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Zeolites. Efficient and Eco-friendly Catalysts for the Synthesis of Benzimidazoles

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Summary. A superior method of synthesis of 2-substituted benzimidazoles by means of the heterogeneous catalysis of synthetic and natural zeolites in the reaction of 1,2-diaminobenzene with acid chlorides is described.

Keywords. Benzimidazole; Zeolite; Heulandite; Heterocyclization; 1,2-Diaminobenzene.

Introduction

Benzimidazoles are crucial structures, which are contained in agrochemicals, dyestuffs, and high temperature polymer products [1], and have interesting biological and pharmacological activities [2, 3], including inhibition of phosphodiesterase IV [4], neuropeptide Y binding [5], and anti-arrythmic and antiviral indications [6, 7]. 2-Aryl and 2-alkyl-substituted benzimidazoles also exhibit activity against HIV [8], influenza [9], and HSV-1 viruses [10]. Thus, these compounds have recently received considerable attention in diverse areas of chemistry [11].

A vast variety of synthesis methods have been developed in recent years to uncover a number of new reagents for the synthesis of 2-substituted benzimidazoles [12–18]. A major drawback of these classical methods is the poor yields, use of expensive and hazardous reagents and solvents, tedious work-up procedure, and in some cases failure of the method. In addition, the synthesis of fine chemicals under environmentally friendly conditions represents a challenging goal in the field of synthetic organic chemistry [19].

In the last decade there has been a tremendous development mainly due to the use of solid acids, such as clays and zeolites [20]. Zeolites are strong *Bronsted* and

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Lewis acids and have been used as catalyst for various organic reactions. An extensive application of heterogeneous catalysis in synthetic organic chemistry can help to render more attractive the processes from both environmental and also the economic point of view [21]. Despite this interest and advantage, however, heterogeneous catalysis in heterocyclization has been largely overlooked.

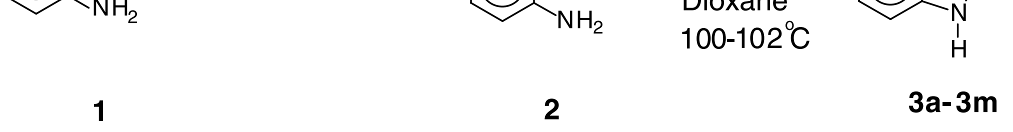
Because of the importance of benzimidazoles [1–18], in continuation of our interest in the synthesis of heterocyclic compounds containing nitrogen [22], and ongoing research in heterogeneous catalysis [23], we wish to report our results for the synthesis of benzimidazoles using synthetic and natural zeolites.

Results and Discussion

The synthesis of 2-substituted benzimidazoles from the reaction of 1,2-diaminobenzene and an acid chloride using $BF_3 \cdot Et_2O$ has been reported [24]. We have recently introduced a new heulandite type of zeolite (HEU) and used it to catalyze the *Biginelli* reaction [25]. During the course of our studies towards the development of this zeolite as an efficient heterogeneous catalyst, we employed it for the one-pot formation of 2-phenylbenzimidazole (**3a**) from reaction of 1,2-diaminobenzene with benzoyl chloride *via* heterocyclization of *N*-benzoyl-1,2-diaminobenzene (**2**) (Scheme 1).

In a first attempt, 1,2-diaminobenzene (**1**) was added to benzoyl chloride (1 equiv) at 0°C in dry dioxane and stirred for 30 min at ambient temperature to give *N*-benzoyl-1,2-diaminobenzene. To this crude, natural heulandite type zeolite (0.25 g) was added and the mixture was heated to 100°C. The progress of reaction was monitored by TLC using (*Ac*O*Et*:hexane 1:2) as eluent. Upon completion of the reaction and usual work-up, the product was identified as 2-phenylbenzimidazole (**3a**). However, the yield of this reaction was 58%. By doubling of the amount of zeolite and increasing of reaction time, the yield improved only slightly to 60%. To compare the performance of the catalyst with the synthetic zeolites such as HY and HZSM-5, we carried out this reaction with the latter two catalysts in various solvents at different reaction times and temperatures. Our results are summarized in Tables 1 and 2. These results clearly indicate that HEU and HY zeolites despite having a greater number of *Lewis* acid sites (Al) [26], are less effective than the HZSM-5 zeolite for this heterocyclization.

Inspection of TDP profiles for these zeolites [25], show that the TDP curve for HZSM-5 zeolite consists of a low temperature (LT) and a high temperature (HT) peak corresponding to weak and strong acidic sites. In the TDP curves for HY and



1 **2** **3a-3m**

Scheme 1

Table 1. Comparison of efficiency of zeolites in preparation of 2-phenylbenzimidazole

Entry	Catalyst	Catalyst weight/g[a]	Time/h	Yield/%
1	HZSM-5	0.25	3	61
2	HZSM-5	0.25	7	63
3	HZSM-5	0.25	12	64
4	HZSM-5	0.5	3	81
5	HY	0.25	3	60
6	HY	0.25	7	63
7	HY	0.5	3	61
8	HEU	0.25	3	58
9	HEU	0.25	7	50
10	HEU	0.5	3	60

[a] Catalyst weight per 0.01 mol *o*-phenylenediamine

Table 2. The effect of solvent, temperature, and catalyst amount (HZSM-5) on 2-phenylbenzimidazole synthesis

Entry	Catalyst weight/g	Solvent	Time/h	Temp/°C	Yield%
1	0.25, 0.5, 1	Dioxane	3	100–102	61, 81, 82
2	0.5	Xylene	1.5	140–150	82
3	0.5	Tetrahydrofuran	3	70–72	69
4	0.5	Tetrahyrofuran	7	70–72	71
5	0.5	Acetonitrile	3	80–82	82.5

HEU no HT peak is observed. Since by using HZSM-5 in comparison with HEU and HY zeolites, this heterocyclization gives a higher yield, it seems that the presence of strong acidic sites rather than the greater number of *Lewis* acidic sites favor this reaction.

As shown in Table 2, the heterocyclization reaction is facilitated by increasing the reaction temperature. The reaction proceeded in xylene at 140–150°C to give a high yield at a shorter reaction time, whereas the yield was low in *THF* at 70–72°C. Also we observed a high yield using acetonitrile due to increased solvent polarity under the same reaction conditions. On the other hand, the amount of catalyst was optimized at 0.5 g *per* 0.01 mol of *o*-phenylenediamine, and a larger amount of catalyst is not effective (Entry 1, Table 2).

The results disclosed in Table 3 show the scope and generality of the method with the HZSM-5 catalyst. One of the salient features of this method is that electron poor or rich benzoyl chlorides as well as alkanoyl chlorides give excellent yields and purities. The catalyst can be used up to 5 times without any activity loss or appreciable changes in product yields.

In conclusion, we have compared the performance of synthetic and natural zeolites as commercial available, inexpensive, and reusable catalysts in the synthesis of 2-substituted benzimidazoles. The reasonable reaction times, high yields, simple work-up procedure, and a one-pot reaction without the necessity to isolate the *N*-acylphenylenediamines are main merits of this method.

Table 3. HZSM-5 catalyzed synthesis of benzimidazole derivatives

	R	Time/h	Yield/%[a]	mp/°C[b]	
				Found	Ref.
3a	C_6H_5	3	81	292–294	290–293 [27]
3b	$2\text{-}NO_2C_6H_4$	5	71	262–265	264–265 [27]
3c	$2\text{-}ClC_6H_4$	3	83	263–234	234 [28]
3d	$3\text{-}ClC_6H_4$	3	82	235–239	238 [28]
3e	$2\text{-}OMeC_6H_4$	3	80	178–181	179–180 [29]
3f	$3\text{-}OMeC_6H_4$	3	81	201–204	205 [29]
3g	$3\text{-}NO_2C_6H_4$	5	70	204–207	204–206 [14]
3h	$4\text{-}NO_2C_6H_4$	5	69	324–327	322–323 [27]
3i	$2\text{-}BrC_6H_4$	3	79	241–244	246 [28]
3j	$4\text{-}MeC_6H_4$	3	80	261–263	264–265 [27]
3k	CH_3	3	72	168–169	168–170 [30]
3l	C_2H_5	3	73	179–180	177–179 [30]
3m	C_3H_7	3	71	160–164	160–162 [24]

[a] Yields refer to isolated products; [b] all compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples

Experimental

General Procedure for the Synthesis of 2-Substituted Benzimidazoles

To a stirred solution of 10 mmol *o*-phenylenediamine in 30 cm^3 dry dioxane were added dropwise 10 mmol appropriate acid chloride in 40 cm^3 dry dioxane at 0°C for 20 min. After about 30 min of stirring at room temperature, 0.5 g zeolite were added. The mixture was heated at 100–102°C for 3 h. Then it was cooled to room temp and the resulting solid was collected by filtration and dissolved in 60 cm^3 $CHCl_3$. The catalyst was removed by filtration and the solution was washed with NaOH (5% *w*/*w*). After evaporation of the solvent, the resulting solid product was recrystallized from ethanol to give the pure product. All products are known compounds and were characterized by mp, IR, ^1H NMR, and MS.

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