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Ethyl Cyanoacetate: A New Cyanating Agent for the Palladium-Catalyzed Cyanation of Aryl Halides

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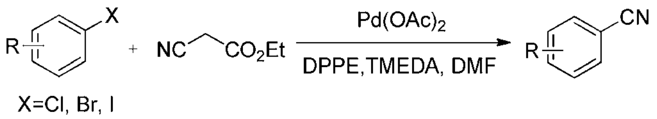
ABSTRACT



A new Pd-catalyzed cyanation reaction has been discovered using ethyl cyanoacetate as the cyanating reagent. A variety of electron-rich and electron-deficient aryl halides were efficiently converted into their corresponding nitriles in good to excellent yields.

The nitrile functional group is a versatile functional group in organic synthesis and can be easily transformed into a variety of functional groups, such as amines, aldehydes, amides, acids, esters, tetrazoles, triazoles, oxazoles, and thiazoles.[1] Aryl nitriles are not only integral parts of dyes and pigments but are also important building blocks of certain pharmaceuticals.[2] For example, Casodex (bicalutamide, Zeneca, antineoplastic, anticancer), Aolept (pericyazine, Bayer, antipsychotic, neuroleptic), and Femara (letrozole, Novartis Pharma, antineoplastic, aromatase inhibitor) all contain an aryl nitrile moiety.[1,2]

Many methods have been developed to introduce cyano groups into molecules. The traditional approaches for the preparation of aryl nitriles[1,3]involve the Rosenmund–von Braun reaction from the corresponding halides or the Sandmeyer reaction from aniline. In an industrial setting, the ammoxidation reaction is typically used.[4] Recently, a useful alternative for the preparation of aryl nitriles was developed using transition-metal-catalyzed cyanation of aryl-X compounds (X = Cl, Br, I, and H). The cyanation agents used in this approach include MCN (M = Cu, K, Na, Zn), TMSCN, and $K_4Fe(CN)_6$ (Scheme 1, entry a).[5] However, there is still great interest in finding safer and more environmentally friendly cyanation reagents.

Very recently, a few new cyanation reagents were identified. Nitromethane was used as the –CN source for the cyanation of 2-phenylpyridine by Yu's group (Scheme 1, entry b).[6] Chang and co-workers reported a combined –CN source of DMF and ammonia for the cyanation of a 2-arylpyridine via C–H bond activation (Scheme 1, entry c).[7] DMF alone can also be used as a –CN source, as demonstrated by Jiao's group (Scheme 1, entry f).[8] Cheng and co-workers reported a reaction using DMF and NH_4HCO_3 for the cyanation of aryl halides (Scheme 1,

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[†] These authors contributed equally to this work.

(1) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049.

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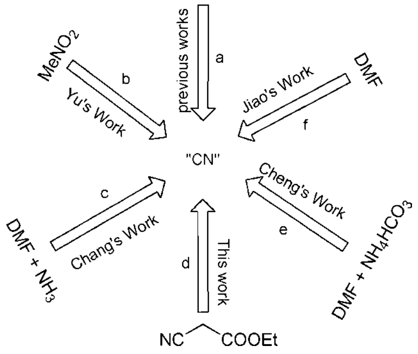
entry e).[9] However, most of these cyanation procedures involve the use of an aryl iodide or a highly reactive aryl bromide and the use of specific substrates; thus, the scope of the applications of these reactions is limited.

Scheme 1. Sources of $-CN$ in Cyanation Reactions

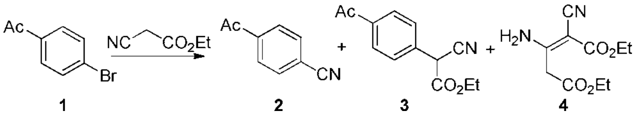


Herein, we describe for the first time the direct cyanation of aryl halides using ethyl cyanoacetate as a source of $-CN$ (Scheme 1, entry d). Palladium acetate was used as the catalyst, and the reaction was conducted in the presence of 1,2-bis(diphenylphosphino)ethane (DPPE), potassium iodide, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Since the ethyl cyanoacetate is an inexpensive, nontoxic and easily handling organic reagent, this method may potentially have wide applications.

The cyanation of 4′-bromoacetophenone was selected as a model reaction to identify essential additives and to optimize the reaction conditions. Selected results are presented in Table 1. Various palladium catalysts, phosphate ligands, organic bases, and inorganic salts were screened. It was found that palladium acetate in the presence of TMEDA, DPPE, sodium carbonate and potassium iodide gave the best results. Both DPPE and TMEDA were believed to reduce the deactivation of the palladium catalyst. Either DPPE or TMEDA can be used alone; however, the combination of these two compounds results in better reaction yields. In addition, it was found that a greater amount of palladium catalyst and a higher reaction temperature will increase the yield and reduce the reaction time. The reaction yield can also be significantly improved by adding potassium iodide to the reaction mixture. The mechanism for this improvement may be due to the exchange between the iodide with bromide or chloride in the molecule. Both DMF and DMSO can be used as the reaction solvent without drying. The reaction is quite clean, and only small amounts of ethyl 2-(4-acetylphenyl)-2-cyanoacetate were detected as a byproduct under most of the reaction conditions.

A number of aryl nitriles were synthesized using this new method (Table 2). In general, the standard conditions (Table 1, entry 6) gave good to excellent reaction yields. However, for certain inert species, NaH replaced Na_2CO_3 when no conversion was observed (Table 2, entries 18, 19, 23, 24, and 29).

Table 1. Reaction Conditions for the Cyanation of 4′-Bromoacetophenone[a]



entry	ligand	catalyst	ratio of **2**:**3**:**1**[b] (%)	yield of **2**[c] (%)
1	TMEDA	$Pd(OAc)_2$	36:1:63	35
2	DPPE	$Pd(OAc)_2$	37:30:33	30
3	DPPE + TMEDA	$Pd(OAc)_2$	84:11:5	75
4[d]	BINAP + TMEDA	$Pd(OAc)_2$	81:9:10	78
5	TMEDA	$Pd(dppf)Cl_2$	69:30:1	63
6[e]	**DPPE + TMEDA**	**$Pd(OAc)_2$**	**94:4:2**	**90**
7[e]	BINAP + TMEDA	$Pd(OAc)_2$	87:5:8	81
8	DPPE + TMEDA	$Pd(PPh_3)_2Cl_2$	83:12:5	78
9	DPPE + TMEDA	$Pd(PPh_3)_4$	36:62:2	25
10[f]	DPPE + TMEDA	$Pd(OAc)_2$	63:36:1	50
11[g]	DPPE + TMEDA	$Pd(OAc)_2$	35:61:4	31
12[h]	DPPE + TMEDA	$Pd(OAc)_2$	82:16:2	74
13[e]	DPPE + TMEDA	$Pd(PPh_3)_2Cl_2$	48:46:6	37

[a] Typical reaction conditions: substrate (1.0 mmol), ethyl cyanoacetate (3.0 mmol), palladium catalyst (0.2 mmol), base (3.0 mmol), ligand (0.3 mmol), TMEDA (1.0 mmol), and DMF (5 mL) stirred at 130 °C under an Ar atmosphere for 22 h. [b] The ratio of 2:3:1 was determined by HPLC; the results are the averages of two identical experiments. [c] The yield represents isolated yield. [d] BINAP (2, 2′-bis(diphenylphosphino)-1,1′-binaphthyl). [e] 1.0 mmol of KI was added. [f] K_3PO_4 was used. [g] Cs_2CO_3 was used. [h] NaOtBu was used.

Different aryl halides with various substituents at the ortho, meta and para positions were investigated, and most of the reactions proceeded smoothly under the standard conditions. In addition, a number of interesting observations were made. The reactivity of aryl halides decreases as the bond-dissociation energy of the C–X bonds increases (reactivity: I > Br > Cl) (Table 2, entries 3, 4, 5, 18, 19).[1,10] Substituents containing active protons such as phenol groups or amine groups seem not to inhibit the reaction (Table 2, entries 2, 9). The presence of two or more strong electron-withdrawing groups (F, NO_2) on the aromatic ring completely inhibits the cyanation reaction. A nucleophilic aromatic substitution proceeds instead (Table 3).

When the reaction is scaled up to the gram scale, the addition of 1.0 mmol of water is needed,[11] and the reaction time must be extended. In certain specific cases, due to the inertness of the substrate with respect to this cyanation reaction, compound **4** becomes the major reaction product.

For certain highly electron-deficient aromatic compounds, phenylacetonitrile derivatives were produced

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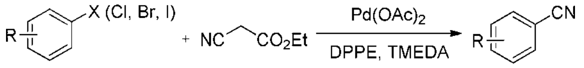
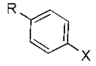
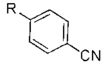
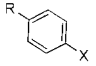
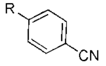
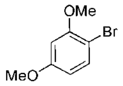
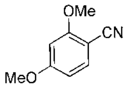
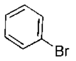
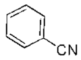
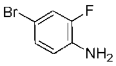
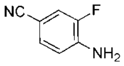
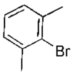
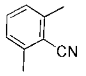
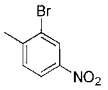
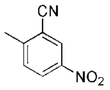
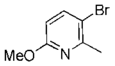
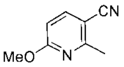
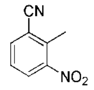
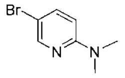
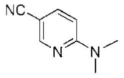
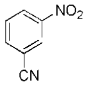
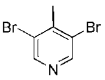
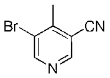
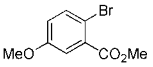
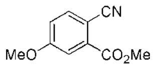
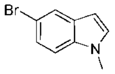
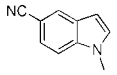
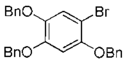
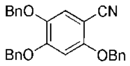
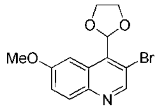
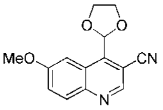
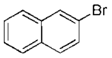
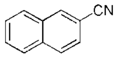
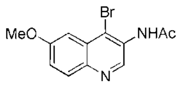
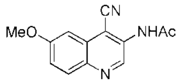
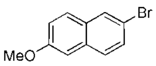
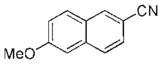
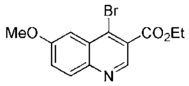
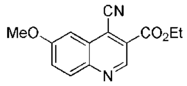
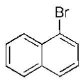
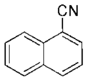
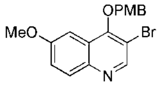
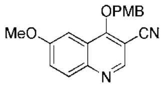
Table 2. Pd-Catalyzed Cyanation with Ethyl Cyanoacetate[a]

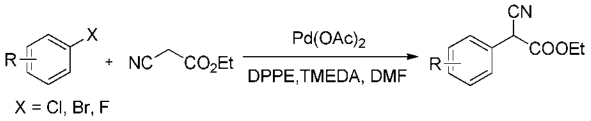


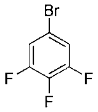
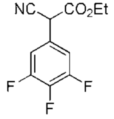
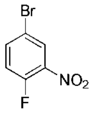
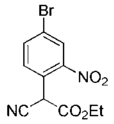
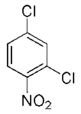
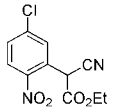
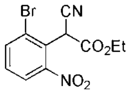
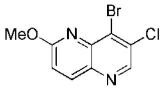
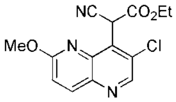
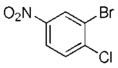
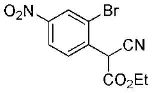
entry	starting material	product	yields (%)	entry	starting material	product	yields (%)
							
1	R = -Ac, X = Br	**2**	90	18[c]	R = -NHAc, X = Cl	**19**	28
2	R = -OH, X = Br	**5**	72	19[c]	R = -NHAc, X = Br	**19**	40
3	R = -NO_2, X = Cl	**6**	65	20	R = -CO_2Me, X = Br	**20**	85
4[b]	R = - NO_2, X = Br	**6**	91	21[b]	R = -OMe, X = Br	**21**	98
5[b]	R = - NO_2, X = I	**6**	99	22	R = -Ph, X = Br	**22**	76
6	R = -Br, X = Br	**7**	61	23[c]	R = -NMe_2, X = Br	**23**	64
7	R = -CN, X = Br	**8**	55	24[c]	R = -Morpholine, X = Br	**24**	39
8		 **9**	72	25		 **25**	34
9		 **10**	49	26		 **26**	38
10		 **11**	43	27		 **27**	78
11		 **12**	82	28		 **28**	81
12		 **13**	88	29[c]		 **29**	48
13		 **14**	67	30		 **30**	52
14		 **15**	43	31		 **31**	40
15		 **16**	95	32		 **32**	63
16		 **17**	90	33		 **33**	55
17		 **18**	52	34		 **34**	45

[a] Unless otherwise noted, all substrates used were aryl bromides. Standard reaction conditions: substrate (1.0 mmol), ethyl cyanoacetate (3.0 mmol), $Pd(OAc)_2$ (0.2 mmol), DPPE (0.3 mmol), TMEDA (1.0 mmol), Na_2CO_3 (3.0 mmol), KI (1.0 mmol), DMF (5 mL) stirred at 130 °C under Ar for 22 h. The products were confirmed by ^1H NMR, MS, IR and ^{13}C NMR. [b] KI was not added. [c] Na_2CO_3 was replaced by NaH (55−60%).

instead of aryl nitriles under the standard reaction conditions (Table 3). Normally, these highly electron-deficient aromatic compounds were aryl halides bearing two or more strong electron-withdrawing groups such as NO_2 and halides at the ortho and para positions. Thus, nucleophilic aromatic substitution was the preferred reaction under the cyanation reaction conditions. In fact, the aromatic substitution reaction

Table 3. Phenylacetonitrile Produced by Pd-Catalyzed Cyanation with Ethyl Cyanoacetate[a,b]



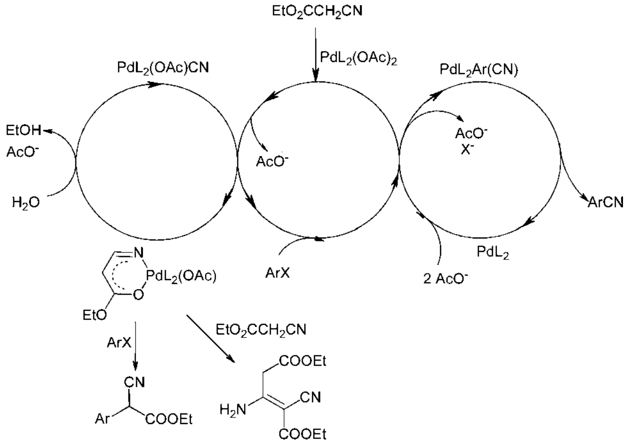
entry	starting material	products	yields (%) ([c])
1		 **35**	87 (72)
2		 **36**	90 (83)
3		 **37**	93 (78)
4		 **38**	88 (81)
5		 **39**	86 (69)
6		 **40**	95 (77)

[a] The standard reaction conditions are same as for the preparation of aryl nitriles. [b] The yield was obtained by isolation. [c] The yield was obtained under the conditions of Na_2CO_3/DMF/130 °C/22 h.

can proceed smoothly even in the absence of the palladium catalyst.

Based on the above results, mechanistic studies of the reactions were performed. First, the control experiment was performed in the absence of ethyl cyanoacetate. It was found that the reaction does not proceed at all under these conditions. Then, DMSO was used as the reaction solvent instead of DMF, and this reaction yielded the same results. These results indicated that the "CN" was originated from ethyl cyanoacetate. An ^{1}H NMR tracking experiment was also performed. An acetate signal and an ethanol signal were detected by ^{1}H NMR after $Pd(OAc)_2$ was reacted with ethyl cyanoacetate in DMSO-d_6 at 100 °C for 2.5 h. Furthermore, we also found that a small amount of water will improve the reaction, especially at the gram scale. This observation hinted that the existence of water may increase the solubility of inorganic salts. On the basis of all of the information available, a preliminary mechanism was proposed as shown in Scheme 2.

Scheme 2. Proposed Mechanism of the "CN" Transformation



It was assumed that the complex of the enolated ethyl cyanoacetate and the palladium catalyst plays the key role in the reaction. This complex can form an intermediate with the aryl halide and can undergo the cyanation reaction. It can also undergo nucleophilic aromatic substitution when electron-deficient aryl halides are used. If the aryl halide is too inert, the complex will react with another molecule of ethyl cyanoacetate and form a dimer instead.

In summary, we have discovered a new Pd-catalyzed cyanation reaction using ethyl cyanoacetate as the cyanating reagent. A variety of electron-rich and electron-deficient aryl halides were efficiently converted into their corresponding nitriles in good to excellent yields. Further optimization to reduce the high loading of palladium acetate and studies to obtain a deeper understanding of the reaction mechanism and to determine the synthetic applications of this reaction are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, characterization, and copies of ^{1}H and ^{13}CNMR for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.