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Microporous material: an efficient and recyclable catalyst for expedite regioselective synthesis of pyrimidobenzimidazoles

Kapil arya*[a] Anshu Dandia[b]
[a]Indian Oil Corporation Limited, R & D center, Faridabad-121007, India
[b]Chemistry department, university of Rajasthan, Jaipur-302004, India
E-mail: aryakapil2001@yahoo.com

Abstract

Microporus materials are active catalysts in regioselective synthesis of pyrimidobenzimidazoles. Five kinds of zeolites were studied and they showed quite different catalytic activities due to their wide acid sites distributions and various pore structures. Hβ zeolite was found to be the best in activity for synthesis of isomer 5 while the basic catalyst NaY zeolite found suitable for synthesis of isomers 4. The main acid sites of H-zeolites were Brönsted acid sites, and H^+ was the catalytic acid site. The methodology involves a ring closure by different ways based on the reaction medium was confirmed by NOE and X-ray studies.

Keywords Microporus materials, Zeolite, Pyrimido[1,2-*a*]benzimidazole, Microwave irradiation

1 Introduction

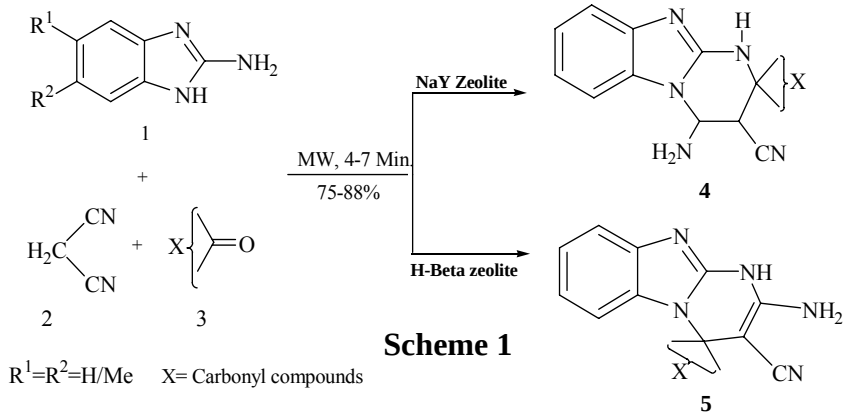
Organic synthesis involving green processes and under solvent-free conditions have been investigated world widely due to stringent environment and economic regulations.[1] In recent years, organic reactions on solid supports such as zeolites[2] or mesoporous molecular sieves[3,4] have attracted much attention because of advantages these catalysts possess, such as acidic properties, shape-selectivities, environment friendly nature of catalysts, the easy work-up, the high purity of the products, and the recycling of catalysts and decrease waste production.[5] These materials are reported to have Brønsted acid sites in the micropores and on the external surface, and Lewis acid sites predominantly at the internal surface due to the local defects.[6]

Pyrimido[1,2-*a*]benzimidazoles represent core structures that are useful templates for the design of a variety of compounds. From high throughput screening, a number of analogues have been found to be of pharmacological interest.[7-11] Usefulness of alkenenitriles as starting materials in heterocyclic syntheses has been amply demonstrated.[12-14] An extensive literature survey of reactions of 2-aminobenzimidazole with alkenenitrile leading to the formation of pyrimido[1,2-a]benzimidazoles indicated that there is a definite need to study the detailed mechanistic pathway and regiochemistry of the synthetic processes and the development of new methods for the regioselective synthesis of these compounds. Conventionally, these compounds have been synthesized by different route.[15-18] However, many of these methodologies suffer from the drawback of green chemistry1[9-21] and have been associated with several shortcomings such as long reaction times, expensive reagents, low product yields and difficulty in recovery and reusability of the catalysts. Due to these problems, development of an efficient and versatile method for the preparation of pyrimido benzimidazole is an important aspect and which is an active going on research area and there is a scope for the further improvement towards mild

reaction conditions and improved yields. Reactions under microwave irradiation[22] are clean, fast and economical and provide a non-conventional energy source that has the advantage of short reaction times with high yields and regioselectivity. Our ongoing programme to develop benign and expeditious methods for organic transformation under solvent-free conditions using microwaves irradiation,[23]and our interest in green chemistry, we planned to synthesise a compound structurally related to the biologically important pyrimido[1,2-*a*] benzimidazoles by reacting 2-aminobenzimidazole with malononitrile and cyclohexanone using various type of zeolites and studied their catalytic effect on reaction mechanism (**Scheme 1**).

2 Result and discussion

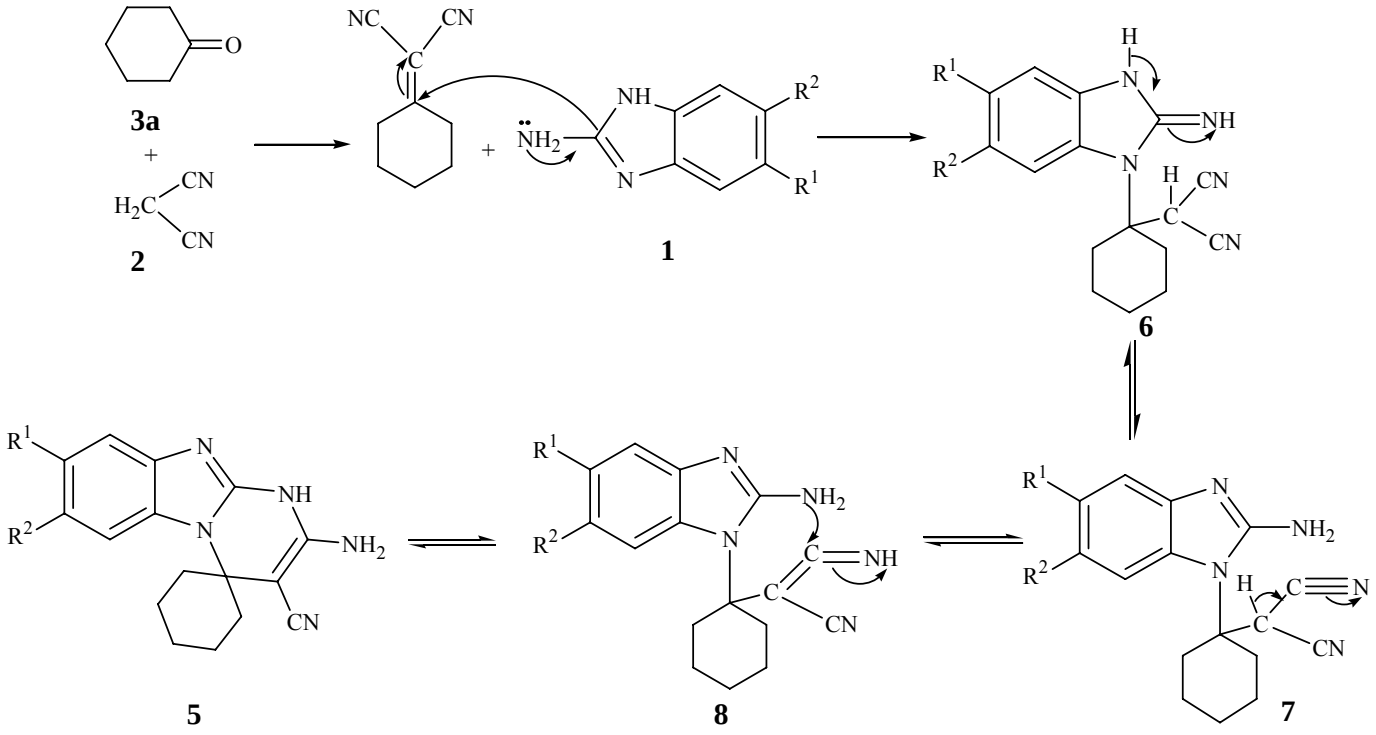
We found that the reaction of substituted or unsubstituted aminobenzimidazoles **1** with alkenenitrile **2** proceeds by two possible pathways depending on the reaction conditions. In conventional manner alkenenitrile **3a** were treated with aminobenzimidazoles **1** under reflux in N, N-dimethylformamide or ethanol for 72 hrs., the reaction being monitored by TLC. When the reaction under reflux in N,N-dimethylformamide was stopped after 18 hours, spectral data showed that traces of the starting materials, unconjugated enaminic nitrile **7**, traces of conjugated enaminic nitrile 8 and some of the pyrimidobenzimidazole **5** were in the mixture. However, after 48 hrs of reaction, all the starting materials had been used up and the intermediate enaminic nitriles converted to the final product in near quantitative yield. When the reaction was carried out in ethanol for 72 days, the unconjugated adduct **7** was the sole product. Compounds **8** show broad twin stretching bands in the IR spectra between 3150-3450 cm^{-1} due to NH_2, intense stretching bands due to C=N between 1640-1650 cm^{-1} and to C = C between 1600-1610 cm^{-1}, while in compound **7** shows absorption band at 3180-3460 cm^{-1} due to NH_2, 2300-2320 cm^{-1} (C≡N) and absence of C=C at 1600-1620 cm^{-1} confirm the formation of **7**. In ^1H NMR spectra CH protons showed at 3.42 ppm further confirmed the formation of **7**. In microwave irradiation 2-aminobenzimidazole (**1a**) react with alkenenitrile in presence of HY zeolite gave 7'-amino-8'H-spiro [cyclohexane-1,5'-pyrimido[1,2-a]benzimidazole]-6'-carbo-nitrile **5a-e** in good yield. While NaY zeolite give 6'-amino-8'H-spiro[cyclohexane-1,7'-[1,2,4]triazolo[4,3-a]pyrimidine]-5'-carbonitrile (**4)** in quantitative yield.(**Scheme 1**).



Scheme 1

The reaction of aminobenzimidazoles with alkenenitrile may proceed by two possible mechanistic pathways (**Schemes 2 or 3**) depending on whether the initial attack of the alkenenitrile is by ring nitrogen (**Scheme 2**) or by the nitrogen of the side chain (**Scheme 3**), to give the isomeric pyrimidobenzimidazoles **4** or **5**. In order to distinguish between the isomeric benzimidazoles 4 and 5, 1H nuclear Overhauser effect (NOE) experiments involving the spectral substitution technique (difference NOE)[24,25] was used. Enhancement of the H-6 signal (26%) was observed when the C-12 methine proton was irradiated in compound 5a, whereas irradiation of H-6 induced enhancement of H-7 (23%) and H-12 (20%) signals, thus indicating that H-6 and H-12 protons are in close spatial proximity. These results confirm that the pyrimidobenzimidazoles obtained in this work are of structure **5**. The NOE experiment also permitted the unambiguous assignment of all the proton signals in structure **5**.

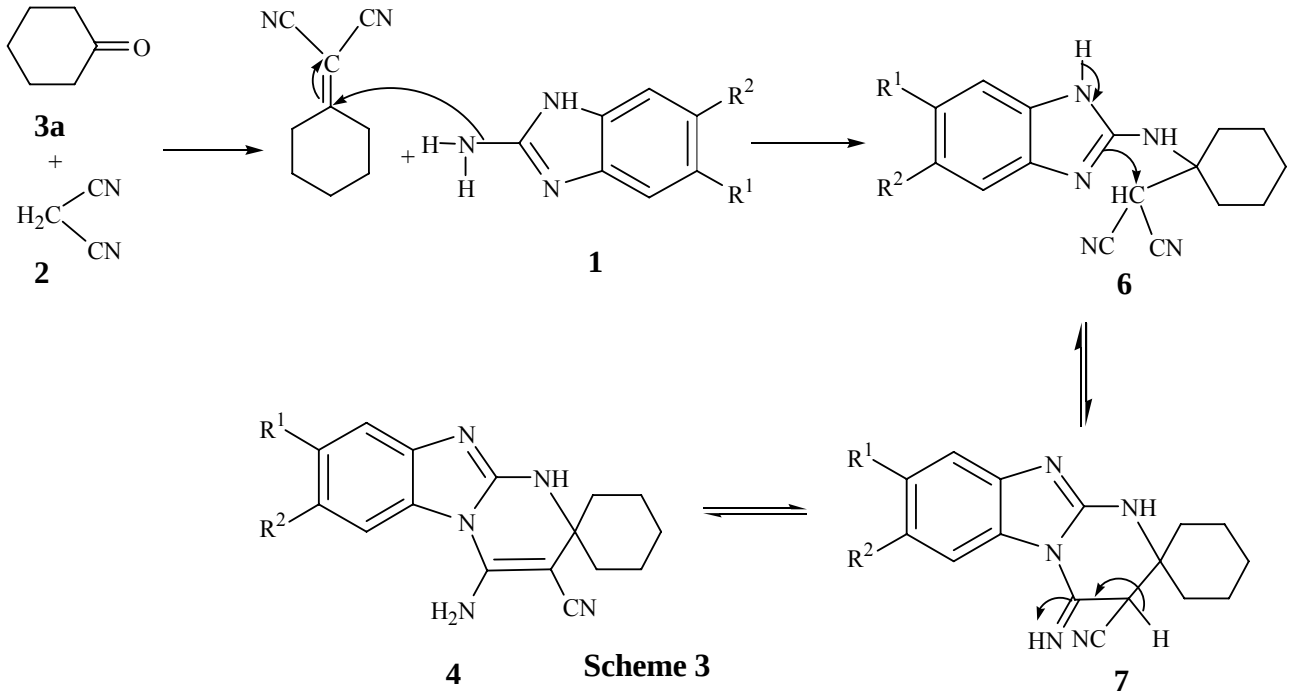
X-Ray crystallographic analyses of reaction products from the reaction of 2-aminobenzimidazoles and dimethyl allene- 1,3-dicarboxylate[26] have proved that the product obtained results from the attack of the alkene by the ring nitrogen in case of HY zeolite.



Scheme 2

In basic medium using NaY zeolite the ring nitrogen is protected by the base and not available to attack on alkenenitrile, so the side chain nitrogen attack and yielded the 4 and no enhancement of signal was observed in NOE. This involves the condensation of carbonyl compound with active

methylene reagent to afford the corresponding β−arylacrylonitrile derivative (**6**) followed by addition of exocyclic amino function of 2-aminobenzimidazole (**1**) to the activated double bond system in (**6**) to form Michael adduct (7) which undergoes intramolecular cyclization to give (**4**).



Scheme 3

X-ray crystallographic analysis of the product of multi-component reaction of (**1**), (**2**) and (**3**) has proved the structure (**4**) [27] The assignment of structure **5** and **4** obtained in this work is thus confirmed conclusively.

Five kinds of zeolites were studied, and the results were listed in **Table 1**. It is obvious to observe that both low conversion and selectivity was obtained when catalyst was not employed in reaction mixture. However, they could be improved by using these zeolites. For sake of comparisons we prepared a range of pyrimidobenzimidazole in the same optimized reaction conditions using conventional heating. Microwave conditions showed the beneficial effect on the reaction with considerably decreased reaction time and increasing yield.

Table 1. Effect of various zeolite and reaction method on synthesis of pyrimidobenzimidazole

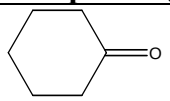
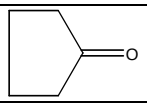
Entry	Compound no.	Reaction conditions	Method	Time (min.)	Temp. (°C)	Yield (%)[a]
1.	5a	Hβ	Δ	600	R.T.	62
2.		Hβ	MW	4	140	86
3.	5a	HUSY	Δ	720	R.T.	45
4.		HUSY	MW	15	140	68

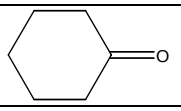
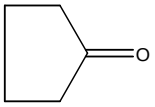
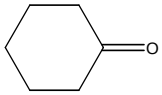
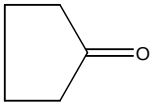
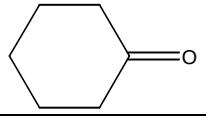
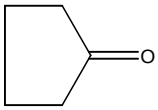
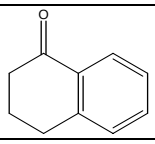
5.	5a	HY	Δ	1200	R.T.	38
6.		HY	MW	18	140	64
7.	5a	HM	Δ	1080	R.T.	47
8.		HM	MW	20	140	55
9.	5a	HZSM-5	Δ	720	R.T.	58
10.		HZSM-5	MW	7	140	72
11.	4a	NaY	Δ	900	R.T.	64
12.		NaY	MW	6	140	88
13.	4a	CeY	Δ	1080	R.T.	45
14.		CeY	MW	10	140	68
15.	4a	LaY	Δ	1320	R.T.	Mixture of products
16.		LaY	MW	15	140	40
17.	4a	Neat	Δ	1440	R.T.	Traces of Products
18.		Neat	MW	8	140	45

[a]= Isolated yeild

As shown in **Table 1** that Hβ exhibited the high conversion while HM showed low conversion under microwave irradiation. The percentages of conversion and the selectivity for the target product **5** could be arranged in the order Hβ> HZSM-5>HUSY > HY> HM. In case of basic zeolite the product selectivity of targeted product was NaY> CeY> LaY. Since the number and strength of acid site in zeolite increase with metal cation exchanged in the order of $H^+ < Na^+ < Ce^2 < La^{3+}$ [23b]. Such results could be explained by the difference of zeolite channel structures and acidic properties.

Table 2. Physical data of synthesized compounds

Cmpd no.	**R^1**	**R^2**	**Carbonyl compound (X)**	**Reaction medium**	**Time (Min.)**	**M.P. (^oC)**	**Yield (%)**
4a	H	H		NaY Zeolite	6	240[27]	88
4b	H	H		NaY Zeolite	5	170	92

4c	CH_3	CH_3		NaY Zeolite	5	205	85
4d	CH_3	CH_3		NaY Zeolite	8	225	82
5a	H	H		H-Beta Zeolite	4	285	86
5b	H	H		H-Beta Zeolite	4	296	90
5c	CH_3	CH_3		H-Beta Zeolite	8	272	82
5d	CH_3	CH_3		H-Beta Zeolite	6	340	84
5e	H	H		H-Beta Zeolite	7	325	79

3 Conclusions

In conclusion, we have demonstrated that Hβ and NaY zeolite is a new efficient and green catalyst for synthesis of pyrimidobenzimidazole derivatives via a three-component reaction of 2-aminobenzimidazole, cabonyl compound and alkenenitrile using microwave irradiation. The remarkable advantages offered by this method are: catalyst is inexpensive, non-toxic, easy handling and reusable, simple work-up procedure, short reaction time, high yields of product with better purity and green aspect by avoiding toxic catalyst and hazardous solvent.

4 Experimental

Melting points were determined. Thin layer chromatography on silica gel 'G' coated glass plates using benzene, ethanol (8: 2) as eluent was used for monitoring the progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer, ^{1}H and ^{13}C NMR spectra [CDCl3] were taken on a Bruker –300DX spectrometer at 300 and 200 MHz respectively, using TMS as an internal standard for PMR as external standard and mass spectra were recorded on Jeol D–300 spectrometer at an ionisation potential of 70 e.v. Microwave assisted reactions were carried out on Maxidigest MX 350 Prolabo (50 W), operating 2450 MHz frequency. Perkin–Elmer 2400 automatic CHNS analyzer used for elemental analyses. All anilines were purchased used as received. NaY, HUSY, HZSM-5, HM and Hβ zeolite were obtained from Zeolyst International, Netherland. The SiO_2/Al_2O_3 ratio is 5.12 in NaY, 8.10 in

HUSY, 60 in HZSM-5, 20 in HM. Hβ zeolite was prepared by following the methods described in literature[28].

General Procedure

Synthesis of 4'-amino-1'H-spiro[cyclohexane-1,2'-(pyrimido[1,2-a]benzimidazole)]-3'-carbonitrile (**4**)This was carried out following the procedures below.

(a) Conventional method: 2-Aminobenzimidazole (**1**) (.01 mol), malononitrile (**2**) (.01 mol) and cyclohexanone (**3**) (.01 mol) and NaY zeolite (2g) were heated to refluxed in ethanol (50 ml) for appropriate time (TLC control). The reaction mixture was kept overnight at room temperature and the resulting precipitate of **4** was filtered off, washed with ethanol, dried and recrystallised from ethanol.

(b) Microwave heating: Pyrex glass vial contaning an equimolar (.01 mol) mixture of **1**, **2** and **3** was mixed with NaY zeolite (2g) was placed in a screw capped Teflon vessel. Microwave irradiation was applied for 3-10 min at 140°C. After the completion of reaction (TLC analysis), recyclable zeolite was separated by filtration after eluting the product with ethanol under reduced pressure and the residue was washed with methanol give pure product in high yield **(Table 2)**.

7'-amino-8'H-spiro [cyclohexane-1,5'-pyrimido[1,2-a]benzimidazole]-6'-carbonitrile (**5)** This was carried out following the procedures below.

(a) Conventional method: 2-Aminobenzimidazole (**1**) (.01 mol), malononitrile (**2**) (.01 mol) and cyclohexanone (**3**) (.01 mol) and Hβ zeolite (2g) were heated to refluxed in ethanol (50 ml) for appropriate time (TLC control). The reaction mixture was kept overnight at room temperature and the resulting precipitate of **4** was filtered off, washed with ethanol, dried and recrystallised from ethanol.

(b) Microwave heating: Pyrex glass vial contaning an equimolar (.01 mol) mixture of 1, 2 and 3 was mixed with Hβ zeolite (2g) was placed in a screw capped Teflon vessel. Microwave irradiation was applied for 3-10 min at 140°C. After the completion of reaction (TLC analysis), recyclable zeolite was separated by filtration after eluting the product with ethanol under reduced pressure and the residue was washed with methanol give pure product in high yield **(Table 2)**.

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