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Bis-Suzuki reactions of 2,3-dihaloindoles. A convenient synthesis of 2,3-diarylindoles

Yanbing Liu and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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Abstract

A convenient, one-pot synthesis of 2,3-diarylindoles **4** is described via a bis-Suzuki palladium-catalyzed cross coupling of 2,3-dihalo-1-(phenylsulfonyl)indoles **1** with arylboronic acids **2**, followed by cleavage of the *N*-protecting group to give **4**. The anti-inflammatory drug indoxole (**4c**) is prepared in high yield.

Keywords: Suzuki reaction; palladium-catalyzed cross coupling; 2,3-diarylindoles; indoxole.

Diarylheterocycles have important anti-inflammatory properties and the early discovery by Szmuszkovicz that 2,3-diarylindoles are active in this regard[1] opened the door for the recent development of Celebrex and Vioxx as potent COX-2 inhibitors for arthritic pain relief.[2] 'Indoxole' (2,3-bis(4-methoxyphenyl)indole) is a potent anti-inflammatory, anti-arthritic, and antipyretic drug in animals, with activity comparable to, or greater than aspirin and indomethacin in certain assays.[3] In view of the continuing interest in the biological activity of 2,3-diarylindoles,[4] we now describe a convenient synthesis of these compounds via a bis-Suzuki cross-coupling reaction[5] between 2,3-dihaloindoles **1** and arylboronic acids **2**.[6] The resulting products **3** can be easily cleaved to the corresponding 2,3-diarylindoles **4**.

Dihaloindoles **1** are readily prepared from indole (**5**) as previously described[7] (Scheme 1), and the arylboronic acids **2** are commercially available. Our results are summarized in Table 1.

* Corresponding author. Tel: 1-603-646-3118; fax: 1-603-646-3946; e-mail: grib@dartmouth.edu

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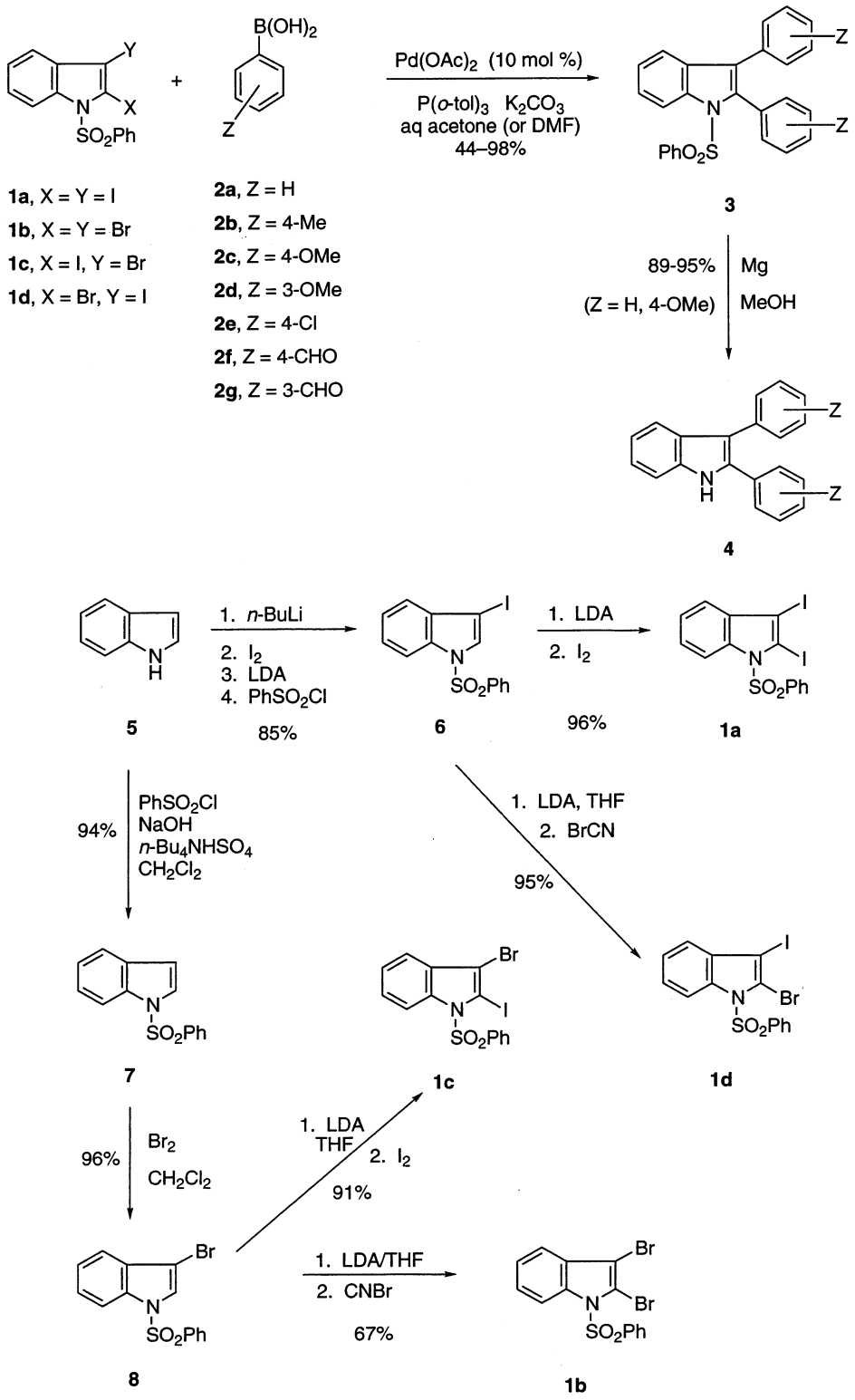
B(OH)2
Pd(OAc)2 (10 mol %)
P(o-tol)3 K2CO3
aq acetone (or DMF)
44–98%
1a, X = Y = I
1b, X = Y = Br
1c, X = I, Y = Br
1d, X = Br, Y = I
2a, Z = H
2b, Z = 4-Me
2c, Z = 4-OMe
2d, Z = 3-OMe
2e, Z = 4-Cl
2f, Z = 4-CHO
2g, Z = 3-CHO
3
89-95%
(Z = H, 4-OMe)
Mg
MeOH
4
5
1. n-BuLi
2. I2
3. LDA
4. PhSO2Cl
85%
6
1. LDA
2. I2
96%
1a
94%
PhSO2Cl
NaOH
n-Bu4NHSO4
CH2Cl2
1. LDA, THF
2. BrCN
95%
7
1c
1d
96%
Br2
CH2Cl2
1. LDA
THF
2. I2
91%
8
1. LDA/THF
2. CNBr
67%
1b

Scheme 1.

Table 1
Reaction of 2,3-dihaloindoles **1** with arylboronic acids **2** to give 2,3-diarylindoles **3**[a]

1[b]	**2**[c] (Z)	Solvent	**3**, Yield, %[d]
1a	**2a** (H)	Acetone–water (2:1)	**3a**, 83
1a	**2b** (4-Me)	Acetone–water (2:1)	**3b**, 98
1a	**2c** (4-OMe)	Acetone–water (2:1)	**3c**, 85
1a	**2d** (3-OMe)	Acetone–water (2:1)	**3d**, 87
1a	**2e** (4-Cl)	Acetone–water (2:1)	**3e**, 55
1a	**2f** (4-CHO)	DMF	**3f**, 50
1a	**2g** (3-CHO)	DMF	**3g**, 44
1b	**2a** (H)	Acetone–water (2:1)	**3a**, 83
1c	**2b** (4-Me)	Acetone–water (2:1)	**3b**, 95
1d	**2b** (4-Me)	Acetone–water (2:1)	**3b**, 95

[a] Typical conditions: **1** (0.196 mmol), **2** (0.432 mmol), $Pd(OAc)_2$ (0.0196 mmol), P(*o*-tol)$_3$ (0.0394 mmol), K_2CO_3 (2.4 mmol), acetone–water (2:1) (15 mL), 70°C, 5 h.
[b] Prepared according to procedures given in Ref. 6.
[c] Commercially available.
[d] Yields refer to isolated and purified (flash chromatographed) products.

Two equivalents of boronic acids **2** are used under typical Suzuki conditions[8] with 10 mol% $Pd(OAc)_2$. Electron-rich boronic acids **2b–d** give excellent yields of 2,3-diarylindoles (85–98%), while electron-deficient boronic acids **2e–g** afford lower yields (44–55%). In fact, these latter arylboronic acids (**2f**,**2g**) only gave the desired products when DMF was employed as the solvent. Although most of our work was done with diiodoindole **1a**, brominated indoles **1b–d** performed equally well in the few cases studied (Table 1, last three entries).

Attempts thus far to achieve tandem bis-Suzuki reactions leading to unsymmetrical 2,3-diarylindoles have not been successful. For example, reaction of **1a–d** each with one equivalent of **2b** affords mixtures of monosubstituted products, **3**, and **1**. In an attempt to circumvent this lack of specificity, we are currently examining tandem-Suzuki reactions of **1** where one of the halogens is chlorine, which will presumably be less reactive than bromine or iodine under standard Suzuki conditions. In this regard, Fu has recently developed new catalysts for effecting Suzuki cross-coupling of aryl chlorides,[5,9] and, thus, a tandem sequence giving unsymmetrical 2,3-diarylindoles seems feasible. Shen has reported mono-Suzuki reactions of 1,1-dibromo-1-alkenes.[5b]

The 2,3-diarylindoles **3** can be readily cleaved with Mg/MeOH[10] to afford the unsubstituted indoles **4**. Thus, treatment of **3a** (Z = H) and **3c** (Z = 4-OMe) affords **4a** and **4c** (indoxole) in 89 and 95% yields, respectively. All new 2,3-diarylindoles **3** exhibited satisfactory spectral and elemental analytical data,[11] and known compounds were in agreement with literature data. The general procedure is given.[12]

All of the previous syntheses of 2,3-diarylindoles **4** have involved de novo indole ring construction (e.g. Fischer, Bischler, Larock, Fürstner).[1,4,13] Our method, starting with indole and, presumably, ring-substituted indoles, should lend itself to the efficient and convergent preparation of libraries of 2,3-diarylindoles given the availability of arylboronic acids.

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11. 2,3-Diphenyl-1-(phenylsulfonyl)indole (**3a**) (83%): Mp 174–176°C; IR (KBr) υ_{max} 1446, 1356, 1176, 1086 cm^{-1}; ^1H NMR (CDCl3) δ 8.43 (m, 1H), 7.51–7.41 (m, 5H), 7.36–7.21 (m, 11H), 7.11–7.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.4, 137.5, 137.0, 133.7, 132.8, 132.3, 131.0, 130.7, 130.0, 128.9, 128.7, 128.4, 127.5, 127.2, 127.1, 125.5, 125.1, 124.5, 120.2, 116.5. HRMS m/z calcd for $C_{26}H_{19}NO_2S$ (M^+) 409.1137, found 409.1138. Anal. calcd for $C_{26}H_{19}NO_2S$: C, 76.26; H, 4.68; N, 3.42; S, 7.83. Found: C, 76.34; H, 4.73; N, 3.50; S, 7.82. 2,3-Bis(4-methylphenyl)-1-(phenylsulfonyl)indole (**3b**) (98%): Mp 153–155°C; IR (KBr) υ_{max} 1444, 1383, 1180, 1079, 1000, 826 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.35 (m, 1H), 7.62 (m, 1H), 7.54 (m, 2H), 7.48–7.40 (m, 4H), 7.32 (m, 1H), 7.19 (m, 2H), 7.13 (m, 2H), 7.09 (m, 2H), 7.02 (m, 2H), 2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 137.5, 137.0, 136.8, 133.7, 132.1, 131.0, 129.8, 129.2, 128.8, 128.3, 128.1, 127.1, 125.3, 124.9, 124.4, 120.2, 116.5, 21.7, 21.4. HRMS m/z calcd for $C_{28}H_{23}NO_2S$ (M^+) 437.1450, found 437.1446. Anal. calcd for $C_{28}H_{23}NO_2S$: C, 76.86; H, 5.30; N, 3.20; S, 7.33. Found: C, 76.98; H, 5.37; N, 3.26; S, 7.30. 2,3-Bis(4-methoxyphenyl)-1-(phenylsulfonyl)indole (**3c**) (85%): Mp 197–199°C; IR (KBr) υ_{max} 1607, 1500, 1444, 1287, 1242, 1175, 1076, 1030, 832 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.35 (m, 1H), 7.61–7.42 (m, 7H), 7.32 (m, 1H), 7.20 (m, 2H), 7.06 (m, 2H), 6.85 (m, 4H), 3.84 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8. 158.6, 138.4, 137.5, 136.6, 133.7, 133.6, 131.1, 130.9, 128.8, 127.1, 125.2, 125.1, 124.41, 124.39, 123.2, 120.1, 116.5, 113.9, 113.0, 55.4, 55.3. HRMS m/z calcd for $C_{28}H_{23}NO_4S$ (M^+) 469.1348, found 469.1353. Anal. calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.94; N, 2.98; S, 6.82. Found: C, 71.44; H, 5.03; N, 3.03; S, 6.71. 2,3-Bis(3-methoxyphenyl)-1-(phenylsulfonyl)indole (**3d**) (87%): Mp 112.5–114.5°C; IR (KBr) υ_{max} 1597, 1446, 1374, 1262, 1178, 1090 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.37 (m, 1H), 7.63–7.58 (m, 3H), 7.50–7.45 (m, 4H), 7.35 (m, 1H), 7.25–7.19 (m, 2H), 6.96 (m, 1H), 6.89 (m, 2H), 6.81–6.76 (m, 2H), 6.66 (m, 1H), 3.74 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 158.7, 138.4, 137.5, 136.8, 134.1, 133.8, 132.2, 130.5, 129.4, 128.9, 128.5, 127.2, 125.5, 124.9, 124.8, 124.5, 122.4, 120.3, 117.6, 116.4, 115.2, 114.8, 113.3, 55.5, 55.3. HRMS m/z calcd for $C_{28}H_{23}NO_4S$ (M^+) 469.1348, found 469.1344. Anal. calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.94; N, 2.98; S, 6.82. Found: C, 71.42; H, 5.03; N, 3.04; S, 6.71. 2,3-Bis(4-chlorophenyl)-1-(phenylsulfonyl)indole (**3e**) (55%): Mp 150.5–152°C; IR (KBr) υ_{max} 1495, 1444, 1371, 1186, 1090, 995, 832 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.36 (m, 1H), 7.65 (m, 1H), 7.58 (m, 2H), 7.51–7.33 (m, 11H), 7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.5, 135.8, 135.1, 134.0, 133.43, 133.40, 131.2, 130.9, 130.2, 129.2, 129.0, 128.9, 128.1, 127.0, 125.9, 124.8, 124.4, 120.1, 116.5. HRMS m/z calcd for $C_{26}H_{17}NCl_2O_2S$ (M^+) 477.0357, found 477.0350. Anal. calcd for $C_{26}H_{17}NCl_2O_2S$: C, 65.28; H, 3.58; N, 2.93; Cl, 14.82. Found: C, 65.29; H, 3.68; N, 2.92; Cl, 14.74. 2,3-Bis(4-formylphenyl)-1-(phenylsulfonyl)indole (**3f**) (50%): Mp 208–210°C; IR (KBr) υ_{max} 1702, 1607, 1444, 1376, 1186, 1085, 843 cm^{-1}, ^1H NMR ($CDCl_3$) δ 10.07 (s, 1H), 9.97 (s, 1H), 8.44 (m, 1H), 7.84 (m, 2H), 7.77 (m, 2H), 7.53–7.43 (m, 7H), 7.38–7.32 (m, 3H), 7.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 192.0, 191.9, 138.9, 137.8, 137.7, 136.8, 136.3, 136.2, 135.3, 134.3, 132.8, 130.6, 130.0, 129.8, 129.2, 129.0, 127.0, 126.5, 125.2, 125.1, 120.2, 116.7. HRMS m/z calcd for $C_{28}H_{19}NO_4S$ (M^+) 465.1035, found 465.1041. Anal. calcd for $C_{28}H_{19}NO_4S$: C, 72.24; H, 4.12; N, 3.01. Found: C, 71.87; H, 4.31; N, 2.99. 2,3-Bis(3-formylphenyl)-1-(phenylsulfonyl)indole (**3g**) (44%): Mp 152–154°C; IR (KBr) υ_{max} 1700, 1450, 1376, 1189, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.01 (s, 1H), 9.95 (s, 1H), 8.40 (m, 1H), 7.97–7.37 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 192.1, 191.8, 138.1, 137.5, 136.8, 136.4, 136.0, 135.9, 135.7, 134.3, 133.5, 133.2, 131.8, 130.9, 130.1, 129.9, 129.5, 129.2, 129.1, 128.6, 126.9, 126.3, 125.0, 124.6, 120.1, 116.4. HRMS m/z calcd for $C_{28}H_{19}NO_4S$ (M^+) 465.1035, found 465.1032. Anal. calcd for $C_{28}H_{19}NO_4S$: C, 72.24; H, 4.12; N, 3.01. Found: C, 71.72; H, 4.14; N, 2.95.
12. General procedure: A mixture of **1a** (0.100 g, 0.196 mmol), arylboronic acid (0.432 mmol), palladium acetate (4.4 mg, 0.0196 mmol), tri(*o*-tolyl)phosphine (12 mg, 0.039 mmol), and potassium carbonate (0.33 g, 2.4 mmol) in a 3-neck round bottom flask was flushed with nitrogen for 10 min. A solution of acetone (10 mL) and water (5 mL) was added by syringe and the mixture was heated at 70°C (reflux) for 5 h under nitrogen (monitored by TLC). The cooled reaction mixture was extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to afford crude product. Flash chromatography over silica gel (EtOAc/hexane, 30/70) gave pure products.[11] Recrystallization from mixtures of ether and hexane afforded analytical samples.[11]
13. For a recent review of these and other indole ring syntheses, see Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.