A Comparison of Phenylboronic Acid and Phenyltrimethyltin in the Palladium-Catalyzed Arylation of 1,5-Dialkylimidazoles

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A comparison of phenyltrimethyltin *vs.* phenylboronic acid in the palladium-catalyzed arylation of brominated 5-methyl-1(phenylmethyl)imidazoles is described.

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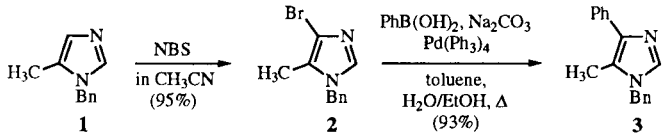
The palladium-catalyzed coupling of a haloarene and an arylstannane [1] or arylboronic acid [2] has become a method of choice in the preparation of unsymmetrical biaryl systems. The reaction is of broad scope, tolerating many different functionalities in carbocyclic arenes while also being applicable to a variety of heterocyclic substrates [3]. In the course of some synthetic studies, we have briefly examined the feasibility of palladium-catalyzed coupling when one component is a mono- or dibromo-1,5-dialkylimidazole. We report here the relative effectiveness of different palladium-catalyzed arylation conditions using such substrates.

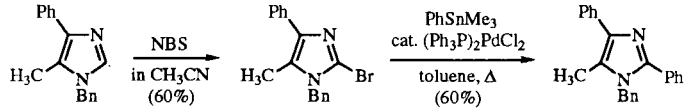
According to literature procedures [4], 5-methyl-1-(phenylmethyl)imidazole (**1**, Scheme 1) was prepared from commercially available 4-methylimidazole (Aldrich). Using this material, we first examined the arylation of the 4-position. Exposure of **1** to *N*-bromosuccinimide (NBS) afforded the 4-bromo product (**2**, 95%). We subjected this bromoimidazole to palladium-catalyzed coupling using phenylboronic acid and phenyltrimethyltin as the arylating agents. With 1.25 equivalents of phenyltrimethyltin and as much as 8 mole % of the catalyst bis(triphenylphosphine)palladium(II) chloride, the coupling could not be run to complete conversion of the starting material. At best a 20% yield of the 4-phenyl product **3** was obtained, with 51% of the bromoimidazole recovered. Much more satisfying results were obtained by using phenylboronic acid. In this case, reaction with **2** catalyzed by 6 mole % tetrakis(triphenylphosphine)-palladium(0) provided a 93% yield of **3**.

Scheme 1



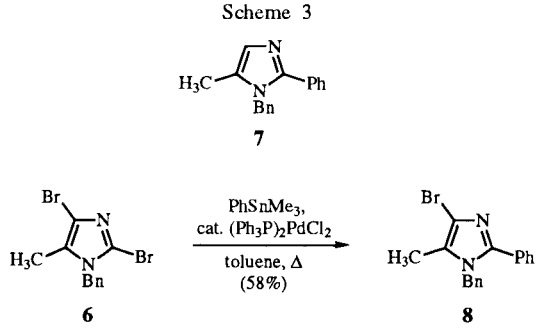
For arylation of the 2-position of **3**, this imidazole was first brominated (Scheme 2) to give **4** in 60% yield (the relative instability of **4** requires that heat be avoided during the isolation process). Phenyltrimethyltin was a satisfactory reagent in replacing the single bromine of **4**, giving a 60% yield of diphenylimidazole **5**. The use of phenylboronic acid for this transformation gave a comparable yield of **5** (57%).

Scheme 2



To achieve a regioselective arylation of **1** at the 2-position, we considered proceeding through dibromoimidazole **6** (Scheme 3). This compound is conveniently prepared from **1** in 80% yield by treatment with excess NBS. No marked regioselectivity was seen when **6** and phenylboronic acid were used in a one to one stoichiometry. We observed instead a 43% yield of diphenyl imidazole **5** as the major product. Imidazoles **3** and **7** were also obtained as minor products from this reaction in a one to three ratio. Dibromoimidazole **6** can be converted to the diphenyl product **5** in 56% yield by using two equivalents of phenylboronic acid. A useful selectivity for the 2-position was observed in the coupling between **6** and phenyltrimethyltin. This substrate/reagent combination provided a 58% yield of the desired 2-phenyl product **8**.

Scheme 3



In summary, we find that the 4-position of a 1,5-dialkylimidazole can be brominated with excellent selectivity and subsequently phenylated (boronic acid reagent)

in high yield. Alternatively, selectivity for the 2-position can be achieved *via* the dibromoimidazole using an aryltin reagent, although the yield is moderate.

EXPERIMENTAL

Melting points were determined on a Meltemp apparatus from Laboratory Devices and are uncorrected. The infrared spectra were recorded on a Nicolet 520 FT-IR spectrometer using chloroform solutions unless otherwise specified. The 300 MHz ^{1}H spectra were recorded on a Varian Gemini 300 FT-NMR spectrometer. The high resolution mass spectra were recorded on a VG Instruments 70-SE mass spectrometer. The elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

4-Bromo-5-methyl-1-(phenylmethyl)imidazole (**2**).

N-Bromosuccinimide (3.133 g, 17.6 mmoles) was added to a solution of **1** (3.018 g, 17.5 mmoles) in dry acetonitrile (400 ml) at 0°. The reaction was stirred for 30 minutes at this temperature. Pyridine (0.025 ml) was added and the mixture was concentrated *in vacuo*. Triethylamine (2.5 ml) was added to the concentrated solution. Flash column chromatography (acetone/hexane, 3:7) afforded **2** as a pale yellow powder. Crystallization from acetone/hexane (1:1) gave colorless prisms (4.196 g, 95%); mp 95-98°; ir: 3110, 3028, 1679, 1562, 1487-1439, 1242, 808, 726 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.41 (s, 1 H), 7.37-7.34 (m, 3 H), 7.07 (d, J = 5.9 Hz, 2H), 5.06 (s, 2 H), 2.07 (s, 3 H); ms: m/z 252.1 (33.0), 250.1 (33.8), 92.2 (14.8), 91.2 (100.0), 65.0 (17.3).

Anal. Calcd. for $C_{11}H_{11}N_2Br$: C, 52.61; H, 4.41; N, 11.15; Br, 31.82. Found: C, 52.40; H, 4.37; N, 11.15; Br, 31.86.

5-Methyl-4-phenyl-1-(phenylmethyl)imidazole (**3**).

Bromoimidazole **2** (216 mg, 0.86 mmole) and tetrakis-(triphenylphosphine)palladium(0) (50 mg, 0.043 mmole, 5 mole %) were combined in toluene (2 ml). Phenylboronic acid (118 mg, 0.97 mmole) in absolute ethanol (1.25 ml) and aqueous sodium carbonate (2*M*, 2 ml) was added, and the reaction was heated to reflux for 24 hours. The product was then extracted with methylene chloride. Combined extracts were washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give an amber colored glass. Flash column chromatography (acetone/hexane, 1:4) gave **3** as a white powder (200 mg, 93%). Crystallization from acetone/hexanes gave analytically pure material, mp 90-91.5°; ir: 3079, 1597, 1500, 1459, 1362, 1258, 781, 739, 704 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.68 (dd, J = 1.1, 8.2 Hz, 4 H), 7.58 (s, 1 H), 7.41-7.26 (m, 3 H), 7.10 (d, J = 6.7 Hz, 2H), 5.11 (s, 2 H), 2.30 (s, 3 H); ms: m/z 249.2 (25.0), 248.2 (100.0), 91.1 (55.3), 89.1 (9.6), 65.0 (9.3).

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.10; H, 6.25; N, 11.22.

2-Bromo-5-methyl-4-phenyl-1-(phenylmethyl)imidazole (**4**).

N-Bromosuccinimide (76 mg, 0.43 mmole) was added to a solution of **3** (85 mg, 0.34 mmole) in dry acetonitrile (5 ml). The reaction was stirred at room temperature for 45 minutes, pyridine (2 drops) was added, and the mixture was concentrated *in vacuo*. Flash column chromatography (acetone/hexane, 1:3) afforded **4** as an amber glass (67 mg, 60%): ir (dichloromethane): 3073, 3038, 2947, 2933, 1951-1800, 1719, 1614, 1495, 1453, 1354, 1326, 760, 744, 716, 421 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.63 (m, 2 H), 7.36-7.23 (m, 6 H), 7.05 (d, J = 3.0 Hz, 2H), 5.19 (s, 2 H), 2.25 (s, 3 H); ms: m/z 329.1 (12.8), 328.0 (37.9), 327.0 (13.1), 326.0 (37.9), 246.1 (9.0), 91.0 (100.0), 65.1 (22.2); hrms Found: 326.0397. M$^+$ Calcd. for $C_{17}H_{15}BrN_2$: 326.0415.

5-Methyl-2,4-diphenyl-1-(phenylmethyl)imidazole (**5**).

Method A.

Bis(triphenylphosphine)palladium(II) chloride (4.2 mg, 0.006 mmole, 1.7 mole %), phenyltrimethyltin (0.084 ml, 0.46 mmole), and **4** (116 mg, 0.35 mmole) were added to toluene (1 ml). The reaction was heated at reflux under nitrogen for 12 hours. After cooling, the reaction was treated with aqueous potassium fluoride (38% by weight, 3 ml) and stirred for a further 10 minutes. The mixture was extracted with methylene chloride, and the combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Flash column chromatography (acetone/hexane, 5:95) and evaporation of the product fractions gave **5** as colorless needles (68 mg, 60%), mp 136-138°; ir: 3056, 2948, 1600, 1496, 1453, 774, 743, 732, 702 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.76 (d, J = 8.1, 2H), 7.57 (d, J = 3.4 Hz, 2H), 7.57-7.33 (m, 9 H), 7.07 (d, J = 6.65 Hz, 2H), 5.24 (s, 2 H), 2.31 (s, 3H); ms: m/z 325.1 (32.2), 324.1 (99.2), 234.1 (24.0), 233.1 (100.0), 130.1 (11.6), 104.0 (19.4), 91.0 (68.2), 89.0 (54.9); hrms Found: 324.1624. (M$^+$ Calcd. for $C_{23}H_{20}N_2$: 324.1622).

Method B.

Phenylboronic acid (160 mg, 1.31 mmoles) in ethanol (2 ml), imidazole **6** (see below; 210 mg, 1.31 mmoles), tetrakis-(triphenylphosphine)palladium(0) (35 mg, 0.03 mmole, 2.3 mole %), and aqueous sodium carbonate (2*M*, 2 ml) were added to toluene (2 ml) and the mixture was heated to reflux for 24 hours. An isolation procedure identical to that for **3** gave crystalline **5** (115 mg, 56%).

2,4-Dibromo-5-methyl-1-(phenylmethyl)imidazole (**6**).

N-Bromosuccinimide (2.62 g, 14.7 mmoles) was added to a solution of **1** (1.26 g, 7.33 mmoles) in chloroform (100 ml) at 0°, and the reaction was stirred for 80 minutes. An isolation procedure identical to that for **2** and subsequent crystallization (acetone/hexane, 1:3) gave **6** as colorless prisms (1.91 g, 80%), mp 98-100°; ir: 3060, 2970, 1559, 1428, 1300, 729 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.36-7.25 (m, 3H), 7.05 (d, J = 7.0 Hz, 2H), 5.13 (s, 2H), 2.11 (s, 3H); ms: m/z 331.9 (11.1), 329.9 (18.9), 92.0 (13.4), 91.0 (100.0), 65.1 (17.2).

Anal. Calcd. for $C_{11}H_{10}Br_2N_2$: C, 40.03; H, 3.05; N, 8.49; Br, 48.42. Found: C, 40.01; H, 2.82; N, 8.51; Br, 48.68.

4-Bromo-5-methyl-2-phenyl-1-(phenylmethyl)imidazole (**8**).

Phenyltrimethyltin (0.10 ml, 0.55 mmole), imidazole **6** (150 mg, 0.45 mmole), and bis(triphenylphosphine)palladium(II) chloride (32.8 mg, 0.047 mmole, 10 mole %) were combined in toluene (1.2 ml), and the mixture was heated to reflux for 12 hours. Extractive isolation as for **5**, and flash column chromatography (acetone/hexane, 1:5) gave a yellow powder. Crystallization (acetone/hexane, 5:95) gave **8** as pale yellow cubes (85 mg, 58%), mp 132.5-136°; ir: 3023, 2956, 1979, 1805, 1571, 1457, 1403, 1363, 1236, 770, 704 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.51-7.47 (m, 2 H), 7.40-7.21 (m, 6 H), 7.03-7.01

(d, J = 7.1 Hz, 2H), 5.19 (s, 2H), 2.09 (s, 3H); ms: m/z 328.1 (27.2), 326.1 (28.1), 92.1 (10.2), 91.1 (100.0), 65.0 (10.9); hrms Found: 326.0460. M^+ Calcd. for $C_{17}H_{15}N_2Br$: 326.0415.

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