RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 5815

Received 31st October 2013
Accepted 12th December 2013

DOI: 10.1039/c3ra46314a

www.rsc.org/advances

Visible-light-initiated photo-oxidative cyclization of phenolic amidines using CBr_4 – A metal free approach to 2-aminobenzoxazoles†

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A mild and efficient one-pot operation for the amination of benzoxazoles has been achieved *via* ring opening of benzoxazoles followed by visible-light-mediated aerobic photo-oxidative cyclization of the resulting *o*-phenolic amidines using CBr_4 as a mild oxidant. The protocol is economical and environmentally benign as it utilizes visible light and does not require any photosensitizers, additives, heating or inert conditions.

Introduction

The potential of developing new synthetic methodologies using visible light has recently received much attention from a number of research groups.[1] This is because solar energy (visible light) is clean, easy to handle and an unlimited energy source having great prospects for the development of sustainable and eco-friendly protocols for organic synthesis.[2] Most visible-light-initiated photochemical organic reactions generally require expensive and potentially toxic ruthenium and iridium complexes as photosensitizers or photocatalysts.[3] Thus, the search for novel synthetically useful photochemical reactions without the need for visible-light photosensitization would be a welcome move, especially in terms of economical and environmental issues. The 2-aminobenzoxazole scaffold is a key structural motif in promising pharmaceuticals for the treatment of various disorders, such as Alzheimer's disease, schizophrenia, HIV and inflammatory diseases.[4] Fascinated by the medicinal worth of 2-aminobenzoxazoles, great efforts have been made for their synthesis.

2-Aminobenzoxazoles have been generally synthesized by direct amination of benzoxazoles with an amine or its surrogates through transition-metal-catalyzed C–H bond activation.[5] These methods are quite beneficial and appreciable compared to the traditional C–N bond formation involving nucleophillic displacement of 2-halogenated benzoxazoles or their precursors with amines.[6] However, various metal-based established methods have disadvantages of using toxic and/or expensive metal catalysts, even traces of which are to be removed for pharmaceutical applications. Hence, several metal-free methods employing various reagents or catalysts such as TEMPO, TBAI, I_2, and NIS have been reported.[7] Furthermore, elegant synthetic routes to access 2-aminobenzoxazoles utilising aminophenols as substrates have also been developed.[8,9] Besides, Chang and co-workers have recently developed an elegant method for the synthesis of 2-aminobenzoxazoles through a unique ring opening of benzoxazoles with secondary amines followed by an oxidative ring closure of the resulting *o*-phenolic amidines with iodobenzene diacetate (DIB).[10] Later on, Bhanage and co-workers have implemented this strategy using 2-iodobenzoic acid (IBX) as the oxidant.[11] These metal-free methods use expensive and potentially explosive oxidants. Very recently, we have developed a convenient synthesis of 2-aminobenzoxazoles from *o*-phenolic amidines using $Ru(dpy)_2Cl_2$ as a visible-light photoredox catalyst.[12]

In view of the above discussion and our continued efforts for developing efficient heterocyclization reactions,[12,13] we envisioned that a metal- and photosensitizer-free visible-light-initiated cyclization of *o*-phenolic amidines to the corresponding 2-aminobenzoxazoles could be feasible and highly interesting (Scheme 1). For this purpose, we focused on CBr_4, which is solid, easy to handle, and absorbs visible light to generate active radical species,[14] hence expected to be suitable for our envisaged cyclization reaction.

Results and discussion

In order to realize our goal, we commenced the study with a model reaction of 2-(piperidin-1-yl-methyleneamino)phenol **1a** using a stoichiometric amount of CBr_4 in acetonitrile as a solvent under visible light irradiation with an 18 W CFL for 1 h in the presence of air at rt. To our delight, 2-aminobenzoxazole

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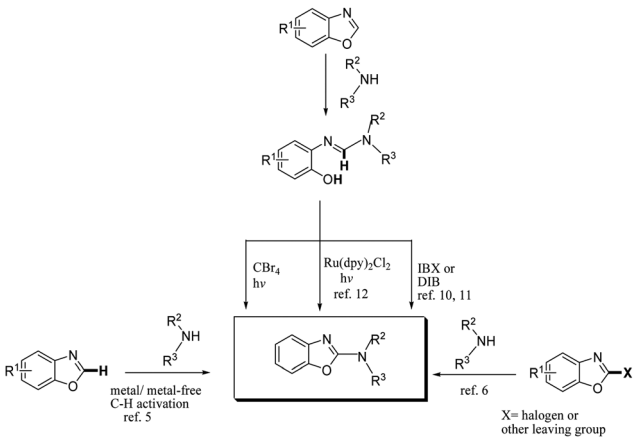
† Electronic supplementary information (ESI) available: Detailed procedures, ^1H, ^{13}C NMR and HRMS spectral data of all the products. See DOI: 10.1039/c3ra46314a

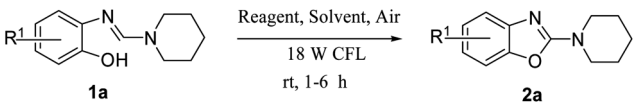


Scheme 1 Amination of benzoxazoles.

2a was obtained in 92% yield after 1 h. To ensure the necessity of the reaction parameters such as CBr_4, air and visible light for the present photo-oxidative cyclization, a series of control experiments were performed which revealed that in the absence of any one of the parameters, a little or no product formation was observed (Table 1, entries 10–12). On performing the cyclization under inert argon atmosphere, a decrease in the yield was observed (Table 1, entry 11). Next, optimization of the solvent was carried out which revealed CH_3CN to be the best solvent for the reaction (Table 1, entry 1). However, several other solvents such as THF, dioxane, DCM, CH_3NO_2, and toluene were also explored which did not give satisfactory results (Table 1, entries 2–6). Notably, a radical generating bromine source was also found to be one of the major parameters necessary for the initiation of the cyclization reaction. Thus, various bromine sources were tested and it was found that CBr_4 was the best in terms of the yield and reaction time (Table 1, entry 1). However, in the case of tetrabutyl ammonium bromide (TBNBr) no cyclization of *o*-phenolic amidine **1a** was observed which might be due to inability of TBNBr to give bromine radical under the given reaction conditions (Table 1, entry 9).

Keeping in view the potential of CBr_4 as an efficient reagent for visible-light-initiated photo-oxidative cyclization of *o*-phenolic amidines in CH_3CN (Table 1, entry 1), we switched to investigate the substrate scope of the reaction. As depicted in Table 2, phenolic amidines bearing electron-neutral, electron-donating or electron-withdrawing substituents generally afforded 2-aminobenzoxazoles in excellent yields (80–92%). This shows little electronic effect of the substituents on the oxidative cyclization reaction. Interestingly, amidines with various functionalites such as CH_3, OCH_3, NO_2, Cl, Ph and CF_3 were easily tolerated to give aminobenzoxazoles in excellent yields and high purity. However, on the part of secondary amines, structurally diverse cyclic and acyclic amines were evaluated and found to undergo the photo-oxidative cyclization very smoothly.

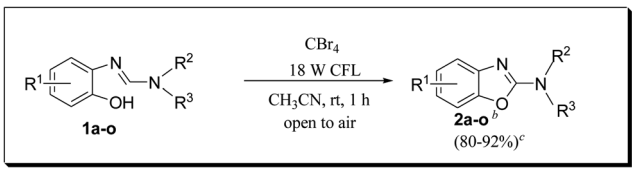
Table 1 Optimization of reaction conditions[a]

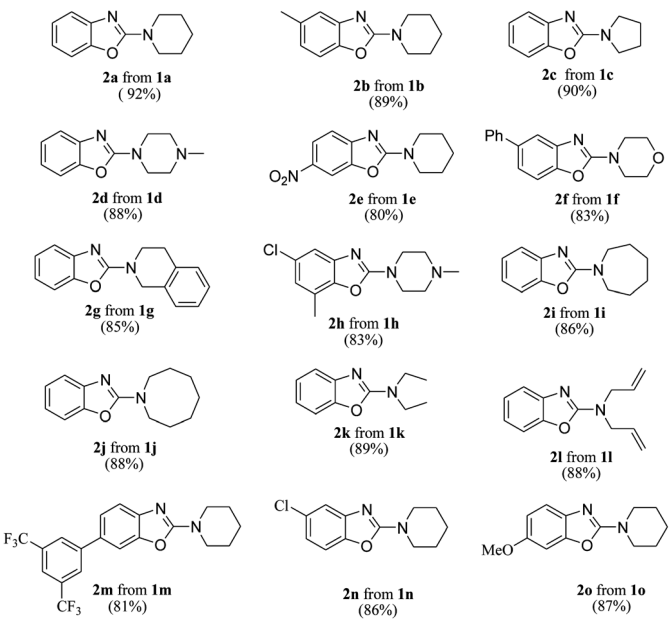


Entry	Reagent	Solvent	Time (h)	Yield (%)[e]
1	CBr_4	CH_3CN	1	92
2	CBr_4	THF	6	25
3	CBr_4	Dioxane	6	30
4	CBr_4	DCM	6	35
5	CBr_4	CH_3NO_2	6	20
6	CBr_4	Toluene	6	15
7	Br_2	CH_3CN	1	71
8	NBS	CH_3CN	3	67
9	TBNBr	CH_3CN	6	0
10[b]	CBr_4	CH_3CN	6	0
11[c]	CBr_4	CH_3CN	6	12
12[d]	—	CH_3CN	6	0

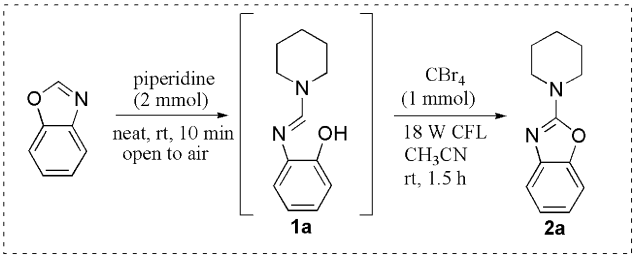
[a] *Reaction conditions*: *o*-phenolic amidine (1 mmol), reagent (1 mmol), solvent (3 mL), under 18 W CFL (Compact fluorescent lamp; Philips, 6500 k, 1010 1 m, 85 mA) irradiation under an air atmosphere at rt. [b] In dark. [c] Under inert Ar atmosphere. [d] Absence of bromine source. [e] Isolated yield of **2a** after flash chromatography.

Table 2 Photo-oxidative cyclization of *o*-phenolic amidines to yield 2-aminobenzoxazoles[a]





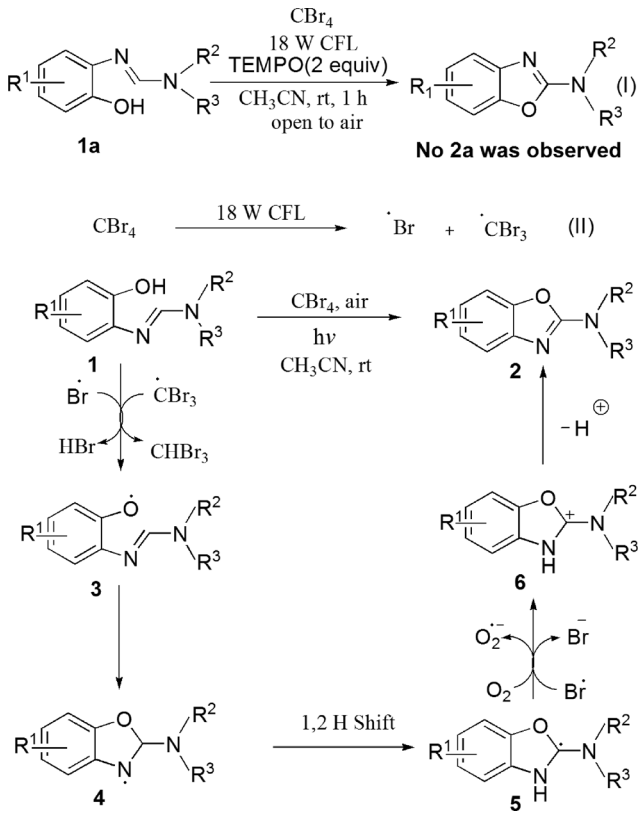
[a] See ESI for detailed procedure. [b] All compounds are known and were characterized by comparison of their ^1H, ^{13}C NMR and HRMS data with those reported in the literature.[10,15,16] [c] Yields of isolated pure compounds.



Scheme 2 One-pot sequential amination of benzoxazoles.

Furthermore, owing to an easy, rapid and high yielding conversion of benzoxazoles into *o*-phenolic amidines,[10] we proceeded for one-pot synthesis of 2-aminobenzoxazoles starting from benzoxazoles and secondary amines (Scheme 2). Thus, we stirred benzoxazole (1 mmol) and piperidine (2 mmol) under neat condition at rt for 10 min. After confirming the complete conversion of benzoxazole to corresponding amidine by TLC, CH_3CN (3 mL) and CBr_4 (1 mmol) were added and the reaction mixture was irradiated with an 18 W CFL for 1.5 h. To our delight, the one-pot procedure was also effective and the desired product, 2-aminobenzoxazole **2a** was obtained in a decent yield (89%).

On the basis of the above observations and the literature precedents,[12,14,17,18] a plausible mechanism for the present visible-light-initiated photo-oxidative cyclization of *o*-phenolic amidines **1** to afford 2-aminobenzoxazoles **2** is depicted in Scheme 3. The cyclization of amidines might follow a radical pathway, as the reaction was quenched on addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), which is a traditional radical scavenger (Scheme 3, eqn (I)).



Scheme 3 Plausible pathway for the photo-oxidative amination of benzoxazoles.

The key steps include: (i) on photo-irradiation, CBr_4 is activated to give $^{\bullet}Br$ and $^{\bullet}CBr_3$ radicals which initiate the reaction (Scheme 3, eqn (II)). (ii) $^{\bullet}CBr_3$ or $^{\bullet}Br$ radical abstracts phenolic H to give **3** which undergoes intramolecular cyclization to generate an aminyl radical **4**. (iii) The aminyl radical **4** is prone to undergo 1,2 H shift to form a more stable carbon radical **5**, and (iv) the radical **5** is efficiently oxidized by giving an electron to $^{\bullet}Br$ or O_2 to generate a highly stabilised carbocation **6**, which finally aromatizes through deprotonation to give the product **2**.

Conclusion

In summary, we have developed a highly efficient, mild and unique strategy for a one-pot synthesis of 2-aminobenzoxazoles. The protocol involves ring opening of benzoxazoles with secondary amines followed by photo-oxidative intramolecular cyclization of the resulting *o*-phenolic amidines using visible-light as a mild source of energy and CBr_4 as an oxidant. The use of visible-light irradiation without the need for any metal or non-metal photosensitizers or photocatalysts makes our method sustainable, ecofriendly and superior to the other existing methods for the amination of benzoxazoles.

Acknowledgements

We sincerely thank SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra. T. K. is grateful to the CSIR, New Delhi, for the award of a junior Research Fellowship (File no. 09/001(0370)/2012-EMR-1). V. P. S. is grateful to the Department of Science and Technology (DST) Govt. of India, for the award of a DST-Inspire Faculty position (Ref. IFA-11CH-08) and financial support.

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