One-Pot Synthesis of Unsymmetrical 2,3-Diarylindoles by Site-Selective Suzuki–Miyaura Reactions of *N*-Methyl-2,3-dibromoindole

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Received 16 November 2009

Abstract: The Suzuki–Miyaura reaction of *N*-methyl-2,3-dibromoindole with two equivalents of boronic acids gave symmetrical 2,3-diarylindoles. The reaction with one equivalent of arylboronic acid resulted in site-selective formation of 2-aryl-3-bromoindoles. The one-pot reaction of 2,3-dibromoindole with two different arylboronic acids afforded unsymmetrical 2,3-diarylindoles containing two different aryl groups.

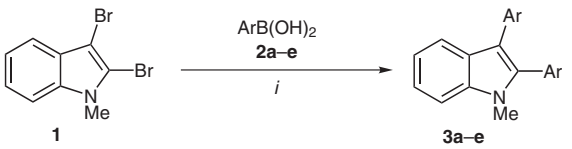
Key words: catalysis, palladium, Suzuki–Miyaura reaction, site-selectivity, indole

2,3-Diarylindoles are of considerable pharmacological relevance, due to their anti-inflammatory, anti-arthritic, and antipyretic properties.[1] For example, 2,3-bis(4-methoxyphenyl)indole ('indoxole') has been shown to possess a stronger anti-inflammatory activity than common drugs, such as aspirin and indomethacin.[2] Based on these findings, novel COX-2 inhibitors for the treatment of arthritic pain have recently been developed.[3] Classic syntheses of 2,3-diarylindoles include the diaza-Cope rearrangement of arylhydrazones (Fischer) and the reaction of anilines with α-halo ketones (Napieralski).[1,4] Modern methods to assemble the indole system include the Fürstner variant of the McMurry reaction and Pd-catalyzed cross-coupling reactions.[4]

An alternative approach to substituted indoles relies on the functionalization of the indole core structure. In recent years, a number of site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated heterocycles have been developed. The site-selectivity of these reactions is generally influenced by electronic and steric parameters.[5] Recently, we have reported the synthesis of aryl-substituted thiophenes,[6] pyrroles,[7] and selenophenes[8] by site-selective Suzuki reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, and tetrabromoselenophene, respectively. A number of Suzuki–Miyaura reactions of monohalogenated indoles have been reported.[9] Ohta et al. reported site-selective Suzuki–Miyaura reactions of *N*-TBDS-3,6-dibromoindole.[10] The first attack occurred at carbon atom C-6. Recently, we have reported Heck reactions of *N*-methyl-2,3-dibromoindole which proceed without site-selectivity.[11] Gribble and Liu reported the synthesis of symmetrical *N*-phenylsulfonyl-2,3-diarylindoles by twofold Suzuki–Miyaura reactions of 2,3-dihalo-*N*-(phenylsulfonyl)indoles.[12] The main part of this study was carried out with *N*-phenylsulfonyl-2,3-diiodoindole, but its 2,3-dibromo-, 2-iodo-3-bromo-, and 2-bromo-3-iodoindole derivatives were also employed. The reactions were carried out using $Pd(OAc)_2/P(o\text{-}Tol)_3$ and K_2CO_3 in acetone–H_2O (2:1) or DMF (70 °C). It is important to note that the authors report that all attempts to develop site-selective reactions and to prepare monocoupling products or unsymmetrical 2,3-diarylindoles, containing two different aryl groups, were unsuccessful. In fact, site-selective palladium(0)-catalyzed cross-coupling reactions of 2,3-dihaloindoles have, to the best of our knowledge, not yet been reported.

We have earlier observed[7] that Suzuki–Miyaura reactions of *N*-sulfonyl- and *N*-acyl-2,3,4,5-tetrabromopyrrole and of unprotected 2,3,4,5-tetrabromopyrrole gave unsatisfactory results (with regard to yield and site-selectivity). In contrast, the reactions of *N*-methyl-2,3,4,5-tetrabromopyrrole proceeded in good yields and with excellent site-selectivity. Therefore, we decided to study the use of *N*-methyl-2,3-dibromoindole as a substrate in Suzuki–Miyaura reactions. Gratifyingly, we have found that the reactions indeed proceed in high yields and with excellent site-selectivity. The results of our efforts are reported herein.

N-Methyl-2,3-dibromoindole (**1**) was prepared as previously reported.[11] The Suzuki–Miyaura reaction of **1** with various arylboronic acids (2.3 equiv) afforded the symmetrical 2,3-diarylindoles **3a–e** (Scheme 1, Table 1).[13,14] All products were isolated in high yields (79–91%). This includes derivatives prepared from both electron-rich and electron-poor arylboronic acids. In contrast, reactions of *N*-phenylsulfonyl-2,3-diiodoindole with electron-poor arylboronic acids were reported to proceed in only moderate yields (44–55%).[12]



Scheme 1 Synthesis of **3a–e**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), **2a–e** (2.3 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 6 h.

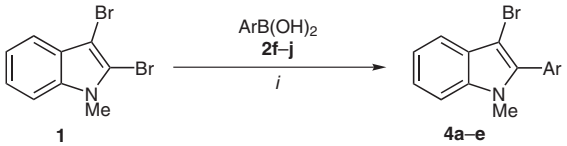
SYNLETT 2010, No. 3, pp 0411–0414
Advanced online publication: 15.01.2010
DOI: 10.1055/s-0029-1219201; Art ID: G38909ST

Table 1 Synthesis of Symmetrical *N*-Methyl-2,3-diarylindoles **3a–e**

2, 3	Ar	Yield of **3** (%)[a]
a	Ph	91
b	4-MeC_6H_4	90
c	4-EtC_6H_4	86
d	4-*t*-BuC_6H_4	79
e	4-ClC_6H_4	83

[a] Yields of isolated products.

The reaction of **1** with arylboronic acids **2f–j** (1.1 equiv) resulted in site-selective formation of the (rather unstable) *N*-methyl-2-aryl-3-bromoindoles **4a–e** (Scheme 2, Table 2).[13,15] Excellent yields were again obtained for products derived from both electron-rich and electron-poor arylboronic acids.



Scheme 2 Synthesis of **4a–e**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), **2f–j** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 70 °C, 6 h.

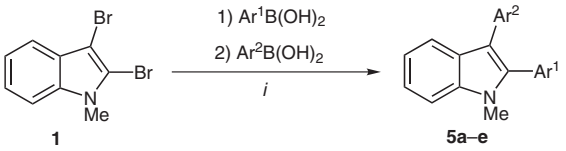
Table 2 Synthesis of 2-Aryl-3-bromoindoles **4a–e**

2	4	Ar	Yield of **4** (%)[a]
f	**a**	3,5-$Me_2C_6H_3$	86
g	**b**	2-$MeOC_6H_4$	71
h	**c**	2-$EtOC_6H_4$	73
i	**d**	3,4-$(MeO)_2C_6H_3$	79
j	**e**	4-$F_3CC_6H_4$	84

[a] Yields of isolated products.

Our next target was to prepare unsymmetrical 2,3-diarylindoles containing two different aryl groups. Due to the unstable nature of the monocoupling products **4**, we developed a one-pot protocol. The Suzuki–Miyaura reaction of *N*-methyl-2,3-dibromoindole with two different arylboronic acids afforded the unsymmetrical 2,3-diarylindoles **5a–e** in good yields (Scheme 3, Table 3).[16,17]

In all reactions, the best yields were obtained when $Pd(PPh_3)_4$ was used as the catalyst (3–4 mol%). The use of $Pd(OAc)_2$ in the presence of XPhos[18] or SPhos[18] gave similar results in terms of yield. However, the employment of $Pd(PPh_3)_4$ is significantly cheaper. For the monocoupling (synthesis of **4a–e** and the first step of the one-pot synthesis of **5a–e**) it proved to be important to carry out the reaction at 70 °C in order to achieve a good site-selectivity. In contrast, the synthesis of **3a–e** and the second step of the one-pot synthesis of **5a–e** were carried out at 110 °C. Potassium phosphate was employed as the base. The structures are established by 2D NMR experiments and X-ray structural analyses.



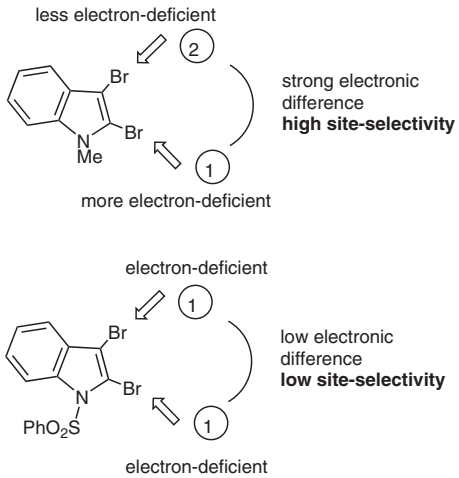
Scheme 3 Synthesis of **5a–e**. *Reagents and conditions*: (*i*) 1) **1** (1.0 equiv), **2k** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (4 mol%), 1,4-dioxane, 70 °C, 6 h; 2) **2a**,**e**,**f**,**j**,**l** (1.2 equiv), K_3PO_4 (1.5 equiv), 110 °C, 8 h.

Table 3 Synthesis of Unsymmetrical 2,3-Diarylindoles **5a–e**

2	5	Ar^1	Ar^2	Yield of **5** (%)[a]
k,**a**	**a**	2,5-$(MeO)_2C_6H_3$	Ph	69
k,**f**	**b**	2,5-$(MeO)_2C_6H_3$	3,5-$Me_2C_6H_3$	67
k,**e**	**c**	2,5-$(MeO)_2C_6H_3$	4-ClC_6H_4	59
k,**l**	**d**	2,5-$(MeO)_2C_6H_3$	4-FC_6H_4	71
k,**j**	**e**	2,5-$(MeO)_2C_6H_3$	4-$F_3CC_6H_4$	63

[a] Yields of isolated products.

The oxidative addition of palladium usually occurs first at the most electron-deficient carbon atom.[5] The site-selective formation of **4a–e** and **5a–e** can be explained by the fact that carbon atom C-2 is more electron-deficient than C-3 (Scheme 4). The nitrogen protective group seems to play an important role. Gribble and Liu reported[12] that the reaction of *N*-phenylsulfonyl-protected 2,3-diiodo-, 2,3-dibromo-, 2-iodo-3-bromo-, and 2-bromo-3-iodoindole with one equivalent of (4-methylphenyl)boronic acid resulted in the formation of mixtures of the 2,3-diarylindoles and of the starting material instead of the



Scheme 4 Possible explanation for the site-selectivity of the Suzuki–Miyaura reactions of **1**

monocoupling product. This might be explained by the strong electron-withdrawing effect of the sulfonyl group which results in an increased reactivity of both carbon C-2 and C-3 of the indole moiety and a less pronounced difference between their electronic character. In case of *N*-methyl-2,3-dibromoindole (**1**) the electronic character of C-2 and C-3 appears to be sufficiently different because site-selective transformations are observed.

In conclusion, we have reported the synthesis of symmetrical and unsymmetrical 2,3-diarylindoles by Suzuki–Miyaura reactions of *N*-methyl-2,3-dibromoindole. The nitrogen protective groups play an important role for the site-selectivity.

Acknowledgment

Financial support by State of Pakistan (HEC scholarships for M.H. and I.U.), by the DAAD (scholarships for M.F.I., A.A. and O.-U.-R.A.), and by the State of Mecklenburg-Vorpommern (scholarship for M.H.) is gratefully acknowledged.

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(13) **General Procedure for the Synthesis of 3a–e and 4a–e**
The reaction was carried out in a pressure tube. A 1,4-dioxane solution (4 mL) of **1**, K_3PO_4, $Pd(PPh_3)_4$, and arylboronic acid **2** was stirred at 110 °C or 70 °C for 6 h or 8 h. After cooling to 20 °C, a sat. aq solution of NH_4Cl was added. The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, heptanes).

(14) **2,3-Bis(4-ethylphenyl)-1-methyl-1*H*-indole (3c)**
Starting with **1** (289 mg, 1.0 mmol), **2c** (262 mg, 2.3 mmol), K_3PO_4 (446 mg, 2.1 mmol), $Pd(PPh_3)_4$ (3 mol%), and 1,4-dioxane (4 mL), **3c** was isolated as a yellowish oil (291 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.05 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.40 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.48 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.42 (s, 3 H, NCH_3), 6.90–6.96 (m, 3 H, ArH), 7.02–7.10 (m, 7 H, ArH), 7.25 (d, *J* = 8.2 Hz, 1 H, ArH), 7.51 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.8 (CH_3), 16.0 (CH_3), 29.1 (CH_2), 29.2 (CH_2), 31.2 (CH_3), 110.7 (CH), 115.4 (C), 120.0 (CH), 121.0 (CH), 123.0 (CH), 128.1 (C), 128.5 (2 CH), 128.7 (2CH), 130.3 (C), 130.6 (2 CH), 132.0 (2 CH), 133.7 (C), 138.3 (C), 138.4 (C), 142.0 (C), 144.9 (C). IR (ATR): ν = 3047 (w), 3022 (w), 2961 (s), 2928 (w), 1797 (w), 1765 (w), 1726 (w), 1519 (m), 1463 (s), 1362 (m), 1325 (m), 1257 (m), 1131 (w), 1115 (w), 1089 (m), 1060 (w), 1017 (m), 967 (w), 923 (w), 869 (m), 836 (s), 801 (w), 740 (s), 652 (w), 629 (m), 545 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 340 (28) $[M + 1]^+$, 339 (100) $[M^+]$, 324 (34), 309 (5), 294 (5), 281 (5), 278 (4), 146 (5). HRMS (EI): *m/z* calcd for $C_{25}H_{25}N$ $[M^+]$: 339.19815; found: 339.197901.

(15) **3-Bromo-2-(3,4-dimethoxyphenyl)-1-methyl-1*H*-indole (4d)**
Starting with **1** (289 mg, 1.0 mmol), **2i** (200 mg, 1.1 mmol), K_3PO_4 (318 mg, 1.5 mmol), $Pd(PPh_3)_4$ (3 mol%), and 1,4-dioxane (4 mL), **4d** was isolated as a yellowish solid (272 mg, 79%), mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3 H, NCH_3), 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.93–6.95 (m, 2 H, ArH), 7.11–7.27 (m, 4 H, ArH),

7.50–7.53 (m, 1 H, ArH). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 30.6 (CH_3), 54.9 (OCH_3), 55.0 (OCH_3), 88.9 (C), 108.6 (CH), 109.9 (CH), 112.8 (CH), 118.2 (CH), 119.5 (CH), 121.7 (CH), 121.8 (C), 122.4 (CH), 126.1 (C), 135.7 (C), 137.0 (C), 147.8 (C), 148.4 (C). IR (ATR): ν = 3052 (w), 2960 (w), 2924 (w), 1607 (w), 1584 (w), 1502 (m), 1462 (m), 1445 (m), 1404 (w), 1379 (w), 1339 (w), 1317 (w), 1257 (s), 1239 (s), 1168 (m), 1136 (s), 1022 (s), 945 (m), 911 (w), 858 (m), 812 (m), 777 (w), 750 (s), 654 (m), 575 (w), 547 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 348 (18) [M + 1, ^{81}Br]$^+$, 347 (100) [M$^+$, ^{81}Br], 346 (19) [M + 1, ^{79}Br]$^+$, 345 (98) [M$^+$, ^{79}Br], 331 (3), 302 (5), 302 (5), 300(4), 267 (3), 251 (5), 223 (24), 180 (10), 152 (7), 102 (5), 89 (2). HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{16}O_2NBr$ [M$^+$, ^{81}Br]: 347.03385; found: 347.033958; *m/z* calcd for $C_{17}H_{16}O_2NBr$ [M$^+$, ^{79}Br]: 345.03589; found: 345.035679.

(16) **General procedure for the synthesis of 5a-e**

The reaction was carried out in a pressure tube. To a dioxane suspension (4 mL) of **1** (215 mg, 0.75 mmol), $Pd(PPh_3)_4$ (3 mol%), and $Ar^1B(OH)_2$ (0.82 mmol) was added K_3PO_4 (238 mg, 1.1 mmol), and the solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 70 °C under argon atmosphere for 6 h. The mixture was cooled to 20 °C. To the solution was added $Ar^2B(OH)_2$ (0.90 mmol) and K_3PO_4 (238 mg, 1.1 mmol), and the solution was degassed again. The reaction mixture was heated under argon atmosphere for 8 h at 110 °C. After cooling to 20 °C, the solution was diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, heptanes).

(17) **2-(2,5-Dimethoxyphenyl)-1-methyl-3-phenyl-1*H*-indole (5a)**

Starting with **1** (215 mg, 0.75 mmol), **2k** (150 mg, 0.82 mmol), **2a** (110 mg, 0.9 mmol), K_3PO_4 (488 mg, 2.3 mmol), $Pd(PPh_3)_4$ (4 mol%), and 1,4-dioxane (4 mL), **5a** was isolated as a yellowish oil (177 mg, 69%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.40 (s, 3 H, NCH_3), 3.44 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 6.54 (d, *J* = 3.1 Hz, 1 H, ArH), 6.77–6.82 (m, 1 H, ArH), 6.87–6.98 (m, 3 H, ArH), 7.04–7.18 (m, 5 H, ArH), 7.28 (d, *J* = 8.3 Hz, 1 H, ArH), 7.56 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.7 (NCH_3), 55.9 (OCH_3), 56.3 (OCH_3), 110.5 (CH), 113.3 (CH), 115.7 (C), 115.8 (CH), 119.5 (CH), 119.8 (CH), 120.6 (CH), 122.5 (C), 122.6 (CH), 126.2 (CH), 127.7 (C), 129.0 (2 CH), 130.1 (2 CH), 135.7 (C), 136.7 (C), 138.1 (C), 153.7 (C), 154.4 (C). IR (ATR): ν = 3051 (w), 2936 (w), 2832 (w), 1736 (w), 1712 (w), 1602 (w), 1549 (w), 1502 (m), 1485 (m), 1463 (m), 1366 (m), 1273 (m), 1225 (m), 1210 (m), 1039 (m), 1020 (m), 941 (w), 918 (w), 876 (w), 805 (w), 772 (m), 735 (s), 700 (s), 616 (w), 570 (w), 531 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 344 (26) [M + 1]$^+$, 343 (100) [M$^+$], 342 (15), 328 (6), 311 (4), 297 (7), 268 (5), 230 (5), 171 (4), 121 (5). HRMS (EI, 70 eV): *m/z* calcd for $C_{23}H_{21}O_2N$ [M$^+$]: 343.15668; found: 343.156144.

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