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A palladium-catalyzed one-pot procedure for the regioselective dimerization and cyanation of indoles

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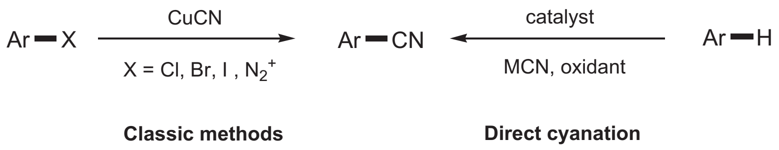
ABSTRACT

A one-pot method for the regioselective dimerization and cyanation of indoles has been developed. The reaction uses safe and nontoxic $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanating agent which introduces selectively a cyano group into the 3-position of biindoles with high efficiency.

Indoles and biindoles constitute an important motif of aromatic compounds and are found in many natural products and pharmaceuticals.[1] Despite the development of methods for indole functionalization at the 2- or 3-positions via C–H activation reactions,[2] little attention has been paid to the development of procedures for direct 2,3-disubstitution of indoles. Due to the unavailability of methods for direct 2,3-disubstitution of this type of heterocyclic system and the need for efficient routes to synthesize more elaborate structures possessing biological activity, the development of convenient procedures for the preparation of indole derivatives still remains an active research area.

Aromatic nitriles are not only the key components of numerous commercial compounds such as natural products, pharmaceuticals, agrochemicals, pigments, and dyes,[3] they are also valuable for the installation of functional groups, including aldehydes, amines, amidines, tetrazoles, carboxylic acids, and carboxylic acid derivatives.[4] The Rosenmund-von Braun and Sandmeyer reactions are two traditional methods for the synthesis of aromatic nitriles from aryl halides (Scheme 1).[5] On the other hand, direct cyanation of a C–H bond of heterocyclic systems using, CuCN, $K_3Fe(CN)_6$, $K_4Fe(CN)_6$, or a combined source of *N*,*N*-dimethylformamide and ammonia has been reported in recent years.[6] Compared to the classic methods, direct cyanation through C–H bond functionalization is more attractive due to the use of readily available reactants.

Considering the above reports, and as a part of our current studies on the development of efficient methods in organic synthesis and on the preparation of heterocyclic compounds,[7] herein, we report a palladium-catalyzed one-pot procedure for the regioselective dimerization and cyanation of indoles through C–H bond activation. The reaction uses safe and nontoxic $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanating agent and introduces selectively a cyano group to the 3-position of biindoles with high efficiency.



Scheme 1. Cyanation methods.

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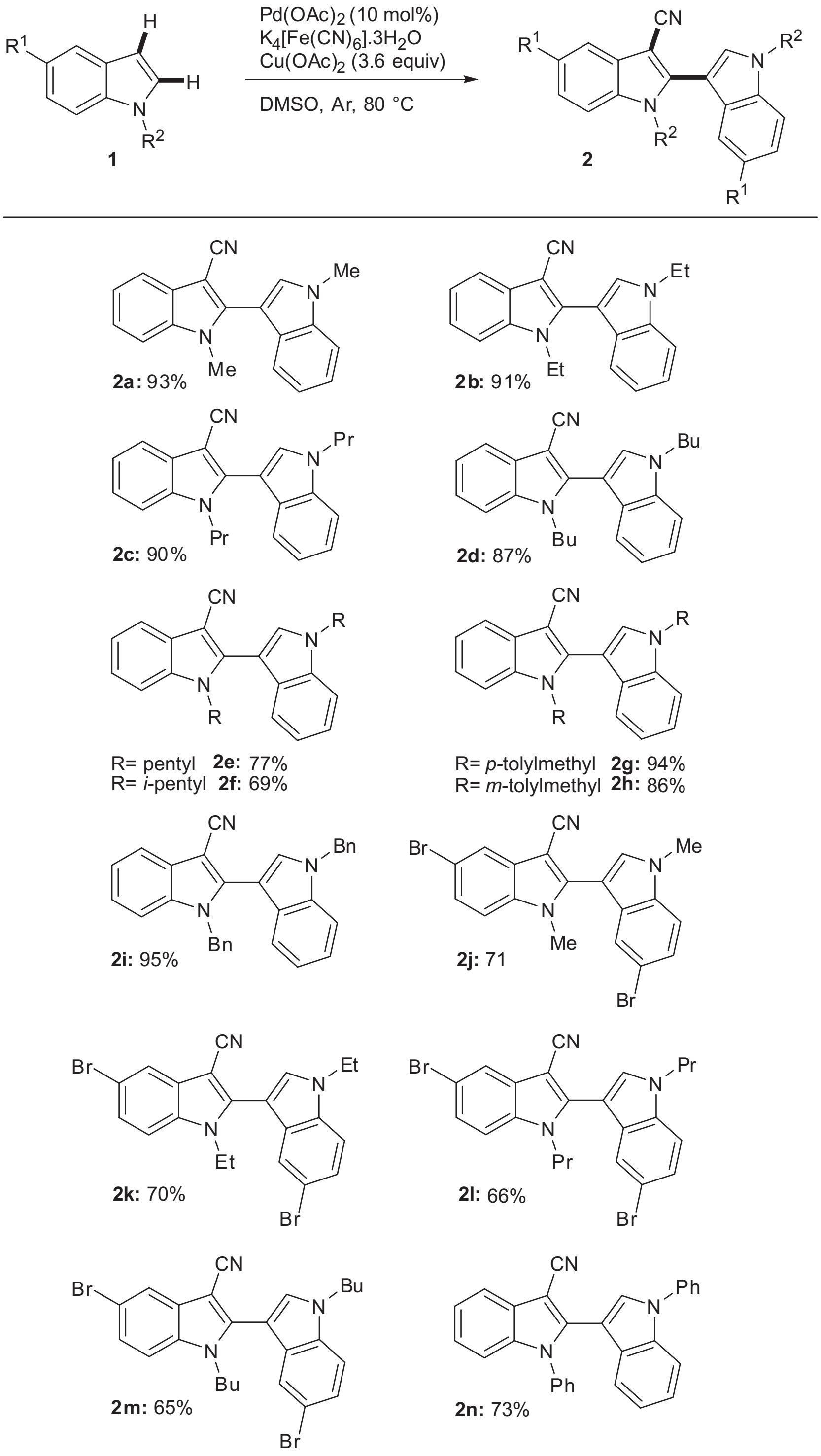
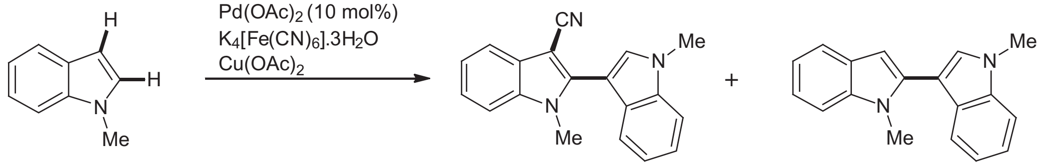


Figure 1. Synthesis of cyanated biindoles. Optimized reaction conditions: **1a** (1 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (3.6 equiv), DMSO (3 ml), 80 °C, 24 h, Ar. Yields are of isolated products.

At the outset of our study, we used *N*-methylindole (**1a**) as a model substrate with $K_4[Fe(CN)_6]\cdot 3H_2O$ in the presence of palladium catalysts. It was found that the dimerization reaction proceeded with the formation of a C-3 cyanated biindole. Cyanation took place in the presence of $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 equiv), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (1.8 equiv) in DMSO under an argon atmosphere at 80 °C (Table 1, entry 1). We investigated the reaction conditions for the selective formation of cyanated biindole **2a** versus **3a** as shown in Table 1. The use of DMF, DMAc, and DMSO-DMF as solvents resulted in lower yields or no reaction (entries 2–4). The yield of the reaction was slightly improved by increasing the reaction time to 36 h (entry 5). When we performed the reaction at 120 °C, the yield of **2a** decreased (entry 6). It was found that the amount of oxidant played a key role in the formation of **2a** (entry 7). For example, only 42% of cyanated product was detected when the reaction was performed with 1.8 equiv of

Table 1
Selected optimization screening results[a]



1a **2a** **3a**

Entry	Solvent	$Cu(OAc)_2$ (equiv)	Yield of **2a**[b] (%)	Yield of **3a**[b] (%)
1	DMSO	1.8	42	41
2	DMF	1.8	Trace	26
3	DMAc	1.8	Trace	23
4	DMF–DMSO (10:1)	1.8	29	28
5[c]	DMSO	1.8	45	38
6[d]	DMSO	1.8	33	29
7	DMSO	3	80	Trace
8	DMSO	3.6	93	–
9[e]	DMSO	3.6	–	–

[a] Reaction conditions: *N*-methylindole (**1a**) (1 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$, anhydrous solvent (3 ml), 80 °C, 24 h, Ar.

[b] Isolated yield based on *N*-methylindole.

[c] The reaction time was 36 h.

[d] The reaction was carried out at 120 °C.

[e] The reaction was carried out in the absence of $Pd(OAc)_2$.

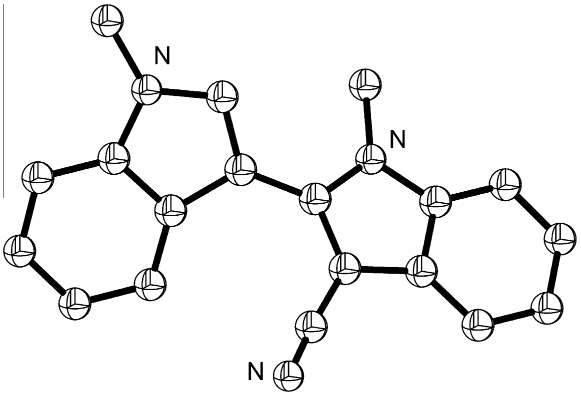


Figure 2. X-ray crystal structure of **2a**.

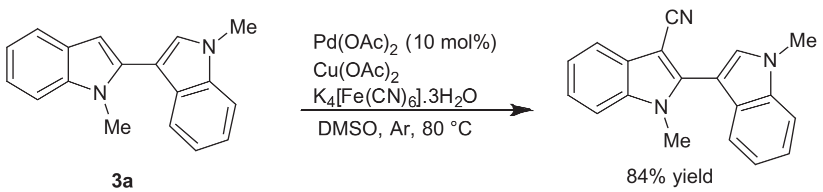
$Cu(OAc)_2$, but the yield of the cyanated product increased to 80% with 3 equiv of $Cu(OAc)_2$ (entries 1 and 7).

As Table 1 (entry 8) shows, the optimum conditions for the formation of the cyanation product were indole derivative (1 equiv), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 equiv), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (3.6 equiv) in DMSO (3 ml) at 80 °C for 24 h under an argon atmosphere. Finally, a control experiment demonstrated that no product **2a** was detected when the reaction was carried out in the absence of $Pd(OAc)_2$ (entry 9). Under the optimized conditions, the substrate scope of this reaction was investigated, and the results are summarized in Figure 1.

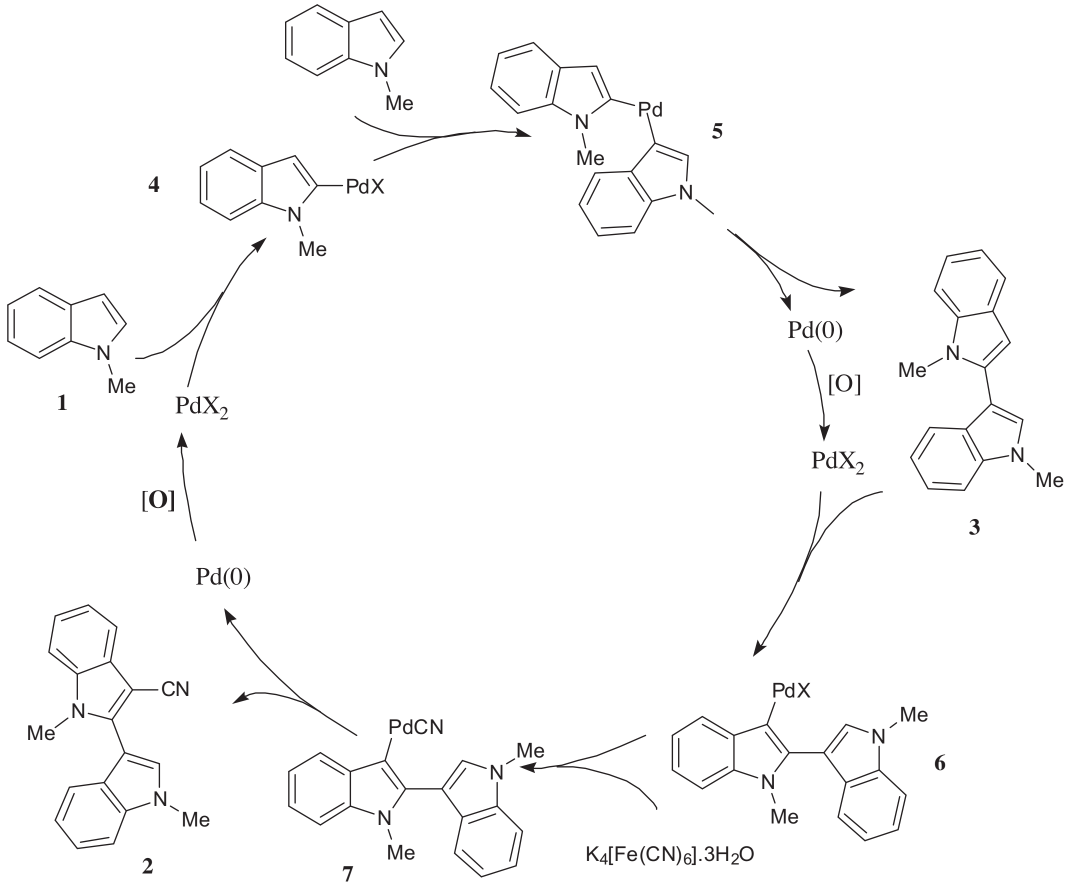
Indoles containing *N*-alkyl and *N*-benzyl substituents reacted smoothly to give the products (**2a–d,g–i**) in high yields. *N*-Isopentylindole (**2f**) and *N*-pentylindole (**2e**) gave lower yields, possibly due to steric hindrance. The presence of bromine on the benzene ring of the indoles did not change the reaction pathway, and satisfactory yields of **2** were obtained using these moderately electron-poor indoles (**2j–m**). *N*-Phenylindole tolerated the reaction conditions well and generated the expected product **2n** in a good yield. The structures of the products were characterized by spectroscopic analysis and further confirmed by an X-ray diffraction study of **2a** as a representative example (Fig. 2).[8]

Reaction of 1,1′-dimethyl-1*H*,1′*H*-2,3′-biindole (**3a**) with $K_4[Fe(CN)_6]\cdot 3H_2O$ under the optimized reaction conditions led to the formation of the 3-cyanated product in an 84% yield (Scheme 2), indicating that the one-pot sequence may proceed through the formation of a biindole.

On the basis of previous chemistry[2a,d,e,g,9] and the results of our study, a plausible Pd(0)/Pd(II) mechanism for the homocoupling reaction as shown in Scheme 3 was proposed. Initially, electrophilic palladation occurs preferentially at the C3-position of the indole and the subsequent migration of PdX to the 2-position leads to the formation of intermediate **4**, which undergoes electrophilic palladation with the second indole to form intermediate **5**. Next, reductive elimination generates the 2,3′-biindole, and Pd(0) is oxidized to Pd(II) by the Cu(II) salt to complete the cycle. Electrophilic palladation of the 2,3′-biindole produced may take place to give intermediate **6**, and subsequent transmetallation with $K_4[Fe(CN)_6]\cdot 3H_2O$ generates intermediate **7**, which undergoes reductive elimination to afford the cyanated biindole. A Pd(II)/



Scheme 2. Direct cyanation of 1,1′-dimethyl-1*H*,1′*H*-2,3-biindole (**3a**).



Scheme 3. A plausible mechanism.

Pd(IV) mechanism is another possible pathway for this regioselective oxidative homocoupling reaction.[10] Further research is required to elucidate the precise reaction mechanism.

In summary, we have developed an efficient method for the dimerization and cyanation of indoles with excellent regioselectivity. The reaction uses safe and nontoxic $K_4[Fe(CN)_6]{\cdot}3H_2O$ as the cyanating agent. This new protocol provides a facile route to the title products via a one-pot sequence.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.129.

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8. CCDC 856401 contains the supplementary crystallographic data for this Letter. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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