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Synthesis of 3-Aryl-2-nitroindoles by Palladium-Catalyzed CH-Activation Reactions

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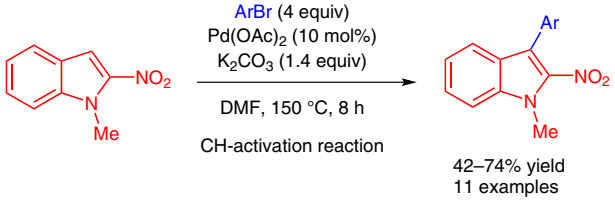

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Abstract 3-Aryl-2-nitroindoles were prepared via CH-activation reactions of *N*-methyl-2-nitroindole.

Key words catalysis, palladium, CH-activation reaction, indole

The indole moiety is found in a wide range of biologically active compounds, drugs, and natural products. Indoles are present as the core of neuromodulators and neurotransmitters, such as serotonin and tryptamine, and of well-known super-potent toxins, such as strychnine and lysergic acid diethylamide. Indoles have been reported to exhibit anticancer, immunomodulatory, vasodilator, antihypertensive, antipsychotic, antidepressant, anti-inflammatory, antiviral, and antimicrobic properties.[1] Recently, it was found that simple 3-aryl-substituted indoles show significant activity against Gram-positive pathogens.[2] Moreover, they exhibit antidepressant, anticancer, and antimicrobial properties (Figure 1).[1]

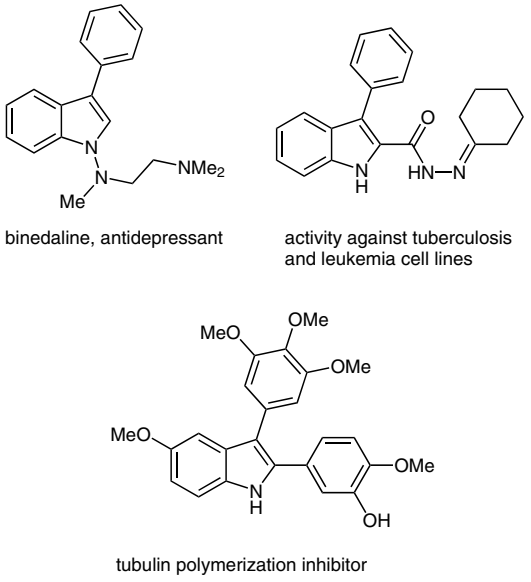


Figure 1 Structure of biologically active 3-arylindoles

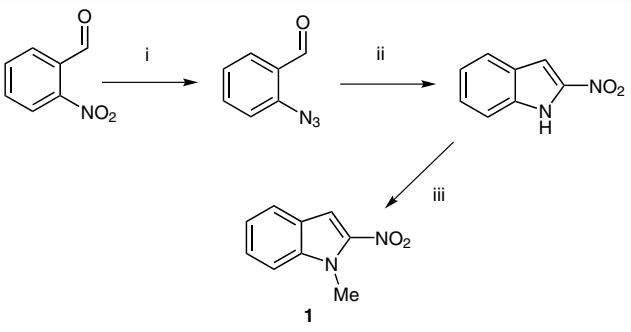
3-Aryl-substituted indoles have been prepared by Suzuki–Miyaura reactions of brominated indoles as the starting materials. Although this synthetic strategy is very efficient,[3] it is limited by the need for additional synthetic steps, such as the synthesis of the required bromoindoles by halogenation and the employment of relatively expensive boronic acids as starting materials. The use of unsubstituted *N*-methylindole as a substrate in CH-activation reactions has been reported,[4] although in several cases expensive catalysts[4a] or reagents[4b] had to be used to avoid the formation of regioisomeric mixtures of 2- and 3-arylindoles.[4c] In this context, a study of the regioselectivity depending on the conditions has also been reported.[5] It was shown that for N-unsubstituted indoles the regioselectivity can be controlled by the choice of a base; namely a magnesium salt. For *N*-methyl indoles, the authors developed a convenient method for the selective synthesis of 2-arylindoles (Scheme 2).[6] A synthesis of 2-nitro-3-phenylindole was developed before by Walser et al. based on the functionalization of 2-acetyl-3-nitro-3-phenyl-3*H*-indole. The synthesis is, however, rather complicated and no study of the preparative scope was reported.[7]

Regioselective palladium-catalyzed CH-activation reactions of indoles at C-3 have, to the best of our knowledge, not been reported to date. Nearly all reactions known so far lead to functionalization of the more electron-poor and, thus more reactive, C-2. It has been reported that, in case of

unsubstituted benzofuran, the desired 3-substituted product could be obtained, however, only as a minor component in a 9:1 mixture.[8] Corresponding reactions for benzothiophenes are possible, but require expensive catalysts and proceed in low yields.[9] Recently, a more efficient protocol using simple palladium on carbon has been reported.[10]

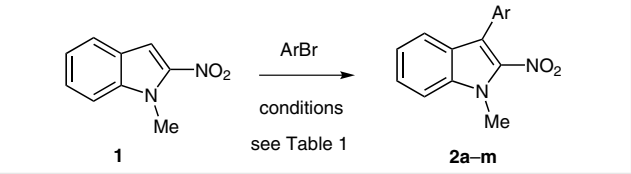
Our aim was to develop a new synthesis of 3-arylated indoles by CH-activation cross-coupling reactions of suitable 2-functionalized indole derivatives. We chose the nitro group[11] as an activating group, as it exhibits a strong electron-withdrawing effect and can be efficiently used as a catalyst-directing group in CH-activation reactions.[12] In addition, the nitro group can be transformed to the biologically relevant amino group.

1-Methyl-2-nitroindole (**1**) was prepared, by the method developed by Pelkey and Gribble,[6] starting with *o*-nitrobenzaldehyde. The nitro group of the latter was transformed into an azide. Subsequent cyclization gave 2-nitroindole which was methylated (Scheme 1).[12]



Scheme 1 Synthesis of the starting indole **1**. *Reagents and conditions*: (i) NaN_3, DMF, 60 °C; (ii) 1) $MeNO_2$, KOH, EtOH, 0 °C; 2) Ac_2O, pyridine, 0 °C to 25 °C; 3) xylenes, 140 °C; (iii) NaH, MeI, DMF, 25 °C.

The conditions of the reaction of **1** with 1-bromo-3-(trifluoromethyl)benzene were optimized (Scheme 2, Table 1). The reaction of the starting materials in the presence of $Pd(PPh_3)_2Cl_2$, CuI, PivOH, and K_2CO_3 in DMF resulted in low conversion (Table 1, entry 1). The use of $Pd(OAc)_2$ (10 mol%) proved to be the most efficient. Interestingly, the use of ligands or the employment of higher catalyst amounts did not result in an improvement of the yield. Best results were found for a simple catalyst system using $Pd(OAc)_2$ and K_2CO_3 in DMF, using four equivalents of the aryl bromide (Table 1, entry 6).



Scheme 2 Synthesis of 3-aryl-2-nitroindoles **2a–m**

Table 1 Optimization of the Synthesis of **2b**

Entry	Catalyst (mol%)	Additive	Yield of **2b** (%)[a]
1	$Pd(PPh_3)_2Cl_2$ (10)	PivOH, CuI	–[c]
2	$Pd(PPh_3)_4$ (10)	–	–[c]
3	$Pd(OAc)_2$ (10)	–	57
4	$Pd(OAc)_2$ (10)	PCy_3	60
5	$Pd(OAc)_2$ (10)	PivOH, CuI	54
6	$Pd(OAc)_2$ (10)	–[b]	74
7	$Pd(OAc)_2$ (10)	Ph_3P	56
8	$Pd(OAc)_2$ (20)	–	55
9	$Pd(OAc)_2$ (10)	PivOH	62
10	$Pd_2(dba)_3$ (10)	–	–[c]

[a] Isolated yields. Conditions: catalyst, ArBr (Ar = 3-$F_3CC_6H_4$, 3.0 equiv), K_2CO_3, 150 °C, 8 h, DMF.
[b] 4.0 equiv of ArBr.
[c] Low conversion.

Using our optimized reaction conditions, the scope of the reaction was studied. The reaction of **1** with various aryl bromides afforded indoles **2a–k** in moderate to good yields (Table 2). The best yields were observed for reactions of aryl bromides containing electron-withdrawing substituents (**2b–e**,**h**). Reactions of **1** with electron-rich 3- and 4-methoxybromide resulted in the formation of mixtures.

Table 2 Synthesis of **2a–m**[13,14]

2	Ar	Yield of **2** (%)[a]
2a	Ph	52
2b	3-$F_3CC_6H_4$	74
2c	4-$F_3CC_6H_4$	71
2d	3-$O_2NC_6H_4$	57[b]
2e	4-NCC_6H_4	63[b]
2f	3-ClC_6H_4	55
2g	4-$OHCC_6H_4$	59
2h	4-$EtO_2CC_6H_4$	62
2i	3-pyridyl	44
2j	1-naphtyl	42
2k	9-phenanthrene	48
2l	4-$MeOC_6H_4$	–
2m	3-$MeOC_6H_4$	19[c]

[a] Yield of isolated products.
[b] A small amount of impurity could not be separated.

The structures of **2a** and **2b** were independently confirmed by X-ray crystal-structure analysis (Figure 2 and Figure 3).

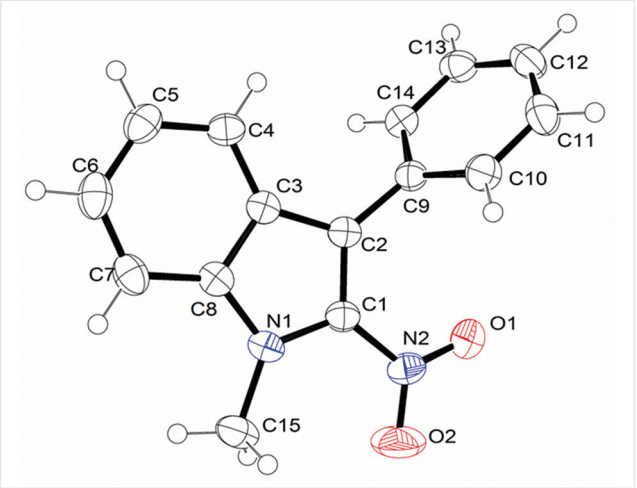


Figure 2 Ortep plot of **2a** (50% probability level)

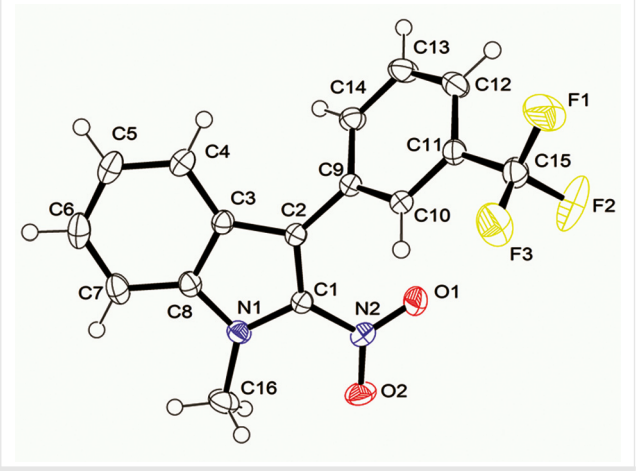


Figure 3 Ortep plot of **2b** (50% probability level)

In summary, we have developed a convenient approach to 3-aryl-2-nitroindoles by palladium-catalyzed CH-activation reactions of 3-nitroindole **1** with a range of aryl bromides. These reactions provide a convenient approach to indole derivatives that are not readily available by other methods.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560053.

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(13) **General Procedure for the Synthesis of 2a–m**
In a Schlenk flask **1** (100 mg, 0.57 mmol), appropriate aryl bromide (2.28 mmol, 4 equiv), $Pd(OAc)_2$ (0.057 mmol, 10 mol%), K_2CO_3 (0.8 mmol, 1.4 equiv), and DMF (5 mL) were added under argon atmosphere and stirred at 150 °C overnight. The reaction mixture was then evaporated to dryness, and the product was isolated by column chromatography (silica gel, hexane–EtOAc) or via semipreparative HPLC (MeOH–H_2O).
(14) **1-Methyl-2-nitro-3-phenylindole (2a)**
Starting with **1** (100 mg, 0.57 mmol), bromobenzene (358 mg, 0.24 ml, 2.28 mmol), $Pd(OAc)_2$ (12.8 mg, 0.057 mmol, 10 mol%), K_2CO_3 (111 mg, 0.8 mmol), and DMF (5 mL), **2a** was isolated as a yellow solid (72 mg, 52%), mp 118–119 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.09 (s, 3 H, CH_3), 7.28 (t, $^3J_{H-H}$ = 7.52 Hz, 1 H, ArH), 7.49–7.61 (m, 7 H, ArH), 7.78 (d, $^3J_{H-H}$ = 8.5 Hz, 1 H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.6 (CH_3), 111.8 (CH), 118.6 (C), 121.8 (C), 122.4 (CH), 124.0 (C), 127.8 (CH), 127.9 (CH), 128.42 (CH), 129.9 (CH), 131.3 (C), 136.1 (C), 138.1 (C). IR (KBr): 1612 (w), 1548 (w), 1501 (m), 1458 (s), 1365 (s), 1303 (s), 1246 (s), 1208 (m), 1178 (m), 1157 (m), 1130 (m), 1113 (m), 1091 (m), 1069 (m), 1028 (m), 978 (w), 923 (m), 897 (m), 858 (w), 779 (m), 769 (m), 753 (s), 740 (s), 699 (s), 642 (m), 604 (s), 550 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 253 (18), 252 (M^+, 100), 235 (15), 223 (10), 222 (20), 221 (10), 207 (25), 206 (12), 205 (21), 204 (20), 195 (12), 194 (15), 192 (10), 191 (24), 190 (36), 181 (21), 178 (12), 166 (10), 165 (49), 164 (19), 163 (20), 152 (15), 151 (10). HRMS (EI, 70 eV): *m/z* calcd for $C_{15}H_{12}O_2N_2$ [M^+]: 252.08933; found: 252.08938.