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Pd-catalyzed direct C–H cyanation of picolinamides via bidentate chelation assistance

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A bidentate-chelation assistant palladium-catalyzed direct C-H cyanation of picolinamides with TMSCN is described. The reaction of various derivatives gave the corresponding cyanated products in moderate to good yields under mild conditions. In addition, the cyanated product could transform into some valuable functional groups in good yields. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords: bidentate chelation; palladium catalysis; C–H activation; cyanation; TMSCN

Introduction

Aryl nitriles exist in numerous drugs, agrochemicals and natural products, and can also be converted into carboxylic acids, amines, amides and heterocyclic compounds by functional group transformations.[1] Therefore, the preparation of nitriles has always been an attractive topic in organic synthesis. Common methods for preparing aryl nitriles are Sandmeyer and Rosenmund–von Braun reactions (Scheme 1(a)).[2] These two classical transformations have a few limitations, such as the requirement for harsh reaction conditions and the use of stoichiometric amounts of toxic metal cyanides. Although inorganic metal cyanides like $Zn(CN)_2$,[3] CuCN,[4] NaCN[5] and KCN[6] have been shown to be effective reagents, the waste and pollution of metals and toxicity of reagents are inevitable, and the solubility of these reagents is not good in organic solvents. Developing and using low-toxicity organic cyanation sources[7] have become an attractive topic. But the preparation of new organic cyanation sources suffers from high costs and multiple steps. In comparison, trimethylsilycyanide (TMSCN) is a promising alternative, being simple, easy to handle and most soluble cyanide ion source.[8]

In the past few decades, transition-metal-catalyzed direct C–H functionalization has been an appealing strategy for the synthesis of aromatic nitriles.[9] A number of metal-based catalysts, such as Pd,[10] Fe,[11] Rh,[12] Cu[13] and Co.,[14] in the presence of oxidants have been reported for the direct cyanation of aromatic compounds (Scheme 1(b)). Meanwhile, the use of bidentate directing groups in the transformation of C–H bonds has seen a swift growth. Efforts have been made in the use of bidentate chelation systems.[15] To the best of our knowledge, few studies have employed TMSCN as a cyanating reagent to obtain aromatic nitriles by the direct cyanation of C–H bonds.[16] Inspired by these pioneer works, we report here a method for direct Pd-catalyzed C–H cyanation of *N*-(naphthalen-1-yl)picolinamides, which are important intermediates in biologically active products and medicinal chemistry.[17]

Experimental

All commercial reagents and solvents were purchased from TCI and Aladdin Chemicals Company. They were used without further purification unless specified. The starting materials were synthesized using a reported method.[18] ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ or deuterated dimethylsulfoxide (DMSO-d_6). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet, and br = broad. Chemical shifts were measured in ppm with tetramethylsilane as internal standard, and coupling constants (*J*) were measured in Hz. Reaction progress was monitored using TLC, and column chromatography was carried out on silica gel (200–300 mesh). Melting points were measured using a digital melting point apparatus without correction. Infrared spectra were recorded with an SP-100 Fourier transform infrared spectrometer. UV–visible spectra were measured with a Shimadzu UV-2501PC UV–visible spectrophotometer.

Procedure for preparation of starting materials

A 100 ml three-necked round-bottomed flask was charged with substituted 1-naphthylamine (10 mmol), 2-picolinic acid (12.5 mmol) and Et_3N (20 mmol, 2.8 ml) in dichloromethane (DCM; 40 ml). Then, 1.88 ml of $POCl_3$ was added dropwise at 0 °C.

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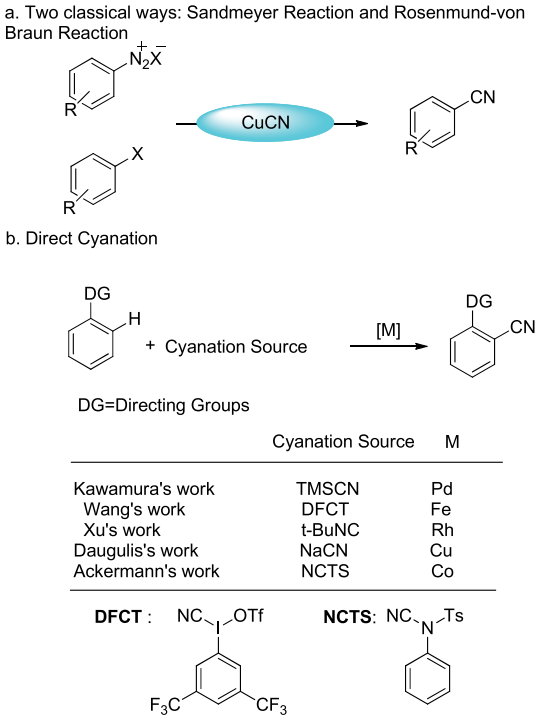


Scheme 1. Strategies for the synthesis of aromatic nitriles.

The resulting mixture was kept stirring at 0 °C for 0.5 h. After warming to room temperature, the mixture was stirred for another 2 h. Then the reaction mixture was cooled to 0 °C. Ice water was added slowly to quench the reaction. The organic layer was collected, and the aqueous phase was extracted with DCM. The combined organic phase was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was recrystallized from cyclohexane to afford the desired product.

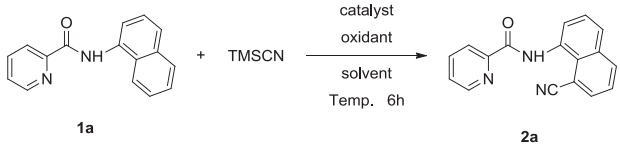
General procedure for palladium-catalyzed C–H Cyanation

A reaction vial (10 ml) was charged with substrate (0.4 mmol), Pd$(PPh_3)_4$ (46.22 mg, 0.04 mmol; 10 mol%), $Cu(OAc)_2$ (145.31 mg, 0.8 mmol), TMSCN (47.62 mg, 0.48 mmol) and dry dimethylformamide (DMF; 6 ml). The reaction tube was placed into a preheated oil bath at 130 °C and was heated for 6 h. The reaction mixture was cooled and poured into water (50 ml). The mixture was extracted with ethyl acetate (3 × 20 ml). Organic layers were combined, washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired cyanated product.

Results and discussion

In the initial phase of this study, we investigated the reaction of *N*-(naphthalen-1-yl)picolinamide in the presence of Pd$(PPh_3)_4$ as catalyst and TMSCN as cyanide source along with $Cu(OAc)_2$ as oxidant in DMSO at 130 °C with stirring for 12 h. To our delight, the desired product was isolated in 46% yield (Table 1, entry 1). In order to improve the yield, the reaction was conducted by changing the reaction parameters, such as catalyst, oxidant and solvent. Various oxidants, including $Cu(OAc)_2$, $CuBr_2$, $Cu(OTf)_2$, $PhI(OAc)_2$, BQ and $K_2S_2O_8$, were tested, among which $Cu(OAc)_2$ is found to be the most effective (Table 1, entries 1–6). Without $Cu(OAc)_2$, no desired product is obtained (Table 1, entry 7). After preliminary solvent screening (Table 1, entries 1 and 8–12), we identified that the reaction in DMF affords the desired product in 85% yield (Table 1, entry 10). The yield decreases to 17% when the reaction is carried out under a nitrogen atmosphere (Table 1, entry 13). Moreover, the reaction is totally shut down when the temperature is changed to 120 or 140 °C (Table 1, entries 14 and 15). A yield of 60% is observed when using $Pd(OAc)_2$ as catalyst (Table 1, entry 16). Also, $IrCl_3$ as catalyst does not work (Table 1, entry 17). Finally, a control experiment shows that a palladium catalyst is necessary for this reaction (Table1, entry 18). According to these experimental results, the optimal reaction conditions are: **1a** (0.4 mmol), TMSCN (1.2 equiv.), Pd

Table 1. Optimization of reaction conditions[a]

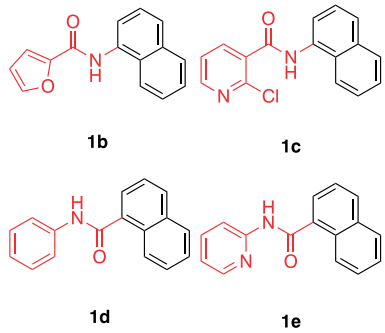


Entry	Catalyst	Oxidant	Solvent	Temp. (°C)	Yield (%)[b]
1	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMSO	130	46
2	$Pd(PPh_3)_4$	$CuBr_2$	DMSO	130	Trace
3	$Pd(PPh_3)_4$	$Cu(OTf)_2$	DMSO	130	32
4	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DMSO	130	40
5	$Pd(PPh_3)_4$	BQ	DMSO	130	8
6	$Pd(PPh_3)_4$	$K_2S_2O_8$	DMSO	130	10
7	$Pd(PPh_3)_4$	—	DMSO	130	0
8	$Pd(PPh_3)_4$	$Cu(OAc)_2$	NMP	130	75
9	$Pd(PPh_3)_4$	$Cu(OAc)_2$	MeCN	130	50
10	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMF	130	85
11	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMAc	130	68
12	$Pd(PPh_3)_4$	$Cu(OAc)_2$	1,4-Dioxone	130	63
13[c]	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMF	130	17
14	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMF	120	52
15	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DMF	140	64
16	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	130	60
17	$IrCl_3$	$Cu(OAc)_2$	DMF	130	0
18	—	$Cu(OAc)_2$	DMF	130	Trace

[a]Reaction conditions: **1a** (0.4 mmol), TMSCN (1.2 equiv.), $Pd(PPh_3)_4$ (10 mol%) and $Cu(OAc)_2$ (2 equiv.) in DMF (6 ml) for 6 h under air atmosphere.

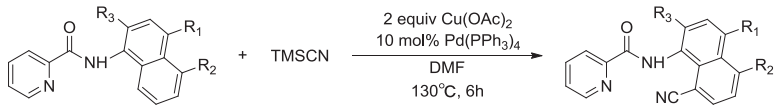
[b]Isolated yields after silica gel column chromatography.

[c]Under nitrogen atmosphere.

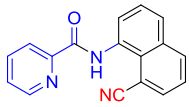


Scheme 2. Ineffective directing groups.

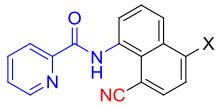
Table 2. Substrate scope of palladium-catalyzed C–H cyanation[a]



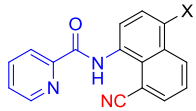
1 2



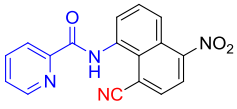
2a 85%



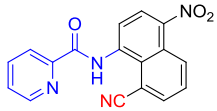
2f X=Cl 80%
2g X=Br 76%
2h X=I 70%



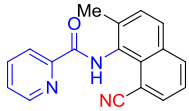
2i X=Cl 76%
2j X=Br 70%
2k X=I 68%



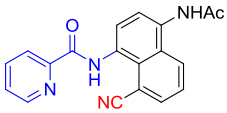
2l 89%



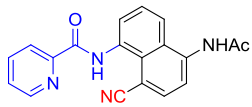
2m 85%



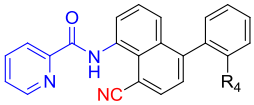
2n 70%



2o 71%

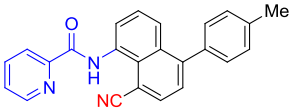


2p 73%

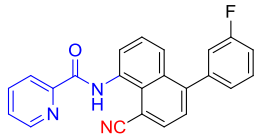


2q R_4=H 75%
2r R_4=Cl 70%

2s 11%



2t trace



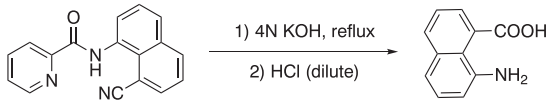
2u 8%

[a]Reaction conditions: **1** (0.4 mmol), TMSCN (1.2 equiv.), $Cu(OAc)_2$ (2 equiv.) and $Pd(PPh_3)_4$ (10 mol%) in DMF (6 ml) at 130 °C for 6 h.

$(PPh_3)_4$ (10 mol%) and $Cu(OAc)_2$ (2 equiv.) in DMF (6 ml) at 130 °C for 6 h under air atmosphere.

We next examined the effect of directing groups (Scheme 2). The reaction does not proceed at all when *N*-(naphthalen-1-yl)furan-2-carboxamide (**1b**) or 2-chloro-*N*-(naphthalen-1-yl)nicotinamide (**1c**) are used as starting materials. The use of other directing groups such as **1d** or **1e** also results in no reaction.

Having established the optimized reaction conditions, the generality of the reaction was investigated using various substrates. As evident from Table 2, the reaction tolerates a range of different functional groups, including chlorine, bromine and iodine (**2f**–**2 h**). Changing the substituents from C5 to C4 position also gives the desired products in good yields (**2i**–**2 k**). Due to the electronic effect on the aromatic rings increasing the reactivity to some extent, the nitro-containing compounds **2 l** and **2 m** are converted into the corresponding products in 89 and 85% yields, respectively. Moreover, C4 substituents and C5 substituents are found to be more favorable than C2 substituents (**2f**, **2i** versus **2n**). Also, substrates with acetylamino group smoothly afford the cyanation products in 71 and 73% yield, respectively (**2o** and **2p**). It is worth noting that the reaction can be applied to substituted substrates

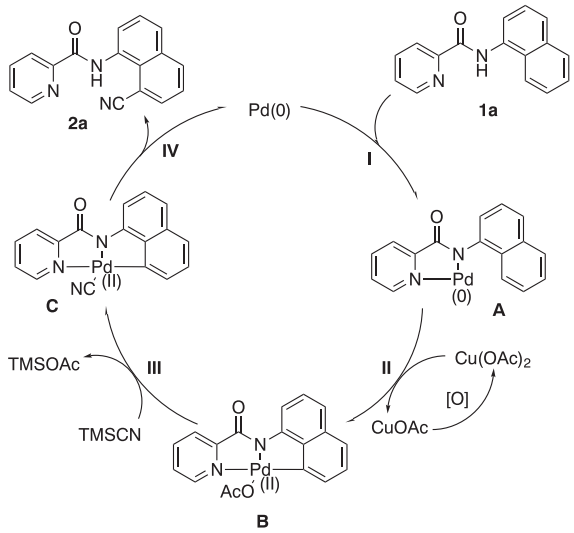


3a 74%

Scheme 3. Application of **3a**.

bearing either phenyl or *o*-chlorophenyl groups (**2q** and **2r**). Unfortunately, the naphthalene-containing substrate afforded the product in only 11% yield (**2 s**). And bulky groups such as tolyl and *m*-fluorophenyl substituted at C5 position do not undergo reaction smoothly under the present reaction conditions (**2 t** and **2u**).

The cyano moiety is a key component for a broad range of functional groups, such as amines, amides, acids and tetrazoles. Therefore, we tried to transform aromatic nitriles into some valuable compounds. As shown in Scheme 3, a solution of **3a** and KOH was heated to reflux and subjected to hydrolysis to afford 8-amino-1-naphthoic acid in 74% yield. In the past few years, 1-amino-8-naphthoic acid as an intermediate of pharmaceuticals and dyes has been synthesized using phosgenation, the naphthalene



Scheme 4. Proposed reaction pathways.

sulfonic acid method and so on.[19] However, these methods have drawbacks such as complex substrates and multiple steps. In comparison, we have developed a simple route to 1-amino-8-naphthoic acid in good yield. The melting point (177–182 °C) has been measured to prove the structure.

According to previous reports[9–13] and our results, we propose the following mechanism of cyanation (Scheme 4). The first step involves the bidentate chelation-directed cyclopalladation to provide the intermediate **A**. Then, **A** undergoes oxidative addition to give the key intermediate **B**. Transmetalation of palladacycle **B** with TMSCN affords the intermediate **C**. In the final step, the reductive elimination of intermediate **C** gives the desired product **2a** along with Pd(0).

Conclusions

We have developed a palladium-catalyzed direct C–H cyanation of picolinamides via bidentate chelation assistance. The present approach is convenient with easy operation, uses an inexpensive catalytic system and has broad substrate scope. In addition, the cyanated product could transform into valuable compounds in good yields. A plausible mechanism is proposed to account for the formation of products. Further experiments are currently underway in our laboratory.

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