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Synthesis of functionalized benzimidazoles and quinoxalines catalyzed by sodium hexafluorophosphate bound Amberlite resin in aqueous medium

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ABSTRACT

A very simple, eco-friendly, and versatile method for the selective synthesis of 1,2-disubstituted benzimidazoles and quinoxalines in water–methanol (1:1) mixture with the aid of resin bound hexafluorophosphate ion as catalyst is reported. The method is also effective for the incorporation of quinoxaline nucleus at the A ring of pentacyclic triterpenoid, friedelin. A plausible mechanism for the formation of disubstituted benzimidazole has also been suggested.

Functionalized benzimidazoles represent an important class of N-containing heterocyclic compounds and have received considerable attention due to their applications as antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistamines among others.[1–7] They are important intermediates in many organic reactions[8–10] and have found biomimetic applications as well.[11,12] In addition, the therapeutic effects of benzimidazoles in diseases such as ischemia–reperfusion injury,[13] hypertension,[14] obesity,[15] etc. have recently been reported. Furthermore, to facilitate evaluation of the exact mechanism of the observed biological activity, it will be beneficial for a simple, eco-friendly, and versatile synthesis of these heterocycles. Current literature is well vast in documenting various synthetic methodologies for the synthesis of benzimidazoles. Generally, the condensation of *o*-phenylenediamines and carboxylic acids (or their derivatives such as nitriles, imidates, and orthoesters) had been widely used for the benzimidazole synthesis, but harsh dehydrating conditions (170–180 °C) are usually required.[16–18] Alternative approaches such as palladium catalyzed tandem carbonylation–cyclization reaction of *o*-phenylenediamine,[19] palladium catalyzed tandem dehydration coupling reaction of 2-bromoaniline,[20] rhodium catalyzed hydroformylation reaction of *N*-alkenyl phenylenediamines,[21] reductive cyclization reaction of *o*-nitroaniline with aldehydes,[22] solid-phase supported synthesis,[23] etc. have also been developed to prepare functionalized benzimidazoles. However, one pot condensation–aromatization reaction of *o*-phenylenediamines and aldehydes under oxidative condition turned out to be the most facile and effective method for the synthesis of 2-substituted benzimidazoles,[24–32] **4** and 1,2-disubstituted benzimidazoles,[33–37] **3**.

Among the reactions of *o*-phenylenediamine with aldehyde, the selectivity in forming 1,2-disubstituted benzimidazole, **3** and 2-substituted benzimidazole, **4** is an issue of high interest. Although, a large body of protocols have been established for synthesizing benzimidazoles of type **4**, there are only a few methods available for the direct synthesis of 1,2-disubstituted benzimidazole, **3** with ideal selectivity.[30–37] Recently, several elegant catalyst systems have been developed to prepare **3** in excellent chemoselectivity by employing water as the medium in the presence of costly organometallic catalysts or rare ionic liquids.[34,36,37] Recently we have also reported a new method for the selective synthesis of benzimidazole of type **3** in water catalyzed by SDS.[30]

The synthesis of quinoxaline is usually achieved by the reaction of *o*-phenylenediamine with dicarbonyl compounds,[38] the oxidative cascade reactions of *o*-phenylenediamine with α-hydroxy ketones,[39,40] epoxides,[41] and diols[42] in the presence of either noble metal, additional oxidants or are microwave assisted. The synthesis using multicomponent reactions has also been recently reported.[43] Interestingly, as an equivalent precursor of α-hydroxyketones, α-bromoketones have been claimed in much less cases as reaction partners of *o*-phenylenediamine to prepare quinoxalines.[44,45] People have so far reported the synthesis of quinoxaline derivatives from α-bromoketones and *o*-phenylenediamine in the presence of either $HClO_4$–SiO_2[44] or TMSCl[45] as catalytic systems. Although, useful, $HClO_4$ has huge hazardous nature than its potential usefulness, whereas application of TMSCl requires a higher temperature with a lower yield of the products.

Herein we report the excellent catalytic ability of (i) sodium hexafluorophosphate (SHFP) and (ii) PF_6^- ion bound Amberlite

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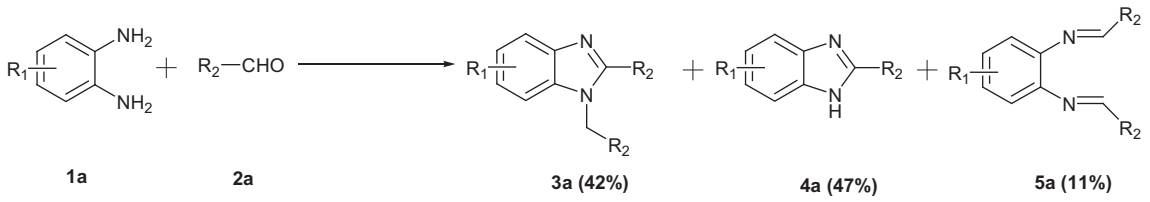
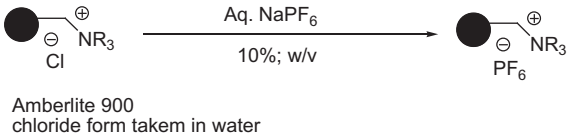


Scheme 1. Plausible transformations.

900 (Cl^-) for the synthesis of 1,2-disubstituted benzimidazole and quinoxaline derivatives. This is the first report of the synthesis of 1,2-disubstituted benzimidazole and quinoxaline derivatives using the above catalysts in water.

Initially *o*-phenylenediamine and benzaldehyde were used in a 1:1 molar ratio in water for the titled transformation, but it failed to produce the desired 1,2-disubstituted benzimidazole **3a** as a major product, instead a mixture of products was isolated (Scheme 1). Increase in the reaction time, temperature, and variation in the molar proportion of the reactants did not make any influence on the ratio of the product distribution. At this juncture and based on the literature report[46,47] on SHFP (sodium hexafluorophosphate) we undertook the above study by using 1 mmol of anhydrous SHFP in the above reaction mixture of *o*-phenylenediamine and benzaldehyde (1:2 mmol). This revised protocol after a very simple work-up gave only a single isolated product in 76% yield.

However, considering the recent emphasis on the development of greener protocols we further worked on the above transformation to replace with a suitable greener catalyst the use of SHFP, which has been reported to produce even more hazardous waste due to its decomposition to phosphorus oxides and toxic hydrofluoridric acid.[47] Working in this direction and looking into the recent literature of resin bound greener catalyst we used PF_6^- ion bound



Scheme 2. Preparation of PHP.

Amberlite 900 (Cl^-) as a potential catalyst for the above transformation.

Polymeric resin bound hexafluorophosphate ion (PHP) was prepared[48] (Scheme 2) by washing Amberlite 900 resin (Cl^-) packed in a column with 10% aqueous sodium hexafluorophosphate solution repeatedly until the washing gave a negative response for the chloride ion (Scheme 6). Finally the solid was washed several times with water and then dried under vacuum. The binding of hexafluorophosphate ion on the surface of Amberlite 900 resin was confirmed by IR spectroscopy[49] in the following way. IR spectrum of PHP was taken in KBr discs (Fig. 1). PF_6^- belongs to O_h point group, where six kinds of vibration modes are included in the molecule, whose basic frequency number is 15. From the characteristics of O_h point group, it can be calculated that for PF_6^- two energy levels belonging to F_{1u} have infrared activity which results from the flexing vibration and bending vibration of F–P bonds, respectively. Therefore, two strong absorption peaks of PF_6^- should appear at 820–860 and 550–565 cm^{-1}. In the IR spectra of PHP, strong absorption peak appeared at 557 and 832 cm^{-1}, respectively (Fig. 1). Appearance of the above said peaks did confirm the binding of PF_6^- ion on polymeric resin (Amberlite 900).

This resin bound PF_6^- ion (PHP) was then applied in place of SHFP as the catalyst and it also showed excellent chemoselectivity by giving **3a** as the major product in water at room temperature (Scheme 3). In a bid to increase the yield of the desired product, we performed the same reaction in other green solvents, such as ethanol, methanol, and mixtures of both water–methanol and water-ethanol in varying proportions at room temperature as well as in 50 °C (Table 1). Of the entire solvent systems studied, methanol gave similar results as water, but ethanol performed poorly (entry 3). A further study with mixed solvent systems indicated

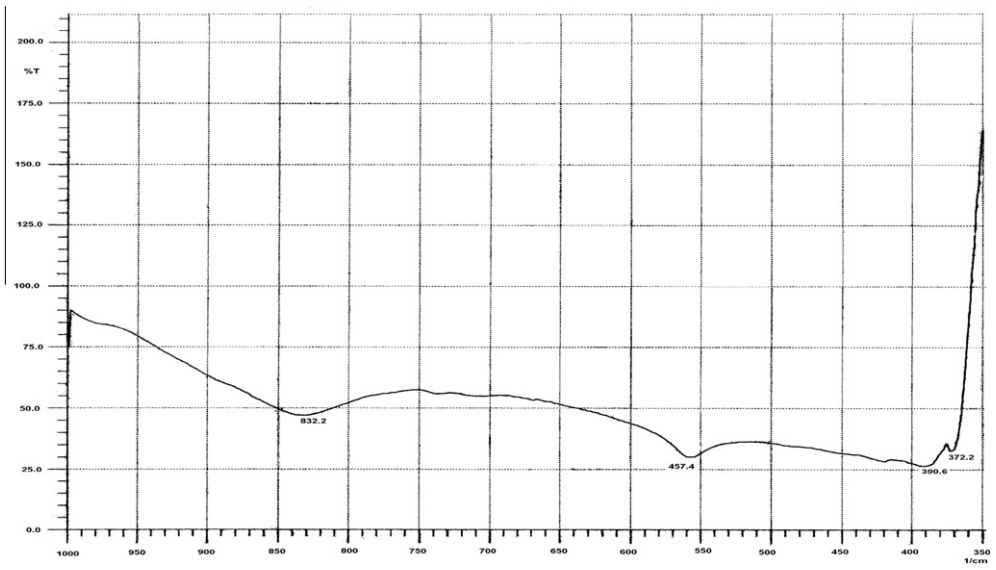
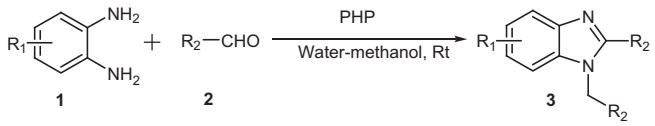


Figure 1. IR spectrum of the PF_6^- bound Amberlite 900 (PHP).



Scheme 3. Preparation of 1,2-disubstituted benzimidazole.

Table 1
Selection of solvent

Entry	Solvent	Temperature (°C)	Time (h)	%Yield of 3
1	Water	rt	1	76
2	Water	50	2	76
3	Ethanol	rt	10	55
4	Water + ethanol 7:3	rt	10	72
5	Water + ethanol 3:2	rt	10	70
6	Water + ethanol 1:1	rt	10	74
7	Water + ethanol 1:1	50	10	76
8	Methanol	rt	2	74
9	Methanol	50	10	76
10	Water + methanol (7:3)	rt	2	82
11	Water + methanol (3:2)	rt	2	86
12	Water + methanol (3:2)	50	8	88
13	Water + methanol (1:1)	rt	1	96
14	Water + methanol (1:1)	50	1	96

%Yield refers to the isolated yield of all the compounds.

that a 1:1 mixture of water and methanol gave an excellent yield of **3a** within 1 h at ambient temperature (Table 1, entry 13); increase in reaction temperature had no effect on the isolated yield of the reaction (entry 14).

The generality of this methodology[50] had been investigated using a wide variety of 1,2-diamines and aldehydes. Except for valeraldehyde (Table 2, entry 25) the developed process was found to be excellent both in terms of yield, selectivity, and time (Table 2). The synthesis of such kind of benzimidazole derivatives from aliphatic aldehydes was not addressed by many of the existing methods. The aldehydes with electron donating (Table 2, entries 6, 7, and 12) as well as with electron withdrawing groups (Table 2, entries 2–5, 8, 11, 20, and 21) participated in the reaction uniformly. Apparently, the nature and position of substitution on the aryl ring did not make much difference in reactivity except for 3-nitrobenzaldehyde which required 24 h for completion (Table 2, entry 8). Sensitive molecules like furan-2-aldehyde, 5-bromothiophene-2-aldehyde, and pyridine-4-carboxaldehyde (Table 2, entries 13, 14, and 23) produced the corresponding benzimidazoles easily. Naphthalene-1-carboxaldehyde also underwent the reaction and gave an excellent yield of the corresponding benzimidazole (Table 2, entry 16). The study in addition indicated that unsubstituted aromatic aldehydes gave better yields of the products compared to the substituted systems and that the response of aliphatic aldehydes toward the conversion is not so encouraging.

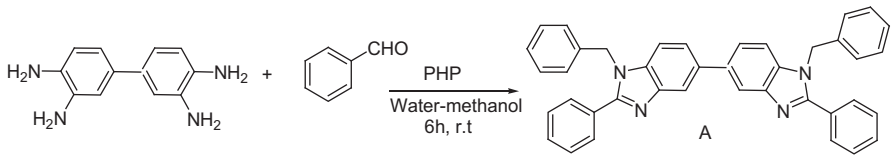
Based on these encouraging results, the utility of this selective greener method was further extended to design some large benzimidazole derivatives that can serve as lead compounds in pharmaceutical research. To our delight we were able to synthesize a large benzimidazole derivative **A** (Scheme 4) from the reaction.

Encouraged by the above findings and based on the literature reports we extended our aim to synthesize quinoxalines, another novel class of heterocyclic compounds from α-bromoketones and *o*-phenylenediamine (1:1) under similar condition[51] (Scheme 5) in excellent yields. The choice of α-bromoketones was made because they are less reactive, comparatively safe, light insensitive, and easy to prepare/handle under ordinary reaction condition. A number of both structurally and electronically diversified α-bromoketones were then tried to affect the quinoxaline synthesis effectively under the optimized reaction condition. To our delight, all the employed α-bromoketones furnished the respective

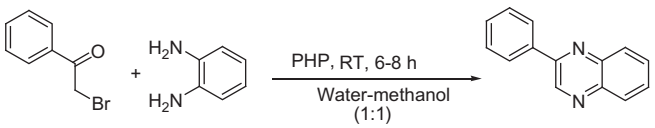
Table 2
Synthesis of diversified benzimidazole derivatives in aqueous SHFP

Entry	R_1	R_2	Time (h)	Temperature	Product	Yield (%)
1	H	Ph	1	rt	3a	96
2	H	4-$CH_3OC_6H_4$	2	rt	3b	88
3	H	4-FC_6H_4	1.5	rt	3c	87
4	H	4-ClC_6H_4	1.5	rt	3d	85
5	H	4-$NO_2C_6H_4$	8	rt	3e	79
6	H	4-$NMe_2C_6H_4$	2	rt	3f	85
7	H	4-Isopropyl C_6H_4	1.5	rt	3g	83
8	H	3-$NO_2C_6H_4$	24	rt	3h	82
9	H	3-$OH_2C_6H_4$	5	rt	3i	85
10	H	3-$OPhC_6H_4$	3	rt	3j	82
11	H	2-ClC_6H_4	1.5	rt	3k	79
12	H	2-OHC_6H_4	15	90 °C	3l	82
13	H	Furan-2-yl	4	rt	3m	85
14	H	5-Bromo-thiophene-2-yl	6	rt	3n	75
15	H	$PhCH{=}CH_2$	5	rt	3o	78
16	H	1-Naphthyl	6	rt	3p	69
17	3-CH_3	4-Isopropyl C_6H_4	2	rt	3q	82
18	3-CH_3	3-$OPhC_6H_4$	7	rt	3r	76
19	3-CH_3	5-Bromo-thiophene-2-yl	8	rt	3s	74
20	3-CH_3	2-ClC_6H_4	5	rt	3t	72
21	3-Benzoyl	4-ClC_6H_4	12	rt	3u	75
22	3-Benzoyl	Ph	14	rt	3v	84
23	H	Pyridine 4-carboxaldehyde	14	90 °C	3w	82
24	H	H	8	rt	3x	68
25	H	Valeraldehyde	12	rt	3y	Trace
26	H	Cyclohexyl	4	rt	3z	84

%Yield refers to the isolated yield of all the compounds after chromatographic separation. R_1 and R_2 belong to Scheme 3.



Scheme 4. Preparation of a bis benzimidazole.



Scheme 5. Preparation of quinoxaline derivatives from α-bromoketone.

quinoxalines in excellent yields (Table 3). Substituents on both the ketone part as well as the amine had minimal effect on the course of the reaction. The overall results are tabulated in Table 3.

In another interesting attempt, we were successfully able to incorporate the quinoxaline moiety in ring A of pentacyclic triterpenoid, friedelin according to Scheme 6.

Table 3
Synthesis of quinoxaline derivatives

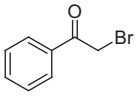
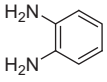
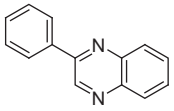
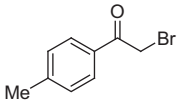
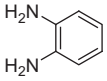
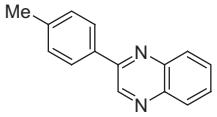
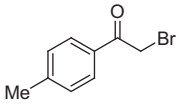
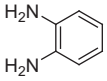
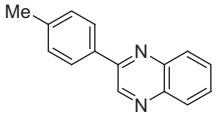
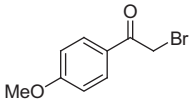
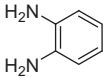
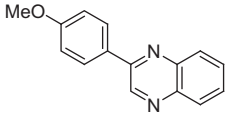
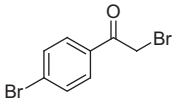
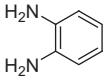
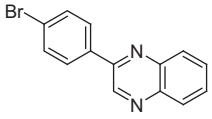
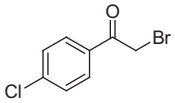
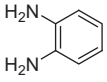
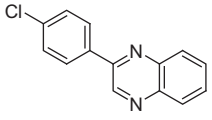
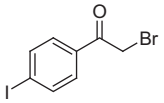
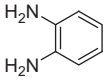
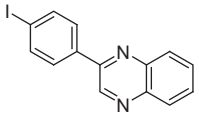
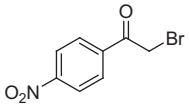
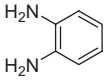
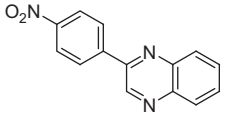
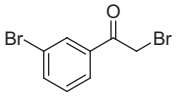
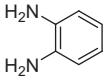
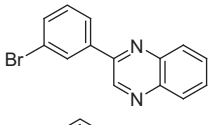
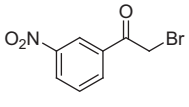
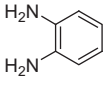
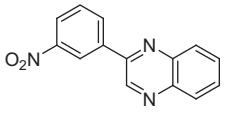
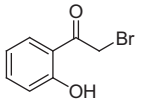
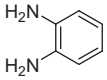
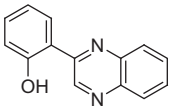
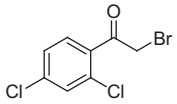
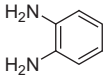
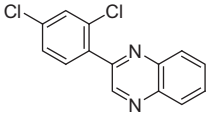
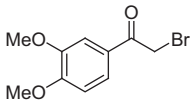
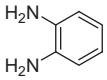
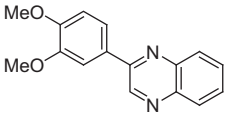
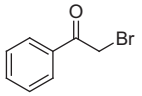
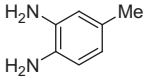
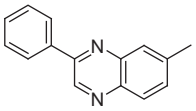
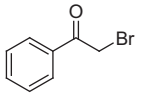
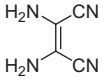
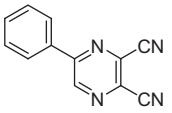
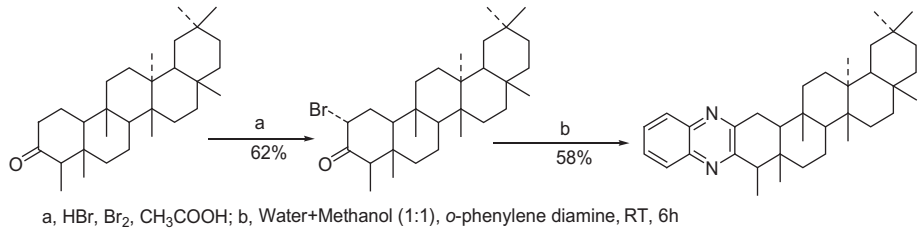
Entry	α-Bromo carbonyl compound	Diamine	Time (h)	Product	%Yield
1			6		94
2			6		92
3			6		92
4			6		86
5			6		92
6			6		89
7			6		87
8			7		84
9			6		87
10			8		85

Table 3 (*continued*)

Entry	α-Bromo carbonyl compound	Diamine	Time (h)	Product	%Yield
11			7		83
12			6.5		98
13			7		82
14			6		92
15			5		84

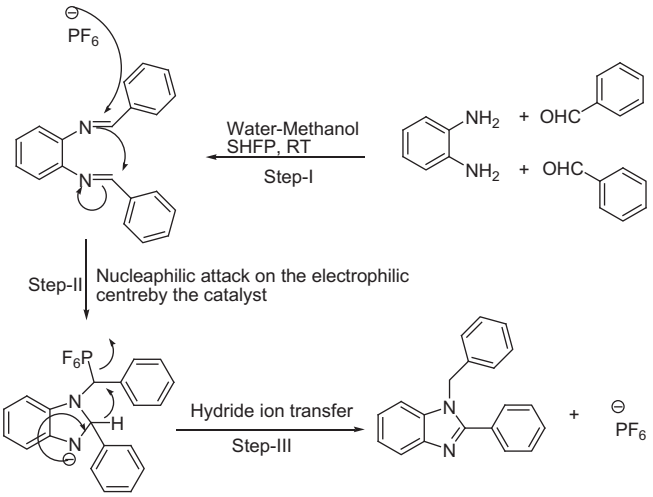
%Yield refers to the isolated yield of all the compounds.



Scheme 6. Preparation of quinoxaline derivative of friedelin.

On the basis of the above experimental results as well as the formation of a Schiff's base as intermediate, which has been isolated and characterized by NMR spectroscopy, a plausible mechanism of functionalized benzimidazole formation has been proposed (Scheme 7). Involvement of the Schiff's base as intermediate is further supported by the fact that, separately prepared Schiff's base when subjected to undergo the same reaction under identical condition, that is, at room temperature gave the target product in an excellent yield. It is then followed by the nucleophilic attack of the catalyst on one of the electrophilic imino carbon. Subsequent cyclization and 1,3-hydride shift lead to the formation of benzimidazoles (Scheme 7).

Based on the above discussions, it can be concluded that commercially available sodium hexafluorophosphate binds on Amberlite 900 (Cl^-) and PHP can be used as a cheap and greener source compared to sodium hexafluorophosphate itself and may also efficiently replace the use of costly, rare ionic liquids for the synthesis of 1,2-disubstituted benzimidazole or quinoxaline derivatives in an expeditious and selective way in water–methanol at ambient temperature. The study also established that it is the hexafluorophosphate ion and not the counter cation which plays the key role for the above transformation. We have also confirmed the catalyzing ability of hexafluorophosphate ion in which it successfully binds to Amberlite 900 resin and promotes the reaction. Several functional groups such as chloro, bromo, nitro, methoxy, and sensitive molecules like 5-bromo thiophene-2-carboxaldehyde and furan-2-carboxaldehyde are compatible with the reaction conditions. The



Scheme 7. Plausible mechanism of benzimidazole formation in water–methanol catalyzed by hexafluorophosphate ion.

reaction procedure is operationally straightforward, mild, and is environmentally friendly. Since benzimidazole derivatives are often used in synthetic, medicinal, and biological chemistry, the reaction procedure, being endowed with so many attractive features, could find applications as alternative green reaction

methodology. In a nutshell, we have developed a green and novel protocol for the selective synthesis of some heterocyclic compounds using PHP as catalyst at ambient temperature. Explorations of further applications of the newly developed green protocol and biological activities of the synthesized compounds are underway in our laboratory.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.045.

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48. Synthesis of polymeric resin bound PF_6^-: Polymeric resin bound hexafluorophosphate ion (PHP) was prepared (Scheme 6) by washing Amberlite 900 resin (Cl^-) packed in a column with 10% aqueous sodium hexafluorophosphate solution repeatedly until the washing gave a negative response for the chloride ion (Scheme 6). Finally the solid was washed several times with water and then dried under vacuum. The binding of hexafluorophosphate ion on the surface of Amberlite 900 resin was confirmed by IR spectroscopy.
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50. General procedure for 1,2-disubstituted benzimidazole: In a typical experimental procedure, *o*-phenlylenediamine and benzaldehyde in 1:2 molar ratios was taken in a 100 ml round bottom flask. To this water–methanol (1:1) and 100 mg PHP was admixed. The reaction mixture was then allowed to stir with magnetic spinning bar, after some time a yellowish mass appeared which settles down like a precipitate after the completion of the reaction (checked by TLC). It was then filtered; the solid reaction mixture was dissolved with dichloromethane (25 mL) and evaporated under vacuum. The crude product was then crystallised from ethanol. The desired product was pure on TLC and characterized by spectral (IR, ^1H and ^{13}C NMR) data and compared to those reported in literature.
51. General procedure for quinoxalines. In a typical experimental procedure, *o*-phenylenediamine and α-bromo ketone in 1:1 molar ratios was taken in a 100 mL round bottom flask. To this water–methanol (1:1) and 100 mg PHP was admixed. The reaction mixture was then allowed to stir with magnetic spinning bar, after some time a yellowish mass appeared which settles down like a precipitate after the completion of the reaction (checked by TLC). It was then filtered; the solid reaction mixture was dissolved with dichloromethane (25 mL) and evaporated under vacuum. The crude product was then crystallised from ethanol. The desired product was pure on TLC and characterized by spectral (IR, ^1H and ^{13}C NMR) data and compared to those reported in literature.