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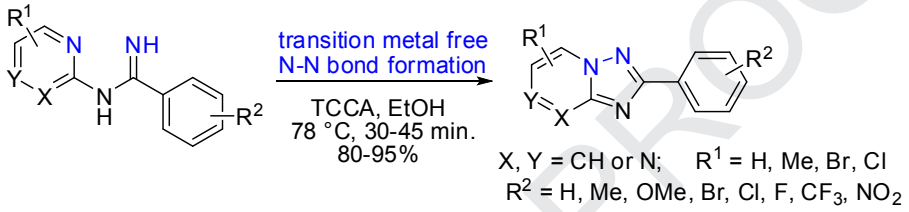

X, Y = CH or N; R^1 = H, Me, Br, Cl
R^2 = H, Me, OMe, Br, Cl, F, CF_3, NO_2

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Trichloroisocyanuric acid-mediated synthesis of 1,5-fused 1,2,4-triazoles from *N*-heteroaryl benzamidines *via* intramolecular oxidative N–N bond formation

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ABSTRACT

A convenient synthesis of 1,5-fused 1,2,4-triazoles from readily available *N*- heteroaryl benzamidines is reported. The reaction is efficiently promoted by trichloroisocyanuric acid to afford the desired products, mostly in high yields and in relatively short time, through direct metal-free oxidative N–N bond formation. The mild nature of the synthesis and short reaction time are notable advantages of the developed protocol. This protocol is effective toward various substrates having different functionalities.

Introduction

The 1,2,4-triazole nucleus is an important structural motif present in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry, agricultural chemistry, materials science, and organocatalysis [1]. 1,2,4-Triazole scaffolds are found in many biologically active molecules [2] and valuable pharmaceuticals, including maraviroc, triazolam, sitagliptin, and penipanoid (Figure-1)[3]. In particular, compounds containing *N*-fused 1,2,4-triazoles, such as triazolopyridine and triazolopyrazine substructures exhibit a wide spectrum of biological activity including antifungal, antimicrobial, antiviral, anti-inflammatory, antiasthmatic, antiproliferative and hypotonic [4]. In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules [5]. On the other hand, they also play important roles as ligands in transition-metal complexes and metal-organic frameworks, exhibiting tremendous application prospects [6].

Due to their importance, many efficient methods have been developed to access *N*-fused 1,2,4-triazoles [7]. Oxidative cyclization of *N*-(2-pyridyl) amidines is one of the most straightforward strategies for the construction of the 1,2,4-triazolo[1,5-a]pyridine framework, which previously has been achieved by utilizing oxidants, such as NaClO/base [8], $Pb(OAc)_4$ [9], and MnO_2 [10]. Nevertheless, these methods are associated with some disadvantages, including low yields, multistep synthetic procedures, limited scopes and inferior regioselectivity.

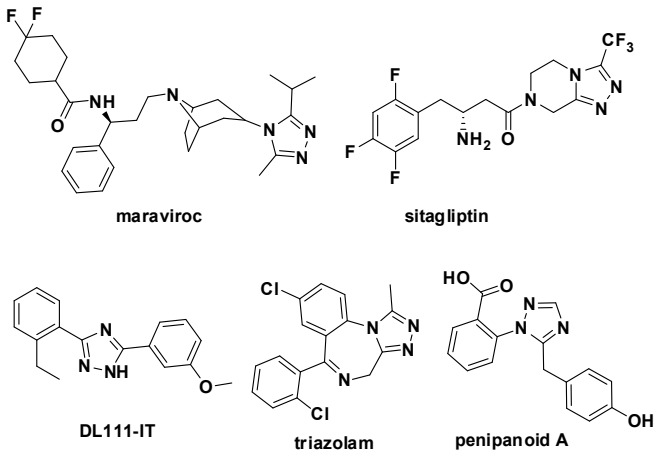


Figure 1. Representative bioactive molecules and natural compounds possessing a 1,2,4-triazole core

In 2009, Ueda and Nagasawa [11] reported a copper-catalyzed tandem addition−oxidative cyclization of 2-amino pyridines and aryl nitriles to 2-aryl-1,2,4-triazolo[1,5-a]pyridines. Alternatively, Zhao and co-workers [12] developed a recyclable Cu−Zn/Al−Ti catalyst for the same transformation. Recently, Xia, Huang, and co-workers [13] described a Cu-catalyzed oxidative cyclization of Nitriles with 2-Aminopyridines or Amidines. However, in almost all cases, copper and other transition metal catalysts with higher loadings (typically 5–20 mol%) were used to achieve high yields, and they are difficult to separate from the reaction mixture and they are not recyclable. These problems are of particular environmental and economic concerns in large-scale syntheses and in industry. Moreover, these transition metal catalysis might cause metal contamination

of the desired product because 1,2,4-triazoles are strong ligands for transition metals and could coordinate with metal to form stable complexes [6c-e]. Therefore, it is still of importance to develop transition metal free synthetic methods to access this kind of compound class.

However, some transition metal free synthetic methods have also been reported to access *N*-fused 1,2,4-triazoles. For example, Du, Zhao, and co-workers [14] reported a PIFA-mediated cyclization of *N*-(pyridin-2-yl) amidines to 2-aryl/2-alkyl triazolopyridines. Further, in 2015, Song, Tian and co-workers [15] reported a new and efficient I_2/KI-mediated methodology for the synthesis of both 2-aryl and 2-alkyl substituted 1,2,4-triazolo[1,5-a]pyridines. But these existing methods suffer from some drawbacks in one or another respect, such as use of expensive catalyst, formation of byproduct like 20% iodinated product along with desired product in I_2/KI-mediated methodology, inferior regioselectivity and a limited substrate scope.

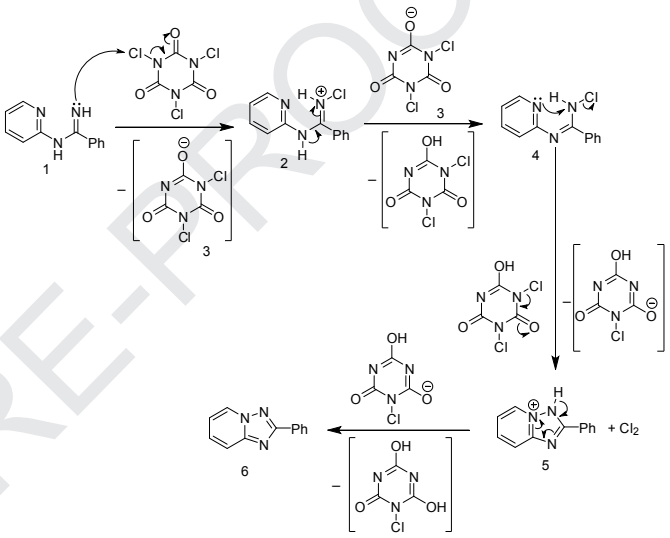
Despite these elegant achievements made, it is still of importance to develop novel and general approaches to access this compound class.

Trichloroisocyanuric acid (TCCA) is a versatile reagent and is becoming increasingly popular because of its commercial availability at low cost. TCCA has been extensively used as an oxidant for a wide variety of functional groups [16,17]. This reagent also acts as a chlorinating agent [18], as oxidant for aromatization of various nitrogen heterocycles [19], and as oxidizing reagent to construct the C–O bond in isoxazole synthesis [20]. However, to the best of our knowledge, there is no report of TCCA-mediated N–N bond formation reactions. Encouraged by the results of our previous work [21,22], in this paper, we disclose a new and efficient TCCA-mediated methodology for the synthesis of 2-aryl substituted 1,2,4-triazolo[1,5-a]pyridines, as well as their pyrazido- and pyrimidotriazole derivatives, from *N*-heteroaryl benzamidines through the construction of N−N bonds.

Result and Discussion

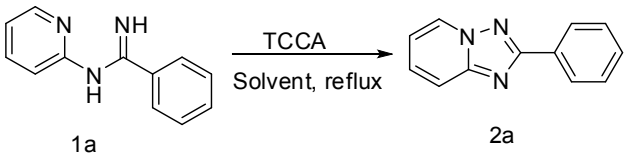
Herein, we describe a convenient synthesis of 1,2,4-triazolo[1,5-a]pyridines, as well as their pyrazido- and pyrimidotriazole derivatives, from their corresponding *N*-aryl amidines. The required substrates *N*- heteroaryl benzamidines **1a-t** were prepared via the addition reaction of corresponding heteroaryl amines to substituted nitriles as per the reported literature procedure [23]. Our preliminary investigation began with the reaction of *N*-(2-pyridyl) amidine **1a** with TCCA (0.5 equiv.) in methanol under reflux at 65 °C. We were delighted to observe the formation of the desired product **2a**, albeit in a low yield of 70% (Table 1, entry 1), as an isolated yield obtained after column chromatography. Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents were screened under reflux condition and the results are summarized in Table 1. It was found that ethanol was the superior solvent in terms of the reaction time and yield of the product (Table 1, entry 2). Once, we had established a suitable solvent for the synthesis of 1,2,4- triazolo[1,5-a]pyridine, we then focused on the quantity of TCCA. An increase in the amount of TCCA (from 0.5 equiv. to 1.5 equiv.) not only decreased the reaction time from 1.5 h to 30 minute, but also increased the product yield from 75% to 95% (Table 1, entry 7). Further increasing the quantity of TCCA (from 1.5 equiv. to 2 equiv.) led to a decrease in the yield to 75% (Table 1, entry 8). Therefore, we decided to perform the subsequent reactions of the various *N*- heteroaryl benzamidines with TCCA (1.5 equiv.) in ethanol under reflux at 78 °C. The effect of temperature on the reaction rate as well as on the yields of the products were also investigated. Faster reactions occurred on increasing the temperature but the product yields were not satisfactory. The progress of the reactions was monitored by TLC analysis (using EtOAc–hexane as the eluent).

Plausible Mechanism: Based on our experimental data and previous report [15,22], a plausible reaction mechanism for the formation of 1,5-fused 1,2,4-triazole **6** is proposed (Scheme 2). According to this route, *N*-heteroaryl benzamidine **1** on treatment with Trichloroisocyanuric acid first provides N-chloro amidinium cation **2** and cyanurate anion **3** as a proton acceptor. N-chloro amidinium cation further by the cleavage of N-Cl bond, deprotonation and after rearomatization provides the desired 1,5-fused 1,2,4-triazole framework **6**.



Scheme 2. Plausible mechanism for the synthesis of 1,5-fused 1,2,4-triazole from *N*-heteroaryl benzamidine

Table-1 Optimization of the Reaction Conditions



1a 2a

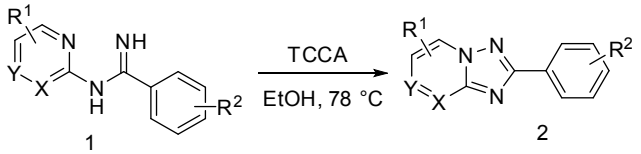
Entry	Solvent	TCCA (eq.)	Time	Yield (%)
1	MeOH	0.5	1.5 h	70
2	EtOH	0.5	1h	75
3	Isopropanol	0.5	2.5 h	50
4	Toluene	0.5	3 h	45
5	AcOH	0.5	2 h	50
6	EtOH	1.0	45 min.	85
7	EtOH	1.5	30 min.	95
8	EtOH	2	15 min.	75

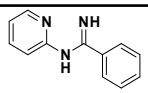
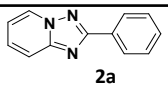
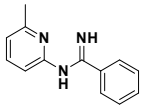
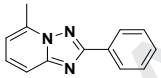
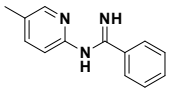
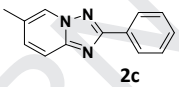
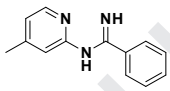
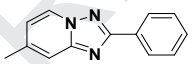
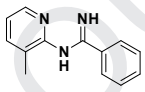
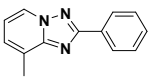
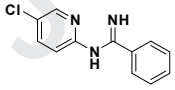
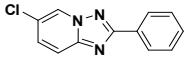
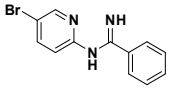
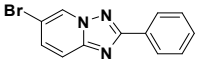
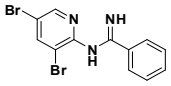
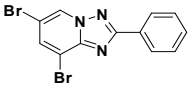
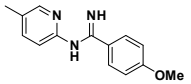
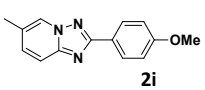
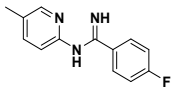
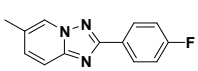
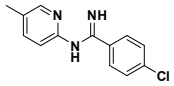
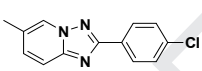
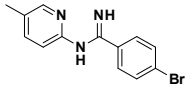
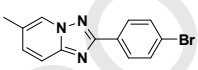
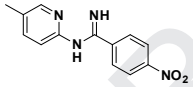
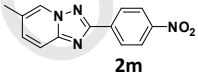
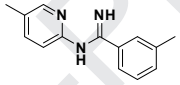
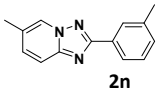
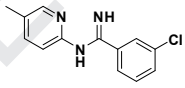
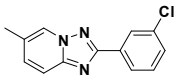
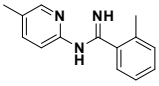
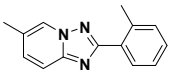
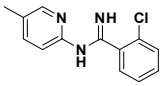
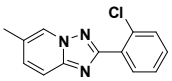
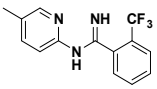
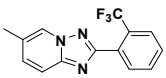
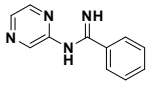
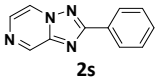
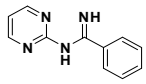
With the optimized reaction conditions established (Table 1, entry 7), the scope of the newly discovered oxidative N−N bond formation reaction was investigated (Table 2). Because **2a** was afforded in an excellent yield from its corresponding substrate **1a**, the effect of substituents on the pyridine ring (R^1) was first examined. This heterocyclic ring was found to be tolerant of both

electron-rich groups such as methyl **2b-e** and electron-deficient groups such as halogens **2f−h**. Reactions of halogen-containing substrates provided yields slightly lower than that of the methyl-containing substrate, which was probably due to the relatively low nucleophilicity of the pyridines affected by the halogens (Table 2, entries **1−8**). The substitution effect of the R^2 group was then examined. It was found that When R^2 is a substituent in aromatic ring, this methodology is compatible with both electron-donating and electron-withdrawing groups at para-, meta-, and ortho-positions of the benzene ring **2i−r**. Even the nitro-group-bearing substrate **1m** was smoothly transformed into the desired 1,2,4-triazolo[1,5-a]pyridine **2m** under the optimal reaction conditions. Ortho-substitution on the 2-phenyl moiety did not affect either the reaction rate or the yields of the products **2p−r**.

Additionally, pyrazido- **2s** and pyrimidotriazoles **2t** were prepared via the oxidative cyclization of *N*-pyrazyl **1s** and *N*-pyrimidyl substituted benzimidamides **1t**, respectively, in good yields.

Table-2 Synthesis of various 1,5-fused 1,2,4-triazoles with the scope of substituents R^1 and R^2 on *N*-heteroaryl benzamidine



Entry	Substrate (1)	Product (2)	Time (min)	Yield (%)
1		 **2a**	30	95
2		 **2b**	35	92
3		 **2c**	30	93
4		 **2d**	30	94
5		 **2e**	40	91
6		 **2f**	30	89
7		 **2g**	35	88
8		 **2h**	35	87
9		 **2i**	30	92
10		 **2j**	30	88
11		 **2k**	30	87
12		 **2l**	35	85
13		 **2m**	45	81
14		 **2n**	30	90
15		 **2o**	30	87
16		 **2p**	35	88
17		 **2q**	35	87
18		 **2r**	40	84
19		 **2s**	30	91
20		**2t**	35	87

Conclusion

In conclusion, we have developed a short and efficient synthesis of 1,5-fused 1,2,4-triazoles using a mild oxidative cyclization method with Trichloroisocyanuric acid through the construction of N-N bond. This facile and transition-metal-free synthetic process works well with a wide range of substituted *N*-heteroaryl benzamidine. A variety of substituents are tolerated allowing the synthesis of diverse products in good to excellent yields. The main advantage of this procedure is to access 1,5-fused 1,2,4-triazoles with high yields and short reaction time. The newly developed synthetic route is believed to be valuable for the

construction of building blocks but also for medicinal chemistry studies comprising 1,5-fused 1,2,4-triazole moiety.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/xxxx/j.tetlet.xxxxxxxx.

References and notes

[1] (a) Moulin, A.; Bibian, M.; Blayo, A.-L.; El Habnouni, S.; Martinez, J.; Fehrentz, J.-A. *Chem. Rev.* **2010**, *110*, 1809. (b) Al-Soud, Y. A.; Heydel, M.; Hartmann, R. W. *Tetrahedron Lett.* **2011**, *52*, 6372. (c) Kaur, R.; Dwivedi, A. R.; Kumar, B.; Kumar, V. *Anti-Cancer Agents Med. Chem.* **2016**, *16*, 465. (d) Keri, R. S.; Patil, S. A.; Budagumpi, S. Nagaraja, B. M. *Chem. Biol. Drug Des.* **2015**, *86*, 410. (e) Paprocka, R.; Wiese, M.; Eljaszewicz, A.; Helmin-Basa, A.; Gzella, A.; Modzelewska-Banachiewicz, B.; Michalkiewicz, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2664.

[2] (a) Sebeika, M. M.; Jones, G. B. *Curr. Org. Synth.* **2014**, *11*, 732. (b) Maddila, S.; Pagadala, R.; Jonnalagadda, S. B. *Lett. Org. Chem.* **2013**, *10*, 693.

[3] (a) Haycock-Lewandowski, S. J.; Wilder, A.; Ahman, J. *Org. Process Res. Dev.* **2008**, *12*, 1094. (b) Turner, K. *Org. Process Res. Dev.* **2012**, *16*, 727. (c) Siddaiah, V.; Basha, G. M.; Srinuvasarao, R.; Yadav, S. K. *Catal. Lett.* **2011**, *141*, 1511. (d) Hansen, K. B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivera, N.; Steinhuebel, D.; Armstrong, J. D.; Askin, D.; Grabowski, E. J. *Org. Process Res. Dev.* **2005**, *9*, 634.

[4] (a) Collin, X.; Sauleau, A.; Coulon, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2601. (b) Papakonstantinou-Garoufalias, S.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. *Farmaco* **2002**, *57*, 973. (c) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115. (d) Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **2007**, *15*, 1976. (e) Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019. (f) Saha, A. K.; Liu, L.; Simoneaux, R.; Decorte, B.; Meyer, C.; Skrzat, S.; Breslin, H. J.; Kukla, M. J.; End, D. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5407. (g) Hester, J. B. Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.

[5] Hitotsuyanagi, Y.; Motegi, S.; Fukaya, H.; Takeya, K. *J. Org. Chem.* **2002**, *67*, 3266. 10.1021/jo010904i

[6] (a) Liu, K.; Shi, W.; Cheng, P. *Dalton Trans.* **2011**, 8475. (b) Wu, P. L.; Feng, X. J.; Tam, H. L.; Wong, M. S.; Cheah, K. W. *J. Am. Chem. Soc.* **2009**, *131*, 886. (c) Zhang, J.-P.; Lin, Y.-Y.; Huang, X.-C.; Chen, X.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5495. (d) Klingele, M. H.; Brooker, S. *Coord. Chem. Rev.* **2003**, *241*, 119. (e) Haasnoot, J. G. *Coord. Chem. Rev.* **2000**, *200*, 131. (f) Tao, Y.; Wang, Q.; Ao, L.; Zhong, C.; Yang, C.; Qin, J.; Ma, D. *J. Phys. Chem. C* **2010**, *114*, 601.

[7] Holm, S. C.; Straub, B. F. *Org. Prep. Proced. Int.* **2011**, *43*, 319. 10.1080/00304948.2011.593999

[8] Grenda, V. J.; Jones, R. E.; Gal, G.; Sletzinger, M. *J. Org. Chem.* **1965**, *30*, 259. 10.1021/jo01012a061

[9] Potts, K. T.; Burton, H. R.; Bhattacharyya, J. *J. Org. Chem.* **1966,** *31*, 260. 10.1021/jo01339a058

[10] Raval, J. P.; Desai, K. R. *ARKIVOC* **2005**, *13*, 21. 10.3998/ark.5550190.0006.d03

[11] Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080-15081. 10.1021/ja905056z

[12] Meng, X.; Yu, C.; Zhao, P. *RSC Adv.* **2014**, *4*, 8612. 10.1039/C3RA47029F

[13] Xia, J.; Huang, X.; Cai, M.; *Synthesis* **2019**, *51*, 2014-2022. 10.1055/s-0037-1611712

[14] Zheng, Z.; Ma, S.; Tang, L.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2014**, *79*, 4687. 10.1021/jo500298j

[15] Song, L.; Tian, X.; Lv, Z.; Li, E.; Wu, J.; Liu, Y.; Yu, W.; Chang, J. *J. Org. Chem.*, **2015**, *80*, 7219-7225. 10.1021/acs.joc.5b01183

[16] Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamshiro, G. S.; Hiberath, L. A. *Synth. Commun.* **1996**, *26*, 2633. 10.1080/00397919608004579

[17] Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, *22*, 1589. 10.1080/00397919208021632

[18] Jing , Y.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 4932. 10.1021/ol5024568

[19] Panarese, J. D.; Waters, S. P. *Org Lett.* **2010**, *12*, 4086. 10.1021/ol101688x

[20] Zhang, W.; Su, Y.; Wang, Ke-Hu; Wu, L.; Chang, B.; Shi, Y.; Huang. D.; Hu, Y. *Org. Lett.* **2017**, *19*, 376. 10.1021/acs.orglett.6b03582

[21] Bhatt, A.; Singh, R. K.; Kant, R. *J. Heterocycl. Chem*. **2019**, *56*, 696. 10.1002/jhet.3451

[22] Bhatt, A.; Singh, R. K.; Kant, R. *Synth. Commun.* **2019**, *49*, 1083. 10.1080/00397911.2019.1590848

[23] (a) Khalifaa, M. M.; Bodnera, M. J.; Berglund, J. A.; Haley, M. M. *Tetrahedron Lett.* **2015**, *56*, 4109-4111. (b) Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969-1972.

Highlights

- Trichloroisocyanuric acid mediated synthesis of 1,5-fused 1,2,4-triazoles from *N*- heteroaryl benzamidines
- A transition-metal free intramolecular oxidative N−N bond formation
- Various substituted *N*- heteroaryl benzamidines tolerated and gave 1,5-fused 1,2,4-triazoles in good yields.