Direct Transformation of *N*,*N*-Dimethylformamide to −CN: Pd-Catalyzed Cyanation of Heteroarenes via C−H Functionalization

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S *Supporting Information*

ABSTRACT: This paper describes the direct cyanation of indoles and benzofurans employing *N*,*N*-dimethylformamide (DMF) as both reagent and solvent. Isotopic labeling experiments indicated that both the N and the C of the cyano group derived from DMF. This transformation offers an alternative method for preparing aryl nitriles, though it is currently limited in scope to indoles and benzofurans.

Aryl nitriles are versatile building blocks in organic synthesis for natural products, pharmaceuticals, agricultural chemicals, materials, and dyes.[1] Their great importance in chemistry and biology has consistently stimulated the development of novel methods for their preparation.[2−4] Metal-catalyzed cyanation of aryl halides or cyanation via C−H bond functionalization of arenes has been significantly developed.[5] Generally, −CN sources containing the whole −CN unit, such as metal cyanide salts (CuCN, KCN, NaCN, ZnCN), TMSCN, $K_3Fe(CN)_6$, and acetone cyanohydrin, have been developed in the above cyanation reactions (Scheme 1a).[5] The discovery of new sources of −CN generated in situ from simple and readily available regents is still an extremely attractive yet challenging goal. An interesting cyanation of 2-phenylpyridine using nitromethane as the −CN source (Scheme 1b) was discovered by Yu's group.[6] Chang and co-workers reported a combined −CN source in which the carbon originates from *N*,*N*-dimethylformamide (DMF) and the nitrogen from ammonia (Scheme 1c).[7a] Besides being an effective polar solvent, DMF has been used as a multipurpose precursor providing O, −CO, −NMe₂, −CONMe₂, −Me, and −CHO units, etc.[8] However, to the best of our knowledge, employing DMF as a source of the −CN unit has not been disclosed. Herein we report a novel Pd-catalyzed cyanation of indoles and benzofurans through C−H bond functionalization in which DMF is disclosed for the first time as a source of −CN (Scheme 1d).

We recently demonstrated a direct dehydrogenative annulation (DDA) reaction of indole derivatives with internal alkynes through C−H functionalization.[9] Recent efforts regarding the synthesis of nitriles by direct C−H functionalization[4] encouraged us to try the cyanation of indoles. We initially investigated the cyanation of 2-(4-methoxyphenyl)-1-methyl-1*H*-indole (**1a**) using different sources of −CN. Intriguingly, a 44% yield of the cyano product **2a** was directly produced in DMF in the absence of any metal cyanide salt (Table 1, entry 1). After extensive screening of different parameters, the optimum reaction conditions were determined to be Pd(OAc)₂ (10 mol %), CuBr₂ (1.1 equiv), FeCl₂ (10 mol %), TBAOAc (1.1 equiv), K₂CO₃ (1.1

**Scheme 1. Sources of −CN in Cyanation Reactions**
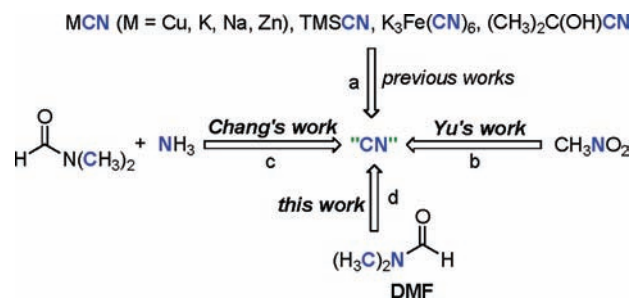
equiv), DMF (2 mL; i.e., 0.1 M **1a** in DMF), and O₂ (1 atm) at 130 °C, which provided **2a** in 79% yield along with a minor amount of **3a** as a byproduct (**2a**:**3a** = 16:1) (entry 2). Both palladium and copper species were required for the direct cyanation (entries 3 and 4), while FeCl₂, K₂CO₃, and TBAOAc promoted the efficiency of the transformation (entries 5−7). The yield decreased to 41% with poor selectivity when *N*,*N*-dimethylacetamide (DMA) was employed as the solvent (entry 8). Notably, both DMF solvent and O₂ atmosphere were essential (entries 9 and 10). Interestingly, **3a** was obtained as the major product when KOAc was used instead of K₂CO₃ (entry 11).

Under these optimized reaction conditions, substrates bearing either electron-donating (para-, meta-, or ortho-substituted) or -withdrawing substituents on the 2-aryl indole could be smoothly transformed into the desired products in moderate yields (51−79%; Table 2, entries 1−5). Except for the unprotected indole **1f**, indoles with N-protecting groups such as Me, MOM, and Bn were well-tolerated, giving the desired nitrile products **2** with excellent chemoselectivity (**2**:**3** > 22:1; entries 7−10). When the dimer of 1-methyl-1*H*-indole was employed as the substrate, only the monocyano product **2l** was obtained as the product in 45% yield without the observation of the dicyano product (entry 13). It is noteworthy that 3-phenylindole could also afford the corresponding cyano product (entry 15). In addition, the strategy was also applicable to the cyanation of other compounds, such as 2-phenylbenzofuran and 3-phenylbenzofuran, which highly selectively gave the corresponding cyano products in moderate yields (entries 16 and 17). Moreover, 2-alkyl-substituted indole **1q** executed this transformation well, producing **2q** in 44% yield

Table 1. Effects of the Reaction Parameters in the Transformation of DMF to "CN"[a]

R = 4-methoxyphenyl
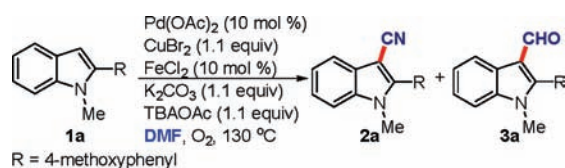
| entry	change from the "standard conditions"	yield of 2a(%)[b]	2a:3a[c]
1	Cu(OAc)$_2$ (2.0 equiv) instead of CuBr$_2$; TBAB (1.0 equiv) instead of TBAOAc; no FeCl$_2$	44	5:1
2	none	79	16:1
3	no Pd(OAc)$_2$	0	—
4	no CuBr$_2$	0	—
5	no FeCl$_2$	53	3:1
6	no K$_2$CO$_3$	20	1:1.1
7	no TBAOAc	20	1:1.3
8	DMA instead of DMF	41	4.5:1
9	solvent 1 instead of DMF[d]	0	—
10	N$_2$ instead of O$_2$	0	—
11	KOAc instead of K$_2$CO$_3$	12	1:4

[a] Reaction conditions: 1a (0.20 mmol), Pd(OAc)$_2$ (10 mol %), CuBr$_2$ (1.1 equiv), FeCl$_2$ (10 mol %), K$_2$CO$_3$ (1.1 equiv), and TBAOAc (1.1 equiv) in dry DMF (2 mL) stirred at 130 °C under O$_2$ (1 atm) for 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Solvent 1 = 1,1-dimethoxy-N,N-dimethylmethanamine.

without the detection of aldehyde **3q** (entry 18). The reaction scope could be expanded to simple N-protected indoles and pyrroles, albeit with low efficiencies (entries 19 and 20). Notably, the reaction on a 1 mmol scale performed well with similar yields (entries 7 and 8).

To probe the mechanism of the conversion of DMF into a −CN unit, a series of labeling experiments involving the essential DMF and O$_2$ were performed (Table 3). Interestingly, the result of the reaction with ^{15}N-labeled DMF indicated that the nitrogen of the −CN group originated completely from DMF (99% incorporation; entry 1). It is noteworthy that the formyl group of DMF could hardly serve as the carbon source for the −CN unit in **2a** and the −CHO unit in **3a** (<5% incorporation; entry 2). Further investigation demonstrated that the carbons of the −CN (88.7% incorporation) and −CHO (93.0% incorporation) units were mainly provided by the dimethylamino moiety of DMF-dimethyl-$^{13}C_2$ (99% ^{13}C).[10] The reason for the less than 99% ^{13}C incorporation is that the −NMe and −OMe methyl groups can be cleaved and exchange with −^{13}CH$_3$ generated from DMF-dimethyl-$^{13}C_2$ [see the Supporting Information (SI)]. In addition, the labeling experiments with ^{18}O$_2$ and H$_2$^{18}O showed that the O in the generated −CHO group in **3a** originated from O$_2$ (entries 4 and 5).

It is noteworthy that the reaction was scarcely influenced in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (79% yield; see the SI), which suggests that a single electron transfer (SET)-based mechanism is unlikely to operate in this case. None of the desired product **2a** was detected when 1,1-dimethoxy-N,N-dimethylmethanamine was employed instead of DMF (Table 1, entry 9). In contrast, **2a** was obtained in 41% yield when the reaction was carried out in DMA (Table 1, entries 8 and 9). We therefore considered that complex 5 (see Scheme 2), which was previously reported to occur in DMF in the presence of Cu(II),[11] would be an involved intermediate.

Additional mechanistic studies with all the possible key intermediates were also carried out (Table 4). It was found that

Table 2. Pd-Catalyzed Cyanation Using DMF as the −CN Source[a]
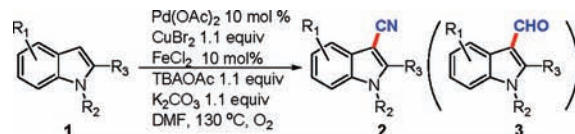
Entry	product	yield of 2 (%)[b]	2:3[c]
1		2a: R = 4-OMe	79	16:1
2		2b: R = 3-OMe	61	6.8:1
3		2c: R = 2-OMe	51	3.4:1
4		2d: R = 4-Me	79	10:1
5		2e: R = 4-F	65	25:1
6		2f: R = H	0	—
7		2g: R = Me	66	>99:1
8[d]		2g: R = Me	65	22:1
9		2h: R = MOM	69	>99:1
10		2i: R = Bn	83	55:1
11		2j	45	2.3:1
12[e]		2k	60	30:1
13		2l	45	>99:1
14		2m + 2m'	56 5	50:1 >99:1
15[e]		2n	38	>99:1
16		2o	66	>99:1
17[e]		2p	48	>99:1
18[f]		2q	44	>99:1
19[f]		2r	18	1.3:1
20		2s	7	>40:1

[a] Reaction conditions: substrate (0.20 mmol), Pd(OAc)$_2$ (10 mol %), CuBr$_2$ (1.1 equiv), FeCl$_2$ (10 mol %), K$_2$CO$_3$ (1.1 equiv), and TBAOAc (1.1 equiv) in dry DMF (2 mL) stirred at 130 °C under O$_2$ (1 atm). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] The reaction was carried out on a 1 mmol scale. [e] Pd(OAc)$_2$ (20 mol %) was employed. [f] Cu(OAc)$_2$ (1.1 equiv) was employed instead of CuBr$_2$ (1.1 equiv). The reaction was stirred at 100 °C under O$_2$ (1 atm).
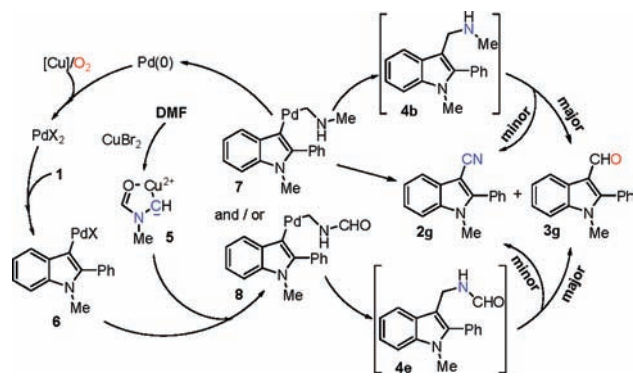
4c−e could not be converted into **2g**, the major product from the normal reaction (entries 3−5). Indeed, **4c** and **4e** preferentially

Table 3. Isotope Incorporation Experiments[a]

Entry	"DMF"	"O₂"	-CN	-CHO
1[b]	H-C(=O)-N(¹⁵N-CH₃)(CH₃)	O₂	-CN 99% ¹⁵N incorporation	
2[b]	H-¹³C(=O)-N(CH₃)(CH₃)	O₂	-CN <5% ¹³C incorporation	-CHO <5% ¹³C incorporation
3[b]	H-C(=O)-N(¹³CH₃)(¹³CH₃)	O₂	-CN 88.7% ¹³C incorporation	-CHO 93% ¹³C incorporation
4[c]	H-C(=O)-N(CH₃)(CH₃)	¹⁸O₂		-CH¹⁸O
5[c]	H-C(=O)-N(CH₃)(CH₃)	O₂ (10 eq. of H₂¹⁸O addition)		-CHO

[a] For the method used to calculate ¹³C incorporation, see ref 10 and the SI. [b] For the reaction conditions, see Table 1, entry 1. [c] For the reaction conditions, see Table 1, entry 11.

Scheme 2. Plausible Mechanism for This Transformation

Table 4. Reaction of Possible Intermediates 4 under the Standard Conditions[a]

entry	4	R	yield of 2g (%)[b]	yield of 3g (%)[b]
1	4a	—NH₂	12	20
2	4b	—NH-Me	18	53
3	4c	=N-Me	trace	76
4	4d	—N(CHO)(Me)	0	0
5	4e	—NH-CHO	trace	37

[a] For the reaction conditions, see Table 2, entry 1. [b] Isolated yields.

Table 5. Reactions of 1g under Various Conditions

Pd(OAc)₂ (10 mol %)
CuBr₂ (1.1 equiv)
FeCl₂ (10 mol %)
K₂CO₃ (1.1 equiv)
TBAOAc (1.1 equiv)
DMF, O₂, 130 °C
1g → 2g + 3g

entry	change from the "standard conditions"[a]	yield (%)[b] 2g	yield (%)[b] 3g
1	MeNHCHO instead of DMF as the solvent	28	tr
2	t-Bu-NC instead of DMF as the solvent	0	0
3	Bn-NC instead of DMF as the solvent	0	0
4	additional CuCN (1.1 equiv) was added	tr	0
5	additional CuCN (1.1 equiv) was added; DMSO instead of DMF as the solvent	0	0
6	CuCN (1.1 equiv) instead of CuBr₂	0	0
7	CuCN (1.1 equiv) instead of CuBr₂; DMSO instead of DMF as the solvent	0	0
8	additional H₂O (5.0 equiv) was added	32	4

[a] For the reaction conditions, see Table 2, entry 1. [b] Isolated yields. tr = trace.

formed the minor product **3g** (entries 3 and 5). Under the normal conditions, **2g** would be formed in 66% yield and 99:1 **2g:3g** ratio. Although the reaction of **4a** or **4b** produced **2g** in 12 and 18% yield, respectively, the aldehyde product **3g** was obtained as the major product (entries 1 and 2). Neither **2g** nor **3g** was obtained in the reaction of **4d** (entry 4). **4e** was mainly converted into **3g** in 37% yield (entry 5).

However, the reaction of **1g** in *N*-methylformamide instead of DMF gave **2g** in 28% yield with a trace of **3g** (Table 5, entry 1). Since the isonitrile could be generated from DMF and then undergo this transformation as an intermediate, *tert*-butyl isonitrile or benzyl isonitrile was used as the solvent instead of DMF. However, no product was detected in either case (entries 2 and 3). In order to further understand the possible mechanism, the reactions of **1g** with additional CuCN or H₂O were investigated. Unfortunately, the reactions under the standard conditions with an additional 1.1 equiv of CuCN did not produce the desired cyano product **2g** (entries 4 and 5). The expected products **2g** and **3g** were also not observed in the reactions using CuCN instead of CuBr₂ in DMF or DMSO (entries 6 and 7). In

addition, the reactions under the standard conditions in the presence of H₂O (5.0 equiv) produced **2g** in 32% yield (entry 8), which is much lower than that under standard conditions (66%; Table 2, entry 7). These results suggest that CuCN is not involved.[12]

On the basis of above results, a plausible mechanism for the reaction is illustrated in Scheme 2. The initial electrophilic aromatic palladation affords Pd[II] intermediate **6**, which undergoes an electrophilic reaction with complex **5**[11] via cleavage[8] to form intermediates **7** and/or **8**. Subsequent reductive elimination generates intermediates **4b** and/or **4e**, respectively. The formed Pd(0) complex could be reoxidized to Pd(II) by O₂ (1 atm) and/or Cu(II) salts to complete the catalytic cycle. The cyano product

2g is likely generated either directly from active **7** or via **4b** as the intermediate in situ.[13,14] On the other hand, intermediate **4e** could be oxidized to aldehyde **3g**. Although all the possible intermediates have been investigated, the mechanism is not yet clear. The evidence suggests that intermediates **4** are capable of forming **2g** and **3g**, with **3g** predominating, and it is unclear what factors control the **2g**:**3g** ratio. More studies are needed to more accurately elucidate this mechanism.

In conclusion, we have demonstrated a novel Pd-catalyzed cyanation of indoles and benzofurans through C—H bond functionalization. Isotopic labeling experiments indicated that both the nitrogen and the carbon incorporated into the cyano group are derived from DMF. This protocol not only extends the application of DMF in organic transformations but also offers an alternative method for preparing aryl nitriles, though it is currently limited in scope to indoles and benzofurans. Further studies to gain a deeper understanding of the reaction mechanism and discover synthetic applications are ongoing in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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