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# Direct oxidative coupling of amidine hydrochlorides and methylarenes: TBHP-mediated synthesis of substituted 1,3,5-triazines under metal-free conditions†

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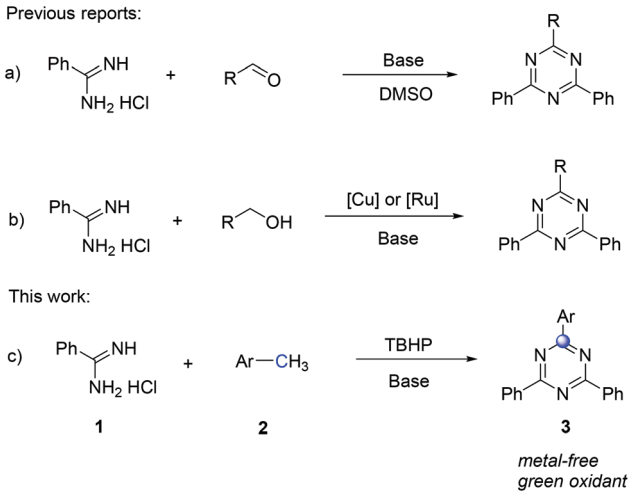
**Various 2,4,6-trisubstituted 1,3,5-triazines were smoothly formed *via* TBHP-mediated direct oxidative coupling of amidine and methylarenes. This tandem oxidation–imination–cyclization transformation exhibits a straightforward protocol to prepare 1,3,5-triazines from easily available starting materials and green oxidants under metal-free conditions.**

## Introduction

1,3,5-Triazines are very important scaffolds found in many natural products and synthetic drugs or drug candidates exhibiting a wide range of biological activities, including anticancer,[1] antiviral,[2] antibacterial,[3] antimalarial,[4] anti-inflammatory,[5] and anti-angiogenesis activities,[6] as well as acting as enzymatic inhibitors.[7] In addition, applications in liquid crystals,[8] foams,[9] molecular probes,[10] and photoluminescent, fluorescent, electronic and magnetic materials have also been described.[11] Despite these fascinating functions, approaches for the preparation of this type of compound still remain scarce. The most frequent routes to 1,3,5-triazines typically involve the Suzuki cross-coupling reaction of halogenated 1,3,5-triazines with all kinds of nucleophiles.[12] Díaz-Ortiz reported the preparation of symmetrically substituted 1,3,5-triazines by the cyclotrimerization of nitriles.[13] Li and coworkers further developed domino [3 + 2 + 1] heterocyclization of isothiocyanates with aryl amidines leading to polysubstituted 1,3,5-triazine derivatives.[14] Recently, Biswas afforded the cyclization of aromatic aldehydes with amidines using DMSO as an oxidant for the synthesis of aryl substituted 1,3,5-triazines (Scheme 1a).[15] Xie *et al.* and Zhang *et al.* also further successfully developed new strategies for the synthesis of 2,4,6-triaryl-1,3,5-triazines based on transition-metal (Ru and Cu) catalyzed reaction of alcohols and amidines; the reaction involved the oxidation of alcohols to aldehydes (Scheme 1b).[16] However, all of the above mentioned methods suffer from limitations such as the requirement of harsh reaction conditions (microwaves, high temperatures), metal catalysts and less-environmentally benign or not readily available substrates. Therefore, the development of facile and efficient methods for the synthesis of 1,3,5-triazines from simple precursors continues to be a challenging task.




**Scheme 1** Selected synthetic methods for 1,3,5-triazines.

In recent years, the use of abundant and sustainable methylarenes for carbon–carbon (C–C) and carbon–nitrogen (C–N) bond formation has received considerable attention.[17] There is no doubt that methylarenes are cheap, stable, less toxic, commercially available, and easy to handle, thus making it advantageous to use them as ideal starting materials. In the exploration of suitable oxidant systems, the oxidation of methylarenes leading to *in situ* formation of aldehydes is considered to be the key step for the formation of the desired

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products.[18] Based on these elegant contributions, we believed that methylarenes could be applied as aldehyde precursors for the synthesis of aryl substituted 1,3,5-triazines. Recently, we also reported a facile one-step synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from amidines and methylarenes by copper-catalyzed cascade annulation, followed by $Csp^3$–H oxidation of methylarenes using TBHP as an oxidant under mild conditions.[19] On the other hand, burgeoning metal-free organo-catalytic strategies have attracted much attention in recent years in many oxidation processes with TBHP as an oxidant, and showed outstanding performances and advantages such as being inexpensive, safe, environmentally benign and requiring mild conditions.[20] Herein, we further develop a novel method for the synthesis of 2,4,6-trisubstituted 1,3,5-triazines directly from methylarenes and amidines mediated by TBHP under metal-free conditions (Scheme 1c). The reaction involves an efficient oxidation–imination–cyclization tandem process.

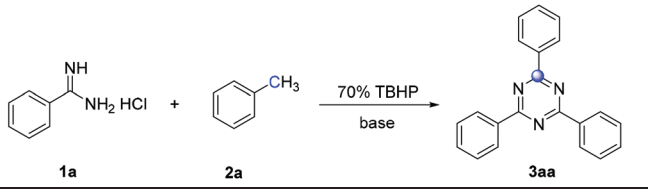
## Results and discussion

We began our study by investigating the TBHP mediated oxidative coupling of benzamidine hydrochloride **1a** and toluene **2a** under basic conditions. We were pleased to obtain the desired product 2,4,6-triphenyl-1,3,5-triazine **3aa** in 43% isolated yield when the reaction was performed using $K_3PO_4$ as the base in the presence of 70% TBHP (3 equiv.) in toluene at 100 °C (Table 1, entry 1). For optimizing the reaction conditions, the effect of oxidants was investigated, and we found that the oxidant plays an important role in this oxidation process. 70% TBHP was found to be superior to TBHP and DTBP (Table 1, entries 2 and 3). Other oxidants such as $H_2O_2$, $O_2$, and $PhI(OAc)_2$ were proved completely ineffective (Table 1, entries 4–6). Various bases such as $K_2CO_3$, KOAc, KOH, $Cs_2CO_3$, $Et_3N$, DBU and DABCO were also screened (Table 1, entries 7–13), of which $Cs_2CO_3$ was found to be the optimum choice (Table 1, entry 10). No products were obtained in the absence of a base or oxidant (Table 1, entries 14 and 15). When the amount of oxidant was decreased, dramatic lowering of yields was observed (Table 1, entries 16 and 17). Overall, **3aa** was successfully formed in 85% isolated yield under the optimized conditions ($Cs_2CO_3$ (2 equiv.), 70% TBHP (3 equiv.) in toluene at 100 °C).

After optimization of the reactions conditions, the substrate scope of the reaction of benzamidines with different substituted methylarenes was investigated, and the results are listed in Table 2. Most of the reactions using methylarenes proceeded smoothly and furnished the desired products in moderate to good isolated yields (**3aa–3al**). Relatively low yields were obtained when methylarenes were substituted with electron-withdrawing substituents such as $CF_3$, Br and $NO_2$ (**3af**, **3ag**, **3ah**). Besides, *para* and *meta* substituted substances gave higher yields than those with *ortho* substituents because of the steric hindrance (**3aj–3am**). When the toluene derivatives were substituted with more than one methyl group, the reaction only took place on one methyl group and the others remained (**3aj**). This result might be attributed to the fact that one of the methyl groups on the aromatic ring was involved in the reaction and its electron-withdrawing properties were unfavourable to the subsequent oxidation.[18a,19] α-Methylnaphthalene also could be employed to react with benzamidine hydrochloride giving moderate yield (**3an**). To our delight, the heterocyclic methylthiophene was also compatible in this transformation regardless of the lower yield (**3ao**).

To further demonstrate the applicability of the procedure, different amidines and toluene were exploited under the standard conditions. As shown in Table 3, a range of functional groups with different electronic properties, including $CH_3$, $OCH_3$, Cl and $CF_3$, were well-tolerated, providing the corresponding substituted products in 49–72% yields (**3ba–3ea**). On the whole, benzamidines with an electron-donating group on the benzene ring gave the corresponding products in slightly higher yields than those with an electron-withdrawing group on the benzene. *meta*-Substituted substances also underwent the transformation in good yield (**3fa**). However, the *ortho* group substituted benzamidines afforded lower yields (**3ga–3ha**). Meanwhile, cyclopropanecarboxamidine was subjected to this reaction system and provided **3ia** only in 34% yield partly due to the moisture-sensitivity of amidines, and a small amount of amidines undergoing hydrolysis to amides was also observed by GC-MS.

**Table 1** Optimization of the reaction conditions[a]



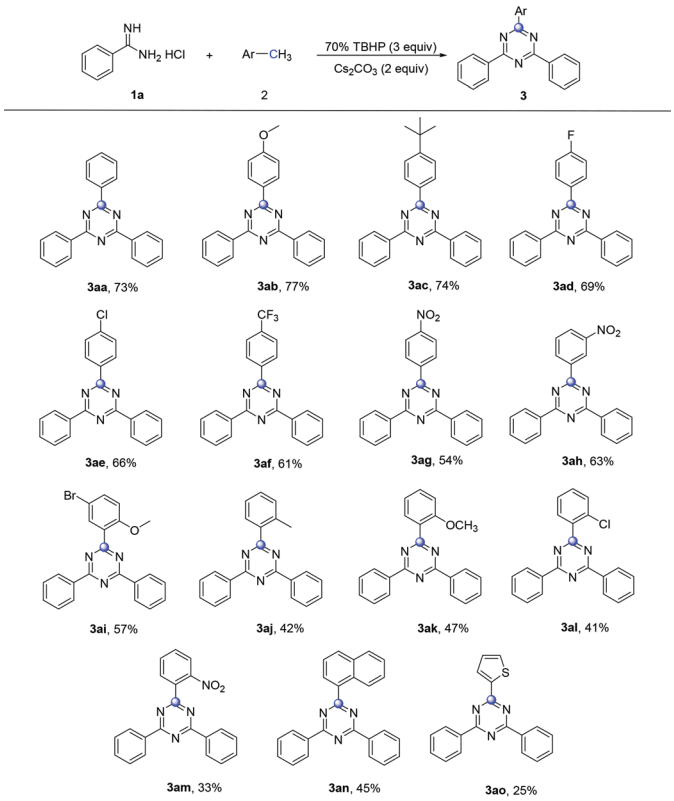

1a 2a 3aa

| Entry | Oxidant | Base | Yield[b] (%) |
|---|---|---|---|
| 1 | 70% TBHP | $K_3PO_4$ | 43 |
| 2 | TBHP | $K_3PO_4$ | 31 |
| 3 | DTBP | $K_3PO_4$ | 39 |
| 4 | $H_2O_2$ | $K_3PO_4$ | 0 |
| 5 | $O_2$ | $K_3PO_4$ | 0 |
| 6 | $PhI(OAc)_2$ | $K_3PO_4$ | 0 |
| 7 | 70% TBHP | $K_2CO_3$ | 49 |
| 8 | 70% TBHP | KOAc | 32 |
| 9 | 70% TBHP | KOH | 66 |
| 10 | 70% TBHP | $Cs_2CO_3$ | 73 |
| 11 | 70% TBHP | $Et_3N$ | 0 |
| 12 | 70% TBHP | DBU | 0 |
| 13 | 70% TBHP | DABCO | 0 |
| 14 | 70% TBHP | — | 0 |
| 15 | — | $Cs_2CO_3$ | 0 |
| 16[c] | 70% TBHP | $Cs_2CO_3$ | 35 |
| 17[d] | 70% TBHP | $Cs_2CO_3$ | 27 |

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.25 mmol), oxidant (3 equiv.) and base (2 equiv.) in 1.0 mL toluene (**2a**) at 100 °C for 24 h under air. [b] Isolated yield based on **1a**. [c] 1.5 equiv. 70% TBHP was used. [d] 1.5 equiv. $Cs_2CO_3$ was used.

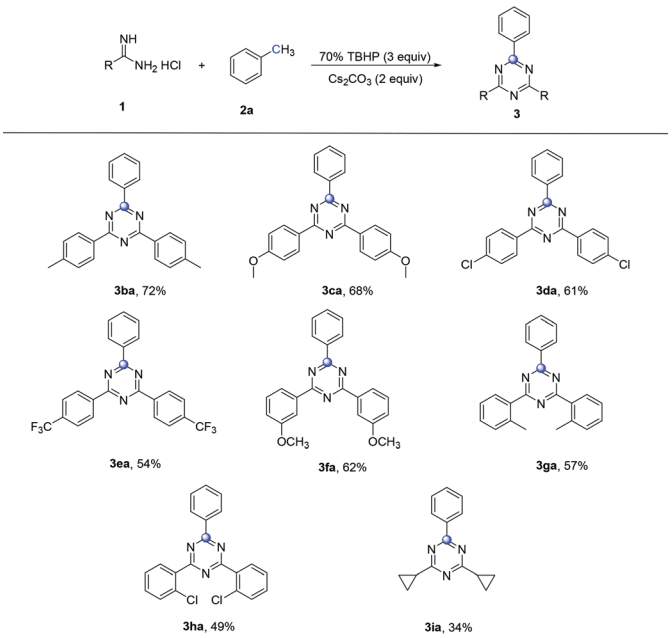
 

**Table 2** Scope of aryl methyl substrates[a]



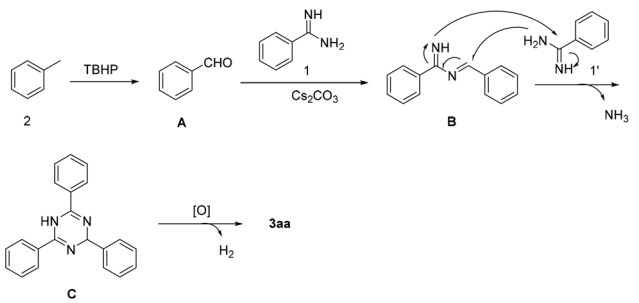

[a] Reaction conditions: **1a** (0.25 mmol), 70% TBHP (3 equiv.), $Cs_2CO_3$ (2 equiv.) and **2** (1 mL) were stirred at 100 °C for 24 h under air. Isolated yield based on **1a**.

**Table 3** Scope of amidine substrates[a]




[a] Reaction conditions: **1** (0.25 mmol), 70% TBHP (3 equiv.), $Cs_2CO_3$ (2 equiv.) and **2a** (1 mL) were stirred at 100 °C for 24 h under air. Isolated yield based on **1a**.

On the basis of great progress in TBHP mediated methylarene oxidation and the conventional 1,3,5-triazine syntheses,[15,16] a plausible pathway for the formation of 2,4,6-triphenyl-1,3,5-triazine was proposed as shown in Scheme 2. Initially, an aldehyde **A** was formed by TBHP mediated toluene oxidation.[18a] Then the reaction of **A** and benzamidine was performed under $Cs_2CO_3$ to give azadiene **B**; benzamidine **1′** neutralized by $Cs_2CO_3$ from its hydrochloride salt **1** then condensed with **B**, which further underwent nucleophilic addition and oxidation processes to form the desired product **3aa**.




**Scheme 2** Possible reaction mechanism.

## Conclusions

In conclusion, we have developed an efficient and straightforward method for the preparation of 2,4,6-trisubstituted-1,3,5-triazines *via* the reaction of TBHP mediated amidines with methylarenes under metal-free conditions. Toluene derivatives can be used as effective aldehyde precursors in the oxidation–imination–cyclization transformation. The reaction featured good functional group tolerance. The mild reaction conditions provide opportunities for applying this methodology in the synthesis of various natural products, drugs and functional materials in the future.

## Experimental

### General information

Melting points were measured using a melting point instrument and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz NMR spectrometer. IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. GC-MS data were obtained using electron ionization. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). TLC was performed using commercially available 100 − 400 mesh silica gel plates (GF254). Unless otherwise noted, the purchased chemicals were used without further purification.

**Typical experimental procedure for the synthesis of 3**

A mixture of amidine hydrochloride **1** (0.25 mmol), toluene derivatives **2** (1 mL), $Cs_2CO_3$ (159 mg, 2 equiv.), and 70% TBHP (96 mg, 3 equiv.) was taken in a test tube (10 mL) equipped with a magnetic stirring bar. The mixture was stirred at 100 °C for 24 h. After the reaction was completed, 10 mL ethyl acetate (3 × 10 mL) was added into the tube. The combined organic layers were washed with brine until neutral, dried over anhydrous $MgSO_4$, and concentrated in a vacuum. Purification of the residue on a preparative TLC afforded **3** as a white solid.

## Acknowledgements

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