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A Novel Straightforward Synthesis of 2,4-Disubstituted-1,3,5-triazines via Aerobic Copper-Catalyzed Cyclization of Amidines with DMF

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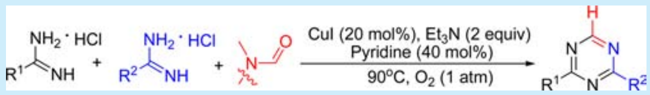
Supporting Information

ABSTRACT: A novel straightforward synthesis of both symmetrical and unsymmetrical 2,4-disubstituted-1,3,5-triazines via aerobic copper-catalyzed cyclization of amidines with DMF as a one-carbon synthon has been developed. The presented method allows synthesizing the products that are currently inaccessible or challenging to prepare with the advantages of operational simplicity, broad substrate scope, and no need for prefunctionalized reagents, making it a highly practical approach to access various 2,4-disubstituted-1,3,5-triazines.

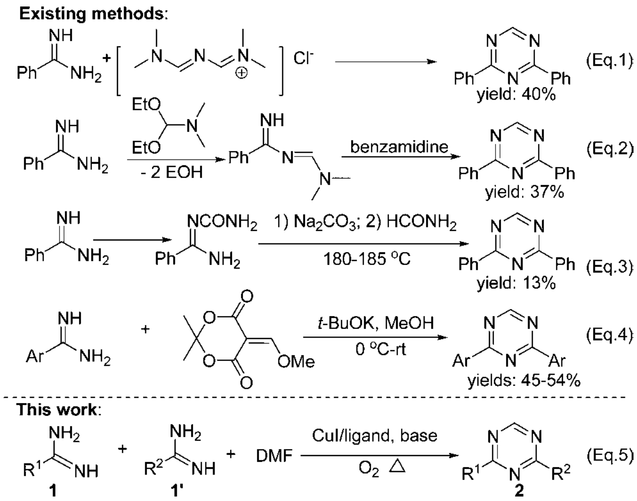


Aryl-substituted 1,3,5-triazines constitute a significant important class of nitrogen-containing heterocycles that exhibit diverse biological activities.[1] In addition, these compounds could serve as chelating ligands for the preparation of organometallic materials,[2] liquid crystals,[3] and transition-metal catalysts.[4] Despite their multiple functions, there are only a few methods reported for the synthesis of this type of compound. During the past decades, much attention has been focused on developing alternative methods to access symmetrical 2,4,6-triaryl-1,3,5-triazines.[5−7] Nevertheless, the synthesis of 2,4-disubstituted-1,3,5-triazines still remains now as before a challenging goal. Conventionally, such a goal can be realized by the cyclization reactions of aryl amidines with special prefunctionalized formylating reagents such as diimino salt,[8a] *N*-[(dimethylamino)methylene]benzamidine,[8b] *N*-carbamoyl benzamidine,[8c] and α-methoxymethylene Meldrum's acid[8d] (Scheme 1, eqs 1−4). However, these methods suffer either harsh reaction conditions such as high temperature (180−185 °C) or low product yields and limited substrate scope that is restricted to the synthesis of only symmetrical 2,4-diaryl-1,3,5-triazines. Moreover, the prefunctionalization steps could constantly increase the complexity of the workup procedure and result in a detrimental influence on the environment. Hence, the development of efficient methods for direct synthesis of 2,4-disubstituted-1,3,5-triazines from easily available feedstock is of significant importance.

Herein, we wish to report a novel straightforward synthesis of both symmetrical and unsymmetrical 2,4-disubstituted-1,3,5-triazines via aerobic copper-catalyzed cyclization of amidines with DMF, a one-carbon supplier (Scheme 1, eq 5).

Actually, our initial intention was to develop a dehydrogenative synthesis of imidazoles from amidines with abundant and sustainable alcohols[9] using a cost-effective copper catalyst.[10] Thus, the reaction of benzamidine hydrochloride **1a** with ethylene glycol in *N*,*N*-dimethylformamide (DMF) was

Scheme 1. Methods Accessing 2,4-Disubstituted-1,3,5-triazines



performed at 90 °C for 14 h by using Cs_2CO_3 as the base, CuI/pyridine (L1) as the catalyst system, and O_2 as the oxidant. Unexpectedly, we observed, instead of the anticipated imidazole product, the 2,4-diphenyl-1,3,5-triazine **2a** in 18% yield (Table 1, entry 1). Interestingly, the reaction in absence of ethylene glycol gave a higher product yield (standard conditions: Table 1, entry 2). However, replacing DMF with ethylene glycol as the reaction solvent failed to yield even a trace of **2a** (Table 1, entry 3), indicating DMF is an essential component while ethylene glycol was not involved in the formation of **2a** and the C−H unit at position-6 of **2a** might come from DMF. Then,

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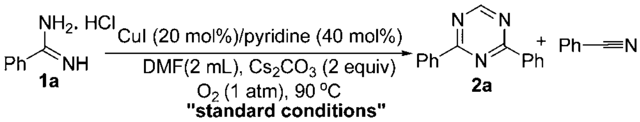
Table 1. Screening of Optimized Reaction Conditions[a]



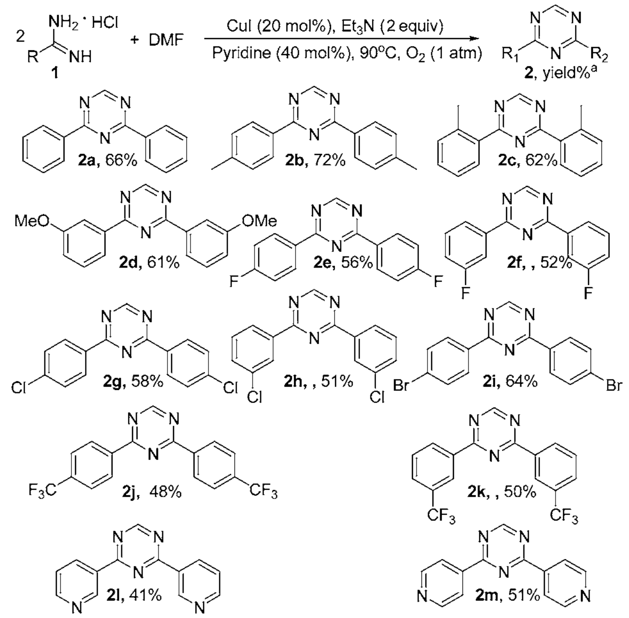
entry	change of the initial conditions	2a, yield[b] (%)
1	addition of 1 equiv of ethylene glycol	18
2	standard conditions	43
3	ethylene glycol instead of DMF	
4	DMSO instead of DMF	19
5	DMA instead of DMF	15
6	no CuI	
7	N_2 instead of O_2	
8	without L1 (pyridine)	29
9[c]	L2 or L3 or L4 or L5 or L6	<40
10	15 mol % instead of 20 mol % CuI	36
11	25 mol % instead of 20 mol % CuI	41
12	K_3PO_4 or K_2CO_3 or DABCO instead of Cs_2CO_3	<20
13	NEt_3 (2 equiv) instead of Cs_2CO_3	85
14	NEt_3 (3 equiv) instead of Cs_2CO_3	85
15	NEt_3 (2 equiv), 100 °C instead of Cs_2CO_3, 90 °C	68
16	NEt_3 (2 equiv), 80 °C instead of Cs_2CO_3, 90 °C	65
17	CuBr or CuCl or $Cu(OAc)_2$ or $CuCl_2$ with NEt_3	<15

[a]Reaction conditions: Unless otherwise stated, the reaction of amidine hydrochloride **1a** (1 mmol), catalyst (20 mol %), base (2 mmol), solvent (2.0 mL), pyridine ligand (40 mol %) was performed at 90 °C under 1 atm O_2 atmosphere for 14 h. [b]NMR yield using mesitylene as an internal standard. DMSO: dimethyl sulfoxide; DMA: *N,N*-dimethylacetamide. [c]Bidentate nitrogen ligand: 20 mol %.

when representative one-carbon suppliers[11a−d] (DMSO, DMA) were tested, product **2a** could also be detected but in relatively lower yields (Table 1, see entries 4 and 5). Further, it was shown that the copper catalyst, O_2, and pyridine ligand (L1) were essential in the formation of **2a** (Table 1, entries 6−8).[11e] Among various nitrogen ligands tested (see Supporting Information, Scheme S1), pyridine (L1) was the most effective one (Table 1, entries 2 and 9), and a decrease or increase of catalyst loading would decrease the product yields (Table 1, entries 10 and 11). Furthermore, we examined several inorganic and organic bases (Table 1, entries 12 and 13), and the use of NEt_3 led to exclusive formation of **2a** in 85% yield. However, an increase NEt_3 amount failed to improve the product yield (Table 1, entry 14). Finally, we chose NEt_3 and DMF as the preferred base and solvent, respectively. Both increase and decrease of reaction temperatures resulted in decreased product yields (Table 1, entries 15 and 16), and other copper catalysts were proven to be inferior to CuI (Table 1, entry 17). Thus, the optimal reaction conditions can be as indicated in entry 13 of Table 1.

With the optimized reaction conditions in hand, we then examined the generality and the limitations of the synthetic protocol. First, we focused on the synthesis of symmetrical 2,4-diaryl-1,3,5-triazines by testing a variety of aryl amidines **1** (see Supporting Information, Scheme S2). As shown in Scheme 2, all of the reactions proceeded smoothly and furnished the desired products in moderate to good yields upon isolation. It was found that electron-donating groups (i.e., -Me, -OMe) containing amidines afforded the products in higher yields (Scheme 2, **2b**−**2d**) than the electron-deficient ones (i.e., -F and -CF_3) (Scheme 2, **2e**−**2k**). By means of GC and GC−MS analyses, this phenomenon can be rationalized as the amidines

Scheme 2. Synthesis of Symmetrical 2,4-Diaryl-1,3,5-triazines



[a]Isolated yield.

bearing electron-withdrawing groups being able to more easily undergo the deammoniation reaction, leading to partial formation of benzonitriles. Gratifyingly, nicotinamidine **1l** and isonicotinamidine **1m** could also be transformed in combination with DMF into the 2,4-dipyridyl products (Scheme 2, **2l**, **2m**). These examples demonstrate the potential of the methodology for further construction of various 2,4-diheteroaryl products. However, the homocoupling of acetamidine **1n** failed to give even trace of desired product. It is conceivable that the alkyl amidines disfavor the formation of essential intermediates owing to lack of aryl stabilizing groups. Noteworthy, all of the obtained products possess a nonsubstituted C−H unit at position 6, providing the potential for further elaboration of complex molecules via direct C−H bond functionalization.[12] Moreover, owing to the aryl groups are *ortho* to the nitrogen atom of the 1,3,5-triazine, they could serve as C^N or C^N^C ligands for the preparation of organometallic materials[13] and especially pincer complexes.[14]

Subsequently, we turned our attention to synthesize unsymmetrical 2,4-disubstituted-1,3,5-triazines with the synthetic protocol. By employing different combinations of aryl amidines (for the reactant molar amount, see Supporting Information, Table S1), all of the cross-coupling reactions underwent efficient cyclization to afford the desired products in moderate to good yields. Similar to the results described in Scheme 2, the electron-rich amidines gave the products in relatively higher yields (Scheme 3, **2n** and **2o**) than the electron-poor ones (Scheme 3, see **2p**−**2t**). Interestingly, the reactions of 1 equiv of aryl amidines with 4 equiv of acetamidine **1n** could also be transformed into the desired 2-aryl-4-alkyl-triazine products in reasonable yields (Scheme 3, see **2u** and **2v**). Hence, the examples presented herein have demonstrated the first straightforward synthesis of unsymmetrical 2,4-disubstituted-1,3,5-triazines, offering an important basis for the further elaboration of various C^N or C^N^C types of organometallic complexes or materials.[13,14]

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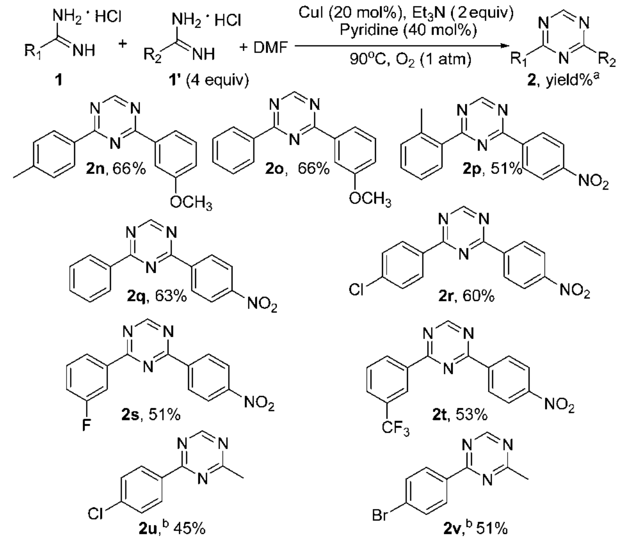
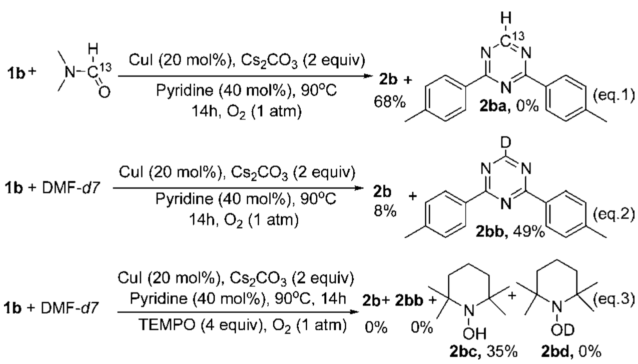
Scheme 3. Synthesis of Unsymmetrical 2,4-Diaryl-1,3,5-triazines and 2-Aryl-4-alkyl-1,3,5-triazines



[a]Isolated yield. [b]Reaction time: 24 h.

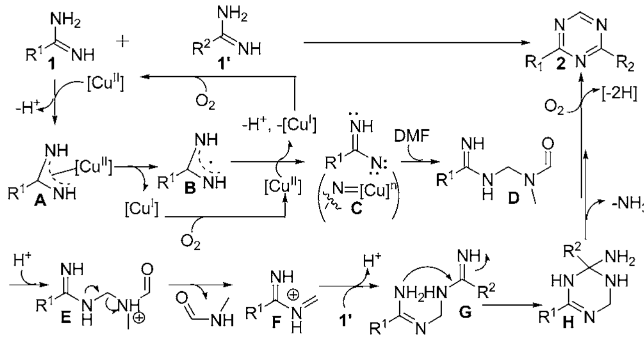
In order to determine how the C−H unit at position-6 of the obtained products is provided (for detailed information, see Supporting Information, Scheme S3), the reaction of **1b** with carbonyl ^{13}C-labeled DMF did not afford ^{13}C-labeled product **2ba** (Scheme 4, eq 1). Further, the reaction with DMF-d_7 gave both deuterated and nondeuterated products (**2b**, **2bb**) with a comparable D/H ratio (49:8) (Scheme 4, eq 2). These results strongly support the methyl group of DMF serve as the C−H supplier. The formation of product **2b** (^{1}H NMR: δ 9.12 ppm) is the result of base-induced partial H/D exchange of **2bb**, suggesting H^+ is produced during the catalytic process. However, the formation of **2b** and **2bb** were totally suppressed upon addition of 4 equiv of radical scavenger (TEMPO), and product **2bc** via TEMPO-trapped hydrogen radical was observed exclusively in 35% yield (Scheme 4, eq 3), which is 1.4 equiv of **1b**, implying the reaction undergoes a dual single-electron oxidation process on amidine **1b**, and an iminium cation intermediate derived from oxidation of DMF is less favored.[15]

Scheme 4. Verification Experiments



Based on our experimental results and some related research,[16] a possible reaction pathway is depicted in Scheme 5. Initially, highly reactive nitrene intermediate **C** (copper nitrene complex) is generated via a sequential dual single-electron oxidation of amidine (Scheme 5, from **1** to **C**), which then proceeds by direct insertion into the C(sp^3)-H bond of DMF to afford intermediate **D**.[17,18] The N-protonation of **D** would facilitate the C−N bond cleavage of the diaminomethyl moiety of **E** and produce an iminium cation **F** by eliminating one molecule of *N*-methyl formamide. The electrophilic addition of **F** to amidine **1′** and subsequent tautomerization give intermediate **G**. Then, intramolecular nucleophilic addition of amino group to the imino center of **G** would generate aminals **H**. Finally, the thermodynamic favorable deammoniation of **H** and O_2-promoted dehydrogenative aromatization steps would afford desired product **2**.

Scheme 5. Possible Pathway for the Formation of Product 2



In summary, we have developed a novel straightforward synthesis of 2,4-disubstituted-1,3,5-triazines from easily available amidines with DMF as a one-carbon supplier. By employing a CuI/pyridine catalyst system and molecular O_2, both symmetrical 2,4-diaryl- and unsymmetrical 2,4-diaryl, 2-aryl-4-alkyl products could be furnished efficiently. The presented method allows synthesizing the products that are currently inaccessible or challenging to prepare with the advantages of operational simplicity, broad substrate scope, and no need for prefunctionalized reagents, making it a highly practical approach for the synthesis of various 2,4-disubstituted-1,3,5-triazines. On the basis of the importance of 2,4-disubstituted-1,3,5-triazines in biological, material, and coordination chemistry, the presented method has the potential to be frequently employed for various applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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