Water Extract of Onion Catalyst: An Economical Green Rou for the Synthesis of 2-substituted and 1,2-disubstituted Benzimidazole Derivatives with high selectivity

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Abstract. An efficient, environmental friendly and substrate controlled method of synthesis of 2-substituted benzimidazole derivatives **3** and 1,2-disubstituted benzimidazole derivatives **4** with high selectivity has been achieved from the reaction of o-phenylenediamine **1** and aldehydes **2** in the presence of water extract of onion and selecting suitable reaction medium. This method is widely applicable for variety of aldehydes such as aromatic/aliphatic/heterocyclic aldehydes and 1,2-diamines to afford 2-substituted benzimidazole derivatives **3** and 1,2-disubstituted benzimidazole derivatives **4** in good to excellent yields (up to 96%). The developed method of water extract of onion catalysis produced 2-substituted benzimidazoles **3** from aromatic aldehydes having electron-withdrawing groups, whereas aromatic aldehydes bearing electron donating groups selectively furnished 1,2-disubstituted benzimidazole **4** derivatives. The process described here has several advantages of cheap, low energy consumption, commercially available starting materials, operational simplicity and nontoxic catalyst. The use of water extract of onion makes this present methodology green and giving a useful contribution to the existing methods available for the preparation of benzimidazole derivatives. In addition, Hammett correlation of substituent constant (σ) versus percentage (%) yield has been established.

Keywords: Water Extract of Onion, 2-substituted benzimidazoles, 1,2-disubstituted benzimidazoles Selectivity, Green Catalyst, 1,2-Diamines

Introduction

Benzimidazole is a bicyclic aromatic heterocyclic compound, consists of fusion of benzene and imidazole unit.[1] The imidazole core is a common moiety present in a large number of natural products and pharmacologically active compounds. It is an important pharmacophore and a privileged structure in medicinal chemistry.[2] Benzimidazole and their derivatives have displayed excellent biological activities such as antihistaminic, antifungal, antiulcer,[3] antipyretic, and anesthetic[4] and antiviral activities like HIV,[5] influenza, RNA,[6] human cytomegalovirus[5] and herpes (HSV-1).[7] In addition, act as antibacterial agents against *gram-negative* bacteria, MRSA, topoisomerase inhibitors,[8a-c] selective neuropeptide YY1 receptor antagonists,[9] factor Xa inhibitor,[10] angiotensin II inhibitors, and 5-HT_3[11] (Figure. 1). Therefore the synthesis of benzimidazole derivatives have received great attention nowadays. The well-known and exploited route to benzimidazole **3** involves the direct condensation of 1,2-diamines **1** with aldehydes **2** or carboxylic acids in the presence of strong dehydrating agent like H_2SO_4.[12] Other improved procedures have also been subsequently reported which include reductive cyclization reaction of *o*-nitroaniline with aldhehyde, palladium catalyzed tandem carbonylation- cyclization reaction[13] and the reaction of aldehydes **2** with 1,2-diamines **1** in the presence of catalysts such as trifluoroacetic acid,[14] $TiCl_4.SiO_2$,[15] $Bi(OTf)_3$,[16] $Bi(NO_3)_3$,[17] TMSCl,[18] ZnO-NPs,[19] *L*-proline,[20] $Fe(ClO_4)_3$,[21] solvent free $SiO_2/ZnCl_2$,[22] $Fe_3O_4@SiO_2@(NH_4)_6Mo_7O_{24}$,[23] SDS micelles,[24] CAN,[25] $Cu(OTf)_2$,[26] Phospho sulfonic acid,[27] $ZrOCl_2.nH_2O$/montmorillonite K10,[28] montmorillonite K-10,[29] NaPTSA,[30] DBSA,[31]

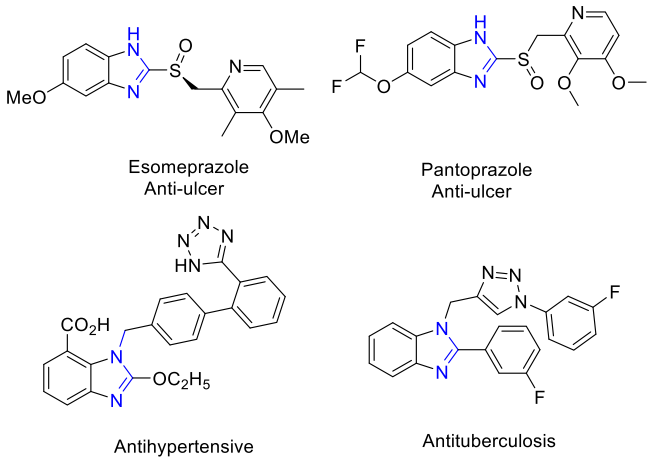

Figure 1. Representative biologically active molecules containing 2-substituted benzimidazole **3** and 1,2-disubstituted benzimidazole **4** moiety.

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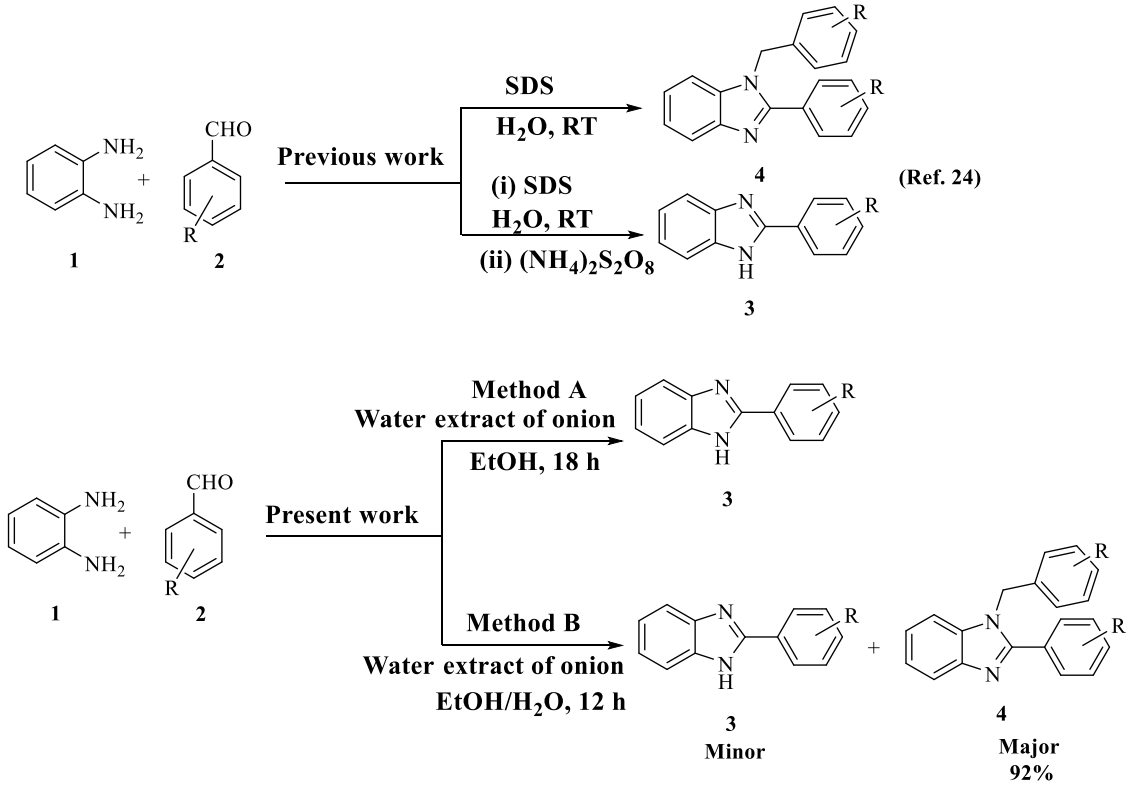
Alumina-sulfuric acid,[32] γ-Fe_2O_3@SiO_2 NPs,[33] $RuCl_2(PPh_3)_3$,[34] Lewis acidic ionic liquids,[35] $CoCl_2.6H_2O$,[36] PSFSI/SBA-15,[37] $FeCl_3$-PANI,[38] $Sm(OTf)_3$,[39] $Na_2S_2O_5$,[40] $In(OTf)_3$,[41] microwave irradiation,[42] 1-heptanesulfonic acid sodium salt,[43] and $BF_3{\cdot}OEt_2$.[44] Unluckily, many of these are have major or minor limitations such as employing considerable amounts of toxic solvents, drastic reaction conditions, highly expensive catalyst and some of the metal based Lewis acid catalyzed reactions toxic to the environment. One of the major limitations is poor selectivity of N-1 substitution, results in the formation of mixture of 1,2-disubstituted benzimidazole **4** and 2-substituted benzimidazole **3.** To best of our knowledge, only one report available for selective synthesis of both 2-substituted benzimidazole derivatives **3** and 1,2-disubstituted benzimidazole derivatives **4** with a particular catalyst[24] (Scheme 1), where $(NH_4)_2S_2O_8$ has been employed as additional oxidizing agent for the synthesis of 2-disubstituted benzimidazoles **3**.



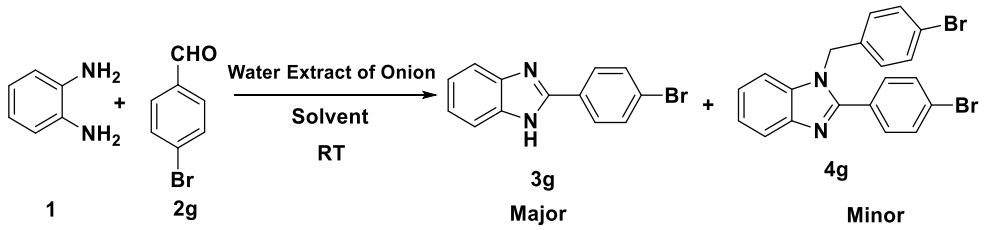
Scheme 1. General scheme for the synthesis of benzimidazole derivatives.

Development of environmentally benign and cost reductive synthesis is one of the important aspects in organic synthesis. Elimination of harmful solvents and substances are shown the regards due to inexpensive, readily available and environmentally benign. We report herein, chemoselective synthesis of 2-substituted benzimidazole derivatives **3** and 1,2-disubstituted benzimidazole derivatives **4** by using water extract of onion as a green catalyst under mild conditions.

Results and Discussion

In continuation of our previous work for the development of green synthetic procedure[45-47] using water extract of onion as catalyst, we are very much interested to develop the cost reductive, chemoselective synthesis of 2-substituted benzimidazole derivatives **3** and 1,2-disubstituted benzimidazole derivatives **4**, we have examined the reaction of *o*-phenylenediamine (1 equiv) **1** with aldehyde (2 equiv) **2** in the presence of water extract of onion (3 mL) at 90 ^oC for 12 h in DMF (5 mL) gave the mixture of 2-substituted **3** benzimidazoles (67%) and 1,2-disubstituted (28%) **4** benzimidazoles (Table 1, entry 1). The method of preparation of required water extract of onion reported earlier from our research group[45]. Primarily, efforts were undertaken towards chemoselective synthesis of 2-substituted benzimidazole derivatives **3** (scheme 1; method A). Accordingly, to achieve the target we have play around three parameters such as equivalent of the substrates, polarity of the solvent, and loading of the catalyst. For optimization study we have choose o-phenenylenediamine **1** and 4-bromobenzaldehyde **2g** as the substrates. The results are summarized in table 1.

Table 1. Optimization of reaction conditions with various solvents and loading of the catalyst for the synthesis of compound **3**



Entry[a]	Substrate (equiv.)		Solvent	Cat. (mL)	Temp (^{o}C)	Time (h)	Product (equiv.) Yield (%)[b]	
	1	**2g**					**3g**	**4g**
1[c]	1	2	DMF (5 mL)	3	90	12	67	28
2[d]	1	2	EtOH (5 mL)	3	70	12	53	24
3	1	1	EtOH (5 mL)	3	70	12	77	10
4	1	1	EtOH (5 mL)	1.5	70	16	89	5
5	1	1	EtOH (15 mL)	0.5	RT	18	93	-
6	1	1	EtOH/H_2O (2:1) (15 mL)	0.5	RT	24	62	10

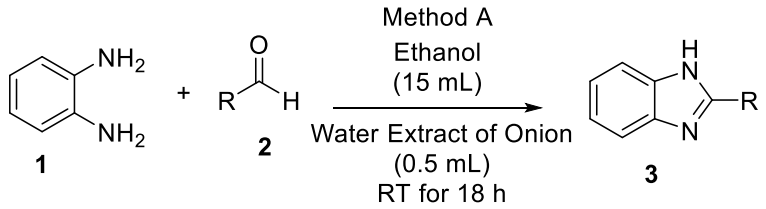
[a)] Unless otherwise mentioned, all the reactions were carried out using *o*-phenylenediamine **1** (1 equiv.), 4-bromo benzaldehyde **2g** (1 equiv.) in various solvent and water extract of onion; [b)] The products were characterized by using HR-MS, IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques and the yields are all isolated products. [c)] The reaction was carried out using *o*-phenylenediamine **1** (1 equiv.), 4-bromo benzaldehyde **2g** (2 equiv.) in DMF (5 mL) and water extract of onion (3 mL) at 90 ^{o}C.; [d)] The reaction was performed using *o*-phenylenediamine **1**(1 equiv.), 4-bromo benzaldehyde **2g** (2 equiv.) in EtOH (5 mL) and water extract of onion (3 mL) at 70 ^{o}C.

When the reaction was carried out using *o*-phenylenediamine **1** (1 equiv.), an aldehyde **2g** (2 equiv.) in EtOH (5 mL) at 70 ^{o}C for 12 h in the presence of onion extract (3 mL) gave compounds **3g** and **4g** with 53% and 24% yields respectively (Table 1, entry 2). The reaction was repeated under the same condition except substrate ratio (1:1) to obtain products **3g** and **4g** with 77% and 10% yields respectively (Table 1, entry 3). In order improve the yield of compound **3g**, the reaction was carried out using *o*-phenylenediamine **1** (1 equiv.) with aldehyde **2g** (1 equiv.) in EtOH (5 mL) at 70 ^{o}C for 16 h in the presence of onion extract (1.5 mL) gave the desired products **3g** and **4g** with 89% and 5% yields respectively (Table 1, entry 4). We thought that the dilution as well as loading of the catalyst may affect the selectivity.

Accordingly, we have examined the reaction of *o*-phenylenediamine **1** (1 equiv.) with 4-bromobenzaldehyde **2g** (1 equiv.) in EtOH (15 mL) at room temperature for 18 h in the presence of onion extract (0.5 mL), gave compound **3g** in 93% yield and did not observed any traces of compound **4g** (Table 1, entry 5). An increasing the polarity of the solvent may interfere in the selectivity, therefore, we have carried out the reaction of *o*-phenylenediamine **1** (1 equiv.) with 4-bromobenzaldehyde **2g** (1 equiv.) in EtOH:H_2O (2:1; 15 mL) at room temperature for 24 h in the presence of onion extract (0.5 mL), gave compounds **3g** and **4g** in 62% and 10% yields respectively (Table 1, entry 6).

Under the above optimized conditions, we have examined the scope of the reaction for the construction of various 2-substituted benzimidazoles **3** by altering the substituted aldehydes **2** and *o*-phenylenediamine **1**. As shown in Table 2, a wide range of substituted groups of aldehyde gave excellent yields, which include methoxy, methyl, fluoro, chloro, bromo, ester, cyano and nitro groups. It is noteworthy that strong electron withdrawing substituent containing aldehyde such as ester, cyano and nitro had high yields (Table 2, entries 8-10). In addition, it should be noted that good yields were also obtained by using other aromatic systems containing electron donating substituents (Table 2, entries 2-3), furfuraldehyde (Table 2, entry 12), thiazole-2-carboxaldehyde (Table 2, entry 13) and aliphatic aldehydes (Table 2, entries 14-15). However, aromatic aldehyde contains strong electron donating hydroxyl group (Table 2, entry 1) gave only 1,2-disubstituted benzimidazole **4a**, not

Table 2. Synthesis of 2-substituted benzimidazole derivatives **3**



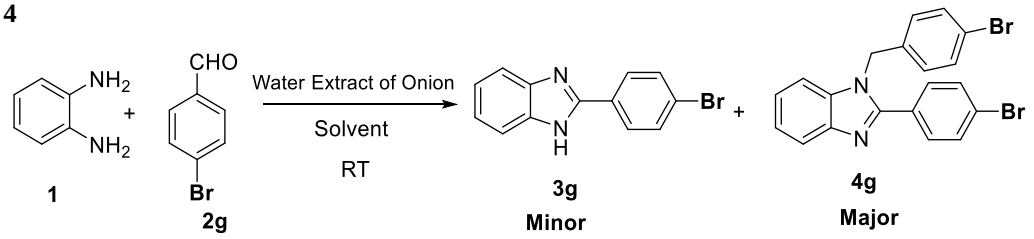
Entry [a]	R		Time (h)	Products **3**/**4**[b]	Method A Yield (%)[c]	
					3	**4**
1	4-OH-C_6H_4	**2a**	21	**4a**	-	88
2	4-OMe-C_6H_4	**2b**	24	**3b**	80	Trace
3	4-Me-C_6H_4	**2c**	24	**3c**	83	Trace
4	C_6H_{5-}	**2d**	18	**3d**	84	-
5	4-F-C_6H_4	**2e**	18	**3e**	86	-
6	4-Cl-C_6H_4	**2f**	18	**3f**	88	-
7	4-Br-C_6H_4	**2g**	18	**3g**	93	-
8	4-CO_2Me-C_6H_4	**2h**	18	**3h**	94	-
9	4-CN-C_6H_4	**2i**	18	**3i**	93	-
10	4-NO_2-C_6H_4	**2j**	18	**3j**	96	-
11	2-NO_2-C_6H_4	**2k**	18	**3k**	84	-
12	2-Furfuryl	**2l**	18	**3l**	88	-
13	2-Thiophenyl	**2m**	18	**3m**	83	-
14	n-Butyl	**2n**	20	**3n**	72	-
15	Cyclohexyl	**2o**	18	**3o**	79	-

[a)] All the reaction were carried out using *o*-phenylenediamine **1** (1 equiv.) and aldehyde **2** (1 equiv.), EtOH (15 mL) and water extract of onion (0.5 mL) at room temperature, appropriate time mentioned in the table. [b)] All the products were characterized by using ^{1}H NMR, ^{13}C NMR, HR-MS and IR spectroscopic techniques. [c)] The yields are all isolated.

observed even traces of 2-substituted benzimidazole **3** under similar conditions. Probably, the strong electron donating hydroxyl group prevent the intramolecular cyclization results to form diimine intermediate **9** and then cyclized.

In addition, the scope of the reaction using onion extract catalyst with 1,2-diamine: aldehyde (1:2) in EtOH: Water (2:1) to give 1,2-disubstituted benzimidazoles **4** was evaluated. The above observation (Table 1. Entry 6), we thought that to increase the equivalent of aldehyde and polarity of the solvent may prevent the intramolecular cyclization of imine **6**. Accordingly, we have examined the reaction of 1,2-diamine **1** (1 equiv.) with an aldehyde **2g** (2 equiv.) in EtOH (5 mL) in the presence of onion extract (2 mL) at room temperature for 24 h to give 2-substituted **3g** and 1,2-disubstituted **4g** benzimidazoles 31% and 66% yields respectively (Table 3, entry 2) . In order to obtain good yields, the reaction was carried out similar conditions, gave 2-substituted benzimidazole **3g** and 1,2-disubstituted **4g** benzimidazole 22% and 68% yields (Table 3, entry 3), here the catalyst water extract of onion was added after 3 h. The results are summarized in table 3. Under the same conditions, to increase the equivalent of aldehyde **2g** from 2.0 to 2.5 at 70 ^{o}C gave **3g** and **4g** 24% and 73% yields respectively (Table 3, entry 4). We felt that to increase the solvent polarity, we could able to achieve selectively compound **4g**. Accordingly, the reaction was carried out by using 1,2-diamine **1** (1 equiv.) with an aldehyde **2g** (2.5 equiv.) in EtOH: Water (2:1; 6 mL) in the presence of onion extract (2 mL) at room temperature for 12 h gave 2-substituted benzimidazole **3g** and 1,2-disubstituted benzimidazole **4g** in 9% and 81% yields (Table 3, entry 5). Further increase the polarity of the medium would not give better yield (Table 3, entries 6-7).

Table 3. Optimization of reaction condition with various solvents and loading of onion extract for the synthesis of compound **4**



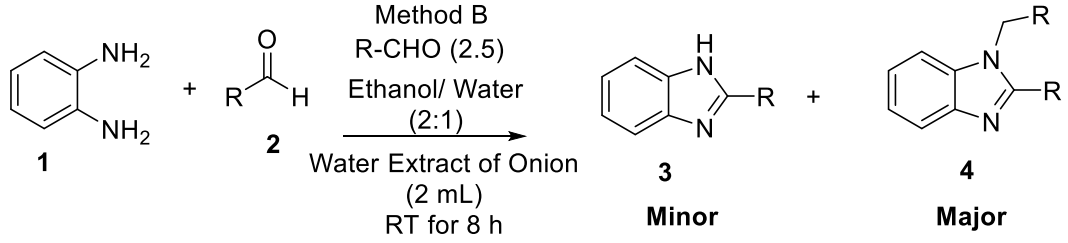
Entry[a]	Substrate (equiv.)		Solvent	Cat. (mL)	Temp (^{o}C)	Time (h)	Product (equiv.) Yield (%)[b]	
	1	**2**					**3g**	**4g**
1	1	2	EtOH (5 mL)	0.1	RT	12	32	55
2	1	2	EtOH (5 mL)	2	RT	24	31	66
3[c]	1	2	EtOH (5 mL)	2	RT	24	22	68
4	1	2.5	EtOH (5 mL)	2	70	12	24	73
5	1	2.5	EtOH/H_2O (2:1; 6 mL)	2	RT	12	09	81
6	1	2.5	EtOH/H_2O (1:2; 6 mL)	2	RT	36	18	43
7	1	2.5	H_2O (6 mL)	2	RT	12	26	51

[a)] Unless otherwise mentioned, all the reactions were carried out using *o*-phenylenediamine **1** (1 equiv.), 4-bromo benzaldehyde **2g** (2.5 or 2 equiv.) in different solvent and water extract of onion at room temperature. [b)] The products were characterized by using Mass, IR, ^{1}H NMR, ^{13}C NMR and HPLC spectroscopic techniques and the yields are all isolated products. [c)] The reaction was carried out using o-phenylenediamine **1** (1 equiv.), 4-bromo benzaldehyde **2g** (2 equiv.) in EtOH (5 mL) stirred at RT for 3 h, then water extract of onion (2 mL) was added and further stirred at same temperature for 24 h.

Once optimized conditions in hand, we have examined the scope of the reaction for the construction of various 1,2-substituted benzimidazoles **4** by altering the substituted aldehydes **2** and *o*-phenylenediamines **1**. It is noteworthy that strong electron donating substituted groups of aldehyde such as hydroxyl, methoxy, methyl, electron withdrawing fluoro, chloro, bromo and heteroaromatic systems like 2-furfuryl and 2-thiophenyl groups had high yields (Table 4, entries 1-3, 5-7 and 11-12). It was observed that under the same conditions, the strong

electron withdrawing groups such as ester, cyano and nitro (Table 4, entries 8-10) gave exclusively compound **3.** This may be due to the electron withdrawing nitro group increase the electrophilicity of the imine **6** carbon so that an intramolecular cyclization happened to form compound **3.**

Table 4. Synthesis of 1,2-disubstituted benzimidazole **4** derivatives



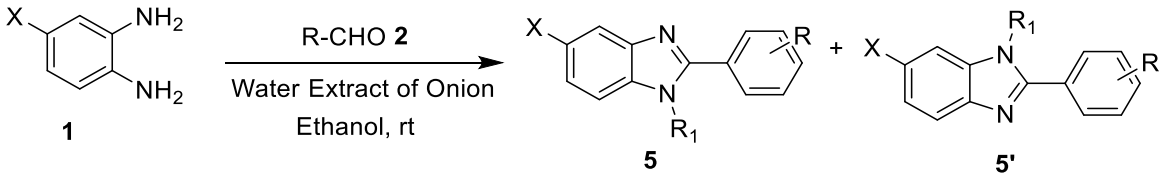
Entry[a]	R		Time (h)	Products **4/3**[b]	Yield (%)[c] Method B	
					3	**4**
1	4-OH-C_6H_4	**2a**	10	**4a**	-	92
2	4-OMe-C_6H_4	**2b**	12	**4b**	09	89
3	4-Me-C_6H_4	**2c**	12	**4c**	-	86
4	C_6H_5	**2d**	12	**4d**	-	83
5	4-F-C_6H_4	**2e**	10	**4e**	trace	80
6	4-Cl-C_6H_4	**2f**	10	**4f**	11	78
7	4-Br-C_6H_4	**2g**	8	**4g**	18	81
8	4-CO_2Me-C_6H_4	**2h**	8	**3h**	84	-
9	4-CN-C_6H_4	**2i**	8	**3i**	87	-
10	4-NO_2-C_6H_4	**2j**	8	**3j**	96	-
11	2-Furfuryl	**2l**	8	**4h**	-	91
12	2-Thiophenyl	**2m**	8	**4i**	12	80

[a] All the reaction were carried out using *o*-phenylenediamine **1** (1 equiv.) and aldehyde **2** (2.5 equiv.), EtOH/ water (2: 1) and water extract of onion (2 mL) at room temperature, appropriate time mentioned in the table. [b] All the products were characterised by using ^{1}H NMR, ^{13}C NMR, HR-MS and IR spectroscopic techniques. [c] The yields are all isolated products.

To further expand the scope of the diamine substrates, we employed 4-OMe, H and 4-NO_2 benzaldehydes as model substrates and examined different diamines. When the reaction was carried out using 1,2-diamine **1a** and aldehydes (1 equiv.) (method A) such as 4-OMe-C_6H_4 **2b**, -C_6H_5 **2d**, 4-F-C_6H_4 **2e**, 4-NO_2-C_6H_4 **2j,** the reaction proceeded smoothly to provide good yields of 2-substituted benzimidazoles with different ratios of isomers **5** and **5'.** In the case of 4-OMe-C_6H_4 and benzaldehyde derivatives, the isomers **5a, 5a'** and **5b, 5b'** were clearly seen in the ^{1}H NMR spectrum but could not able to isolate. For example, compound **5b** and **5b'** the ^{1}H NMR at δ 2.42, 2.44

corresponds to methyl and δ 12.74, 12.77 corresponds to imidazole –NH (Table 5, entries 1-2 see supplementary, page No. S36-S37).. Whereas, the compound containing electron withdrawing 4-F-C_6H_4 **2e**, 4-NO_2-C_6H_4 **2j,** derivatives, the isomeric separation were not observed (Table 5, entries 3-4 see supplementary, page No. S38-S39). When we examined the reaction with 4-methylphenylene-1,2-diamine **1a** and aldehydes (2.5 equiv) such as 4-OMe-C_6H_4 **2b**, -C_6H_5 **2d**, in Ethanol:water (2:1) system (method B), gave isomeric mixture of 1,2-disubstituted benzimidazoles **5h/5h'** and **5i/5i'** respectively (Table 5, entries 8-9 see supplementary, page No. S43-S44). Whereas in the case of aldehyde (2.5 equiv) 4-NO_2-C_6H_4 **2j**, gave only 2-substituted benzimidazoles **5d**. In the case of 4- chlorobenzene-1,2-diamine **1b** with aldehydes (1 equiv. or 2.5 equiv) failed to give isomeric mixture of 1,2-disubstituted benzimidazoles, Instead gave only 2-substituted benzimidazole in moderate to good yields (Table 5, entries 5-7 and 11-13; see supplementary, page No. S40-S42). In general, electron withdrawing group present in X or R position gave only 2-substituted benzimidazoles. This may probably, due to fast exchange of hydrogen between imidazole nitrogen the isomeric separation of the product could not see in ^{1}H NMR spectrum.

Table 5. Synthesis of 1,2-disubstituted benzimidazole **5/5'** derivatives able Caption.



Entry[a]	X	R		R_1	Time (h)	Product **5/5'**	Yield (%)[b] **5/5'**
1	Me (**1a**)	4-OMe	(**2b**)	H	18	**5a/5a'**	81
2	Me (**1a**)	H	(**2d**)	H	16	**5b/5b'**	89
3	Me (**1a**)	4-F	(**2e**)	H	16	**5c**	87
4	Me (**1a**)	4-NO_2	(**2j**)	H	16	**5d**	93
5	Cl (**1b**)	4-OMe	(**2b**)	H	16	**5e**	79
6	Cl (**1b**)	H	(**2d**)	H	18	**5f**	65
7	Cl (**1b**)	4-NO_2	(**2j**)	H	24	**5g**	73
8[c]	Me (**1a**)	4-OMe	(**2b**)	4-OMe- $C_6H_4CH_2$-	12	**5h/5h'**	83
9[c]	Me (**1a**)	H	(**2d**)	$C_6H_5CH_2$	8	**5i/5i'**	87
10[c]	Me (**1a**)	4-NO_2	(**2j**)	H	12	**5d**	82
11[c]	Cl (**1b**)	4-OMe	(**2b**)	H	15	**5e**	73
12[c]	Cl (**1b**)	H	(**2d**)	H	12	**5f**	91
13[c]	Cl (**1b**)	4-NO_2	(**2j**)	H	24	**5g**	56

[a)] Unless otherwise mentioned, all the reaction were carried out using 1,2-diamine **1a/1b** (1 equiv.) and aldehyde **2** (1 equiv.), EtOH (15 mL) and water extract of onion (0.5 mL) at room temperature, appropriate time mentioned in the table. [b)] Yields are all isolated yields. [c)]All the reaction were carried out using 1,2-diamine **1a** /**1b** (1 equiv.) and aldehyde **2** (2.5 equiv.), EtOH/ water (2: 1; 6 mL) and water extract of onion (2 mL) at room temperature, appropriate time mentioned in the table.

In order to understand clearly the formation of the products **3** (Table 2) and **4** (Table 4**)**, the plot were drawn substituent constant (σ) vs yields of the products (%) of **3** and **4** as shown in Figure 2. The strong electron donating substituent 4-OH-C_6H_4 having σ value -0.37 gave only 1,2-disubstituted benzimidazole **4** with 92% yield. In the same

way the strong electron withdrawing substituent 4-NO_2-C_6H_4 having σ value 0.78 gave only 2-substituted benzimidazole **3** with 96% yield. The figure 2, clearly shows that the substituent constant σ increases, the yield of compound **3** also increases and yield of compound **4** decreases. Substituent constant σ directly proportional to yield of compound **3** and indirectly proportional to compound **4**. At the neutral point substituent constant is 0, both the product **3** and **4** are formed almost same yield.

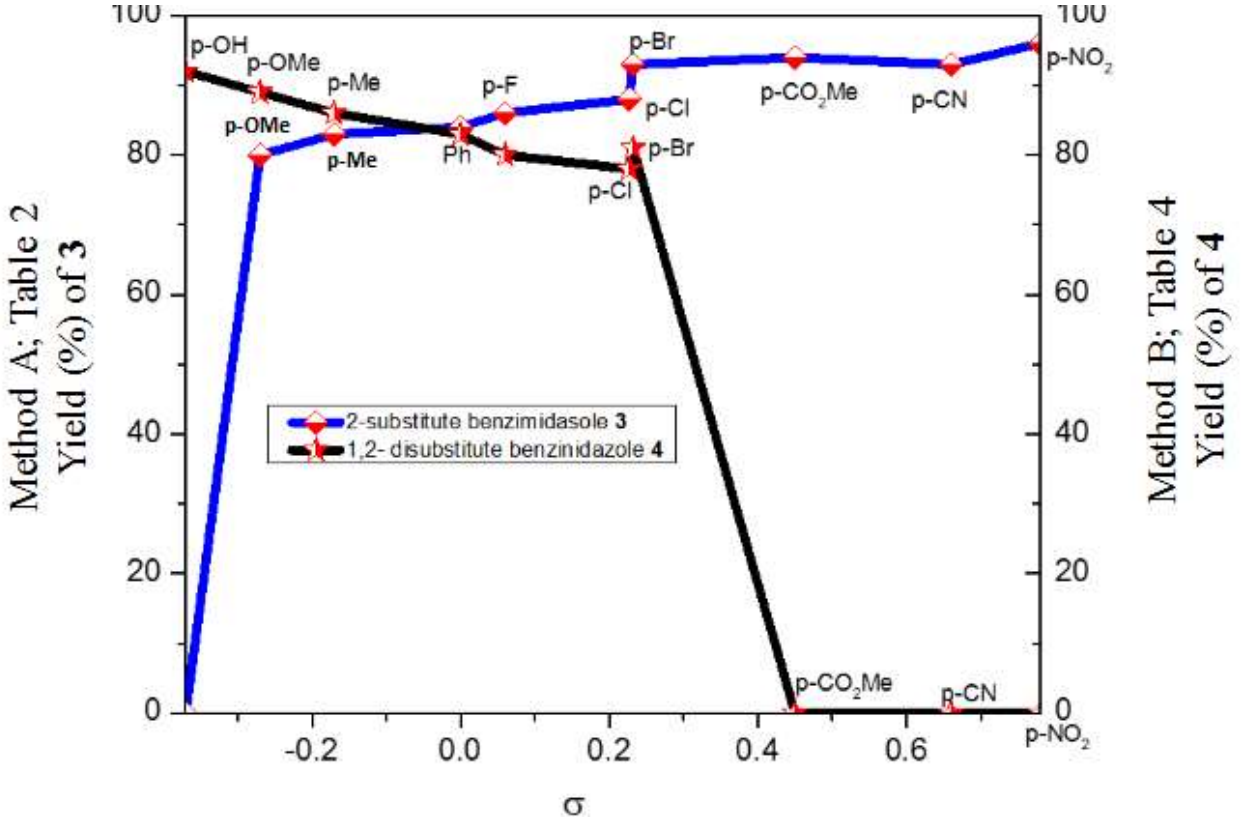


Figure 2. Plot of substituent constants Vs yields (%) of the products **3** and **4**

Although the effect of reaction conditions to direct the subsequent processes to 2-substituted benzimidazole **3** and 1,2-disubstituted benzimidazole **4** systems respectively remains to be fully clarified, the polarity of the solvent and equivalent of substrate must play a role in determining the product distribution.

In order to evaluate the possibility of applying this methodology in a large scale, we carried out the reaction of equimolar amounts (10 mmol) of diamine **1** with 4-NO_2 benzaldehyde **2j**. The 2-substituted benzimidazole **3j** was obtained in similar yield as that of the small scale reaction (2 mmol).

To probe the mechanism of the reaction, several control experiments were performed. The reaction was carried out with **1** (1 equiv) and **2** (1 equiv) in the presence of water extract of onion (0.5 mL) in EtOH (15 mL) and the reaction of **1** (1 equiv) and **2** (2.5 equiv) in the presence of onion extract (2 mL) in EtOH: water (2:1; 6 mL) at room temperature, with TLC monitoring the formation of intermediates **6** and **9** respectively, which was separated and identified by ^{1}H NMR spectral technique. Based on the observations and the similar mechanisms conferred in the literature[22,33,48] a plausible mechanism for this reaction was proposed as shown in Figure 3. Initially, the imine intermediate **6** was formed from the condensation of aldehyde **2** and *o*-phenylenediamine **1,** facilitated by onion extract. Then the formed imine **6** contains electron withdrawing group the electrophilicity of imine attached carbon (-N=C-) increased. Hence, another amine nucleophile present in the **1** immediately attacked electrophilic carbon center in an intramolecular fashion to form 2-substituted benzimidazole **3**. The formed imine contains electron donating group the electrophilicity of imine attached carbon (-N=C-) decreased. Therefore, another -NH_2 of the o-phenylenediamine **1** condensed with available aldehyde **2** to form intermediate **9**. Further, the intermediate **9** undergo intramolecular cyclization followed by 1,3-hydride transfer[49] to form 1,2-disubstituted benzimidazole **4**.

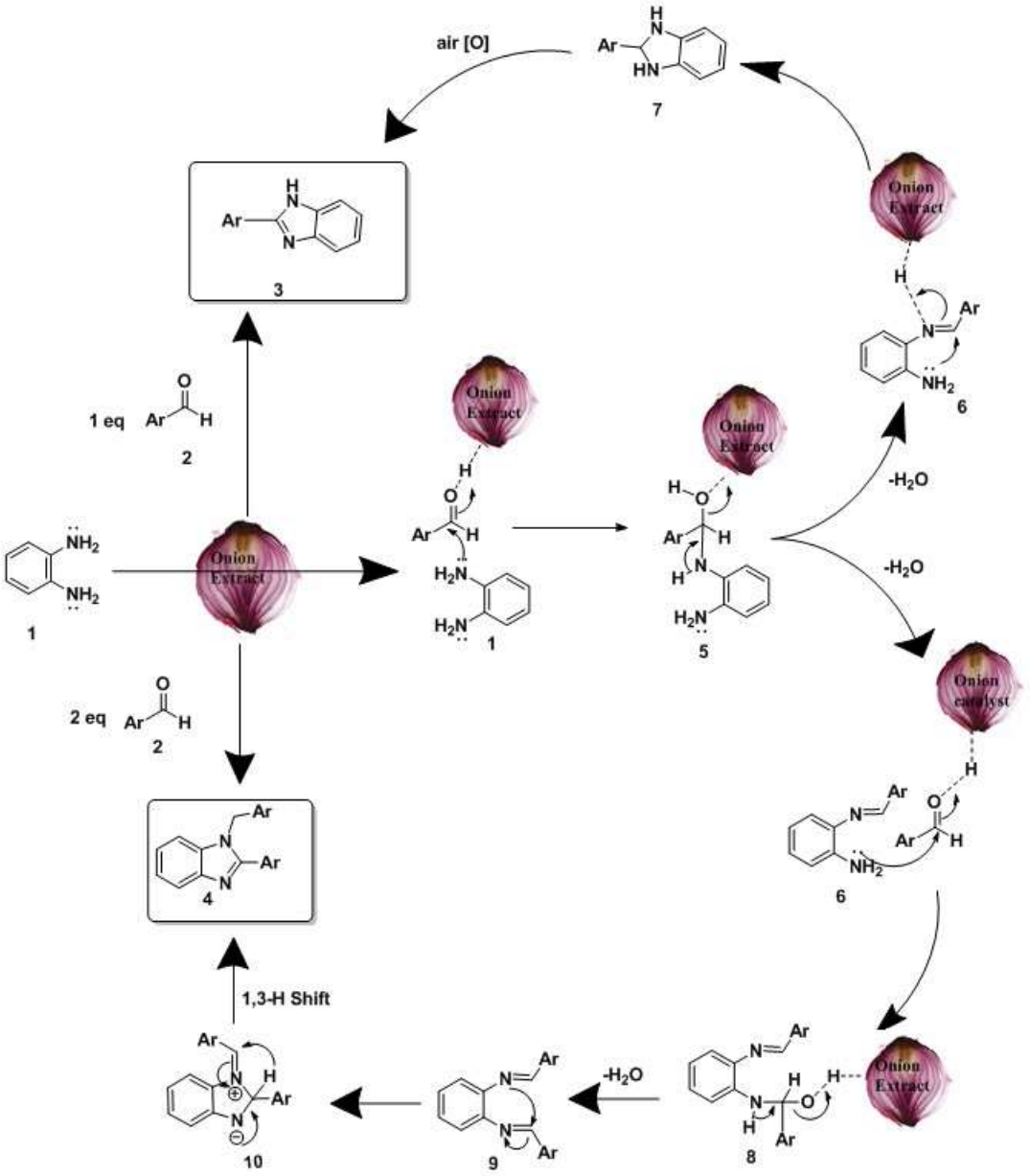


Figure 3. Plausible mechanism

Conclusions

In conclusions, we have demonstrated an efficient and practical approach for the chemoselective synthesis of 2-substituted benzimidazole derivatives **3** and 1,2-disustituted **4** benzimidazole derivatives from 1,2-diamines **1** and aldehydes **2** in the presence of water extract of onion as green catalyst. The broad substrate scopes of 1,2-diamines such as 1,2-phenylenediamine **1**, 4-methyl-1,2-phenylenediamine **1a**, 4-chloro-1,2-phenylenediamine **1b** and aldehydes like aromatic/aliphatic/heteroaromatic were also studied. The intermediates **6** and **9** were also isolated, characterized and plausible mechanism was discussed. The high yields of the products, operational simplicity, non-toxic and high chemoselectivity are the main advantages of this method. The use of onion extract makes this procedure is cheap, safe and environmentally benign.

Supplementary information

The Supplementary information file containing general procedure for the preparation of 2-substituted benzimidazoles **3** (Method A), 1,2-disubstituted benzimidazoles **4** (Method B) ; Characterization data for compounds **3**, **4**, **5** and intermediates **6 & 9** (**3c-3o ; 4b-4i**, **5a-5i**) ; and Copies of NMR spectra.

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References

[1] G. C. Wadhawa, V. S. Shivankar, D. D. Patil, Y. A. Gaikwad, L. V. Gavali, C. H. Gill, World. J. Pharm. Sci. *2016*, 5, 624.

[2] M. J. Tebbe, W. A. Spitzer, F. Victor, S. C. Miller, C. C. Lee, T. R. Sattelberg, S. E. McKinney, J. C. Tang, J. Med. Chem. *1997***,** 40, 3937.

[3] (a) H.-J. Federsel, M. Larsson, Asymmetric Catalysis on Industrial Scale, (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, *2004*, p 413. (b) H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sçrensen, S. V. Unge, Tetrahedron: Asymmetry *2000*, 11, 3819. (c) H.-J. Federsel, Nat. Rev. Drug Discovery *2005*, 4, 685. (d) H.-J. Federsel, Drug Discovery Today *2006,* 11, 966. (e) M. Seenivasaperumal, H. J. Federsel, K. J. Szabó, Adv. Synth. Catal. *2009*, 351, 903. (f) M. Seenivasaperumal, H. J. Federsel, A. Ertan, K. J. Szabó, Chem. Commun. *2007*, 2187.

[4] (a) S. H. Nile, B. Kumar, S. W. Park, ChemBiol Drug Des. *2013*, 82, 290. (b) C. Zhang, B. Zhong, S. Yang, L. Pan, S. Yu, Z. Li, S. Li, B. Su, X. Meng, Bioorg. Med. Chem. *2015*, 23, 3774.

[5] (a) A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach, L. B. Townsend, J. Med. Chem. *1998*, 41, 1252. (b) T. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Buckheit, C. J. Michejda, J. Med. Chem. *1997*, 40, 4199.

[6] L. Tamrn, P. B. Sehgal, Adv. Virus. Res. *1978*, 22, 187.

[7] M. T. Migawa, J. L. Girardet, J. A. Walker II, G. W. Koszalka, S. D. Chamberlain, J. C. Drach, L. B. Townsend, J. Med. Chem. *1998*, 41, 1242.

[8] (a) N. H. Hauel, H. Nar, H. Priepke, U. Ries, J. M. Stassen, W. Wienen, J. Med. Chem. *2002*, 45, 1757. (b) J. S. Kim, Q. Sun, B. Gatto, C. Yu, A. Liu, L. F. Liu, E. J. Lavoie, Bioorg. Med. Chem. *1996*, 4, 621. (c) J. S. Kim, B. Gatto, C. Yu, A. Liu, L. F. Liu, E. J. LaVoie J. Med. Chem. *1996*, 39, 992.

[9] H. Zarrinmayeh, D. M. Zimmerman, B. E. Cantrell, D. A. Schober, R. E. Bruns, S. L. Gackenheimer, P. L. Ornstein, P. A. Hipskind, T. C. .Britton, D. R. Gehlert, Bioorg. Med. Chem. Lett. *1999*, 9, 647.

[10] Z. Zhao, D. O. Arnaiz, B. Griedel, S. Sakata, J. L. Dallas, M. Whitlow, L. Trinh, J. Post, A. Liang, M. M. Morrissey, K. J. Shaw, Bioorg. Med. Chem. Lett. *2000*, 10, 963.

[11] M. L. L. Rodriguez, B. Benhamu, J. M. Morcillo, I. D. Tejada, L. Orensanz, J. M Alfaro, I. M. Martin, J. Med. Chem. *1999*, 42, 5020.

[12] (a) N. S. El-Gohary, M. I. Shaaban, Eur. J. Med. Chem. *2017*, 131, 255. (b) Z. Hu, T. Zhao, M. Wang, J. Wu, W. Yu, J. Chang, J. Org. Chem. *2017*, 82, 3152. (c) T. H. Kim, H. Y. Yang, B. G. Park, S. Y. Jung, J. H. Park, K. D. Park, S. J. Min, J. Tae, H. Yang, S. Cho, S. J. Cho, H. Song, I. M. Jung, J. Lee, A. N. Pae, Eur. J. Med. Chem. 2017, 125, 1172. (d) H. Saral, O. Ozdamar, I. Ucar, J. Mol. Struct. *2017*, 46, 1130.

[13] J. E. R. Sadig, R. A. A. Foster, F. Wakenhut, M. C. Willis, J. Org. Chem. *2012*, 77, 9473.

[14] M. R. Mohammadizadeh, S. Z. Taghavi, Eur. J. Chem. *2011*, 8, 101.

[15] L. Zamani, B. B. F. Mirjalili, K. Zomorodian, M. Namazian, S. Khabnadideh, E. F. Mirzaei, FARMACIA, *2014*, 62, 467.

[16] J. S. Yadav, B. V. S. Reddy, K. Premalatha, K. S. Shankar, Can. J. Chem. *2008*, 86, 124.

[17] V. N. Mahire, P. P. Mahulikar, Chin. Chem. Lett. *2015*, 26, 983.

[18] J. P. Wan, S. F. Gan, J. M. Wu, Y. Pan, Green. Chem. *2009*, 11, 1633.

[19] H. Sharma, N. Kaur, N. Singh, D. O. Jang, Green. Chem. *2015*, 17, 4263.

[20] R. Varala, A. Nasreen, R. Enugala, S. R. Adapa, Tetrahedron. Lett. *2007*, 48, 69.

[21] H. A. Oskooie, M. M. Heravi, A. Sadnia, F. K. Behbahani, F. Jannati, Chin. Chem. Lett. *2007*, 18, 1357.

[22] R. G. Jacob, L. G. Dutra, C. S. Radatz, S. R. Mendes, G. Perin, E. J. Lenardao, Tetrahedron. Lett. *2009*, 50, 1495.

[23] G. Bai, X. Lan, X. Liu, C. Liu, L. Shi, Q. Chen, G. Chen, Green Chem. *2014*, 16, 3160.

[24] K. Bahrami, M. M. Khodaei, A. Nejati, Green Chem. *2010*, 12, 1237.

[25] M. Kidwai, A. Jahan, D. Bhatnagar, J. Chem. Sci. *2010*, 122, 607.

[26] M. M. Guru, M. A. Ali, T. Punniyamurthy, J. Org. Chem. *2011*, 76, 5295.

[27] S. Rezayati, M. Mehmannavaz, E. Salehi, S. Haghi, R. Hajinasiri, S. A. S Abad, J. Sci. I. R. Iran, *2016*, 27,51.

[28] S. Rostamizadeh, A. M. Amani, R. Aryan, H. R. Ghaieni, L. Norouzi, Monatsh. Chem. *2009*, 140, 547.

[29] S. Perumal, S. Mariappan, S. Selvaraj, ARKIVOC *2004.* viii, 46.

[30] S. Kamble, G. Rashinkar, A. Kumbhar, R. Salunkhe, Synth. Commun. *2012*, 42, 756.

[31] V. Kumar, D. G. Khandare, A. Chatterjee, M. Banerjee, Tetrahedron Lett. *2013*, 54, 5505.

[32] A. Pramanik, R. Roy, S. Khan, A. Ghatak, S. Bhar, Tetrahedron Lett. *2014*, 55, 1771.

[33] (a) E. Rafiee, N. Rahpeima, S. Eavani, Acta Chim. Slov. *2014*, 61, 1771. (b) V. Elumalai, J. H. Hansen, Synlett. *2020*, 31, 547.

[34] C. S. Cho, J. U. Kim, Bull. Korean Chem. Soc. *2008*, 29, 1097.

[35] Y. Liang, J. Wang, C. Cheng, H. Jing, RSC Adv. *2016*, 6, 93546.

[36] A. T. Khan, T. Parvin, L. H. Choudhury, Synth. Commun. *2009*, 39, 2339.

[37] Z. H. Ma, S. Lin, J. Nie, Synth. Commun. *2012*, 42, 506.

[38] M. A. Alibeik, M. Moosavifard, Synth. Commun. *2010*, 40, 2686.

[39] A. V. Narsaiah, A. R. Reddy, J. S. Yadav, Synth. Commun. *2011*, 41, 262.

[40] G. N. Vazquez, H. M. Diaz, S. E. Soto, M. T. Piedra, I. L. Rivera, H. Tlahuext, O. M. Muniz, H. T. Gomez, Synth. Commun. *2007*, 37, 2815.

[41] R. Trivedi, S. K. De, R. A. Gibbs, J. Mol. Catal. A: Chem. *2006*, 245, 8.

[42] A. Hasaninejad, K. Niknam, A. Zare, E. Farsimadan, M. Shekouhy, Phosphorus, Sulfur, and Silicon, *2009*, 184, 147.

[43] G. R. Jadhav, M. U. Shaikh, C. H. Gill, R. P. Kale, Chin. Chem. Lett. *2009*, 20, 535.

[44] Y. K. Bommegowda, G. S. Lingaraju, S. Thamas, K. S. V. Kumar, C. S. P. Kumara, K. S. Rangappa, M. P. Sadashiva, Tetrahedron Lett. *2013*, 54, 2693.

[45] K. Prabakaran, M. Sivakumar, M. S. Perumal, ChemistrySelect. *2017*, 2, 2363.

[46] K. Prabakaran, M. Sivakumar, M. S. Perumal, Asian J. Green Chem. *2019*, 3, 137.

[47] K. Prabakaran, S. Loganathan, M. S. Perumal, S. Philip Anthony, ChemistrySelect. *2020*, 5, 8773.

[48] (a) S. J. Thomson, P. Rippon, C. Butts, S. Olsen, M. Shaw, N. I. Joyce, C. C. Eady, J. Agric. Food. Chem. *2013*, 61, 10574. (b) S. Imai, N. Tsuge, M. Tomotake, Y. Nagatome, H. Sawada, T. Nagata, H. Kumagai, Nature *2002*, 419, 685. (c) P. Ascenzi, A. Azzi, IUBMB Life, *2003*, 55, 49. (d) E. Block, Sci. Am. *1985*, 252, 114.

[49] (a) R. Chebolu, D. N. Kommi, D. Kumar, N. Bollineni, A. K. Chakraborti, J. Org. Chem. *2012*, 77, 10158. (b) W. Senapak , R. Saeeng, J. Jaratjaroonphong , V. Promarak, U. Sirion, Tetrahedron Lett**.** *2019*, 75, 3543.

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