Suzuki Coupling Reactions in Heterocyclic Chemistry: Synthesis of 3-Substituted Pyrrolines and Pyrroles

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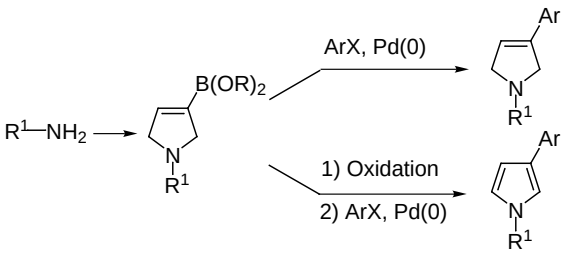
Abstract: A simple preparation of N-substituted 3-pyrroline boromic esters from primary amines is described. The Suzuki–Miyaura coupling of these heterocycles with aryl halides proceeds in good yields. Alternatively, oxidation with DDQ or MnO_2 gives the corresponding pyrroles, which can be also engaged in subsequent palladium cross-coupling reactions.

Key words: boronic esters, pyrroline, pyrrole, Suzuki–Miyaura coupling reactions

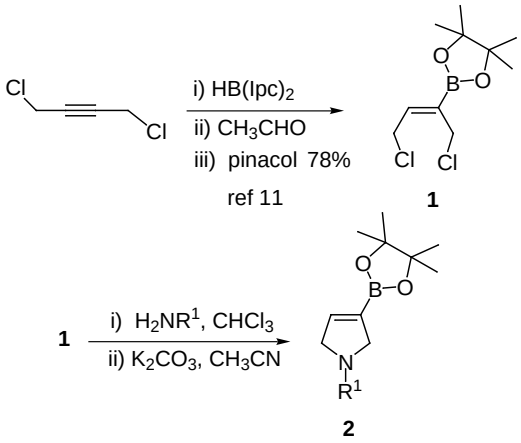
Nitrogen five-membered heterocyclic units occur widely in a range of natural products, drugs, dyes and polymers, and, as such, represent important synthetic targets.[1] A wide variety of chemistry has been developed to prepare this class of molecules,[2] but, in contrast to the significant number of syntheses of polysubstituted compounds, there are relatively few methods for the construction of simple 3-substituted derivatives.[3] Recent preparations of 3-arylpyrroles are based on rhodium-catalyzed hydroformylation of β-alkynylamines with CO/H_2,[4] and condensation of tosylmethylisocyanide with activated alkenes.[5] 3-Arylpyrrolines were preferentially obtained by ring closure methathesis.[6] Palladium catalyzed reactions, a powerful method for preparing biaryls, have also found some applications in the synthesis of nitrogen five-membered heterocycles.[7] However, in the case of the Suzuki–Miyaura reaction, the relative inaccessibility of starting boronic acids often restricts the interest of this method to particular substrates.[8–10]

Herein, we report an easy and versatile access to 3-substituted pyrrolines and pyrroles from primary amines and aryl halides (Scheme 1).



Scheme 1

To initiate our work, commercially available 1,4-dichlorobut-2-yne was first hydroborated with diisopinocampheylborane. Dealkylation with acetaldehyde and ester exchange with pinacol were then effected, as reported by Miyaura and coworkers.[11] The reaction of the resulting alkenylboronate **1** with three equivalents of amine in chloroform at room temperature was followed by elimination of the solvent. The treatment with excess of potassium carbonate in acetonitrile afforded pyrrolines **2**, which were isolated in good to moderate yields by distillation (Scheme 2, Table 1).[12,13] They can be stored at –15 °C for several weeks, but slowly decompose at room temperature. Only traces of product were observed with ammonia (R^1 = H).



Scheme 2

Table 1 Synthesis of *N*-Substituted 3-Pyrrolines **2**

Entry	R^1	Product	Yield (%)
1	$C_6H_5CH_2$	**2a**	78
2	$(CH_3)_2CH$	**2b**	65
3	CH_2=CH-CH_2	**2c**	50
4	C_6H_5	**2d**	72
5	$(C_6H_5)_2CH$	**2e**	60
6	(2-furyl)-CH_2	**2f**	75
7	*n*-(C_4H_9)	**2g**	40

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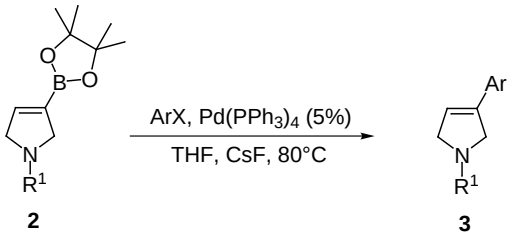
With boronic esters **2a**–**2g** in hand, we then turned our attention to the reactivity of these compounds in Suzuki–Miyaura coupling reactions. Due to the wide availability of aryl or heteroaryl halides, such transformations would extend the utility of this class of compounds in the preparation, and the further synthetic elaboration, of pyrroline derivatives. Palladium-mediated reaction of **2** with aromatic substrates led to the desired cross-coupled products **3** in good yields. In addition, depending on the nature of palladium catalyst, variable amounts (3–12%) of 3-arylpyrroles were formed, presumably via a dehydrogenative aromatization during coupling.[14] Best results were obtained with tetrakis(triphenylphosphine)palladium as catalyst (5%), CsF as a base in THF at reflux (Scheme 3, Table 2). Purification was readily achieved by extraction of the pyrroline with 1 M HCl. The resulting hydrochloride was treated with 1 M NaOH to give pure **3a**–**3e** after bulb-to-bulb distillation.[15]

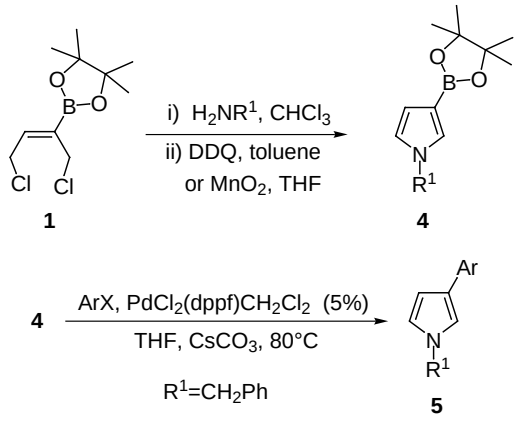


Scheme 3

Table 2 Palladium Catalyzed Coupling Reaction of **2** with Aryl Halides

Entry	R^1	Ar	Product	Yield (%)
1	$C_6H_5CH_2$	C_6H_5	**3a**	80
2	$C_6H_5CH_2$	4-MeO-C_6H_4	**3b**	78
3	$(CH_3)_2CH$	4-MeO-C_6H_4	**3c**	67
4	C_6H_5	4-Me-C_6H_4	**3d**	58
5	(2-furyl)-CH_2	4-Me-C_6H_4	**3e**	78

Compounds **2** are also good precursors of the corresponding pyrrole-3-boronates **4**. Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[16] was achieved without isolation of the corresponding pyrrolines **2**. After condensation of the primary amine with alkenyl boronic ester **1** and chloroform elimination, the crude mixture was stirred overnight in toluene with one equivalent of DDQ (Scheme 4, Table 3).[17] The aromatization of *N*-isopropyl derivative **2b** failed under these conditions and was accomplished by action of MnO_2 at reflux (entry 2).[18,19] *N*-benzyl pyrrole **3a** was then chosen to test the efficiency of Suzuki–Miyaura coupling reaction with this class of heterocyclic boronates. Dichloro [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) was used as catalyst in the presence of $CsCO_3$ in THF at 80 °C.[20] Good yields of the desired cross-coupling products were obtained after purification by bulb to bulb distillation (Scheme 4, Table 3).



Scheme 4

Table 3 Synthesis of Pyrroles **4** and **5**

Entry	R^1	Ar	Product	Yield (%)
1	$C_6H_5CH_2$	–	**4a**	80
2	$(CH_3)_2CH$	–	**4b**	72
3	CH_2=CH-CH_2	–	**4c**	30
4	C_6H_5	–	**4d**	68
5	(2-furyl)-CH_2	–	**4e**	74
6	$C_6H_5CH_2$	4-MeO-C_6H_4	**5a**	72
7	$C_6H_5CH_2$	C_5H_4N	**5b**	68
8	$C_6H_5CH_2$	4-Me-C_6H_4	**5c**	60
9	$C_6H_5CH_2$	C_6H_5	**5d**	74

In summary, we have reported a new route to a series of *N*-substituted pyrroline boronic esters from primary amines. Subsequent aromatizations to pyrroles were easily achieved with DDQ or MnO_2. Suzuki–Miyaura coupling reactions of these two heterocyclic boronates afford the corresponding 3-aryl derivatives in good yields.

Acknowledgement

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References

(1) *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 1–257.

(2) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 119–206. (b) Patel, A. V.; Crabb, T. A. *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds, Heterocyclic Compounds, Part A: Three, Four and Five Membered*

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Monoheterocyclic Compounds; Sainsbury, M., Ed.; Elsevier: Oxford, **1997**, 457–556. (c) Ketcha, D. M. In *Progress in Heterocyclic Chemistry*, Vol. 11; Gribble G. W., Gilchrist T. L., Pergamon-Elsevier: Oxford, **1999**, 124–143. (d) Black, D. S. In *Hetarenes and Related Ring Systems: Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom*, Vol. 9; Maas, G.; Regitz, M.; Ley, S. V., Eds.; Georg Thieme Verlag: Stuttgart, New York, **2001**, 441–552.

(3) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.

(4) Campi, E. M.; Fallon, G. D.; Jackson, W. R.; Nilsson, Y. *Aust. J. Chem.* **1992**, *45*, 1167.

(5) (a) Bean, G. P. In *Pyrroles Part 1., The Synthese and the Physical and Chemical Aspects of the Pyrroles Ring*; Jones, R. A., Ed.; John Wiley and Sons: New York, **1990**, 182–183. (b) Lamberth, C. *J. Prakt. Chem./Chem.-Ztg.* **1998**, *340*, 483.

(6) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8785.

(7) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Baldwin, J. E.; Williams, R. M., Eds.; Pergamon-Elsevier: Oxford, **2000**.

(8) Chung, Y. J.; Lee, C. W. *Tetrahedron Lett.* **2000**, *41*, 3423.

(9) For some examples of synthesis and reactivity of pyrrole-2-boronic ester, see: (a) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025. (b) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653. (c) D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513. (d) Martina, S.; Enkelmann, V.; Wegner, G.; Schluter, A. D. *Synthesis* **1991**, 613.

(10) For a recent preparation of a *N*-(Boc)pyrrole-3-boronic ester, see: Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *34*, 7995.

(11) Kamabuchi, A.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 4827.

(12) For similar reactions without the boronic moiety, see: (a) Margaret, M.; Bowers, N.; Lee, J.; Jouille, M. M. *Synth. Commun* **1983**, *13*, 1117. (b) Taylor, E. C.; Ahmed, Z. *J. Org. Chem.* **1991**, *56*, 5443.

(13) A representative procedure is as follows: A solution of alkenylboronate **1** (1 mmol) and three equivalents of the amine in chloroform (5 mL) was stirred overnight at r.t. The residue obtained upon evaporation of the solvent was dissolved in 7 mL of acetonitrile and stirred for 2 h at r.t. with 6 mmol (828 mg) of K_2CO_3. Solids were removed by filtration and solvents were evaporated to dryness to afford a crude product, which was subjected to distillation under reduced pressure. *Selected data*: **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.3 Hz, 6 H), 1.28 (s,12 H), 2.60 (sept, *J* = 6.3 Hz, 1 H), 3.52–3.63 (m, 4 H); 6.52 (s broad, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 24.7, 54.1, 59.0, 59.4, 83.3, 143.2. HRMS *m/z* calcd for $C_{13}H_{24}BNO_2$ (M^+) 237.1899, found 237.1902.

(14) Bläckvall, J. E.; Nyström, J. E. *J. Chem. Soc., Chem. Commun.* **1981**, 59.

(15) A representative procedure is as follows: A mixture of pyrroline boronic ester **2** (1 mmol), aryl halide (1.5 mmol), $Pd(PPh_3)_4$ (0.05 mmol) and CsF (4 mmol) in freshly distilled THF (10 mL) was heated at reflux under argon for 2 h. Saturated NH_4Cl solution (10 mL) and diethyl ether (30 mL) were added to the cooled solution. Aqueous layer was extracted with diethyl ether and the combined extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the resulting solution was treated with 1 mL of 1 M HCl. After evaporation of the solvents, the mixture was washed with diethyl ether. The organic layer was discarded before treatment with 1 M NaOH (1 mL). The free pyrroline was extracted with CH_2Cl_2. Distillation of the solvent afforded oil, which was distilled with Kugelrohr. *Selected data*: **3e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 3.67–3.74 (m, 2 H), 3.85–3.93 (m, 4 H), 6.05 (dd, *J* = 1.7 and 2.0 Hz, 1 H), 6.25 (dd, *J* = 1.7 and 3.2 Hz, 1 H), 6.34 (dd, *J* = 2.0 and 3.2 Hz, 1 H), 7.10 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 7.35–7.40 (m, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 51.9, 59.6, 60.2, 107.6, 110.0, 120.7, 125.3, 129.1, 131.5, 137.3, 139.4, 142.0, 153.0. HRMS *m/z* calcd for $C_{16}H_{17}NO$ (M^+) 239.13101, found 239.1312.

(16) Pawda, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041.

(17) A representative procedure is as follows: A chloroform solution (5 mL) of alkenylboronate **1** (1 mmol) and three equivalents of the amine was stirred overnight at r.t. The solvent was then evaporated in vacuo. After dilution of the residue in toluene (6 mL), 1 mmol of DDQ (227 mg) was added to the solution. The slurry was stirred at r.t. over night. The solvent was removed and the residue was washed with 2 × 20 mL of pentane, filtered through a pad of celite and concentrated in vacuo. The pyrrole **4** was purified by column chromatography on silica gel (EtOAc–heptane, 10:90). *Selected data* **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 12 H), 5.05 (s, 2 H), 6.56 (t, *J* = 1.8 Hz, 1 H), 6.72 (t, *J* = 1.8 Hz, 1 H), 7.16–7.33 (m, 6 H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.9, 53.4, 82.8, 114.6, 122.3, 127.4, 127.8, 128.8, 130.3, 137.6. HRMS *m/z* calcd for $C_{17}H_{22}BNO_2$ (M^+) 283.1743, found 283.11754.

(18) Yagi, T.; Aoyama, T.; Shiori, T. *Synlett* **1997**, 1063.

(19) A representative procedure is as follows: A mixture of pyrroline **2b** (1 mmol) and activated manganese oxide (870 mg, 10 mmol) in THF (12 mL) was heated under reflux for 48 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo The residue was purified by column chromatography on silica gel (EtOAc–Heptane, 10:90). *Representative data for the selected compound* **3e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 12 H), 1.43 (d, *J* = 6.7 Hz, 6 H), 4.24 (sept., *J* = 6.7 Hz, 1 H), 6.47 (dd, *J* = 2.5 and 1.7 Hz, 1 H), 6.74 (t, *J* = 2.5 Hz, 1 H); 7.19 (t, *J* = 1.7 Hz, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.9, 24.8, 50.9, 82.7, 113.7, 119.7, 127.3. HRMS *m/z* calcd for $C_{13}H_{22}BNO_2$ (M^+) 235.1746, found 235.11743.

(20) A representative procedure is as follows: To a solution of pyrrole-3-boronate **4** (1 mmol) in THF (10 mL), under an argon atmosphere, were added $CsCO_3$ (978 mg, 3 mmol), $PdCl_2(dppf)CH_2Cl_2$ (72 mg, 0.090 mmol), aryl or heteroaryl iodide (290 mg, 1.5 mmol) and water (1 mL). The reaction mixture was stirred at reflux temperature for 18 h, then cooled to r.t. and partitioned between water (20 mL) and diethyl ether (50 mL × 3). The combined extracts were washed with 1 N HCl (20 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (eluting with EtOAc–Heptane 10:90). *Selected data*: **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2 H), 6.55 (dd, *J* = 1.8 and 2.8 Hz, 1 H), 6.73 (dd, *J* = 2.3 and 2.8 Hz, 1 H), 7.11 (dd, *J* = 2.3 and 1.8 Hz, 1 H), 7.20–7.35 (m, 5 H), 8.46–8.54 (m, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 53.8, 106.8, 119.4, 119.7, 122.3, 123.1, 127.2, 128.0, 128.9, 137.2, 143.2, 149.9. HRMS *m/z* calcd for $C_{16}H_{14}N_2$ (M^+) 234.1157, found 234.1165.

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