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Research Article

Synthesis and characterization of a porous acidic polymer containing pendant pyrazine moieties based on calix[4]resorcinarene: A green and retrievable solid acid catalyst for preparation of benzimidazole heterosystems

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ABSTRACT

In this work, for the first time, a cationic polymer containing pendant pyrazine groups was synthesized via post-functionalization of the porous polymeric backbone based on a calix[4]resorcinarene. The formation of this cationic polymer was confirmed by elemental analysis, scanning electron microscopy (SEM), thermal gravimetric analysis (TGA) and derivative thermogravimetric (DTG) analysis. Subsequently, HSO_4 anion was incorporated into the polymer along the pyrazine pendant groups via a well-known ion exchange reaction. Elemental analysis data revealed that the cationic polymer was conveniently loaded with the desired Bronsted acid anion; therefore, it provides a novel heterogeneous acid catalyst for achieving synthetic goals. The acidic organocatalyst enables environmentally benign synthesis of benzimidazole heterocyclic compounds in ethanol. The unique features of this catalyst, such as superior thermal stability, recyclability, excellent catalytic activity in terms of yield and reaction time are potentially important for the applications of this catalyst in the industry.

Keywords: Acidic organocatalyst, polymer supported ionic liquid, heterogeneous solid acid catalyst, pendant pyrazine groups, porous polymer, heterocyclic compounds, benzimidazole.

1. Introduction

The synthesis of heterocyclic moieties through new methods has attracted tremendous attention due to the utilization of heterocyclic compounds in biological, biochemical, pharmaceutical, and asymmetric chemical investigations. Benzimidazole heterosystems are present in many natural and synthetic biological activity structures and are of great interest in medical chemistry and pharmacology. Benzimidazole derivatives are distinguished for antimicrobial [1–4], antifungal [5–7], antiviral [8], anthelmintic [9, 10], antihypertensive [11], antihistaminic [12], analgesic [13], and anti-HIV [14] actions. Also, some of benzimidazoles are used in coordination chemistry [15, 16], in optoelectronics [17], etc. Although a few methods, with distinct advantages, have recently been reported for preparation of these compounds, by use of a variety of catalysts, the methods suffer from such disadvantages as extended reaction times, unsatisfactory yields, high cost, harsh reaction conditions, and use of toxic solvents and stoichiometric amounts of catalyst; the catalysts are also environmentally hazardous. Therefore, discovery of new catalysts for preparation of benzimidazole derivatives under mild conditions is of prime importance.

Ionic liquids (IL), have received much attention for synthesis of heterogeneous catalysts. Owing to their high solubility, heterogenization of IL is a very attractive means of overcoming the difficulty of recovery [18]. Development of supported ionic liquid catalysts requires smaller amounts of ionic liquid and simultaneously minimizes limitations associated with their viscosity, separation, corrosiveness, and toxicity. supported ionic liquid catalysts have such interesting advantages as facilitating separation workup and good recyclability. It has also been reported that supported IL are more efficient than homogenous ionic liquids [19].

Moreover, Brønsted ionic solid acids (BISA), which contain an acid component in the cation or anion, can act as catalysts in organic reactions. Many typical acid-catalyzed organic reactions have been successfully performed in the presence of BISA [20, 21]. Substantial effort has been devoted to immobilization of IL on the surface of supports, for example organic polymers, silica, and metal oxides [22–24]. Silica is usually used as a support for ionic liquids, because of its ready availability and low cost. However, the wide-range pore distribution, irregular pore shape, low pore volume, and low specific surface area of silica often result in attachment of small amounts of ionic liquids, high mass-transfer resistance, and poor catalytic activity [25].

Compared with inorganic supports, polymers have shown adjustable hydrophobicity and good stability for various acids. These features, coupled with their biodegradability and green nature, make polymeric supports attractive materials to organic and industrial chemists [26].

Having the above points in mind, as part of our continuing efforts to develop high performance and environmentally friendly procedures for various important reactions and transformations [27-32] and our new interest in the application of the 3D-network porous polymer based on calix[4]resorcinarene for the preparation of biologically important molecules [33-35], herein, we propose, for the first time, the functionalization of polymeric calix[4]resorcinarene *via* covalently anchored acidic ionic liquid containing pyrazine moieties under mild reaction conditions and the investigation of its efficiency as a new solid acid catalyst for the synthesis of benzimidazole heterosystems.

2. Experimental

2.1. General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies and used without further purification. Products were characterized by physical data, IR, ^{1}H NMR and^{13}C NMR spectra. IR spectra were obtained on a Bomen MB:102 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker spectrometer at 400 MHz and 100 MHz, respectively, in $CDCl_3$ or dimethyl sulfoxide (DMSO) with tetramethylsilane as an internal standard. Elemental analyses were performed at a Thermo Finnigan Flash EA 1112 CHNS-Analyzer. The polymer morphology was examined by SEM (LEO-1455VP). Thermal stability of the functionalized polymer was investigated by NETZSCH STA 409 PC/PG under nitrogen atmosphere (rate of $N_2 \approx$ 1Lit/h).

Monitoring of the reactions and the purity determination of the products were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates.

2.2. Synthesis of calix[4]resorcinarene (1)

Calix[4]resorcinarene was prepared according to the literature procedures [36].

2.3. Synthesis of the 3D-network polymer based on calix[4]resorcinarene (2)

To a magnetically stirred mixture of formaldehyde (42 mmol), and the prepared calix[4]resorcinarene (14 mmol), 40 cm^3 NaOH solution (10%) was added dropwise under an inert atmosphere at room temperature. After completion of NaOH addition, the mixture was heated to 90°C and remained at this temperature for 20 h. Then the reaction mixture was cooled down and the resultant gel was washed consecutively with cold water to make sure that excess alkali was removed. In the following, the gel became acidic in treatment with 0.1 M HCl solution. Finally, the resultant solid product was dried at 100°C for 10 h [37].

2.4. Synthesis of novel functionalized polymer (3) through one-step chemical modification

The mixture of 12 mmol (3-chloropropyl)trimethoxysilane and 12 mmol of pyrazine was refluxed at 95 °C for 24 h under nitrogen atmosphere. The reaction mixture was cooled down and desired ionic liquid was obtained with 98 % yield. Then, 0.5 g of the synthesized polymer was added to ionic liquid. After heating the slurry at 90 °C for 20 h the solid was isolated by filtration. Owing to the solubility of unreacted ionic liquid in water, the desired cationic polymer was collected by filtration and washed with deionized water several times before drying at 80 °C.

2.5. Determination of the amount of grafted cationic moieties onto polymer

The amount of grafted cationic moieties onto polymer was achieved by elemental analysis. The amount of grafted pyrazine moieties was generally found to be 2.1 mmol per gram of the dry cationic polymer.

2.6. Preparation of polymer-supported acidic catalyst (4)

Dried cationic polymer (1.0 g) was suspended in 10 mL CH_2Cl_2. During vigorous stirring, 3.5 mmol of concentrated H_2SO_4 (96%) was introduced drop by drop at 0 °C. Then, the mixture was warmed up to room temperature and refluxed for 48 h. The desired catalyst was collected by filtration and washed with deionized water several times.

2.7. Determination of the capacity of the polymer-supported

Catalyst The capacity of the polymer-supported catalyst was determined by elemental analysis. The capacity was generally found to be 1.035 mmol H^+ per gram of the dry polymer-supported catalyst 4.

2.8. General procedure for the synthesis of benzimidazole derivatives (5)

To a mixture of aldehyde (1 mmol) and ortho-phenylene diamine (1 mmol) in ethanol (5 mL), 0.01 g of catalyst was added. The resultant mixture was stirred at room temperature, and after completion of the reaction (TLC monitoring), the solvent was removed by filtration and a viscous solid was obtained. Then, hot ethanol (10 mL) was added to the residue and the catalyst was separated by filtration. Evaporation of the ethanol under reduced pressure afforded the products, which were then purified by recrystallization in a suitable solvent (ethanol).

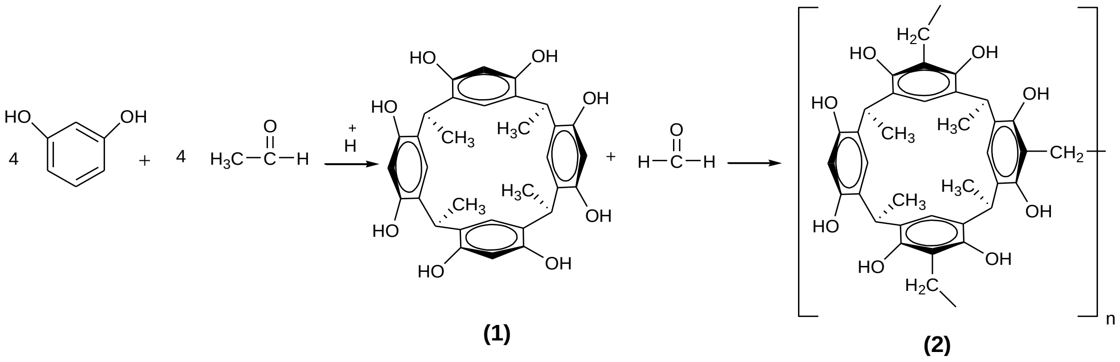
The recovered catalyst was washed with water, ethanol and ethyl acetate, respectively. Then was dried under vacuum and reused for the next reaction.

3. Results and Discussion

Sustainable chemistry focuses on the design, manufacture, and use of chemicals and chemical processes that cause little or no pollution potential or environmental risk and are both economically and technologically feasible.1 Since optimization of existing chemical processes together with the development of novel, environmentally friendly processes depend greatly on improvement of catalyst performance; the catalysis has a strong impact on the development of modern sustainable chemistry. Recently, solid acid-support heterogeneous catalysis have drawn great interest in industrial processes owing to their potential advantages over solution-based homogeneous catalysis, such as the easier operation/purification and recycling catalysts from reaction environments which lead to improved processing steps, better process economics, and environmentally friendly manufacturing [38].

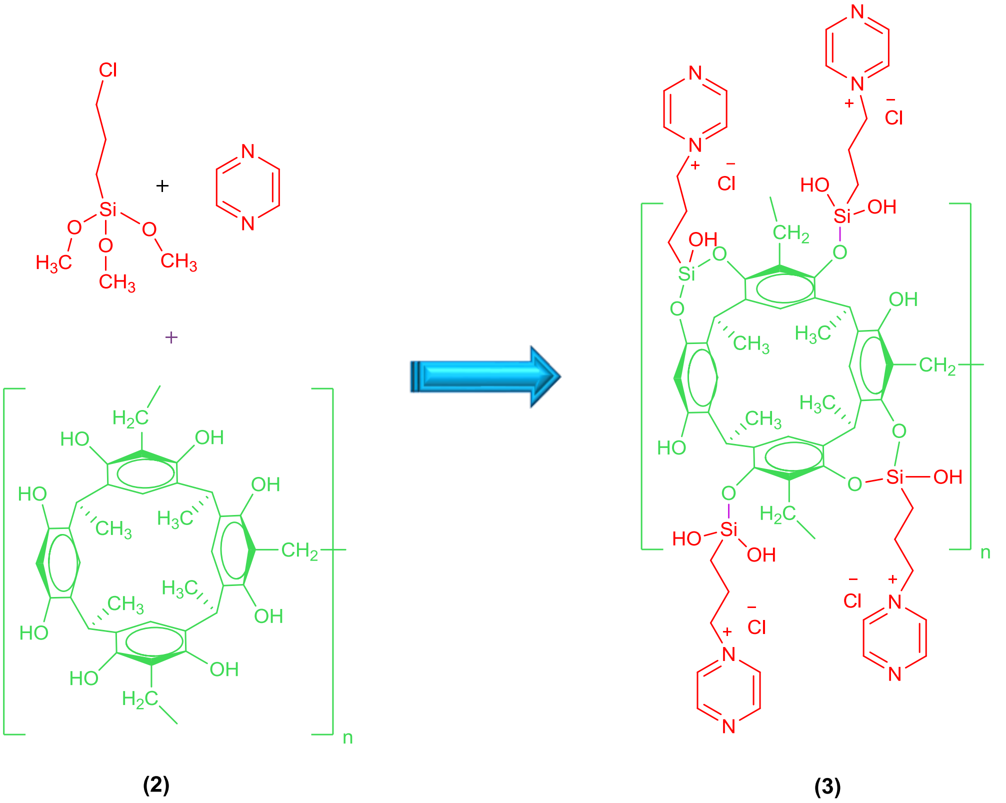
Considering this fact, we have chosen the immobilization of Bronsted acidic ionic liquid onto a 3D-network polymer based on calix[4]- resorcinarene via two post-functionalization steps.

To achieve this objective, the 3D-network polymer 2 was prepared by the reaction of resorcinol and acetaldehyde, followed by the polycondensation of calix[4]resorcinarene 1 with formaldehyde [36, 37] and the synthesis steps are shown in Scheme 1. The structure of compound 1 was established unambiguously from the spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data (see ESI†). The formation of polymer 2 was also confirmed and characterized by atomic force microscopy (AFM), X-ray diffraction (XRD) and scanning electron microscope (SEM) [39] (available in the ESI†).



Scheme .1. Synthesis of calix[4]resorcinarene (**1**) and the 3D-network polymer (**2**).

Subsequently, two post-functionalization steps were performed on the prepared polymer 2, respectively. The first step consists of the synthesis of novel cationic polymer 3 via the immobilization of IL onto polymeric backbone (Scheme 2), and the second step consists of cationic polymer transformation into acidic polymer by an ion-exchange reaction 4 (Scheme 3).



Scheme .2. Synthesis of cationic polymer (**3**) through one-pot chemical modification of (**2**).

The loading amount of the cationic moieties on the polymer was determined by elemental analysis. The nitrogen analysis of supported IL 3 (N, 4.96%) indicates that 2.1 mmol of the pyrazine moieties were grafted onto the surface per 1 g of the polymer.

The formation of 3 was also confirmed by SEM, TG and DTG analyses. In order to gain an insight into the morphology of the synthesized polymer 3, scanning electron microscopy was used (Fig. 1). Since the cationic polymer 3 shows smaller pores (about 98 nm in diameter) than polymer 2 (300 nm in diameter, see ESI†), it can be concluded that the ILs are successfully grafted onto the polymeric backbones.

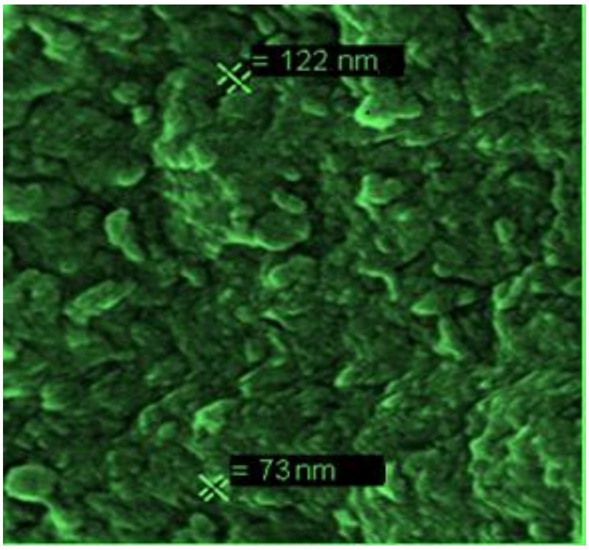


Fig .1.SEM image of synthesized polymer **3**.

The stability of the functionalized polymer 3 was determined by thermo gravimetric analysis at a heating rate of 10 °C per minute under a nitrogen atmosphere (Fig. 2). The TG curve indicates an initial weight loss of 7.68% up to 100 °C due to the adsorbed water and organic solvent in the polymeric support, which is common in the cases of immobilized catalysts onto organic or inorganic supports 40-44. A complete loss of the IL chains is seen in the range of 300–400 °C. The weight loss in the temperature range of 500–1100 °C can be assigned to the decomposition of the polymeric support. Thus, the TGA and DTG curves also convey the clear information that IL chains are successfully grafted onto the polymeric backbones.

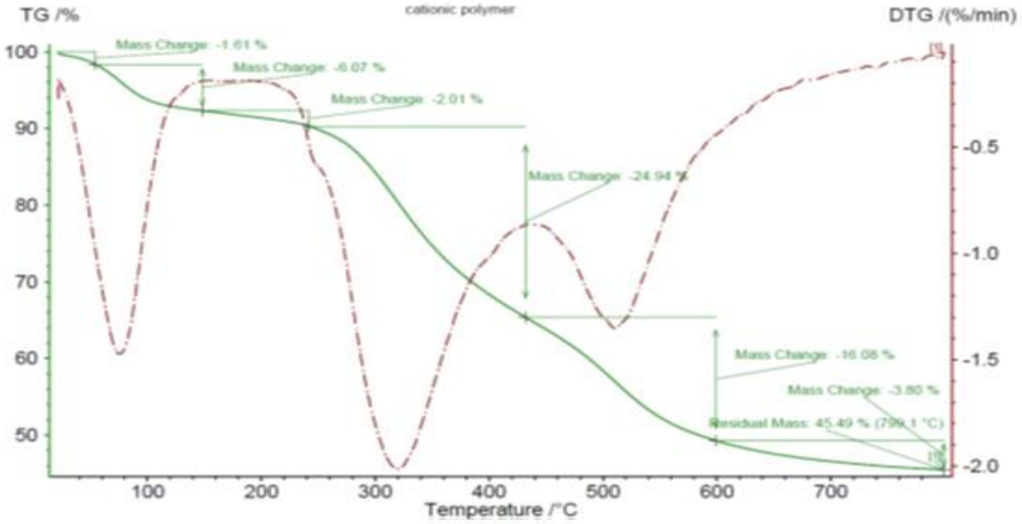
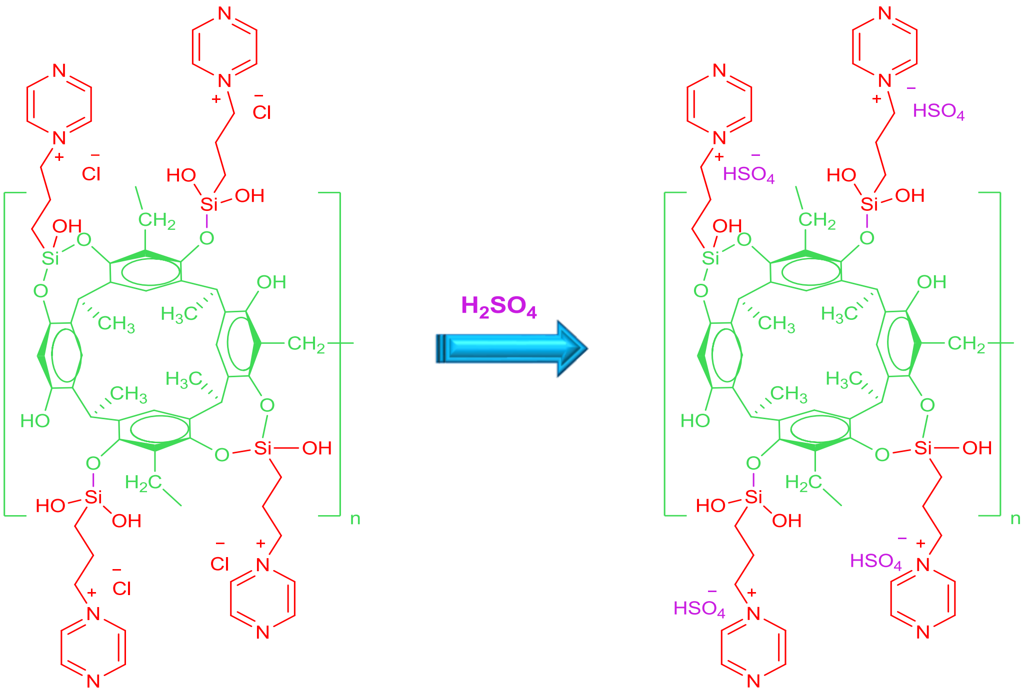


Fig .2. TGA and DTG curves of cationic polymer **3**.

After the characterization of 3, as stated earlier, in the second step of post-functionalization, the resultant cationic polymer was further reacted with H_2SO_4 in dichloromethane to form the corresponding 3D-network polymer-supported acidic catalyst 4 (Scheme 3). The sulfur content of the catalyst, measured by CHNS analysis, showed the value of about 8.6%. Based on this value, the amount of HSO_4 anions, which were supported on the polymer, is about 1.035 mmol per gram polymer.



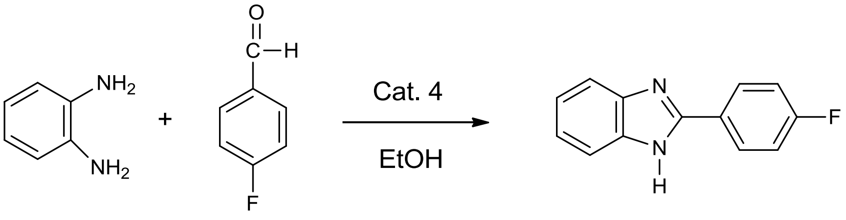
(3) (4)

Scheme .3. Synthesis of polymer supported Bronsted acid ionic liquid (**4**).

This result gave us confidence that the pyrazine side-chains and polymeric backbones are completely stable under acidic conditions. It is noteworthy that this polymeric support showed more potential for covalently anchored acidic ionic liquids in comparison with some previous solid supports reported in literature [45, 46]. Moreover, the synthesized polymer supported acid catalyst (4) is effectively insoluble in various solvents, including H_2O, CH_3OH, EtOH, DMSO, DMF, CH_3CN, CH_2Cl_2, and $CHCl_3$. These features render it suitable for conducting chemical transformations in various reaction media as an efficient heterogeneous acid catalyst.

In light of the aforementioned points and owing to the widespread applications of benzimidazole derivatives, we became interested to investigate the synthetic applicability of 4 as an acid catalyst for the rapid and efficient construction of benzimidazole derivatives.

To develop suitable reaction conditions, the reaction of ortho-phenylene diamine with 4-fluorobenzaldehyde was chosen as a model reaction (Scheme 4) and parameters such as solvent, temperature and amount of catalyst (4) were examined in detail.



(**5**)

Scheme . 4. the reaction of ortho-phenylene diamine with 4-fluorobenzaldehyde

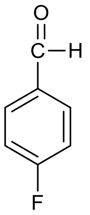
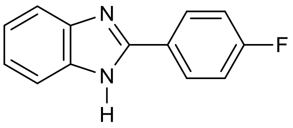
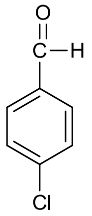
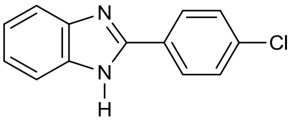
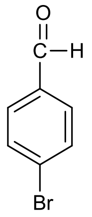
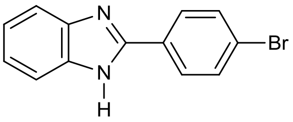
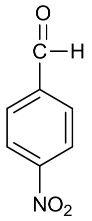
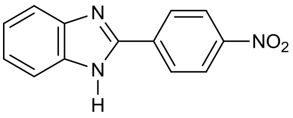
After some experiments, it was found that the use of 0.01 g of the catalyst **4** at room temperature in the ethanol as solvent, were the best conditions.

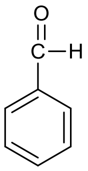
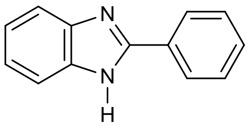
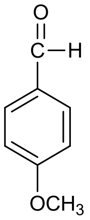
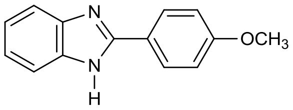
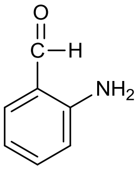
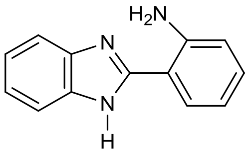
To confirm the catalyst efficiency, further experiments were carried out. Initially, in a control experiment, we carried out the model reaction in the absence of any catalyst. In this case, only a trace amount of product was detected after 6 h.

Next, the model reaction was examined in the presence of H_2SO_4. The yield of desired product was much higher with solid protic acid (4) compared with sulfuric acid. The superiority of this solid analog of sulfuric acid to commercial sulfuric acid is attributed to its porosity. The adsorption of substrate onto the surface of the functionalized polymer based on hydrophobic interaction between the substrates and polymeric backbone could increase the local concentration of substrates around the active sites of the polymer and effectively promote the reaction. These observations clearly highlight the existence of a synergistic effect between the cavities of the polymeric support and the immobilized acidic ILs, which leads to high catalytic activities.

These results encouraged us to demonstrate the efficiency and the applicability of the present acid-catalyzed reaction. For this purpose, the optimized reaction conditions were applied to a variety of aldehydes containing electron-withdrawing or electron-donating groups. Representative results of this synthetic modification are listed in Table 1. Both electron-rich and electron-deficient aldehydes gave the benzimidazole in good to excellent yields (entries A–G, Table 1).

Table . 1. Reaction of various aldehydes with ortho-phenylene diamine in the present of the representative catalyst in ethanol

Entry	Various aldehydes	Product	Time (min.)	Yield (%)
A			1	95
B			4	96
C			1	99
D			4	92

E			1	99
F			4	99
G			5	92

All products were identified by comparing their physical and spectral data with those of authentic samples [47].

Under these results, we expect that this porous acidic catalyst (**4**) will be a suitable alternative to the existing catalysts.

4. Conclusion

Bronsted acid ionic liquid has been immobilized onto a 3D-network polymer based on calix[4]resorcinarene to form a novel heterogeneous solid acid catalyst. Following the characterization of functionalized polymer, the application of this functionalized porous polymer as solid acid catalyst for the preparation of benzimidazole derivatives was investigated. The synthesized catalyst shows remarkably and somewhat extraordinary catalytic activity. The porosity of the polymeric support and covalently anchored acidic ionic liquid might indeed provide a synergistic means for the efficient approach of the starting materials to acidic sites, enough space for the preparation of product and a suitable hydrophobicity to drive out the water formed during the reaction from the support. The synthesized catalyst possesses a combination of a stable and hydrophobic polymeric support, strong acid strength, excellent catalytic activity and good recyclability in acid catalyzed reactions, and may open up a new route for the synthesis of novel and efficient heterogeneous acid catalysts via modification of the 3D-network polymer based on calix[4]resorcinarene.

Thus, this study suggests that the 3D-network polymer based on calix[4]resorcinarene can be used as an important and versatile green solid support for a variety of acid catalysts.

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