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Iodine-Promoted Multicomponent Synthesis of 2,4-Diamino-1,3,5-triazines

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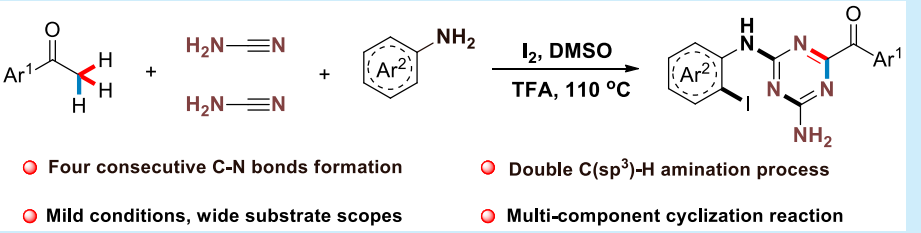
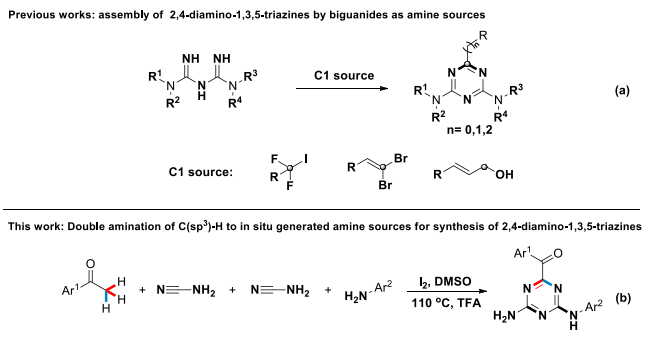


ABSTRACT: A novel and efficient multicomponent cyclization of methyl ketones, cyanamides, and arylamines for the synthesizing 2,4-diamino-1,3,5-triazines via consecutive formation of four C−N bonds is reported. This multicomponent reaction is characterized by the employment of two molecules of cyanamide for double C(sp^3)−H amination of methyl ketones, avoiding complicated prepreparation of substrates and expanding the substrate scope. Furthermore, this multicomponent cyclization strategy provides a new approach for generating diverse 2,4-diamino-1,3,5-triazines with a broad substrate scope under mild conditions.

1,3,5-Triazines and their derivatives are an important class of multi-*N*-containing heterocycles found in various pharmaceuticals and natural products.[1] In particular, 2,4-diamino-1,3,5-triazines exhibit excellent biological activities, such as antibacterial and anticancer activities.[2] Recently, several elegant methods for the formation 2,4-diamino-1,3,5-triazines have been achieved by developing novel C1 sources to expand the reaction complexity and novelty. For example, Liang and Zhang have disclosed appealing studies of the construction 2,4-diamino-1,3,5-triazines via transition-metal-catalyzed or photocatalyzed processes. Notably, perfluoroalkyl halides,[3] 1,1-dibromoalkenes,[4] and alcohols[5] have been used as unusual C1 synthons in these transformations (Scheme 1a). Despite the great progress, these methods are usually limited to using biguanides as substrates,[6] which require harsh preparation conditions and limited narrow substrate scopes. Accordingly, the development of new methods for the synthesisis 2,4-diamino-1,3,5-triazines remains an important goal.

Scheme 1. Recent Progress in the Synthesis of 2,4-Diamino-1,3,5-triazines



Recently, the synthesis of multi-*N*-containing heterocycles from nitriles and methyl ketones has received attention.[7] In 2018, the Zhou group disclosed an appealing cascade cyclization of two nitrile molecules with methyl ketones to construct pyrimidines. In this work, methyl ketones acts as nucleophiles, which attack the nitriles to realize the cascade cyclization process (Figure 1a).[8] Inspired by the involvement of nitriles in heterocyclic synthesis, we envisaged employing methyl ketones as electrophiles via iodination/Kornblum oxidation sequences, which could attack two molecule cyanamides to achieve a double C(sp^3)−H amination process.[9] Then the naked electrophilic nitrile unit can be attacked by anilines to generate guanidines *in situ*. Finally, triazines were delivered by the amination/cyclization process (Figure 1b). Herein, we first developed a novel strategy for the synthesizing the devised 2,4-diamino-1,3,5-triazines from readily available cyanamides, methyl ketones, and anilines via consecutive construction of four C−N bonds (Scheme 1b). This multicomponent cyclization strategy provides a new synthesis for generating 1,3,5-triazines.[10]

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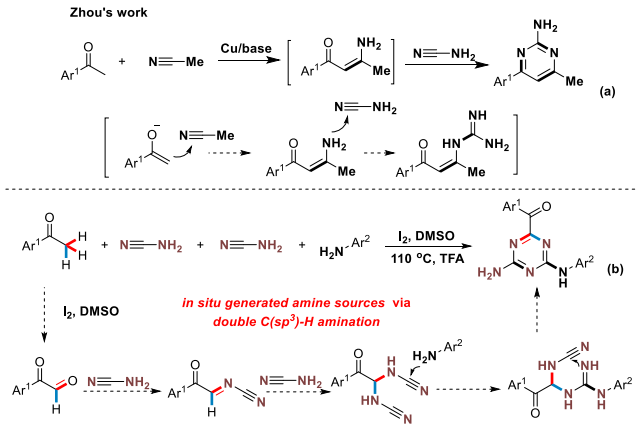
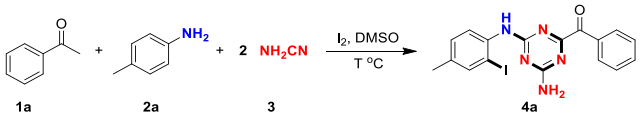


Figure 1. Use of nitriles and methyl ketones in multi-*N*-containing heterocycle synthesis.

Owing to continued interest in the synthesis of nitrogen-containing heterocycles.[11] First, cyanamide **3** was used as the amine source to react with methyl ketone **1a** and *p*-toluidine **2a** at 100 °C in the presence of DMSO and I_2. Fortunately, the corresponding 1,3,5-triazines were afforded in 48% yield (Table 1, entry 1), and X-ray crystallographic analysis showed

Table 1. Representative Optimization of the Amination Reaction[a]



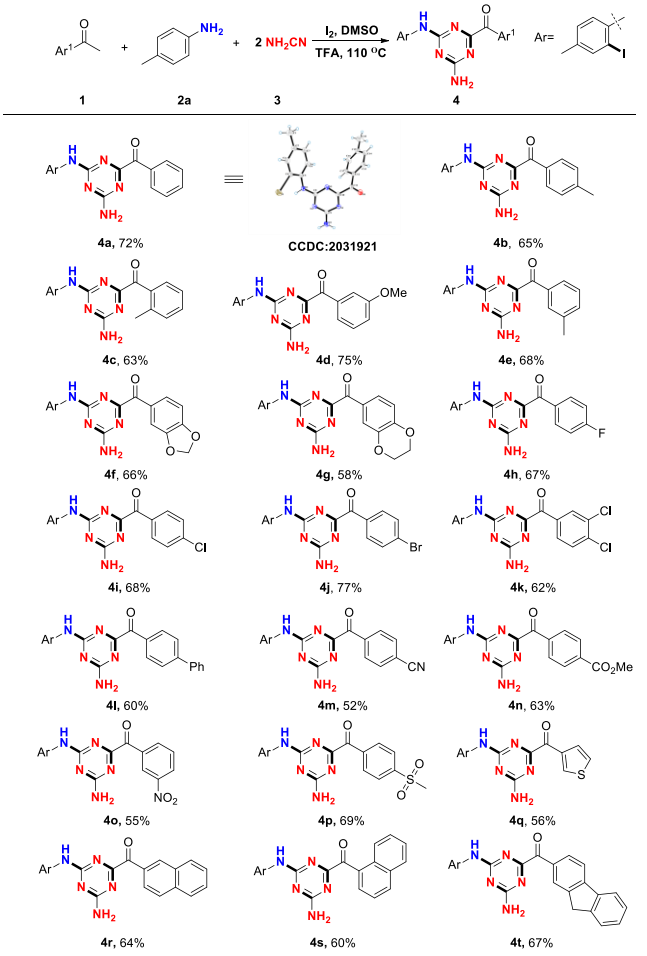
entry	I_2 (equiv)	temp (°C)	additive	yield[b] (%)
1	3.2	100		48
2	3.2	110		55
3	3.2	120		52
4	3.2	130		50
5	3.2	140		46
6	3.2	110	TFA	65
7	3.2	110	TfOH	58
8	3.2	110	$CuCl_2$	49
9	3.2	110	$FeCl_3$	42
10	3.2	110	HCl	38
11	2.0	110	TFA	72
12	1.6	110	TFA	62
13	1.0	110	TFA	22
14		110	TFA	ND

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (2.0 mmol), I_2 (equiv), additive (1.0 equiv), indicated temperature, DMSO 4 mL, 24 h, unless otherwise noted. [b]Isolated yields.

that the *ortho*-position of aniline in the triazine product was iodo substituted (for details, see the SI). Next, the effect of different reaction temperatures was investigated, with 110 °C found to give the best result (Table 1, entries 2−5). A series of acids were then screened, with the results indicating that TFA significantly improved the reaction yield (Table 1, entries 6−10). Finally, different amounts of iodine were tested, and **4a** was obtained in 72% yield when limited to 2 equiv (Table 1, entries 11−14).

With the optimized conditions in hand, the effect of different substituents on methyl ketones on this transformation was investigated (Scheme 2). Methyl ketones with electron-

Scheme 2. Scope of Aryl Methyl Ketones[a,b]



[a]1.0 mmol scale. [b]Isolated yield of products **4**.

donating (Me, OMe, 3,4-OCH_2O, 3,4-$O(CH_2)_2O$) and halogen (F, Cl, Br, 3,4-di-Cl) substituents were compatible with this multicomponent reaction under the optimized conditions, affording the corresponding triazines in good yields (**4a**−**4k**, 58−77%). Furthermore, methyl ketones with electron-deficient substituents (Ph, NO_2, CN, CO_2Me, SO_2Me) reacted smoothly, affording 1,3,5-triazines in satisfactory yields (**4l**−**4p**, 52−69%). Notably, treating 3-acetylthiophene **1q** with cyanamide and *p*-toluidineunder standard conditions, afforded corresponding product **4q** in 56% yield. Gratifyingly, sterically hindered 2-naphthyl methyl ketone **1r**, 1-naphthyl methyl ketone **1s**, and 1-(9*H*-fluoren-2-yl)ethenone **1t** substrates afforded products **4r**−**4t** in 60−67% yields.

Next, to further broaden the substrate scope of this polyamination process, a range of arylamines were investigated under the optimal conditions (Scheme 3). Arylamines with electron-rich ($C(CH_3)_3$,$CH(CH_3)_2$, CH_2CH_3, 3,4-di-Me) and halogen (F, Cl) substituents reacted well, affording **5a**−**5f** in 62−75% yields. Furthermore, halogen-substituted arylamines reacted with halogen-substituted methyl ketones under the optimal conditions, generating desired products **5g**−**5h** in 58−64% yields. Interestingly, arylamines bearing multiple halogen functional groups (2-F-4-Cl, 3,4,5-tri-Cl) afforded the corresponding uniodinated products (**5i**−**5j**, 52−56%), perhaps owing to the electron deficiency produced by multiple

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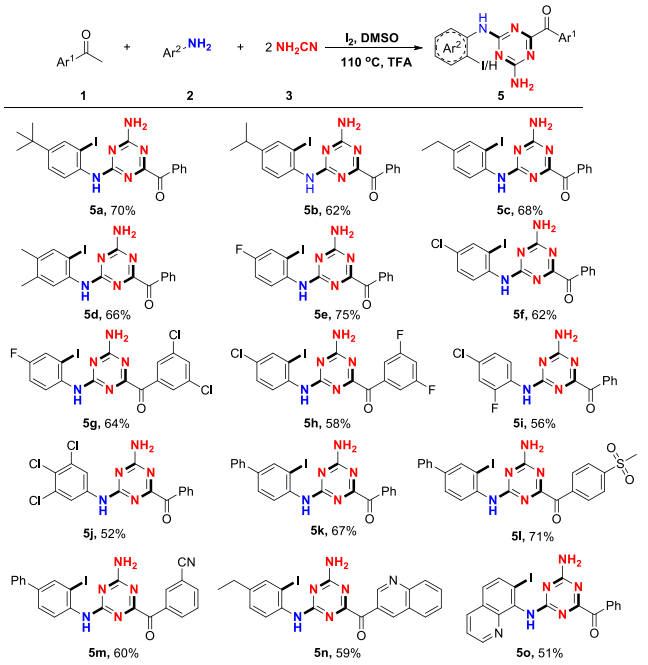
Scheme 3. Scope of Anilines[a,b]

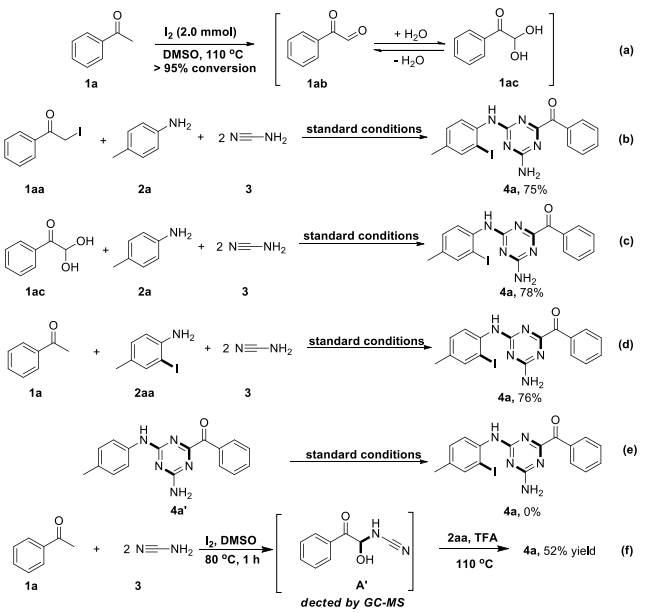


[a]1.0 mmol scale. [b]Isolated yield of products **5**.

halogen substituents reducing the nucleophilicity of the aniline *ortho*-position. Furthermore, biphenyl-4-amine reacted smoothly with methyl ketones, affording **5k**–**5m** in 60%–71% yields. Finally, elegant biheterocyclic products were also synthesized using 1-(quinolin-3-yl)ethanone and quinolin-8-amine as substrates, respectively (**5n** and **5o**, 59% and 51%, respectively).

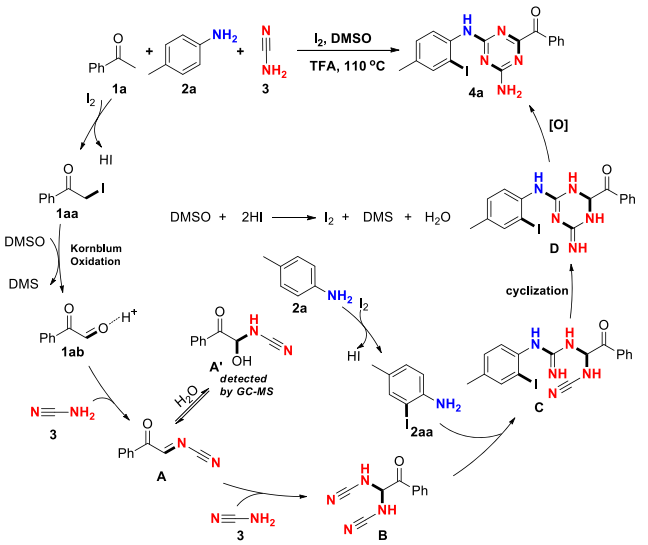
To further explore the reaction mechanism, a series of control experiments were conducted. Initially, methyl ketone **1a** produced phenylglyoxal and a hydrated species in quantitative yield under the optimal conditions (Scheme 4a). Next, α-iodoacetophenone **1aa** as substrate reacted with *p*-toluidine **2a** and cyanamide **3** under the optimal conditions to afford unsymmetrical triazine **4a** in 75% yield (Scheme 4b). Subsequently, the reaction of phenylglyoxal hydrate **1ac** with **2a** and **3** under the optimal conditions afforded diamino-1,3,5-triazine **4a** in 78% yield (Scheme 4c). These results showed that the **1aa** and **1ac** were important intermediates in the amination/cyclization reaction. Moreover, 2-iodo-4-methylaniline **2aa** as substrate reacted smoothly, affording **4a** in 76% yield (Scheme 4d). Compound **4a′** was prepared[12] and shown to be unable to transform into final product **4a** under the optimal conditions (Scheme 4e). These results indicated that the iodination process occurred at the initial reaction stage. Furthermore, 2-(4-methylphenyl)guanidine was unable to be transformed into **4a**, excluding the possibility of in situ generation of guanidine by aniline and cyanamide (for details, see SI). Finally, **1a** was reacted with **3** and iodine at 80 °C for 1 h, affordingintermediate **A′** (detected by GC–MS), which was converted into **4a** by adding **2aa** and TFA at 110 °C (Scheme 4f).

Scheme 4. Control Experiment



Based on the above experimental results and previous work,[13] we have proposed a plausible mechanism for multicomponent reaction (Scheme 5). Acetophenone **1a** undergoes iodination to produce α-iodoacetophenone **1aa**, which further transforms into phenylglyoxal **1ab** via Kornblum oxidation. Phenylglyoxal **1ab** activated by acid can undergo continuous reaction with two molecules of cyanamide to form intermediate **B** via the construction of two C–N bonds. Simultaneously, the aniline *ortho*-position is iodinated, generating *o*-iodoaniline **2aa**, which can undergo nucleophilic attack on intermediate **B** to deliver intermediate **C**. Finally, intermediate **C** undergoes a cyclization sequence to afford intermediate **D**, which further transforms into desired product **4a** via an oxidative aromatization process.

Scheme 5. Proposed Mechanism



In summary, a new and efficient multicomponent amination/cascade cyclization strategy to prepare trisubstituted 1,3,5-triazines has been developed. In this transformation, amine sources are generated in situ from cyanamides to construct 1,3,5-triazines, combining with methyl ketones and aryl amines to expand the substrate scopes. Furthermore, this multicomponent cyclization strategy proceeds via a novel pathway, in which cyanamides are employed as nucleophiles

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and electrophiles in the consecutive formation of four C−N bonds, which avoids complicated substrate prepreparation. Further research on the construction of other nitrogen heterocycles using this multicomponent amination/cascade cyclization strategy is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03130.

Experimental procedures, product characterization, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2031921 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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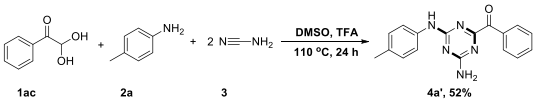
(12) **4a′** was obtained in absence of iodine.



(13) (a) Xue, W. J.; Guo, Y. Q.; Gao, F. F.; Li, H. Z.; Wu, A. X. A Novel Self-Sequence Reaction Network Involving a Set of Six Reactions in One Pot: The Synthesis of Substituted Benzothiazoles from Aromatic Ketones and Anilines. *Org. Lett.* **2013**, *15*, 890−893. (b) Wu, X.; Gao, Q.; Geng, X.; Zhang, J.; Wu, Y. D.; Wu, A. X. Iodine-Promoted Oxidative Cross-Coupling of Unprotected Anilines with Methyl Ketones: A Site-Selective Direct C-H Bond Functionalization to C4-Dicarbonylation of Anilines. *Org. Lett.* **2016**, *18*, 2507−2510.

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