

A New Combined Source of “CN” from *N,N*-Dimethylformamide and Ammonia in the Palladium-Catalyzed Cyanation of Aryl C–H Bonds

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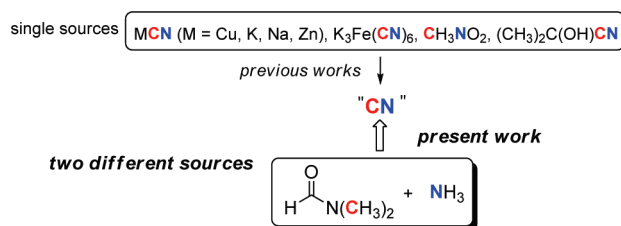
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Abstract: An unprecedented protocol for cyanation at arene C–H bonds has been developed by employing *N,N*-dimethylformamide and ammonia as a combined source for the cyano “CN” unit. Isotopic incorporation experiments revealed that the carbon and nitrogen of the “CN” originate from the *N,N*-dimethyl moiety of DMF and ammonia, respectively. The present cyanation reaction shows an excellent degree of regioselectivity, producing only monosubstituted nitriles at the less hindered C–H position, and it allows for the preparation of doubly labeled nitrile compounds for the first time.

Aromatic nitriles possess versatile utilities and are indispensable not only in organic synthesis but also in chemical industry.¹ In fact, the nitrile group is an important precursor for various functional groups such as aldehydes, amines, amidines, tetrazoles, amides, and their carboxyl derivatives.² Representative methods for the preparation of organonitriles with cyanide-containing reagents are the Sandmeyer³ and Rosenmund–von Braun reactions.⁴ Recently, a catalytic route to aryl nitriles has been reported on the basis of the chelation-assisted C–H bond activation⁵ or metal-catalyzed cyanation of haloarenes.⁶ In those cyanation protocols, the “CN” unit is provided from metal-bound precursors of MCN (M = Cu, K, Na, Zn), TMS-CN, or K₃Fe(CN)₆.⁶ Additionally, it can be generated in situ from nitromethane^{5a} or acetone cyanohydrin.⁷ Herein, we report the first example of generating “CN” from two different, readily available precursors, ammonia and *N,N*-dimethylformamide (DMF) (Scheme 1). In addition, its synthetic utility is demonstrated through the Pd-catalyzed cyanation of arene C–H bonds.

Scheme 1



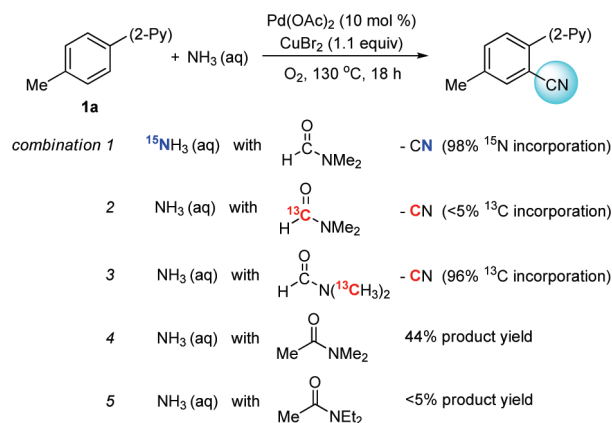
During the course of our studies on the C–H functionalization of arenes,⁸ we were interested in the employment of readily available and nonexpensive reagents such as ammonia.⁹ With the use of 2-(*p*-tolyl)pyridine (**1a**) as a model substrate, amination of the tolyl moiety was initially tried using aqueous ammonia.¹⁰ Quite surprisingly, instead of the anticipated product 5-methyl-2-(pyridin-2-yl)aniline (**3a**), its cyano variant **2a** was obtained in 85% NMR yield under the standard conditions (Table 1, entry 1). Both palladium and copper species were required for the cyanation

Table 1. Effects of the Reaction Parameters in the Pd-Catalyzed Cyanation

entry	change from the “standard conditions”	yield of 2a (%) ^a
1	none	85
2	no Pd(OAc) ₂	0
3	no CuBr ₂	0
4	no NH ₃ (aq)	0 ^b
5	DMSO instead of DMF	0
6	N ₂ instead of O ₂ [with 1 equiv of Pd(OAc) ₂]	0
7	0.5 equiv of CuBr ₂ instead of 1.1 equiv	49
8	Cu(OAc) ₂ instead of CuBr ₂	20
9	CuCN instead of CuBr ₂	0
10	Pd(OCOCF ₃) ₂ instead of Pd(OAc) ₂	42

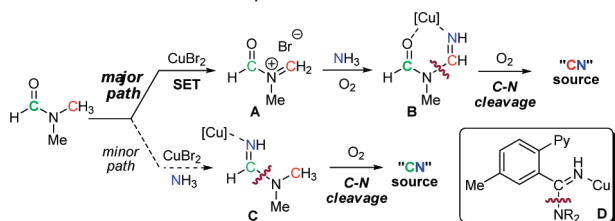
^a ¹H NMR yield (internal standard: 1,1,2,2-tetrachloroethane). ^b The 2,2'-dimer of **1a** was exclusively obtained in 90% yield.

Scheme 2. Cyanation with Different “CN” Sources



(entries 2 and 3). It was also observed that both DMF solvent and oxygen atmosphere were essential (entries 5 and 6). While lower loading of CuBr₂ decreased the product yield (entry 7), palladium or copper species other than Pd(OAc)₂ and CuBr₂ gave inferior results (entries 8–10). The reaction was highly regioselective, affording the cyano product exclusively at the position ortho to the 2-pyridyl group. On the other hand, when 4-methylbiphenyl was employed, no cyanated product was observed, suggesting the importance of a directing group for the conversion.

In order to obtain a clue concerning how the “CN” unit is provided in this unique cyanation procedure, a series of experiments were next performed (Scheme 2). When **1a** was allowed to react with ¹⁵N-labeled aqueous ammonia under the standard conditions, almost complete isotopic incorporation into the 2-cyano moiety was

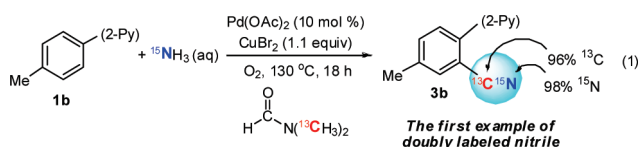
Scheme 3. Mechanistic Proposal for the “CN” Formation

observed (combination 1),¹¹ strongly indicating that ammonia serves as the nitrogen source of “CN”. It was interesting to note that the carbon source of “CN” was supplied from the dimethylamino moiety rather than formyl group of DMF (combinations 2 and 3).¹² In addition, while the use of *N,N*-dimethylacetamide resulted in just a moderate product yield relative to that for DMF, its diethylamino derivative did not afford **2a** (combinations 4 and 5), implying that the *N,N*-dimethylamino moiety of amides is an efficient carbon source of “CN” in the present cyanation protocol.

Although the details of this way of generating the cyano unit “CN” are not clear at the present stage, it is proposed that the copper complex is presumably involved in the single electron transfer (SET) step to give an imine species **A**, which is attacked by ammonia to provide an amidine intermediate **B** (Scheme 3).¹³ C–N bond cleavage in **B** is envisioned to occur under the aerobic conditions, leading to “CN” (major pathway).¹⁴ It was observed that the reaction is completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).¹⁵ On the basis of the above isotope experiments (Scheme 2), a path generating “CN” from the formyl group of DMF and ammonia can be regarded as a minor contribution. However, an alternative route to cyanation that, instead of using prior-generated “CN”, proceeds via reaction of the substrate with proposed amidine species such as **B** to form an intermediate **D** cannot be completely ruled out at the moment. On the other hand, it is postulated that the palladium catalyst is involved only in the C–H bond activation of **1a**, and a large intramolecular kinetic isotope effect ($k_H/k_D = 3.3$) was observed from **1a-d**.¹⁶

Irrespective of the exact mechanistic path offering the “CN” unit, the standard cyanation conditions were briefly applied to a range of substrates (Table 2). 2-(2-Pyridyl)arenes bearing various substituents at the para, meta, or ortho position were readily cyanated, although electron-deficient groups led to slightly lower product yields (**2a–j**). A substituted pyridyl group did not cause any difficulties (**2k**). Cyanation of arenes containing other pyridine-like directing groups also proceeded smoothly. In fact, the reactions of 1-phenylisoquinoline (**2l**), benzo[*h*]quinoline (**2m**), and 2-phenylpyrimidine (**2n**) afforded the corresponding cyanated products in high efficiency. It should be noted that the reaction is highly regioselective, affording only one isomeric product in cases where two different reacting sites are present (e.g., **2h**, **2i**, and **2j**).

Since the present cyanation protocol employs two different sources for the in situ generation of “CN”, it was envisioned that doubly labeled benzonitriles could readily be obtained. Indeed, when isotopic aqueous ammonia (¹⁵NH₃) and *N,N*-dimethyl-¹³C₂ DMF were used under our conditions, a doubly labeled product was isolated in 40% yield¹⁷ with >96% isotopic incorporation at each carbon and nitrogen of “CN” (eq 1), representing to the best of our knowledge the first example of making such nitriles.

**Table 2.** Pd-Catalyzed Cyanation with NH₃(aq) and DMF^a

1	Reaction Conditions	2
	Pd(OAc) ₂ (10 mol %) CuBr ₂ (1.1 equiv) NH ₃ (aq) (4.4 equiv) O ₂ , DMF, 130 °C, 18 h	
2a : R ¹ = Me; 78%		
2b : R ¹ = H; 82%		
2c : R ¹ = OMe; 60%		
2d : R ¹ = Ph; 70%		
2e : R ¹ = F; 61% ^b		
2f : R ¹ = COOMe; 30% ^b		
2g (3-Me): 61% ^b		
2h (4-Me): 65%		
2i : 62% ^b		
2j : 45% ^b		
2k : 51% ^b		
2l : 48% ^b		
2m : 75% ^b		
2n : 86% ^c		

^a Substrate (0.3 mmol), NH₃(aq, 28%), DMF (1.5 mL), and O₂ (1 atm). ^b Reaction time 48 h. ^c Using 2.2 equiv of CuBr₂ and 8.8 equiv of NH₃(aq) for 48 h.

In summary, we have discovered a new protocol for generating a cyano “CN” unit from two readily available precursors, NH₃(aq) and DMF. Its synthetic utility has been demonstrated in the Pd-catalyzed cyanation of aryl C–H bonds. Mechanistic studies on the detailed path of generating the cyano group are underway.

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Supporting Information Available: Experimental details and ¹H, ¹³C, and ¹⁵N NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) See the Supporting Information for details.
- (17) The lower yield is presumably due to the lower concentration of aqueous ammonia employed. See the Supporting Information for details.

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