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Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of aryl nitriles by palladium-assisted cyanation of aryl iodides using *tert*-butyl isocyanide as cyano source

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ARTICLE INFO

Article history:

Received 18 March 2015

Received in revised form 15 April 2015

Accepted 18 April 2015

Available online xxx

Keywords:

Palladium-catalyzed synthesis

Cyanation

tert-Butyl isocyanide

Aryl nitriles

Aryl iodides

ABSTRACT

A palladium-catalyzed synthesis of aryl nitriles by the cyanation of aryl iodides with *tert*-butyl isocyanide as cyano source has been developed. This novel and efficient method avoids the use of toxic cyanides. The reaction is easy-to-handle and shows good functional group compatibility.

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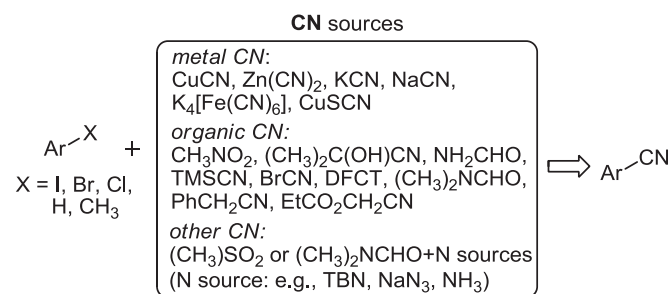
1. Introduction

Aryl nitriles are an integral part of many natural products, pharmaceuticals, agrochemicals, herbicides, pigments, and dyes.¹ In addition, they are easily transformed into other functional groups, such as amines, acids, amides, aldehydes, and heterocycles.² As a result, a number of methods to introduce cyano group to aromatic ring have been developed. Of these transformations, transition-metal-catalyzed cyanation of aryl halides^{2e} or aromatic C–H bond activation was an elegant route to benzonitriles (Scheme 1). However, typical protocols utilized toxic cyanides (e.g., Cu(CN)₂,³ Zn(CN)₂,⁴ NaCN, and KCN⁵), CH₃NO₂,⁶ acetone cyanohydrin,⁷ cyanogen halides,⁸ TMSCN,⁹ *N*-cyano-*N*-phenyl-*para*-toluenesulfonamide (NCTS),¹⁰ and aryl(cyano)iodonium triflates (DFCT)¹¹ as cyanating agents. Low toxic CN source was thus highly desired. K₄[Fe(CN)₆] was first used by Beller and co-workers to introduce CN into organic molecules.¹² Recently, other CN sources such as ammonium salts or organic amine/DMSO,¹³ DMF,¹⁴ formamide,^{14f,g} ethyl cyanoacetate,^{15a} benzyl cyanide,^{15b–d} CuSCN,¹⁶ NaN₃,¹⁷ NH₃, and *tert*-butyl nitrite (TBN)¹⁸ have been demonstrated to deliver nitriles. However, poor functional group tolerance and maneuverability restricted their application.

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<http://dx.doi.org/10.1016/j.tet.2015.04.059>

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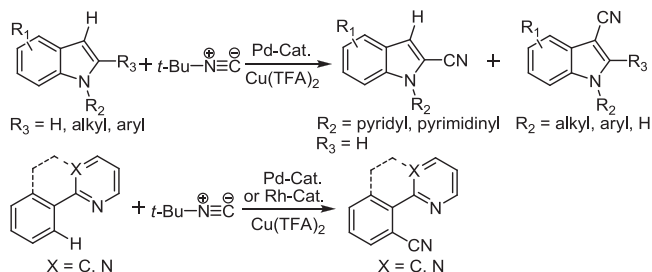


Scheme 1. Approaches to aryl nitriles.

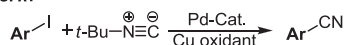
Isocyanides, which are well known as isoelectronic equivalent of CO, are powerful C₁ building blocks in organic synthesis since the pioneer work of Passerini and Ugi.¹⁹ Palladium-catalyzed isocyanide insertion has been widely applied in the synthesis of nitrogenous compounds.²⁰ Our group has successfully constructed C–O, C–C, C–N and aldehydes via metal-catalyzed isocyanide insertion into C–X bonds.²¹ Nevertheless, the use of isocyanides as a cyano source has been less explored.²² Palladium-catalyzed direction C–H cyanation of phenylindole and phenylpyridine was only reported by Xu and Zhu.^{22e–g} However, those reactions limit the scope to electron-rich and regioselective nitrogen-containing indoles or 2-phenylpyridine derivatives. Herein, for further broadening the application of isocyanides as CN source in the

synthesis of aromatic and heteroaromatic nitriles, we describe an efficient palladium-catalyzed cyanation of aryl iodides using *tert*-butyl isocyanide as CN source (Scheme 2).

previous work: only indoles or 2-phenylpyridine derivatives with 28%–92% yields



this work:



Scheme 2. Cyanation using isocyanide as CN source.

2. Results and discussion

Our investigation began with examining the reaction of 4-phenyliodobenzene and *t*-BuNC (1.2 equiv) utilizing Pd(OAc)₂ (5 mol %) as catalyst, copper(II) trifluoroacetate hydrate (3 equiv) as oxidant and Na₂CO₃ (1 equiv) as base at 130 °C. To our delight, 4-phenylbenzonitrile was produced in 46% yield in DMF under N₂ for 12 h (Table 1, entry 1). In the presence of 3 equiv of *t*-BuNC, completed conversion was achieved under 2 equiv of Cu(TFA)₂·xH₂O and the yield was increased to 83% (Table 1, entry 2). Base had no significant effect on this reaction (Table 1, entry 3 and

Table 1
Optimization of reaction conditions^a

Entry	Catalyst	Oxidant	Additive	Solvent	Temp (°C)	Yield ^b (%)
1	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	Na ₂ CO ₃	DMF	130	46 ^c
2	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	Na ₂ CO ₃	DMF	130	83
3	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMF	130	82
4	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	NaHCO ₃	DMF	130	84
5	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMF	130	76
6	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	98
7	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	toluene	130	35
8	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	dioxane	120	28
9	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	110	59
10	PdCl ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	93
11	Pd(TFA) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	95
12	Pd ₂ (dba) ₃	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	92
13	—	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	86
14	Pd(OAc) ₂	—	—	DMSO	130	trace ^d
15	Pd(OAc) ₂	AgTFA	—	DMSO	130	23
16	Pd(OAc) ₂	CuCl ₂	—	DMSO	130	45
17	Pd(OAc) ₂	Cu(OAc) ₂	—	DMSO	130	38
18	Pd(OAc) ₂	Cu(NO ₃) ₂ ·2.5H ₂ O	—	DMSO	130	87
19	Pd(OAc) ₂	CuSO ₄	—	DMSO	130	59
20	Pd(OAc) ₂	CuSO ₄ ·5H ₂ O	—	DMSO	130	76
21	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	CaCl ₂	DMSO	130	51
22	Pd(OAc) ₂	CuCl ₂	H ₂ O	DMSO	130	52
23	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O/O ₂	—	DMSO	130	trace ^e
24	Pd(OAc) ₂	Cu(TFA) ₂ ·xH ₂ O	—	DMSO	130	18 ^f

^a Conditions: All reactions were performed with **1a** (0.7 mmol), *tert*-butyl isocyanide (3 equiv), catalyst (5 mol %), oxidant (2 equiv), and additive (1 equiv) in 2.5 mL of solvent under nitrogen for 12 h in a sealed tube unless otherwise noted.

^b Isolated yield.

^c *tert*-Butyl isocyanide (1.2 equiv), oxidant (3 equiv).

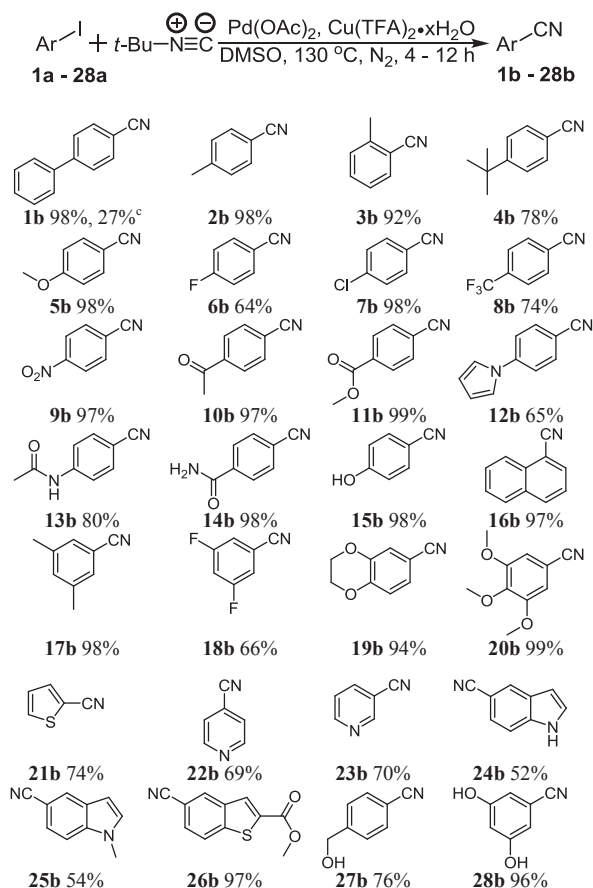
^d With DPPP (10 mol %).

^e Performed with 10 mol % of oxidant under O₂.

^f Cyclohexyl isocyanide (3 equiv).

4). Both of 76% yield of the corresponding benzonitrile and 4-phenylbenzaldehyde were obtained in absence of base, which might be attributed to the solvent DMF (Table 1, entry 5). Solvent screening showed that DMSO was better than other non-polar solvents in the reaction (Table 1, entries 6–8). Lower temperature led to decrease in the yield of desired product (Table 1, entry 9). Compared to other palladium catalysts such as PdCl₂, Pd(TFA)₂, and Pd₂(dba)₃, Pd(OAc)₂ gave better result (Table 1, entries 10–12). The absence of Pd(OAc)₂ decreased the yield of the product (Table 1, entry 13), and trace amounts of the desired product was produced without Cu(TFA)₂·xH₂O (Table 1, entry 14). With using CF₃COOAg as oxidant, only 23% yield was got (Table 1, entry 15). Different Cu(II) oxidants were tested (Table 1, entries 16–20). And we observed that the presence of H₂O promoted this reaction (Table 1, entries 16, 19, and 20–22). When the reaction was run with 10% of Cu(TFA)₂·xH₂O under O₂, no desired product was detected (Table 1, entry 23). However, attempt to utilize other isocyanides such as cyclohexyl isocyanide was not successful (Table 1, entry 24). Thus, the optimized reaction conditions was aryl halide (1 equiv), *tert*-butyl isocyanide (3 equiv), Pd(OAc)₂ (5 mol %), and Cu(TFA)₂·xH₂O (2 equiv) in DMSO at 130 °C under N₂ atmosphere.

Next we explored the scope and limitation of the new protocol (Scheme 3). Only 27% yield of nitrile was obtained when using 4-bromobiphenyl (Scheme 3, **1b**). Both electron neutral (Scheme 3, **1b–5b**, **15b**, **16b**, **17b**, **19b**, and **20b**) and electron deficient (Scheme 3, **6b–14b**, and **18b**) aryl iodides were transformed to the desired aryl nitriles smoothly with 64%–99% yields. Steric hindrance has a slight effect on the reaction (Scheme 3, **2b** and **3b**). Various of



^a Conditions: All reactions were performed with **1** (0.7 mmol), *tert*-butyl isocyanide (3 equiv), Pd(OAc)₂ (5 mol %), Cu(TFA)₂·xH₂O (2 equiv) and DMSO (2.5 mL) under nitrogen at 130 °C for 4–12 h in a sealed tube unless otherwise noted. ^b Isolated yield. ^c 4-Bromobiphenyl.

Scheme 3. Synthesis of aryl nitriles.^{a,b}

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