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Synthesis of diarylpyrimidinones (DAPMs) using large pore zeolites

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ABSTRACT

A series of diarylpyrymidin-2(1H)-one (DAPM) belongs to one of the important class of therapeutic and pharmacological active hetrocycles, were synthesized through the multicomponent reactions (MCRs) of aldehydes, ketone and urea, followed by the heterogeneous catalysis. The synthetic utility of this method is well demonstrated by avoiding expensive reagent TMSCl, using large pore zeolites (H-MOR, HY and H-BEA) as potential solid acid catalyst. Key role of textural properties such as surface acidity, hydrophobicity and porosity on catalytic activity of the zeolites on the synthesis of DAPMs has also been described.

1. Introduction

Concurrent research in organic synthesis focuses on economy. In fact, the efficiency of a synthetic sequence is more than ever corroborated with its conciseness and sustainability issues, as witnessed by the remarkable efforts currently aimed at the development of multiple bond forming and catalytic chemical processes. The efficiency of a chemical synthesis can be measured not only by parameters such as selectivity and overall yield, of course, but also by its raw material, time, human resources, and energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved. It is thus now recognized that the step count is one of the most important criteria when evaluating the efficiency of a synthesis [1]. In this context Multicomponent reactions (MCRs) have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry. The MCRs strategy offers significant advantages over conventional multistep synthesis due to its flexible, convergent, and atom economic nature. In a true sense, MCRs represent environmentally friendly processes by reducing the number of steps, energy consumption, and waste production. These features make MCRs well-suited for the easy construction of diversified arrays of, *e.g.*, valuable heterocyclic scaffolds [2].

Owing to the wide range of pharmaceutical and therapeutic properties of pyrimidinones (PMs) such as antitumor action in the treatment of B16 melanoma and P388 leukemia [3,4] or antagonize cell proliferation and induce cell differentiation by inhibiting (a nontelomeric) endogenous reverse transcriptase [5]. The syntheses of these heterocycles have recently received a great deal of consideration for the innovation of improved protocols towards milder reaction conditions, clean and high yielding approaches. Many procedures have been reported for the preparation of these heterocycles [6] but only few methods exist for the synthesis of pyrimidin-2(1H)-ones [7–9]. Thus the development of facile synthetic methods towards pyrimidin-2(1H)-ones, constitutes an active area of investigation in organic synthesis.

The uses of acidic zeolites in different areas of the organic chemistry have now grabbed significant levels, not only for the possibility to perform environmentally benign synthesis, but also for the good yields [10]. Further, zeolites are broadly used in the synthesis of specialty and fine chemicals [11]. Moreover, excellent reviews have been devoted to a large number of zeolite-catalyzed organic reactions [12,13]. In continuation of our work [14,15] on zeolite catalyzed multicomponent reactions (ZCMCRs), we herein report the synthesis of 4,6-diarylpyrimidinones (DAPMs) using various acidic zeolites as novel heterogeneous "***E***" catalyst (Eco-friendly, Efficient and Economic) (Scheme 1). To the best of our knowledge, no reports are available on the synthesis of DAPMs using zeolite as catalyst.

2. Experimental

2.1. Catalyst preparation and characterization

The zeolites Na-Beta (BEA(12); Si/Al = 12), H-Mordenite (H-MOR(11); Si/Al = 11), Na-Y (Si/Al = 2.43), Na-ZSM-5 (Si/Al = 15) zeolites were obtained from Sud-Chemie India Pvt. Ltd., India. The H-form of zeolite were prepared by ion exchange of the Na-form

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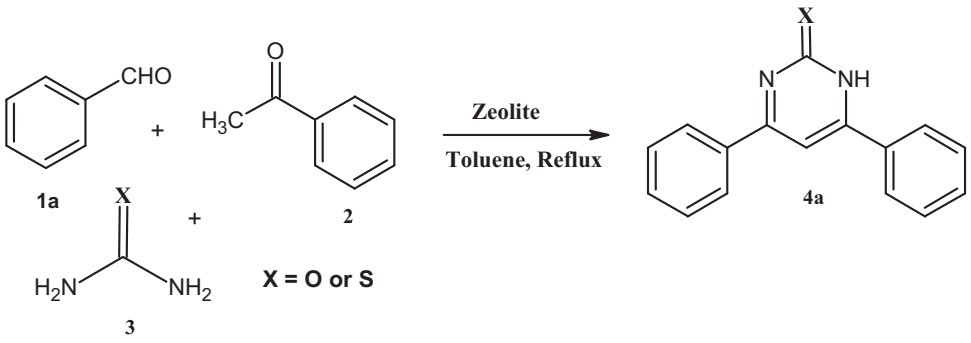


Scheme 1. Zeolite catalyzed synthesis of DAPM.

Table 1
Physiochemical properties of various zeolites.

Catalysts	Si/Al	Pore structure	S_{BET} (m^2/g)	Ammonia uptake (mmol/g)		
				Weak	Strong	Total
H-BEA	12	0.76 × 0.64 0.55 × 0.55	680	0.89	0.70	1.60
H-MOR	11	0.65 × 0.70	412	2.02	2.39	4.41
H-Y	2.43	0.74 × 0.74	480	2.30	–	2.30
H-ZSM-5	15	0.53 × 0.56	320	1.95	1.40	3.35

samples with aqueous solution of NH_4NO_3 (1 M), followed by drying and calcination at 823 K.

The phase purity and crystallinity of the zeolites were analyzed by XRD (D8 Advanced Brucker AXS, Germany) with Cu Kα radiation and nickel filter. Surface area measurement (BET method) was carried out on Micromeritics Gemini at −196 °C using nitrogen adsorption isotherms. Acidity of zeolites were determined on Micromeritics Chemisorb 2720, by a temperature programmed desorption (TPD) of ammonia. Ammonia was chemisorbed at 120 °C and then desorption was carried out up to 700 °C at heating rate of 10 °C/min. The solvents were distilled before use. All reagent used were of analytical grade.

2.2. Typical procedure for the synthesis of DAPM

All zeolites were activated, by heating at higher temperature of 773–823 K for 3–4 h, before loading into the reactor.

All the reactions were carried out in a round bottom flask attached to a condenser and equipped with a magnetic stirrer under heating in an oil bath. In a typical reaction, to a solution of ketone (1.2 mol) and urea (1.5 mol) in toluene, appropriate amount of aldehyde (1 mol) and zeolite (5 wt.%) were added. The reaction mixture was refluxed for 20–30 min and 60–70 min with zeolite H-BEA and H-Y, respectively. After completion of the reaction indicated by TLC, the spent catalysts were collected by filtration and then washed with ethanol. Crude product was recovered by evaporating the solvent under reduced pressure. This product was purified by recrystallization with ethanol to afford pure 4,6-diphenyl-pyrimidin-2(1H)-one having melting point 232–235 °C (reported, 233–240 °C) in 82% yield with zeolite H-BEA and 85% yield with H-Y.

The desire product, 4,6-diphenyl-pyrimidin-2(1H)-one (4a) was characterized by comparison of their physical data with those of known compound [16–20] and the spectral data of novel DAPM (entries 1g–1i) are given below.

4-(2-Chlorophenyl)-6-phenyl-pyrimidin-2(1H)-one (1g). Mp. 205–210 °C; FTIR (KBr) ν_{max} = 3429, 3230, 3083, 1605, 1549, 754 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 7.71 (m, 2H), 7.54–7.31 (m, 6H), 7.30 (dd, 1H, J = 7.5), 7.24–7.19 (m, 1H) ppm.; ^{13}C NMR (125 MHz, DMSO-d_6): 58.6, 126.4, 126.6, 127.4, 129.4, 132.7, 156.6, 157.9; ESI/MS: 284. 1 (M+2).

4-(2-Chlorophenyl)-6-phenyl-pyrimidin-2(1H)-thione (1h). Mp. 200–205 °C; FTIR (KBr) ν_{max} = 3427, 3233, 3081, 1608, 1549, 1509, 1090, 754 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 8.19 (s, 1H), 7.72 (m, 2H), 7.56–7.40 (m, 6H), 7.23–7.19 (m, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 58.2, 126.5, 127.3, 129.4, 132.8, 134.5, 158.6, 160.1; ESI/MS: 300 (M+2).

4-(4-Chlorophenyl)-6-phenyl-pyrimidin-2(1H)-thione (1i). Mp. 220–230 °C; FTIR (KBr) ν_{max} = 3429, 3231, 3080, 1600, 1550, 1506, 1092, 767 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 9.36 (s, 1H, NH), 7.72 (m, 2H), 7.56–7.40 (m, 6H), 7.23–7.19 (m, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 58.8, 115.1, 127.2, 132.9, 156.5, 157.8, 159.9; ESI/MS: 300(M+2).

3. Results and discussion

Zeolites are crystalline, highly ordered, microporous aluminosilicates with intracrystalline channels and cages of molecular dimensions. They have received an increasing attention because of their tunable acidity, the variety of structures and pore dimensions and excellent thermal stability which makes them economically and environmentally feasible [11]. Moreover, zeolite Y exhibits the FAU (faujasite) structure. It has a 3-dimensional pore structure, characterized by supercages of approximately 12 Å in diameter, which are linked through windows about 8 Å in diameter composed of rings of 12 linked tetrahedra (12-rings). These cages and pores permit access to quite large molecules, making this structure useful in catalytic applications (Fig. 1) [21].

Zeolites with different topologies as solid acid catalysts were used to elucidate the role of the zeolite channel system on their activity and selectivity on the synthesis of DAPM (Table 1). Table 2 shows the effect of various structural features such as, geometry (pore structure and dimension), acidity and Si/Al ratio of zeolites on the synthesis of DAPM. H-BEA and H-Y with 3-dimensional 12-membered ring (large pore) showed the high yield of 82% and 85% respectively (runs 1 and 3, Table 2) in considerably shorten reaction time as compared to other zeolites indicating that higher acid strength of the acid centre. Thus, the preferential order to yield DAPM was found to be: H-Y > H-BEA > H-MOR > H-ZSM-5.

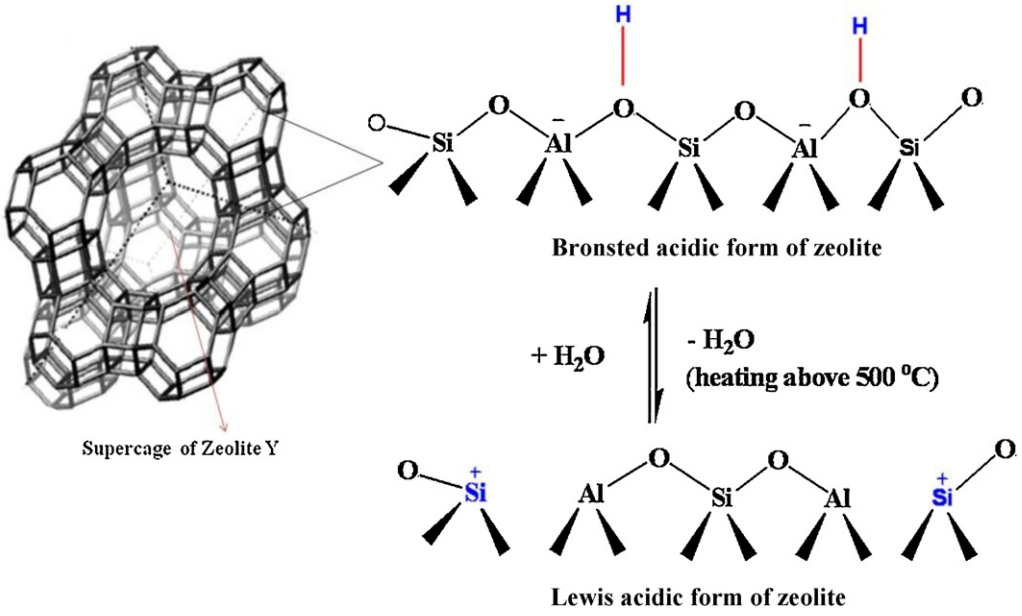


Fig. 1. (a) Faujasite structure of zeolite Y, illustrating the aluminosilicate framework with Lewis and Bronsted acidic form of zeolite.

3.1. Effect of geometry and surface acidity

According to our recent investigation on ZCMCR of Biginelli reaction [15], the low activity of zeolite ZSM-5, is probably ascribed to the diffusional limitation of the pores towards bulkier reactant molecules and geometrical constraints for the formation of intermediates inside the pores. Whereas, MOR exhibits largest number of acid sites compare to other zeolites (Table 1) but it seems that the unidirectional channels system causes either inherent diffusional limitations or pore blocking owing to strong adsorption of the reactant or products. Further, existence of strong acid sites in ZSM-5 and MOR does not favor the reaction due to the possibility of denseness of the active sites. Moreover, BEA zeolite possesses comparatively lower strong acid sites than other zeolite and the surface area of BEA zeolites is higher than other zeolites. Whereas, zeolite H-Y consists of supercages (Fig. 1) of pore structure and contain higher weak Lewis acid sites (Al). The most unexpected observation was the low activity shown by H-Y and H-MOR with respect to the reaction time (60–70 and 35–40 min respectively) compared to H-BEA (Table 2). It should be noted in this case that, there is no geometrical constraints for the diffusion of reactant through the pores but the strong adsorption of reactants and/or products in the pores of the catalyst that poisons or block the active sites and channels. The higher activity of H-BEA may also ascribed to higher Si/Al ratio compared to rest of the zeolites consequently leads to higher hydrophobicity. Moreover, it is noteworthy that, with increasing framework Si/Al ratio, the catalyst becomes more hydrophobic, the concentration of acid sites (both, Bronsted and Lewis) decreases and strength of remaining sites increases [22]. According to the results and conclusions presented above, we could expect that the less polar zeolite should favor the desorption of adsorbed polar product. Hence, it is concluded that low to moderate acidity along with higher surface area and higher Si/Al ratio of zeolite BEA are prime factors for higher catalytic activity towards the synthesis of DAPMs.

Table 2
Synthesis of DAPM using different zeolites.[a]

Catalysts	Time (min)	Yield (%)[b]
H-BEA	20–30	82
H-MOR	35–40	60
H-Y	60–70	85
H-ZSM-5	60–80	25

[a] *Reaction conditions*: aldehyde (1 mmol), acetophenone (1.2 mmol), urea (1.5 mmol), catalyst (5 wt%) under toluene reflux.
[b] Isolated yields.

3.2. Synthesis of substituted DAPMs

In order to optimize the catalyst concentration, the reaction of acetophenone, urea and benzaldehyde, was carried out with varied amount of H-BEA and H-Y (1, 3, 5 up to 10 wt.%) in toluene as a solvent. The best result was obtained by carrying out the reaction with 1.2:1.5:1 molar ratio of acetophenone, urea and benzaldehyde using 5 wt.% of zeolites H-BEA and H-Y under reflux condition (Fig. 2).

Using the optimized reaction conditions, the performance and efficiency of these procedures were explored for the synthesis of a wide range of substituted DAPMs. The results are summarized in Table 3. It is observed that, aromatic aldehydes with both electron withdrawing and electron-donating substituents reacted efficiently with urea and acetophenone in the presence of catalytic

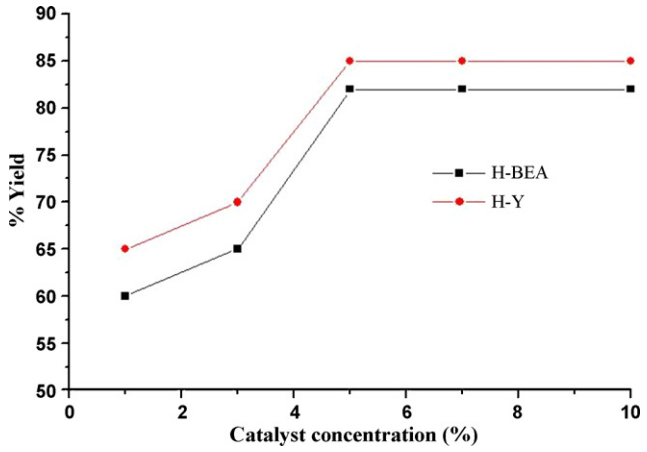


Fig. 2. Optimization of catalyst concentration.

Table 3
Zeolites catalyzed synthesis of 4,6 diaryl pyrimidin-2(1H)-ones under reflux conditions.[a]

Entry	Aldehydes	X	H-BEA		H-Y		
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b,c]	Yield (%)
1a	C_6H_5CHO	O	20–30	82	60–70	85	–
1b	4-Br-C_6H_4CHO	O	20–30	76	60–70	78	–
1c	**4-HO-C_6H_4CHO**	**O**	**20–30**	**76**	**60–70**	**71**	**–**
1d	**4-MeO-C_6H_4CHO**	**O**	**20–30**	**79**	**60–70**	**76**	**–**
1e	4-Cl-C_6H_4 CHO	O	20–30	85	60–70	88	–
1f	4-Me-C_6H_4CHO	O	20–30	83	60–70	85	–
1g	2-Cl-C_6H_4CHO	O	20–30	81	60–70	84	–
1h	2-Cl-C_6H_4CHO	S	20–30	75	60–70	79	–
1i	4-Cl-C_6H_4CHO	S	20–30	80	60–70	83	–
1j	CH_3CHO	O	50–60	–	60–70	–	–
1k	$CH_3CH{=}CHCHO$	O	50–60	–	60–70	–	–
1l	C_6H_5CHO	O	–	–	–	–	75[d,e]
1i	C_6H_5CHO	O	50–60	–	20–30	–	–

Bold values represents the polar reactants.
[a] *Reaction conditions*: aldehyde (1 mmol), acetophenone (1.2 mmol), urea (1.5 mmol), catalyst (5 wt%) under toluene reflux.
[b] Isolated yields.
[c] All known products (except 1g–1i) have been reported previously in the literature and were characterized by comparison of Mp, IR and NMR spectra with authentic samples [16–20].
[d] Reaction was carried in the presence of TMSCl as a catalyst in DMF/CH_3CN at 90 °C according to reported method [23].
[e] Isolated yields in the presence of TMSCl catalyst.

amount of H-BEA and H-Y (5 wt.%) under reflux condition to give the corresponding DAPMs in moderate to high (70–88%) yields without the formation of any side products. Moreover, as could be expected, less polar zeolite H-BEA found to be more efficient with respect to the shorten reaction time and when subjected more polar substrate involved in the reaction (Table 3, entries 1c and 1d) compare to the zeolite H-Y. The scope of the reaction was also investigated with aliphatic aldehydes and α,β-unsaturated aldehydes. In our preliminary attempts with aliphatic aldehydes such as acetaldehyde and crotonaldehyde (Table 3, entries 1j and 1k) the reaction failed to yield the corresponding DAPM. Moreover, reaction in the absence of zeolite catalyst did not give corresponding DAPM (Table 3, entry 1i). The overall 15–20% less yield revels that there is still scope of development of zeolite catalyst with regards to restricted pore size of zeolite which limiting the application of zeolite towards bulkier organic molecule. The XRD patterns of zeolite before and after the reaction revealed that the zeolite retained its crystallinity throughout. Thus, the catalyst can be reused. Further, the catalysts were recycled for five runs without significant loss of activity (Fig. 3).

Recently, Lewis acids such as sulphamic acid, bismuth(III) trifluoroacetate and heteropolyacids along with trimethylsilyl chloride (TMSCl) have been reported as an efficient catalysts for the synthesis of DAPM [16–19]. Scheme 2 shows the merit of the present work in comparison with the above mentioned reported methods. Additionally, it shows that use of TMSCl is essential for this reaction and absence of either one, failed to give the reaction. In this context, we could not found any reasonable explanation about the role of TMSCl in this transformation. In order to ensure the Lewis acidity characteristic of TMSCl, we attempted the synthesis of DAPM using exclusively TMSCl as a catalyst according to the method reported by Wang et al. and afforded 75% yield of corresponding DAPM (Table 3, entry 1i). TMSCl has also been reported as Lewis acid catalyst for many MCRs for the preparation of other heterocyclic compounds [23,24]. Therefore, we assume that the Lewis acidity of the zeolite catalyst in the present study is the main driving force for the desired conversion. The efficiency of zeolite towards this transformation can be explained by the various physiochemical parameters such as both zeolites (H-BEA and H-Y) possess large porosity and higher surface area. The results revealed that zeolite can act as an effective catalyst with respect to acidity profile, reaction times, yields and the obtained products as well as elimination of expensive and toxic reagent TMSCl.

On the basis of our above preliminary results, the mechanism of zeolite catalyzed synthesis of DAPM is shown in Scheme 3. Moreover, we have not found any suggested mechanism for this reaction in the literature except proposed by Heravi et al. [16]. To ensure

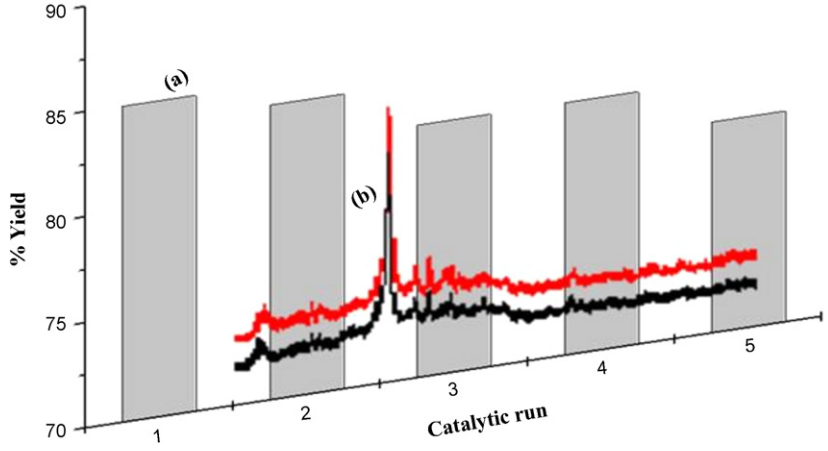
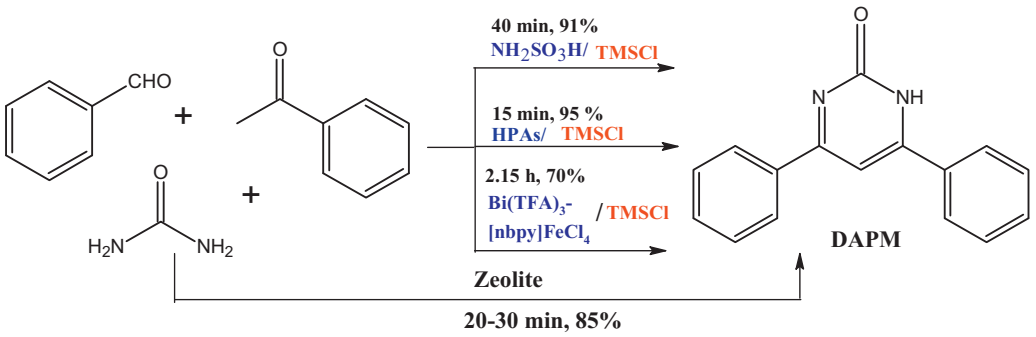
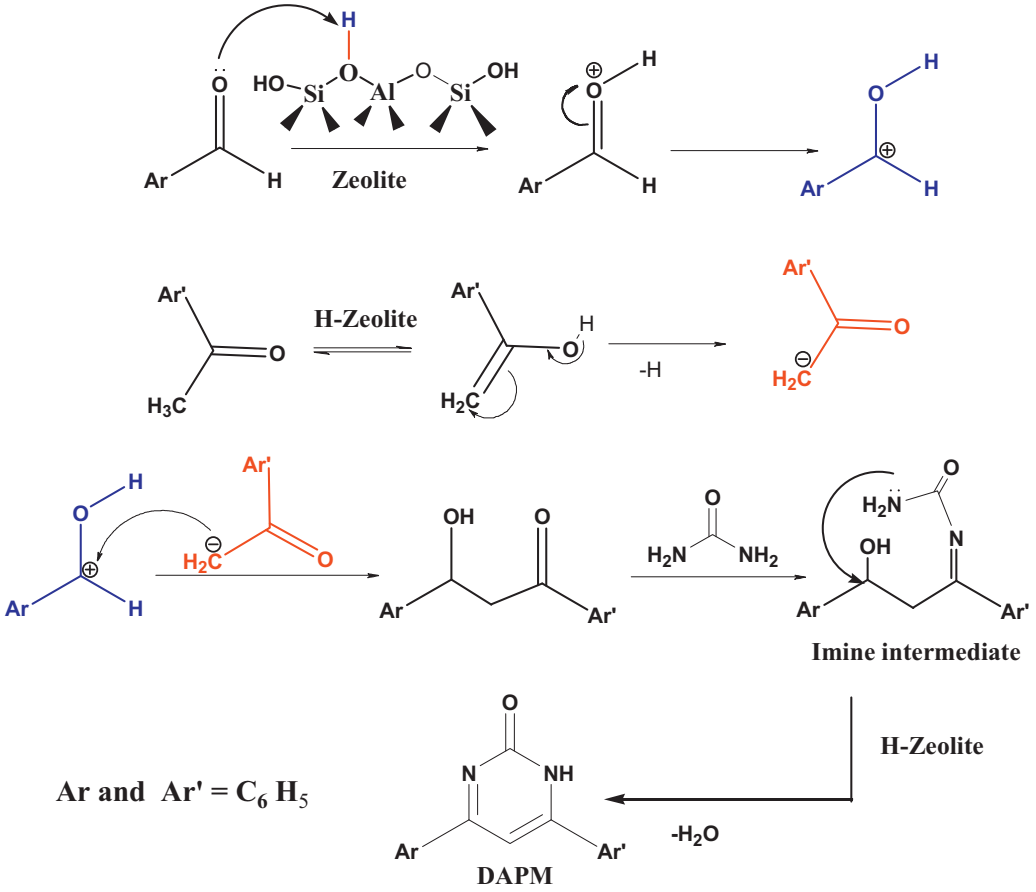


Fig. 3. (a) Reusability of catalyst (b) XRD pattern of zeolite H-BEA fresh (black, lower) and after four run (red, upper). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)



Scheme 2. Comparison of present catalytic system with reported catalyst.



Scheme 3. Plausible mechanism of zeolite catalyzed synthesis of DAPM.

formation of β-hydroxy ketone in the mechanism, the reaction of *p*-chlorobenzaldehyde with acetophenone was carried out separately in the presence of zeolite H-BEA and obtained product 3-(4-chlorophenyl)-3-hydroxy-1-phenylpropan-1-one was confirmed by comparison of their physical data with those of known compound [25] (Mp: 97–99 °C, Reported: 99.4–100.4 °C) On further reaction of β-hydroxy ketone with urea yielded desired DAPM. We have been currently exploring the involvement of nature of acidity (Lewis and Bronsted) in the mechanism aspect of DAPM formation using zeolite.

4. Conclusion

The synthesis of biological active DAPM over various large pore zeolites (H-Y, H-MOR and H-BEA) was studied. Zeolite presents cleaner green technology over the reported Lewis acid catalysts used for the synthesis of DAPMs by eliminating the use of toxic TMSCl. It has been found that the presence of strong acid sites in zeolite does not favor the reaction. Zeolite H-BEA and H-Y showed higher catalytic activity compared to the other zeolites for ZCMCRs under study. Moreover, H-BEA has been found to be more efficient as compared to H-Y with respect to shorter reaction time. This can be attributed to the higher surface area and Si/Al ratio of zeolite H-BEA.

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