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COMMUNICATION

$I_2/K_2S_2O_8$Mediated Direct Oxidative Annulation of Alkyl azaarenes with Amidinesfor the Synthesis of Substituted 1,3,5-Triazines

Jun Zhang,*[a] Tingting Zheng,[a] and Jidong Zhang*[b]

Abstract: A direct method for the synthesis of heteroaryl substituted 1,3,5-triazines from readily available methyl-azaarenes and amidines has been developed. The present method involves iodine mediated cascade aerobic C(sp^3)–H oxidative amination and following condensation, cyclization with amidine. Both of methyl quinoline, pyridine and benzothiazole derivates could be well tolerated to react with various amidines leading to corresponding products in good to excellent yields.

Introduction

Recently, the 1,3,5-triazines have attracted much attentions and widely used as core skeleton introduced to functional supramolecular organic frame exhibiting various founion such as photoredox catalysts,[1] transfer hydrogenation catalysts,[2] gas absorption,[3] magnetism,[4] semiconductor.[5] A large number of small molecules bearing 1,3,5-triazine fragments usually possess a broad spectrum of biological activities such as antitumor,[6a,b] anti-inflammatory,[6c,d] antibacterial,[6e] antiviral[6f] and play a significant role in the discovering of active lead compounds. Moreover, this scaffold exhibits extensive applications in preparation of high performance chelating ligands,[7] liquid crystals,[8] molecular probes,[9] photoelectric materials. [10] (Figure 1)

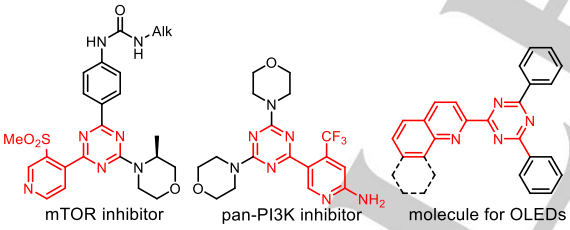

Figure 1. Selected examples of functional molecular bearing 1,3,5-triazine.

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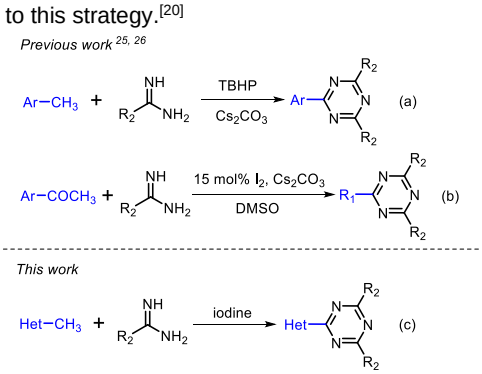
Traditionally, the symmetrically 2,4,6-substituted 1,3,5-triazines could be prepared through the cyclotrimerization of nitriles.[11] For the 1,3,5-triazines bearing three different substituents, the common preapration processes are based on the sequential coupling of each substituent with halogenated 1,3,5-triazines.[12] The domino cyclization of isothiocyanates with aryl amidines is also an effective method to polysubstituted 1,3,5-triazine derivatives.[13] Not long ago, a microwave-assisted cyclo condensation of 4H-pyrido[1,3]oxazin-4-ones with amidines was established leading to asymmetry2,4,6-substituted 1,3,5-triazines bearing pyridyl as well.[14] More recently, a novel visible light promoted the three-component reaction of isothiocyanates, amidines and guanidines were developed by Guo for the construction of amino-containing unsymmetrical trisubstituted 1,3,5-triazines.[15] In addition, transition metal and visible light catalyzed cascade amination of 1,1-dibromoalkenes,[16a] alcohol[16b] or perfluoroalkyl halides[16c] with biguanides to 1,3,5-triazines were also effective methods to introduce various substitutes. In contrast, the formal [3+2+1] annulation of aldehydes with amidines is of particular interets and widely adopted in rapid assembly of triazine skeletons due to its convergent and step-economical features.[17] Based on this strategy, researchers have tried various carbon synthons in cyclization with amidines to improve the synthesis of 1,3,5-triazines and achieved a lot of progresses over the past decades. In previous work, transition-metal Ru,[18a] Cu(II)[18b] and hypervalent iodine[18c] catalyzed aerobic oxidative coupling of alcohols with amidine were respectively developed leading to 2,4,6-triaryl-1,3,5-triazines via aldehydes intermediate. Similarly, polythene glycol mediated aerobic oxidative tandem cyclization of benzylamines with amidines[19a] and oxidative C(sp^3)–H amination of tertiary amines with amidines using Cu(II)[19b] or iodine[19c] as catalysts were also further established as novel strategies for the synthesis of polysubstituted 1,3,5-triazine. As an alternative, other carbon synthons such as aryl acetic acids, styrenes, isatins and alkyl ethers were also developed as C1 coupling precursors introduced to this strategy.[20]



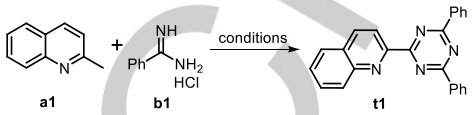
Scheme 1. Synthesis of 1,3,5-triazines via direct oxidative amination.

Despite these previous reactions synthetic exhibit high efficiency, a simple and direct method for the construction of triazine containing biheteroaryls is still needed in consideration of tedious synthetic process, expensive substrates of above methods. Comparing with inaccessible heteroaryl aldehyde, the alkylazaarenes have been widely used as the carbon source in organic synthesis as their cheap, easily available features.[21] With a certain oxidant, the methyl group attached to the aryl ring could be oxidized in-situ to aldehyde and involved in further transformations. To date, copper,[22] elemental sulfur[23] and iodine reagent[24] were successively selected as the catalysts to promote aerobic oxidative C-N, C-S bonds coupling of alkylazaarenes to construct various heterocycles. Nevertheless, to the best of our knowledge, there is still no report using alkylazaarenes as the C-1 carbon source to the oxidative cyclization with amidines to 1,3,5-triazine. In 2015, Guo reported TBHP mediated oxidative C(sp^3)–H amination of methylarenes[25] with amidine for the synthesis of 1,3,5-triazines (Scheme 1, eq. a). However, this protocol needed an excessive amount of methyl arenes as solvent which limited its wide application in heterocyclic substrates. As a green and recyclable catalyst, molecular iodine had attracted much attention in the C(sp^3)-H functionalization of alkylazaarenes for the construction of various heterocycles including quinazolinones,[24a-b] imidazo[1,5-a]-pyridines,[24e] 1,2,4-triazolo[4,3-a]pyridines[24f] and so on. Recently, Bhanage and group utilized molecular iodine as catalyst to facilitate the C(sp^3)-H amination of acetophenone[26] and developed a practical methodology for the synthesis of 1,3,5-triazines (Scheme 1, eq. b). Therefore, we considered that iodine promoted oxidative C(sp^3)-H amination of alkylazaarenes with amidines would be feasible and disclosed a novel route for the synthesis of 1,3,5-triazines bearing heterocycles (Scheme 1, eq. c).

Results and Discussion

At the outset of this study, we employed the reaction of 2-methyl quinoline (**a1**) and benzamidine hydrochloride (**b1**) as the model to optimize the reaction conditions for this tandem oxidative cycloaddition (Table 1). Base on previous iodine promoted oxidative cycloaddition of amidines with tertiary amines[19c] or methyl ketones [26] and our preliminary exploration of reaction conditions (Table s1), iodine combining with DMSO might be the suitable catalytic system in the presence of Cs_2CO_3. However, an excessive amount of iodine did not significantly improve the desirable transformation, hence, we conducted the reaction using 30 mol % iodine as a catalyst with the addition of Cs_2CO_3 in DMSO, firstly (Table 1, entry 1). Fortunately, the reaction mixture converted to desired 1,3,5-triazine **t1** in 20% yield when heated at 120°C for 24h. In consideration of the fast recovery of iodine might promote the oxidation of a1 and then improve the reaction yield, we subsequently investigated the effect of oxidants and found it is essential for the current catalytic system. Then, a series of different oxidants including $K_2S_2O_8$, TBHP, DTBP, TBPB were successively screened, and $K_2S_2O_8$ exhibited the best activity (Table 1, entry 2-5). It is encouraging that the reaction was significantly improved and the yield increased to 50% with the addition of $K_2S_2O_8$ (2.0 equiv.). Further increase or decrease of $K_2S_2O_8$ did not improve the yield of **t1** at all (Table 1, entry 6). Some other iodine sources were also investigated to promote the reaction. However, neither of NH_4I, NIS, TBAI lead to a higher yield of product and only KI showed comparable efficiency (Table 1, entries 7-10). Following, the optimal loading amount of iodine was also explored and 50 mol % iodine was found to be ideal leading to a 70% yield of **t1** (Table 1, entry 12).

Table 1. Optimization of reaction conditions.[a]



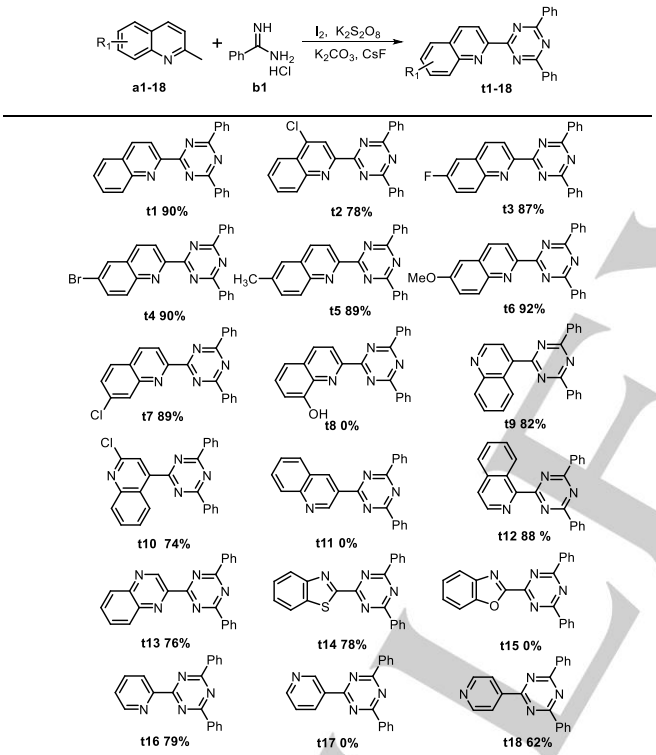
Entry	[I] (mol %)	Oxidant	Base (equiv.)	Solvent	Yield[b]
1	I_2 (30%)		Cs_2CO_3 (2)	DMSO	20
2	I_2 (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	50
3	I_2 (30%)	TBHP	Cs_2CO_3 (2)	DMSO	35
4	I_2 (30%)	DTBP	Cs_2CO_3 (2)	DMSO	25
5	I_2 (30%)	TBPB	Cs_2CO_3 (2)	DMSO	21
6	I_2 (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	38[c], 49[d]
7	KI (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	45
8	NH_4I (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	30
9	NIS (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	25
10	TBAI (30%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	20
11	I_2 (20%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	45
12	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	70
13	I_2 (75%)	$K_2S_2O_8$	Cs_2CO_3 (2)	DMSO	70
14	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (3)	DMSO	72
15	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (4)	DMSO	78
16	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (5)	DMSO	74
17	I_2 (50%)	$K_2S_2O_8$	Na_2CO_3 (4)	DMSO	34
18	I_2 (50%)	$K_2S_2O_8$	K_2CO_3 (4)	DMSO	68
19	I_2 (50%)	$K_2S_2O_8$	KOH(4)	DMSO	38
20	I_2 (50%)	$K_2S_2O_8$	CsOH(4)	DMF	40
21	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (4)	NMP	48
22	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (4)	Toluene	20
23	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (4)	PhCl	25
24	**I_2 (50%)**	**$K_2S_2O_8$**	**Cs_2CO_3 (4)**	**DMSO/PhCl (1:1)**	**90**
25	I_2 (50%)	$K_2S_2O_8$	Cs_2CO_3 (4)	DMSO/PhCl (1:1)	78[e], 85[f]

[a] Reaction condition: **a1** (0.5 mmol), **b1** (1.1 mmol), oxidant (1.0 mmol) and base (1.0 mmol) in 5.0 mL solvent, reacted at 120°C for 24 h.[b] Products were obtained

in isolated yields based on **a1**. [c] 1 equiv. $K_2S_2O_8$ was used. [d] 3 equiv. $K_2S_2O_8$ was used.[e]Reaction performed at 110°C. [f] Reaction performed at 130°C.

Moreover, with the increase of Cs_2CO_3, the transformation was gradually enhanced and achieved a satisfying yield of 78% when 4 equivalents of Cs_2CO_3 was added. Subsequently, the screening of optimal base was conducted while only K_2CO_3 exhibited a satisfied promotion to the reaction (Table 1, entries 16-18). In addition, the results of solvent effects showed that both DMF, NMP, toluene and chlorobenzene were unsuitable for the current reaction system (Table 1, entries 19-22). Nevertheless, the result exhibited that a significant enhancement in yield was achieved when the reaction was conducted in a mixed solvent. With the combination of DMSO and PhCl (1:1), the reaction gratifyingly proceeded and gave the product in excellent yield (Table 1, entry 23). Finally, Increasing or decreasing reaction temperature could be of no advantage to the conversion of reactants, resulting in lower yield (Table 1, entry 25)

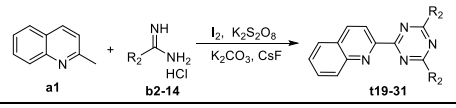
Table 2. Scope of methyl azaarene derivatives.[a]



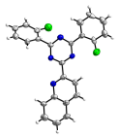
[a] Reaction condition: **a** (0.5 mmol), **b1** (1.1 mmol), $K_2S_2O_8$ (1.0 mmol) and Cs_2CO_3 (2.0 mmol) were stirred in DMSO (2.5 mL)/PhCl (2.5 mL) at 120°C for 24 h. Products were obtained in isolated yields based on **a**.

With the optimized conditions in hand, the scope of 2-aminobenzamides was firstly investigated. As shown in Table 2, substrates with electron-withdrawing groups or electron-donating groups can react smoothly to afford the corresponding products in good to excellent yields (**t1-18**). In general, the electronic nature of substituents showed no significant impact on the yields of target molecules. Both 2-methyl quinoline bearing F, Cl, Br, CH_3, OCH_3 on C-6 and C-7 position could lead to the desired products (**t3-7**) up to about 92% yield. The C-4 chlorine on 2-methyl quinoline well compatible with a current catalytic system with a slight decrease of yield (**t2**). Considering the wide application of fluorescent dyes based on the excited-state intramolecular proton transfer, the 2-methyl quinoline with hydroxy at the C8 position was also examined. However, no target molecular was observed at all, both of increasing reaction time and temperature (**t8)**. Besides the 2-methyl-quinolines, the optimized reaction conditions can also be extended to the oxidative amination of other methyl azaarenes. Gratifyingly, both of 4-methyl quinoline, 1-methyl isoquinolines derivates smoothly underwent the oxidative cycloaddition with **b1**, giving the corresponding products **t9**, and **t12** in 82% and 88% yields, respectively. It was surprising that Cl- at the C-2 position of 4-methyl quinoline was also tolerated well and led to the corresponding products **t10** in good yield (74%). When 3-methyl quinoline was employed as a substrate, unfortunately, no reaction was observed under the present reaction condition. 2-Methylquinoxaline which contains another nitrogen atom was suitable for the protocol to obtain **t13** in 76% yield. The reaction was further successfully applied to sulfur containing five-member heterocycle substrates. The 2-methyl benzothiazole is proved to be suitable for this oxidative cyclization reaction and transformed into corresponding products **t14** in satisfied yield. However, when 2-methylbenzoxazole was employed as a substrate, no reaction was observed either at a higher and lower temperature (**t15**). In addition, 2-methyl pyridines, 4-methyl pyridines all turned out to be suitable substrates for this transformation, leading to the corresponding products **t16**, **t18** in 79% and 62% yields, respectively. Similar to 3-methyl quinoline, 3-methylpyridine did not react at all under the standard condition.

Table 3. Scope of amidine hydrochlorides.[a]



t19 R_2 = 4-F-Ph 81%
t20 R_2 = 4-Cl-Ph 84%
t21 R_2 = 4-Br-Ph 85%
t22 R_2 = 4-CF_3-Ph 70%
t23 R_2 = 4-CH_3-Ph 92%
t24 R_2 = 3-F-Ph 76%
t25 R_2 = 3-Cl-Ph 80%
t26 R_2 = 3-CH_3-Ph 86%
t27 R_2 = 3-OMe-Ph 90%
t28 R_2 = 2-F-Ph 68%
t29 R_2 = 3Cl-4F-Ph 70%
t30 R_2 = thiophene-2-yl 82%
t31 R_2 = cyclopropyl 66%



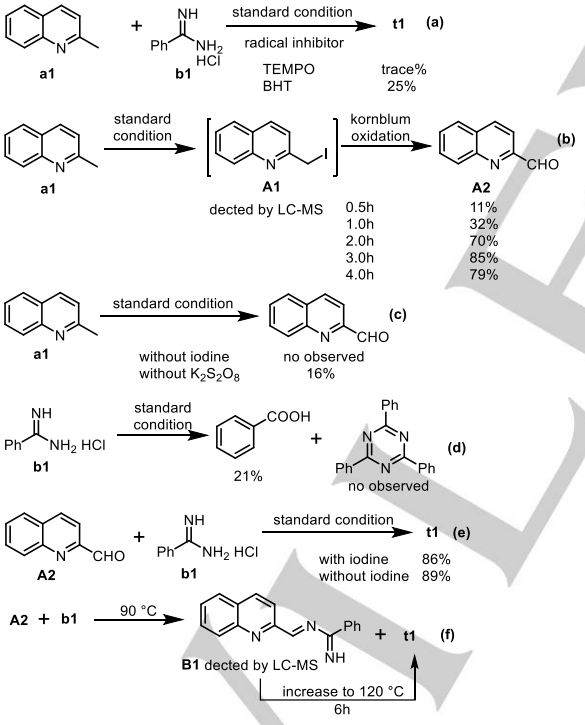
X-ray structure of **t28**

[a] Reaction condition: **a1** (0.5 mmol), **b** (1.1 mmol), $K_2S_2O_8$ (1.0 mmol) and Cs_2CO_3 (2.0 mmol) were stirred in DMSO (2.5 mL)/PhCl (2.5 mL) at 120°C for 24 h. Products were obtained in isolated yields based on **a1**.

To further demonstrate the applicability of the reaction, we next investigated the generality of the current procedure by testing various amidine hydrochlorides with 2-methyl quinoline (**a1**). A wide range of amidine including phenyl, aromatic heterocycles, alkyl substituted derivates could reacted with **a1** smoothly to give the corresponding 1,3,5-triazines. Firstly, a series of functional groups on the phenyl ring of benzamidines including CH_3, OCH_3, F, Cl, Br and CF_3 were tested and tolerated well providing the corresponding products in good to excellent yields. In generally, the benzamidines bearing electron-donating group on the benzene ring showed better reactivity and provided higher yields

than electron-rich ones. It was found that the substrates bearing electron-donating groups like Me or OCH_3 on *para* and *meta* position were highly suitable and provided the desired products (**t23** and **t26-27**) in excellent isolated yields. Both of the halide substituents on *para*, *meta* position were tolerated, providing the respective target products (**t19-21** and **t24-t25**) in 76-85% yields. Furthermore, the amidines bearing strong electron-withdrawing CF_3 group was also employed, while the reaction became sluggish giving the corresponding product in 70% yields. When the *ortho* substituted benzamidine was tested, a slight steric effect was observed and inhibited the reaction. Even so, the desired product **t28** was successfully obtained in 68% yield and further confirmed by X-ray crystallography. The reaction of **a1** with the polysubstituted benzamidines was also feasible and afforded corresponding product **t29** in 70% yields. In addition, 2-thienylamidine was confirmed to be an efficient substrate for this reaction, leading to the triazine **t30** bearing three heterocycles in 79% yield. Gratifyingly, when cyclopropane carboxamidine was subjected to this reaction, dicyclopropyl-substituted 1,3,5-triazines **t31** were successfully obtained in a moderate yield.

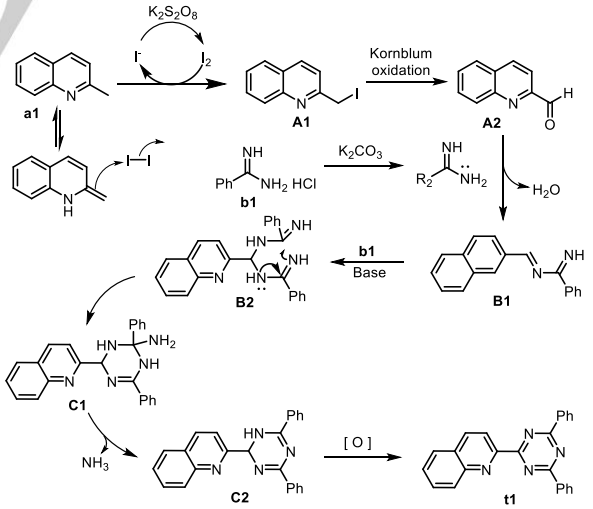
Scheme 2. Several control experiments for mechanism studies.



In order to clarify the mechanism of this reaction, a series of control experiments were carried out as shown in Scheme 2. First, the radical inhibition experiments were performed to investigate the reaction by addition of excess 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tertbutyl-4-methyl phenol (BHT). The results showed that both of TEMPO and BHT have significantly influences on the yields of **t1** (Scheme 2a). Thus, a radical mechanism could be included during the transformation.

Following, to confirm the active intermediate of 2-methyl quinoline (**a1**), the reaction was conducted in the absence of benzamidine. It was found that most of **a1** could be transformed into quinoline-2-carbaldehyde under the standard condition (Scheme 2b). In the presence of iodine, the oxidation of **a1** could be quickly initiated in 0.5 h and transform into quinoline-2-carbaldehyde (**A2**) via the key intermediate 2-iodomethyl-quinoline (**A1**) in the presence of DMSO. With the increase of reaction time, the intermediate **A1** gradually disappeared, the main product **A2** achieved an 84% yield after stirring of 3h. These results indicated that intermediate **A1** acted as a crucial intermediates during the oxidative process while the **A2** might be active species in the cyclization process. Besides, the oxidation of **a1** to **A2** would be completely inhibited with the remove of iodine or $K_2S_2O_8$ (Scheme 2c). Moreover, single **b1** was treated with the standard condition, however, only 21% yield of benzoic acid was obtained in the absence of **a1** (Scheme 2d). Subsequently, the reaction of quinoline-2-carbaldehyde with benzamidine was also investigated and gave the product **t1** in excellent yield which further verified the important role of **A2** (Scheme 2e). Notably, the transformation of **A2** with **b1**seemed entirely unaffected without iodine. This result indicated that the iodine catalyst played an important role in the oxidative in-situ aldehyde generation process while had no obvious promotion and suppression during the condensation and cyclization steps. In addition, when the reaction of **A2** with **b1** was performed at 90°C, the aldimine (**B1**) was proved to the main product and an only trace amount of **t1** was observed (Scheme 2f). However, the intermediate **B1** would be gradually disappeared and converted into **t1** with an additional stirring of 6 h when the temperature was further raised to 120°C.

Scheme 3. Proposed reaction mechanism.



Based on these results and previous reports, a plausible mechanism was proposed and illustrated in Scheme 3 using the reaction of 2-methyl quinoline with benzamidine as an example. Initially, 2-methyl quinoline underwent nucleophilic substitution with iodine to afford the intermediate 2-iodomethyl-quinoline (**A1**) via the more active enamine. The intermediate **A1** would be rapidly oxidized to quinoline-2-carbaldehyde (**A2**) via Kornblum oxidation in the presence of DMSO. Then, the condensation of

quinoline-2-carbaldehyde with benzamidine hydrochloride (**b1**) was initiated to afford imine (**B1**) with the promotion of Cs_2CO_3. Subsequently, in the presence of an excessive base, the nucleophilic addition of **b1** with **B1** was achieved and provided an intermediate **B2**. Finally, **B2** could be rapidly transformed into **C1** which underwent oxidation to the desired product 1,3,5-triazine.

Conclusions

In summary, we have developed a novel and practical strategy for the construction of biheteroaryls bearing quinoline and 1,3,5-triazine ring. Compared with literature procedures, the reaction showed advantages such as cheap starting materials, transition metal-free and good functional group tolerance. The current catalytic system performed via a tandem oxidative in-situ aldehyde generation, amination, condensation and cyclization utilized a catalytic amount of molecular iodine as catalyst in the presence of oxidant. The mild reaction conditions make it suitable for a wide range of methyl quinoline, methylpyridine and methyl benzothiazole as aldehyde precursors leading to respectively substituted 1,3,5-triazines. To the best of our knowledge, this is the first direct method for the synthesis of 2-heteroaryl substituted 1,3,5-triazines with methyl-azaarenes. We believe that the present methodology would have wide applications in organic synthesis, medicinal chemistry and materials science fields.

Experimental Section

The general experimental procedure is as follows: To an oven-dried reaction vessel charged with 2-methyl quinoline (**a1**, 0.5 mmol, 72.5 mg), amidine hydrochloride (**b1**, 1.1 mmol, 171.6 mg), iodine (50 mol %, 0.25 mmol, 63.5 mg), $K_2S_2O_8$ (1.0 mmol, 270.3 mg), Cs_2CO_3 (2.0 mmol, 651.6 mg) was added. Then, a mixture of dried DMSO (2.5 mL) and chlorobenzene (2.5 mL) was used as the solvent. The vessel was sealed and heated to 120°C for 24 h. The reaction progress was monitored using TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The resulting mixture was diluted with brine (50 mL) and extracted with dichloromethane (20 mL) three times. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator to get the crude product. The crude product was purified by silica gel column chromatography (eluent: 15:1 petroleum ether/ethyl acetate). Other 1,3,5-triazine derivates were prepared according to similar procedure to **t1**.

Acknowledgments

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Keywords: azaarenes • biheteroaryls • C(sp^3)-H amination • cyclization • Kornblum oxidation

[1] a) W. Huang, J. Byun, I. Rorich, C. Ramanan, P. W. M. Blom, H. Lu, D. Wang, L. Caire da Silva, R. Li, L. Wang, K. Landfester, K. A. I. Zhang, *Angew Chem Int Ed Engl*. **2018**, *57*, 8316-8320; b) D. Schwarz, Y. Noda, J. Klouda, K. Schwarzova-Peckova, J. Tarabek, J. Rybacek, J. Janousek, F. Simon, M. V. Opanasenko, J. Cejka, A. Acharjya, J. Schmidt, S. Selve, V. Reiter-Scherer, N. Severin, J. P. Rabe, P. Ecorchard, J. He, M. Polozij, P. Nachtigall, M. J. Bojdys, *Adv. Mater*. **2017**, *29*, 1703399; c) S. Yang, W. Hu, X. Zhang, P. He, B. Pattengale, C. Liu, M. Cendejas, I. Hermans, X. Zhang, J. Zhang, J. Huang, *J. Am. Chem. Soc*. **2018**, *140*, 14614-14618.

[2] a) G. H. Gunasekar, K. Park, V. Ganesan, K. Lee, N.K. Kim, K.D. Jung and S. Yoon, *Chemistry of Materials*. **2017**, *29*, 6740-6748; b) S. Padmanaban, G. H. Gunasekar, M. Lee, S. Yoon, *ACS Sustainable Chem. Eng.* **2019**, *7*, 8893-8899.

[3] a) Q. Q. Dang, C. Y. Liu, X. M. Wang and X. M. Zhang, *ACS Appl. Mater. Interfaces*. **2018**, *10*, 27972-27978; b) Y. Zhao, K. X. Yao, B. Teng, T. Zhang and Y. Han, *Energy Environ. Sci*. **2013**, *6*, 3684; c) X. Zhu, C. Tian, S. M. Mahurin, S. H. Chai, C. Wang, S. Brown, G. M. Veith, H. Luo, H. Liu and S. Dai, *J. Am. Chem. Soc*. **2012**, *134*, 10478-10484.

[4] a) Y. Jiang, I. Oh, S. H. Joo, O. Buyukcakir, X. Chen, S. H. Lee, M. Huang, W. K. Seong, J. H. Kim, J. U. Rohde, S. K. Kwak, J. W. Yoo, R. S. Ruoff, *ACS Nano*. **2019**, *13*, 5251-5258; b) W. Yang, X. Wu, T. Liu, T. Wang and X. Hou, *Analyst*. **2018**, *143*, 5744-5753.

[5] a) L. Hao, J. Ning, B. Luo, B. Wang, Y. Zhang, Z. Tang, J. Yang, A. Thomas, L. Zhi, *J. Am. Chem. Soc*. **2015**, *137*, 219-225; b) P. Kumar, R. Boukherroub, K. Shankar, *J. Mater. Chem. A*. **2018**, *6*, 12876-12931.

[6] a) P. Dao, N. Smith, C. Tomkiewicz-Raulet, E. Yen-Pon, M. Camacho-Artacho, D. Lietha, J. P. Herbeuval, X. Coumoul, C. Garbay, H. Chen, *J. Med. Chem*. **2015**, *58*, 237-251; b) R. V. Patel, P. Kumari, D. P. Rajani, K. H. Chikhalia, *Eur. J. Med. Chem*. **2011**, *46*, 4354-4365; c) D. Lazewska, M. Wiecek, J. Ner, K. Kaminska, T. Kottke, J. S. Schwed, M. Zygmunt, T. Karcz, A. Olejarz, K. Kuder, G. Latacz, M. Grosicki, J. Sapa, J. Karolak-Wojciechowska, H. Stark, K. Kiec-Kononowicz, *Eur. J. Med. Chem*. **2014**, *83*, 534-546; d) P. Singh, S. Kaur, P. Kumari, B. Kaur, M. Kaur, G. Singh, R. Bhatti, M. Bhatti, *J. Med. Chem*. **2018**, *61*, 7929-7941; e) A. H. Pang, A. Garzan, M. J. Larsen, T. J. McQuade, S. Garneau-Tsodikova, O. V. Tsodikov, *ACS Chem. Biol*. **2016**, *11*, 3084-3092; f) V. Lozano, L. Aguado, B. Hoorelbeke, M. Renders, M. J. Camarasa, D. Schols, J. Balzarini, A. San-Felix, M. J. Perez-Perez, *J. Med. Chem*. **2011**, *54*, 5335-5348.

[7] a) B. Laramee-Milette, F. Lussier, I. Ciofini and G. S. Hanan, *Dalton Trans*. **2015**, *44*, 11551-11561; b) F. Kallmeier and R. Kempe, *Angew. Chem. Int. Ed.Engl*. **2018**, *57*, 46-60.

[8] a) S. Kotha, D. Kashinath and S. Kumar, *Tetrahedron Lett*. **2008**, *49*, 5419-5423; b) J. Jia, L. Zhu, Y. Wei, Z. Wu, H. Xu, D. Ding, R. Chen, D. Ma, W. Huang, *J. Mater. Chem. C*. **2015**, *3*, 4890-4902; b) H. J. Jung, S. H. Hwang, Y. K. Kim, J. O. Lim, S. H. Han, J. H. Lee, P. U.S. Pat. Appl. US 2013/0099206A1, 2013.

[9] a) R. Banerjee, N. J. Pace, D. R. Brown and E. Weerapana, *J. Am. Chem. Soc*. **2013**, *135*, 2497-2500; b) M. Shellaiah, Y. C. Rajan and H.-C. Lin, *J. Mater. Chem*. **2012**, *22*, 8976.

[10] a) J. Cervenka, A. Budi, N. Dontschuk, A. Stacey, A. Tadich, K. J. Rietwyk, A. Schenk, M. T. Edmonds, Y. Yin, N. Medhekar, M. Kalbac and C. I. Pakes, *Nanoscale*. **2015**, *7*, 1471-1478; b) N. Chakravarthi, U. K. Aryal, K. Gunasekar, H. Y. Park, Y. S. Gal, Y. R. Cho, S. I. Yoo, M. Song and S. H. Jin, *ACS Appl. Mater. Interfaces*. **2017**, *9*, 24753-24762.

[11] a) J. H. Forsberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. A. Kinsley, C. A. Duckworth, J. J. Poteruca, P. S. Brown, J. L. Miller, *J. Org. Chem*. **1987**, *52*, 1017-1021; b) F.Xu, J. Sun, Q. Shen, *Tetrahedron Lett*. **2002**, *43*, 1867-1869; c) J. f. Wang,F. Xu, T. Cai,Q. Shen, *Org.Lett*. **2008**, *10*, 445-448; d) A. Díaz-Ortiz, A. de la Hoz, A. Moreno, A. Sánchez-Migallón and G. Valiente, *Green Chem*. **2002**, *4*, 339-343.

[12] a) T. J. Hagen, X. Mo, A. B. Burgin, D. Fox, 3rd, Z. Zhang and M. E. Gurney, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 4031-4034; b) J. Y. Kim, J. W. Lee, W. S. Lee, H. H. Ha, M. Vendrell, J. T. Bork, Y. Lee and Y. T. Chang, *ACS Comb. Sci*. **2012**, *14*, 395-398; c) C. Li, X. Fan, C. Han and H. Xu, *J. Mater. Chem. C*. **2018**, *6*, 6747-6754.

[13] a) N. Li, M.-S. Tu, B. Jiang, X. Wang and S.-J. Tu, *Tetrahedron Lett*. **2013**, *54*, 1743-1746.

[14] a) L. Le Falher, O. Ben Ayad, O. Ziyaret, A. Mamontov, C. Botuha, S. Thorimbert, F. Slowinski, *J. Org. Chem*. **2014**, *79*, 6579-6589.

[15] W. Guo, M. Zhao, C. Du, L. Zheng, L. Li, L. Chen, K. Tao, W. Tan, Z. Xie, L. Cai, X. Fan, and Kai Zhang, *J. Org. Chem.* **2019**, *84*, 15508-15519.

[16] a) C. Zhang, M. T. Ban, K. Zhu, L. Y. Zhang, Z. Y. Luo, S. N. Guo, D. M. Cui and Y. Zhang, *Org. Lett.* **2017**, *19*, 3947-3949; b) M. Zeng, Z. P. Xie, D. M. Cui and C. Zhang, *Org. Biomol. Chem.* **2018**,*16*, 6140-6145; c) R.Wang, L. Wang, Q. Xu, B.-Y. Ren and F. Liang, *Org. Lett.* **2019**, *21*, 3072-3076.

[17] a) W. Guo, M. Zhao, W. Tan, L. Zheng, K. Tao and X. Fan, *Org. Chem. Front.* **2019**,*6*, 2120-2141; b) S. Biswas and S. Batra, *Eur. J. Org. Chem*. **2012**, *2012*, 3492-3499; c) K. Wang, L.M. Yang, X. Wang, L. Guo, G. Cheng, C. Zhang, S, Jin, B. Tan, *Angew. Chem. Int. Ed*. **2017**, *56*,14149-14153. d) X. Wang, Y. Xu, L. Yang, X. Lu, H. Zou, W. Yang, Y. Zhang, Z. Li and M. Ma, *J Fluoresc*. **2018**, *28*, 707-723.

[18] a) F. Xie, M. Chen, X. Wang, H. Jiang and M. Zhang, *Org. Biomol. Chem*. **2014**, *12*, 2761-2768; b) Q. You, F. Wang, C. Wu, T. Shi, D. Min, H. Chen, W. Zhang, *Org. Biomol. Chem*. **2015**, *13*, 6723-6727; c) A. R. Tiwari, A. T and B. M. Bhanage, *Org. Biomol. Chem*. **2015**, *13*, 10973-10976.

[19] a) A. R. Tiwari and B. M. Bhanage, *Green Chem.* **2016**, *18*, 144-149; b) H. Huang, W. Guo, W. Wu, C. J. Li, H. Jiang, *Org. Lett.***2015**, *17*, 2894-2897; c) Y. Yan, Z. Li, C. Cui, H. Li, M. Shi, Y. Liu, *Org. Biomol. Chem*. **2018**, *16*, 2629-2633.

[20] a) S. D. Pardeshi, P. A. Sathe, B. V. Pawar, K. S. Vadagaonkar, A. C. Chaskar,*Eur. J. Org. Chem*. **2018**, *2018*, 2098-2102; b) A. Llobera, J. M. Saa, A. Peralta,*Synthesis*. **1985**,*1*, 95-98; c) F. C. J, C. Xu, Y. W. Wang, Z. P. Chen, Y. F. Chen, A. X. Wu,*Org. Biomol. Chem*. **2018**, *16*, 4223-4226; d) Y. Yan, Z. Li, H. Li, C. Cui, M. Shi, Y. Liu, *Org. Lett*. **2017**, *19*, 6228-6231.

[21] a) Y. Huang, T. Chen, Q. Li, Y. Zhou and S. F. Yin, *Org. Biomol. Chem*.**2015**, *13*, 7289-7293; b) M. Liu, X. Chen, T. Chen, Q. Xu, S. F. Yin, *Org. Biomol. Chem*. **2017**, *15*, 9845-9854; c) L. Meng, S. Zhang, X. Jia, L. Lv and Y. Yuan, *Tetrahedron Lett*. **2019**, *60*, 1443-1447; d) P. Qian, Z. Yan, Z. Zhou, K. Hu, J. Wang, Z. Li, Z. Zha, Z. Wang, *Org. Lett*. **2018**, *20*, 6359-6363.

[22] a) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu, S. F. Yin and L. B. Han, *Org. Lett*. **2014**, *16*, 3672-3675; b) Z. Li, S. S. Wu, Z. G. Luo, W. K. Liu, C. T. Feng and S. T. Ma, *J. Org. Chem*. **2016**, *81*, 4386-4392; c) X. Pang, M. Wu, J. Ni, F. Zhang, J. Lan, B. Chen, R. Yan, *J. Org. Chem*. **2017**, *82*, 10110-10120.

[23] a) H. Huang, Q. Wang, Z. Xu and G. J. Deng, *Adv. Synth. Catal*. **2018**, *361*, 591-596; b) G. Li, H. Xie, J. Chen, Y. Guo, G. J. Deng, *Green Chem.* **2017**, *19*, 4043-4047; c) H. Xie, J. Cai, Z. Wang, H. Huang, G. J. Deng, *Org. Lett.* **2016**, *18*, 2196-2199.

[24] a) L. Yang, X. Shi, B. Q. Hu, L. X. Wang, *Asian J. Org. Chem*. **2016**, *5*,494–498; b) H. Liu, T. Zhai, S. Ding, Y. Hou, X. Zhang, L. Feng and C. Ma, *Org. Chem. Front.* **2016**, *3*, 1096-1099; c) G. S. Mani, S. P. Shaik, Y. Tangella, S. Bale, C. Godugu and A. Kamal, *Org. Biomol. Chem*. **2017**, *15*, 6780-6791; d) A. Rahim, S. P. Shaik, M. F. Baig, A. Alarifi, A. Kamal,*Org. Biomol. Chem*. **2018**, *16*, 635-644; e) P. Qian, Z. Yan, Z. Zhou, K. Hu, J. Wang, Z. Li, Z.Zhaand Z. Y. Wang, *Org. Lett.* **2018**, *20*, 6359-6363; f) W. Z. Weng, Y. H. Gao, X. Zhang, Y. H. Liu, Y. J. Shen, Y. P. Zhu, Y. Y. Sun, Q. G. Meng and A. X. Wu, *Org. Biomol. Chem*. **2019**, *17*, 2087-2091.

[25] W. Guo, *Org. Biomol. Chem*. **2015**, *13*, 10285-10289.

[26] A. R. Tiwari, S. R. Nath, K. A. Joshi and B. M. Bhanage, *J Org Chem*. **2017**, *82*, 13239-13249.

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A simple and direct approach to 1,3,5-triazines based biheteroaryls from methyl-azaarenes and amidines has been developed, providing the target products with up to 92%. The transformation is achieved via $I_2/K_2S_2O_8$ catalyzed in-situ aldehyde generation of methyl-azaarenes and cascade amination, cyclization.

*C(sp3)–H functionalization, biheteroaryls

Key Topic*

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Page 1. – Page 7.

$I_2/K_2S_2O_8$ Mediated Direct Oxidative Annulation of Alkylazaarenes with Amidines for the Synthesis of Substituted 1,3,5-triazines