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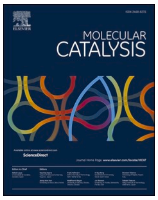

Efficient synthesis of 2-trifluoromethyl-benzimidazoles via cascade annulation of trifluoroacetimidoyl chlorides and amines based on a heterogeneous copper doped g-C_3N_4 catalyst

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ABSTRACT

An efficient approach for the synthesis of 2-trifluoromethyl-benzimidazoles via cascade annulation of trifluoroacetimidoyl chlorides and amines using a heterogeneous copper doped g-C_3N_4 catalyst has been developed. Compared with the previously reported homogeneous catalytic system, the reaction exhibits higher efficiency and the copper doped g-C_3N_4 catalyst can be readily recycled for three times with slightly decreased catalytic reactivity.

Benzimidazole derivatives have widely found in natural products and functional materials, which possess a myriad of biological and pharmaceutical properties.[1] In addition, benzimidazoles have also been applied in the fields of dyes, polymers, fluorescence and corrosion science.[2] The existence of trifluoromethyl group could obviously improve the physicochemical properties of the parent molecules, such as electronegaivity, bioavailability, metabolic stability and lipophilicity.[3] Therefore, the development of efficient methods to the construction of trifluoromethyl substituted benzimidazoles is of great significance and is highly desirable.

The traditional synthetic strategies to 2-trifluoromethyl-benzimidazoles mainly lie in: (1) the condensation of *ortho*-aminoanilines with trifluoroacetic acid or α-perfluoroalkyl aldehydes;[4] (2) the reductive cyclization of *ortho*-nitroanilines with trifluoroacetic acid;[5] (3) the direct trifluoromethylation of benzimidazoles with trifluoromethyl reagents;[6] (4) electrochemical or PIDA (phenyliodine (III) diacetate) mediated oxidative intramolecular cyclization of fluorinated amidines.[7] Some of these methods generally suffered from inaccessible starting materials, narrow substrate scope and harsh reaction conditions. In 2009, Wu and Zhang independently reported a copper-catalyzed tandem C–N bond formation reaction of *N*-(2-haloaryl)trifluoroacetimidoyl chlorides with primary amines for the synthesis of 2-trifluoromethyl-benzimidazoles.[8] Although the positive results have been obtained, we wish to develop a recyclable and heterogeneous catalytic system to enable the preparation of 2-trifluoromethyl-benzimidazoles with higher efficiency under mild reaction conditions.

The properties of nanoscale materials are different from those of bulk materials due to their small size and large surface to volume,[9] and supported metal nano materials have a wide range of applications, especially playing a critical role in the field of catalysis. The loading of nanoscale copper on different carriers has aroused great interest. Graphitic carbon nitrides (g-C_3N_4) can be employed as an effective support due to its high thermal stability against high temperatures and chemical stability against acid, base and organic solvents.[10] The common synthetic methods for the preparation of metal nanomaterials are thermal decomposition or chemical reduction. Herein, we first bonded the terminal amino group of g-C_3N_4 with the acid chloride of the isonicotinoyl chloride hydrochloride in the form of the amide bonds, and then coordinated with copper. The coordinated copper was reduced *in situ* using triethylamine as a reducing agent to prepare copper/graphitic carbon nitride (Cu/g-C_3N_4) composite catalyst. The prepared Cu/g-C_3N_4 was applied to catalyze the cascade annulation of trifluoroacetimidoyl chlorides and amines for the synthesis of 2-trifluoromethyl-benzimidazoles. High catalytic efficiency was observed and the Cu/g-C_3N_4

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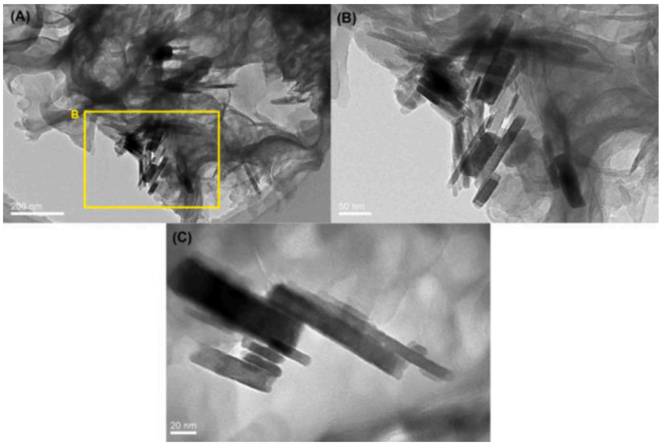
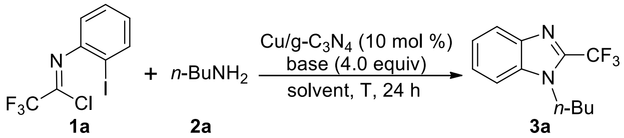


Fig. 1. TEM Images of Cu/g-C_3N_4.

Table 1
Optimization of Reaction Conditions.[a]



Entry	Base (equiv)	Solvent (mL)	Temperature (°C)	Yield[b] (%)
1	K_2CO_3	DMSO	60	55
2	K_2CO_3	CH_3CN	60	15
3	K_2CO_3	THF	60	trace
4	K_2CO_3	toluene	60	trace
5	K_2CO_3	DMF	60	91
6	Na_2CO_3	DMF	60	15
7	K_3PO_4	DMF	60	62
8	Cs_2CO_3	DMF	60	78
9	DIPEA	DMF	60	ND
10	NEt_3	DMF	60	ND
11	K_2CO_3	DMF	50	49
12	K_2CO_3	DMF	80	99 (94)
13	K_2CO_3	DMF	100	99
14	K_2CO_3	DMF	80	99[c]
15	**K_2CO_3**	**DMF**	**80**	**99 (98)**[c,d]

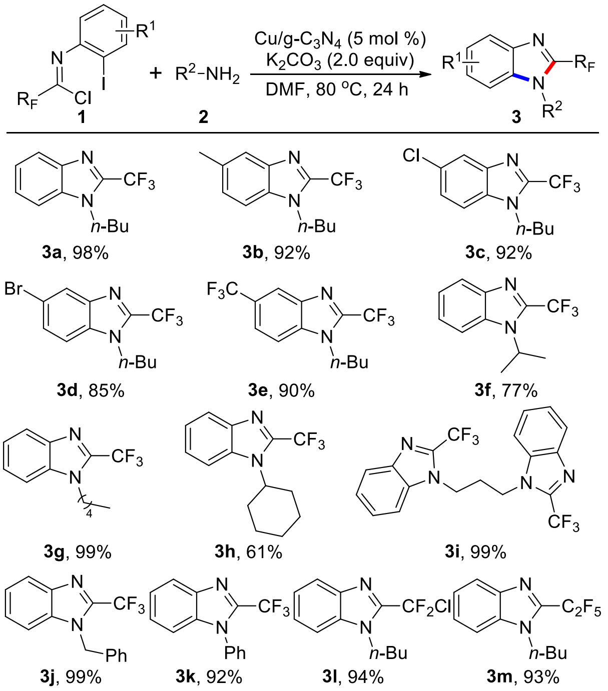
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Cu/g-C_3N_4 (10 mol %) and base (4.0 equiv) in solvent (1.0 mL) under air at specific temperature for 24 h. [b] Yields determined by GC analysis using dodecane as an internal standard and the isolated yields were given in parenthesis. [c] 2.0 equiv. of K_2CO_3 was used. [d] 5 mol % of Cu/g-C_3N_4 was used.

catalyst could be recycled for three times with slight reactivity decrease.

The morphology of the prepared catalyst was observed by TEM. As can be seen from Fig. 1, Cu existed in the form of nanorods. The prepared Cu nanorods were dispersed on g-C_3N_4, and the width of Cu nanorods is about 10-20 nm. The aboved results confirmed that the copper ion could be reduced and grown *in-situ* after coordination by the preparation method. ICP-OES was used to detect the total Cu amount in the Cu/g-C_3N_4 and the Cu amount was 16 wt%.

The reaction conditions were optimized by selecting 2,2,2-trifluoro-*N*-(2-iodophenyl)acetimidoyl chloride **1a** and *N*-butylamine **2a** as model substrates. The reaction performed smoothly in the presence of 10 mol % Cu/g-C_3N_4 and 4.0 equiv. of K_2CO_3 in DMSO at 60 °C for 24 h, producing the desired 2-trifluoromethyl-benzimidazole **3a** in 55% yield (Table 1, entry 1). Then, different solvents were screened and the best result was observed with regard to DMF, where 91% GC yield could be obtained (Table 1, entries 2-5). The effect of base was investigated by testing a variety of inorganic and organic bases, which demonstrated that the organic bases could totally inhibit the reaction (Table 1, entries 6-10). Lowering the reaction temperature to 50 °C resulted in the decrease of the reaction yield and elevating the reaction temperature to 80 °C or 100 °C could greatly promote the reaction to give the almost quantitative yield (Table 1, entries 11-13). Notably, reducing the amounts of base to 2.0 equivalents had no harmful influence upon the reaction's efficiency (Table 1, entry 14). To our delight, when 5 mol % of Cu/g-C_3N_4 catalyst was adopted, the comparable high yield was achieved (Table 1, entry 15), highlighting the excellent catalytic activity of the heterogeneous copper catalyst. It is important to mention that Cu/C (3 wt. %) was tested as the catalyst as well, but only 9% of the target product was obtained under our conditions.

Table 2
Scope of the Reaction.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Cu/g-C_3N_4 (5 mol %) and K_2CO_3 (2.0 equiv) in DMF (1.0 mL) under air at 80 °C for 24 h. Isolated yields.

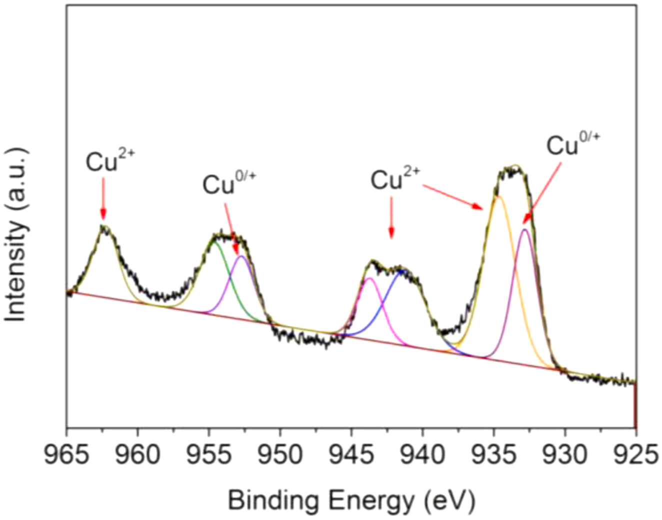


Fig. 2. XPS Spectrum of Cu/g-C_3N_4.

With the establishment of the optimal conditions, the scope and generality of the reaction were examined by the use of diverse fluorinated imidoyl chlorides and amines (Table 2). An array of *N*-

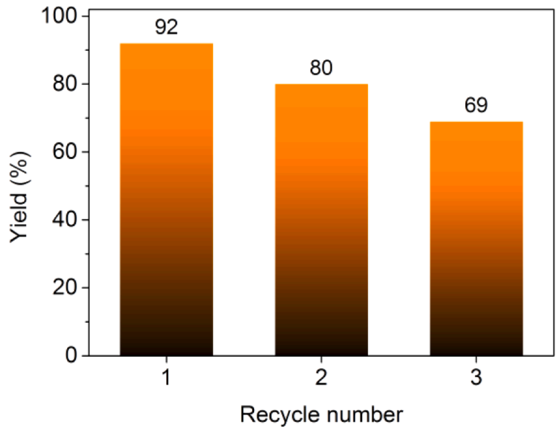
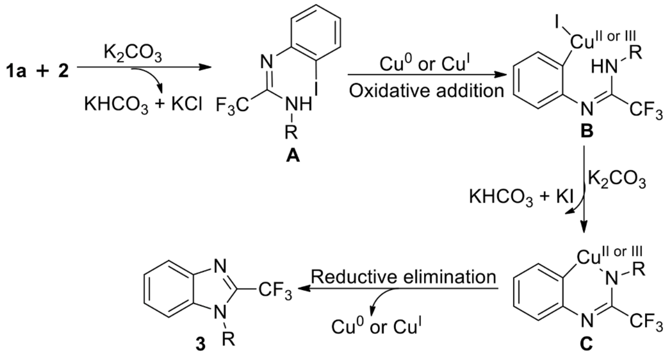


Fig. 3. The Catalytic Reactivity of the Recycled Cu/g-C_3N_4.



Scheme 1. Plausible Reaction Mechanism.

aryltrifluoroacetimidoyl chlorides prepared from differently substituted 2-iodoanilines reacted with *N*-butylamine **2a** under the standard conditions to deliver the corresponding 2-trifluoromethyl-benzimidazole **3a-e** in excellent yields. The transformation also tolerated various kinds of amines, including primary aliphatic amines, diamine, benzylamine and aniline, which could provide the target products **3f-k** in moderate to excellent yields. As for the isopropylamine and cyclohexanamine, the relatively inferior reactivity possibly originates from the steric hindrance (**3f** and **3h**). In addition, other fluorinated imidoyl chlorides were also compatible with the current reaction system for the assembly of fluoroalkyl-substituted benzimidazoles (**3l** and **3m**) in 93-94% yields. This heterogeneous protocol also exhibits the high efficiency compared to that of previously reported methods with homogeneous copper catalysis.[8]

By measuring the XPS, we explored the oxidation state of Cu on the surface of g-C_3N_4.The XPS result of Cu/g-C_3N_4 was shown in Fig. 2. The peaks at 943.7 and 962.3 eV could be assigned to Cu(II), owing to the open $3d^9$ shell of Cu(II). The characteristic peak at 934.6 eV was in accord to the XPS spectrum of Cu 2p, further suggesting the presence of Cu(II).[11] The binding energy located at approximately 932.8 eV and 952.7 eV were attributed to Cu^0 or Cu^+, because there was only a difference of 0.1-0.2 eV between the binding energies of Cu^0 and Cu^+.[12] The XPS results showed that Cu(II) could be reduced to Cu(0) and Cu(I), or underwent disproportionation process to genereate Cu(I), which effectively catalyzed the cascade annulation reaction for the synthesis of 2-trifluoromethyl-benzimidazoles.

On the basis of the valent state of Cu catalyst from XPS analysis and the previous literatures,[8] a plausible reaction mechanism was proposed as depicted in Scheme 1. Initially, the coupling of substrate **1a** and **2** in the presence of base afford the amidine compound **A**. Then, the oxidative addition of the Cu (0) or Cu (I) species to the C-I bond of **A** gave the Cu (II) or Cu (III) complex **B**, which underwent the intramolecular nucleophilic attack with the assistance of base to lead to the copper intermediate **C**. Finally, the reductive elimination of **C** could deliver the benzimidazole product **3** with the regeneration of Cu (0) or Cu (I) species.

The Cu/g-C_3N_4 catalyst could be easily recycled and re-catalyzed the cascade annulation reaction for three times (**Fig. 3**). The reaction yield was gradually decreased to 69% for the third run. The reaction possibly underwent the cascade coupling of trifluoroacetimidoyl chlorides and amines to form the corresponding amidine compounds and copper-catalyzed intramolecular C-N bond formation sequence. The Cu/g-C_3N_4 catalyst generally exhibited high catalytic reactivity for this transformation to construct functionalized heterocycles.

In summary, we have developed an efficient approach for synthesis of 2-trifluoromethyl-benzimidazoles via cascade annulation of trifluoroacetimidoyl chlorides and amines using a heterogeneous copper doped g-C_3N_4 catalyst. Notable advantages of this protocol include a broad substrate scope, high efficiency and recoverability. The higher catalytic reactivity of the Cu/g-C_3N_4 catalyst compared with the homogeneous copper catalyst stimulates us to explore its application into more chemical transformations.

Author statement

XFW, ZC, WL supervised the project. TX prepared the catalyst. YZ performed all the experiments. LY characterized the copper catalysts.

Declaration of Competing Interest

We have no conflict of interest to declaration!

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2021.111767.

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