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Regioselective Suzuki cross-coupling reactions of 2,3,4,5-tetrabromo-1-methylpyrrole

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Abstract

Regioselective Suzuki cross-coupling reactions of 2,3,4,5-tetrabromo-1-methylpyrrole allow a convenient synthesis of functionalized pyrroles.

Keywords: Heterocycles; Pyrroles; Regioselectivity; Suzuki reactions

Pyrroles are of considerable pharmacological relevance. They occur in a number of synthetic drugs (e.g., zomepirac and atorvastatin) and natural products (e.g., in the tetrapyrrole pigments porphobilinogen and bilirubin).[1–3] Oligopyrroles proved to be important as organic materials (e.g., as synthetic metals).[4] Heterocycles have been widely functionalized by palladium(0)-catalyzed cross-coupling reactions.[5] In recent years, it has been shown that polyhalogenated heterocycles may be regioselectively functionalized in such reactions by selective activation of a single halogen atom—a process which is controlled by electronic and steric parameters.[6] Recently, we reported the synthesis of tetraarylthiophenes based on regioselective Suzuki reactions of tetrabromothiophene.[7] Despite their potential synthetic utility, regioselective functionalization reactions of polyhalogenated pyrroles have only scarcely been reported to date. Bach and Schröter recently reported regioselective Suzuki reactions of ethyl 2,3,4-tribromopyrrole-5-carboxylate and of 2,3-dibromo-5-nitropyrrole.[8] Herein, we disclose our preliminary results related to Suzuki cross-coupling reactions of 2,3,4,5-tetrabromo-1-methylpyrrole. Palladium(0)-catalyzed cross-coupling reactions of tetrahalopyrroles have, to the best of our knowledge, not been reported to date. In general, reactions of tetrahalogenated pyrroles are rather rare, which can be explained by the unstable nature of these compounds.[9]

2,3,4,5-Tetrabromo-1-methylpyrrole (**1**) was prepared by NBS-mediated bromination of *N*-methylpyrrole. The published procedure[10] for the synthesis of **1** was modified,[11] as we were not able to isolate the pure product by the original protocol. The reaction was carried out at −78 °C for 8 h. It proved to be helpful for the separation of succinimide to add heptane to the reaction mixture, which results in the precipitation of succinimide and of side-products. The yellowish crude product was purified by repeated washing with cold ethyl acetate to give the pure material in the form of colourless crystals. Noteworthy, impure product fails to undergo the desired Suzuki reactions and also more rapidly decomposes. The solid can be stored under argon at −18 °C for a few weeks. After a few weeks, the compound starts to become slightly yellow and the quality is not sufficient anymore for Suzuki reactions.

The Suzuki reaction of **1** with various boronic acids (1.1 equiv) afforded 5-aryl-2,3,4-tribromopyrroles **2a–f** in good yields and with very good regioselectivity (Scheme 1, Table 1). During the optimization, it proved to be

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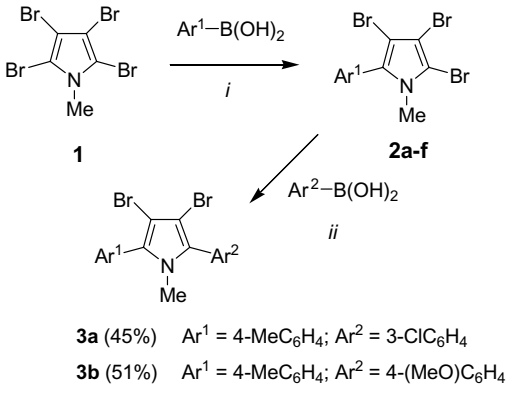


Scheme 1. Synthesis of 5-aryl-2,3,4-tribromopyrroles **2a–f** and of 2,5-diaryl-3,4-dibromopyrroles **3a**,**b**. Reagents and conditions: (i) **1** (1.0 equiv), $Ar^1B(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (6 mol %), K_3PO_4 (4.0 equiv), solvent (see Table 1), 90 °C, 12 h; (ii) **2c** (1.0 equiv), $Ar^2B(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (4.0 equiv), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, 48 h.

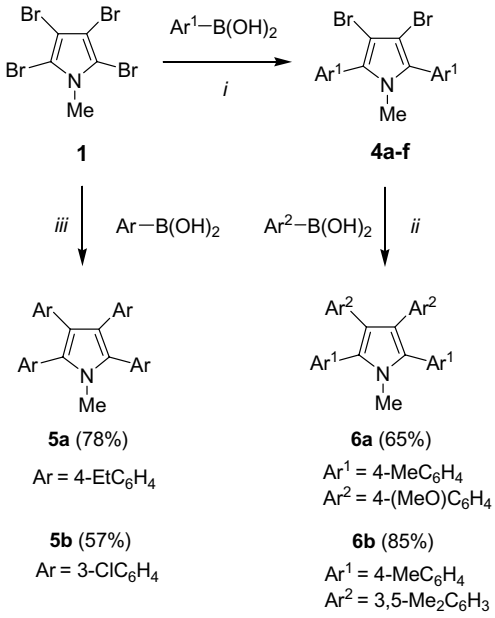
Table 1
Synthesis of **2a–f**

2	Ar	Solvent[a]	Yield[b] (%)
a	3-PhC_6H_4	Toluene/H_2O	66
b	3-ClC_6H_4	Toluene/H_2O	71
c	4-EtC_6H_4	Toluene/H_2O	75
d	2-(MeO)C_6H_4	1,4-Dioxane/H_2O	70
e	4-MeC_6H_4	1,4-Dioxane/H_2O	81
f	3,5-$Me_2C_6H_3$	1,4-Dioxane/H_2O	72

[a] Solvent/H_2O = 4:1.
[b] Yields of isolated products.

important to suppress the formation of 2,5-diaryl-3,4-dibromopyrroles, as their separation from the desired products proved to be difficult and tedious. The stoichiometry, temperature, solvent and the presence of water proved to play an important role in terms of yield (Table 1). Noteworthy, the employment of benzyl-, carbamate- and sulfonyl-protected pyrroles was unsuccessful (decomposition). The reaction of **2e** with 1.1 equiv of (3-chlorophenyl)- and (4-methoxyphenyl)boronic acid resulted in regioselective formation of 2,5-diaryl-3,4-dibromopyrroles **3a** and **3b**, respectively (Scheme 1).

The Suzuki reaction of **1** with 2.5 equiv of various arylboronic acids afforded 2,5-diaryl-3,4-dibromopyrroles **4a–f** in good yields and with very good regioselectivity (Scheme 2, Table 2).[12] The solvent proved again to be a very important parameter during the optimization of the yield. The reaction of **4c** with (4-methoxyphenyl)- and (3,5-dimethylphenyl)boronic acid gave tetraarylpyrroles **6a** and **6b**, respectively, containing two different types of aryl groups. Tetraarylpyrroles **5a**,**b**, containing four identical aryl groups, were prepared by reaction of **1** with (4-ethylphenyl)- and (3-chlorophenyl)boronic acid (5.0 equiv). The best yields of **5a**,**b** and **6a**,**b** were obtained when the reactions were carried out using a quaternary solvent mixture (DMF/toluene/EtOH/H_2O = 4:1:1:1) and an increased amount of catalyst and reagents and when the reaction time was extended. Considerable amounts of 2,3,5-triaryl-



Scheme 2. Synthesis of 2,5-diaryl-3,4-dibromopyrroles **4a–f** and of tetraarylpyrroles **5a**,**b** and **6a**,**b**. Reagents and conditions: (i) **1** (1.0 equiv), $Ar^1B(OH)_2$ (2.5 equiv), $Pd(PPh_3)_4$ (6–10 mol %), K_3PO_4 (4.0 equiv), solvent (see Table 2), 90 °C, 12 h; (ii) **4c** (1.0 equiv), $Ar^2B(OH)_2$ (3.0 equiv), $Pd(PPh_3)_4$ (20 mol %), K_3PO_4 (4.0 equiv), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, (**6a**: 48 h, **6b**: 96 h); (iii) **1** (1.0 equiv), $ArB(OH)_2$ (5.0 equiv), $Pd(PPh_3)_4$ (20 mol %), K_3PO_4 (5.0 equiv), DMF/toluene/EtOH/H_2O (4:1:1:1), reflux, 96 h.

Table 2
Synthesis of **4a–f**

4	Ar^1	Solvent	Yield[a] (%)
a	3-ClC_6H_4	Toluene/H_2O (5:1)	57
b	4-EtC_6H_4	Toluene/H_2O (5:1)	52
c	4-MeC_6H_4	Toluene/H_2O (5:1)	79
d	4-ClC_6H_4	1,4-Dioxane/H_2O (5:1)	67
e	4-(MeO)C_6H_4	1,4-Dioxane/H_2O (5:1)	79
f	Thien-2-yl	Toluene/MeOH/H_2O (2:2:1)	50

[a] Yields of isolated products.

4-bromopyrroles were formed when the amounts of reagents and catalyst were too low. Noteworthy, the bromide groups of 2,5-diaryl-3,4-dibromopyrroles **4a–f** proved to be considerably less reactive than those of 2,5-diaryl-3,4-dibromothiophenes.[7] This must be explained by electronic reasons, as the steric hindrance is similar for both types of substrates. The conditions developed for the synthesis of

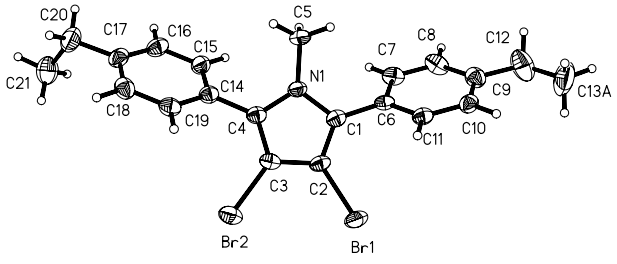


Fig. 1. ORTEP plot of **4b** (50% probability level).

5a,**b** and **6a**,**b** could be successfully applied to the synthesis of related tetraarylpyrroles.

All products were characterized by spectroscopic methods. The structure of **4b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[13]

In conclusion, we have reported a new strategy for the synthesis of 5-aryl-2,3,4-tribromopyrroles, 2,5-diaryl-3,4-dibromopyrroles and tetraarylpyrroles based on regioselective Suzuki cross-coupling reactions of *N*-methyltetrabromopyrrole.

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11. *Synthesis of 2,3,4,5-tetrabromo-1-methylpyrrole* (**1**): To a THF solution (700 mL) of 1-methylpyrrole (40.5 g, 44.5 mL, 0.5 mol) was added *N*-bromosuccinimide (504 g, 2.5 mol) at −78 °C and the solution was stirred at this temperature for 8 h. To the mixture was added *n*-heptane (500 mL) and the tetrahydrofuran was subsequently removed under reduced pressure to give a colourless precipitate of succinimide. The precipitate was filtered off and the solvent of the filtrate was removed in vacuo. To the residue was added a saturated aqueous solution of NaOH and the solution was heated under reflux for 6 h. The aqueous layer and the organic layer were separated. The latter was dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was recrystallized from a 1:1-solution of chloroform and methanol at −18 °C. The crude product (in the form of yellow crystals) was washed with very cold ethyl acetate for several times to give **1** as colourless crystals (174.7 g, 88%), mp = 154–156 °C. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.65$ (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.0$ (CH_3), 101, 103.5 (CBr). IR (KBr, cm^{-1}): $\tilde{\nu} = 2940$ (w), 2862 (w), 2833 (w), 2664 (w), 1492 (m), 1451 (m), 1311 (m), 1079 (m), 988 (w), 861 (w).
12. *General procedure for synthesis of 3,4-dibromo-2,5-diaryl-1-methylpyrroles*: To a toluene solution (4 mL) of **1** (0.199 g, 0.5 mmol) was added $Pd(PPh_3)_4$ (0.058 g, 10 mol %) at 20 °C under argon atmosphere. After stirring for 30 min, the arylboronic acid (1.25 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred under reflux for 24 h. After cooling to 20 °C, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane) and subsequent chromatotron chromatography (Marrison Research, ser. no. Y63, *n*-heptane). *Synthesis of 3,4-dibromo-2,5-di(4-tolyl)-1-methylpyrrole* (**4c**). Starting with **1** (0.199 g, 0.5 mmol) and 4-tolylboronic acid (0.170 g, 1.25 mmol), **4c** was isolated (0.166 g, 79%) as a colourless solid, mp = 145–150 °C. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.32$ (s, 6H, $2CH_3$), 3.26 (s, 3H, CH_3), 7.15, 7.20 (d, $^3J = 8.2$ Hz, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 34.5 (CH_3), 100.0 (CBr), 129.3, 130.4 (CH, Ar), 128.8, 133.0, 138.8 (C). IR (KBr, cm^{-1}): $\tilde{\nu} = 1920$ (w), 1910 (w), 1549 (w), 1535 (w), 1493 (m), 1445 (w), 1318 (m), 1222 (w), 1114 (w), 1020 (w), 973 (w), 825 (m), 802 (m), 770 (w), 726 (w). MS (EI, 70 eV): *m*/*z* (%) = 421 (M^+, [^{81}Br, ^{81}Br], 50), 419 (M^+, [^{81}Br, ^{79}Br], 100), 417 (M^+, [^{79}Br, ^{79}Br], 52), 244 (11). HRMS (EI, 70 eV): calcd for $C_{19}H_{17}Br_2N$ (M^+, [^{79}Br]): 416.9728; found: 416.99725. All products gave satisfactory spectroscopic data and correct elemental analyses and/or high resolution mass data.
13. CCDC-671706 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.