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Visible light promoted tandem dehydrogenation-deaminative cyclocondensation under aerobic conditions for the synthesis of 2-aryl benzimidazoles/quinoxalines from *ortho*-phenylenediamines and arylmethyl/ethyl amines†

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Visible light promoted domino synthesis of 2-aryl benzimidazoles is reported through the reaction of *ortho*-phenylenediamines and arylmethyl amines under aerobic conditions. The methodology has wide substrate scope and tolerates a wide range of functional groups affording the products in high yields. The use of arylethyl amines instead of arylmethyl amines gives 2-aryl quinoxalines.

The strong preponderance of nitrogen containing heterocycles in drug candidate molecules[1] has encouraged medicinal chemists to consider these heterocycles as a privileged structure for new drug design. Among the N-heterocycles, the benzimidazole scaffold has a high occurrence[2] and is in the top five most commonly used five-membered N-heterocyclic containing pharmaceuticals approved by the U.S. FDA. Various benzimidazole derivatives are known to exhibit a wide range of biological activities, such as antimalarial, anti-microbial, anti-inflammatory, anti-tubercular, anti-diabetic, anti-convulsant, anti-protozoal, antihypertensive, and anticancer.[3] This triggered interest from synthetic organic/medicinal chemists toward developing effective synthetic methodologies for the construction of a benzimidazole ring system. The cyclo-condensation of an aldehyde with *o*-phenylenediamines appears to be the simplest approach for this purpose but often encounters the problem of the formation of 2-substituted and 1,2-disubstituted benzimidazoles.[4] This selectivity issue is compounded during the use of unsymmetrically substituted *o*-phenylenediamines as the reacting partner and would require an alternative multistep strategy to control the regioselectivity.[5]

The use of arylmethyl amines as the aldehyde surrogates has emerged as a new strategy for the synthesis of 2-substituted benzimidazoles[6] leading to several methods under transition metal-catalysed and metal free reaction conditions.

However, there is a need to develop new synthetic methods to enrich medicinal chemists' tool box in compliance with green chemistry.[2] In the last few decades, visible light promoted synthesis of N-heterocycles has emerged as an important green chemistry tool. In this context, the limited reports for the synthesis of 2-arylbenzimidazoles include the reaction of *o*-phenylenediamine with aldehydes in atmospheric oxygen,[7] and in the presence of a photocatalyst such as 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (pytz),[8] Rose Bengal,[9] and PDI-SN.[10]

Herein, we report visible light promoted tandem dehydrogenation-deaminative cyclocondensation of *o*-phenylenediamines (**1**) with arylmethyl amines (**2**), used as the aldehyde surrogate, for a transition metal and photocatalyst free synthesis of 2-aryl benzimidazoles (**3**) under aerobic conditions and extension of the protocol for the synthesis of 2-aryl quinoxalines (**5**) by replacing **2** with arylethyl amines (**4**) as the reacting partner of **1** (Fig. 1).

This study began with the model reaction of *o*-phenylenediamine (**1a**) with phenylmethyl amine (**2a**) so as to form the 2-phenyl-benzimidazole (**3a**) (Scheme 1).

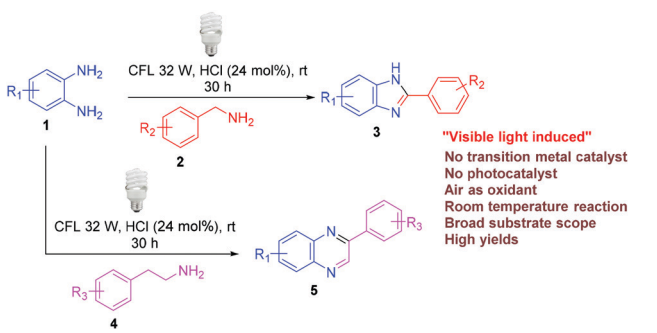

Fig. 1 Visible light promoted synthesis of 2-aryl benzimidazoles/quinoxalines.

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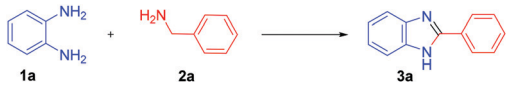


Scheme 1 Visible light promoted reaction of **1a** with **2a** to form **3a**.

During initial attempts, the reaction of **1a** with **2a** under visible light did not result in the formation of **3a** (Table 1, entries 1–3). However, **3a** was produced in 70% yield after 40 h in the presence of conc. HCl (12 mol%: 10 μL of aq. 12 N) (Table 1, entry 4). Increase of the amount of conc. HCl to 24 mol% (20 μl of aq. 12 N) increased the yield of **3a** to 78% in 30 h (Table 1, entry 5). The reaction either did not proceed to form **3a** or produced **3a** in a trace amount when DMSO was replaced by other organic solvents (*e.g.*, MeOH, ^{i}PrOH, MeCN, dioxane, DMF, EtOAc, THF, toulene, hexane, DCE) or water (Table 1, entries 8–18). The use of other protic acids such as HOAc, *p*-TsOH, TFA, and MsOH or metal salts as a Lewis acid like $CuCl_2$ and $Cu(OTf)_2$ in place of conc. HCl as the additive resulted in either no formation of **3a** or a substantial decrease in the yield of **3a** (Table 1, entries 19–25). No formation of **3a** was observed in performing the reaction using a photocatalyst such as Eosin dye (5 mol%) in place of aq. HCl (Table 1, entry 26). The formation of **3a** also did not take place in using H_2O_2 as the additive replacing conc. HCl (Table 1, entry 7). When the light source was changed to a blue LED, the yield of **3a** improved a bit (81%) (Table 1, entry 27). Herein also no formation of **3a** took place in the absence of conc. HCl (Table 1, entry 28).

Table 1 The reaction of **1a** with **2a** under different conditions to form **3a**[a]

Entry	Light source	Additive	Time (h)	Solvent	Yield[b] (%)
1	No light	No additive	24	DMSO	Nil
2	No light	HCl (12 mol%)	24	DMSO	Nil
3	White CFL	Without HCl	24	DMSO	Nil
4	**White CFL**	**HCl (12 mol%)**	**40**	**DMSO**	**70**
5	**White CFL**	**HCl (24 mol%)**	**30**	**DMSO**	**78**
7	White CFL	H_2O_2	24	DMSO	Nil
8	White CFL	HCl (24 mol%)	30	MeOH	Trace
9	White CFL	HCl (24 mol%)	30	MeCN	Nil
10	White CFL	HCl (24 mol%)	30	Dioxane	Nil
11	White CFL	HCl (24 mol%)	30	^{i}PrOH	Trace
12	White CFL	HCl (24 mol%)	30	DMF	Nil
13	White CFL	HCl (24 mol%)	30	EtOAc	Nil
14	White CFL	HCl (24 mol%)	30	THF	Nil
15	White CFL	HCl (24 mol%)	30	Toluene	Nil
16	White CFL	HCl (24 mol%)	30	Hexane	Nil
17	White CFL	HCl (24 mol%)	30	DCE	Trace
18	White CFL	HCl (24 mol%)	30	H_2O	Nil
19	White CFL	AcOH (35 mol%)	30	DMSO	25
20	White CFL	*p*-TsOH (10 mol%)	30	DMSO	40
21	White CFL	TFA (26 mol%)	30	DMSO	35
22	White CFL	MsOH (20 mol%)	30	DMSO	20
23	White CFL	$CuCl_2$ (10 mol%)	30	MeCN	Nil
24	White CFL	$CuCl_2$ (10 mol%)	30	DMSO	Nil
25	White CFL	$Cu(OTf)_2$ (20 mol%)	30	DMSO	Nil
26	White CFL	Eosin dye (5 mol%)	30	DMSO	Nil
27	Blue LED[c]	HCl (24 mol%)	30	DMSO	81
28	Blue LED[c]	Without HCl	30	DMSO	Nil

[a] The mixture of **1a** (1 mmol) and **2a** (1.2 mmol, 1.2 equiv.) in DMSO (4 mL) in an open vessel was treated under light (a 32 W capacity difference light source was used except for entries 1, 2, 27, and 28) in the presence of various additives (wherever applicable the HCl used was aq. 12 N) at room temperature. [b] Isolated yield of **3a**. [c] 18 W capacity light source was used. nil = no formation of **3a**.

Thus, the findings (Table 1) in the present work that the reaction does not require any photocatalyst and instead 24 mol% of aq. HCl can be used has a distinct advantage. Hence, we planned to explore further the general synthetic applicability of this newly developed methodology.

However, though the use of blue LED light afforded comparable results for the model reaction (Table 1, entry 27), inferior product yields were obtained with other substrate combinations (either taking any substituted arylmethyl amine or any substituted *o*-phenylenediamine). Hence, the white compact fluorescent lamp (CFL) was considered for subsequent studies to evaluate the substrate scope of the reaction adopting the reaction conditions of Table 1, entry 5 as the optimized reaction conditions.

For this purpose, arylmethyl amines bearing different substitutions on the aryl ring and substituted *o*-phenylenediamines were considered as coupling partners. With respect to the diversity of the arylmethyl amines, the reaction proceeded well with arylmethyl amines bearing electron withdrawing and electron releasing groups in the aryl moiety. In the case of arylmethyl amines bearing electron withdrawing groups (Fig. 2, entries **3c**, and **3h**) the yields were slightly higher in comparison to those obtained for the reactions involving the arylmethyl amines containing electron releasing groups in the aryl moiety (Fig. 2, entries **3b**, **3d**, **3e**, and **3f**).

The scope with respect to various substituted *o*-phenylenediamines bearing electron withdrawing and electron releasing groups was also explored. With respect to the *o*-phenylenediamine, substrates bearing electron withdrawing groups (Fig. 2, entries **3g**, **3h**, **3i**, **3k**, and **3l**) gave slightly higher yields in comparison to those having an electron releasing group (Fig. 2, entry **3n**). The reaction worked well with disubstituted *o*-phenylenediamines as well (Fig. 2, entries **3i**, **3j**, **3k**, and **3l**).

To gain mechanistic insights into the reaction, several control experiments were designed for the model reaction of

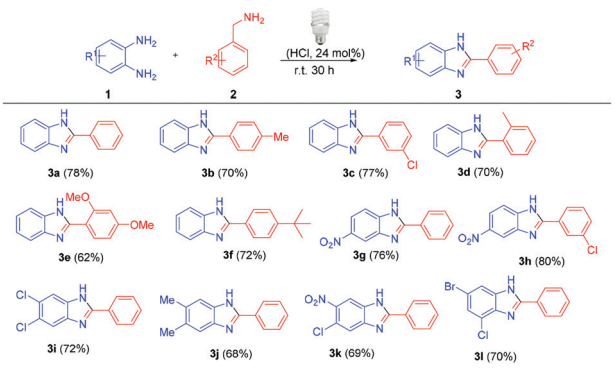


Fig. 2 Substrate scope with respect to arylmethyl amines and *o*-phenylenediamines for the synthesis of 2-aryl benzimidazoles.[a] [a] Reaction conditions: **1** (1 mmol) was reacted with **2** (1.2 mmol, 1.2 equiv.) in DMSO (4 mL) in the presence of conc. HCl (24 mol%; 20 μL of 12 N aq. HCl) under visible light (32 W White CFL) for 30 h at r.t.

1a with **2a** (Fig. 3). The radical pathway of the reaction was established by performing the reaction in the presence of TEMPO (2 equiv.) used as the radical scavenger,[11] which did not result in the formation of **3a** (Fig. 3, entry a). When the reaction was carried out under a nitrogen atmosphere, **3a** was not formed suggesting the necessity of molecular oxygen as the oxidant (Fig. 3, entry c).

As singlet oxygen is far more reactive than triplet oxygen toward organic compounds and is responsible for the photodegradation of many materials,[12] it was felt that the singlet oxygen is involved/responsible in each of the relevant stages of the mechanistic pathways. To establish the involvement of singlet oxygen, the model reaction involving **1a** and **2a** as the coupling partners was performed in the presence of singlet oxygen quencher DABCO[13] (Fig. 3, entry b). The lack of formation of **3a** in the presence of DABCO suggested the involvement of singlet oxygen species during the oxidative transformations. In the absence of visible light only a trace amount of **3a** was formed indicating the crucial role of visible light in promoting the transformation (Fig. 3, entry d).

Based on the results of these control experiments and previous literature reports,[7,9,14] a plausible mechanism has been proposed (Scheme 2). Arylmethyl amine **2a** undergoes oxidation with singlet oxygen leading to the formation of phenylmethanimine **A**. The intermediate **A** upon subsequent coupling with another molecule of **2a** leads to the formation of (*E*)-*N*-benzyl-1-phenylmethanimine **B**,[14] which undergoes *trans*-imination reaction with *o*-phenylenediamine **1a** in the presence of HCl and produces the intermediate imine **C**. The imine **C** is activated under visible light irradiation[7] to the species **D*** which reduces O_2 to superoxide (O^{2-}) and becomes the radical cation **E**. Radical cation **E** upon deprotonation by superoxide generates radical **F**, and subsequent hydrogen radical abstraction by a hydroperoxyl radical ($HOO^{\bullet}$)[7] produces the product 2-phenyl benzimidazole **3a**. Through an alternative pathway the imine may undergo intramolecular nucleophilic attack by the NH_2 nitrogen atom to form the 2-substituted imidazoline

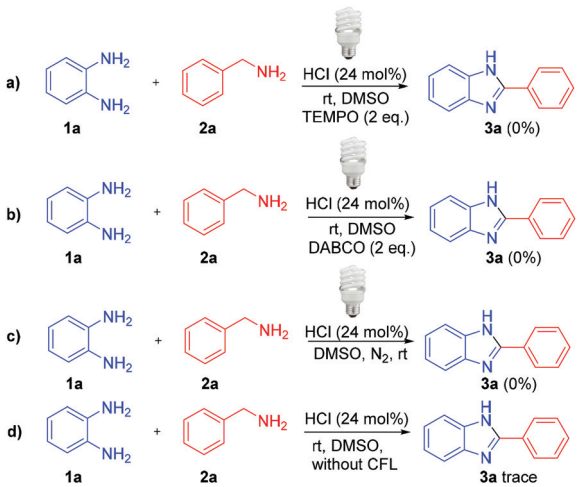
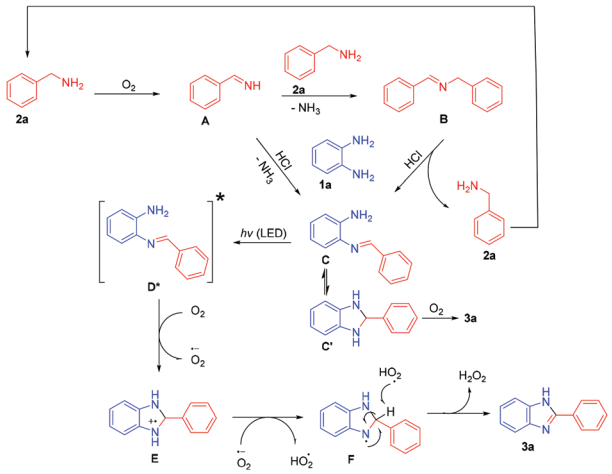


Fig. 3 Control experiments relevant to the understanding of the mechanistic course of the reaction of **1a** (1 mmol) with **2a** (1.2 mmol).



Scheme 2 Plausible mechanism for the visible light promoted reaction of **1a** with **2a** to form **3a**.

intermediate **C′** which on oxidation by singlet oxygen may give rise to the desired product **3a**. However, when the reaction of **1a** with **2a** was performed under thermal conditions (at 40 °C) in place of using visible light, no significant amount of **3a** was formed thus ruling out the probability of this alternate pathway. The visible light mediated activation of **C** to **D*** probably makes the oxidative cyclisation to **E** faster.

We next thought to test the versatility of this methodology with respect to the scope of constructing diverse N-heterocyclic system and realised that the increase of the alkyl carbon chain of aryl methylamine by one carbon (*i.e.*, use of arylethyl amine) would generate 2-aryl quinoxalines. The diverse bioactivities[15] of compounds containing the quinoxaline moiety have generated interest to develop greener synthetic methodologies[16] of this heterocyclic system. Thus, in a model reaction, phenethyl amine **4a** was treated with **1a** under the optimised reaction conditions and to our delight, the 2-phenyl quinoxaline **5a** was obtained in 75% yield. This encouraged us to assess the substrate scope for the reaction of various substituted *o*-phenylenediamines **1** with substitute aryl ethyl amines **4**. The reactions proceeded well. Arylethyl amines bearing electron withdrawing groups (Fig. 4, entries **5b**, **5d**, **5h**, **5j** and **5k**) gave higher yields in comparison to those bearing electron releasing groups (Fig. 4, entries **5c**, **5g** and **5l**). Similarly, *o*-phenylenediamine bearing electron withdrawing groups (Fig. 4, entries **5e**, **5f**, **5g** and **5h**) afforded higher yields in comparson to those containing electron releasing groups (Fig. 4, entries **5i**, **5j**, **5k** and **5l**). In general, unsymmetrical *o*-phenylenediamines resulted in the formation of two regioisomeric products (Fig. 2, entries **5m** and **5n**) but the nitro substituted *o*-phenylenediamine gave only one of the two possible regioisomeric products (Fig. 4, entry **5e**).[17]

For reactions involving unsymmetrical *o*-phenylenediamines the two-regioisomeric products formed could be easily separated by column chromatography. The pure regioisomers were characterized by NMR analysis and comparison with the literature reports.[16a,18] The regioisomers **5n** and **5n^{I}**, were separated by

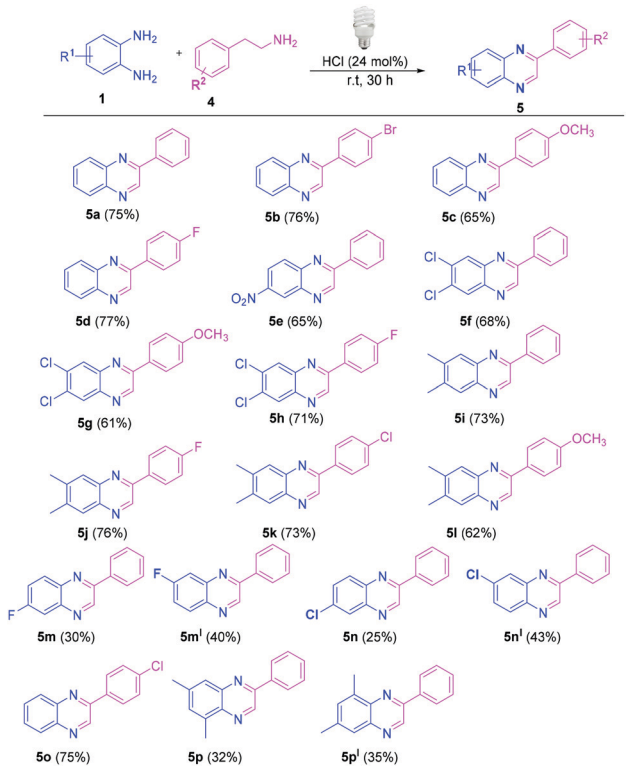
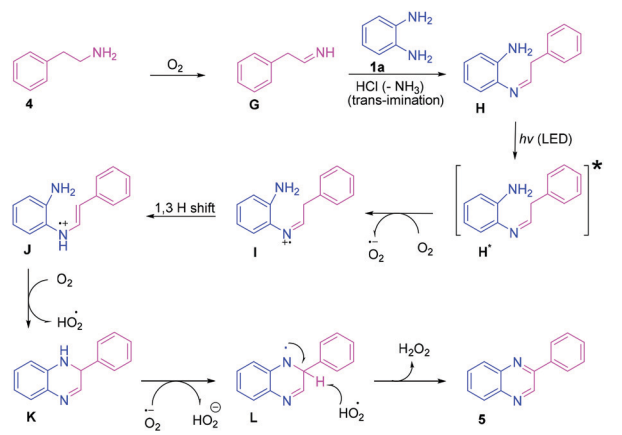


Fig. 4 Evaluation of substrate scope for the visible light promoted reaction of *o*-phenylenediamines with arylethyl amines to form diverse 2-aryl quinoxalines.[a] [a]Reaction conditions: **1** (1 mmol) was treated with **4** (1.2 mmol, 1.2 equiv.) in DMSO (4 mL) under visible light (32 W White CFL) in the presence of conc. HCl (24 mol%; 20 μL of 12 N aq., HCl) for 30 h at r.t.

column chromatography and identified by comparison with the spectral data of the reported authentic compounds formed *via* an unambiguous synthetic route.[16a] Similarly the regioisomers **5m** and **5m^{I}**, were separated using column chromatography and characterized by the spectral data of **5m** with an authentic compound synthesized *via* an unambiguous route.[18]

In view of the chemistry involved for the visible light-promoted oxidative transformations of aryl alkyl amines outlined in Scheme 2, a plausible mechanism for the generation of quinoxalines is depicted in Scheme 3. The reaction is triggered by initial oxidation of the phenethylamines **4** in the presence of oxygen leading to the formation of the intermediate **G** (Scheme 3). The HCl-promoted trans-imination of **G** with **1a** form the imine **H** under visible light induced oxidation by molecular oxygen is converted to the radical cation **I**. The radical cation **I** undergoes 1,3-H shift to **J** which undergoes cyclisation *via* intramolecular nucleophilic attack by the NH_2 nitrogen atom on the enaminic β-carbon followed by oxidation with molecular oxygen to form the intermediate **K**. Following a similar course of oxidation by molecular oxygen, **K** is converted to the quinoxaline **5**.



Scheme 3 Plausible mechanism for the visible light promoted reaction of **1a** with **4** to form **5**.

Conclusions

In summary, in this study an efficient visible light promoted tandem dehydrogenation-deaminative cyclocondensation of arylmethyl amines with *ortho*-phenylenediamines has been achieved for the synthesis of 2-aryl benzimidazoles. Room temperature operation, transition metal and photocatalyst free reaction conditions, and use of air as the oxidant are the distinct green advantages. Furthermore, the reaction has wide substrate scope and functional group tolerability affording good to excellent product yields and is extendable for the synthesis of 2-aryl quinoxalines.

Conflicts of interest

There are no conflicts to declare.

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