



Metal-free cascade reactions of aldehydes and primary amines for the synthesis of 1,3,4-trisubstituted pyrroles



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ABSTRACT

The synthesis of 1,3,4-trisubstituted pyrroles has been realized via the cascade reactions of phenylacetaldehydes and primary amines. It is the first time that this annulation involving the construction of one new C–C and two new C–N bonds has been successfully conducted under metal-free conditions.

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Pyrrole ring is a featured structure in a large number of valuable organic molecules, including natural products¹ and artificial compounds of rich bioactivities.² Being guided by the high potential of this privileged heterocyclic moiety in discovering new lead compounds and drugs, the synthesis of pyrroles is known as an issue of longstanding and renewed interest.³ As classical protocols, the Hantzsch, Paal–Knorr and Huisgen reactions have been utilized as practical methods in the synthesis of pyrroles.⁴ Along with the recent extensive efforts made in designing alternative synthetic strategies, a variety of new methodologies with specific features, such as novel multicomponent reactions,⁵ ring opening-based annulation,⁶ alkyne-based cycloaddition or cyclization,⁷ enamine-based cascade annulation,⁸ cascade reactions initiated by transition metal-catalyzed latent C–H bond functionalization,⁹ and others¹⁰ have emerged as revolutionary advances in pyrrole chemistry.

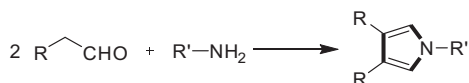
Among the large number of methodologies towards pyrrole synthesis, protocols employing simple and readily available substrates are of particular significance owing to their practicality in operation and low cost. In 2010, Jia and co-workers reported the cascade reactions of alkyl-/aryl acetaldehydes with primary amines as a facile route to the synthesis of polysubstituted pyrroles

via the mediation of AgOAc (A, Scheme 1),¹¹ catalytic version of this pyrrole synthesis has been recently achieved by Huang, Deng and co-workers via the catalysis of Cu(OTf)₂ (B, Scheme 1).¹² While advances on the synthesis of these pyrroles have been witnessed, however, a metal-free version, which can further improve the synthetic sustainability, has not yet been accomplished.¹³ Based on our recent interest in the metal-free cascade multimolecular reactions for heterocycle synthesis,¹⁴ we report herein the first metal-free synthesis of 1,3,4-trisubstituted pyrroles via the cascade reactions of acetaldehydes and primary amines (C, Scheme 1).

To start the investigation, the cascade reaction between phenylacetaldehyde **1a** and *p*-methylaniline **2a** was selected for screening practical reaction conditions. First, a class of oxidants of different features were examined, respectively. The outcome indicated that peroxides were able to promote the formation of **3a** while entries employing other oxidants such as oxygen, K₂S₂O₈, PhI(OAc)₂ and DDQ provided only trace amount of product (entries 1–6). Variation on the loading of the oxidant proved that 2 equiv-mol TBHP gave the best yield (entries 6–8, Table 1). Subsequently, a class of different solvents were also screened, but no superior medium over MeCN was identified (entries 9–15, Table 1). A control experiment carried out in the presence of TEMPO, a radical scavenger, gave the target pyrrole with trace amount, confirming that the key radical-based transformation(s) were involved in this cascade reaction (entry 16, Table 1). Additionally, experiments employing AcOH and FeCl₃ as additive, respectively, gave no improved yield of **3a** (entries 17–18, Table 1).

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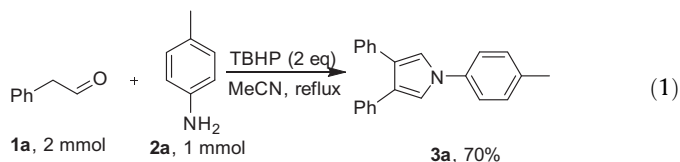


- A) Jia et al: AgOAc (2 equiv) mediated synthesis
 B) Huang, Deng et al: Cu(OTf)₂-catalyzed synthesis
 C) This work: metal-free synthesis

Scheme 1. Synthesis of 1,3,4-trisubstituted pyrroles with different conditions.

To further examine this metal-free protocol for pyrrole synthesis, the scope of reaction was studied by employing different primary amines and acetaldehydes, respectively.¹⁵ The results obtained from this section (Table 2) suggested broad application scope of the present method in the synthesis of pyrroles **3**. For the component of primary amine, anilines with various substituents in *para*-, *meta*- and *ortho*-position of the amino group showed general tolerance for the synthesis of corresponding pyrroles. The electron withdrawing effect as well as steric hindrance both exhibited negative effect to the yield of corresponding products probably because that the nucleophilicity of the amino group was undermined (**3i–3k**, **3m**, Table 2). The entries using sensitive hydroxyl substituted aniline (*p*-hydroxy aniline) failed to provide expect pyrrole (entries 19, Table 2). On the other hand, while conventional electron donating group (EDG) and weak electron withdrawing group (EWG) functionalized phenylacetaldehydes could smoothly take part in the synthesis (**3o–3q**, Table 2), the synthesis of corresponding product with substrate **1e** which contains strong nitro EWG was found unpractical (entry 18, Table 2). In addition, this metal-free protocol did not tolerate expect pyrrole synthesis using aliphatic acetaldehyde or aliphatic amine as substrate(s).

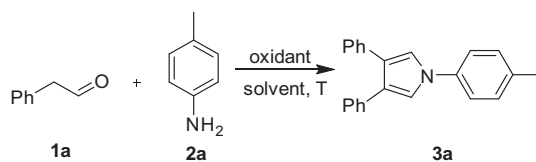
Complementarily, to examine the potential application of this metal-free protocol in the scale-up synthesis, a 1 mmol scale reaction for the synthesis of **3a** was performed, and it was found that the product could be acquired with satisfactory yield (Eq. 1).



Considering the specific function of peroxide in the reactions, the result from the control entry performed in the presence TEMPO as well as the known literature reporting similar reactions wherein the free radicals were involved,^{11,12} a mechanism based on radical intermediates has been proposed for the reactions in the present work. As outlined in Scheme 2, the imine intermediate **4** occurs firstly via the aldehyde-amine condensation, the oxidation of **4** in the presence of TBHP provides imine radical **5**. Bis-imine **6** is then generated via the dimerization of the free radical **5**. As the tautomeric version of **6**, the enamine intermediate **7** undergoes intramolecular cyclization and elimination of amine to afford pyrrole **3**.

In conclusion, we have developed a metal-free protocol for the synthesis of 1,3,4-trisubstituted pyrroles via the cascade reactions between aryl acetaldehydes and primary amines. The major feature of metal-free operation represents a step forward on the basis of previous version employing transition metal catalysis or promotion. The work is thus an important complement for the synthesis of useful pyrrole scaffolds.

Table 1
 Optimization in reaction conditions^a



Entry	Oxidant	Solvent	T (°C)	Yield ^b (%)
1 ^c	O ₂	MeCN	Reflux	Trace
2	K ₂ S ₂ O ₈	MeCN	Reflux	Trace
3	PhI(OAc) ₂	MeCN	Reflux	Trace
4	DDQ	MeCN	Reflux	Trace
5	H ₂ O ₂	MeCN	Reflux	21
6	TBHP	MeCN	Reflux	78
7 ^d	TBHP	MeCN	Reflux	69
8 ^e	TBHP	MeCN	Reflux	71
9	TBHP	EtOH	Reflux	13
10	TBHP	H ₂ O	100	17
11	TBHP	Toluene	100	Trace
12	TBHP	DMF	100	Trace
13	TBHP	DMSO	100	Trace
14	TBHP	Dioxane	100	56
15	TBHP	DCE	100	52
16 ^f	TBHP	MeCN	Reflux	Trace
17 ^g	TBHP	MeCN	Reflux	64
18 ^h	TBHP	MeCN	Reflux	Trace

^a General conditions: **1a** (0.4 mmol), **2a** (0.2 mmol) and oxidant (0.4 mmol) in 2 mL solvent, stirred for 4 h at 100 °C (reflux for MeCN, EtOH); DCE = 1,2-dichloroethane.

^b Yield of isolated product.

^c 1 atm O₂.

^d The loading of TBHP was 1.0 equiv.

^e The loading of TBHP was 3.0 equiv.

^f Reaction in the presence of 5 equiv TEMPO.

^g 20 mol % AcOH was additionally employed.

^h 20 mol % FeCl₃ was additionally employed.

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