EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Facile Synthesis of Polysubstituted Imidazoles via CBr4 Mediated Tandem Cyclization of Amidine with 1,3-Dicarbonyl or Ketone

Authors: Xiaoqiang Zhou, Haojie Ma, Chong Shi, Yixin Zhang, Xingxing Liu, and Guosheng Huang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201601428

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601428

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

COMMUNICATION

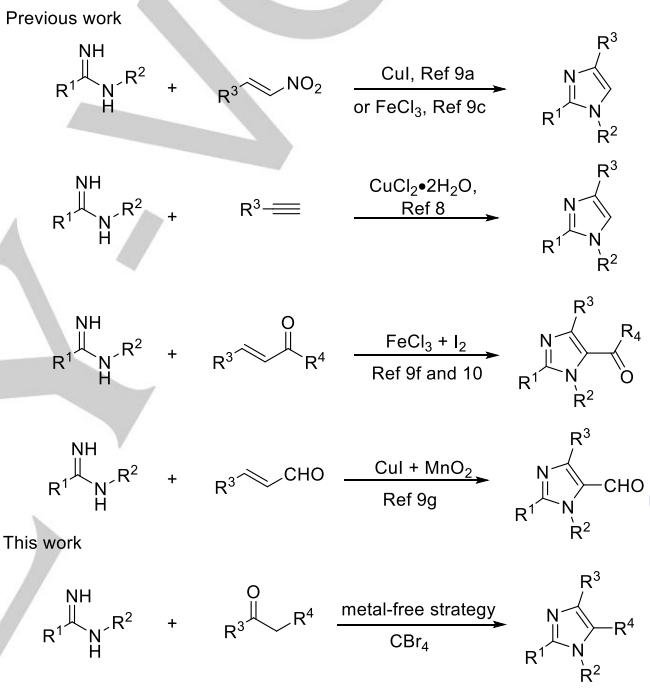
Facile Synthesis of Polysubstituted Imidazoles *via* CBr_4 Mediated Tandem Cyclization of Amidine with 1,3-Dicarbonyl or Ketone

Xiaoqiang Zhou, Haojie Ma, Chong Shi, Yixin Zhang, XingXing Liu and Guosheng Huang*

Abstract: A facile approach to synthesize polysubstituted imidazoles *via* CBr_4 mediated tandem cyclization of amidine with 1,3-dicarbonyl or ketone is described. This metal-free cascade reaction employed CBr_4 as promoter and was carried out with a simple operation under mild conditions.

As one of the most valuable N-heterocyclic compounds, imidazoles have been found in many natural products[1] and pharmaceutical compounds.[2] The importance of this heterocyclic structure motivated an intensive research for the development of new and efficient synthetic strategies.[3-6] Transition metal-catalyzed cycloaddition of amidines has been widely used for rapidly constructing these compounds.[7] In recent years, a series of methods which catalyzed by copper or iron have been developed by the group of Neuville,[8] Chen,[9] and Li[10] (Scheme 1). However, in order to satisfy the low threshold residual tolerance of metals for pharmaceuticals, complicated purifying procedures and high cost have to be paid out for removing trace amounts of residual metal from pharmaceutical precursors such as polysubstituted imidazoles. From this point, developing metal-free strategies for the synthesis of imidazole cores is still important.

In 2015, metal-free I_2 catalyzed synthesis of substituted imidazoles from vinyl azides and benzylamines has been reported by Yan's group.[5] This procedure required highly energetic reagent iodine and over stoichiometric amounts of peroxide oxidants TBHP. α-Halogenated ketones or 1,3-dicarbonyls and their derivatives are versatile synthetic blocks for building complex molecules in organic chemistry. By virtue of simple operation and fewer steps, preparing these α-halogenated products in situ has been highlighted for the construction of heterocycles.[11-12] As an efficient catalyst, carbon tetrabromide has been found to show good reactivity for the formation of C−C bond in cross-dehydrogenative coupling (CDC) reactions and double-oxidative dehydrogenative (DOD) reactions by Huo's group.[13] Recently, Huo's group developed an efficient CBr_4–mediated oxidative C−N bond formation reaction to construct complex imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrimidines.[14] During our preparation of this manuscript, Jaenicke and co-workers reported an in-situ α-bromination strategy which employed $CBrCl_3$ as promoter for the formation of imidazo[1,2-a]pyridines.[15] As part of our continuing work in the development of new and efficient metal-free methods for the construction of N-heterocycles,[16] herein, we describe a facile approach to synthesize polysubstituted imidazoles *via* CBr_4 mediated tandem cyclization of amidine with 1,3-dicarbonyl or ketone.



Scheme 1. Synthesis of imidazole from amidine.

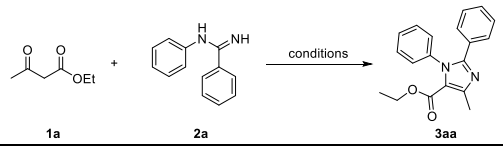
To initiate our study, the reaction conditions were screened for the formation of tetrasubstituted imidazoles by taking ethyl 3-oxobutanoate (**1a**) and N-phenylbenzamidine (**2a**) as model substrates (Table 1). Various brominating reagents were first examined. In a typical procedure, a mixture of **1a** (0.2 mmol, 1 equiv), **2a** (1 equiv), and halogenating reagents (1.0 equiv) in 2 mL of acetonitrile was stirred under air at 70 °C. The desired product ethyl 4-methyl-1,2-diphenyl-1H-imidazole-5-carboxylate **3aa** was detected when NBS, $CBrCl_3$ and CBr_4 were employed in this reaction, respectively (Table 1, entries 1-5). And the desired **3aa** was isolated in 41% yield by the use of 1.0 equiv of CBr_4. Although NBS, a highly energetic reagent, could give a higher yield (44%). To make this transformation milder, CBr_4 was selected to screen the reaction conditions. Increasing the amount of CBr_4 could not improve the yields (Table 1, entry 6). Subsequently, the yield was enhanced obviously by increasing the dosage of amidine **2a** moderately (Table 1, entries 7-8), while no better result was observed when the loading of amidine **2a** was increased to 3.0 equiv (Table 1, entry 9). The use of other solvents

Xiaoqiang Zhou, Haojie Ma, Chong Shi, Yixin Zhang, XingXing Liu and Prof. Guosheng Huang
State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University.
Lanzhou, 730000, China.
E-mail: hgs@lzu.edu.cn

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

such as DCE (17 %) and MeOH (40 %), instead of CH_3CN, was found to be less effective (Table 1, entries 10-11). Finally, the optimized reaction conditions were obtained as follows: 1.0 equiv of CBr_4 was mixed with 1.0 equiv **1a** and 2.0 equiv **2a** in CH_3CN at 70 °C under air (Table 1, entry 8).

Table 1. Optimization of the reaction conditions [a]



1a 2a 3aa

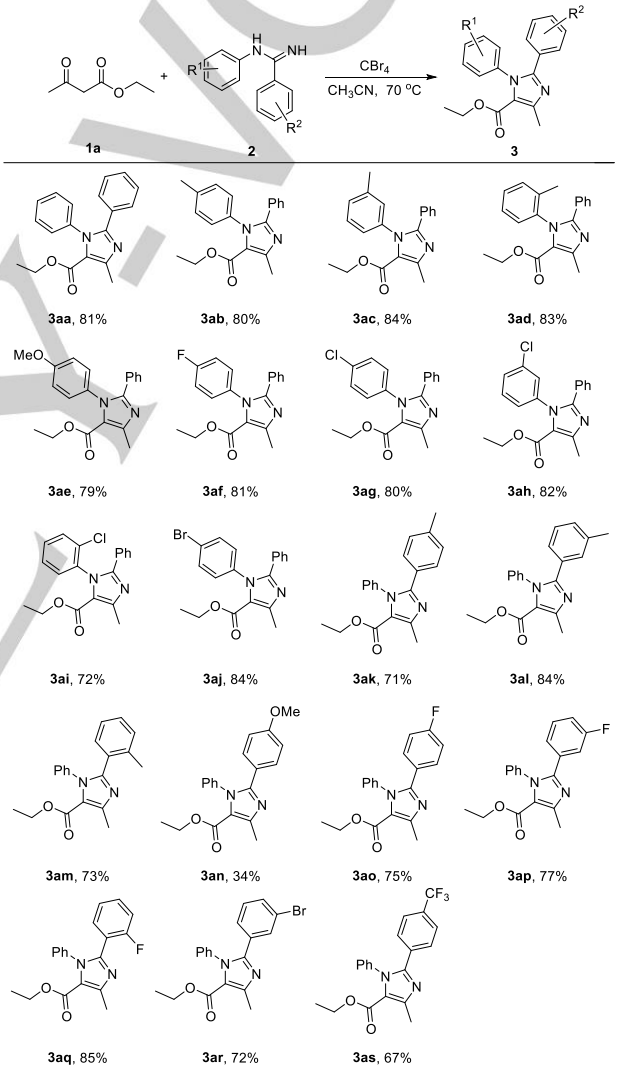
Entry	Hal/equiv	Solvent	Yield [b](%)
1	TBAB(1.0)	CH_3CN	0
2	NBS (1.0)	CH_3CN	44
3	$CBrCl_3$(1.0)	CH_3CN	trace
4	CBr_4 (1.0)	CH_3CN	41
5	CCl_4(1.0)	CH_3CN	0
6	CBr_4(2.0)	CH_3CN	39
7 [c]	CBr_4(1.0)	CH_3CN	57
8 [d]	CBr_4(1.0)	CH_3CN	82
9 [e]	CBr_4(1.0)	CH_3CN	83
10 [d]	CBr_4(1.0)	DCE	17
11 [d]	CBr_4(1.0)	MeOH	40

[a] Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), solvent (2 mL), under 70 °C, overnight and monitored by TLC. [b] Isolated yields. [c] **2a** (1.5 equiv, 0.3 mmol). [d] **2a** (2.0 equiv, 0.4 mmol). [e] **2a** (3.0 equiv, 0.6 mmol).

With the optimized reaction conditions in hand, the scope and generality to different amidines were investigated and the results are summarized in Scheme 2. First, a series of amidines derived from anilines with electron-donating or withdrawing groups were examined using optimized conditions. All these amidines could react with ethyl 3-oxobutanoate **1a** smoothly and the desired tetrasubstituted imidazoles could be obtained efficiently in good yields. The yields remained relatively stable with the nature of the different groups in the aromatic ring of anilines (**3aa**-**3aj**). Then, various amidines derived from benzonitriles with electron-donating or withdrawing groups were carried out in standard conditions. Except of methoxyl (**3an**), all other substrates can give the desired products in moderate to good yields (**3ak**-**3am**, **3ao**-**3as**).

This metal-free oxidative C−N bond formation strategy was further expanded to a range of β-keto esters, 1,3-diones or ketones substrates 1 (Scheme 3). Polysubstituted imidazoles could be obtained smoothly. β-Keto esters with different substituents could provide the corresponding products in good yields (**3aa**-**3da**), while 1,3-diones and ketones gave moderate results (**3ea**-**3ia**).

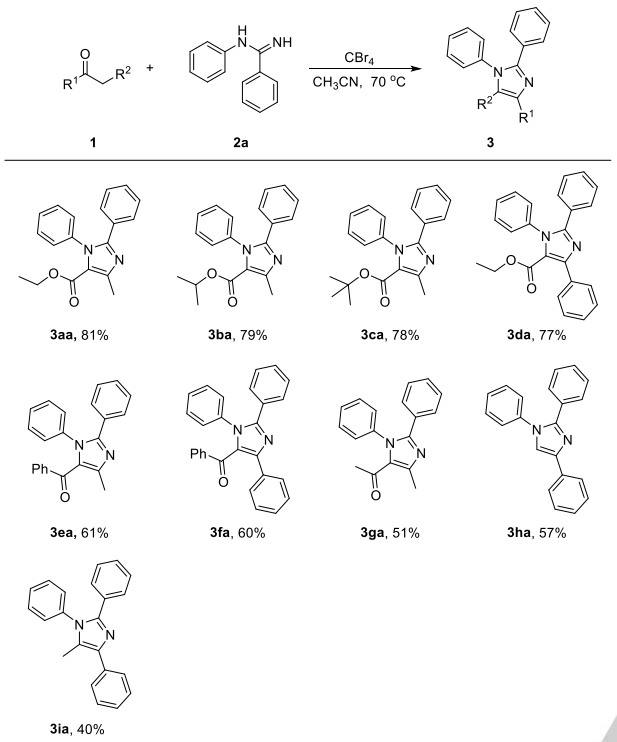
To gain mechanistic insights into this transformation, some control experiments were carried out. Firstly, α-brominated ketone **4h**, as the proposed intermediate, was used to react with amidines **2a** under standard conditions without CBr_4, the desired imidazole **3ha** was obtained in high yield (Scheme 4, a). Furthermore, this α-brominated intermediate **4d** was also isolated from the reaction of **1d** and **2a** under standard conditions by carrying out this reaction at room temperature (Scheme 4, b). These results validated α-brominated product is the intermediate of this conversion. In addition, the reaction of **1a** and **2a** was conducted in the presence of 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under optimized conditions, and no obvious inhibition was observed (Scheme 4, c). This result suggested that no radical process was involved in this CBr_4 mediated C−H bond amination reaction.



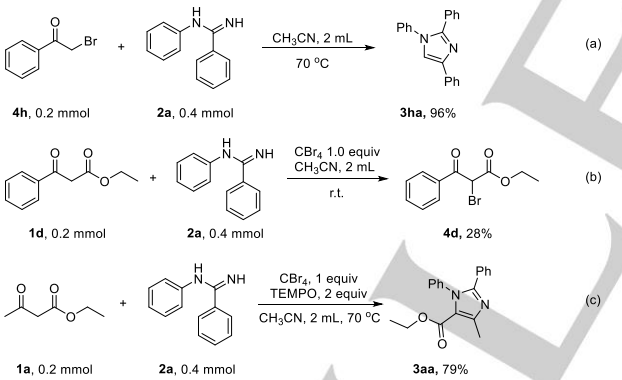
Scheme 2. Scope of amidines.

On the basis of the previous literature reports [12-15] and the above results, the possible mechanism for this transformation is proposed, as illustrated in Scheme 5. Firstly, intermediate **A**, the isomerization of **1a**, reacts with CBr_4 to give α-brominated intermediate **B**. Then the nucleophilic substitution of **2a** with **B** provides imine intermediate **C**. Subsequently, intramolecular

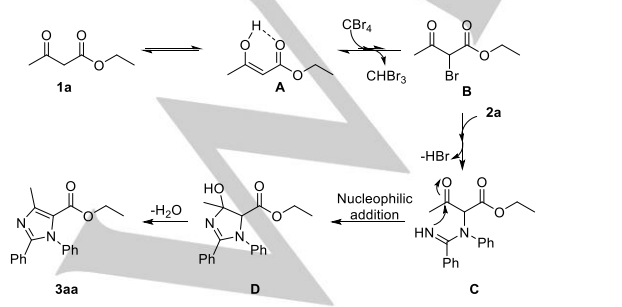
nucleophilic addition of **C** and the connected oxidative aromatization process affords the final imidazole derivative **3aa**.



Scheme 3. Scope of β-keto esters, 1,3-diones and ketones.



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

In conclusion, we have demonstrated a facile metal-free approach to synthesize polysubstituted imidazoles *via* CBr_4 mediated tandem cyclization of amidine with 1,3-dicarbonyl or ketone. CBr_4 was employed to promote this in situ α-C–H bromination process. Simple operation with inexpensive reagents and mild reaction conditions make this efficient protocol practical.

Experimental Section

A test tube equipped with a magnetic stir bar was charged with ketones **1** (0.2 mmol), amidines **2** (0.4 mmol), CBr_4 (66.4 mg, 0.2 mmol), and CH_3CN (2 mL). Then the reaction mixture was stirred at 70 °C (oil bath temperature) under air. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated in vacuo, and the residues were purified by column chromatography, eluting with petroleum ether/EtOAc to afford the desired imidazoles **3**.

Keywords: amidine • amination • bromination • imidazoles • metal-free

[1] a) J. Zhong, *Nat. Prod. Rep.* **2009**, *26*, 382–445; b) B. Forte, B. Malgesini, C. Piutti, F. Quartieri, A. Scolaro and G. Papeo, *Mar. Drugs,* **2009**, *7*, 705–753; (c) P. Midoux, C. Pichon, J.-J. Yaouanc and P.-A. Jaffres, *Br. J. Pharmacol.* **2009**, *157*, 166–178.

[2] a) R. J. C. Lee, P. C. Timmermans, T. F. Gallaghr, S. Kumar, D. McNully, M. Blumenthal and J. R. Heys, *Nature*, **1994**, *372*, 739–746; b) S. E. De Laszlo, C. Hacker, B. Li, D. Kim, M. MacCoss, N. Mantalo, J. V. Pivnichny L. Colwell, G. E. Koch, M. A. Cascieri, M. A. Cascieri and W. K. Hagmenn *Bioorg. Med. Chem. Lett.* **1999**, *9*, 641–646; c) M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi and A. Ursini, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023–1028; d) L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinsky-Mozng, D. Frost, S. H. Rosenberg and H. L. Sham, *J. Med. Chem.* **2002**, *45*, 1697–1711; e) J. Dietrich, V. Gokhale, X.-D. Wang, L. H. Hurley and G. A. Flynn, *Bioorg. Med. Chem.* **2010**, *18*, 292–304.

[3] For a review, see: S. Kamijo and Y. Yamamoto, *Chem. Asian J.* **2007**, *2*, 568–578.

[4] For selected examples, see: a) H. Huang, X. Ji, W. Wu and H. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 170–180, and the references therein; b) Z. Cai, S. Wang and S. Ji, *Org. Lett.* **2012**, *14*, 6068–6071; c) H. Chen, A. Kaga and S. Chiba, *Org. Lett.* **2014**, *16*, 6136–6039; d) Y. Li, L. Cheng, Y. Shao S. Jiang, J. Cai and N. Qing, *Eur. J. Org. Chem.* **2015**, *4325*–4329; e) X. Zhou, Z. Jiang, L. Xue, P. Lu and Y. Wang, *Eur. J. Org. Chem.* **2015**, 5789–5797; f) J. Zhang, Q. Gao, X. Wu, X. Geng, Y. Wu and A. Wu, *Org. Lett.* **2016**, *18*, 1686–1689.

[5] L. Xiang, Y. Niu, X. Pang, X. Yang and R. Yan, *Chem. Commun.* **2015**, *51*, 6598–6600.

[6] J. Cao, X. Zhou, H. Ma, C. Shi and G. Huang, *RSC Adv.* **2016**, *6*, 57232–57235.

[7] a) S. Sanjaya and S. Chiba, *Org. Lett.* **2012**, *14*, 5342–5345; b) Y.-F. Wang, X. Zhu and S. Chiba, *J. Am. Chem. Soc.* **2012**, *134*, 3679–3682; c) S. Sanjaya, S. H. Chua and S. Chiba, *Synlett*, **2012**, *23*, 1657–1661; d) H. Chen, S. Sanjaya, Y.-F. Wang and S. Chiba, *Org. Lett.* **2013**, *15*, 212–215; e) L. Xu, H. Li, Z. Liao, K. Lou, H. Xie, H. Li and W. Wang, *Org. Lett.* **2015**, *17*, 3434–3437.

[8] J. Li and L. Neuville, *Org. Lett.* **2013**, *15*, 1752–1755;

[9] a) D. Tang, P. Wu, X. Liu, Y. Chen, S. Guo, W. Chen, J. Li and B. Chen, *J. Org. Chem.* **2013**, *78*, 2746–2750; b) X. Liu, D. Wang, Y. Chen, D. Tang and B. Chen, *Adv. Synth. Catal.* **2013**, *355*, 2798–2802; c) X. Liu, D. Wang and B. Chen, *Tetrahedron*, **2013**, *69*, 9417–9421; d) D. Tang, X. Li, X. Guo, P. Wu, J. Li, K. Wang, H. Jing and B. Chen, *Tetrahedron*, **2014**, *70*, 4038–4042; e) J. Qu, P. Wu, D. Tang, X. Meng, Y. Chen, S. Guo and B. Chen, *New J. Chem.* **2015**, *39*, 4235–4239; f) P. Wu, J. Qu,

Y. Li, X. Guo, D. Tang, X. Meng, R. Yan and B. Chen, *Adv. Synth. Catal.* **2015**, *357*, 3868–3874; g) Y. Li, Y. Fu, C. Ren, D. Tang, P. Wu, X. Meng and B. Chen, *Org. Chem. Front.* **2015**, *2*, 1632–1636; h) P. Wu, L. Zhang, X. Zhang, X. Guo and B. Chen, *Chin. J. Chem.* **2016**, *34*, 363–367.

[10] Y. Zhu, C. Li, J. Zhang, M. She, W. Sun, K. Wan, Y. Wang, B. Yin, P. Liu and J. Li, *Org. Lett.* **2015**, *17*, 3872–3875.

[11] a) Y. Zhu, M. Lian, F. Jia, M. Liu, J. Yuan, Q. Gao and A. Wu, *Chem. Commun.* **2012**, *48*, 9086–9088; b) C. Wan, J. Zhang, S. Wang, J. Fan and Z. Wang, *Org. Lett.* **2010**, *12*, 2338–2341; c) Y. Xie, J. Wu, X. Che, Y. Chen, H. Huang and G. Deng, *Green Chem.* **2016**, *18*, 667–671; d) M. H. Shinde and U. A. Kshirsagar, *Green Chem.* **2016**, *18*, 1455–1458; e) Q. Gao, Z. Fei, Y. Zhu, M. Lian, F. Jia, M. Liu, N. She and A. Wu, *Tetrahedron*, **2013**, *69*, 22–28; f) Z. Fei, Y. Zhu, M. Liu, F. Jia and A. Wu, *Tetrahedron Lett.* **2013**, *54*, 1222–1226.

[12] a) X. Wang, L. Ma and W. Yu, *Synthesis,* **2011**, 2445–2453; b) L. Ma, X. Wang, W. Yu and B. Han, *Chem. Commun.* **2011**, *47*, 11333–11335; c) J. Xie, H. Jiang, Y. Cheng and C. Zhu, *Chem. Commun.* **2012**, *48*, 979–981; d) I. I. Roslan, K.-H. Ng, G.-K. Chuah and S. Jaenicke, *Adv. Synth. Catal.* **2016**, *358*, 364–369; e) S. K. Lee and J. K. Park, *J. Org. Chem.* **2015**, *80*, 3723–3729.

[13] a) C. Huo, H. Xie, F. Chen, J. Tang and Y. Wang, *Adv. Synth. Catal.* **2016**, 358, 724–730; b) C.Huo, H.Xie, M. Wu, X. Jia, X. Wang, F. Chen and J. Tang, *Chem. Eur. J.* **2015**, *21*, 5723–5726; c) C. Huo, M. Wu, F. Chen, X. Jia, Y. Yuan and H. Xie, *Chem. Commun.* **2015**, *51*, 4708–4711.

[14] C. Huo, J. Tang, H. Xie, Y. Wang and J. Dong, *Org. Lett.* **2016**, *18*, 1016–1019.

[15] I. I. Roslan, K.-H. Ng, J.-E. Wu, G.-K. Chuah and S. Jaenicke, *J. Org. Chem.* **2016**, *81*, 9167–9174.

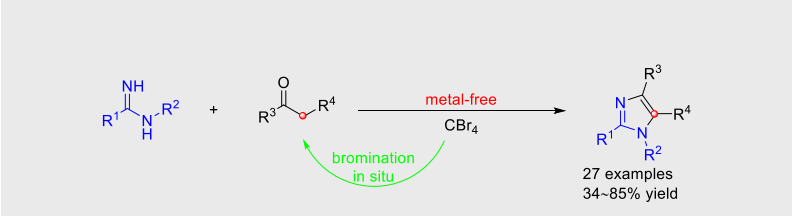
[16] a) Y. Li, X. Zhou, Z. Wu, J. Cao, C. Ma, Y. He and G. Huang, *RSC Adv.* **2015**, *5*, 88214–88217; b) R. Yan, X. Li, X. Yang, X. Kang, L. Xiang and G. Huang, *Chem. Commun.* **2015**, *51*, 2573–2576; c) X. Zhou, H. Ma, J. Cao, X. Liu and G. Huang, *Org. Biomol. Chem.* **2016**, *14*, 10070–10073; d) L. Xiang, Y. Yang, X. Zhou, X. Liu, X. Li, X. Kang, R. Yan and G. Huang, *J. Org. Chem.* **2014**, *79*, 10641–10647.

10.1002/ejoc.201601428

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



A facile metal-free approach to synthesize polysubstituted imidazoles *via* CBr_4 mediated tandem cyclization of amidine with 1,3-dicarbonyl or ketone is described, affording desired products in moderate to good yields with a simple operation under mild conditions.

*Xiaoqiang Zhou, Haojie Ma, Chong Shi, Yixin Zhang, XingXing Liu and Guosheng Huang**

Page No. – Page No.

Facile Synthesis of Polysubstituted Imidazoles via CBr4 Mediated Tandem Cyclization of Amidine with 1,3-Dicarbonyl or Ketone