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Expedite regioselective synthesis of pyrimidobenzimidazoles

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Abstract:
An simple, general, efficient and greener method has been developed for one pot regioselective synthesis of pyrimido[1,2-a]benzimidazole is described. Starting from the 2-aminobenzimidazole, malononitrile and carbonyl compound, the methodology involves a ring closure by different ways based on the reaction medium was confirmed by NOE and X-ray studies.

Introduction:

One of the main aims of green chemistry is the reduction of the use of organic solvents because of the economical and environmental concerns associated with them, and therefore the development of solvent-free synthetic methods[1] is of the utmost importance. The usefulness of alkenenitriles as starting materials in heterocyclic syntheses has been amply demonstrated.[2]

Pyrimido[1,2-*a*] benzimidazoles have been described as antiinflammatory[3], macrofilaricidal[4], antibiotic[5], antiarrythemic[6], anthelmintic[7], antibacterial[8], antifungal[9], anti-histaminic[10], anticancer[11], angiotension receptor antagonist[12], potent and selective 5-HT_4 receptor antagonist, antitumor , antiviral[13] and antiproliferative activities.[14]

A number of synthetic methods have been developed during past two decades.[15-19] Of these methods, a variety of organic solvents and catalyst is used. However, organic solvents, particularly methanol, toluene, dimethylformamide, pyridine, etc. are high on the list of damaging chemicals because of their volatile nature, considerable toxicity and use in large quantities for a reaction. To avoid these disadvantages a couple of modifications using zeolite have been reported recently.[20]

Microwave radiation provides an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The use of microwave irradiation has introduced several new concepts in chemistry, since the absorption and transmission of the energy is completely different from the conventional mode of heating. The microwave technology has been applied to a number of useful research and development processes and several reviews have been published covering various aspects of microwave-assisted chemistry.[21,22]

As a part of our green technology program[23] we would also like to disclose here a more practical green alternative for the regioselective synthesis of pyrimido[1,2-a]benzimidazole by a three-component condensation of carbonyl compounds (aldehydes and ketones), malononitrile

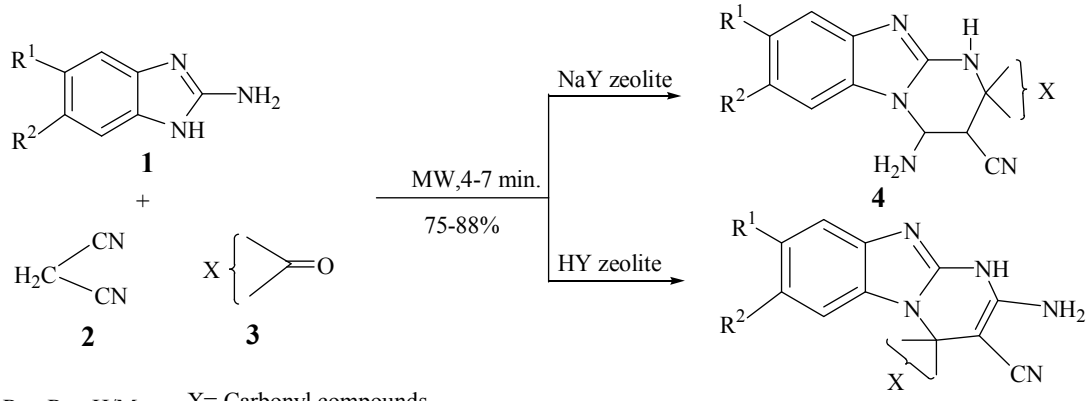
and substituted /unsubstituted aminobenzimidazoles without any hazardous solvent in presence of zeolite.(**Scheme-1**).

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'-carbonitrile **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**).



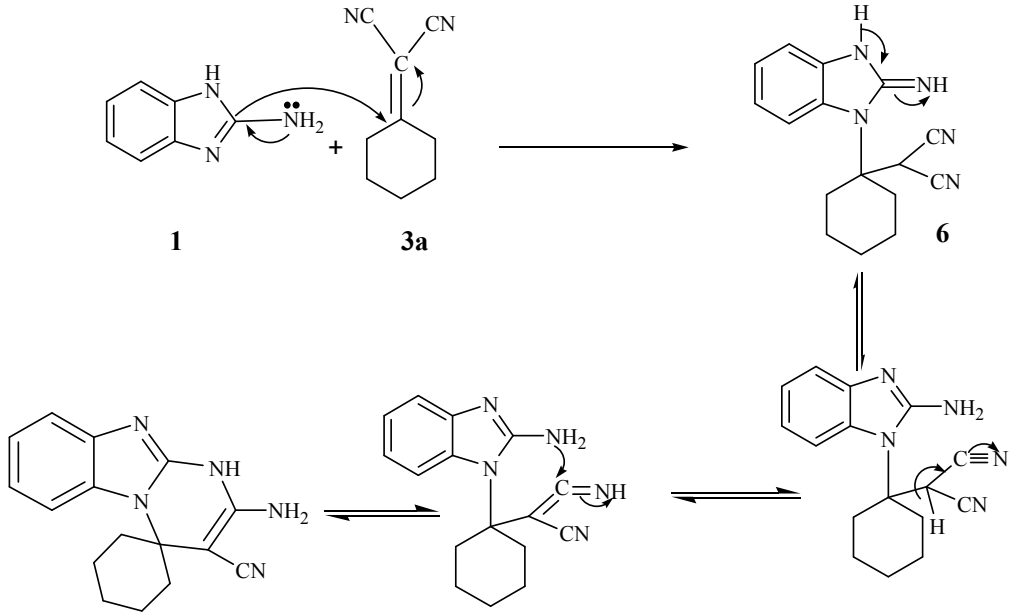
$R_1 = R_2 = H/Me$

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

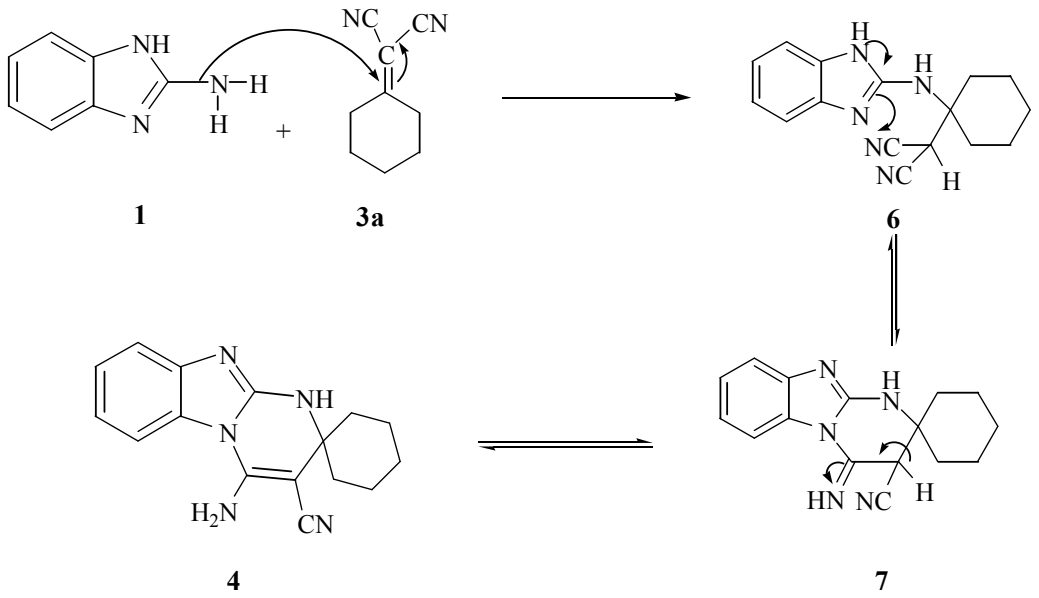
benzimidazoles **4** and **5**, 1H nuclear Overhauser effect (NOE) experiments involving the spectral substitution technique (difference NOE) [24,25] was used. Enhancement of the H-6 signal (26%) was observed when the C-12 methine proton was irradiated in compound **5a**, whereas irradiation of H-6 induced 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)**. The assignment of structure **5** and **4** obtained in this work is thus confirmed conclusively.

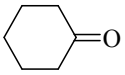
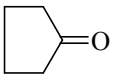
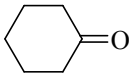
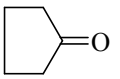
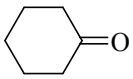
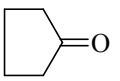
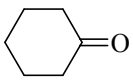
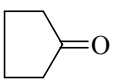
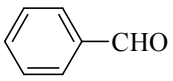
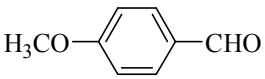
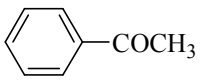
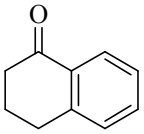
3. Experimental

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, ^{19}F and ^{13}C NMR spectra [$CDCl_3$] were taken on a Bruker –300DX spectrometer at 300 and 200 MHz respectively, using TMS as an internal standard for PMR and hexafluorobenzene as external standard for ^{19}F NMR 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. All anilines were purchased used as received. Perkin–Elmer 2400 automatic CHNS analyzer used for elemental analyses.

General procedure of synthesis:

Substituted aminobenzimidazole, malononitrile and carbonyl compound were dissolved in 50 ml anhydrous benzene. To this solution, 2-4 g of mineral support (NaY and HY zeolite) was added under stirring. After solvent evaporation under low pressure, the obtained solid was exposed to microwaves for appropriate time (**Table-1**). The activated solid was cooled and washed several times with 10 ml of benzene. Then, the solvent was evaporated and the product purified by methanol recrystallization.

Table 1 : Physical data of synthesized compound (4a-d,5a-f)

S.No.	R^1	R^2	Carbonyl compounds (X)	Reaction medium	Time (min.)	M.P. (°c)	Yield (%)
4a	H	H		NaY	6	240	88
4b	H	H		NaY	5	170	92
4c	CH_3	CH_3		NaY	5	205	85
4d	CH_3	CH_3		NaY	8	225	82
5a	H	H		HY	4	285	86
5b	H	H		HY	4	296	90
5c	CH_3	CH_3		HY	8	272	82
5d	CH_3	CH_3		HY	6	340	84
5e	H	H		HY	4	208	88
5f	H	H		HY	5	265	82
5g	H	H		HY	8	298	80
5h	H	H		HY	7	310	79

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