



One-pot synthesis of benzoylacetone nitriles through sequential Pd-catalyzed carbonylation and decarboxylation



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ABSTRACT

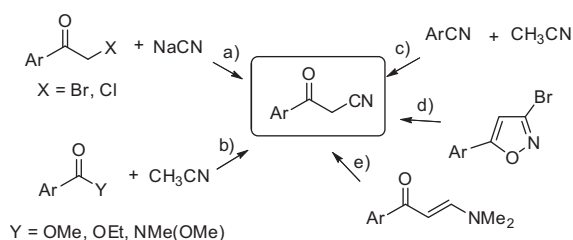
Benzoylacetone nitriles were prepared through sequential carbonylation and decarboxylation. The palladium-catalyzed carbonylation of aryl iodides and methyl cyanoacetate using $\text{Mo}(\text{CO})_6$ as a carbon monoxide source afforded beta-keto cyanoesters, and then the subsequent reaction with $\text{Li}/\text{H}_2\text{O}$ produced the desired benzoylacetone nitriles.

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Introduction

Benzoylacetone nitrile is an important building block because it can be converted to a variety of heterocyclic compounds such as cytosine,¹ triazole,² imidazole,³ furan,⁴ aminopyrazole,⁵ aminoisoxazole,⁶ isoxazole,⁷ and pyridine.⁸ In addition, it has been employed as a starting material for the preparation of biologically active materials, such as antimicrobial,⁹ antineoplastic,¹⁰ and anti-inflammatory agents,¹¹ and HIV inhibitors.¹² A number of preparation methods have been developed as shown in Scheme 1. The substitution of α -haloacetophenones with cyanide (Scheme 1a),¹³ the coupling of an ester (or *N*-methoxy-*N*-methylbenzamide) and acetonitrile in the presence of a strong base (Scheme 1b),¹⁴ the reaction between benzonitriles and acetonitrile (Scheme 1c),¹⁵ the ring opening of 3-bromoisoxazole (Scheme 1d),¹⁶ and the reaction of enaminones with hydroxylamine hydrochloride (Scheme 1e) have been employed to produce benzoylacetone nitriles.¹⁷

Recently, we first reported the synthesis of benzoylacetone nitriles through palladium-catalyzed carbonylation with aryl halides and trimethylsilyl acetonitrile (Scheme 2a).¹⁸ Palladium-catalyzed carbonylation has been used in the synthesis of carbonyl compounds such as amides, esters, and ketones via the couplings of aryl halides and nucleophiles in the presence of carbon monoxide.¹⁹ Although it is a simple and straightforward method, the handling of carbon monoxide gas requires special equipment and is a safety issue. In



Scheme 1. Classical methods for the synthesis of benzoylacetone nitriles.

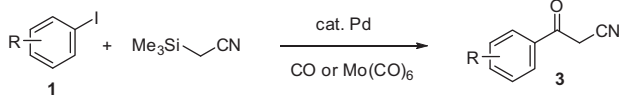
order to address the use of toxic carbon monoxide, we developed an alternative method that utilizes $\text{Mo}(\text{CO})_6$ as a carbon monoxide surrogate. A number of carbonylation methods using $\text{Mo}(\text{CO})_6$ have been reported.²⁰ Although these two methods provided straightforward protocols for the synthesis of benzoylacetone nitriles from aryl halides, they required trimethylsilyl acetonitrile, which may give rise to cost issues. Therefore, the development of a synthetic method that uses much less expensive reagents is still in demand. To meet this requirement, we focused our attention on the carbonylation of aryl iodides with methyl cyanoacetate (**2**) and the subsequent decarboxylation.

The palladium-catalyzed coupling reaction of aryl halides with alkyl cyanoacetates has been reported by other groups.²¹ However, the carbonylation of aryl halides and cyanoacetate in the presence of a carbon monoxide has never been reported. Here, we first report the direct synthesis of benzoylacetone nitriles through the car-

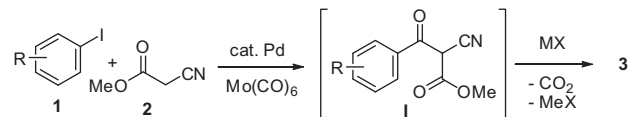
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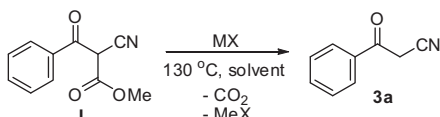
a) Previous our works



b) This work



Scheme 2. Synthesis of benzoylacetone nitriles through carbonylation.

Table 1
Optimization of Krapcho decarboxylation^a

Entry	MX	Solvent	Yield ^b (%)
1	NaCN	DMSO/H ₂ O	43
2	NaCl	DMSO/H ₂ O	90
3	LiCl	DMSO/H ₂ O	84
4	KI	DMSO/H ₂ O	43
5	LiI	DMSO/H ₂ O	55
6	NaCN	DMF/H ₂ O	23
7	NaCl	DMF/H ₂ O	43
8	LiCl	DMF/H ₂ O	38
9	KI	DMF/H ₂ O	77
10	LiI	DMF/H ₂ O	88
11	NaCl	NMP/H ₂ O	51
12	LiI	NMP/H ₂ O	91

^a Reaction conditions: **I** (0.3 mmol) and MX (0.6 mmol) were reacted at 120 °C for 6 h.

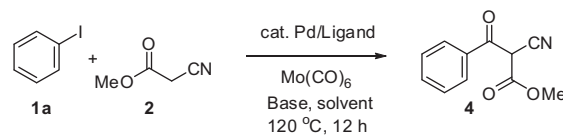
^b Determined by gas chromatography with an internal standard.

carbonylation of aryl halides with alkyl cyanoacetates and a subsequent decarboxylation.

To achieve this goal, we first attempted to find the optimized conditions for the decarboxylation of methyl 2-cyano-3-oxo-3-phenylpropanoate (**I**), which can be obtained through the coupling reaction of an aryl iodide and the corresponding cyanoacetate in the presence of a carbon monoxide source. This decarboxylation of an ester bearing an electron-withdrawing group at the β -position is known as the Krapcho reaction.²² The results are summarized in Table 1.

When NaCN, NaCl, and LiCl, which showed good activity in the Krapcho decarboxylation, were employed in DMSO, desired product **3a** was formed in 43%, 90%, and 84% yields, respectively (entries 1–3). However, KI and LiI gave product **3a** in 43% and 55% yields, respectively (entries 4 and 5). Bearing in mind the subsequent reaction, the decarboxylation was tested in DMF, which was a good solvent in the palladium-catalyzed carbonylation for the synthesis of benzoylacetone nitriles. We found that NaCN, NaCl, and LiCl provided lower yields of the product than they did in DMSO (entries 6–8). KI and LiI showed good yields in DMF (entries 9 and 10). When the reaction was conducted in NMP (*N*-methyl-2-pyrrolidinone), NaCl was inferior to LiI (entries 11 and 12).

In order to accomplish the one-pot sequential synthesis of benzoylacetone nitriles, we attempted the palladium-catalyzed carbonylation of an aryl iodide and a cyanoacetate in the presence of Mo(CO)₆ (Table 2). As a model reaction, iodobenzene and methyl cyanoacetate were tested in the synthesis of the intermediate,

Table 2
Optimization of the carbonylation^a

Entry	Catalyst	Ligand	Base	Solvent	Yield ^b (%)
1	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Na ₂ CO ₃	NMP	40
2	Pd(PPh ₃) ₂ Cl ₂	dppb	Na ₂ CO ₃	NMP	54
3	Pd ₂ (dba) ₃	PPh ₃	Na ₂ CO ₃	NMP	36
4	Pd ₂ (dba) ₃	dppb	Na ₂ CO ₃	NMP	57
5	[(allyl)PdCl] ₂	PPh ₃	Na ₂ CO ₃	NMP	55
6	[(allyl)PdCl] ₂	dppb	Na ₂ CO ₃	NMP	87
7	[(allyl)PdCl] ₂	dppf	Na ₂ CO ₃	NMP	60
8	[(allyl)PdCl] ₂	Xantphos	Na ₂ CO ₃	NMP	70
9	[(allyl)PdCl] ₂	BINAP	Na ₂ CO ₃	NMP	62
10	[(allyl)PdCl] ₂	dppb	K ₂ CO ₃	NMP	61
11	[(allyl)PdCl] ₂	dppb	Cs ₂ CO ₃	NMP	73
12	[(allyl)PdCl] ₂	dppb	Na ₃ PO ₄	NMP	51
13	[(allyl)PdCl] ₂	dppb	Na ₂ CO ₃	DMF	81
14	[(allyl)PdCl] ₂	dppb	Na ₂ CO ₃	DMSO	53

^a Reaction conditions: iodobenzene (0.3 mmol), methyl cyanoacetate (0.6 mmol), Mo(CO)₆ (0.3 mmol), palladium catalyst (0.015 mmol), ligand (0.015 mmol), and base (0.6 mmol) were reacted in NMP (1.0 mL) at 120 °C for 12 h.

^b Isolated yield.

methyl 2-cyano-3-oxo-3-phenylpropanoate, in the subsequent reaction. First, we employed Pd(PPh₃)₂Cl₂, which had shown good activity in the coupling reaction in the presence of Mo(CO)₆, as the palladium catalyst. When PPh₃ and 1,4-bis(diphenylphosphino)butane (dppb) were used as ligands, desired carbonyl compound **4** was formed in 40% and 54% yields, respectively (entries 1 and 2). When the palladium catalyst was changed to Pd₂(dba)₃ with PPh₃ and dppb as ligands, the yields did not improve (entries 3 and 4). When [(allyl)PdCl]₂ was employed as the palladium catalyst, the reactions with PPh₃ and dppb as ligands afforded the desired product in 55% and 87% yields, respectively (entries 5 and 6). However, other chelating phosphine ligands such as 1,1'-bis(diphenylphosphino)ferrocene (dppf), Xantphos, and BINAP were not superior to dppb and did not give satisfactory results (entries 7–9). When K₂CO₃, Cs₂CO₃, and Na₃PO₄ were used as bases instead of Na₂CO₃, the desired product was formed in 61%, 73%, and 51% yield, respectively (entries 10–12). The reaction in DMF gave an 81% yield of the product (entry 13). However, the reaction in DMSO, which is a good solvent in the decarboxylation, did not give a satisfactory result (entry 14).

Finally, we combined the carbonylation and the decarboxylation for the sequential one-pot synthesis of benzoylacetone nitriles. The optimized conditions were as follows: aryl iodide, methyl cyanoacetate, Mo(CO)₆, [(allyl)PdCl]₂, dppb, and Na₂CO₃ were reacted in NMP at 120 °C for 12 h, and then LiI/H₂O was added to the resulting mixture and stirred at 130 °C for 6 h. To evaluate this methodology, a variety of aryl iodides was tested under the optimized conditions. As shown in Table 3, moderate yields were obtained in most cases. As expected, iodobenzene provided the desired benzoylacetone nitrile in 76% isolated yield (entry 1). Methyl-, ethyl-, and methoxy-substituted iodobenzenes gave desired products **3b**, **3c**, and **3d** in 70%, 71%, and 69% yields, respectively (entries 2–4). Halide-substituted aryl iodides afforded the desired benzoylacetone nitriles in yields ranging from 55% to 71% (entries 5–11). 4-Iodoacetophenone gave desired product **3l** in 57% yield (entry 12). 2-Naphthyl iodide and 2-thiophenyl iodide provided corresponding products **3m** and **3n** in 83% and 44% yields, respectively (entries 13 and 14). However, aryl iodides bearing ester or cyano groups did not give the desired products (entries 15 and 16).²³

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