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Montmorillonite K10: An Efficient Organo-Heterogeneous Catalyst for Synthesis of Benzimidazole Derivatives

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Abstract: The use of toxic solvents, high energy consumption, the production of waste and the application of traditional processes that do not follow the principles of green chemistry are problems for the pharmaceutical industry. The organic synthesis of chemical structures that represent the starting point for obtaining active pharmacological compounds, such as benzimidazole derivatives, has become a focal point in chemistry. Benzimidazole derivatives have found very strong applications in medicine. Their synthesis is often based on methods that are not convenient and not very respectful of the environment. A simple montmorillonite K10 (MK10) catalyzed method for the synthesis of benzimidazole derivatives has been developed. The use of MK10 for heterogeneous catalysis provides various advantages: the reaction yields are decidedly high, the work-up procedures of the reaction are easy and suitable, there is an increase in selectivity and the possibility of recycling the catalyst without waste formation is demonstrated. The reactions were carried out in solvent-free conditions and in a short reaction time using inexpensive and environmentally friendly heterogeneous catalysis. It has been shown that the reaction process is applicable in the industrial field.

Keywords: heterogeneous catalysis; montmorillonite; benzimidazoles

1. Introduction

Benzimidazole is a hetero bicyclic aromatic organic compound consisting in the fusion of benzene and imidazole. The benzimidazole ring is very well known in nature thanks to its various therapeutic applications. Its "nucleus" is present in many important molecules such as, for example, vitamin B_{12} [1].

In the early nineties, various benzimidazole derivatives were synthesized, obtaining fluorine, propylene and tetrahydroquinoline derivatives with greater stability and biological activity [2,3], while derivatives with an electron-donating group have proven to have good antiulcer activity [4,5], such as omeoprazole.

Recently, the therapeutic effects of benzimidazole derivatives in diseases such as ischemia-reperfusion injury or hypertension have been demonstrated [6].

Thanks to their various pharmacological properties, various synthetic methodologies have been developed in the field of organic synthesis.

The first synthetic methodologies reported in the literature are based on the reaction between *o*-phenylenediamine and carboxylic acids or their derivatives [7,8].

Subsequently, the reaction process was made easier by replacing the carboxylic acids with aldehydes, obtaining 2-substituted and 1,2-substituted benzimidazole derivatives. Numerous methods

are reported for the condensation of substituted *o*-phenylenediamine with aldehydes catalyzed by metal triflate such as $Sc(OTf)_3$ or Yb $(OTf)_3$ [9], $TiCl_3OTf$ [10], different oxidizing agents [11–14] and lanthanides such as Lewis acid catalysts [15,16]. However, these protocols present several problems that make the methods less convenient due to long reaction times and the use of expensive reagents and toxic organic solvents. Furthermore, non-recoverable, difficult to prepare and poorly selective catalysts are often used [17–22].

Since the development of new synthetic methods to produce potential drug compounds has always played a relevant role in scientific research, in recent years, the use of recyclable heterogeneous catalysts has become very important. Their use is favored because of their particularly versatile properties, low cost and thermal stability. In addition, reactions catalyzed by solid supports or in a solid state provide better selectivity in the products, compared to solution phase reactions.

These heterogeneous catalysts have found widespread application in eco-sustainable organic synthesis, showing higher activity than homogeneous catalysts [23,24]. Their use in the pharmaceutical industry is favored because of their easy recovery and stability and their ability to minimize waste. The synthesis of Lewis acid heterogeneous catalysts from waste materials has become increasingly popular over recent years **[25]**, such as in the case of sulfonic-acid-functionalized activated carbon prepared from matured tea leaf, tested for synthesis of 2-substituted benzimidazole and benzothiazole [26].

The use of toxic solvents in the pharmaceutical industry is a serious problem for the environment and human health, but in recent years, green chemistry principles have influenced the activities of the drug industry, introducing less use of classic organic solvents [27–30], cuts in waste production with the use of recyclable reagents [31–35] and the use of environmental organic synthetic methods.

Various research studies have been conducted on the use of "green" solvents [36], principally bio-solvents [37–42], ionic liquids [43–45], deep eutectic solvents [46–51], supercritical fluids [52,53] or water [54–62]. Certainly, the use of experimental methods based on solvent-free or solid state reaction conditions may reduce pollution. Green reactions may be also carried out using the reactants alone. Often the same reactions involve the use of solid supports (clays, zeolites, silica, alumina or other matrices), easing the experimental and work-up procedures, improving yields, increasing the reaction rate and considerably lowering the environmental impact [63–65]. In this context, therefore, solid Lewis acid catalysts are widely used and thermal process [66,67] can be employed to lead the reactions.

The use of microwaves (MW) in solvent-free reactions [68–71] has been particularly important for industrial production. MW irradiation increases the rate of chemical reactions, thus showing great potential in innovative chemical reaction processes [72]. This improvement is particularly demonstrated in heterogeneous catalytic systems, compared with conventional heating under identical temperature conditions, presumably due to interaction(s) between the MW radiation fields and the catalyst itself. For the above reason, it has given rise, over the years, to a strong interest in the field of the synthesis of pharmaceutical compounds [73–83].

In this regard, montmorillonite represents an ideal heterogeneous eco-sustainable catalyst thanks to its low cost, ease of handling, easy recovery by filtration method and possibility of use in chemical reactions in solvent-free conditions under microwaves or ultrasound irradiation [84]. Like other clay catalysts, it is widely available and has a high surface area containing both Brønsted and Lewis acid sites catalyzing organic reactions [85–88].

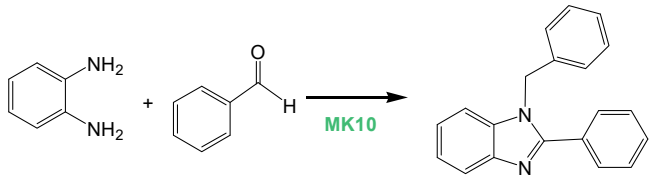
Recently, a simple and eco-friendly protocol for the synthesis of some novel substituted 2-arylbenzimidazoles was developed using $ZrOCl_2 \cdot nH_2O$ supported on montmorillonite K10 [89,90]. The synthetic process involves only the formation of the 2-benzimidazole derivative, and requires the preparation of a catalyst and the use of water as a solvent. Moreover, acid treated modified montmorillonite clay was used as a catalyst precursor for the synthesis of benzimidazoles, but the pretreatment of the catalyst and the use of toluene as a solvent makes the synthetic process unsustainable [91]. Other zeolites have been tested for the synthesis of benzimidazoles, but the experimental procedures do not show selectivity [92–94].

Considering the stability, catalytic activity and selectivity of MK10 tested in the synthesis reactions of bifunctionalized cyclopentenones [95] and our experience in developing environmental reactions for the synthesis of pharmaceutical azo-compounds [96–100], we present a new and selective synthetic method to obtain benzimidazole derivatives in a solvent-free reaction, testing MK10 as a heterogeneous catalyst.

2. Results

In our preliminary experiment, we choose *o*-phenylenediamine, *o*-PDA, (1 mmol) and benzaldehyde as starting materials to selectively obtain 1,2-disubstituted benzimidazole derivative **1a** (Table 1).

Table 1. Optimization of the reaction conditions. [a]



Entry	MK10 wt (%) [b]	Molar Ratio *o*-PDA: Benzaldehyde	Temp (°C)	Time (min)	Conversion (%)[c]	Selectivity (%) [d]
1	10	1:1	rt	120	19.3	12.0
2	10	1:2	rt	120	20.9	53.0
3	10	1:2	60	120	79.6	65.1
4	10	1:1	80	120	80.9	33.3
5	10	1:1	100	60	99.9	38.3
6	10	1:2	100	60	99.9	75.0
7	-	1:2	100	90	45.0	49.0
8 [e]	20	1:1	60	5	99.9	18.2
9 [e]	**20**	**1:2**	**60**	**5**	**99.9**	**98.5**

[a] General reaction conditions: *o*-PDA (1 mmol) and benzaldehyde (1 or 2 mmol) were stirred for 5–120 min at different temperatures and different wt (%) of MK10. [b] wt % with respect to amine. [c] Percent conversion of the *o*-PDA calculated from GC/MS data. [d] Percent yield calculated from GC/MS data of the corresponding disubstituted benzimidazole derivative. By-product obtained is constituted by 2-phenyl-benzimidazole (**1b**). [e] Reaction mixture under MW irradiation; the temperature was controlled in the microwave reactor.

Initially, we tested the effect of MK10 on the model reaction by performing the reaction (Table 1, entry 1) using 10 wt% of MK10 with respect to *o*-phenylendiamine. The reaction mixture, stirred at room temperature for 2 h, consists of diamine and benzaldehyde in a 1:1 and 1:2 molar ratio, respectively (Table 1, entries 1 and 2). The reaction is monitored by thin layer chromatography (TLC) and gas chromatography/mass spectrometry (GC/MS) analysis.

The GC/MS analysis showed the low conversion of the reagents within 120 min and low selectivity even when using 2 mmol benzaldehyde (Table 1, entry 2). At the higher temperature, 60 °C, the 1,2-disubstituted benzimidazole derivative **1a** was favored (65.1% yields), but the 2-substituted benzimidazole derivative **1b** in 34.9% yields was also obtained (Table 1, entry 3), thus not improving selectivity. The selectivity was worsened using 1 mmol benzaldehyde at 80 °C (Table 1, entry 4). The GC-MS analysis showed the presence of the corresponding 2-phenyl-benzimidazole by-product (66.7% yield) in 2 h. The model reaction showed the complete conversion of *o*-phenilendiammine when the same reaction was performed at higher temperatures (100 °C) (Table 1, entries 5 and 6) in 1 h. By increasing the molar ratio of benzaldeide (2 mmol) at the same temperature in the same reaction time (60 min), a better selectivity was observed (Table 1, entry 6). When the same reaction was carried out in the absence of a catalyst and in a longer reaction time (90 min), no complete conversion of *o*-PDA and more by-product formation were observed (Table 1, entry 7).

We obtained the complete conversion when the amount of catalyst was increased to 20 wt% of MK10 at 60 °C under MW irradiation (Table 1, entry 8), achieving 2-phenyl-benzimidazole as the

principal product (81.2% yield) and using 1 mmol of benzaldehyde. Surprisingly, we gained the desired product, 1-benzyl-2-phenyl-benzimidazole **1a**, in 98.5% yield and in only 5 min at 60 °C (Table 1, entry 9) using 2 mmol of benzaldehyde.

The use of the heterogeneous catalyst has made the reaction process even more eco-sustainable than the previously developed methodologies, in terms of both faster reaction times and greater selectivity of product formation.

The fundamental contribution that a heterogeneous catalyst makes to the sustainability of a reaction process is its being recyclable.

To demonstrate this, after testing MK10 in the reaction model system using the best reaction conditions (Table 1, entry 9), the final reaction mixture was treated with ethyl acetate. The MK10 was recovered from the organic solution by filtration, washed with ethyl acetate (3 mL) four times and dried in an oven (40 °C). The combined organic phases were concentrated by vacuum rotary evaporation.

The percent conversion and selectivity were analyzed by GC/MS. The recovered catalyst was used directly for the next run, adding new, fresh reagents following the procedures reported in the literature [91] (Figure 1).

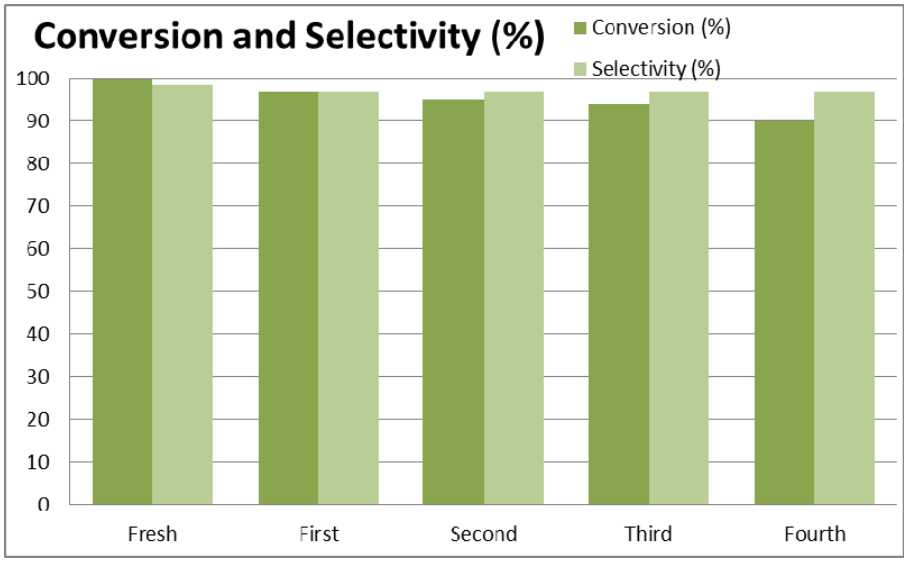


Figure 1. Cycling performance of MK10 in synthesis of 1-benzyl-2-phenyl-benzimidazole **1a** under MW irradiation.

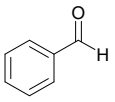
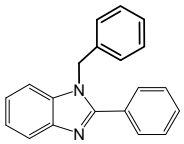
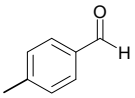
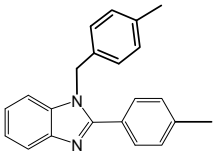
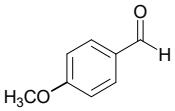
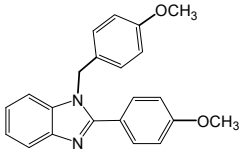
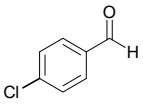
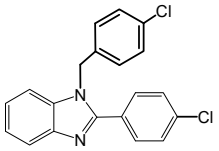
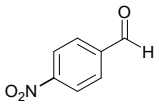
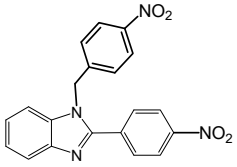
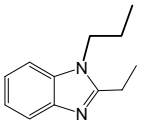
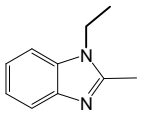
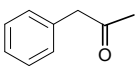
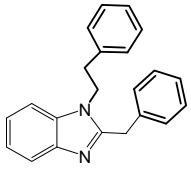
In order to demonstrate the potential industrial applicability as a green procedure, the model reaction was tested on a large scale using 10 mmol of *o*-phenylendiammine, 20 mmol of benzaldehyde and the respective amount of MK10. The reaction was completed in 25 min with excellent yield (95%) after simple extraction with ethyl acetate.

The experimental method was applied using *o*-PDA and different aldehydes to obtain 1,2-disubstituted benzimidazole derivatives. Quantitative yields superior to 90% were obtained in cases of aldehydes containing electron-donor groups (Table 2, entries 1–3 and entries 6 and 7).

The reactions performed with aldehydes containing electron-withdrawing groups such as *p*-chloro or *p*-nitro benzaldehyde (Table 2, entries 4 and 5) did not afford the disubstituted derivative, but did afford the corresponding 2-monosubstituted benzimidazoles (**4b** and **5b**) in good yields (detected by GC/MS). In this case, the monosubstituted product can be separated from the excess of benzaldehyde through chromatographic separation.

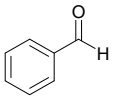
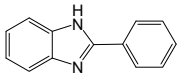
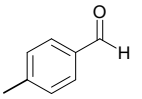
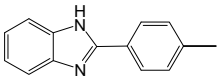
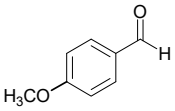
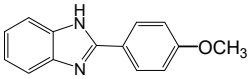
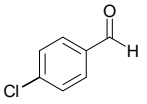
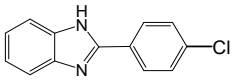
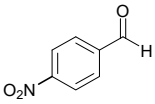
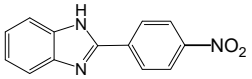
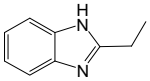
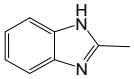
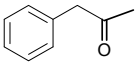
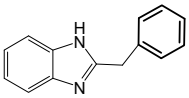
The same reactions performed using 1 molar amount of aldehydes afforded the corresponding 2-monosubstituted benzimidazoles (**1b–8b**) in good yields demonstrating, once again, the selectivity of the adopted reaction process (Table 3). This result was in accordance with the data reported in the literature [50,99].

Table 2. Synthesis of 1,2-disubstituted benzimidazoles. [a]

Entry	Aldehyde	Product	Conversion (%)	Yield (%) [b]
1		 **1a**	99.9	95.0
2		 **2a**	98.7	96.6
3		 **3a**	99.9	99.6
4 [c]		 **4a**	982	0
5 [c]		 **5a**	97.3	0
6		 **6a**	91.0	90.8
7		 **7a**	97.8	95.1
8		 **8a**	96.8	93.8

[a] General reaction conditions: 1 mmol of *o*-OPD and 2 mmol of aldehyde are added to 20% mw to amine of MK10. The reaction was conducted in a Synthos 3000 microwave oven (Anton-Paar) at 60 °C for 5 min. The reaction mixture was then washed with AcOEt (3 × 3 mL) and filtered to obtain MK10. The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the corresponding products **1a**–**8a**. [b] Percent yield calculated from GC/MS data. The corresponding 1,2-disubstituted benzimidazole derivative was recovered as the only product. [c] Product a was not detected. Only the corresponding 2-substituted derivatives, 4b and 5b (Conversion 98% and 97%, respectively, of *o*-OPD calculated from GC/MS) were detected by GC/MS.

Table 3. Synthesis of 2-monosubstituted benzimidazoles. [a]

Entry	Aldehyde	Product	Conversion (%)	Yield (%) [b]
1		 **1b**	99.9	95.0
2		 **2b**	95.9	97.8
3		 **3b**	99.9	99.0
4		 **4b**	90.6	98.3
5		 **5b**	89.6	97.3
6		 **6b**	91.0	90.8
7		 **7b**	97.8	94.8
8		 **8b**	96.8	94.1

[a] General reaction conditions: 1 mmol of *o*-PDA and 1 mmol of aldehyde are added to 20% mw to amine of MK10. The reaction was conducted in a Synthos 3000 microwave oven (Anton-Paar) at 60 °C for 5 min. The corresponding products, monosubstituted benzimidazoles **1b**–**8b**, were isolated as previously described to obtain disubstituted benzimidazoles (Table 2, footnote a). [b] Percent yield calculated from GC/MS data.

In conclusion, in the development of a green procedure, the recyclability of the heterogeneous catalyst MK10 is an essential feature. All reactions were performed in short reaction times (5 min) and with reaction yields of 90% to 99% (Tables 2 and 3).

Unlike the reaction procedures reported in the literature, the described method does not require the use of solvents [99] or the synthesis of deep eutectic solvents [50] essential to perform the complete reaction process. The proposed method reduces energy consumption and reaction time, making the process industrially acceptable.

3. Materials and Methods

3.1. General Methods

Montmorillonite K10 clay and all chemical reagents were obtained from Sigma-Aldrich. The chemical composition (wt%) of the clay (main elements) was SiO_2: 67.6; Al_2O_3: 14.6; Fe_2O_3: 2.9; MgO: 1.8.

All reactions were monitored by a GC-MS Shimadzu workstation. It is constituted by a GC 2010 (equipped with a 30 m QUADREX 007-5MS capillary column, operating in the "split" mode, 1 mL min^{-1} flow of He as carrier gas, (Shimadzu Corporation, Kyoto, Japan).

^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz and at 75 MHz, respectively, using a Bruker WM 300 system, (Bruker Corporation, Massachusetts, USA). The samples were solubilized in $CDCl_3$ using tetramethylsilane (TMS) as a reference (δ 0.00). Chemical shifts are given in parts per million (ppm), and coupling constants (J) are given in hertz. For ^{13}C-NMR, the chemical shifts are relative to $CDCl_3$ (δ 77.0).

A Synthos 3000 instrument from Anton Paar, (Minoh City, Osaka, Japan), equipped with a 4 × 24MG5 rotor, was used for the MW-assisted reactions. An external IR sensor monitored the temperature at the base of each reaction vessel.

3.2. General Procedure for the Synthesis of 1,2-Substituted Benzimidazoles **1a**–**8a**

The aldehyde (2 mmol) was added to the *o*-PDA (1 mmol) and MK10 (20 mg). The obtained mixture was reacted for 5 min under microwave heating, at a temperature of 60 °C (IR limit). After complete conversion of *o*-phenilendiammine, the MK10 was separated from the reaction mixture by filtration and washed with ethyl acetate (4 × 3 mL). The products were isolated after evaporation of the solvent to afford compounds in 90–99% yields. The NMR spectral data were in accordance with those reported in the literature [50] (See Supplementary Materials).

3.3. General Procedure for the Synthesis of 2-Substituted Benzimidazoles **1b**–**8b**

The synthesis procedure of the mono-substituted imidazoles derived was carried out under the same conditions used for the synthesis of the 1,2-substituted benzimidazoles. In this case, however, the aldehydes were used in an amount equal to 1mmol. After complete conversion of *o*-PDA in the 2-monosubstituted benzimidazoles (5 min), the products were isolated as previously described. The NMR spectral data were in accordance with those reported in the literature [50] (See Supplementary Materials).

3.4. Catalyst Recycling

The MK10 was separated from the reaction mixture by rapid filtration, then washed with ethyl acetate (3 mL) four times and dried in an oven (50 °C).

4. Conclusions

A fast, cheap, simple and environmentally sustainable method has been developed for the synthesis of 1,2-bisubstituted benzimidazoles and 2-substituted benzimidazoles. Microwave assistance was crucial to obtain the products in only five minutes.

Moreover, this proposed method produces very low quantities of reaction waste. MK10 was recycled and reused for four consecutive cycles without any significant loss in catalytic activity, as previously demonstrated [92].

Furthermore, compared to recently reported procedures, the proposed method does not require a previous treatment for the preparation of deep eutectic solvents (DESs) as eco-friendly and sustainable solvent and catalytic systems (the procedure of preparation of DESs requires 2 h at 80 °C), necessary to perform the subsequent synthesis reaction of benzimidazoles [50].

All this means that the use of the heterogeneous catalyst MK10 provides a synthetic procedure that considerably reduces reaction times and energy costs, further promoting industrial application.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/8/845/s1. Experimental Section, General Procedure for the Synthesis of 1,2-Substituted Benzimidazoles 1a–8a, General Procedure for the Synthesis of 2-Substituted Benzimidazoles 1b–8b, Catalyst recycling, ^{1}H NMR and ^{13}C NMR of compounds 1a–3a, 6a–8a, ^{1}H NMR and ^{13}C NMR of compounds 1b–8b.

Author Contributions: M.N. conceived and designed the experiments; S.B. performed the experiments; G.I., S.M., P.N. and S.T. analyzed the data; S.B. and R.P. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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