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Metal Free, I_2-Catalyzed [3+1+1] Cycloaddition Reactions to Synthesize 1,2,4-Trisubstituted Imidazoles

Dong Tang, [a] Xin Guo, [a] Yu Wang, [a] Jing Wang, [a] Jihui Li,[b] Qiangwei Huang [a] and Baohua Chen* [a]

[a] *State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou 730000, P.R.of China;*
[b] *College of Materials and Chemical Engineering, Hainan University, Haikou, 570228, China*

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ABSTRACT

We have successfully developed an operationally simple and economical one-pot three-component cycloaddition reaction to synthesize 1,2,4-trisubstituted imidazoles by employing aldehydes, α-amino carbonyl compounds and ammonium acetate. The transformation is environmentally friendly and metal free by employing I_2 (10 mol %) as a catalyst and EtOH as a solvent, and a wide range of function groups and heterocyclics are well tolerated resulting in moderate to good yields.

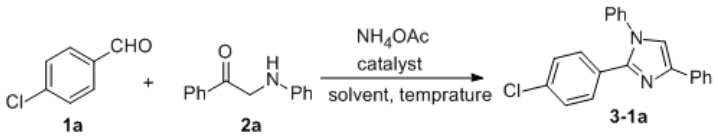
Introduction

Imidazole represents an important class of heterocycles found in many natural products and thereby the structure can exhibit an array of biology and pharmacological activities.[1] In particular, imidazole, as a privileged structural motif, is a kind of important N-heterocyclic carbene (NHC) [2] and chiral ligands.[3] The development of convenient and efficient methods for imidazole derivatives has attracted considerable attention. To get high substituted imidazoles, the usual strategy involves 1,2-diketone, aldehyde, a primary amine and ammonium acetate to afford multi-substituted imidazoles in one-pot.[4] Transition metal catalyzed N-arylation[5] and C-arylation[6] of imidazoles are also versatile tools to construct imidazole derivatives. In recent years, our groups has reported some works about the synthesis of multisubstituted imidazoles.[7] For example, copper-catalyzed [3+2] cycloaddition reaction to synthesize multi-substituted imidazoles[8] and iron (III)-catalyzed synthesis of 1,2,4-trisubstituted imidazoles.[9] Since transition metal addition, high temperature, environmental toxic and scope limitation may be a restriction of these methods, and an efficient and general access to imidazole derivatives under mild condition is anticipated.

The multi-component reactions (MCR) emerged as useful methods because the combination of components to generate new products in a single step is energy saving, low waste and environmentally friendly.[10] With the conception in mind, our continuous research focus on new strategies for multi-substituted imidazoles in moderate condition. Hence, the results of I_2-catalyzed α-amino carbonyl compounds,[11] aldehyde and ammonium acetate to synthesize 1,2,4-trisubstituted imidazoles is reported in the current work.

We initiated our studies by using 4-chlorobenzaldehyde (**1a**) and 1-phenyl-2-(phenylamino)ethanone (**2a**) as model substrates to optimize the reaction conditions. Treatment of **1a** with **2a** used an equiv of iodine as the catalyst in ethanol overnight and the desired product (**3-1a**) was isolated in 24% yield (Table1, entry1). Other lewis acids, such as $FeCl_3$, ZnI_2 and $Cu(OTf)_2$, did not show any catalytic activities to this transformation (Table 1, entries 2-4). Iodine sources including KI and tetrabutylammonium iodide (TBAI) were conducted into the reaction and only 19% and 14% yields were isolated, respectively (Table 1, entries 5-6). Moreover, reducing the amount of iodine to 0.1 equiv could significantly increase the yield to 57% (Table 1, 7-8). To our delight, the yield increased to 81% when the temperature changed into 40 °C (Table 1, entries 9-12). Different solvents including dioxane, toluene, DMF, DMSO and DCE were tested (Table 1, entries 13-17), and EtOH proved to be the best solvent. Therefore, the subsequent reactions were performed in the presence of iodine (0.1 equiv) in EtOH under 40 ^{o}C overnight.

Table 1. Optimization of the Reaction Conditions [a]

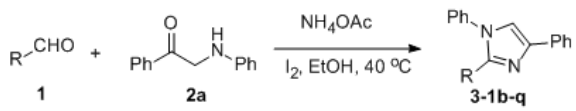


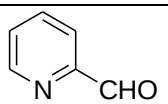
entry	catalyst (equiv)	temprature (°C)	solvent	yield (%) [b]
1	I_2 (1.0)	100	EtOH	24
2	$FeCl_3$ (0.2)	100	EtOH	NR
3	ZnI_2 (0.1)	100	EtOH	NR
4	$Cu(OTf)_2$ (0.1)	100	EtOH	NR
5	KI (0.1) / TBHP (6.0)	100	EtOH	19
6	TBAI (0.1) / TBHP (6.0)	100	EtOH	14
7	I_2 (0.5)	100	EtOH	38
8	I_2 (0.1)	100	EtOH	57
9	I_2 (0.1)	80	EtOH	62
10	I_2 (0.1)	60	EtOH	66
11	**I_2 (0.1)**	**40**	**EtOH**	**81**
12	I_2 (0.1)	RT	EtOH	72
13	I_2 (0.1)	40	Dioxane	38
14	I_2 (0.1)	40	Toluene	NR
15	I_2 (0.1)	40	DMF	26
16	I_2 (0.1)	40	DMSO	NR
17	I_2 (0.1)	40	DCM	NR

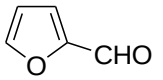
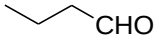
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), ammonium acetate (0.4 mmol), solvent (2 mL), overnight. [b] Isolated yield

With the optimal conditions in hand, **2a** was used as a starting material to determine the scope of aldehydes under the optimized conditions. The results were shown in Table 2. For aromatic aldehyde, the reaction often afforded the corresponding products in moderate to good yields (Table 2, entries 1-11). In regard to the electronic effects, the use of benzaldehyde bearing electron-withdrawing groups at different positions gave higher yields (Table 2, entries 3, 9 and 10), and benzaldehyde bearing an electron-donating group gave a lower yield (Table 2, entries 1, 2 and 4). In addition, the substrates with methyl were well tolerated and afforded the **3-1f**, **3-1g** in 75% and 74%, respectively (Table 2, entries 5 and 6). In contrast, the substrate with fluorine did not archive the desired product in a good yield (Table 2, entry 8). We were pleased to note that hydroxyl was well tolerated and gave **3-1h** yield in 57% (Table 2, entry 7). Notably, heterocyclic aldehyde, such as picolinaldehyde and furan-2-carbaldehyde, were also tolerated and performed smoothly (Table 2, entries 12 and 13). Nevertheless, alkyl aldehydes, such as butyraldehyde, and the substrates with nitro, such as 4-nitrobenzaldehyde and 2-nitrobenzaldehyde, were not applied to in this transformation.

Table 2. Substrate Scope of Aldehydes [a]



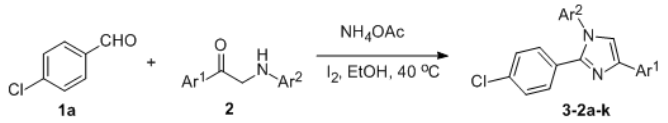
entry	R	product	yields (%) [b]
1	2-OMe-Ph	**3-1b**	55
2	4-OMe-Ph	**3-1c**	53
3	4-CN-Ph	**3-1d**	87
4	2,5-OMe-Ph	**3-1e**	67
5	4-Me-Ph	**3-1f**	75
6	3-Me-Ph	**3-1g**	74
7	4-OH-Ph	**3-1h**	57
8	2-F-Ph	**3-1i**	54
9	2-Cl-Ph	**2-1j**	71
10	3-Cl-Ph	**3-1k**	77
11	Ph	**3-1l**	54
12		**3-1m**	65

13		**3-1n**	26
14		**3-1o**	NR
15	4-NO_2-Ph	**3-1p**	NR
16	2-NO_2-Ph	**3-1q**	NR

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), EtOH (2 mL), 40 °C, overnight. [b] Isolated yield

To further expand the scope of the process, a number of α-amino carbonyl compounds were investigated for the cycloaddition reaction with 4-chlorobenzaldehyde (**1a**) (Table 3). Generally, electron-donating substituents on Ar^1 and electron-withdrawing substituents on Ar^2 showed excellent results in these reactions and the yields were above 71% (Table 3, entries 3, 4, 6 and 10). However, electron-deficient ones on Ar^1 and electron-rich ones on Ar^2 might obtain low yields (Table 3, entries 1, 2, 5, 7 and 8). Additionally, the substrate with bromine on Ar^2 conducted in the reaction and the product **3-2h** only converted into 41%, which might due to the poor solubility of the substrate (Table 3, entry 8). Noteworthy, the substrate with methyl on the ortho-position only 23% desired product (**3-2a**) was isolated. Moreover, the substrate with bulky group, such as naphthyl, could not achieve this transformation (Table 3, entries 1 and 11), and steric effect might remarkable influence on the formation of products.

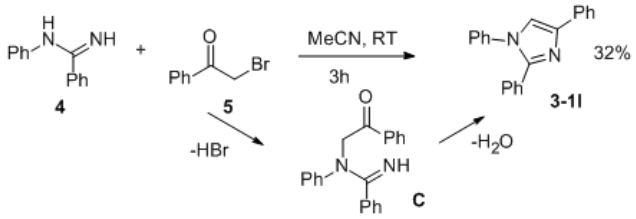
Table 3. Substrate Scope of α-Amino Carbonyl Compounds [a]



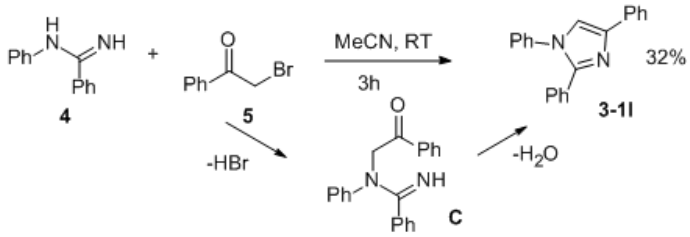
entry	Ar^1	Ar^2	product	yield (%) [b]
1	Ph	2-Me-Ph	**3-2a**	23
2	Ph	4-iPr-Ph	**3-2b**	60
3	Ph	4-Cl-Ph	**3-2c**	80
4	4-OMe-Ph	Ph	**3-2d**	82
5	Ph	4-OMe -Ph	**3-2e**	42
6	Ph	4-F-Ph	**3-2f**	71
7	Ph	3, 4-Me-Ph	**3-2g**	56
8	Ph	4-Br-Ph	**3-2h**	41
9	Ph	4-Me-Ph	**3-2i**	70
10	4-Me-Ph	Ph	**3-2j**	77
11	Ph	1-Nap	**3-2k**	NR

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), I_2 (10%), EtOH (2 mL), 40 °C, overnight. [b] Isolated yield

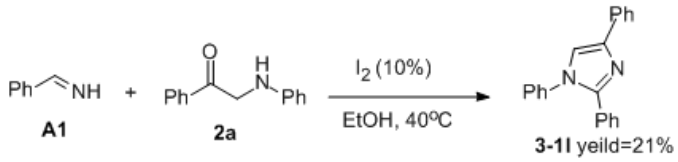
To obtain more information to understand the mechanism of this catalytic process, 1-phenyl-2-(phenylamino)ethanone (**1a**), 4-chlorobenzaldehyde (**2a**) and ammonium acetate were carried out to study the model reaction under condition 1, condition 2 and condition 3. The results indicated that air or iodine were necessary to make this transformation efficiently, as shown in scheme 1. Additionally, N-phenylbenzamidine (**4**) reacted with 2-bromo-1-phenylethanone (**5**) in presence of MeCN as solvent under room temperature for 3 hours, and the desire product 1,2,4-triphenyl-1H-imidazole (**3-1l**) was isolated in 32 % yield.[12] Notably, the reaction might through an important intermediate (**C**) to get the final product, as shown in scheme 2. The phenylmethanimine (**A1**) was also prepared to react with **2a**,[13] and the desired product **3-1l** was isolated in 21% yield (as shown in scheme 3).



Scheme 1. The Control Experiments for the Model Reaction.

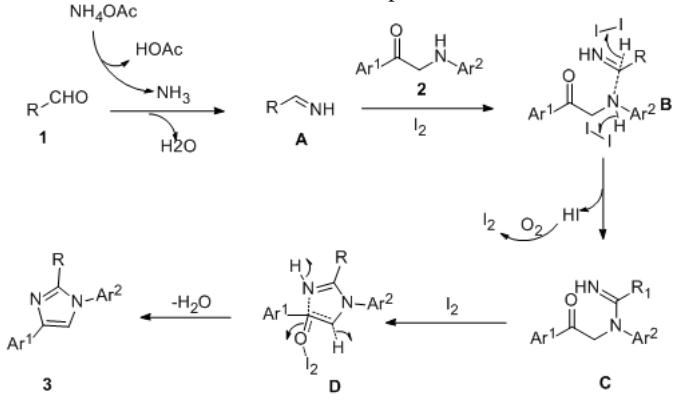


Scheme 2. Preparation of 1,2,4-Triphenyl-1H-Imidazole (**3-1l**) from 2-Bromo-1-Phenylethanone and N-Phenylbenzamidine



Scheme 3. The Investigation of Reaction Process.

On the basis of the results obtained above, a proposed mechanism of this reaction is illustrated in Scheme 3. Initially, aldehyde **1** reacts with ammonia released from ammonium acetate to generate imine A, which gave the intermediate complex B via oxidative addition with α-amino carbonyl compounds **2** in the presence of iodine.[14] Subsequently, intermediate **B** converted into the intermediate **C**, and the species of I_2 is regenerated via reoxidized by oxygen to continue the catalytic cycle. In the end, the intermediate **C** is through a transition status **D** to form the desired product **3**.



Scheme 3. Plausible Reaction Pathway

In conclusion, an interesting strategy for the synthesis of multi-imidazoles via [3+1+1] three-component cycloaddition reactions had developed. The transformation employed environmentally friendly and inexpensive I_2 (10 mol%) as a catalyst, and all components were easily available or economical. Moreover, the reactions, using EtOH as a solvent in 40 ^{o}C in one-pot, were mild conditions and operationally simple. Otherwise, various function groups including furan, pyridine and hydroxyl were tolerated resulting in moderate to good yields.

Experimental Section

Typical Procedure for the Preparation of multisubstituted imidazole 3. Synthesis of 2-(4-chlorophenyl)-1,4-diphenyl-1H-imidazole (3-1a):

The reaction was carried out in a sealed tube (10 mL), **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), ammonium acetate (0.4 mmol) and EtOH (2 mL) were added to the tube with a magnetic stirring bar at 40 ^{o}C under air. Allowed for stirring at this temperature overnight, the tube was took out and cooled to room temperature. Then, the mixture was filtered with ethyl acetate, and the filtrate was concentrated under reduced pressure to get the crude product. Subsequently, the residue was further purified by silica gel chromatography (petroleum/ethyl acetate = 20/1 as eluent) to obtain product **3-1a**. ^{1}H NMR and ^{13}C NMR spectra were determined on 300 MHz and 75 MHz in $CDCl_3$ or DMSO-D_6. The products were further characterized by HRMS (TOF-ESI), the melting of solid products points were determined on a microscopic apparatus**.**

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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11. Typical experimental procedure for α-amino carbonyl compounds. A mixture of aromatic amine (0.02 mol), 2-bromo-1-arylethanone (0.02 mol), $NaHCO_3$ (0.024 mol) and ethanol (50ml) was added into a 100 ml flask. Then, the flask was stirred overnight under room temperature. The crude products were filtered and washed with water, the final products was further purified by recrystallization in ethanol.

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Graphical Abstract

we have successfully developed an operationally simple and economical one-pot three-component cycloaddition reaction to synthesize 1,2,4-trisubstituted imidazoles by employing aldehydes, α-amino carbonyl compounds and ammonium acetate. The transformation is environmentally friendly and metal free by employing I_2 (10 mol %) as a catalyst and EtOH as a solvent, and a wide range of function groups and heterocyclics are well tolerated resulting in moderate to good yields.

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