2,5,6-Trisubstituted *N*-Methylindoles from Site-Selective Suzuki–Miyaura Cross-Coupling, Twofold Heck and 6π-Electrocyclization–Dehydrogenation Reactions of 2,3,5-Tribromo-*N*-methylpyrrole

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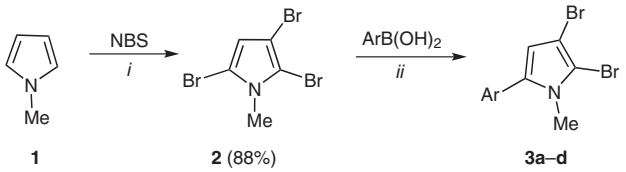
Abstract: Site-selective Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole afforded 5-aryl-2,3-dibromo-*N*-methylpyrroles. These products were transformed into 2,5,6-trisubstituted *N*-methylindoles by twofold Heck reactions and subsequent 6π-electrocyclization–dehydrogenation reactions.

Key words: catalysis, palladium, Heck reaction, electrocyclization, indoles

Indole derivatives are found in many natural, synthetic, agrochemical and pharmaceutical compounds.[1] Indole derivatives influence the neurotransmitter serotonin,[2] act as hallucinogen agents,[3] potent PPAR-c binding agents with potential application for the treatment of osteoporosis,[4] neuroprotective agents affecting oxidative stress,[5] potent anti-inflammatory agents,[6] and antimicrobial agents.[7] Indoles constitute a privileged scaffold capable of providing useful ligands for diverse receptors.[8] Indoles can be prepared by various classical methods, e.g. the Fischer indole synthesis, the Plieninger indole synthesis, the Madelung cyclization of *N*-acyl-*o*-toluidines, the Bischler indole synthesis, the Batcho–Leimgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetals, and the reductive cyclization of *o*-nitrobenzyl ketones.[9] Most of the known methods allow to vary the substituents located at positions 2 and 3 of the indole moiety. Positions 5 and 6 are much more difficult to access.

De Meijere and co-workers reported the synthesis of benzene derivatives by twofold Heck reactions of 1,2-dibromocycloalk-1-enes and related substrates and subsequent 6π-electrocyclization.[10] In recent years, we have studied the application of this approach to the synthesis of heterocyclic systems, such as carbazoles, benzothiophenes, dibenzofurans, and benzimidazoles.[11] We have also studied site-selective Suzuki reactions of 2,3,4,5-tetrabromothiophene, 2,3,4,5-tetrabromoselenophene, pentachloropyridine, 2,3,4-tribromothiophene, 2,3,4,5-tetrabromo-*N*-methylpyrrole and other substrates.[12] Due to the importance of indoles in organic and medicinal chemistry, we studied a new approach to 2,5,6-trisubstituted indoles based on the combination of hitherto unknown site-selective Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole with twofold Heck and 6π-electrocyclization reactions. The building block strategy reported herein provides a powerful method for the synthesis of indoles which are not readily available by other methods.

2,3,5-Tribromo-*N*-methylpyrrole (**2**) was prepared by reaction of *N*-methylpyrrole (**1**) with NBS (3.1 equiv) in 88% yield (Scheme 1).[13] The Suzuki–Miyaura reaction of **2** with arylboronic acids (1.1 equiv) afforded the 5-aryl-2,3-dibromo-1-methyl-1*H*-pyrroles **3a–d** (Scheme 1, Table 1).[14,15] The best yields were obtained when the reactions were carried out using $Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base in a 1:1 mixture of dioxane and toluene (100 °C, 12 h). The formation of **3a–d** proceeded with excellent site-selectivity. Palladium-catalyzed reactions of **2** have, to the best of our knowledge, not been previously reported.



Scheme 1 Synthesis of **2** and **3a–d**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), NBS (3.1 equiv), THF, –78 °C → 20 °C, 12 h; (*ii*) **2** (1.0 equiv), $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (4.0 equiv), 1,4-dioxane–toluene (1:1), 100 °C, 12 h

Table 1 Synthesis of **3a–d**

3	Ar	Yield (%)[a] of **3**
a	4-MeC_6H_4	82
b	4-EtC_6H_4	73
c	4-*t*-BuC_6H_4	64
d	3,5-$Me_2C_6H_3$	58

[a] Yields of isolated products.

The first attack in palladium-catalyzed reactions of polyhalogenated substrates usually occurs at the electronically most deficient and sterically least hindered position. The site-selective formation of products **3a–d** can be ex-

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plained by the fact that carbon atom C-5 of tribromopyrrole **2** is, on the one hand, more electron-deficient than C-3 and, on the other hand, less sterically hindered than C-2 (Figure 1).

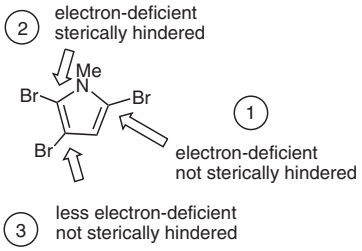
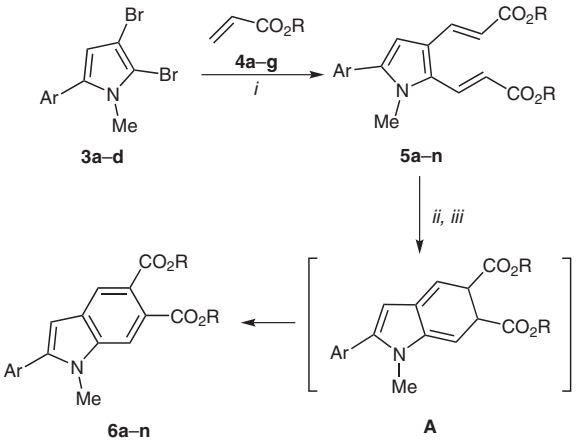


Figure 1 Possible explanation for the site-selectivity of the reactions of **2**

The Heck reaction of **3a–d** with acrylates **4a–g** afforded the 5-aryl-2,3-di(alkenyl)-*N*-methylpyrroles **5a–n** in 47–76% yield (Scheme 2, Table 2).[16,17] The best yields were obtained when the reactions were carried out using $Pd(OAc)_2$ (5 mol%) as the catalyst in the presence of tricyclohexylphosphine (TCHP, 10 mol%; Table 3). The yields significantly dropped when $Pd(PPh_3)_4$ was employed.



Scheme 2 Synthesis of **5a–n** and **6a–n**. *Reagents and conditions*: (i) **3a–d** (1 equiv), **4a–g** (2.5 equiv), $Pd(OAc)_2$ (5 mol%), TCHP (10 mol%), Et_3N, DMF, 100 °C, 24 h; (ii) diphenyl ether, 200 °C, 24 h; (iii) Pd/C (10 mol%), diphenyl ether, 200 °C, 48 h

The reactions were carried out at 100 °C in DMF. The yields dropped when the temperature was increased or decreased (Table 4). The employment of styrene instead of acrylates proved to be unsuccessful, due to decomposition under the reaction conditions employed.

5-Aryl-2,3-di(alkenyl)-*N*-methylpyrroles **5a–n** were transformed into the indoles **6a–n** in 69–94% yield.[18,19] The pyrroles were heated in diphenyl ether for 24 hours at 200 °C. Subsequently, Pd/C was added and the mixture was heated for further 48 hours at 200 °C. The indoles were formed by 6π-electrocyclization and subsequent dehydrogenation. The yields dropped when the reaction was carried out at 160 °C for 96 hours instead of at 200 °C for 72 hours (Table 5).

Table 2 Synthesis of **5a–n** and **6a–n**

3	**4**	**5**,**6**	Ar	R	Yield (%)[a] of **5**	Yield (%)[a] of **6**
a	**a**	**a**	4-MeC_6H_4	*i*-Bu	72	91
a	**b**	**b**	4-MeC_6H_4	*n*-Hex	75	80
b	**a**	**c**	4-EtC_6H_4	*i*-Bu	69	72
b	**c**	**d**	4-EtC_6H_4	*t*-Bu	65	74
b	**b**	**e**	4-EtC_6H_4	*n*-Hex	60	90
b	**d**	**f**	4-EtC_6H_4	Et	47	69
b	**e**	**g**	4-EtC_6H_4	$CH_2CH(Et)(CH_2)_3Me$	61	94
c	**f**	**h**	4-*t*-BuC_6H_4	CO_2Me	53	70
c	**a**	**i**	4-*t*-BuC_6H_4	*i*-Bu	76	77
c	**g**	**j**	4-*t*-BuC_6H_4	*n*-Bu	56	89
c	**b**	**k**	4-*t*-BuC_6H_4	*n*-Hex	71	81
c	**d**	**l**	4-*t*-BuC_6H_4	Et	48	75
d	**e**	**m**	3,5-$Me_2C_6H_3$	$CH_2CH(Et)(CH_2)_3Me$	51	77
d	**g**	**n**	3,5-$Me_2C_6H_3$	*n*-Bu	66	88

[a] Yields of isolated products.

Table 3 Influence of the Catalyst

Catalyst	Yield (%)[a] of **5c**	Yield (%)[a] of **5f**	Yield (%)[a] of **5j**
10 mol% $Pd(PPh_3)_4$	37	45	19
5 mol% $Pd(OAc)_2$ + 10 mol% THCP	69	47	56

[a] Yields of isolated products.

Table 4 Influence of the Temperature

Temp (°C)	Yield (%)[a] of **5a**	Yield (%)[a] of **5l**	Yield (%)[a] of **5j**
90	59	30	50
100	72	48	56
120	63	41	42

[a] Yields of isolated products.

Table 5 Influence of the Temperature on the 6π-Electrocyclization

Temp (°C)	time (h)	Yield (%)[a] of **6a**	Yield (%)[a] of **6b**
160	96	63	71
200	72	91	80

[a] Yields of isolated products.

In conclusion, we have reported an efficient synthesis of 2,5,6-trisubstituted indoles based on Suzuki and Heck reactions of 2,4,5-tribromo-*N*-methylpyrrole and subsequent 6π-electrocyclization–dehydrogenation reactions. This methodology provides a convenient access to various indoles which are not readily available by other methods.

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(14) **Synthesis of 5-Aryl-2,3-dibromo-*N*-methylpyrroles 3a–d**: To a mixture of **2**(0.159 g, 0.5 mmol), aryl boronic acid (0.55 mmol), and $Pd(PPh_3)_4$ (5 mol%) was added a mixture of 1,4-dioxane and toluene (1:1; 5 mL) and K_3PO_4 (4.0 equiv, 424 mg) under an argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h and was subsequently allowed to cool to 20 °C. The solution was poured into H_2O and EtOAc (25 mL each) and the organic and the aqueous layers were separated. The latter was extracted with EtOAc (3 × 25mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (flash silica gel, eluent: *n*-heptane).

(15) **Synthesis of 2,3-Dibromo-5-(4-*tert*-butylphenyl)-*N*-methylpyrrole (3c)**: Starting with **2** (0.318 g, 1.0 mmol) and 4-*tert*-butylphenylboronic acid (0.178 g, 1.1 mmol), **3c** was isolated (237 mg, 64%) as a colorless oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.34 (s, 9 H, 3 × Me), 3.61 (s, 3 H, NMe), 6.29 (s, 1 H, $CH_{pyrrole}$), 7.34 (d, 2 H, *J* = 8.6 Hz, ArH), 7.59 (d, 2 H, *J* = 8.6 Hz, ArH). ^{13}C NMR (62 MHz, acetone-d_6): δ = 31.6 (3 × Me), 35.2 (C), 35.4 (NMe), 98.5, 105.5 (CBr), 111.3 ($CH_{pyrrole}$), 126.4 (2 × CH), 129.4 (2 × CH), 130.2, 137.4, 151.7 (C). IR (KBr): 2959 (m), 2903, 2866, 1783, 1697, 1650, 1606, 1537 (w), 1499, 1456, 1362, 1318, 1265 (m), 1216, 1201 (w), 1109, 1086, 1017, 946 (m), 837 (s), 821, 779 (m), 741, 668, 595 (w), 574 (m), 532 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 373 (36) [M^+ (^{81}Br, ^{81}Br)], 371 (73) [M^+ (^{79}Br, ^{81}Br)], 369 (36) [M^+, (^{79}Br, ^{79}Br)], 358 (50), 357 (16), 356 (100) [M^+], 354 (53), 164 (15). HRMS (EI, 70 eV): *m*/*z* [M^+ (Br, ^{81}Br)] calcd for $C_{15}H_{17}NBr_2$: 370.97018; found: 370.97046.

(16) **Synthesis of 2,3-Di(alkenyl)pyrroles 5a–n**: In a pressure tube (glass bomb) a suspension of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5 mol%) and TCHP (28.04 mg, 0.10 mmol, 10 mol%) in DMF (5 mL) was purged with Ar and stirred at 20 °C to give a yellowish or brownish clear solution. To the stirred solution were added **3a–d** (1.0 mmol), Et_3N (1.1 mL, 8.0 mmol) and the acrylate (5.0 equiv). The reaction mixture was stirred at 100 °C for 24 h. The solution was cooled to 20 °C, poured into H_2O and CH_2Cl_2 (25 mL each), and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (flash silica gel, eluent: heptanes–EtOAc).

(17) **(2*E*,2′*E*)-Isobutyl 3,3′-[5-(4-Ethylphenyl)-*N*-methylpyrrole-2,3-diyl]diacrylate (5c)**: Compound **5c** was prepared starting with **3b** (343 mg, 1.0 mmol) as a brown highly viscous oil (301 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, 6 H, *J* = 6.7 Hz, 2 × Me), 0.91 (d, 6 H, *J* = 6.7 Hz, 2 × Me), 1.20 (t, 3 H, *J* = 7.6 Hz, Me), 1.87–1.99 (m, 2 H, 2 × CH), 2.62 (q, 2 H, *J* = 7.6 Hz, CH_2), 3.57 (s, 3 H, NMe), 3.90 (d, 2 H, *J* = 6.8 Hz, CH_2O), 3.92 (d, 2 H, *J* = 6.8 Hz, CH_2O), 6.10 (d, 1 H, *J* = 16.0 Hz, CH), 6.18 (d, 1 H, *J* = 15.6 Hz, CH), 6.42 (s, 1 H, $CH_{pyrrole}$), 7.20–7.25 (m, 4 H, Ar), 7.71 (d, 1 H, *J* = 16.0 Hz, ArH), 7.78 (d, 1 H, *J* = 15.7 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): d = 15.4 (Me), 19.2 (4 × Me), 27.8, 27.9 (CH), 28.6 (CH_2), 33.9 (NMe), 70.4,

70.8 (CH_2O), 107.7, 116.5, 117.5 (CH), 123.7 (C), 128.2 (2 × CH), 129.0 (C), 129.1 (2 × CH), 130.9 (C), 131.1, 136.3 (CH), 140.7, 144.6 (C), 167.2, 167.5 (CO). IR (KBr): 2959 (m), 2932, 2872 (w), 1699, 1615 (s), 1548, 1504 (w), 1468, 1453 (m), 1424, 1392 (w), 1368, 1284, 1260, 1241, 1220 (m), 1148 (s), 1015, 966, 839, 799 (m), 773, 723, 703, 672, 610, 533 (w) cm^{-1}. EI^+ (70 eV): *m*/*z* (%) = 437 (7) $[M]^+$, 280 (14), 236 (11), 66 (13), 44 (16), 43 (100), 42 (30), 41 (55). HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{27}H_{35}O_4N$: 437.25606; found: 437.25529.

(18) **Synthesis of Indoles 6a–n**: A diphenyl ether solution (3 mL) of **5a–n** was stirred at 200 °C for 24 h in a pressure tube. The solution was allowed to cool to 20 °C and Pd/C (30 mg, 10 mol%) was added. The solution was stirred at 200 °C for 48 h under an argon atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, eluent: heptanes–EtOAc).

(19) **Dibutyl 2-(4-*tert*-Butylphenyl)-*N*-methylindole-5,6-dicarboxylate Diacrylate (6j)**: Compound **6j** was prepared starting with **5j** (465 mg, 1.0 mmol) as a brown highly viscous oil (412 mg, 89%). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, 6 H, *J* = 8.7 Hz, 2 × Me), 1.29 (s, 9 H, 3 × Me), 1.33–1.42 (m, 4 H, 2 × CH_2), 1.61–1.72 (m, 4 H, 2 × CH_2), 3.71 (s, 3 H, NMe), 4.23 (t, 2 H, *J* = 6.7 Hz, CH_2O), 4.25 (t, 2 H, *J* = 6.7 Hz, CH_2O), 6.52 (s, 1 H, $CH_{pyrrole}$), 7.36 (d, 2 H, *J* = 8.4 Hz, ArH), 7.43 (d, 2 H, *J* = 8.5 Hz, ArH), 7.65 (s, 1 H, ArH), 7.92 (s, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (2 × Me), 18.2 (2 × CH_2), 29.6, 29.7 (CH_2), 30.3 (3 × Me), 30.5 (NMe), 33.7 (C), 64.1, 64.3 (CH_2O), 101.5, 110.1, 121.1 (CH), 123.2, 124.5 (C), 124.6 (2 × CH), 127.8 (C), 128.0 (2 × CH), 128.0, 137.2, 144.1, 150.7 (C), 167.8, 168.0 (CO). IR (KBr): 2956 (m), 2870 (w), 1711 (s), 1611, 1562, 1494 (w), 1475, 1461 (m), 1430, 1390 (w), 1360, 1339 (m), 1256, 1243 (s), 1209, 1157 (m), 1103 (s), 1060, 1036, 1004 (m), 962, 944, 896 (w), 839, 783, 736 (m), 672, 625, 602, 565 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 463 (100) $[M]^+$, 448 (13), 407 (10), 355 (14), 334 (54), 318 (13), 290 (11). HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{29}H_{37}O_4N$: 463.27171; found: 463.27286.