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A facile tandem decyanation/cyanation reaction of α-iminonitriles toward cyano-substituted amides†

Zhengwang Chen, *[a,b] Pei Liang,[a] Botao Liu,[a] Haiqing Luo,[a] Jing Zheng,[a] Xiaowei Wen,[a] Tanggao Liu[a] and Min Ye*[a]

A new tandem decyanation/cyanation reaction of α-iminonitriles has been developed. A variety of cyano-substituted aryl amides and heteroaryl amides are synthesized in good yields. Both electron-rich and electron-deficient groups are compatible with the standard conditions. This reaction features a nonmetallic cyano source, tandem decyanation and cyanation reaction, waste utilization of the HCN from the hydrolysis of α-iminonitriles, formation of two important functional groups in one-step operation, *etc*.

Nitrile and amide groups are considered as one of the most fundamental groups in organic chemistry. Aryl and heteroaryl nitriles are well represented throughout natural products, pharmaceuticals, agrochemicals, and electronic materials.[1] Moreover, the nitrile moiety is a versatile precursor for the preparation of aldehydes, amides, amines, amidines, tetrazoles, and other carboxy derivatives.[2] The Sandmeyer reaction and Rosenmund–von Braun protocol are the most conventional methods to aryl nitriles, which require stoichiometric amounts of CuCN and relatively harsh reaction conditions.[3] Transition-metal-catalyzed cyanation of aromatic halides with a range of cyanating reagents has made great progress in the past decades.[4] However, most of these approaches use highly toxic and environmentally hazardous metal cyanide sources such as CuCN, KCN, NaCN, $Zn(CN)_2$, *etc*., restricting their widespread applications. Recently, nonmetallic organic cyano-group sources in the metal-catalyzed cyanation of aryl halides have attracted significant attention, as they avoid producing hazardous HCN gas and stoichiometric metal waste. These cyanating reagents include NCTS, acetone cyanohydrin, MeCN, $CNCH_2CN$, $CNCH_2CO_2Et$, BnCN, $HCONH_2$, DMF/NH_4X, and so on.[5] Despite the significance of these methods, continuing to explore new nonmetallic cyano-group sources involving high efficiency and practicability would be highly desirable.[6]

Amides are ubiquitous in natural products, pharmaceuticals, polymers and synthetic intermediates.[7] Accordingly, above 50% of known drugs contain amide moieties.[8] As a result, over the past decades many efforts have been devoted to the acquisition of amide compounds. Considering the importance of these kinds of compounds, the alternative platform for their preparation is of great interest in organic synthesis. Typically, pyridyl benzamides and cyano-substituted arylamides are frequently found in a variety of natural products, pharmaceuticals and bioactive molecules.[9] Conventionally, the construction of cyano-substituted amides needs multistep processes and metal cyanides to introduce different functional groups.[10] Consequently, the development of efficient and versatile methods for organic molecules with nitrile and amide functionalities presents an important synthetic challenge.

α-Iminonitriles are valuable synthetic intermediates for the preparation of amidines, α-keto acids, amides, *N*-alkyl ketene imines, cyanoenamides, triazoles, aminopyrroles, and nitrogen heterocycles.[11] Several mild and practical routes have been established and thus have increased the attractiveness of α-iminonitriles in organic synthesis.[12] Recently, Zhu's group reported an unprecedented alumina-promoted hydrolysis of α-iminonitriles to amides with microwave irradiation.[13] However, the production of the HCN byproduct may cause environmental issue and limit the application in large scale synthesis. In contrast, there are few reports involving the retention of the CN group in the product through the activation of the C–CN bond.[14] Herein, we present the first cyanation reaction of iodo-substituted α-iminonitriles *via* the cleavage and formation of the C–CN bond, thereby providing an effective and unusual strategy for the synthesis of cyano-substituted amides.

Our investigation began with an unexpected discovery; the original purpose was to carry out the Suzuki reaction between

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[a] *Key Laboratory of Organo-Pharmaceutical Chemistry of Jiangxi Province, Gannan Normal University, Ganzhou, 341000, China. E-mail: chenzwang@126.com, yemin811@gnnu.cn; Fax: +86 797-8793670; Tel: +86 797-8793670*

[b] *Key Laboratory of Functional Molecular Engineering of Guangdong Province, South China University of Technology, Guangzhou, 510640, China*

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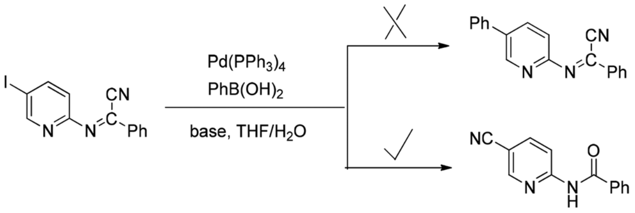
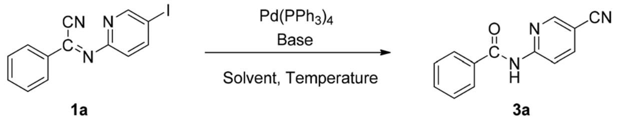


Scheme 1 Cyanation reaction of iodo-substituted α-iminonitriles to cyano-substituted amides.

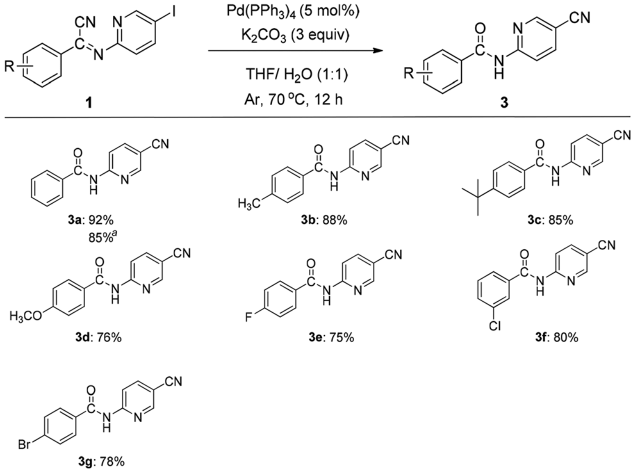
an iodo-substituted α-iminonitrile and phenylboronic acid under palladium-catalyzed conditions. However, the cyanation reaction occurred to afford cyano-substituted amides instead of the Suzuki reaction (Scheme 1). Firstly, the reaction of (*Z*)-*N*-(5-iodopyridin-2-yl)benzimidoyl cyanide **1a** and $Pd(PPh_3)_4$ catalyst was chosen as the model reaction to optimize the reaction conditions. As shown in Table 1, the solvent played an important role in transformation, and besides that THF–H_2O can promote the reaction, other co-solvents or water led to significantly lower yields (entries 1–7). Then a variety of common inorganic and organic bases were probed, and K_2CO_3 was found to give the best results with the isolated yield improved to 92% (entries 8–14). The reaction temperature was also evaluated, and decreasing the temperature resulted in declined yields (entries 15 and 16). Finally, it was unfavorable when the reaction time was shortened to 8 hours (entry 17). Thus, it was determined that K_2CO_3 at 70 °C in THF–H_2O for 12 h was the optimal reaction condition (entry 10).

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Base	Temp.	Yield[b] (%)
1	H_2O	Na_2CO_3	70	n.p
2[c]	THF/H_2O	Na_2CO_3	70	65
3[c]	DMF/H_2O	Na_2CO_3	70	26
4[c]	DMSO/H_2O	Na_2CO_3	70	n.p
5[c]	EtOH/H_2O	Na_2CO_3	70	n.p
6[c]	Dioxane/H_2O	Na_2CO_3	70	n.p
7[c]	CH_3CN/H_2O	Na_2CO_3	70	n.p
8[c]	THF/H_2O	NaO*t*-Bu	70	Trace
9[c]	THF/H_2O	Cs_2CO_3	70	95
10[c]	**THF/H_2O**	**K_2CO_3**	**70**	**98(92)**
11[c]	THF/H_2O	K_3PO_4	70	n.p
12[c]	THF/H_2O	TEA	70	30
13[c]	THF/H_2O	DABCO	70	50
14[c]	THF/H_2O	DBU	70	n.p
15[c]	THF/H_2O	K_2CO_3	50	90
16[c]	THF/H_2O	K_2CO_3	25	52
17[c,d]	THF/H_2O	K_2CO_3	70	78

[a] Reaction conditions: **1a** (0.2 mmol) with catalyst (5 mol%) in 1 mL solvent for 12 h. [b] Determined by GC with mesitylene as the internal standard. Number in parentheses is isolated yield. [c] The volume ratio of water and other solvents is 1 : 1. [d] Reacted for 8 h.



Scheme 2 The synthesis of cyano-substituted pyridyl amides from iminonitriles. Isolated yields. [a]10 mmol scale of the reaction.

With the optimal reaction conditions available, we next investigated the scope and generality of this facile tandem decyanation/cyanation approach to cyano-substituted amides. The iodo-substituted pyridyl α-iminonitriles were prepared conveniently based on our procedure.[15] Initially, the phenyl moiety was evaluated and the results are summarized in Scheme 2. Both electron-rich and electron-deficient groups on the benzene ring were well tolerated and furnished the corresponding products in good yields (Scheme 2, **3b–g**). The substrates bearing a bulky *tert*-butyl group provided the product in satisfactory yield (Scheme 2, **3c**). To our excitement, the reaction could be carried out on gram scale, furnishing the product in high yield (**3a**). The structure of **3a** was further determined based on X-ray diffraction (Fig. 1).[16]

Next, we tested the substrate scope of the 2-amino pyridine moiety under the standard conditions (Scheme 3, **4a–h**). The reaction conditions were compatible with a series of substituents, such as methyl, methoxy, fluoro, chloro, bromo and trifluoromethyl functional groups. We were pleased to find that the bromo group was able to maintain in the palladium-catalyzed cross coupling reaction. Especially aryl bromide can be used for further synthetic application under transition-metal-catalyzed conditions (Scheme 3, **4g**). Moreover, the strong electron-withdrawing group, trifluoromethyl group, was also suitable for the reaction and gave high yield (Scheme 3, **4h**).

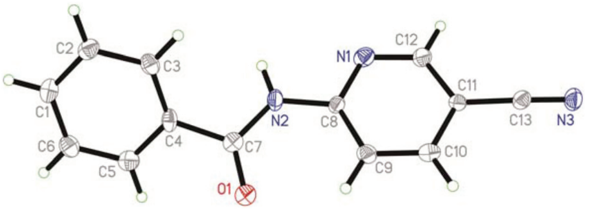
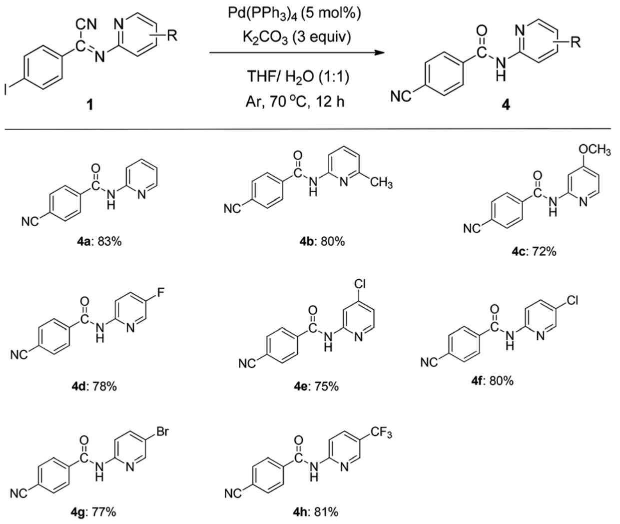
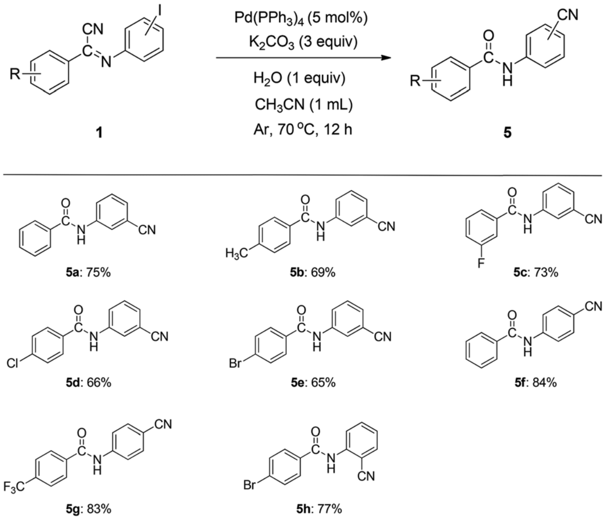


Fig. 1 X-ray crystal structure of **3a**.

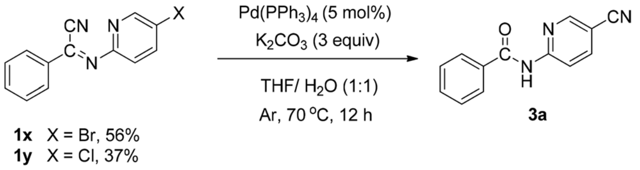


Scheme 3 The synthesis of cyano-substituted pyridyl amides from iminonitriles. Isolated yields.

On the other hand, we continued to extend the strategy to *N*-phenyl α-iminonitriles. The α-iminonitrile substrates were synthesized according to Zhu's oxidative Strecker approach.[12a] We tried the palladium-catalyzed intramolecular cyanation reaction under the standard conditions mentioned above, however, it failed to form the desired products. After some attempts, we found that solvent is essential to the transformation, and the reaction proceeded smoothly in acetonitrile solvent. As illustrated in Scheme 4, substituted α-iminonitriles with the iodo group at different positions of the aniline moiety underwent smooth reaction to afford the products in moderate to good yields (Scheme 4, **5a–h**). Irrespective of the electronic nature of the substituents, the reactions were well tolerated (Scheme 4, **5b–e**). To our delight, the trifluoromethyl substituted product was obtained in high yield (Scheme 4, **5g**). Interestingly, the reaction worked well when *ortho* iodo substituted aniline was employed, and gave better yield compared to the *meta* iodo substrate (Scheme 4, **5e** and **5h**). Disappointingly, the reaction failed to work when the iodo was attached to the benzoyl moiety.



Scheme 4 The synthesis of cyano-substituted phenyl amides from iminonitriles. Isolated yields.

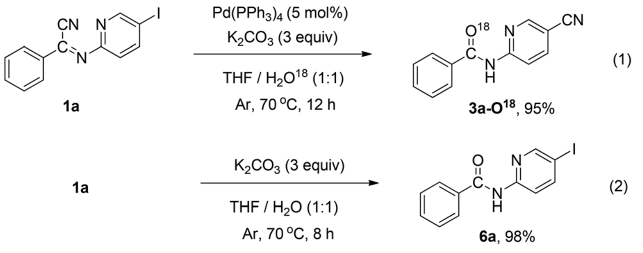


Scheme 5 The synthesis of **3a** from bromo or chloro-substituted α-iminonitriles.

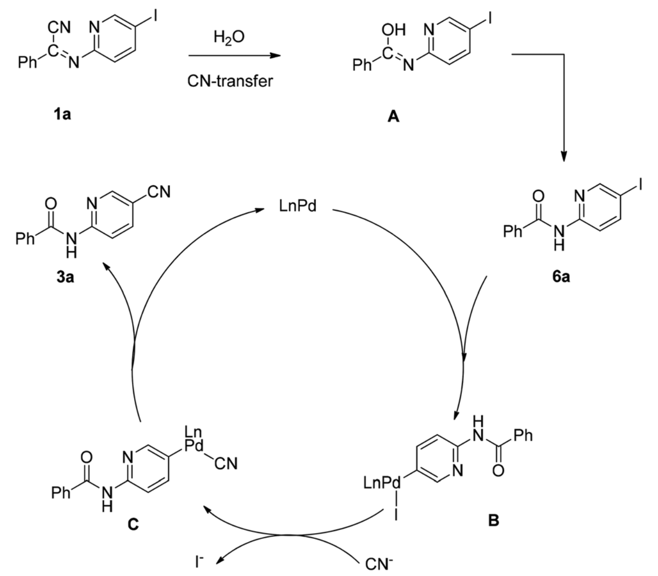
Besides iodo-substituted α-iminonitriles, bromo or chloro-substituted substrates were also tried under the standard conditions, however, **1x** afforded **3a** in moderate yield and **1y** furnished the product in low yield (Scheme 5). Moreover, when the substrates contained I and Br or I and Cl, the cyanation reaction mainly happened with the C–I bond.

To understand the origin of the carbonyl oxygen atom in the amide product, an isotope-labeled reaction was performed to gain evidence under standard conditions with $H_2{}^{18}O$, and GCMS spectra demonstrated that **3a-O^{18}** was obtained in 95% yield. This isotope-labeled experiment showed that the oxygen was from water (Scheme 6, eqn (1)). Moreover, **1a** could be hydrolysed to the corresponding amide under the standard conditions without palladium catalyst with 98% yield for 8 h (Scheme 6, eqn (2)). Based on the previous reports[4,13] and our experimental observations, we proposed a possible mechanism shown in Scheme 7. Initially, α-iminonitrile **1a** was hydrolysed to amide **6a** and the CN anion was released under base conditions. Then oxidative addition of palladium to aryl iodide to formed intermediate **B**, which *via* transmetalation yielded intermediate **C**. Finally, reductive elimination afforded product **3a** and regenerated the palladium catalyst to complete the catalytic cycle (Scheme 7).

In conclusion, we have developed a novel tandem decyanation and cyanation reaction with various iodo-substituted α-iminonitriles. Under mild conditions, a broad range of cyano-substituted aryl amides were obtained in good yields. This methodology will prevent or reduce the release of hazardous HCN gas in the hydrolysis of α-iminonitriles through



Scheme 6 Controlled experiments.



Scheme 7 Possible reaction mechanism.

waste utilization and lead to valuable products. Moreover, the cyanation reaction results in the simultaneous formation of two important functional groups in one-step operation. Further studies on the utilization of α-iminonitriles are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 CCDC 1844390† contains the supplementary crystallographic data for this paper (compound **3a**).