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Synthesis of Benzoylacetonitriles from Pd-Catalyzed Carbonylation of Aryl Iodides and Trimethylsilylacetonitrile

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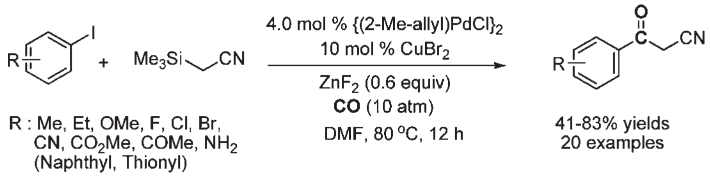
ABSTRACT



Palladium-catalyzed carbonylation of aryl iodides and trimethylsilylacetonitrile to produce benzoylacetonitrile derivatives through a one-pot, three-component reaction is described. This preparation method provides good yields of the carbonylated products without any additional ligands. It has a broad substrate scope with a high tolerance for a variety of functional groups.

Benzoylacetonitrile analogues, namely 3-oxo-3-arylpropanenitriles, have been used as starting materials for the synthesis of various biologically and pharmacologically active compounds, such as nonsteroidal anti-inflammatory drugs and inhibitors against HIV.[1] Moreover, they have been employed as precursors for the synthesis of optically active β-hydroxy carboxylic nitriles,[2] which are the key building blocks for the synthesis of 1,3-amino alcohol moieties and a variety of heterocyclic structures, including aminopyrazoles,[3] aminoisoxazoles,[4] imidazoles,[5] furanes,[6] and triazoles.[7] The classical preparation methods for benzoylacetonitriles involve the coupling of acetonitriles and esters in the presence of a strong base[8] and a cyanide displacement reaction with α-bromoketones[9] (Scheme 1a and b respectively). Recently, several new methods have been developed, such as the *C*-arylation of resin-bound cyanoacetates and indium-mediated coupling of bromoacetonitriles with acyl cyanides.[10] These methods have drawbacks such as the need for a preparation step for the starting materials, low functional group tolerance, and low yields. Since Heck reported the palladium-catalyzed carbonylation of aryl halides with carbon monoxide and nucleophiles,[11]

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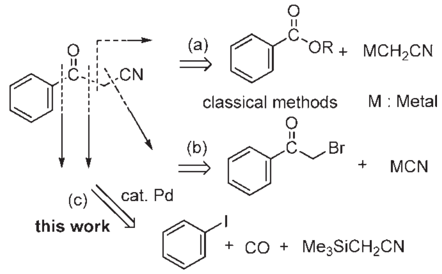
10.1021/ol300035u

Scheme 1. Synthetic Methods of Benzoylacetonitrile

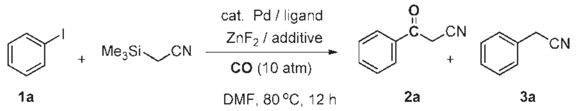


a variety of carbonylation methodologies have been reported.[12] The use of alcohols and amines as nucleophiles has produced carboxylic acid derivatives.[13] Carbonylative cross-coupling reactions such as the Stille, Suzuki, Sonogashira, and Heck carbonylations have produced a variety of aryl ketones.[14] Recently, the use of reductive carbonylation to produce aromatic aldehydes under milder conditions using CO/H_2 (synthesis gas) has been reported.[15] Similarly, carbonylative C−H activation has been used to produce aryl ketones.[16] In addition, a variety of sp^3 carbon nucleophiles have been used as coupling partners in the palladium-catalyzed carbonylation.[17] However, there have been no reports on the use of aliphatic nitrile anions in the transition-metal-catalyzed carbonylation of aryl halides including aryl iodides, though they have been employed in direct coupling reactions with aryl halides in the α-arylation of nitriles.[18] Here, we report the use of palladium-catalyzed carbonylation for the synthesis of benzoylacetonitrile derivatives through a one-pot three-component reaction for the first time (Scheme 1c).

Because of its functional group tolerance and mild conditions, we used an activated nitrile such as trimethylsilylacetonitrile as the nitrile source. To find the optimized conditions, the coupling reaction of iodobenzene, trimethylsilylacetonitrile, and carbon monoxide was chosen as a model.

Table 1 shows the yields under various conditions of the desired carbonylated compound **2a** and the noncarbonylated coupling product **3a**.

Table 1. Optimization of the Bases and the Solvents for the Carbonylation[a]



				yield (%)[c]	
entry	Pd	ligand	additive[b]	**2a**	**3a**
1	$Pd_2(dba)_3$	Xantphos[d]	–	0	0
2[c]	$Pd_2(dba)_3$	dppf[e]	–	0	0
3	$Pd(OAc)_2$	Xantphos	–	0	0
4	$Pd(PPh_3)_4$	Xantphos	–	0	0
5	$\{(cinnamyl)PdCl\}_2$	Xantphos	–	9	13
6	$\{(allyl)PdCl\}_2$	Xantphos	–	21	trace
7	$\{(2\text{-Me-allyl})PdCl\}_2$	Xantphos	–	43	trace
8	$\{(2\text{-Me-allyl})PdCl\}_2$	dppf	–	trace	0
9	$\{(2\text{-Me-allyl})PdCl\}_2$	$^tBu_3P\cdot HBF_4$	–	28	0
10	$\{(2\text{-Me-allyl})PdCl\}_2$	–	–	41	0
11	$\{(2\text{-Me-allyl})PdCl\}_2$	–	CuCl	56	14
12	$\{(2\text{-Me-allyl})PdCl\}_2$	–	CuBr	32	8
13	$\{(2\text{-Me-allyl})PdCl\}_2$	–	$CuCl_2$	45	0
14	$\{(2\text{-Me-allyl})PdCl\}_2$	–	$CuBr_2$	82	6
15	–	–	$CuBr_2$	0	0

[a] Reaction conditions: **1a** (0.30 mmol), trimethylsilylacetonitrile (0.36 mmol), Pd (0.024 mmol), ZnF_2 (0.18 mmol), and CO (10 atm) were reacted in DMF (*N*,*N*-dimethylformamide) at 80 °C for 12 h. [b] 0.03 mmol was added. [c] Determined by gas chromatography with internal standard. [d] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [e] 1,1′-Bis(diphenylphosphino)ferroecene.

Employing ZnF_2 as an activator, the model reaction was conducted in the presence of $Pd_2(dba)_3$ and Xantphos, which had shown good activity in coupling reactions with aryl halides and trimethylsilylacetonitrile in studies by the Hartwig group.[18g] No product was formed in the presence of carbon monoxide (entry 1), by using dppf as a ligand (entry 2), or in the presence of $Pd(OAc)_2$ and $Pd(PPh_3)_4$ (entries 3 and 4). In carbonylation, and when used as a Pd source, $\{(cinnamyl)PdCl\}_2$ showed limited activity, yielding 9% of product **2a** and 13% of product **3a** (entry 5). Both $\{(allyl)PdCl\}_2$ and $\{(2\text{-Me-allyl})PdCl\}_2$ yielded only a trace amount of product **3a** but yielded, respectively, 21% and 43% of product **2a** (entries 6 and 7). With $\{(2\text{-Me-allyl})PdCl\}_2$ as a palladium source, both dppf and $^tBu_3P\cdot HBF_4$ were used as a ligand; however, the yields of the desired product were unsatisfactory (entries 8 and 9).

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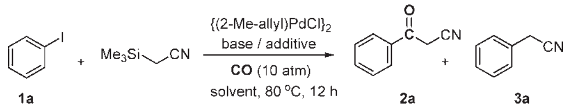
Interestingly, the reaction conditions in the absence of a ligand showed a similar yield to that in the presence of Xantphos (entry 10). We also took into account cost effectiveness by testing the reaction conditions without ligands. To increase the yield of **2a**, we used copper complexes CuCl, CuBr, $CuCl_2$, and $CuBr_2$ as cocatalysts. $CuBr_2$ gave the best result, yielding 82% of carbonylated compound **2a** and a small amount of **3a** (entry 14). No coupled product formed using $CuBr_2$ as a catalyst (entry 15) in the absence of Pd.

Table 2 shows the results of the effect of changing the base, additive, or solvent in the carbonylation reaction to study the role of fluorides.

Table 2. Effect of Base, Additive, and Solvent[a]



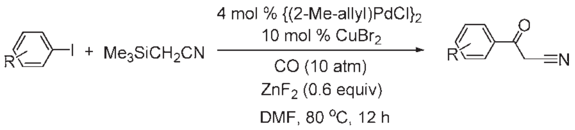
				yield (%)[b]	
entry	base	additive	solvent	**2a**	**3a**
1	KF	–	DMF	0	20
2	CsF	–	DMF	0	0
3	CsF	$CuBr_2$	DMF	0	0
4	$CuBr_2$	–	DMF	0	0
5	$CuCl_2$	–	DMF	0	0
6	FeF_2	$CuBr_2$	DMF	5	0
7	CoF_2	$CuBr_2$	DMF	3	0
8	NiF_2	$CuBr_2$	DMF	trace	12
9	CuF_2	–	DMF	69	19
10	ZnF_2	$CuBr_2$	NMP	32	0
11	ZnF_2	$CuBr_2$	DMSO	33	0
12[c]	ZnF_2	$CuBr_2$	DMF	38	2

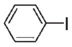
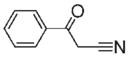
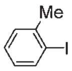
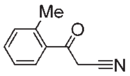
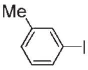
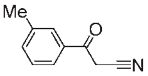
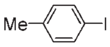
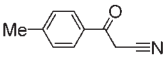
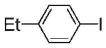
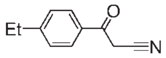
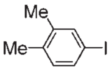
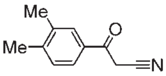
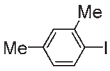
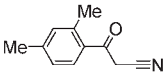
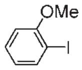
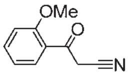
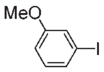
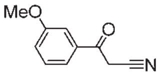
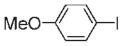
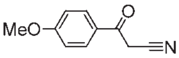
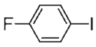
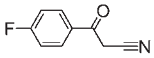
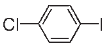
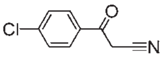
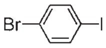
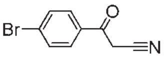
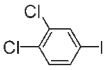
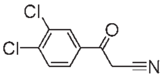
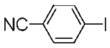
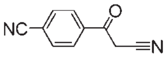
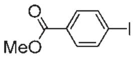
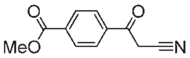
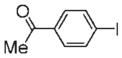
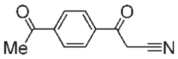
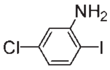
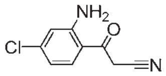
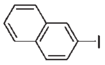
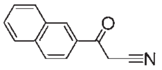
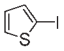
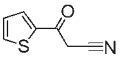
[a] Reaction conditions: **1a** (0.30 mmol), trimethylsilylacetonitrile (0.36 mmol), $\{(2\text{-Me-allyl})PdCl\}_2$ (0.012 mmol), base (MF = 0.36 mmol, MF_2 = 0.18 mmol), CO (10 atm), and additive (0.03 mmol) were reacted in DMF at 80 °C for 12 h. [b] Determined by gas chromatography with internal standard. [c] CO (5 atm).

KF, used as a fluoride source to activate trimethylsilylacetonitrile, gave 20% of the noncarbonylated product, **3a** (entry 1). Whether $CuBr_2$ was added or not, CsF did not give any coupled product (entries 2 and 3), nor did $CuBr_2$ or $CuCl_2$ (entries 4 and 5). Using late transition metal fluorides such as FeF_2, CoF_2, and NiF_2 instead of ZnF_2 produced a very low yield of **2a** (entries 6–8).

The use of CuF_2 as a base afforded 69% of **2a** and 19% of **3a**. Among the tested solvents, NMP and DMSO yielded, respectively, 32% and 33% of **2a** and no **3a** (entries 10 and 11).[19] By decreasing the pressure of carbon monoxide to 5 atm, the yield decreased to 38% (entry 12). From these results, we found that the combination of ZnF_2 and $CuBr_2$ is essential to obtain the desired benzoylacetonitrile in good yield.

Table 3. Synthesis of Benzoylacetonitrile from Aryl Iodide[a]



entry	R	product		yield (%)[b]
1			**2a**	80
2			**2b**	72
3			**2c**	65
4			**2d**	75
5			**2e**	65
6			**2f**	79
7			**2g**	71
8			**2h**	72
9			**2i**	69
10			**2j**	73
11			**2k**	65
12			**2l**	74
13			**2m**	82
14			**2n**	63
15			**2o**	41
16			**2p**	83
17			**2q**	43
18			**2r**	67
19			**2s**	68
20			**2t**	79

[a] Reaction conditions: aryl iodides (3.0 mmol), trimethylsilylacetonitrile (3.6 mmol), $\{(2\text{-Me-allyl})PdCl\}_2$ (0.12 mmol), ZnF_2 (1.8 mmol), and $CuBr_2$ (0.3 mmol) were reacted under CO (10 atm) in DMF at 80 °C for 12 h. [b] Isolated yield.

With the optimized conditions defined, we examined the scope of the carbonylative coupling reactions using various aryl iodides. As shown in Table 3, most aryl iodides produced the corresponding benzoylacetonitrile in moderate to good yields. Notably, benzoylacetonitrile (**2a**) was

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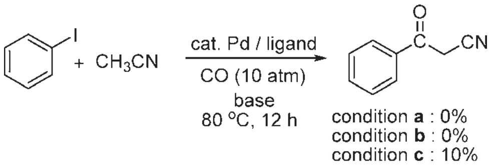
(19) No product was formed in diglyme and toulene.

successfully isolated in 80% yield (entry 1). Aryl iodides bearing an alkyl group at the *ortho*, *meta*, or *para* position produced a 65–75% yield (entries 2–5). Dimethyl-substituted phenyl iodides led to good yields (entries 6 and 7), but iodoanisole derivatives produced slightly lower yields (entries 8–10). Aryl iodides bearing a halo group, viz. fluoro, chloro, and bromo, which are electron-withdrawing groups, produced yields of 65%, 74%, and 82%, respectively (entries 11–13). The yield from aryl iodides with nitrile, ester, ketone, and amine groups, which are sensitive to a base, ranged from 41% to 83% (entries 15–18). In addition, 2-iodonaphthalene and heteroaryl iodides such as 2-iodothiophene also gave good yields (entries 19 and 20).

Taking atom economy into consideration, we attempted to employ acetonitrile instead of trimethylsilylacetonitrile in the synthesis of benzoylacetonitrile. As shown in Scheme 2, none of the desired product was obtained when iodobenzene and acetonitrile were reacted with carbon monoxide under the optimized conditions (Scheme 2, condition a). We used a strong base to activate the α-proton of acetonitrile. In the presence of $\{(\text{cinnamyl})PdCl\}_2$ and Xantphos, NaHMDS (HMDS = hexamethyldisilane) did not produce benzoylacetonitrile. However, benzoylacetonitrile was obtained in 10% yield when the reaction was carried out with NaO^tBu in the presence of $Pd(OAc)_2$ and dppf.[20]

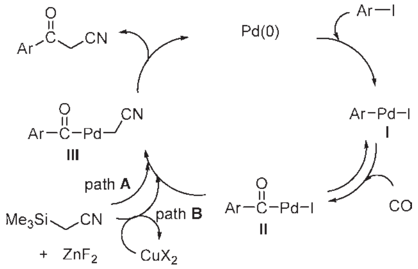
Scheme 2. Synthesis of Benzoylacetonitrile from Acetonitrile[a]



[a] Reaction conditions: iodobenzene (3.0 mmol), acetonitrile (6.0 mmol), and carbon monoxide (10 atm) were reacted at 80 °C for 12 h in the following conditions: (**a**) $\{(\text{2-Me-allyl})PdCl\}_2$ (0.12 mmol), ZnF_2 (1.8 mmol), and $CuBr_2$ (0.3 mmol) were used in DMF; (**b**) $\{(\text{cinnamyl})PdCl\}_2$ (0.12 mmol), Xantphos (0.30 mmol), and NaHMDS (6.0 mmol) were used in toluene; (**c**) $Pd(OAc)_2$ (0.15 mmol), dppf (0.15 mmol), and NaO^tBu (6.0 mmol) were used in toluene.

Scheme 3 shows our proposed mechanism for the palladium-catalyzed carbonylation of aryl iodides and Me_3SiCH_2CN to produce benzoylacetonitriles.

Scheme 3. Proposed Mechanism



The oxidative addition of aryl iodides to Pd(0) form the palladium complex **I**. Next, the insertion of carbon monoxide into the aryl palladium iodide complex **I** occurs. This process might be reversible because the noncarbonylated product was formed in the presence of high-pressure carbon monoxide. In the transmetalation step, two pathways might exist: Path A as direct transmetalation, and Path B as copper-catalyzed transmetalation from the reaction with trimethylsilylacetonitrile and ZnF_2. We did not observe any change when ZnF_2 and trimethylsilylacetonitrile were reacted in DMF-d_7, as Hartwig reported.[18g] However, the amount of trimethylsilylacetonitrile was decreased and trimethylsilylfluoride was identified in ^{19}F NMR (−159.0 ppm, J_{H-F} = 7.3 Hz),[21] when ZnF_2 and trimethylsilylacetonitrile were reacted in the presence of $CuBr_2$ (10 mol %) in DMF-d_7. Based on the experimental results, path B would be predominant over path A. Finally, the reductive elimination of complex **III** affords the desired product.

In summary, we developed a novel method of synthesizing benzoylacetonitriles from the palladium-catalyzed carbonylation of aryl iodides and trimethylsilylacetonitrile. This method provides a broad scope and good yields of the carbonylated products without any additional ligands. In addition, it shows high functional group tolerance. To the best of our knowledge, this is the first report on the construction of benzoylacetonitriles from palladium-catalyzed carbonylation. Mechanistic studies are ongoing in our laboratory.

Acknowledgment. This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (2009-0072357).

Supporting Information Available. Reaction procedures and spectral and analytical data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The yield of product was not improved even in the presence of $CuBr_2$.

(21) For reference of the chemical shift of ^{19}F NMR H, see: Burger; Moritz, P. *J. Organomet. Chem.* **1992**, *427*, 293.