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$Pd(OAc)_2$-catalyzed C–H activation of indoles: a facile synthesis of 3-cyanoindoles

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ABSTRACT

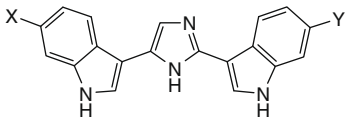
Indoles undergo smooth cyanation with CuCN in the presence of 20 mol % $Pd(OAc)_2$ and 40 mol % $CuBr_2$ in DMF to produce a wide range of the corresponding 3-cyanoindoles in good yields with high regioselectivity.

Indole nucleus is frequently found in medicinal chemistry and is considered as 'privileged scaffolds'.[1] Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[2–4] Of these, 3-substituted indoles have played a major role in the synthesis of various biologically active molecules. In particular, 3-cyanoindoles are key intermediates for the synthesis of antibacterial, antiviral and cytotoxic natural products such as nortopsentins (Fig. 1).[5]

Therefore, the introduction of cyanide functionality onto indole moiety is considered to be very important, because nitriles are valuable precursors for the synthesis of heterocycles such as oxazolines, tetrazoles and imidazoles.[6] Consequently, various methods have been developed for the cyanation of indoles.[7,8] Recently, the direct cyanation of aromatic and heteroaromatic systems has been reported using CuCN in the presence of Pd(II).[9] However, there have been no reports on the cyanation of indoles using CuCN/Pd(II) system.

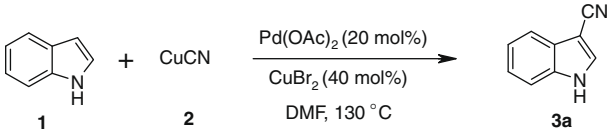
In continuation of our interest on the functionalization of indoles,[10] we herein report the direct Pd(II)-catalyzed cyanation of indoles through C–H bond activation using CuCN as the cyanating agent. We first attempted the cyanation of indole (**1**) with CuCN (**2**) using 0.1 equiv of $Pd(OAc)_2$ and 0.4 equiv of $CuBr_2$ in DMF. The reaction proceeds well at 130 °C under air to give the desired product **3a** in good yield (Scheme 1).

Further attempts were made to improve the yields. However, no improvement in yield or reaction time was achieved even by increasing the amount of the catalyst from 10 mol % to stoichiometric amounts. Next, we turned our attention to various indoles. Interestingly, several indoles such as 5-bromo-, 5-methoxy-, 2-methy-, 2-phenyl, 5-chloro, 6-methoxy derivatives (Table 1, entries b–f) underwent smooth cyanation to yield the corresponding 3-cyanoindoles. In addition, *N*-methyl- and *N*-benzyl-indoles (Table 1, entries g and h) also gave the respective 3-cyanated derivatives. The reaction works well even with sterically hindered and electron-deficient indoles such as 5-nitro, 2-methyl-5-nitro, 6-methoxy-2-carbethoxy derivatives (Table 1, entries i–l) to produce the corresponding 3-cyanated indoles. Thus, a large number



Nortopsentin A: X=Y=Br, Nortopsentin B: X=Br, Y=H
Nortopsentin C: X=H, Y=Br

Figure 1. Examples of natural products.



1 2 3a

Scheme 1. Preparation of 3-cyanoindole.

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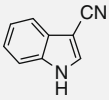
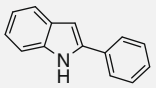
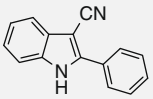
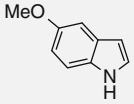
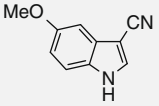
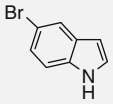
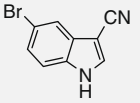
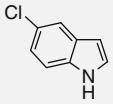
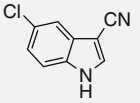
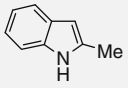
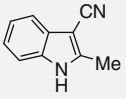
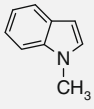
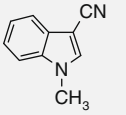
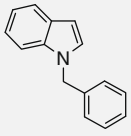
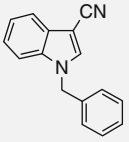
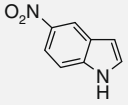
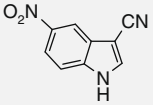
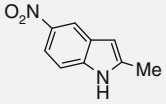
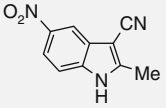
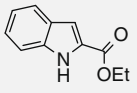
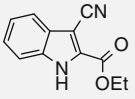
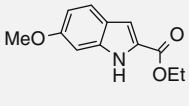
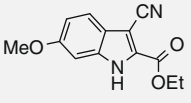
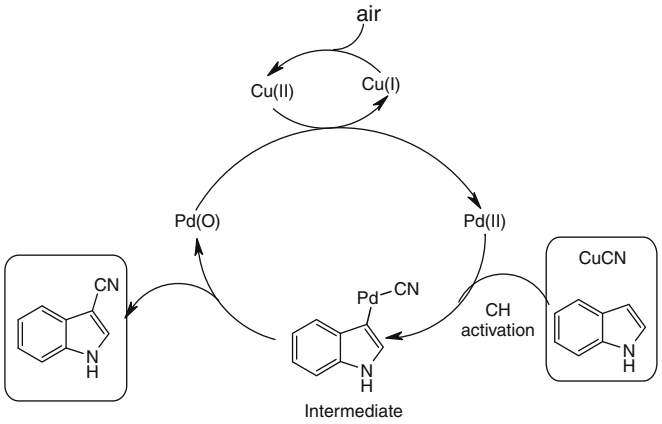
Table 1
Pd(OAc)2 -catalyzed regioselective cyanation of indoles via C–H activation

Entry	Indole	Product[a]	Time (h)	Yield[b] (%)
a			24	60
b			22	72
c			22	65
d			24	62
e			24	67
f			22	68
g			22	66
h			24	63
i			22	62
j			23	70
k			75	85
l			45	84

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.

of 3-cyanoindole derivatives were prepared using this procedure. Though reaction proceeded at lower temperature (100 °C), the yields were low (30–50%). No over cyanation was observed even by increasing the amount of CuCN or by extending the reaction time. Unlike indoles, pyrrole and carbazole failed to give the desired product under identical conditions. The products were characterized by ^{1}H NMR, IR and mass spectrometry. In the absence of either Pd(II) or Cu(II), the reaction failed to give the desired product. It is a direct and selective method for the cyanation of indoles at C-3 position. The possible reaction mechanism is depicted in Scheme 2. First, the cyanide anion is transferred



Scheme 2. A plausible reaction mechanism.

from CuCN to palladium, to form Pd(II) species, which undergoes electrophilic palladation at the C-3 position of the indole. Reductive elimination of carbo-palladium gave the desired product along with Pd(0), which was oxidized to Pd(II) by Cu(II) and/or air to complete the catalytic cycle.[11] The scope of the palladium-catalyzed selective cyanation of indoles is illustrated with respect to various indoles and the results are presented in Table 1.[12]

In summary, we have developed a novel protocol for the cyanation of indoles at C-3 position via C–H activation. This method provides an easy access to a wide range of potentially valuable 3-cyanoindoles thereby providing the precursors for the synthesis of natural products such as nortopsentins.

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12. *General procedure*: A mixture of indole (1 mmol), CuCN (1 mmol), $Pd(OAc)_2$ (10 mol %) and $CuBr_2$ (40 mol %) in dry DMF (1 mL) was stirred under air. The mixture was kept stirring at 130 °C for 24 h. After the completion of the reaction, as monitored by TLC, the reaction mixture was diluted with water and extracted with diethylether (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure 3-cyanoindoles. *1H-Indole-3-carbonitrile* (**3a**): white solid, mp 175–177 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.85 (br s, 1H), 7.88 (s, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.14–7.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 134.4, 126.6, 123.2, 121.6, 118.3, 116.3, 112.8, 84.1; IR (KBr): ν 3256, 2924, 2854, 2221, 1707, 1521, 1458, 1403, 1237, 741 cm^{-1}; LC–MS: 142 $[M]^+$. *2-Phenyl-1H-indole-3-carbonitrile* (**3b**): white solid, mp 228–230 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.08 (brs, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.61–7.75 (m, 1H), 7.40–7.60 (m, 5H), 7.13–7.27 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 144.3, 135.3, 129.3, 128.7, 126.6, 123.3, 121.5, 118.1, 116.7, 112.2, 81.4; IR (KBr): ν 3221, 2923, 2217, 1626, 1489, 1451, 1422, 1375, 1242, 736 cm^{-1}; LC–MS: 219 [M+H]; HRMS calcd for $C_{15}H_{11}N_2$ 219.022, found: 219.093. *5-Chloro-1H-indole-3-carbonitrile* (**3e**): white solid, mp 164–166 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.5 (br s, 1H), 8.56 (d, J = 1.7 Hz, 1H), 8.22 (s, 1H), 8.13 (dd, J = 1.7, 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 142.4, 136.0, 133.7, 123.5, 117.6, 114.6, 88.7; IR (KBr): ν 3444, 2921, 2854, 2224, 1713, 1633, 1528, 1464, 1280, 1236, 781 cm^{-1}; LC–MS: 176 $[M]^+$. *5-Nitro-2-methyl-1H-indole-3-carbonitrile* (**3j**): white solid, mp 248–250 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.98 (br s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 2.0, 8.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 150.1, 144.9, 114.0, 138.0, 118.0, 114.9, 112.6, 84.7, 12.7; IR (KBr): ν 3445, 3207, 2224, 1627, 1560, 1519, 1475, 1421, 1338, 1255, 1138, 742 cm^{-1}; LC–MS: 224 [M+Na]. HRMS calcd for $C_{10}H_7N_3O_2Na$ 224.0435, found: 224.0444.