Palladium-Catalyzed Carbonylation with $Mo(CO)_6$ for the Synthesis of Benzoylacetonitriles

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Abstract: Benzoylacetonitriles were synthesized by the palladium-catalyzed carbonylation of aryl iodides and trimethylsilylacetonitrile using $Mo(CO)_6$ as a carbon monoxide source. $Pd(PPh_3)Cl_2$ and CuF_2 were employed as the catalyst and activator, respectively. A variety of aryl iodides bearing alkyl, alkoxy, fluoro, chloro, bromo, nitrile, ester, and ketone groups afforded the corresponding benzoylacetonitriles in moderate to good yields.

Key words: carbonylation, cross-coupling, palladium, arylation, molybdenum

Palladium-catalyzed carbonylation is one of the most important methods in the field of organic chemistry.[1] Heck first reported the synthesis of aryl amides and esters from the coupling of aryl halides, carbon monoxide, and nucleophiles such as amines and alcohols in the presence of a palladium catalyst.[2] Since then, a variety of nucleophiles that have been employed in Heck,[3] Negishi,[4] Stille,[5] Suzuki,[6] Hiyama,[7] and Sonogashira[8] cross-coupling reactions have also been employed in palladium-catalyzed carbonylation. Recently, the α-carbon atoms of carbonyl compounds[9] and C–H activated compounds[10] have been used as nucleophiles. In addition, formylation[11] and oxidative carbonylation[12] have also been reported. Very recently, we first reported the use of palladium-catalyzed carbonylation for the synthesis of benzoylacetonitriles, which are very useful building blocks in the pharmaceutical and material chemistry fields.[13] For example, they have been employed as precursors for the synthesis of cytosine,[14] aminopyrazoles,[15] 2-pyridones,[16] β-hydroxy carboxylic acids,[17] furanes,[18] and triazoles.[19]

Although palladium-catalyzed carbonylation using carbon monoxide is very simple and straightforward, it has some drawbacks in that special equipment is required. Because the handling of toxic carbon monoxide is troublesome in the general organic laboratory, a number of alternative methods that do not involve the direct use of carbon monoxide have been developed.[20] As alternative carbonyl sources, formic acid derivatives, aldehydes, and metal carbonyls have been used. Among them, $Mo(CO)_6$ has been widely used in a number of palladium-catalyzed carbonylations.[21] However, in most cases, the reactions required the assistance of microwave radiation to obtain the desired carbonylated compounds in good yields.[22] The requirement for special equipment has limited the usage of the carbonyl system in the general organic laboratory. Therefore, it is necessary to develop a more easily accessible method for use in common organic laboratories. Herein, we report a simple and convenient method for the synthesis of benzoylacetonitriles from the three-component coupling of aryl iodides, activated acetonitriles, and a carbon monoxide surrogate.

As a model reaction, phenyl iodide and trimethylsilylacetonitrile were reacted with ZnF_2 in the presence of $\{(2\text{-Me-allyl})PdCl\}_2$ and $CuBr_2$. First, a variety of CO gas surrogates were tested to find a suitable CO source for the synthesis of benzoylacetonitrile. None of the desired product was formed when the reaction was conducted in the absence of CO source at 150 °C. (Table 1, entry 1).[23] Among the tested metal carbonyl complexes, $Mo(CO)_6$ was considered to be a suitable CO source, although the use of $Cr(CO)_6$ gave a similar yield of the product (entries 2–5). Instead of the combination of ZnF_2 and $CuBr_2$, which afforded a good yield using carbon monoxide,[13] the employment of CuF_2 gave 55% yield of the product (entry 6). Next, we tested sources of palladium complexes. Palladium complexes bearing an allyl group such as cinnamyl and allyl afforded 31 and 46% yields, respectively (entries 7 and 8). No product was obtained from $Pd(OAc)_2$ or $Pd(dba)_2$ (entries 9 and 10). Use of $Pd(PPh_3)_2Cl_2$ gave 61% yield of the product (entry 11). Unfortunately, the addition of ligands such as Xantphos, dppb and PCy_3 did not improve the yield of the product (entries 12–14). Increasing the amount of $Mo(CO)_6$ decreased the yield of the product (entry 15). However, the yield of the product was improved when the amount of $Mo(CO)_6$ was decreased to 0.5 and 0.2 equivalents (entries 16 and 17). None of the desired product was formed when the reaction was run with $Mo(CO)_6$ in the absence of palladium (entry 18).[24] Screening of the solvents demonstrated that acetonitrile was optimal (entry 21), however, acetonitrile was found not to work as a substrate because no product was formed in the absence of trimethylsilylacetonitrile (entry 22). Considering the cost of the reagents and yield of the product, we employed the following conditions for the synthesis of benzoylacetonitriles; aryl iodide (1.0 equiv), trimethylsilylacetonitrile (1.2 equiv), $Mo(CO)_6$ (0.5 equiv), CuF_2 (0.6 equiv), and $Pd(PPh_3)_2Cl_2$ (5.0 mol%) in acetonitrile at 80 °C for 16 hours.

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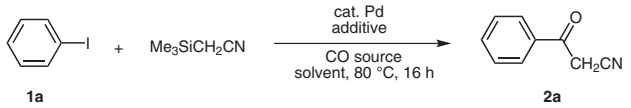
Table 1 Optimized Conditions for the Synthesis of Benzoylacetonitrile[a]



1a 2a

Entry	Pd	CO source (equiv)	Additive[b]	Solvent	Yield (%)[c]
1	$\{(2Me\text{-}allyl)PdCl\}_2$	*t*-BuOK	A	DMF	0
2	$\{(2Me\text{-}allyl)PdCl\}_2$	$Mo(CO)_6$ (1.0)	A	DMF	48
3	$\{(2Me\text{-}allyl)PdCl\}_2$	$Cr(CO)_6$ (1.0)	A	DMF	46
4	$\{(2Me\text{-}allyl)PdCl\}_2$	$Co_2(CO)_8$ (1.0)	A	DMF	28
5	$\{(2Me\text{-}allyl)PdCl\}_2$	$W(CO)_6$ (1.0)	A	DMF	21
6	$\{(2Me\text{-}allyl)PdCl\}_2$	$Mo(CO)_6$ (1.0)	B	DMF	55
7	$\{(cinnamyl)PdCl\}_2$	$Mo(CO)_6$ (1.0)	B	DMF	31
8	$\{(allyl)PdCl\}_2$	$Mo(CO)_6$ (1.0)	B	DMF	46
9	$Pd(OAc)_2$	$Mo(CO)_6$ (1.0)	B	DMF	trace
10	$Pd(dba)_2$	$Mo(CO)_6$ (1.0)	B	DMF	trace
11	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (1.0)	B	DMF	61
12[d]	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (1.0)	B	DMF	51
13[e]	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (1.0)	B	DMF	27
14[f]	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (1.0)	B	DMF	19
15	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (2.0)	B	DMF	7
16	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.5)	B	DMF	71
17	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.2)	B	DMF	61
18	–	$Mo(CO)_6$ (0.5)	B	DMF	0
19	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.5)	B	toluene	6
20	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.5)	B	dioxane	45
21	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.5)	B	MeCN	81
22[g]	$Pd(PPh_3)_2Cl_2$	$Mo(CO)_6$ (0.5)	B	MeCN	0

[a] Reaction conditions: Phenyl iodide (0.3 mmol), $TMSCH_2CN$ (0.36 mmol), and Pd (0.015 mmol) were reacted with the carbon monoxide source in the presence of an additive at 80 °C for 16 h.
[b] Additive **A**: ZnF_2 (0.18 mmol), $CuBr_2$ (0.03 mmol); **B**: CuF_2 (0.18 mmol).
[c] Determined by gas chromatography with internal standard 2-methoxynaphthalene.
[d] Xanthphos was used as ligand.
[e] dppb was used as ligand.
[f] PCy_3 was used as ligand.
[g] The reaction was conducted in the absence of trimethylsilylacetonitrile.

We then evaluated the optimized conditions for the synthesis of benzoylacetonitrile by examining a variety of aryl iodides; the results are summarized in Table 2. As expected, benzoylacetonitrile was obtained in 77% isolated yield (entry 1). Mono- and dialkyl-substituted aryl iodides produced the corresponding products in good yields (entries 2–6). 2-Methoxyphenyl iodide afforded 65% yield of the product (entry 7). *ortho*-Substituted substrates also gave good yields (entries 6 and 7). Use of aryl iodides bearing monohalo groups such as fluoro, chloro, and bromo gave good yields of the corresponding products (entries 8–12). Neither the carbonylation nor coupling reaction occurred at the bromo position in the case of bromoiodobenzenes (entries 11 and 12). Dihalo-substituted aryl iodides gave 53–60% yields (entries 13–15). Aryl iodides bearing acid- or base-sensitive groups such as cyano, keto, and ester moieties produced the desired products in 49, 64, and 57% yields, respectively (entries 16–18). However, 5-chloro-2-iodoaniline gave a poor yield (11%; entry 19), even though it gave a good yield (67%) in the

presence of carbon monoxide.[13] 2-Naphthyl iodide and 2-thiophenyl iodide afforded the corresponding products in 83 and 53% yield, respectively (entries 20 and 21). However, the desired carbonylated products were not obtained from 2-iodopyridine and 4-iodophenol (entries 22 and 23).

Table 2 Synthesis of Benzoylacetonitrile from Aryl Iodide[a]

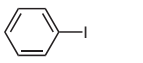
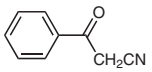
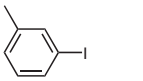
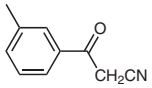
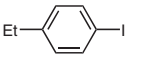
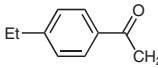
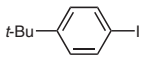
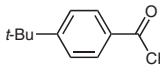
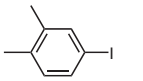
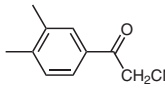
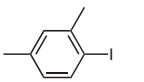
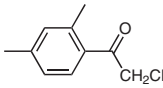
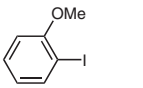
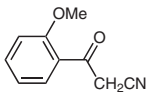
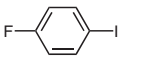
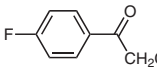
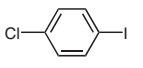
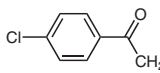
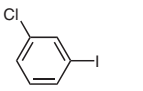
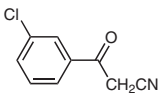
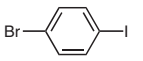
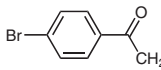
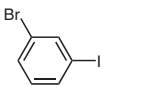
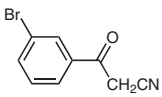
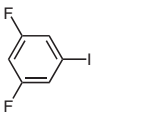
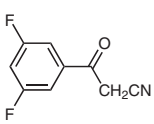
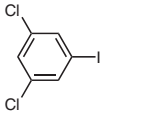
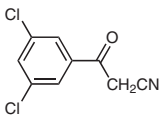
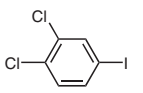
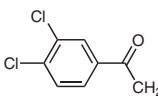
Entry	R	Product		Yield (%)
1			**2a**	77
2			**2b**	77
3			**2c**	71
4			**2d**	84
5			**2e**	64
6			**2f**	63
7			**2g**	65
8			**2h**	61
9			**2i**	66
10			**2j**	57
11			**2k**	68
12			**2l**	61
13			**2m**	60
14			**2n**	56
15			**2o**	53

Table 2 Synthesis of Benzoylacetonitrile from Aryl Iodide[a] (continued)

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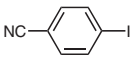
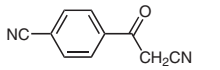
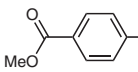
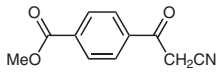
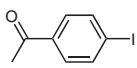
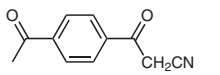
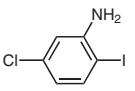
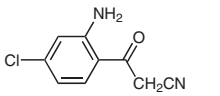
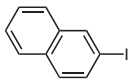
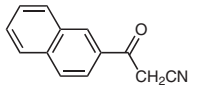
16			**2p**	49
17			**2q**	64
18			**2r**	57
19			**2s**	11
20			**2t**	83
21			**2u**	35
22			**2v**	0
23			**2w**	0

[a] Reaction conditions: aryl iodide (3.0 mmol), trimethylsilylacetonitrile (3.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.15 mmol), $Mo(CO)_6$ (1.5 mmol), CuF_2 (1.8 mmol), MeCN, 80 °C, 16 h.

To study the role of CuF_2, trimethylsilylacetonitrile was reacted with CuF_2 in DMF-d_7.[25] The generation of $(CH_3)_3SiF$ was identified in the ^{19}F NMR (δ = –156.7 ppm) and ^1H NMR (δ = 0.23 ppm, J_{H-F} = 7.5 Hz) spectra. This result suggests that CuF_2 cleaves the C–Si bond of the δ-silylacetonitrile, in contrast to the reaction with ZnF_2.[26] Based on this result, we propose the mechanism shown in Scheme 1. The oxidative addition intermediate is first formed from the reaction of Pd(0) and aryl iodide. This then reacts with the carbon monoxide generated from $Mo(CO)_6$ to afford the acyl palladium iodide complex **B**. Complex **C** is then formed by transmetallation with the preformed copper acetonitrile species, which is formed from the reaction with trimethylsilylacetonitrile and CuF_2. The desired product is finally formed through reductive elimination.

Scheme 1 Proposed mechanism

In summary, we have developed a simple and easy-to-handle method for the synthesis of benzoylacetonitriles through palladium-catalyzed carbonylation using $Mo(CO)_6$. Trimethylsilyl acetonitrile was activated by CuF_2 and transmetallated with acyl palladium iodide. The reaction showed good tolerance toward functional groups such as alkoxy, fluoro, chloro, bromo, nitrile, ester, and ketone moieties. Instead of using toxic carbon monoxide gas, the employment of $Mo(CO)_6$ afforded several advantages with respect to handling and safety.

Synthesis of Benzoylacetonitriles; General Procedure

Aryl iodide (3.0 mmol), trimethylsilylacetonitrile (408 mg, 3.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.015 mmol), CuF_2 (2.25 mmol), $Mo(CO)_6$ (1.5 mmol), and MeCN (10.0 mL) were mixed in a 20 mL vial. The reaction mixture was stirred for 16 h at 80 °C and then cooled to r.t. The reaction mixture was poured into 1 M HCl (25 mL) and extracted with EtOAc (5 × 20 mL). The combined organic extracts were washed with brine (90 mL), dried over $MgSO_4$, and passed through Celite. The resulting crude product was purified by flash chromatography on silica gel (EtOAc–hexane).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(25) To simplify the analysis, DMF-d_7 was employed instead of CD_3CN. See the Supporting Information.

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