

Zeolite H-BEA catalysed multicomponent reaction: One-pot synthesis of amidoalkyl naphthols – Biologically active drug-like molecules

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Abstract. Zeolite has been used as an efficient and a novel heterogeneous catalyst for one-pot synthesis of biologically active drug-like molecules, amidoalkyl naphthols. This green route involves multicomponent reaction of 2-naphthol, aromatic aldehydes and amide in the presence of a catalytic amount of zeolite H-Beta (H-BEA) under solvent reflux as well as solvent-free conditions.

Keywords. Zeolite; multicomponent reaction; amidoalkyl naphthol; green chemistry.

1. Introduction

The use of acidic zeolites in different areas of the organic chemistry has now reached significant levels, not only for the possibility to perform environmentally benign synthesis, but also for the good yields.¹ Further, zeolites are broadly used in the synthesis of specialty and fine chemicals. They have received an increasing attention because of their tunable acidity and the variety of structures and pore dimensions. The other salient features of zeolite include their low cost and excellent thermal stability which make them economically and environmentally feasible.² The use of zeolites as a catalyst is important in the development of clean technologies, since it avoids the drawbacks of the conventional technologies, mainly environmental pollution and corrosion of the equipment (figure 1).

Multicomponent reactions (MCRs) have attracted considerable attention since an increasing number of organic chemical compounds are formed by multicomponent reactions (MCRs) that convert more than two educts directly into their products by one-pot reactions. Further, they are performed without need to isolate any intermediate during their processes; this reduces time and saves both energy and raw material. They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.³

One of these MCRs is the preparation of amidoalkyl naphthols. It is worthy to note that by amide hydrolysis

reaction, 1-amidomethyl-2-naphthols can be converted to important biologically active 1-aminomethyl-2-naphthol derivatives. The hypotensive and bradycardiac effects of these compounds have been reported.⁴ The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol and acetonitrile or amide in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10 clay,⁵ HClO₄-SiO₂,⁶ iodine,⁷ heteropolyacids,⁸ *p*-TSA,⁹ sulfamic acid,¹⁰ and cation-exchange resins.¹¹ However, some of these methods associated with prolonged reaction time, toxicity and low yields of desired product. Further, when a solid aldehyde or high amounts of catalyst is used, an organic solvent such as dichloroethane is needed.¹⁰ In this context, there is growing interest in development of clean processes involving green catalysts. Increasing demand for environmentally benign procedures with heterogeneous and reusable catalyst¹² encourage us to develop a safe alternate method for the synthesis of amidoalkyl naphthols using acidic zeolite. To the best of our knowledge, no reports are available on the synthesis of amidoalkyl naphthol using zeolite as catalyst (scheme 1).

2. Experimental

2.1 Materials and methods

The composition of anhydrous Na-BEA zeolite was obtained from Sud-Chemie India Pvt Ltd., India. The

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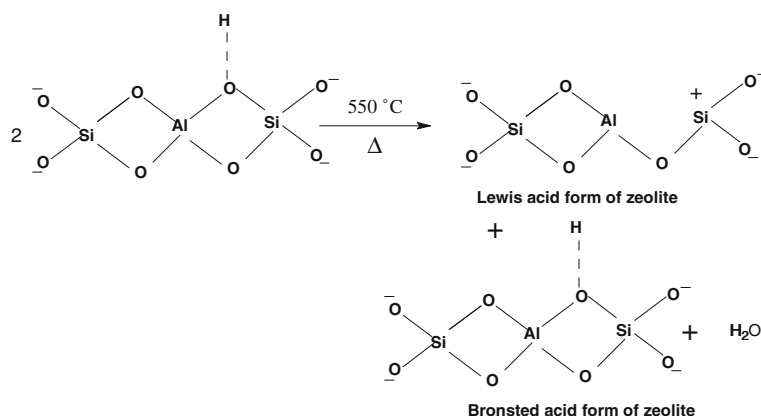


Figure 1. Lewis and Bronsted acidic form of zeolite.

H-form zeolite was prepared by ion exchange of the Na-form sample with aqueous solution of NH_4NO_3 (1M) or alkali metal acetate, followed by drying and calcination at 823 K.

The X-ray diffractogram ($2\theta = 5\text{--}65^\circ$) were obtained on X-ray diffractometer (D8 Advanced Bruker AXS, Germany) with Cu- K_α 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 of ammonia. Ammonia was chemisorbed at 120°C and then desorption was carried out up to 700°C at heating rate of $10^\circ\text{C}/\text{min}$.

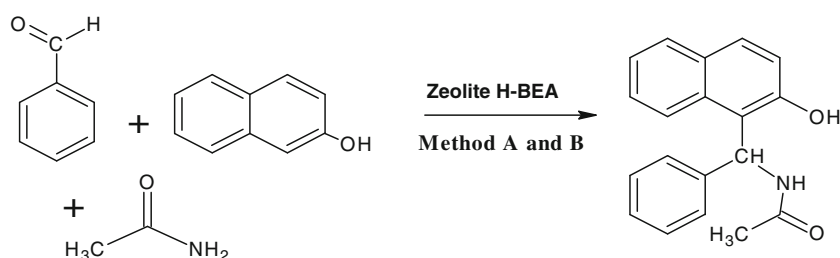
The solvents were distilled before use. All reagents used were of analytical grade. NMR spectra were recorded on a Varian 200 MHz. IR spectra were run on a (FT-IR) (Shimadzu make, model 8400 S) using KBr powder. Mass spectra were recorded on VG micromass 7070 H. The purity of the substances and the progress of the reactions were monitored by TLC on silica gel.

2.2 Procedure for the synthesis of amidoalkyl naphthols

To a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol) and acetamide (1.2 mmol), effective amount of zeolite H-BEA was added. The mixture was stirred under thermal solvent-free condition at 120°C in oil bath for 5–7 min and the reaction was followed by TLC. After completion of reaction, mass was cooled to 25°C , then the solid residue was dissolved in EtOAc and the mixture stirred for 5 min. The catalyst was recovered. Then solvent was evaporated, the remaining solid product was recrystallized in aqueous EtOH (15%).

All products are known and compounds were characterized by melting point (mp), $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and FT-IR and MS. Some physical data of these compounds are represented below:

2.2a *N*-[Phenyl-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (table 2, entry 1): White solid; *M.p.*



Method A: Under toluene reflux

Method B: Thermal Solvent-Free conditions

Scheme 1.

244–245°C; ¹H NMR (DMSO-d₆): δ = 1.98 (s, 3H), 7.18–1.10 (m, 4H), 7.25–7.20 (m, 4H), 7.33 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 10.02 (s, 1H) ppm; ¹³C NMR (125 MHz, DMSO-d₆): 23.3, 40.1, 119.2, 119.4, 122.4, 123.8, 126.6, 126.9, 128.4, 128.6, 128.9, 129.1, 129.8, 132.9, 143.1, 153.7, 168.9 ppm; IR (KBr): 3400, 3250, 3063, 1640, 1581, 1514, 1372, 1337, 1060, 808, 742, 696, 623 cm⁻¹; MS *m/z*: 292 ([M+H]⁺).

2.2b *N*-[(4-Methylphenyl)-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide (table 2, entry 2): *M.p.* 222–224 °C; ¹H NMR (DMSO-d₆): δ = 1.96 (s, 3H), 2.21 (s, 3H), 7.08–7.03 (m, 5H), 7.19 (d, J = 8.8 Hz, 1H), 7.24 (t, J = 7.1 Hz, 1H), 7.34 (m, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.82 (brd, 1H), 8.36 (d, J = 8.1 Hz, 1H), 9.91 (s, 1H) ppm; ¹³C NMR (125 MHz, DMSO-d₆): 20.4, 22.6, 47.6, 118.4, 118.9, 122.2, 123.1, 125.9, 126.1, 128.3, 128.4, 128.9, 132.2, 134.9, 139.4, 143.3, 152.9, 168.9 ppm; IR (KBr): 3419, 3316, 3070, 1621, 1595, 1561, 1514, 1466, 1392, 1283, 1202, 1141, 1051, 939, 884, 784, 745, 712 cm⁻¹; MS *m/z*: 305 ([M+H]⁺); Anal. Calcd. for C₂₀H₁₉NO₂: C: 78.66; H: 6.27; N: 4.59 %. Found: C: 78.75; H: 6.19; N: 4.62 %.

2.2c *N*-[(4-Methoxy-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (table 2, entry 9) *M.p.* 181–183°C: ¹H NMR (DMSO-d₆): δ = 10 (s, 1H), 8.4 (d, 1H), 7.80–7.73 (m, 4H), 7.35–7.05 (m, 6H), 2.51 (s, 3H), 1.94 (s, 3H). IR (KBr): 3399, 3063, 3000, 2964, 2830, 2785, 2704, 1626, 1581, 1514, 1438, 1372, 1337, 1280, 1257, 1180, 1086, 1060, 1045, 928, 879, 847, 820, 746 cm⁻¹; MS *m/z*: 322 ([M+H]⁺).

2.2d *N*-[(2-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (table 2, entry 11) *M.p.* 213–215°C: ¹H NMR (DMSO-d₆): δ = 1.91 (s, 3H), 7.08–7.56 (m, 8H), 7.73 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 6.1 Hz, 1H), 8.00 (t, J = 7.0 Hz, 1H), 8.50 (s, 1H), 9.75 (s, 1H) ppm; IR (KBr): 3427, 3061, 1640, 1514, 1438, 1268, 808, 752, 501 cm⁻¹; MS *m/z*: 325 ([M+H]⁺).

3. Results and discussion

In order to carry out synthesis of amidoalkyl naphthol in a more efficient way that minimizes time and the amount of catalyst, the reaction of 2-naphthol, benzaldehyde and acetamide was selected as a model reaction. The best result was obtained by carrying out the reaction with 1:1:1.2 molar ratios of 2-naphthol, benzaldehyde acetamide and 7 wt% of zeolite H-BEA. Further, looking towards the % yield (85%) and shorter reaction time (5–7 min), thermal solvent-free condition is found to be more beneficial compared to the solvent reflux condition (table 1).

Thus, we have made an attempt to prepare a range of amidoalkyl naphthols under the optimized reaction conditions i.e., 2-naphthol (1 mmol), aryl aldehydes (1 mmol), and acetamide (1.2 mmol) in the presence of zeolite H-BEA (7 wt%). A series of amidoalkyl naphthols were prepared in high to excellent yields in thermal solvent-free conditions (table 2). In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups gave the desired products in Method A and B with yield of 70–90%. 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 (figure 2).

Table 1. Optimization of catalyst concentration.^a

Entry	H-BEA	Reflux condition		Thermal solvent-free condition	
		Time (h)	Yield (%)	Time (min)	Yield ^b (%)
1	2 wt %	10-11	55	10-15	61
2	5 wt %	7-9	69	9-10	75
3	7 wt %	4-6	78	5-7	85
4	10 wt %	4-6	70	5-7	79
5	15 wt %	4-6	72	5-7	73

^aReaction condition:

2-naphthol/aldehyde/acetamide (1/1/1.2) under toluene reflux,

2-naphthol/aldehyde/acetamide/catalyst (1/1/1.2) under thermal solvent-free condition, oil bath, 120°C

^bYields refers to the pure isolated products

Table 2. Synthesis of amidoalkyl naphthols using zeolite H-BEA.^a

Entry	Aldehydes	Time (min)/yield (%) ^c
1	C ₆ H ₅ CHO	5-7/85
2	4-Me C ₆ H ₄ CHO	5-7/73
3	4-NO ₂ -C ₆ H ₄ CHO	5-7/90
4	4-NMe ₂ C ₆ H ₃ CHO	5-7/70
5	4-Cl-C ₆ H ₄ CHO	5-7/80
6	4-Br-C ₆ H ₄ CHO	5-7/82
7	4-F- C ₆ H ₄ CHO	5-7/78
8	2,4-Cl ₂ - C ₆ H ₃ CHO	5-7/80
9	4-MeOC ₆ H ₄ CHO	5-7/82
10	3-MeO C ₆ H ₄ CHO	5-7/80
11	2-Cl-C ₆ H ₄ CHO	5-7/76
12	2-NO ₂ -C ₆ H ₄ CHO	5-7/80
13	C ₆ H ₅ CH=CHCHO	5-7/65
14	CH ₃ CHO	10/-
15	CH ₃ (CH ₂) ₂ CHO	10/-

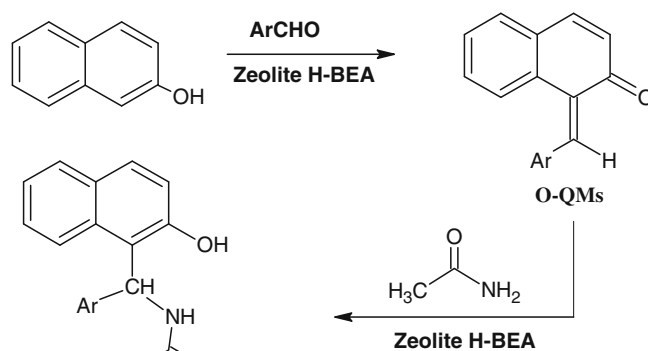
^aReaction conditions:

2-naphthol/aldehyde/acetamide/catalyst (1/1/1.2/7 wt%) under thermal solvent-free condition, oil bath, 120°C

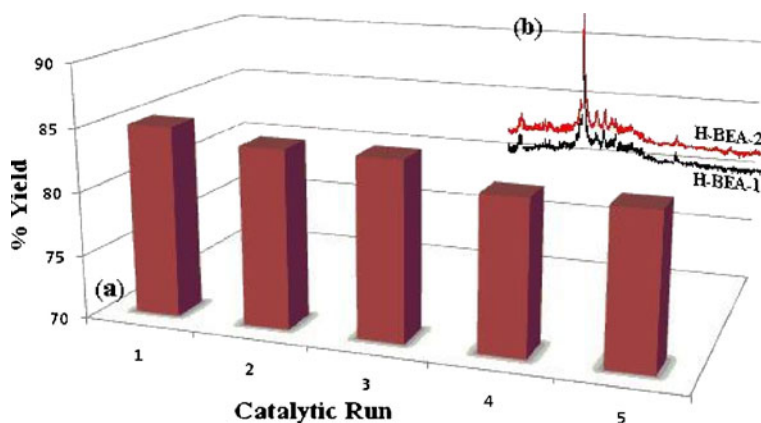
^bYields refer to the pure isolated products^cAll known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.¹³⁻¹⁹

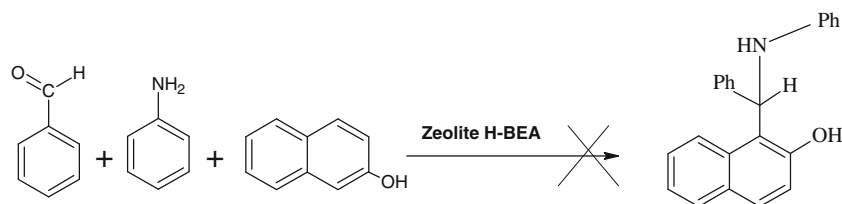
The proposed mechanism for the H-BEA catalysed preparation of amidoalkyl naphthols from the reaction of 2-naphthol, aromatic aldehydes and acetamide under reflux and thermal conditions is shown in scheme 2.

As can be seen from the results (table 2), this reaction is affected by electronic and steric factors. Aldehydes with electron-withdrawing groups, gave higher yields than those with electron-donating groups. A reasonable explanation for this result has been suggested

**Scheme 2.**

by Shaterian *et al.*¹³ The condensation of 2-naphthol with aldehydes under acid catalysts gave ortho-quinone methides (o-QMs). The generated o-QMs reacted with acetamide via the conjugated addition to afford 1-amidoalkyl-2-naphthols. Electron-withdrawing groups on the benzaldehydes in the o-QMs increase the rate of the 1,4-nucleophilic addition reaction because the alkene LUMO is at lower energy in the presence of electron-withdrawing groups compared with electron-donating groups. *Ortho* substituents decrease the yield of the reaction probably due to the steric effect (table 2, entry 11, 12). The scope of the reaction was also investigated with aliphatic aldehydes and α, β -unsaturated aldehydes. In our preliminary attempts with aliphatic aldehydes¹³ such as acetaldehyde and butyraldehyde (table 2, entry 14 and 15 respectively) the reaction failed to yield the corresponding amidoalkyl naphthols. However, in case of α, β -unsaturated aldehydes i.e., cinnamaldehyde, we have isolated the product, amidoalkyl naphthol along with impurity (table 2, entry 13). In

**Figure 2.** (a) Recyclability of zeolite H-BEA, (b) XRD patterns of H-BEA before used (H-BEA-1) and after four run (H-BEA-2).



Scheme 3.

Table 3. Comparison of catalytic activity of H-BEA with several catalysts for synthesis of amidoalkyl naphthol.

Entry	Catalyst	Time	Solvent (temp)	Yield (%)	Ref
1	Montmorillonite K-10 clay	1 h	— (125°C)	84	[4]
2	HClO ₄ -SiO ₂	40 min	— (110°C)	89	[5]
3	I ₂	4.5 h	— (125°C)	87	[7]
4	K ₅ CoW ₁₂ O ₄₀ ·3H ₂ O	2 h	— (125°C)	90	[8]
5	NaHSO ₄	20 h	ACN (85°C)	80	[13]
6	Fe(HSO ₄) ₃	50 min	— (85°C)	93	[14]
7	Wet TCT (Cyanuric chloride)	10 min	— (100°C)	91	[15]
8	[TEBSA][HSO ₄] (Bronsted acidic Ionic liquid)	10 min	— (120°C)	87	[16]
9	FeCl ₃ -SiO ₂	11 min	— (120°C)	86	[17]
10	H-BEA	4–6	Toluene (110°C)	78	This work
11	H-BEA	5–7 min	— (120°C)	90	This work

Table 4. Characterization of zeolite.

Catalysts	Channel structure	Pore structure (nm)	SiO ₂ /Al ₂ O ₃ ratio	S _{BET} (m ² /g)	Ammonia uptake (mmol/g)		
					Weak	Strong	Total
H-BEA	3D	0.76 × 0.64 0.55 × 0.55	25	710	0.89	0.70	1.60

our laboratory, we have been working in the direction to optimize the yield of amidoalkyl naphthols using various conjugated aldehydes. On the other hand, the reactions with thiourea were considered, but no corresponding products were produced. Also, amine such as aniline was utilized and no aminoalkyl naphthol was obtained (scheme 3).

Moreover, table 3 shows the merit of the present work in comparison with the results reported in the literature. The results revealed that zeolite H-BEA can act as an effective catalyst with respect to reaction times, yields and the obtained products. The efficiency of zeolite H-BEA towards these reactions can be explained by the various physiochemical parameters (table 4) as it possess higher surface area and weak to moderate acidity which are the prime factor for higher catalytic activity of zeolite catalyst. Further, the loss of 10–20% yields in these reactions are probably ascribed to geometry of

zeolite catalyst as restricted pore architecture of zeolite (BEA - 0.76 × 0.64 nm, table 4) sometimes limiting the diffusion of bulkier reactant molecules as well as geometrical constraints for the formation of intermediates inside the pores. Moreover, we observed that solid aldehydes are reacted smoothly where as trace amount of liquid aldehydes were found unreacted during the reaction.

4. Conclusion

In conclusion, we demonstrated a new application of zeolite H-BEA in the synthesis of amidoalkyl naphthols. A series of amidoalkyl naphthols were obtained in high yields via three-component reaction of 2-naphthol, aromatic aldehydes and amide under two different conditions (Method A and B). The thermal solvent-free

(Method B) green procedures offer advantages such as shorter reaction times, simple work-up, environmentally benign, excellent yield, cost effective recovery and reusability of catalyst for a number of times without significant loss of activity. Further applications of zeolite in organic transformations are currently in progress in our laboratories.

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