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Direct C–H aminocarbonylation of *N*-heteroarenes with isocyanides under transition metal-free conditions†

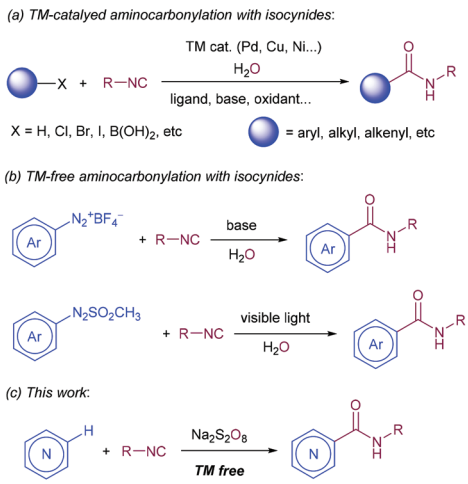
Zhong Zhou,[a] Huihui Ji,[a] Qing Li,[a] Qian Zhang*[a] and Dong Li *[a,b]

A C–C bond forming amide synthesis through direct C–H aminocarbonylation of *N*-heteroarenes with isocyanides was developed. The reaction was mediated by an inorganic persulfate salt under transition metal-free conditions. Mechanistic studies suggested a radical pathway for this reaction without the participation of H_2O and O_2. This method also showed merits of substrate availability, easy operation and atom economy. It provided an efficient route for straightforward synthesis of *N*-heteroaryl amides.

Introduction

Amides are of great importance because of their ubiquitous existence and essential role in natural products, biologically active molecules, functional materials and organic synthesis intermediates.[1] Great efforts have been devoted to the development of facile and efficient methods for amide synthesis all the time. The amide bond is typically constructed *via* C–N bond formation reactions between carboxylic acid surrogates and appropriate amine sources in both laboratories and industries.[2] In recent decades, C–C bond forming aminocarbonylation has been developed as an efficient route to this end, which significantly broadened the avenue of amide synthesis methodologies.[3] Among these methods, isocyanides have been revealed as efficient building blocks.

Isocyanides have attracted increasing attention in organic synthesis because they feature high synthetic efficiency and molecular diversity in many heterocycle syntheses and multi-component reactions.[4] As isoelectronic species of carbon monoxide, isocyanides exhibit a strong metal coordination ability and are widely involved in organometallic chemistry.[5] In recent years, the employment of isocyanates as C1 synthons has emerged as an efficient strategy for the amide synthesis. These methods are generally performed through transition metal-catalyzed aminocarbonylation with isocyanides and stoichiometric H_2O and/or terminal oxidants (Scheme 1a).[6] Considering the cost of transition-metal catalysts and the requirement for removal of trace amounts of metal residues in the products especially in pharmaceutical manufacturing, development of metal-free methodologies is also highly desired.[7] Several groups successfully achieved the transition metal-free aminocarbonylation with isocyanides through base or visible light-promoted reactions of aryl diazonium salts or azo sulfones (Scheme 1b).[8,9] However, the application of these methods is limited by the pre-functionalized substrates. The development of a direct C–H aminocarbonylation method with isocyanides under transition metal-free conditions will be intriguing and attractive.



Scheme 1 Amides synthesis through aminocarbonylation with isocyanides.

[a]*Hubei Provincial Key Laboratory of Green Materials for Light Industry, Hubei University of Technology, Wuhan 430068, China.*
E-mail: zhangqian620@hotmail.com, dongli@mail.hbut.edu.cn
[b]*Hubei Key Laboratory of Drug Synthesis and Optimization, Jingchu University of Technology, Jingmen 448000, China*

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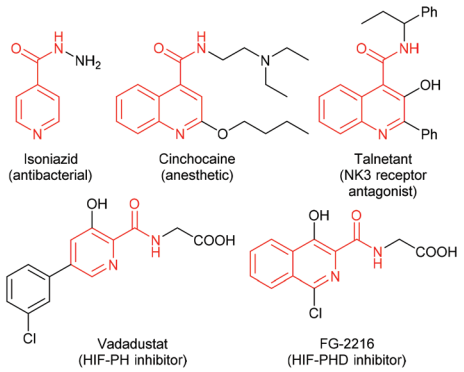


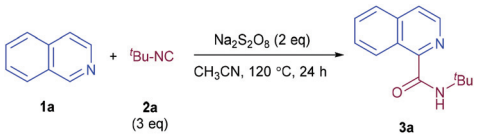
Fig. 1 Representative drugs containing *N*-heteroaryl amide moieties.

On the other hand, *N*-heteroarenes such as pyridines, quinolines and isoquinolines are important structure motifs which pervasively exist in natural products, pharmaceuticals, functional materials and organic synthesis ligands.[10] The development of new methodologies for synthesis of *N*-heteroarene derivatives has attracted great attention.[11] Represented by the Minisci-type reaction, a number of methods have been developed for the direct C–H functionalization of *N*-heteroarenes.[12] The amide bond attached to *N*-heteroarenes is also an important class of moieties which is present in many drugs and biologically active molecules (Fig. 1).[13] Previously, *N*-heteroaryl amides were mainly prepared through the reaction of *N*-heteroarenes or heteroarene *N*-oxides with amide counterparts such as formamides, hydrazine carboxamides or oxamic acids.[14] However, this transformation still required transition metal catalysts, or pre-functionalized substrates. To the best of our knowledge, the preparation of *N*-heteroaryl amides through the C–H aminocarbonylation reaction between *N*-heteroarenes and isocyanides has been undeveloped. Recently, we paid attention to both the development of amide synthesis methods and functionalizations of *N*-heteroarenes.[15,16] Herein, we reported the first transition metal-free direct C–H aminocarbonylation of *N*-heteroarenes with isocyanides (Scheme 1c). The reaction was promoted by a cheap, stable and readily available inorganic persulfate salt under transition metal-free conditions.[17] It provided an efficient route for straightforward synthesis of *N*-heteroaryl amides in an atom economical manner.

Results and discussion

We carried out our initial study with the reaction between isoquinoline (**1a**) and a commercially available *t*-butyl isocyanide as the model reaction (**2a**). After examining a series of reaction parameters, we were pleased to find out that **1a** reacted with 3 equiv. of **2a** in the presence of 2 equiv. of $Na_2S_2O_8$ in CH_3CN at 120 °C for 24 hours to provide the aminocarbonylation product **3aa** in 75% yield with 15% recovery of the starting materials (Table 1, entry 1). Notably, the reaction can be handled under air without requirements of anhydrous solvents

Table 1 Optimization of the reaction conditions[a]

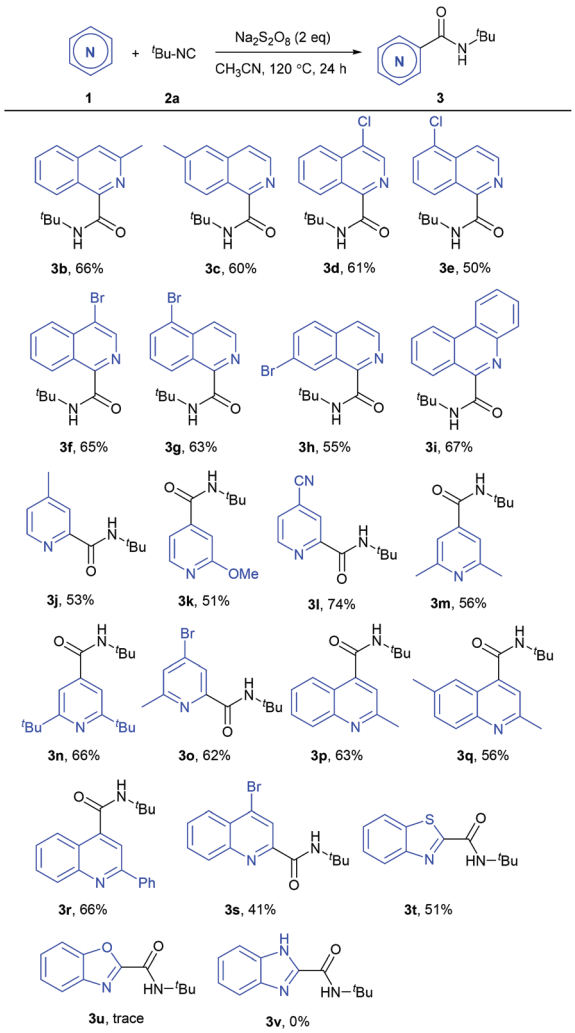


Entry	Deviations from the standard conditions	Yield[b] (%)
1	None	75(15)[c]
2	$K_2S_2O_8$ instead of $Na_2S_2O_8$	24
3	$(NH_4)_2S_2O_8$ instead of $Na_2S_2O_8$	Trace
4	Oxone instead of $Na_2S_2O_8$	Trace
5	TBHP instead of $Na_2S_2O_8$	0
6	DTBP instead of $Na_2S_2O_8$	0
7	*m*CPBA instead of $Na_2S_2O_8$	34
8	DCE instead of CH_3CN	48
9	DMF instead of CH_3CN	0
10	HFIP instead of CH_3CN	0
11	H_2O instead of CH_3CN	0
12	CH_3CN/H_2O (1 : 1) instead of CH_3CN	0
13	1.5 equiv. of $Na_2S_2O_8$	66
14	2 equiv. of ^{t}BuNC	36
15	100 °C	58
16	80 °C	14
17	12 h	61
18	4 h	50

[a] Reaction conditions: Isoquinoline (**1a**) (0.2 mmol), *t*-butyl isocyanide (**2a**) (0.6 mmol), and $Na_2S_2O_8$ (0.4 mmol) in CH_3CN (2.0 mL) under stirring at 120 °C for 24 h. [b] Isolated yield. [c] Recovery of the starting materials.

or anaerobic conditions. Using $K_2S_2O_8$ instead of $Na_2S_2O_8$ led to a drastic decrease of the product yield (entry 2). Other inorganic persulfate salts such as $(NH_4)_2S_2O_8$ and oxone were not effective for this reaction (entries 3 and 4). Organic peroxide oxidants such as TBHP, DTBP and *m*CPBA were also tested. Except for *m*CPBA which afforded 34% yield, the others resulted in no reaction (entries 5–7). Other solvents such as DCE, DMF, HFIP and H_2O were not suitable (entries 8–11). Unlike most previous studies of aminocarbonylation with isocyanides, a mixed solvent of CH_3CN and H_2O was unfavorable for this reaction (entry 12). On reducing the amount of $Na_2S_2O_8$ to 1.5 equiv., the yield decreased to 66% (entry 13). A much lower yield was obtained after reducing the amount of **2a** to 2 equiv. (entry 14). The temperature was also essential for this reaction. A lower yield was obtained when the temperature was reduced to 100 °C (entry 15). And the reaction hardly proceeded at a much lower temperature (entry 16). Finally we also investigated the effect of reaction time. Shortening the reaction time to 12 hours only generated 61% product yield (entry 17). A much lower yield was obtained within 4 hours (entry 18).

After the optimization of the reaction conditions, we then investigated the substrate scope of this method. At first, a series of *N*-heteroarenes (**1**) were examined for reactions with *t*-butyl isocyanide (**2a**) (Scheme 2). Different substituents such as methyl, chlorine and bromine were tolerated on the C3-, 4-, 5-, 6- or 7-position of isoquinoline. 2-Aminocarbonylation products were obtained selectively in similar yields without a significant electronic or steric hindrance effect (**3b–3h**). Generally

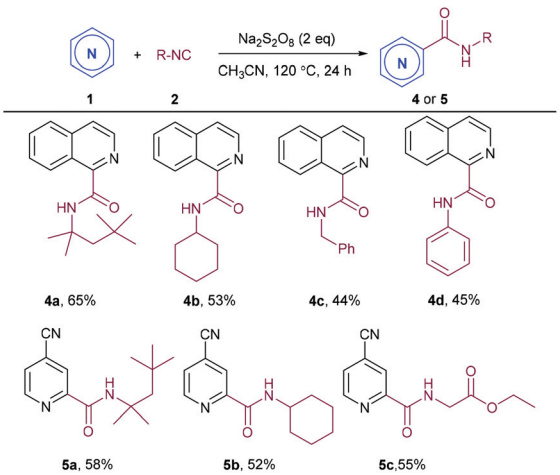


Scheme 2 Substrate scope of *N*-heteroarenes (**1**). Reaction conditions: heteroarene (**1**) (0.2 mmol), *t*-butyl isocyanide (**2a**) (0.6 mmol), and $Na_2S_2O_8$ (0.4 mmol) in CH_3CN (2.0 mL) under stirring at 120 °C for 24 h. Isolated yield.

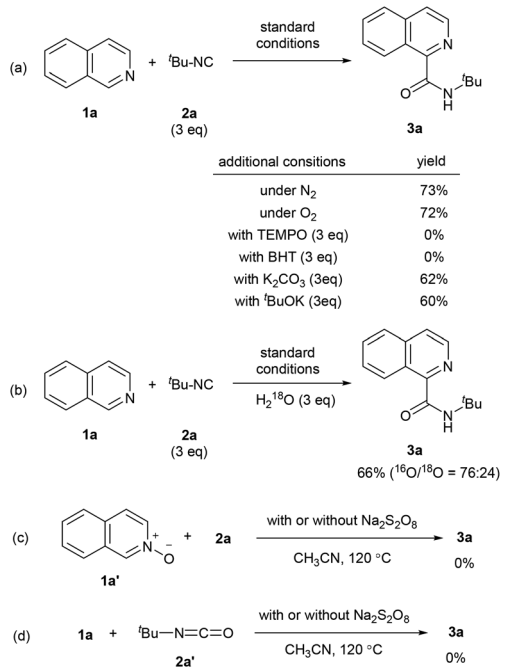
unreacted starting materials remained after reaction without obvious by-product observed. A polycyclic phenanthridine also reacted well to provide the corresponding product in good yield (**3i**). Pyridines with various substituents were examined subsequently. Functional groups such as methyl, *t*-butyl, methoxyl, CN and Br were tolerated on the pyridine ring (**3j–3o**). Generally, 2-aminocarbonylation occurred on 4-substituted pyridines and 4-aminocarbonylation on 2-substituted pyridines (**3j–3l**). Di-substituted pyridines also undergo this transformation to provide the desired products in moderate to excellent yields (**3m–3o**). Quinolines were also applicable in this method to give the desired products in moderate to good yields (**3p–3s**). Notably, the reaction of 2-phenylquinoline occurred on the C4-position of quinoline without the influence of the phenyl ring (**3r**). Finally, an *N*,*S*-containing heteroarene benzo[*d*]thiazole was tested which also reacted to give the aminocarbonylation product in moderate yield (**3t**). However, benzo[*d*]oxazole and benzo[*d*]imidazole were not suitable for this reaction (**3u** and **3v**).

The scope of isocyanides was then investigated with the reactions of isoquinoline and 4-cyanoquinoline (Scheme 3). 2,4,4-Trimethyl-2-pentanyl isocyanide reacted well with both isoquinoline and 4-cyanoquinoline, affording the desired amide products in moderate to good yields (**4a** and **5a**). The reactions of cyclohexyl isocyanide also proceeded with isoquinoline and 4-cyanoquinoline in moderate yields (**4b** and **5b**). Benzyl and phenyl isocyanides reacted with isoquinoline to give the desired products; however the yields were low (**4c** and **4d**). A reaction of 4-cyanoquinoline with an ester-containing isocyanide occurred to generate the corresponding products in moderate yield (**5c**).

Subsequent studies were carried out to investigate the reaction mechanism (Scheme 4). At first, the reaction was conducted under an atmosphere of N_2 and O_2 respectively (Scheme 4a). Both reactions proceeded smoothly without a significant change in the product yields. It excluded the involvement of oxygen in this reaction. Then the addition of the radical scavenger TEMPO or BHT was examined. Both the reagents inhibited the reaction entirely. It indicated the existence of radical intermediates in the reaction pathway. However, the reaction was not significantly influenced by the addition of a base (K_2CO_3 or ^{t}BuOK), which suggested that the proton was not essential for this reaction. Isotopic labeling experiment with $H_2{}^{18}O$ was also conducted. With 3 equiv. of $H_2{}^{18}O$, the product was formed in 66% yield in which the ^{16}O product still predominated (Scheme 4b). This suggested that H_2O didn't participate in this reaction as the oxygen source either. As heteroarene *N*-oxides and isocyanates might be formed from the oxidation of heteroarenes and isocyanides respectively,[18] we tested these two possible intermediates independently. The reaction between isoquinoline *N*-oxide (**1a′**) and *t*-butyl isocyanide (**2a**) didn't proceed with or without an



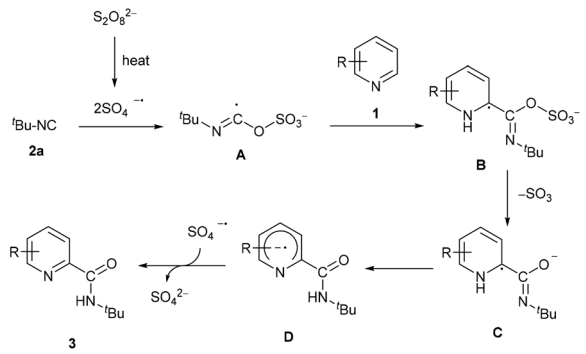
Scheme 3 Substrate scope of isocyanide (**2**). Reaction conditions: heteroarene (**1**) (0.2 mmol), isocyanide (**2**) (0.6 mmol), and $Na_2S_2O_8$ (0.4 mmol) in CH_3CN (2.0 mL) under stirring at 120 °C for 24 h. Isolated yield.



Scheme 4 Control experiments.

oxidant (Scheme 4c). The same outcomes were obtained with the reaction between isoquinoline (**1a**) and *t*-butyl isocyanate (**2a′**) (Scheme 4d). These results ruled out the involvement of *N*-oxides and isocyanates as reaction intermediates.

On the basis of the above results and previous literature, a plausible mechanism for this reaction was proposed (Scheme 5). At first, homolytic cleavage of the persulfate anion under heating generated sulfate anion radicals.[17] This oxygen-centered radical was trapped by isocyanide (**2a**) to form a C-radical intermediate **A**.[19] The radical intermediate **A** added to heteroarene **1** in a Minisci-type pathway to generate the intermediate **B**. It converted to intermediate **C** after the release of SO_3, which could rearrange to an anion radical **D**. Finally, a single electron transfer (SET) between **D** and the sulfate anion radical produced the heteroaryl amide product **3**.



Scheme 5 Proposed mechanism.

Conclusions

In summary, we have developed a novel protocol for persulfate salt-mediated direct C–H aminocarbonylation of *N*-heteroarenes with isocyanides under transition metal-free conditions. Isocyanates act as C1 synthons which make the amide synthesis atom economical. Mechanistic studies suggested a radical pathway for this reaction. It also indicated that neither H_2O nor O_2 participate as the oxygen source, unlike most previous reports on isocyanide-involving aminocarbonylation. But the reaction was moisture and air tolerable which can be easily handled under air. It also showed broad *N*-heteroarene substrate scope and good functional group compatibility. It provided an efficient route for straightforward synthesis of *N*-heteroaryl amides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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