Synthesis of 2,5,6-Trisubstituted Benzimidazoles by Heck and Subsequent 6π-Electrocyclization–Dehydrogenation Reactions of 2,4,5-Tribromo-*N*-methylimidazole and 2-Aryl-4,5-dibromo-*N*-methylimidazoles

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Abstract: 2,5,6-Trisubstituted benzimidazoles were prepared by Heck reactions of 2,4,5-tribromo-*N*-methylimidazole and 2-aryl-4,5-dibromo-*N*-methyl-imidazoles and subsequent 6π-electrocyclization–dehydrogenation reactions.

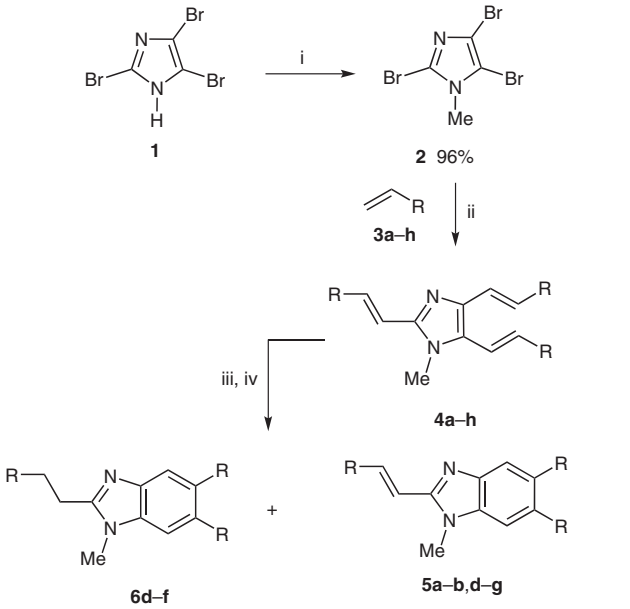
Key words: catalysis, palladium, Heck reaction, electrocyclization, benzimidazole

Benzimidazoles are of great relevance in medicinal chemistry and crop protection.[1] They show a wide range of pharmacological activities. Benzimidazoles have been used, for example, as antifungals,[2] antibacterials,[2,3] antihelminthics,[4] 5-HT receptor antagonists,[5] and thrombin receptor antagonists.[6] Benzimidazole drugs (antihelmintic compounds albendazole, fenbendazole, oxfenbendazole, thiabendazole, mebendazole, and inhibitors of proton pump omeprazole, lansoprazole, pantoprazole) represent substances used in both human and veterinary medicine. The benzimidazole benomyl is a widely used plant fungicide. The benzimidazole moiety occurs in a number of natural products. The most prominent one is vitamine B_{12}.[1]

Polyhalogenated molecules represent interesting substrates in palladium(0)-catalyzed cross-coupling reactions.[7] Recently, we have reported Suzuki–Miyaura and Heck reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, tetrabromoselenophene, dibromobenzofuran, dibromo-*N*-methylindole, and other polyhalogenated heterocycles.[8] Suzuki–Miyaura, Negishi, and Stille cross-coupling reactions of protected 2,4,5-tribromo- and 2,4,5-triiodoimidazole have been reported.[9] The first attack generally occurs at carbon atom C-2. Heck reactions of di- or trihalogenated imidazoles have, to the best of our knowledge, not yet been reported. Herein, we report the synthesis of 2,5,6-trisubstituted benzimidazoles[10] by Heck reactions of 2,4,5-tribromo-*N*-methylimidazole and 2-aryl-4,5-dibromo-*N*-methylimidazoles and subsequent domino[11] '6π-electrocyclization–dehydrogenation' reactions.[12] The products are not readily available by other methods.

Commercially available tribromoimidazole (**1**) was transformed into tribromo-*N*-methyl-imidazole (**2**) by reaction with potassium carbonate and methyl iodide in DMF (Scheme 1). The Heck reaction of **2** with acrylates **3a**–**g** (3.3 equiv) afforded the tri(alkenyl)-*N*-methyl-imidazoles **4a**–**g** in 73–86% yield (Table 1).[13,14] The Heck reaction of **2** with styrene **3h** gave product **4h**. The best yields were obtained when $Pd(OAc)_2$ (5 mol%) in the presence of tris(cyclohexyl)phosphane (TCHP, 10 mol%) was employed as the catalyst. During the optimization, the temperature also proved to be an important parameter. A clean transformation was observed when the reaction was carried out at 100 °C. Significant amounts of 2-alkenyl-4,5-dibromoimidazoles (0–10%) and of 2,5-di(alkenyl)-4-bromoimidazoles (15–30%) were formed when the reactions were carried out at 90 °C.

Heating of **4a**,**b** and **4d**–**g** in diphenyl ether for 24 hours at 200 °C resulted in 6π-electrocyclization. Subsequent addition of Pd/C and heating for further 48 hours at 200 °C afforded products **5a**,**b** and **5d**–**g**. Products **5a**,**b**,**g**



Scheme 1 Synthesis of **4a**–**h**, **5a**,**b**,**d**–**g** and **6d**–**f**. *Reagents and conditions*: *i*, **1** (1 equiv), MeI (2 equiv), K_2CO_3 (2 equiv), DMF, 20 °C, 14 h; *ii*, **2** (1 equiv), **3a**–**h** (3.3 equiv), $Pd(OAc)_2$ (5 mol%), TCHP (10 mol%), Et_3N, DMF, 100 °C, 24 h; *iii*, diphenylether, 200 °C, 24 h; *iv*, Pd/C (10 mol%), diphenylether, 200 °C, 48 h.

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were isolated in excellent yields. In case of **4c** and **4h**, the formation of a complex mixture was observed. In case of the **5d–f**, considerable amounts of the hydrogenated products **6d–f** were formed. Their formation can be explained by formation of one equivalent of hydrogen during the Pd/C-catalyzed dehydrogenation. The hydrogen thus formed reacts, again catalyzed by Pd/C, with the alkenyl group located at carbon atom C-2 to give products **6d–f**. It is surprising that the formation of hydrogenated products **6a**,**b**,**g** was not observed. This might be explained by the assumption that the electrocyclization, dehydrogenation and, thus, the formation of hydrogen, is slower for **4a**,**b**,**g** than for **4d–f**. Therefore, there is not sufficient time for the hydrogenation of products **5a**,**b**,**g**. On the other hand, the formation of products **6a**,**b**,**g** was observed when the reaction time was extended.

Table 1 Synthesis of **4a–h**, **5a**,**b**,**d–g**, and **6d–f**

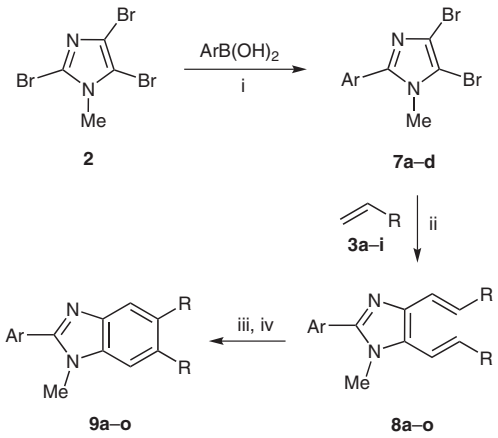
3–6	R	Yield of 4 (%)[a]	Yield of 5 (%)[a]	Yield of 6 (%)[a]
a	CO_2n-Bu	86	90	0
b	CO_2i-Bu	84	92	0
c	CO_2t-Bu	81	0[c]	0[c]
d	CO_2n-Hex	74	60	32
e	CO_2Et	73	48	40
f	CO_2Me	76	40	34
g	CO_2R[b]	82	88	0
h	4-MeC_6H_4	46	0[c]	0[c]

[a] Yields of isolated products.
[b] R = $CH_2CH(Et)(CH_2)_3CH_3$.
[c] Formation of a complex mixture.

The Suzuki–Miyaura reaction of tribromoimidazole **2** with different arylboronic acids afforded the 2-aryl-4,5-dibromoimidazoles **7a–d** in 78–96% yield (Scheme 2, Table 2). The best yields for this transformation were obtained using $Pd(PPh_3)_4$ (5 mol%) as the catalyst and an aqueous solution of K_2CO_3 (2 M) as the base (solvent: 1,4-dioxane–toluene).

The Heck reaction of **7a–d** with acrylates or styrenes **3a–i** afforded the 2-aryl-4,5-di(alkenyl)imidazoles **8a–o** in 52–91% yield (Scheme 2, Table 3).[13,15] The reactions were carried out under the same conditions as the synthesis of **4a–h**. Products **8a–o** were transformed to the benzimidazoles **9a–o** in 65–93% yield.[16,17]

In conclusion, we have reported an efficient synthesis of 2,5,6-trisubstituted benzimidazoles by Heck reactions of 2,4,5-tribromo-*N*-methylimidazole and 2-aryl-4,5-dibromo-*N*-methylimidazoles and subsequent 6π-electrocyclization–dehydrogenation reactions.



Scheme 2 Synthesis of **7**, **8a–o**, and **9a–o**. *Reagents and conditions*: *i*, **2** (1.0 equiv), $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 M), 1,4-dioxane–toluene (1:1), 100 °C, 12 h; *ii*, **7a–d** (1 equiv), **3a–i** (3.3 equiv), $Pd(OAc)_2$ (5 mol%), TCHP (10 mol%), Et_3N, DMF, 100 °C, 24 h; *iii*, diphenylether, 200 °C, 24 h; *iv*, Pd/C (10 mol%), diphenylether, 200 °C, 48 h.

Table 2 Synthesis of **7a–d**

7	Ar	Yield of 7 (%)[a]
a	4-(MeO)C_6H_4	78
b	4-MeC_6H_4	88
c	4-t-BuC_6H_4	96
d	3,5-$Me_2C_6H_3$	90

[a] Yields of isolated products.

Table 3 Synthesis of **8a–o** and **9a–o**

7	8,9	Ar	R	Yield of 8 (%)[a]	Yield of 9 (%)[a]
a	**a**	4-$MeOC_6H_4$	CO_2n-Bu	91	81
a	**b**	4-$MeOC_6H_4$	CO_2i-Bu	85	77
a	**c**	4-$MeOC_6H_4$	CO_2t-Bu	89	90
a	**d**	4-$MeOC_6H_4$	CO_2n-Hex	78	84
a	**e**	4-$MeOC_6H_4$	4-MeC_6H_4	63	79
a	**f**	4-$MeOC_6H_4$	4-t-BuC_6H_4	52	71
b	**g**	4-MeC_6H_4	4-(MeO)C_6H_4	77	83
b	**h**	4-MeC_6H_4	CO_2n-Hex	75	87
c	**k**	4-t-BuC_6H_4	4-$MeOC_6H_4$	64	65
c	**l**	4-t-BuC_6H_4	CO_2Et	81	93
c	**m**	4-t-BuC_6H_4	4-MeC_6H_4	56	77
d	**n**	3,5-$Me_2C_6H_3$	CO_2n-Bu	74	90
d	**o**	3,5-$Me_2C_6H_3$	4-t-BuC_6H_4	65	72

[a] Yields of isolated products.

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(13) **General Procedure for the Synthesis of 4a-h and 8a-d**
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 **2** or **7** (1.0 mmol), Et_3N (1.1 mL, 8.0 mmol) and the alkene (2.5 equiv per bromine atom of the substrate). The reaction mixture was stirred at 100 °C for 24 h. The solution was cooled to 20 °C, poured into a mixture of H_2O and CH_2Cl_2 (25 mL each), and the organic and the aqueous layer 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, heptanes–EtOAc).

(14) **(2*E*,2′*E*,2″*E*)-Trimethyl 3,3′,3″-(1-Methyl-1*H*-imidazole-2,4,5-triyl)triacrylate (4f)**
Starting with **2** (318 mg, 1.0 mmol), **4f** was isolated as a yellow highly viscous oil (254 mg, 76%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, NCH_3), 3.72, 3.75, 3.76 (s, 3 H, OCH_3), 6.20 (d, 1 H, *J* = 16.2 Hz, CH), 6.74 (d, 1 H, *J* = 15.4 Hz, CH), 6.91 (d, 1 H, *J* = 15.3 Hz, CH), 7.41 (d, 1 H, *J* = 15.3 Hz, CH), 7.53 (d, 1 H, *J* = 16.2 Hz, CH), 7.57 (d, 1 H, *J* = 15.4 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.7 (NCH_3), 51.7 (OCH_3), 52.0 (2 OCH_3), 120.0, 121.0, 124.1, 127.4, 128.4 (CH), 130.7 (C), 133.1 (CH), 140.3, 146.1 (C), 166.5, 166.6, 167.4 (CO). IR (KBr): 3041, 2991, 2948, 2847 (w), 1708, 1695, 1622 (s), 1519 (w), 1431, 1411, 1306 (m), 1279, 1261, 1193, 1165 (s), 1065, 1034, 1014, 984 (m), 959 (s), 931, 879, 869, 811, 748, 713, 700, 665, 611 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 334(74) $[M]^+$, 303(41), 276(13), 275(82), 244(16), 243(100), 231(27), 216(12), 215(18), 199(17), 185(28), 184(10), 171(25), 157(44), 156(21). HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_{18}O_6N_2$ $[M]^+$: 334.11594; found: 334.11621.

(15) **(2*E*,2′*E*)-Dibutyl 3,3′-[2-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole-4,5-diyl]diacrylate (8a)**
Starting with **7** (346 mg, 1.0 mmol), **8a** was isolated as a yellow highly viscous oil (400 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.4 Hz, CH_3), 0.90 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.31–1.41 (m, 4 H, 2 CH_2), 1.55–1.65 (m, 4 H, 2 CH_2), 3.64 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 4.12 (t, 2 H, *J* = 6.6 Hz, CH_2O), 4.16 (t, 2 H, *J* = 6.7 Hz, CH_2O), 6.20 (d, 1 H, *J* = 16.1 Hz, CH), 6.77 (d, 1 H, *J* = 15.3 Hz, CH), 6.92 (dd, 2 H, *J* = 2.0, 6.8 Hz, ArH), 7.48 (dd, 2 H, *J* = 2.1, 6.8 Hz, ArH), 7.62 (d, 1 H, *J* = 16.1 Hz, CH), 7.69 (d, 1 H, *J* = 15.3 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2 CH_3), 19.2 (2 CH_2), 30.7, 30.8 (CH_2), 33.9 (NCH_3), 55.4 (OCH_3), 64.2, 64.8 (CH_2O), 114.2 (2 CH), 119.1, 119.4 (CH), 121.6 (C), 129.1 (CH), 130.0 (C), 130.7 (2 CH), 133.5 (CH), 139.7, 152.1, 160.8 (C), 166.7, 167.5 (CO). IR (KBr): 2957, 2933, 2871 (w), 1694 (s), 1622, 1612 (m), 1578, 1531 (w), 1456, 1443 (m), 1387, 1338 (w), 1278 (m), 1249, 1158 (s), 1114, 1065, 1024, 965, 835 (m), 815, 793 (w), 741 (m), 695, 638, 620, 536 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 440(30) $[M]^+$, 339(25), 338(20), 284(22), 283(100), 281(12), 266(14), 265(71), 240(18), 239(96), 237(17), 41(11). HRMS (EI, 70 eV): *m/z* calcd for $C_{25}H_{32}O_5N_2$ $[M]^+$: 440.23057; found: 440.22968.

(16) **General Procedure for the Synthesis of Benzimidazoles 5a,b,d–g, 6d–f, and 9a–d**
A diphenylether solution (3 mL) of **8a–d** or **4a,b,d–g** 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 argon atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes–EtOAc).

(17) **Dibutyl 2-(4-Methoxyphenyl)-1-methyl-1*H*-benzo[*d*]imidazole-5,6-dicarboxylate (9a)**
Starting with **7** (346 mg, 1.0 mmol), **9a** was prepared over two steps as a yellowish highly viscous oil (354 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 6 H, *J* = 7.3 Hz, 2 CH_3), 1.31–1.43 (m, 4 H, 2 CH_2), 1.61–1.70 (m, 4 H, 2 CH_2), 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, NCH_3), 4.25 (t, 4 H, *J* = 6.7 Hz, 2 CH_2O), 6.96 (dd, 2 H, *J* = 2.0, 6.9 Hz, ArH), 7.64 (dd, 2 H, *J* = 2.0, 6.5 Hz, ArH), 7.65 (s, 1 H, ArH), 8.05 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.7 (2 CH_3), 18.1, 18.2 (CH_2), 29.5, 29.6 (CH_2), 31.1 (NCH_3), 54.4 (OCH_3), 64.3, 64.6 (CH_2O), 111.0 (CH), 113.3 (2 CH), 119.9 (CH), 120.5, 125.9, 126.1 (C), 129.9 (2 CH), 136.5, 143.0, 156.0, 160.3 (C), 167.1, 167.3 (CO). IR (KBr): 2957, 2932, 2872 (w), 1713 (s), 1609 (m), 1577, 1532 (w), 1478, 1463, 1438 (m), 1381, 1358 (w), 1327, 1306, 1271 (m), 1245, 1174 (s), 1099, 1059, 1024, 962, 943, 836, 782, 740 (m), 661, 638, 588, 549 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 438(45) $[M]^+$, 310(19), 309(100), 308(12). HRMS (EI, 70 eV): *m/z* calcd for $C_{25}H_{30}O_5N_2$ $[M]^+$: 438.21492; found: 438.21393.