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One-Pot Protocol for the Synthesis of Imidazoles and Quinoxalines using NBS

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Abstract. NBS-mediated one-pot green, efficient and practical synthesis of substituted imidazoles and quinoxalines has been reported by the reaction of styrenes with *N*-arylbenzamidines and *o*-phenylenediamines, respectively in water:1,4-dioxane mixture. The reaction involves formation of α-bromoketone as an intermediate in the presence of NBS and water, followed by condensation with *N*-arylbenzamidine and *o*-phenylenediamines. Use of an inexpensive NBS as a bromine source as well as an oxidant, water as a solvent and readily available starting materials make this protocol environmentally benign and economically viable. Substituted imidazoles and quinoxalines were obtained in good to excellent yields with wide functional group compatibility.
Keywords: Styrene; *N*-Arylbenzamidine; *o*-Phenylenediamine; Imidazole; Quinoxaline; NBS

In recent years, C-H functionalization has attracted significant attention in organic synthesis owing to selective construction of new bonds leading to rapid assembly of complex molecular framework from easily available simple starting materials. Consequently, numerous synthetic methods have been developed for carbon-carbon and carbon-heteroatom bonds formation by using C-H functionalization.[1,2] Moreover, from green chemistry perspective, it is preferable to use water to replace toxic organic solvents as the reaction medium. Thus, development of new synthetic protocols involving water as a solvent has received great deal of interest among research community. Recently, tandem procedures have been extensively used for the synthesis of nitrogen heterocycles because of their ability to perform multiple reactions in a single step.[3]

Imidazole is an important nitrogen heterocycle, ubiquitous in many natural products[4] and pharmaceutical compounds.[5] Imidazole derivatives are known to display broad range of biological activities[6] such as antifungal,[7] antitumor,[8] antibacterial,[9] antiplasmodium[10] and anti-inflammatory.[11] Moreover, they are integral part of numerous functional materials[12] such as organic semiconductors,[13] dyes,[14] optoelectronic materials,[15] etc. Furthermore, imidazole salts are mostly liquids at room temperature and have been extensively used as catalysts and/or green reaction media as well as electrolytes for solar cells and batteries. Hence, several methods for the synthesis of imidazole scaffolds have been developed Conventionally, imidazoles are synthesized by using 1,2-diketones/α-hydroxyketones/α-haloketones/α-aminoketones, primary amine, an aldehyde and ammonium acetate. Several new methods such as aldimine cross-coupling,[16] catalyst-free domino reaction of 2-azido acrylates and nitrones,[17] cycloaddition of amidines and nitroolefins,[18] multicomponent reactions,[19] Ni-catalyzed dehydrogenation of benzylic-type imines,[20] and Zn-catalyzed cyclization of 2-(tetrazol-5-yl)-2*H*-azirines and imines[21] have also been reported. Chiba et al.[22] described the synthesis of imidazoles from oxime by using copper (I) iodide and K_3PO_4, while Peiman Mirzaei synthesized *N*-substituted 2,4-diarylimidazoles via a multicomponent reaction.[23] Meille accomplished the synthesis of imidazoles through $FeCl_3$ mediated ring opening of 2*H*-azirines.[24]

Multisubstituted imidazoles have also been prepared from amidines through (3+2) cycloaddition reaction or radical pathway. In this context, Chen et al. synthesized trisubstituted imidazoles from acetophenones[25] through an iodine-zinc iodide catalyzed process, whereas Mandal and co-workers[26]

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reported the synthesis of imidazoles from phenacyl bromide by employing $KHCO_3$ as a base. Iron catalyzed three-component protocol was established by using aldehydes, amidines and nitroalkanes,[19c] while (3+2) cycloaddition of nitrovinylbenzene was accomplished in the presence of copper iodide.[18a] Moreover, Luc Neuville prepared trisubstituted imidazoles from phenylacetylene by using copper chloride as a catalyst over the period of 24 hours,[27] whereas Mohinder Mahajan utilized nitrosovinylbenzene in dichloromethane to form imidazoles (Figure 1).[28] 1,3-dicarbonyl compounds, ketones and chalcones have also been successfully used along with amidines for the synthesis of imidazoles.[29]

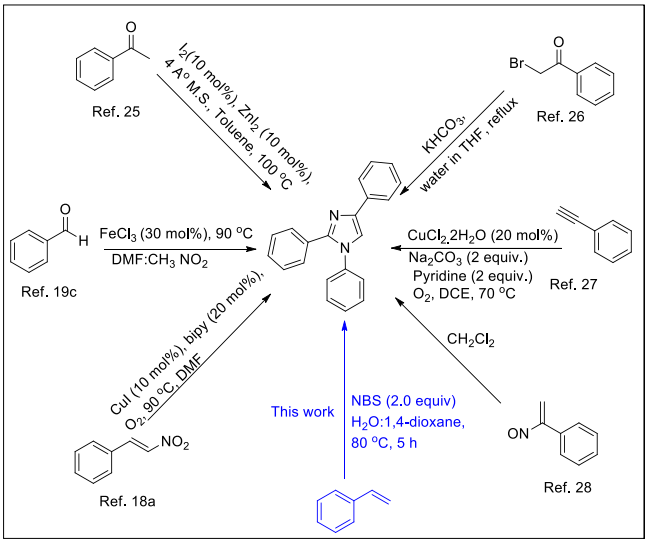


Figure 1. Methods for the synthesis of substituted imidazoles

The quinoxaline system is widely found in numerous dyes,[30,31] organic semiconductors,[32] electroluminescent materials.[33] Quinoxaline derivatives are known[34] to show a wide array of medicinal activities such as antitumor, antibacterial, anti-inflammatory and antidepressant. Particularly, the quinoxaline core is an important component of antibiotics such as echinomycin, levomycin and triostin.[35] In view of these aforementioned applications of quinoxalines, various method have been developed for their synthesis.

Traditionally, quinoxalines are synthesized by condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds,[36] α-hydroxy ketones[37] and α-haloketones.[38] Quinoxalines are also prepared by the reaction of *o*-phenylenediamines with epoxides,[39] α-sulfonyloxy ketones,[40] α-ketocarboxylic acids,[41] diazenylbutenes,[42] hydroxyacetylenes.[43] Moreover, Chen *et al.*[44] reported an efficient synthesis of quinoxalines by the cyclization of 1,2-diaminobenzenes with terminal alkynes in the presence of $Cu(OAc)_2$ as a catalyst and a combination of DMAP and Cs_2CO_3 as a base, whereas Cho *et al.*[45] synthesized quinoxalines *via* oxidative cyclization of *o*-phenylenediamines with vicinal diols by using $RuCl_2(PPh_3)_3$ as a catalyst and KOH as a base.

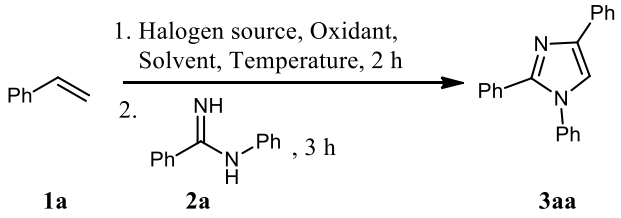
However these methods suffer from drawbacks such as use of transition metal catalysts, toxic reagents, an excess amount of base, higher reaction temperature, longer reaction time, low yield of products and requirement of functionalized substrates. Consequently, process efficiency is reduced and environmental problems arise. Therefore, the development of a simple, green and efficient process for the synthesis of imidazoles and quinoxalines is highly desirable.

In continuation of our research interest in metal-free C-H functionalization mediated tandem synthesis of *N*-heterocycles,[46] we herein report a green one-pot synthesis of substituted imidazoles and quinoxalines via C-H functionalization of readily available styrenes by using NBS as a bromine source as well as an oxidant, followed by condensation with *N*-arylbenzamidines and *o*-phenylenediamines in water:1,4-dioxane mixture.

Initially, the reaction of styrene **1a** with 2.0 equiv. I_2 as a halogen source and 2.0 equiv. TBHP as an oxidant in DMSO was carried out at 80 °C for 2 h. To the resulting mixture *N*-Phenylbenzamidine (1.5 equiv) was added and heating was continued at 80 °C for 3 h (Table 1, entry 1). However, TLC did not show desired product formation. Similar result was obtained when TBHP was replaced with IBX as an oxidant (Table 1, entry 2). The reaction of styrene **1a** with *N*-phenylbenzamidine **2a** in the presence of TBAI (2.0 equiv) and TBHP (2.0 equiv) in water failed to give desired imidazole **3aa** (Table 1, entry 3). Similar result was observed for the reaction in the presence of KI (2.0 equiv) and Oxone (2.0 equiv) (Table 1, entry 4). Next, we studied the effect of different reagents such as Br_2, NIS, NCS, and NBS on this reaction. The reaction by using Br_2 (2.0 equiv) as a halogen source as well as an oxidant offered product **3aa** in 54% yield (Table 1, entry 5). The reaction by using NIS (2.0 equiv) in water afforded 1,2,4-triphenyl-1*H*-imidazole **3aa** in 57% yield (Table 1, entry 6). Use of 2.0 equiv. of NCS and NBS afforded product **3aa** in 70% and 75% yields, respectively (Table 1, entries 7 and 8). We also performed the reaction of styrene **1a** with *N*-phenylbenzamidine **2a** by using 1.0 equiv. NBS. However, the reaction afforded product **3aa** in lower yield (42%, Table 1, entry 9). We also used 1.0 equiv *N*-phenylbenzamidine for this reaction (Table 1, entry 10). But, the reaction gave product **3aa** in moderate yield (65%). To improve reaction yield, we employed different solvent systems such as H_2O:acetonitrile and H_2O:1,4-dioxane in 1:1 ratio for this reaction. The reaction involving the use of H_2O:acetonitrile as solvent system resulted in low yield (39%) of the

product (Table 1, entry 11). To our delight, use of H_2O:1,4-dioxane as a solvent system resulted in formation of desired product in 80% yield (Table 1, entry 12). The same reaction was then carried out at 60 °C and 90 °C, whereupon yields of 56% and 71% were obtained (Table 1, entry 13), thereby indicating 80 °C is the best reaction temperature. Thus, the use of styrene **1a** (1.0 equiv.) with *N*-phenylbenzamidine **2a** (1.5 equiv.) in the presence of NBS (2.0 equiv) in water:1,4-dioxane (1:1) at 80 °C was found to the best reaction condition.

Table 1. Optimization of Reaction Conditions.[a]

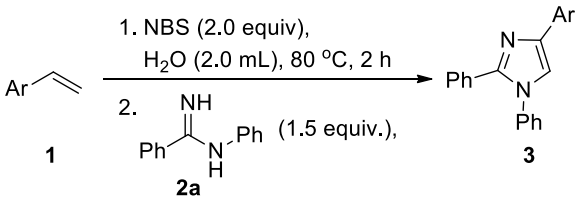


Entry	Halogen Source (equiv)	Oxidant (mol%) [g]	Solvent	Yield (%)[b]
1	I_2	TBHP	DMSO	n.d.
2	I_2	IBX	DMSO	n.d.
3	TBAI	TBHP	H_2O	n.r.
4	KI	Oxone	H_2O	n.r.
5	Br_2		H_2O	54
6	NIS	-	H_2O	57
7	NCS	-	H_2O	70
8	NBS	-	H_2O	75
9	NBS	-	H_2O	42[c]
10	NBS	-	H_2O	65[d]
11	NBS	-	H_2O:acetonitrile	39
12	**NBS**	-	**H_2O:1,4-dioxane**	**80**
13	NBS	-	H_2O:1,4-dioxane	56[e]/ 71[f]

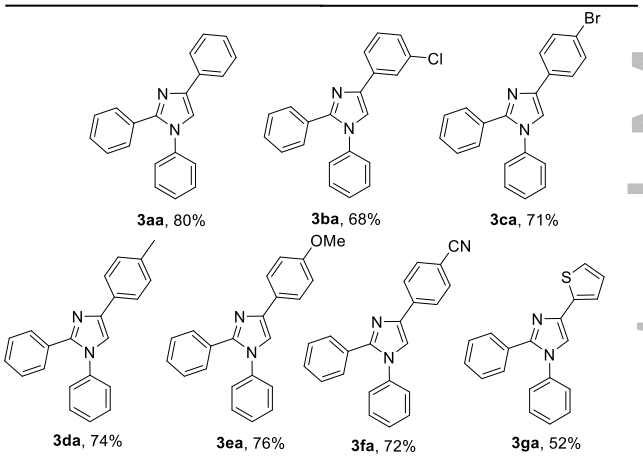
[a]Reaction conditions: Styrene **1a** (1.0 mmol), halogen source (2.0 mmol), oxidant (2.0 mmol), solvent (2.0 mL) were heated at 80 °C for 2 h, *N*-phenylbenzamidine **2a** (1.5 mmol) was added and heating continued at 80 °C for 3 h.
[b]Yield of isolated product after column chromatography.
[c]NBS (1.0 mmol).
[d]*N*-Phenylbenzamidine **2a** (1.0 mmol).
[e]Reaction performed at 60 °C.
[f]Reaction performed at 90 °C.
[g]Abbrevations: TBAI = tetra-butyl ammonium iodide, TBHP = *tert*-butyl hydroperoxide, IBX = 2-idodoxybenzoic acid.

The scope and limitations of this transformation was explored by using various styrenes under the optimized reaction conditions (Table 2). The reaction was found to be robust and unaffected by the nature as well as the position of the substituent present in the aromatic ring. Styrene without any substituent on the phenyl ring offered imidazole **3aa** in 80% yield. Styrenes bearing halogen substituents such as -Cl and -Br at the *meta* and *para* positions reacted smoothly with *N*-Phenylbenzamidine to offer the corresponding imidazoles **3ba** and **3ca** in 68% and 71% yields, respectively. The reaction of styrenes bearing electron donating substituents (4-Me and 4-OMe) proceeded easily with *N*-Phenylbenzamidine to furnish imidazoles **3da** and **3ea** in 74% and 76% yields, respectively. The reaction of styrenes bearing an electron withdrawing substituent (4-CN) with *N*-Phenylbenzamidine resulted in formation of imidazole **3fa** in good yield (72%). We also performed reaction of heterocyclic styrene (2-vinyl thiophene) with *N*-Phenylbenzamidine which gave respective product **3ga** in 52% yield.

Table 2. Scope of Various Styrenes for the Synthesis of 1,2,4-Trisubstituted Imidazoles[a]



Ar= C_6H_5, 3-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-CNC_6H_4, thiophen-2-yl



[a]Reaction conditions: Styrene **1a** (1.0 mmol), NBS (2.0 mmol), water (2.0 mL) were heated at 80 °C for 2 h, *N*-phenylbenzamidine **2a** (1.5 mmol) in 1,4-dioxane (2.0 mL) was added and heating continued at 80 °C for 3 h.

Furthermore, we evaluated the scope of various *N*-arylbenzamidines bearing substituents of varying electronic character and steric effect on both the phenyl rings (Table 3). *N*-Phenylbenzamidines bearing halogen substituents (3-Cl and 4-Cl) produced respective imidazoles **3ab** and **3ac** in 60% and 67% yields, respectively. *N*-Phenylbenzamidines bearing electron-donating substituents (3-Me, 4-Me and 4-OMe) afforded corresponding imidazoles **3ad-3af** in good yields (72-78%). We also tried the reaction of *N*-

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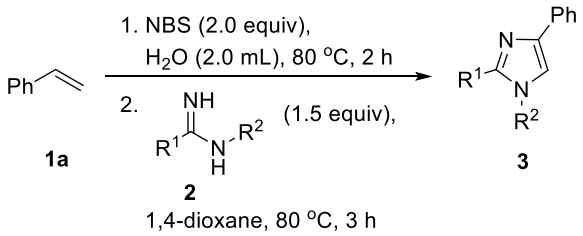
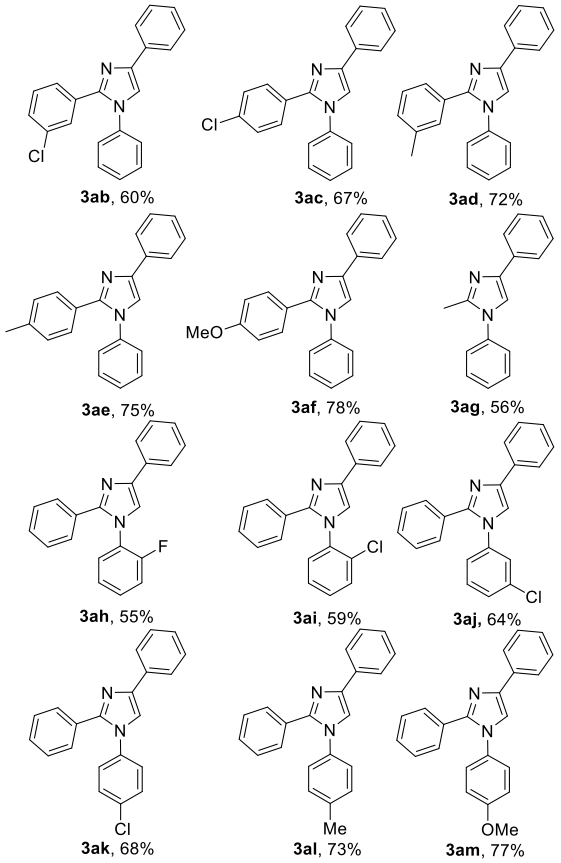
phenylacetamidine with styrene which furnished desired product **3ag** in moderate yield (56%). Likewise, the effect of the substituents on *N*-phenyl ring of *N*-arylbenzamidine was also studied. *N*-arylbenzamidines bearing halogen substituents (2-F, 2-Cl, 3-Cl and 4-Cl) provided corresponding imidazoles **3ah**-**3ak** in moderate to good yields (55-68%). *N*-arylbenzamidines bearing electron-donating substituents (4-Me and 4-OMe) offered corresponding imidazoles in **3al** and **3am** in 73% and 77% yields, respectively.

Table 3. Scope of Various *N*-Substituted Amidines for the Synthesis of 1,2,4-Trisubstituted Imidazoles[a]



R^1= 3-ClC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, -CH_3;

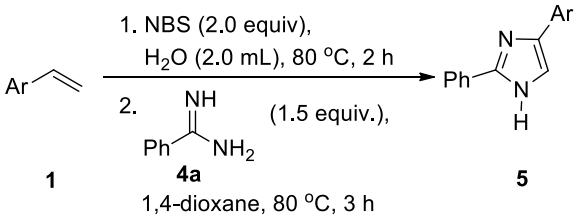
R^2= 2-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$



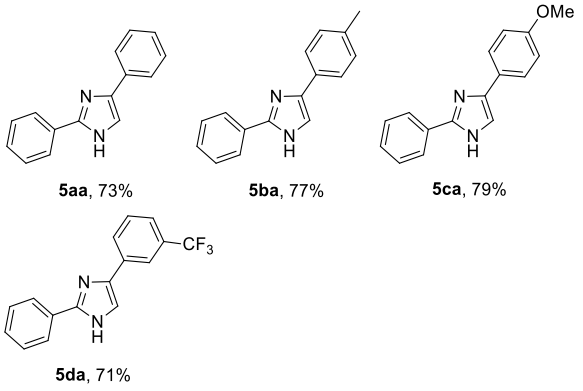
[a]Reaction conditions: Styrene **1a** (1.0 mmol), NBS (2.0 mmol), water (2.0 mL) were heated at 80 °C for 2 h, *N*-arylbenzamidine **2** (1.5 mmol) in 1,4-dioxane (2.0 mL) was added and heating continued at 80 °C for 3 h.

Encouraged with these results, we next focused our attention on the synthesis of disubstituted imidazoles by exploring the reaction of benzamidine with various styrenes (Table 4). Styrene without any substituent on the phenyl ring furnished imidazole **5aa** in 73% yield. Styrene bearing electron-donating (4-Me and 4-OMe) substituents afforded corresponding disubstituted imidazoles **5ba** and **5ca** in 77% and 79% yields, respectively. Styrene bearing an electron-withdrawing substituent (3-CF_3) produced corresponding disubstituted imidazole **5da** in 71% yield.

Table 4. NBS-mediated Synthesis of 2,4-Disubstituted Imidazoles[a]



Ar= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$CF_3C_6H_4$



[a]Reaction conditions: Styrene **1** (1.0 mmol), NBS (2.0 mmol), water (2.0 mL) were heated at 80 °C for 2 h, benzamidine **4a** (1.5 mmol) in 1,4-dioxane (2.0 mL) was added and heating continued at 80 °C for 3 h.

The scope of this method was extended towards the synthesis of quinoxalines (Table 5). We found that reaction by using 1.2 equiv *o*-phenylenediamine under similar reaction conditions offered quinoxalines in good to excellent yields. Styrene on reaction with *o*-phenylenediamine produced quinoxaline **7aa** in 82% yield. Styrenes bearing halogen substituents (2-Br, 3-Cl, 4-Br, 4-Cl and 2,4-Cl_2) afforded corresponding quinoxalines **7ba**-**7fa** in good yield (73-81%). The reaction of styrene bearing electron donating substituents (2-Me, 3-Me, 4-Me, 4-OMe and 2,6-di-OMe) proceeded smoothly to give corresponding quinoxalines **7ga**-**7ka** in good yields (65-74%). 4-Nitrostyrene reacted easily with o-phenylenediamine to afford quinoxaline **7la** in 83% yield. 1-naphthyl and

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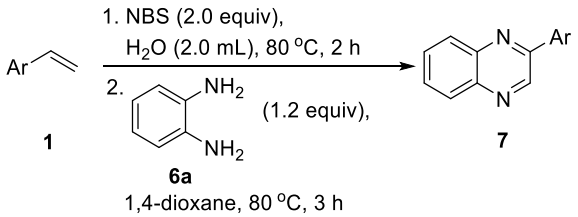
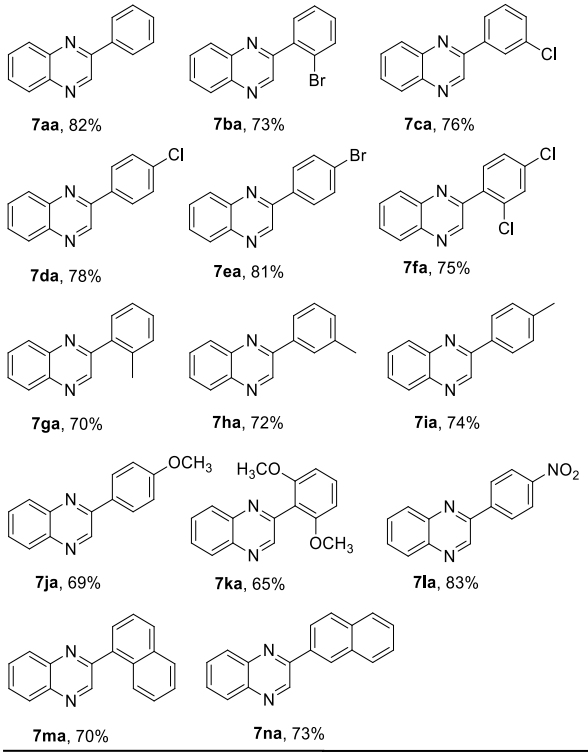
2-naphthylstyrenes offered corresponding products **7ma** and **7na** in 70% and 73% yields, respectively.

Table 5. Scope of Various styrenes for the Synthesis of Quinoxalines[a]



Ar= C_6H_5, 2-BrC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,6-di-$MeOC_6H_3$, 4-$NO_2C_6H_4$, 1-naphthyl, 2-naphthyl

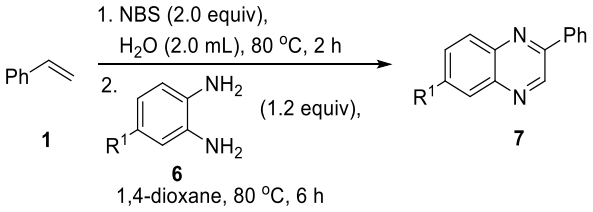


[a]Reaction conditions: Styrene **1** (1.0 mmol), NBS (2.0 mmol), water (2.0 mL) were heated at 80 °C for 2 h, *o*-phenylenediamine **6a** (1.2 mmol) in 1,4-dioxane (2.0 mL) was added and heating continued at 80 °C for 3 h.

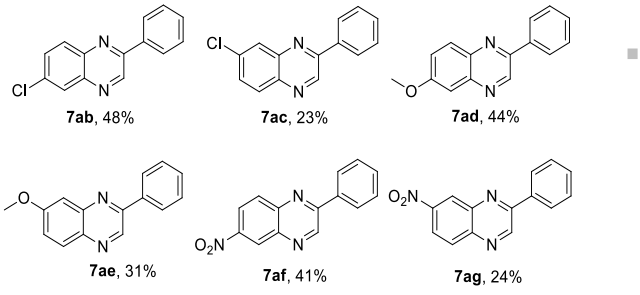
Next, we reacted different *o*-phenylenediamines with styrene in order to explore the effect of substituent on the reactivity and regioselectivity (Table 6). 4-chloro-*o*-phenylenediamine on reaction with styrene produced regioisomers **7ab** and **7ac** in 2:1 ratio with a overall yield of 71%, whereas 4-methoxy-*o*-phenylenediamine reacted easily with styrene to give regioisomers **7ad** and **7ae** in 3:2 ratio with a total yield of 75%. 4-Nitro-*o*-phenylenediamine on reaction with styrene formed regioisomers **7af** and **7ag** in 3:2 ratio with a combined yield of 65%.

To gain insight into the reaction mechanism, few controlled experiments have been performed (Scheme 1). When styrene (**1a**) was reacted with NBS in water at 80 °C for 2 h, formation of α-bromoacetophenone (**D**) was observed. This implied that the reaction involves formation of α-bromoacetophenone (**D**) as

Table 6. Scope of Various *o*-phenylenediamines for the Synthesis of Quinoxalines[a]

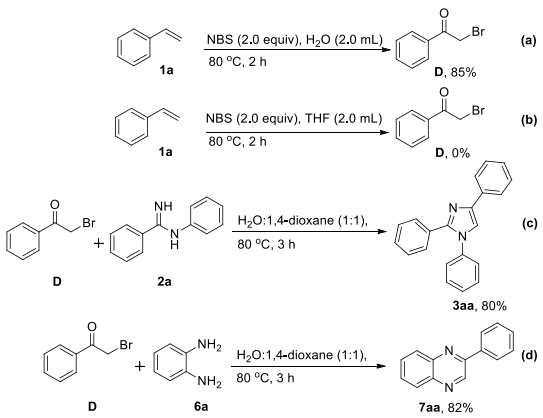


R^1= Cl, OMe, NO_2



[a]Reaction conditions: Styrene **1** (1.0 mmol), NBS (2.0 mmol), water (2.0 mL) were heated at 80 °C for 2 h, *o*-phenylenediamine **6a** (1.2 mmol) in 1,4-dioxane (2.0 mL) was added and heating continued at 80 °C for 3 h

an intermediate. When water was replaced with THF as a solvent, the reaction did not form α-bromoacetophenone (**D**). This highlighted the key role of water in this reaction. α-Bromoacetophenone (**D**) on reaction with *N*-phenylbenzamidine (**2a**) in water afforded imidazole **3aa** in good yields. Similarly, α-bromoacetophenone (**D**) reacted smoothly with *o*-phenylenediamine (**6a**) in water to give quinoxaline **7aa** in good yields.



Scheme 1. Control Experiments

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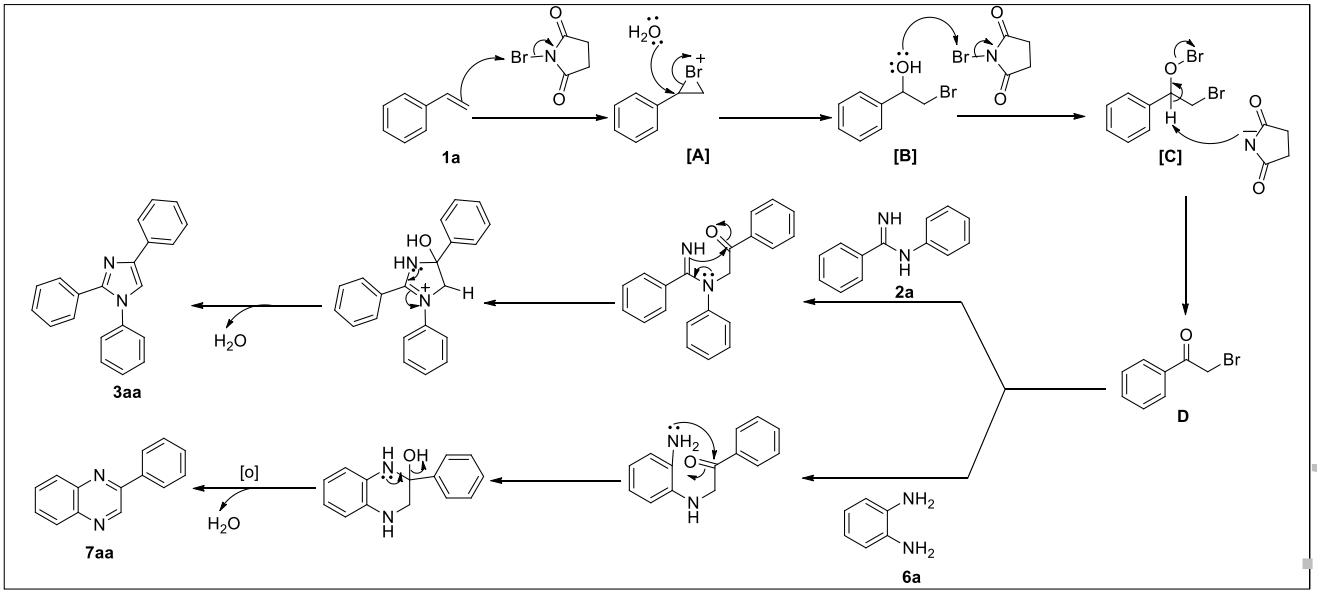

Scheme 2. Proposed reaction mechanism.

On the basis of control experiments and the literature report,[3a] a plausible mechanism is depicted in Scheme 2. Initially, styrene (**1a**) in the presence of NBS forms cyclic bromonium ion [**A**] which undergoes ring opening through nucleophilic attack of H_2O to give intermediate [**B**]. Intermediate [**B**] in the presence of NBS undergoes oxidation to form α-bromoacetophenone [**D**]. Intermediate [**D**] on subsequent condensation with *N*-Phenylbenzamidine (**2a**) and *o*-phenylenediamine (**6a**) offers corresponding products 1,2,4-triphenyl-1*H*-imidazole (**3aa**) and 2-phenylquinoxaline (**7aa**), respectively.

Conclusion

We have developed a one-pot environmentally benign synthesis of substituted imidazoles and quinoxalines through C-H functionalization of easily available styrenes by using *N*-bromosuccinimide as a bromine source as well as an oxidant in water, followed by condensation with *N*-arylbenzamidines and *o*-phenylenediamines. Use of inexpensive reagent, water as a solvent, metal-free conditions, broad substrate scope, good to excellent yields of imidazoles and quinoxalines are notable features of this protocol. We strongly believe that this protocol will serve as an advancement to the existing methods and will be widely adopted for the synthesis of biologically important imidazoles and quinoxalines.

Experimental section

General Experimental Procedure for the Synthesis of Substituted Imidazoles and Quinoxalines.

A round bottom flask equipped with a magnetic stirring bar was charged with Styrene (**1**) (1.5 mmol), NBS (2.0 mmol) and water (2.0 mL) at room temperature. The resulting mixture was heated to 80 °C for 2 h. After disappearance of the reactant (monitored by TLC), substituted *N*-arylbenzamidine **2**/ *o*-phenylenediamine **6** (1.0 mmol) was added and heating continued at 80 °C for 3 h. After completion of the reaction, 10 mL of water was added and the resulting mixture extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with 10% $Na_2S_2O_3$ solution (10 mL) and brine solution (10 mL) successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on 100:200 mesh silica gel by using *n*-hexane:ethyl acetate as the eluent to obtain the corresponding imidazole (**3**)/ quinoxaline (**7**).

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Author contribution

†Authors contributed equally to this work.

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FULL PAPER

One-Pot Protocol for the Synthesis of Imidazoles and Quinoxalines using NBS

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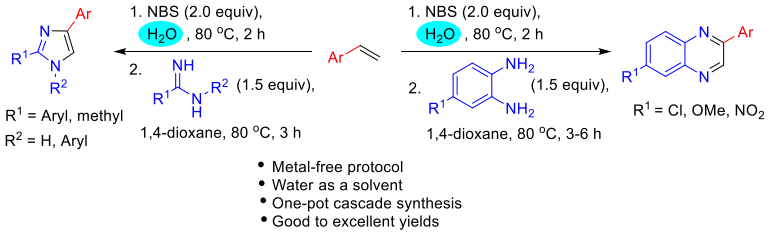

- Metal-free protocol
- Water as a solvent
- One-pot cascade synthesis
- Good to excellent yields