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# $Zn^{2+}$-K10-clay (clayzic) as an efficient water-tolerant, solid acid catalyst for the synthesis of benzimidazoles and quinoxalines at room temperature

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ABSTRACT

A very simple, green and efficient protocol is developed in which zinc chloride-exchanged K10-montmorillonite (clayzic) is employed as a Lewis acid catalyst in aqueous media at room temperature for the synthesis of various benzimidazoles and quinoxalines from carbonyl compounds and *o*-phenylenediamine. Among the various catalysts (including claycop and $Zn^{2+}$–Y) studied, clayzic produces benzimidazoles and quinoxalines in higher yield, and with a flexible diamine such as ethylenediamine only the bis-Schiff base is formed. Other salient features of this protocol include milder conditions, atom-economy, absence of coupling agents, and no wastes.



Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical and biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics.[1–3] The widespread interest in benzimidazole-containing structures has prompted extensive studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamines and carboxylic acids[4] or their derivatives (nitriles, imidates, or orthoesters),[5] which often require strong acidic conditions and sometimes combines with very high temperatures (i.e., PPA, 180 °C) or the use of microwave irradiation.[6] The other way involves a two-step procedure that includes the oxidative cyclodehydrogenation of aniline Schiff's bases, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes. Various oxidative reagents such as nitrobenzene (high-boiling point oxidant/solvent),[7] 1,4-benzoquinone,[8] DDQ,[9] tetracyanoethylene,[10] benzofuroxan,[11] $MnO_2$,[12] $Pb(OAc)_4$,[13] Oxone,[14] $NaHSO_3$,[15] and $Na_2S_2O_5$[16] have been employed.

Recently, a variety of catalysts such as homogeneous Lewis acids,[17] pyridinium-*p*-toluenesulfonate,[18] sulfur/ultrasonic,[19] $I_2/KI/K_2CO_3/H_2O$,[20] ionic liquids,[21] (bromodimethyl)sulfonium bromide,[22] polyaniline-sulfate,[23] and a tandem oxidation process[24] have been used for the synthesis of benzimidazoles. Quinoxaline derivatives are nitrogen containing heterocyclic compounds with widespread importance[25] and catalytic systems[26–28] have been developed for their synthesis. Ranu and co-workers have reported the synthesis of 2-substituted benzimidazoles in the presence of 1-methyl-3-pentylimidazolium tetrafluoroborate as solvent and catalyst.[29] An environmentally benign tandem procedure has also been reported for the synthesis of quinoxaline derivatives with manganese oxide octahedral molecular sieves as reusable catalysts.[30]

Lewis acid catalysis has attracted considerable attention in heterogeneous catalysis.[31] Although various kinds of Lewis acids have been developed, many of them must be used only under strictly anhydrous conditions. In addition, all these processes require stoichiometric or excess amount of catalyst/reagents and most of them employ considerable amounts of hazardous organic solvents which are not environmentally friendly. Also, several of these reactions are carried out at higher temperatures.

Recently, with an objective to develop environmentally benign reaction conditions and media for organic reactions with excellent efficiency and selectivity, water has been shown to be a useful solvent.[32] In this context, in the present study, we report here the use clayzic as an eco-friendly water tolerant Lewis acid catalyst for the synthesis of substituted benzimidazoles and quinoxalines, as shown in Scheme 1. Clayzic has been extensively used as an eco-friendly catalyst 'Envirocat', in Lewis acid-catalyzed reactions, including benzylations, olefinations, and Fridel–Crafts alkylation of benzenoid compounds, a reaction that is facile even at room temperature.[33] Recently, Varala et al. have used zinc montmorillonite as a reusable catalyst for the synthesis of benzodiazepine derivatives.[34]

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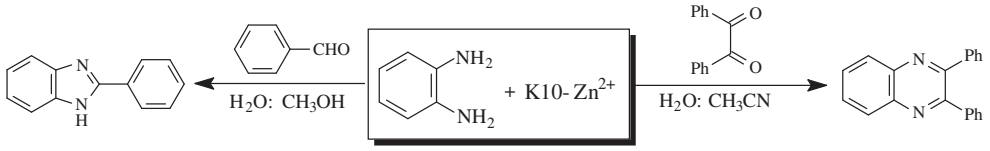



**Scheme 1.** Synthesis of benzimidazoles and quinoxalines.

**Table 1**
Optimization of reaction conditions for the synthesis of 2-phenylbenzimidazole[a]

| Run | Catalyst | Solvent | Time (h) | Percentage conversion[b] |
|---|---|---|---|---|
| 1 | None | $H_2O/CH_3OH$[c] | 24 | — |
| 2 | K10-clay | $H_2O/CH_3OH$[c] | 24 | 26 |
| 3 | Clayzic | Hexane | 24 | 19 |
| 4 | Clayzic | $H_2O$ | 24 | 32 |
| 5 | Clayzic | $CH_3OH$ | 24 | 89 |
| 6 | Clayzic | EtOH | 24 | 91 |
| 7 | Clayzic | ACN | 24 | 84 |
| 9 | Clayzic | $H_2O/CH_3OH$[c] | 24 | 98 |
| 10 | Clayzic | $H_2O/CH_3OH$[c] | 12 | 64 |
| 11 | Clayzic[d] | $H_2O/CH_3OH$[c] | 24 | 15 |
| 12 | Clayzic[e] | $H_2O/CH_3OH$[c] | 24 | 32 |
| 13 | K10-$Cu^{2+}$ | $H_2O/CH_3OH$[c] | 24 | 84 |
| 14 | K10-$Pb^{2+}$ | $H_2O/CH_3OH$[c] | 24 | 30 |
| 15 | $Zn^{2+}$–Y | $H_2O/CH_3OH$[c] | 24 | 26 |

[a] Catalyst (100 mg), *o*-phenylenediamine (0.9 mmol), benzaldehyde (0.9 mmol), solvent (3 mL), rt.
[b] Determined by GC.
[c] 1:1 ratio.
[d] 25 mg of clayzic.
[e] 50 mg of clayzic.

To minimize the formation of byproducts and to achieve a good yield of the desired product, the reaction is optimized by varying the amount of catalyst (25 and 50 mg), time of the reaction, and using various solvents. Equimolar amounts of benzaldehyde and diamine are dissolved in various solvents and the mixture is stirred for the required time. Significant amounts of 2-phenylbenzimidazole (Table 1) are produced under these mild conditions when clayzic is used instead of other Lewis acid catalysts. Also, among the different solvents tried to optimize the reaction conditions, alcoholic solvents seemed to be a better choice in terms of yield of the isolated product. The same trend is also observed when equal amount of water is used along with methanol. Though various catalytic systems have been developed for the synthesis of quinoxaline derivatives, use of aqueous medium is more relevant from the context of green chemistry. Hence, it is proposed to synthesize those heterocyclic compounds in aqueous medium with clayzic as the water tolerant Lewis acid catalyst.

To generalize the scope and versatility of this protocol, different substituted arylaldehydes are used for the synthesis of substituted benzimidazoles.[36] Equimolar amounts of *o*-phenylenediamine and aryl aldehydes are stirred at room temperature in water–methanol

**Table 2**
Synthesis of benzimidazoles and quinoxaline derivatives[a]

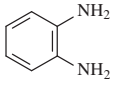
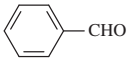
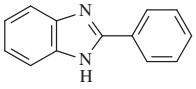
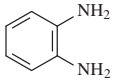
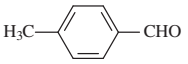
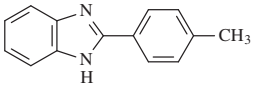
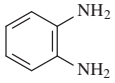
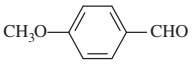
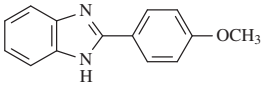
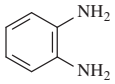
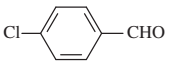
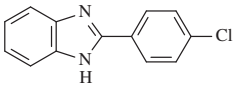
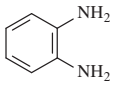
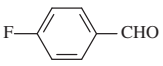
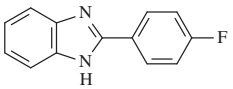
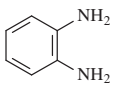
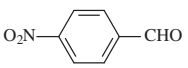
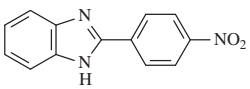
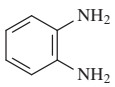
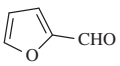
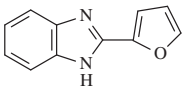
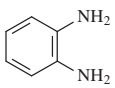
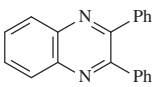
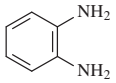
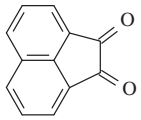
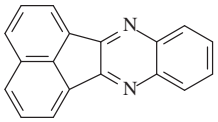
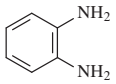
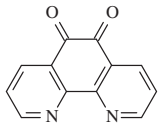
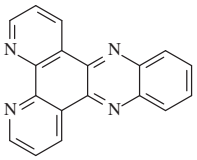
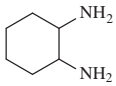
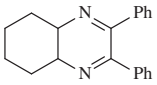
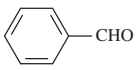
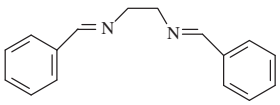
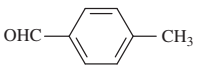
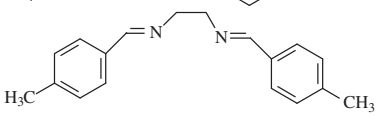
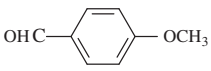
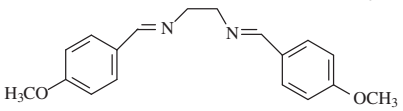
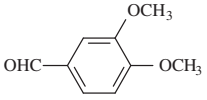
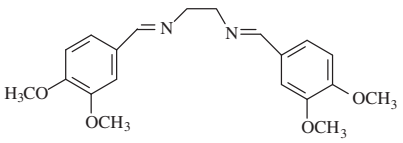
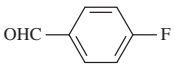
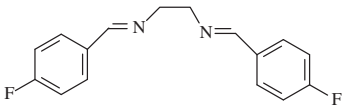
| Entry | Amine | Carbonyl compound | Product | Isolated yield[b] |
|---|---|---|---|---|
| 1 |  |  |  | 94 (89, 88, 84, 83)[c] (78)[d] |
| 2 |  |  |  | 81 |
| 3 |  |  |  | 69 |
| 4 |  |  |  | 92 |
| 5 |  |  |  | 88 |
| 6 |  |  |  | 78 |
| 7 |  |  |  | 72 |
| 8[e] |  |  |  | 89 |

**Table 2** (*continued*)

| Entry | Amine | Carbonyl compound | Product | Isolated yield[b] |
|---|---|---|---|---|
| 9[e] |  |  |  | 89 |
| 10[e] |  |  |  | 84 |
| 11[e] |  |  |  | 81[f] |

[a] Aldehyde (0.9 mmol), diamine (0.9 mmol), clayzic (100 mg), water–methanol (1.5:1.5 mL), rt for 24 h.
[b] Isolated yield.
[c] Yields in successive reused runs 1–4.
[d] Scale up reaction: benzaldehyde (10 mmol), *o*-phenylenediamine (10 mmol), clayzic (1 g), water–methanol (15:15 mL), rt for 24 h.
[e] Ketone (0.4 mmol), diamine (0.4 mmol), clayzic (50 mg), water–acetonitrile (1.5:1.5 mL), rt for 2.5 h.
[f] Isolated as cis/trans mixture.

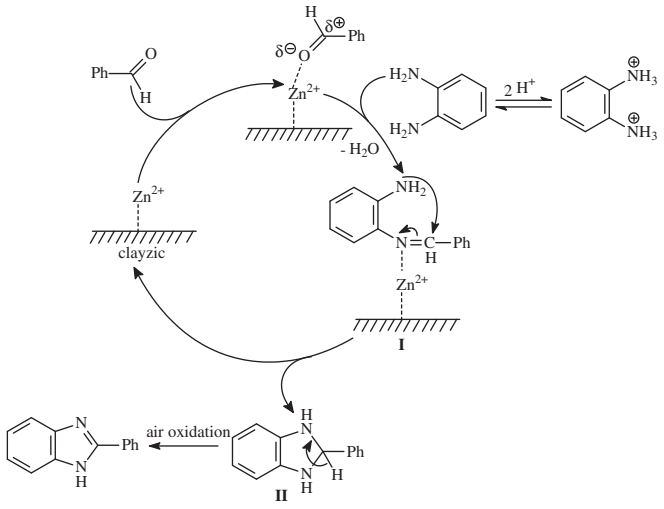
**Table 3**
Synthesis of bis-Schiff base from the reaction between ethylenediamine and aldehydes in the presence of clayzic at room temperature[a]

| Entry | Aldehyde | Bis-Schiff base | Isolated yield |
|---|---|---|---|
| 12 |  |  | 85 |
| 13 |  |  | 90 |
| 14 |  |  | 89 |
| 15 |  |  | 82 |
| 16 |  |  | 80 |

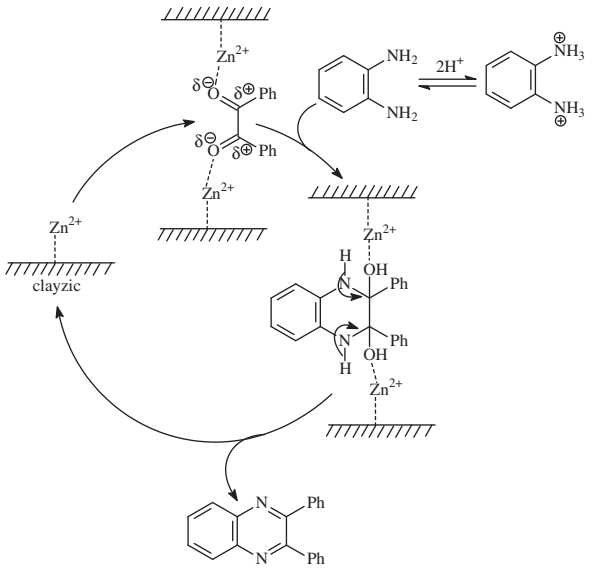
[a] Aldehyde (0.9 mmol), diamine (0.9 mmol), clayzic (100 mg), water–methanol (1.5:1.5 mL), rt for 24 h.

(1:1) mixture and the observed results are given in Table 2. Aldehydes bearing both electron-donating, electron-withdrawing substituents (Table 2, entries 1–4) and heteroaromatic aldehydes (Table 2, entry 7) resulted in the corresponding benzimidazoles in good to excellent yields. In addition, the synthesis of 2-phenylbenzimidazole was also performed in 10 mmol scale of benzaldehyde as mentioned in Table 2. Seventy-eight percent of the desired product was isolated, indicating that this method could also be used for the large scale synthesis without any undesired products. The applicability of the present methodology is further extended to synthesis of quinoxaline derivatives (Table 2, entries 8–11) by performing the reaction in (1:1) water–acetonitrile mixture. The feasibility of the reaction is tested on various 1,2-dicarbonyl compounds with *o*-phenylenediamine in good yield. Also the present protocol works for aliphatic 1,2-diamine with 1,2-dicarbonyl compounds to give the corresponding quinoxaline derivatives in good to moderate yield. This process is thus green, environmental friendly,[17] clean, and can be performed easily at room temperature with no undesirable side reactions. Water displayed a specific functionality in regulating the selectivity, and hence can be considered as a remarkable medium over organic solvents in terms of yields as well as in the work-up procedure of the reactions. In all the cases, the products are isolated and are characterized by their $^1$H NMR and GC–MS data (Supplementary data).

Another advantage of the present methodology is the reusability of the catalyst. After completion of the reaction, the catalyst is removed by simple filtration. The catalyst is again treated with dichloromethane followed by filtration. The catalyst is then dried at 80 °C for 2 h and can be reused for another reaction. The recycled catalyst is used for four consecutive




**Scheme 2.** Proposed mechanism for the synthesis of benzimidazoles.




**Scheme 3.** Proposed mechanism for the synthesis of quinoxalines.

reactions without any appreciable change in its catalytic activity (Table 2).

These interesting results have prompted us to extend a similar protocol to synthesis of imidazoline and its substituted analogs from benzaldehyde and a flexible diamine such as ethylenediamine. However, instead of the anticipated imidazoline (cyclized product) only a bis-Schiff base in which both the amino groups condense with aldehyde groups to give an $N^1$,$N^2$-dibenzylideneethane-1,2-diamine is observed and in the absence of clayzic, the conversion of benzaldehyde was low and a mixture of products are formed. This is confirmed from its $^1$H NMR and GC–MS analyses (Table 3).

To account for the facile formation of benzimidazoles, the following mechanism (Scheme 2) is proposed. The reaction between an aldehyde and a diamine leads to the formation of Schiff base (**I**) which is stabilized by clayzic. Intramolecular attack by the second amino group on C=N double bond facilitates the formation of hydrobenzimidazole (**II**) which undergoes subsequent air oxidation[35] to give the desired benzimidazole as the final product. A control experiment was performed in nitrogen atmosphere for the reaction of benzaldehyde and *o*-phenylenediamine under the conditions described in Table 1 and the formation of 2-phenylbenzimidazole decreases to <2%. This clearly demonstrates the role of oxygen as an oxidant in the present study.

In a similar fashion, clayzic facilitates the formation of quinoxaline derivatives as outlined in the following mechanism (Scheme 3). 1,2-Diketone stabilized in the interlayer of clay via interaction with $Zn^{2+}$ by partial polarization of carbonyl group reacts readily with *o*-phenylenediamine. The resultant amino-1,2-diol undergoes base-induced dehydration to give quinoxaline as the end product.

In summary, a very simple, green, energy-efficient, and atom-economical protocol has been developed for the synthesis of biologically active benzimidazoles and quinoxaline derivatives with a cheap, benign water tolerant Lewis acid catalyst namely clayzic in water–methanol mixture at room temperature. An attempt to prepare imidazoline by a similar methodology is unsuccessful and has resulted in a bis-Schiff base. The advantage of the present protocol is the elimination of corrosive liquid acids, conventional organic solvents, and toxic reagents. The reaction is also characterized by its operational simplicity, high yield of products, and above all the catalyst can be reused for more runs without any loss in its activity. The observed results are rationalized by proposing suitable mechanisms involving Lewis acidic sites ($Zn^{2+}$) of clay.

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## Supplementary data

Complete experimental procedures are provided, including preparation of catalyst, general procedure for the synthesis of benzimidazoles and quinoxalines, $^1$H NMR and MS (EI) spectra of all compounds are available in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.146.

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36. *General procedure for the synthesis of benzimidazoles/quinoxalines:* In a typical reaction, aldehyde/carbonyl compounds (0.9 mmol) and *o*-phenylenediamine (0.9 mmol) were dissolved in 3 mL of water–methanol/acetonitrile mixture (1:1 v/v). To this solution, clayzic (100 mg) was added and stirred for the required time at room temperature. Then the reaction mixture was extracted with dichloromethane (10 mL), filtered, washed with water, and dried with anhydrous sodium sulfate. In some cases, crude products were recrystallized with ethyl acetate.