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Graphical Abstract

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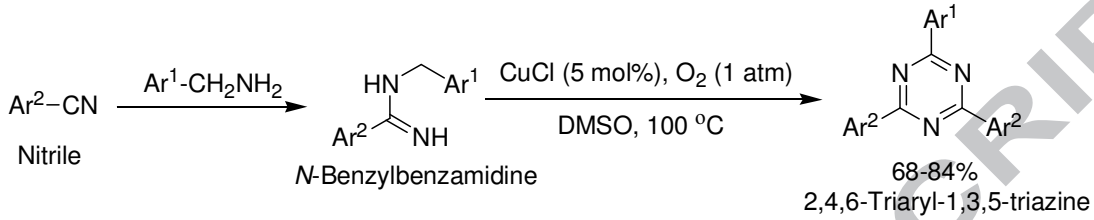

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Abstract: A novel, straightforward method for the synthesis of 2,4,6-triaryl-1,3,5-triazines *via* copper-catalyzed cyclization of *N*-benzylbenzamidines in DMSO has been developed. Compared to other methods, the present protocol has a number of advantages such as- cost-effectiveness, avoidance of aldehydes or alcohols as reaction partners and easy accessibility of starting materials, making it a highly practical approach to access various 2,4,6-triaryl-1,3,5-triazines.

Keywords: Symmetrical and unsymmetrical triazines, benzamidines, copper-catalyst, DMSO.

Introduction:

Aryl-substituted 1,3,5-triazines are a remarkably important class of nitrogen containing heterocycles in the pharmacological area because of their broad range of biological activities.[1] In addition, these compounds serve as chelating ligands for the preparation of organometallic materials,[2] liquid crystals,[3] and transition-metal catalysts.[4] Despite extensive functions, only a few methods are reported for the preparation of this class of compounds. Conventionally, such a goal can be realized by cyclotrimerization of nitriles catalyzed by acids, bases or Lewis acids.[5] However, these methods suffer either harsh reaction conditions such as high temperature, high pressure or low product yields and limited substrate scope that is restricted to the synthesis of only symmetrical 2,4,6-trisubstituted-1,3,5-triazines. Moreover, the cyclotrimerization of nitriles generally needs excess of amines as the co-catalyst which could increase the complexity of work-up procedure. Very recently, Martinez-Alvarez *et al*. described a modified, one-pot synthetic protocol for the

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preparation of 2,4,6-trisubstituted-1,3,5-triazine derivatives *via* controlled cross-cyclotrimerization of nitriles using equimolecular amount of triflic anhydride.[6] Alternative approaches to the synthesis of 2,4,6-trisubstituted-1,3,5-triazine derivatives based on the Suzuki-coupling reactions between halogenated 1,3,5-triazines and aryl boronic acids were developed.[7] Main disadvantage of these approaches is the use of less-environmentally benign halogenated substrates which could produce stoichiometric amounts of undesirable waste and result in a detrimental influence on the environment. Recently, the condensation of aromatic aldehydes with amidines has provided a direct pathway for the synthesis of symmetrical as well as unsymmetrical aryl substituted 1,3,5-triazine derivatives.[8] However, the use of aldehydes as the coupling partners could frequently meet some problems[9] such as- (i) active aldehyde groups may suffer from an oxidation reaction leading to the formation of undesirable by-products; (ii) aldehydes could undergo a decarbonylation reaction under harsh reaction conditions resulting in lower yields of the products; (iii) cost of some aldehydes are high or not readily available. The method, therefore, does not offer unrestricted scope for the synthesis of products with wide variation. Recently, Zhang *et al.*[8a] have applied amidines and primary alcohols as *latent* aldehydes for the synthesis of aryl substituted 1,3,5-triazines by using costly $[RuCl_2(p\text{-Cymene})]_2$ as dehydrogenative catalyst. Although this protocol is effective under relatively mild conditions, high cost of catalyst as well as the use of alcohols as reaction partners are the main disadvantages of this protocol. Hence, search for easily available, inexpensive substrate as well as catalyst would provide a new avenue for direct synthesis of 2,4,6-trisubstituted-1,3,5-triazines and is of high importance.

Scheme 1

Recently, direct oxidation of amines to imines has attracted much attention. By employing suitable catalyst systems, the dehydrogenation of the amines leading to *in situ* formation of methanimine is recognized as the key point for the formation of desired imines. In this context, Adimurthy *et al.*[10a] and Kerton *et al.*[10b] have independently developed copper-based catalytic systems for the direct oxidation of primary and secondary benzylamines to imines. Taking cue from

the aforesaid elegant contributions, it is reasonable to expect that the copper-catalyst could also be applied to the oxidation of benzylic position of *N*-benzylamidines to azadines A (Scheme 1) which on dehydrogenative cyclization with another molecule of amidine would provide 1,3,5-triazines. To our delight, it was found that copper catalysts function well in this context. The present protocol offers a variety of advantages such as - cost-effectiveness, avoids aldehydes or alcohols as reaction partner and easy accessibility of the starting materials.[11] The aforesaid thought led us to undertake a study to explore the synthesis of both symmetrical and unsymmetrical 2,4,6-triaryl-1,3,5-triazines from *N*-benzylbenzamidines. To the best of our knowledge, such a synthetic protocol has not yet been reported.

The possibility of a direct synthesis of 2,4,6-triaryl-1,3,5-triazine has been examined by using commercially available Cu-salts as catalyst. *N*-Benzylbenzamidine (**1a**) was selected as a model substrate. The reactions were carried out at 100 ^{o}C for 15 h using 5 mol % of Cu-salt in DMSO solvent. As indicated in Table 1, among different copper sources examined, Cu^{I} salts were found better than Cu^{II} salts and CuCl was found to be the best catalyst giving product **2a** in 78 % yield (Table 1, entries 1-8). Screening of various solvents in the presence of CuCl as catalyst indicated that polar solvents (DMF, HFIP) and less polar THF or non-polar toluene as solvents are less effective than DMSO (Table 1, entries 9-12). Both decrease and increase of the reaction temperatures resulted in the formation of products in lower yields (Table 1, entries 13 and 14). Moreover, no reduction of reaction time was observed even when the catalyst loading was increased to 10 mol% (Table 1, entry 15). By using the optimized catalyst and solvent, it was found that the rate of reaction was sluggish in open air, and the reaction required 36 h to reach completion as compared to 15 h in the presence of O_2 (1 atm) (Table 1, entry 16). No reaction occurred without copper catalyst (Table 1, entry 17). Hence, the optimized conditions[12] are summarised as follows: 5 mol% of CuCl catalyst, DMSO as the reaction solvent, O_2 (1 atm) and 100 ^{o}C temperature (Table 1, entry 2).

Table 1

With the optimized conditions in hand, the substrate scope of this copper-catalyzed synthetic protocol was examined. First, the compatibility with substituents in the phenyl ring of the benzamidines was investigated (Table 2, entries 2-6). The reaction has also smoothly proceeded with the substrates bearing the substituents in the phenyl ring of *N*-benzyl moiety of the *N*-benzylbenzamidines (Table 2, entries 7-10). Both the electron withdrawing (F, Cl, Br, CF_3) (Table 2, entries 2-5) and electron donating (OMe, Me) (Table 2, entries 6-10) substituents are well tolerated. It was observed that the amidines containing electron-donating groups (OMe, Me) afforded the products in higher yields (Table 2, entries 6-10) than those containing the electron-withdrawing ones (F, Cl, Br, CF_3) (Table 2, entries 2-5). The phenomenon may be explained by assuming that oxidative addition of copper to amidine nitrogen may occur more easily when a more basic amidine (electron-donating) is used (Scheme 2). In the overall process two molecules of *N*-benzylamidine are involved for the formation desired triazines with the release of one molecule of *N*-benzyl amines. Thus the products are comprised of two units of Ar^2 and only one Ar^1. It is also noteworthy that halogen substituted *N*-benzylbenzamidines performed well, leading to halo-substituted 2,4,6-triaryl-1,3,5-triazines which may be used for further transformation to liquid crystalline materials.[7d,13] An attempt to synthesize heteroaryltriazines, a representative reaction of heteroarylamidine (**1k**) using this protocol furnished heteroaryl substituted 1,3,5-dihydrotriazine (**2k**) instead of substituted 1,3,5-triazine.

Table 2

On the basis of copper-catalyzed formation of imines[10] from benzylamines as well as the conventional 1,3,5-triazine synthesis, a plausible pathway for the formation of 2,4,6-triaryl-1,3,5-triazines from *N*-benzylamidines is depicted in Scheme 2. The reaction is initiated by oxidative action of copper catalyst at the benzylic position of *N*-benzylbenzamidine to form azadiene **A**. The subsequent inter- and intra-molecular nucleophilic addition of the amino group to the electrophilic carbon centre may generate the intermediate **B** and racemic aminals **C**. Then, thermodynamically

favourable deamination may release dihydrotriazine **D** and *N*-benzyl amine. Finally, the desired product **2** is formed *via* dehydrogenative aromatization of **D** which is promoted either by copper catalyst or oxygen (oxidation).

Scheme 2

In summary, a new efficient method for the synthesis of 2,4,6-triaryl-1,3,5-triazines from *N*-benzylbenzamidines using easily available CuCl as catalyst has been developed. This is the first report of using readily accessible *N*-benzylbenzamidines as a single component starting material for the synthesis of 2,4,6-triaryl-1,3,5-triazines. The cyclization process proceeds efficiently and furnishes the products in good to excellent yields. This protocol does not require aldehydes or alcohols as reaction partners. Hence, compared to conventional synthetic methodologies, it is a significantly improved protocol with advantages such as- operational simplicity, cost-effectiveness and easy accessibility of the starting materials. On the basis of importance of 2,4,6-triaryl-1,3,5-triazines in biological, material, and coordination chemistry, this protocol has the potential for applications.

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12. Typical procedure for the synthesis of 2,4,6-triphenyl-1,3,5-triazine (**2a**): An oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar was charged with *N*-benzylbenzamidine (105 mg, 0.5 mmol) and CuCl (2.47 mg, 5 mol%, 0.025 mmol). The vessel was flushed with O_2 and then sealed with septum. Dry DMSO (1 mL) was added to the reaction vial using a syringe. The reaction mixture was heated at 100 ^{o}C and stirred for 15 h. The reaction mixture was allowed to reach room temperature and then poured into water (10 mL). This was extracted with dichloromethane (20 mL). The aqueous layer was further extracted with dichloromethane (2 x 10 mL). The combined organic extracts was washed with water (2 x 10 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum. The residue was directly purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate-petroleum ether mixture (1:19) as eluent to give 2,4,6-triphenyl-1,3,5-triazine **2a** as white solid (0.06 g, 78%).

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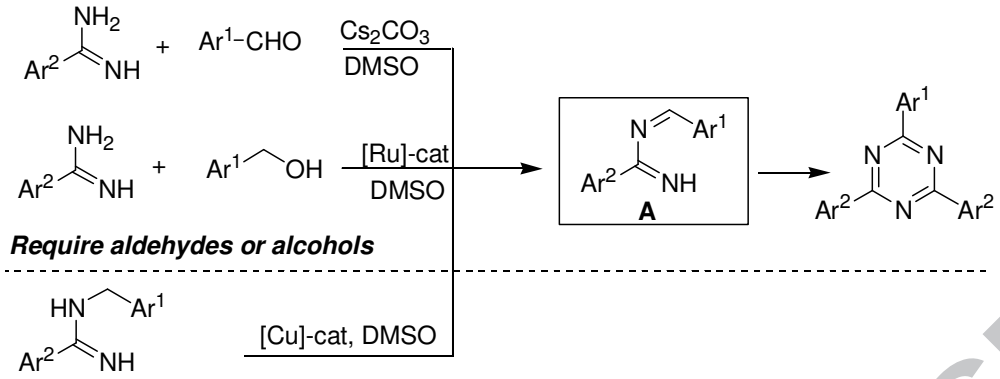
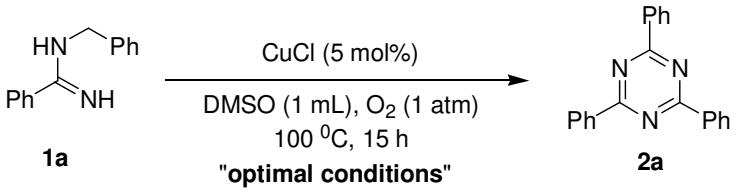
Previous methods:



This method does not require aldehydes or alcohols

Scheme 1. Methods accessing 2,4,6-triaryl-1,3,5-triazines from amidines.

Table 1. Optimization of the conditions for the copper-catalyzed cyclization of *N*-benzylbenzamidine **1**.[a]



1a **2a**

Entry	Catalyst (mol%)	Solvent (1 mL)	Yield (%)[b]
1	CuI (5)	DMSO	52
2	**CuCl (5)**	**DMSO**	**78**
3	CuBr (5)	DMSO	47
4	$CuCl_2$ (5)	DMSO	37
5	$CuBr_2$ (5)	DMSO	40
6	$Cu(OAc)_2$ (5)	DMSO	15
7	CuO (5)	DMSO	20
8	$CuSO_4.5H_2O$ (5)	DMSO	trace
9	CuCl (5)	DMF	55
10	CuCl (5)	HFIP	0
11	CuCl (5)	THF	16
12	CuCl (5)	toluene	trace
13[c]	CuCl (5)	DMSO	55
14[c]	CuCl (5)	DMSO	67
15	CuCl (10)	DMSO	77
16[d]	CuCl (5)	DMSO	57
17	—	DMSO	0

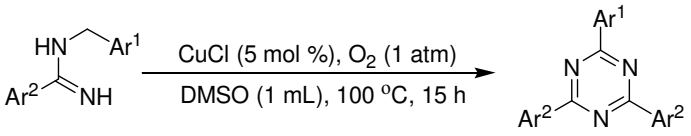
[a] Reaction conditions: **1a** (0.5 mmol), catalyst, O_2 (1 atm), 100 ^{o}C, 15 h.

[b] Isolated yield of **2a**.

[c] Reaction carried out at 90 ^{o}C (entry 13) and at 110 ^{o}C (entry 14).

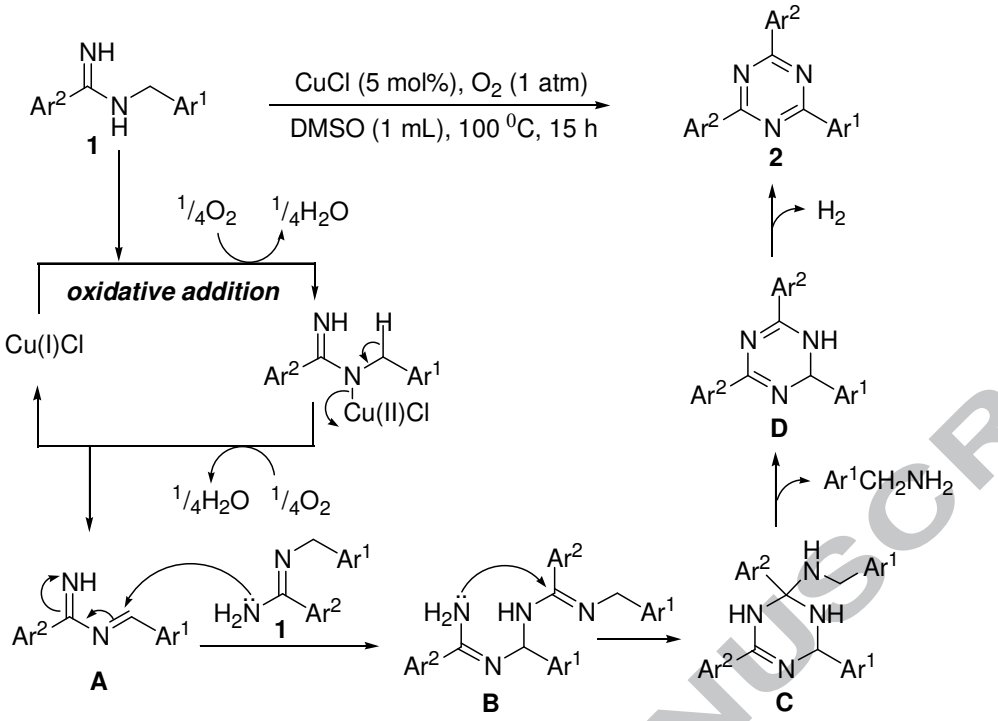
[d] Reaction performed under an open air atmosphere, reaction completed in 36 h (entry 16).

Table 2. Synthesis of 2,4,6-triaryl-1,3,5-triazines from *N*-benzylbenzamidines.[a]



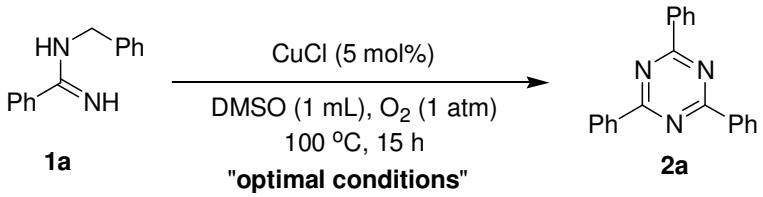
Entry	Substrate **1**	Product **2**	Yield[b] (%)
1	**1a**: Ar^1 = -C_6H_5, Ar^2 = -C_6H_5	**2a**	78
2	**1b**: Ar^1 = -C_6H_5, Ar^2 = 4-Br-C_6H_4	**2b**	76
3	**1c**: Ar^1 = -C_6H_5, Ar^2 = 4-Cl-C_6H_4	**2c**	75
4	**1d**: Ar^1 = -C_6H_5, Ar^2 = 4-F-C_6H_4	**2d**	71
5	**1e**: Ar^1 = -C_6H_5, Ar^2 = 3-CF_3-C_6H_4	**2e**	68
6	**1f**: Ar^1 = -C_6H_5, Ar^2 = 4-OMe-C_6H_4	**2f**	84
7	**1g**: Ar^1 = 4-OMe-C_6H_4, Ar^2 = -C_6H_5	**2g**	80
8	**1h**: Ar^1 = 3,4-di-OMe-C_6H_3, Ar^2 = -C_6H_5	**2h**	82
9	**1i**: Ar^1 = 2,4,6-tri-OMe-C_6H_2, Ar^2 = -C_6H_5	**2i**	84
10	**1j**: Ar^1 = 4-Me-C_6H_4, Ar^2 = -C_6H_5	**2j**	79
11	**1k**: Ar^1 = -C_6H_5, Ar^2 = 	**2k**	68[c]

[a] Reaction conditions: Substrate (0.5 mmol) , CuCl (5 mol%), DMSO (1 mL), 100 °C, O_2 (1 atm), 15 h.
[b] Yield of the isolated product.
[c] Yield of 1,3,5-dihydrotriazine.



Scheme 2. Proposed mechanism for the formation of 2,4,6-triaryl-1,3,5-triazines from *N*-benzylbenzamidines.

Table 1. Optimization of the conditions for the copper-catalyzed cyclization of *N*-benzylbenzamidine **1**.[a]



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9	CuCl (5)	DMF	55
10	CuCl (5)	HFIP	0
11	CuCl (5)	THF	16
12	CuCl (5)	toluene	trace
13[c]	CuCl (5)	DMSO	55
14[c]	CuCl (5)	DMSO	67
15	CuCl (10)	DMSO	77
16[d]	CuCl (5)	DMSO	57
17	-	DMSO	0

[a] Reaction conditions: **1a** (0.5 mmol), catalyst, O_2 (1 atm), 100 °C, 15 h.

[b] Isolated yield of **2a**.
[c] Reaction carried out at 90 ^{o}C (entry 13) and at 110 ^{o}C (entry 14).
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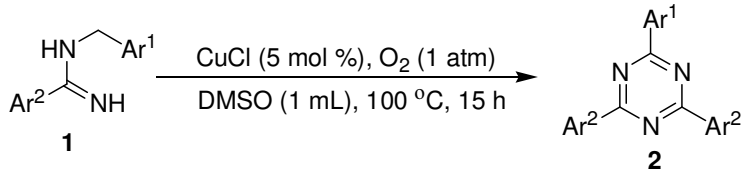

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2	**1b**: Ar^1 = -C_6H_5, Ar^2 = 4-Br-C_6H_4	**2b**	76
3	**1c**: Ar^1 = -C_6H_5, Ar^2 = 4-Cl-C_6H_4	**2c**	75
4	**1d**: Ar^1 = -C_6H_5, Ar^2 = 4-F-C_6H_4	**2d**	71
5	**1e**: Ar^1 =-C_6H_5, Ar^2 = 3-CF_3-C_6H_4	**2e**	68
6	**1f**: Ar^1 =-C_6H_5, Ar^2 = 4-OMe-C_6H_4	**2f**	84
7	**1g**: Ar^1 = 4-OMe-C_6H_4, Ar^2 = -C_6H_5	**2g**	80
8	**1h**: Ar^1 = 3,4-di-OMe-C_6H_3, Ar^2 = -C_6H_5	**2h**	82
9	**1i**: Ar^1 = 2,4,6-tri-OMe-C_6H_2, Ar^2 =-C_6H_5	**2i**	84
10	**1j**: Ar^1 = 4-Me-C_6H_4, Ar^2 = -C_6H_5	**2j**	79
11	**1k**: Ar^1 = -C_6H_5, Ar^2 = thiophen-3-yl	**2k**	68[c]

[a] Reaction conditions: Substrate (0.5 mmol) , CuCl (5 mol%), DMSO (1 mL), 100 °C, O_2 (1 atm), 15 h.
[b] Yield of the isolated product.
[c] Yield of 1,3,5-dihydrotriazine.