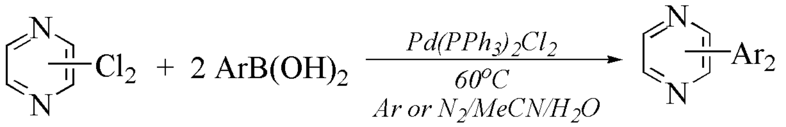
Abstract – The palladium-catalyzed coupling of dichloropyrazines with aryl boronic acids is reported. The reaction proceeds smoothly under anaerobic conditions to give moderate to good yields of the corresponding diarylpyrazines.

INTRODUCTION

Arylpyrazines are of interest due to their potential application as versatile intermediates in the synthesis of pharmaceuticals and as agrochemicals[1] and food flavorings.[2] A variety of traditional synthetic procedures have been developed for the preparation of this family of compounds based on the cyclocondensation of α-amino ketones, or related derivatives[3] and, more recently, the transition metal catalyzed Suzuki coupling of halopyrazines with arylmetals.[4] The latter strategy provides a procedure for the regiocontroled introduction of a range of aryl substitutents starting from the appropriate halopyrazine. Thus Ohta reported the coupling reaction of chloropyrazines with tetraphenyltin to form phenylpyrazines in moderate to good yields.[5] McKillop[6] and Mitchell,[7] however, noted that the coupling of aryl boronic acids with π-deficient heteroaryl chlorides including chloropyrazine was feasible but sensitive to the nature of the palladium catalyst - both authors reporting that [1,4-bis(diphenylphosphine)butane]palladium(II) dichloride was the most effective catalyst. Thompson noted that [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) diacetate was the most efficient catalyst.[8] The Suzuki coupling of halopyrazines with arylboronic acids has proven to be a useful tool for the synthesis of complex molecules.[9] The reaction has also been used in total syntheses of natural products including Dragmacidin D[10] and analogues of psoralen[11] and coelenterazine.[12] In this paper we report the synthesis of diarylpyrazines using the readily available bis(triphenylphosphine)palladium(II) dichloride as catalyst.

RESULTS AND DISCUSSION

A range of arylpyrazines were prepared by palladium-catalyzed cross coupling of chloropyrazines with arylboronic acids according to equation 1. The results are tabulated in Table 1.

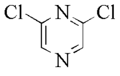
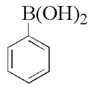
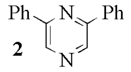
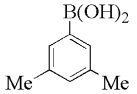
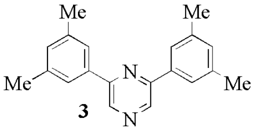
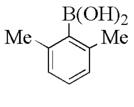
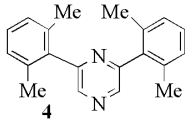
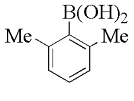
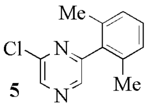
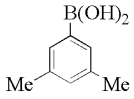
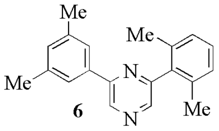
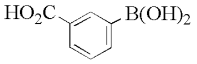
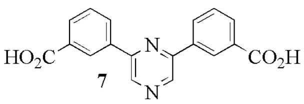
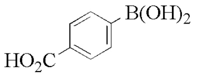
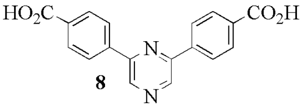
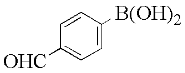
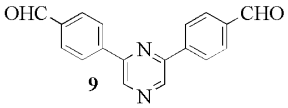
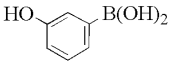
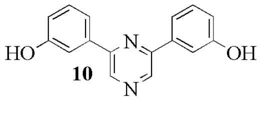
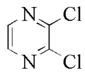
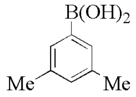
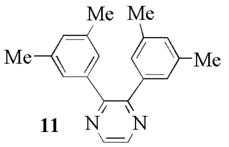
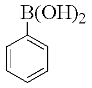
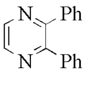
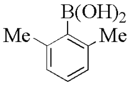
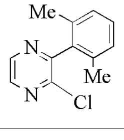


(1)

We used bis(triphenylphosphine)palladium(II) dichloride as a catalyst and performed the reaction with mild heating under basic and heterogeneous conditions in a mixture of acetonitrile and aqueous sodium carbonate. We obtained similar yields of products when tetrahydrofuran was used as the organic solvent. It is important to note that during our first trials we isolated significant amounts of biaryls, derived from the arylboronic acids, when the reaction was performed under an atmosphere of air. Thus, for example, 20-30% of biphenyl was formed during reaction of phenylboronic acid with 2,6-dichloropyrazine. This side reaction was effectively stopped when we purged the reaction mixture with argon and performed the reaction under an argon atmosphere. In this regard it is relevant to note that Moreno-Mañas reported the palladium catalyzed homocoupling of arylboronic acids to yield biaryls in an oxygen atmosphere or in air.[13] Those authors also noted that biaryl formation was significantly retarded in a nitrogen atmosphere. We were surprised to note that reaction of 2,3-dichloropyrazine with an excess of 2,6-dimethylphenylboronic acid yielded the corresponding monoarylated product as the exclusive product even after extended reaction. We isolated the product (**13**) in 52% yield. All attempts to subsequently add a second aryl group were unsuccessful. The same selectivity was not observed with arylboronic acids that did not contain the ortho methyl substituents. Thus ^{1}H NMR spectral monitoring of the reaction of 2,3-dichloropyrazine with 3,5-dimethylphenylboronic acid indicated that a mixture of mono- and diarylated pyrazine were formed during the reaction. The reaction of 2,6-dichloropyrazine with 2,6-dimethylphenylboronic acid was also monitored by ^{1}H NMR at intermediate times. This clearly indicated that the reaction was unselective and reaction with one equivalent of the arylboronic acid yielded a roughly statistical mixture of monoarylated product in about 50 % yield along with approximately 25 % of each of the monoarylated product and the unreacted dichloropyrazine. The monoarylated pyrazine (**5**) was separated by flash chromatography on silica gel and isolated in moderate yield. Subsequent coupling of the monochloropyrazine (**5**) with the isomeric boronic acid, 3,5-dimethylphenylboronic acid, gave the mixed arylpyrazine (**6**) in 84 % yield.

We believe that the selective monosubstitution shown with 2,3-dichloropyrazine is the result of the increased steric demand of the *ortho*-methyl on the aryl group that effectively blocks the adjacent reaction site. In 2,6-dichloropyrazine the two reaction sites are separated by the *N*-atom and the reaction is not selective.

Table. Reaction of dichloropyrazines with aryl boronic acids.

pyrazine	arylboronic acid	arylpyrazine	yield (%)
 **1**		 **2**	91
1		 **3**	94
1		 **4**	90
1		 **5**	90
5		 **6**	94
1		 **7**	71
1		 **8**	54
1		 **9**	68
1		 **10**	56
 **9**		 **11**	72
9		 **12**	74
9		 **13**	90

EXPERIMENTAL

Materials. The dichloropyrazines, arylboronic acids and solvents were purchased from Aldrich and used as received. The palladium catalyst was purchased from Strem. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and elemental analyses were performed by Atlantic Microlabs.

Typical experimental procedure for alkylarylboronic acids: 2,6-Dichloropyrazine (1.61 g, 10.77 mmol), phenylboronic acid (2.62 g, 21.49 mmol), sodium carbonate (2.30 g, 21.9 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.10 g, 0.14 mmol, 0.6 mol%) were added to a round bottom flask. MeCN (40 mL) and H_2O (40 mL) were then added and argon bubbled through the resultant mixture for 15 min. The mixture was heated at 70 °C under an Ar atmosphere until TLC indicated that the reaction was complete. Conventional workup followed by flash chromatography and recrystallization from ethanol yielded the product 2,6-diphenylpyrazine (**2**).[14] Characteristic physical data of the products are: *2,6-Diphenylpyrazine (**2**):* mp 86-88 °C (lit.,[1b] mp 93 °C); *2,6-Bis(3',5'-dimethylphenyl)pyrazine (**3**):* mp 111-113 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 2H), 7.73 (s, 4H), 7.12 (s, 2H), 2.43 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 151.96, 139.94, 138.54, 136.59, 131.50, 124.90, 21.43; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.35; H, 7.16; N, 9.68. *2,6-Bis(2',6'-dimethylphenyl)pyrazine (**4**):* mp 125-127 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 2H), 7.27-7.11 (m, 6H), 2.10 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 155.11, 143.20, 136.79, 135.98, 128.59, 127.59, 20.23; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.00; H, 6.98; N, 9.72. *2-Chloro-6-(2',6'-dimethylphenyl)pyrazine (**5**):* pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.45 (s, 1H), 7.26 (dd, *J*=6.4, 8.4 Hz, 1H), 7.13 (d, *J*=7.4 Hz, 1H), 2.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.17, 148.91, 143.31, 142.49, 136.20, 135.23, 129.13, 127.87, 20.26; Anal. Calcd for $C_{12}H_{11}N_2Cl$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.88; H, 5.22; N, 12.71. *2-(2',6'-Dimethylphenyl)-6-(3",5"-dimethylphenyl)pyrazine (**6**):* ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.44 (s, 1H), 7.67 (s, 2H), 7.30-7.11 (m, 4H), 2.40 (s, 6H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.52, 152.48, 143.29, 139.88, 138.59, 137.12, 136.39, 131.54, 128.66, 127.84, 124.92, 21.37, 20.44; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.10; H, 6.87; N, 9.56. *2,6-Bis(3'-carboxyphenyl)pyrazine (7):* 2,6-Dichloropyrazine (0.19 g, 1.269 mmol), 3-carboxyphenylboronic acid (0.45 g, 2.680 mmol), Na_2CO_3 (0.28 g, 2.7 mmol) and $Pd(PPh_3)_2Cl_2$ (0.025 g, 0.035 mmol, 1.3 mol %) were added to a round bottom flask. H_2O (8 mL) and MeCN (7 mL) were added and N_2 bubbled through the mixture for 20 min. The reaction was heated at 60 °C under a N_2 atmosphere for 48 h later and let cool to rt. The MeCN was removed with a rotary evaporator. The precipitate was filtered and the aqueous solution acidified with 4 mL of 1.0 M HCl and a white precipitate formed. The precipitates were combined and dissolved in 1.0 M K_2CO_3. The solution was washed with dichloromethane (2 x 20 mL) and the organic layer discarded. The aqueous phase was reacidified with

1.0 M HCl (5 mL) to precipitate the product that was recrystallized from DMSO as colorless blocks. mp >300 ^{o}C; ^{1}H NMR (C_2D_6SO) δ 9.33(s, 2H), 8.78 (s, 2H), 8.53 (d, *J*= 6.8 Hz, 2H), 8.14 (d, *J*=6.4 Hz, 2H), 7.78 (t, *J*=6.5 Hz, 2 H); ^{13}C NMR (C_2D_6SO) δ 167.1, 149.7, 140.9, 136.3, 131.8, 131.1, 130.8, 129.5, 127.6; Anal. Calcd for $C_{18}H_{12}N_2O_4.C_2H_6SO$: C, 60.29; H, 4.55; N, 6.93. Found: C, 60.26; H, 4.48; N, 6.93. *2,6-Bis(4'-carboxyphenyl)pyrazine (**8**):* A similar procedure was followed for the 4-carboxy derivative and the product was recrystallized from DMSO as a fine white powder. mp >300 ^{o}C; ^{1}H NMR (C_2D_6SO) δ 13.18 (s, 2H), 9.36 (s, 2H), 8.44 (d, *J*=6.4 Hz, 4H), 8.15 (d, *J*=6.4 Hz, 4H); ^{13}C NMR (C_2D_6SO) δ 166.96, 149.52, 141.47, 139.65, 132.02, 129.97, 127.08; Anal. Calcd for $C_{18}H_{12}N_2O_4.0.2\ H_2O$: C, 66.81; H, 3.77; N, 8.66. Found: C, 66.76; H, 4.00; N, 8.58. *2,6-Bis(4'-formylphenyl)pyrazine (**9**):* 2,6-Dichloropyrazine (0.45 g, 3.01 mmol), 4-formylphenylboronic acid (0.44 g, 2.680 mmol), Na_2CO_3 (0.28 g, 2.7 mmol) and $Pd(PPh_3)_2Cl_2$ (0.025 g, 0.035 mmol, 1.2 mol %) were added to a round bottom flask. MeCN (10 mL) and H_2O (10 mL) were added and N_2 bubbled through mixture for 20 min. The reaction was refluxed for 48 h during which time an extra 5 mL of MeCN was added. The resultant light green precipitate was filtered off allowed to dry and recrystallized from DMSO. mp 186-188 ^{o}C; ^{1}H NMR (C_2D_6SO) δ 10.14 (s, 2H), 9.43 (s, 2H), 8.56 (d, *J*=8.4 Hz, 4H), 8.14 (d, *J*=8.4 Hz, 4H); ^{13}C NMR (C_2D_6SO) δ 191.72, 150.48, 141.54, 141.31, 137.23, 130.35, 127.65; Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 73.10; H, 4.21; N, 9.25. An impurity was detected in ^{13}C NMR spectrum (142.90, 142.50, 134.80 ppm). *2,6-Bis(3'-hydroxyphenyl)pyrazine (**10**):* 2,6-Dichloropyrazine (0.45 g, 3.00 mmol), 3-hydroxyphenylboronic acid (0.90 g, 6.493 mmol), K_2CO_3 (0.45, 3.2 mmol), PPh_3 (0.034 g, 0.13 mmol) and $Pd(PPh_3)_2Cl_2$ (51.3 mg, 0.07 mmol, 1.1 mol %) were added to a round bottom flask. MeCN (12 mL) and H_2O (12 mL) were added and N_2 bubbled through mixture for 20 min. The mixture was heated at 60 °C under a N_2 atmosphere for 5 d. The precipitated product was filtered off and the remaining solution was washed with 100 mL of hexane/EtOAc (1/1). The organic layer was separated and the aqueous layer was allowed to evaporate slowly and to precipitate more product. The combined precipitate was dissolved in hot Me_2CO, filtered and reprecipitated as an off-white powder, mp 229-231 ^{o}C; ^{1}H NMR (C_2D_6SO) δ 9.04 (s, 2H), 7.76 (s, 2H), 7.71 (d, *J*=7.2 Hz, 2H), 7.40 (t, *J*=7.0 Hz, 2H), 7.01 (d, *J*=7.8 Hz, 2H), 4.7-3.6 (br m, 2H); ^{13}C NMR (C_2D_6SO) δ 158.90, 151.74, 140.75, 138.70, 130.84, 118.71, 117.72, 114.42; Anal. Calcd for $C_{18}H_{12}N_2O_4.0.2\ C_3H_6O$ (acetone): C, 72.27; H, 4.82; N, 10.15. Found: C, 72.00; H, 4.64; N, 10.48. *2,3-Bis(3',5'-dimethylphenyl)pyrazine (**11**):* mp 93-97 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 2H), 7.06 (s, 4H), 6.96 (s, 2H), 2.23 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 153.04, 141.72, 138.42, 137.50, 130.16, 127.531, 21.17; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.17; H, 7.04; N, 9.63.

2,3-Diphenylpyrazine (***12***)*:* mp 112-114°C.[14] *2-Chloro-3-(2',6'-dimethylphenyl)pyrazine* (***13***)*:* mp 104-106 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.40 (s, 1H), 7.32-12 (m, 3H), 2.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.93, 149.28, 142.58, 142.49, 135.78, 135.64, 128.99, 127.59, 19.54; Anal. Calcd for $C_{12}H_{11}N_2Cl$: C, 65.85; H, 5.07; N, 12.81. Found: C, 65.87; H, 5.09; N, 12.62.

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