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

Sonia Bonacci, Giuseppe Iriti, Stefano Mancuso, Paolo Novelli, Rosina Paonessa, Sofia Tallarico and Monica Nardi *

Dipartimento di Scienze della Salute, Università Magna Græcia, Viale Europa, Germaneto, 88100 Catanzaro, Italy; s.bonacci@unicz.it (S.B.); giuseppeiriti94@gmail.com (G.I.); stefanoman27@gmail.com (S.M.); paolo.novelli92@gmail.com (P.N.); r.paonessa@unicz.it (R.P.); sofia.tallarico@outlook.it (S.T.)

* Correspondence: monica.nardi@unicz.it; Tel.: +39-0961-3694116

Received: 6 July 2020; Accepted: 25 July 2020; Published: 28 July 2020

**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\textsubscript{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 omeprazole.

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 \textit{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$_3$OTf [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 reagents 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$_2$·nH$_2$O 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).

![Optimization of the reaction conditions](image)

| Entry | MK10 wt (%) | Molar Ratio | Temp (°C) | Time (min) | Conversion (%) | Selectivity (%) |
|-------|-------------|-------------|-----------|------------|----------------|----------------|
| 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     | 20          | 1:1         | 60        | 5          | 99.9           | 18.2           |
| 9     | 20          | 1:2         | 60        | 5          | 99.9           | 98.5           |

* 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. 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-phenylenediamine. 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-phenylenediamine 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 benzaldehyde (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).

![Conversion and Selectivity (%)](image.png)

**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-phenylenediammine, 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-monomosubstituted 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-monomosubstituted 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 [30,99].
Table 2. Synthesis of 1,2-disubstituted benzimidazoles. a

| Entry | Aldehyde | Product | Conversion (%) | Yield (%) b |
|-------|----------|---------|----------------|-------------|
| 1     |          | ![1a](image) | 99.9           | 95.0        |
| 2     |          | ![2a](image) | 98.7           | 96.6        |
| 3     | H$_2$CO | ![3a](image) | 99.9           | 99.6        |
| 4 c   | Cl       | ![4a](image) | 982            | 0           |
| 5 c   | O$_2$N   | ![5a](image) | 97.3           | 0           |
| 6     |         | ![6a](image) | 91.0           | 90.8        |
| 7     |         | ![7a](image) | 97.8           | 95.1        |
| 8     |         | ![8a](image) | 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-Par) at 60 °C for 5 min. The reaction mixture was then washed with AcOEt (3 x 3 mL) and filtered to obtain MK10. The combined organic phases were dried over Na$_2$SO$_4$, 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.
3.2. General Procedure for the Synthesis of 1,2-Substituted Benzimidazoles 1a–8a

The aldehyde (2 mmol) was added to the reaction mixture of DMF-MeOH (1:1), and 2 mmol of o-PDA and 1 mmol of aldehyde are added to 20% mw to 60 °C for 5 min. 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 the corresponding products. c Product a was not detected. Only the corresponding 2-substituted derivatives, 4b and 5b were isolated as previously described to obtain disubstituted benzimidazoles (Table 2, footnote a). b Percent yield calculated from GC/MS data.

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     | H3CO     | 3b      | 99.9           | 99.0        |
| 4     | Cl       | 4b      | 90.6           | 98.3        |
| 5     | O2N      | 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 SiO₂: 67.6; Al₂O₃: 14.6; Fe₂O₃: 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).
1H-NMR and 13C-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 CDCl3 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 13C-NMR, the chemical shifts are relative to CDCl3 (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, 1H NMR and 13C NMR of compounds 1a–3a, 6a–8a, 1H NMR and 13C NMR of compounds 1b–8b.

Author Contributions: M.N. conceived and designed the experiments; S.B. performed the experiments; G.L., S.M., E.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.

Funding: This research received funding from Dipartimento di Scienze della Salute, Università Magna Græcia, Italy.
Conflicts of Interest: The authors declare no conflict of interest.

References

1. Emerson, G.; Brink, N.G.; Holly, F.W.; Koniuszzy, F.; Heyl, D.; Folker, K. Vitamin B12-Like Activity of 5,6-Dimethylbenzimidazole and Tests on related compounds. *J. Am. Chem. Soc.* **1950**, *72*, 3084–3085. [CrossRef]

2. Kubo, K.; Oda, K.; Kaneko, T.; Satoh, H.; Nohara, A. Synthesis of 2-(4-Fluoroalkoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole derivatives as Antifuclor Agents. *Chem. Pharm. Bull.* **1990**, *38*, 2853–2858. [CrossRef] [PubMed]

3. Uchida, M.; Chihiro, M.; Morita, S.; Yamashita, H.; Yamasaki, K.; Kanbe, T.; Yabuuchi, Y.; Nakagawaz, K. Synthesis and Antitumor Activity of 4-Substituted 8-[2-Benzimidazolyl]sulfanyl]methyl]-1, 2, 3, 4-tetrahydroquinolines and Related Compounds. *Chem. Pharm. Bull.* **1990**, *38*, 1575–1586. [CrossRef] [PubMed]

4. Grassi, A.; Ippen, J.; Bruno, M.; Thomas, G.; Bay, P. A thiazolylamino benzimidazole derivative with gastroprotective properties in the rat. *Eur. J. Pharmacol.* **1991**, *195*, 251–259. [CrossRef]

5. Ozkay, Y.; Tunali, Y.; Karaca, H.; Isikdag, I. Antimicrobial activity and a SAR study of some novel benzimidazole derivatives bearing hydrazones moiety. *Eur. J. Med. Chem.* **2010**, *45*, 3293–3298. [CrossRef]

6. Algul, O.; Karabulut, A.; Canacankatan, N.; Gorur, A.; Sucu, N.; Vezir, O. Apoptotic and anti-angiogenic effects of benzimidazole compounds: Relationship with oxidative stress mediated ischemia/reperfusion injury in rat hind limb. *Antiinflamm AntiallergyAgents Med. Chem.* **2012**, *11*, 267–275. [CrossRef]

7. Thakuria, H.; Das, G. An expedient one-pot solvent-free synthesis of benzimidazole derivatives. *ARKIVOC* **2008**, *15*, 321–328.

8. Rithe, S.R.; Jagtap, R.S.; Ubarhande, S.S. One Pot Synthesis of Substituted Benzimidazole Derivatives And Their Characterization. *RASAYAN J. Chem.* **2015**, *8*, 213–217.

9. Liyan, F.; Wen, C.; Lulu, K. Highly chemoselective synthesis of benzimidazoles in Sc(OTf)3-catalyzed system. *Heterocycles* **2015**, *91*, 2306–2314.

10. Bahrami, K.; Khodaei, M.M.; Kavianinia, I. Heterocycles, 1 H2O2/HCl as a new and efficient system for synthesis of 2-substituted benzimidazoles. *J. Chem. Res.* **2006**, *12*, 783–784. [CrossRef]

11. Ma, H.; Han, X.; Wang, Y.; Wang, J. A simple and efficient method for synthesis of benzimidazoles using FeBr3 or Fe(NO3)3·9H2O as catalyst. *ChemInform* **2007**, *38*, 1821–1825. [CrossRef]

12. Du, L.-H.; Wang, Y.-G. A rapid and efficient synthesis of benzimidazoles using hypervalent iodine as oxidant. *Synthesis* **2007**, *5*, 675–678.

13. Sontakke, V.A.; Ghosh, S.; Lawande, P.P.; Chopade, B.A.; Shinde, V.S. A simple, efficient synthesis of 2-aryl benzimidazoles using silica supported periodic acid catalyst and evaluation of anticancer activity. *ISRN Org. Chem.* **2013**, 1–7. [CrossRef] [PubMed]

14. Kumar, K.R.; Satyanarayana, P.V.V.; Reddy, B.S. NaHSO4-SiO2 promoted synthesis of benzimidazole derivatives. *Arch. Appl. Sci. Res.* **2012**, *4*, 1517–1521.

15. Venkateswarlu, Y.; Kumar, S.R.; Leelavathi, P. Facile and efficient one-pot synthesis of benzimidazoles using lanthanum chloride. *Org. Med. Chem. Lett.* **2013**, *3*, 2–8.

16. Martins, G.M.; Puccinelli, T.; Gariani, R.A.; Xavier, F.R.; Silveira, C.C.; Mendes, S.R. Facile and efficient aerobic one-pot synthesis of benzimidazoles using Ce(NO3)3·6H2O as promoter. *Tetrahedron Lett.* **2017**, *58*, 1969–1972. [CrossRef]

17. Mobinikhaleedi, A.; Hamta, A.; Kalhor, M.; Shariatzadeh, M. Simple Synthesis and Biological Evaluation of Some Benzimidazoles Using Sodium Hexafluoroualuminate, Na3 AlF6, as an Efficient Catalyst. *Iran. J. Pharm. Res.* **2014**, *13*, 95–101.

18. Birajdar, S.S.; Hatnapure, G.D.; Keche, A.P.; Kamble, V.M. Synthesis of 2-substituted-1 H-benz[d]imidazoles through oxidative cyclization of O-phenylenediamine and substituted aldehydes using dioxygenated bromide. *Res. J. Pharm. Biol. Chem. Sci.* **2014**, *5*, 487–493.

19. Srinivasulu, R.; Kumar, K.R.; Satyanarayana, P.V.V. Facile and Efficient Method for Synthesis of Benzimidazole Derivatives Catalyzed by Zinc Triflate. *Green Sustain. Chem.* **2014**, *4*, 33–37. [CrossRef]

20. Sehyun, P.; Jaehun, J.; Eun, J.C. Visible-Light-Promoted Synthesis of Benzimidazoles. *J. Org. Chem.* **2014**, *352*, 4148–4154.

21. Vishwanath, D.P.; Ketan, P.P. Synthesis of Benzimidazole and Benzoxazole Derivatives Catalyzed by Nickel Acetate as Organometallic Catalyst. *Int. J. ChemTech Res.* **2014**, *8*, 457–465.
22. Procopio, A.; De Nino, A.; Nardi, M.; Oliverio, M.; Paonessa, R.; Pasceri, R. A New Microwave-Assisted Organocatalytic Solvent-Free Synthesis of Optically Enriched Michael Adducts. *Synlett* **2010**, *12*, 1849–1853. [CrossRef]

23. Deng, Q.; Wang, R. Heterogeneous MOF catalysts for the synthesis of trans-4,5-diaminocyclopent-2-enones from furfural and secondary amines. *Catal. Commun.* **2019**, *120*, 11–16.

24. Thomas, J.M.; Raja, R.; Lewis, D.W. Single-site heterogeneous catalysts. *Angew. Chem. Int. Ed.* **2005**, *44*, 6456. [CrossRef] [PubMed]

25. Osman, A.I.; Abu-Dahrieh, J.K.; McLaren, M.; Laffir, F.; Rooney, D.W. Characterisation of Robust Combustion Catalyst from Aluminium Foil Waste. *ChemistrySelect* **2018**, *3*, 1545–1550. [CrossRef]

26. Goswami, M.; Dutta, M.M.; Phukan, P. Sulfonic-acid-functionalized activated carbon made from tea leaves as green catalyst for synthesis of 2-substituted benzimidazole and benzothiazole. *Res. Chem. Intermed.* **2018**, *44*, 1597–1615. [CrossRef]

27. Nelso, W.M. *Green Solvents for Chemistry Perspectives and Practice*; Oxford University Press: Oxford, UK, 2004.

28. Mikami, K. *Green Reaction Media in Organic Synthesis*; Blackwell: Tokyo, Japan, 2005.

29. Clark, J.H.; Tavener, S.J. *Alternative Solvents: Shades of Green.*

30. Ballini, R.; Bosica, G.; Carloni, L.; Maggi, R.; Sartori, G. Zeolite HSZ-360 as a new reusable catalyst for the direct acetylation of alcohols and phenols under solventless conditions. *Tetrahedron Lett.* **1998**, *39*, 6049–6052. [CrossRef]

31. Bartoli, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Nardi, M.; Procopio, A.; Tagarelli, A. Cerium(III) Triflate versus Cerium(III) Chloride: Anion Dependence of Lewis Acid Behavior in the Deprotection of PMB Ethers. *Eur. J. Org. Chem.* **2004**, *10*, 2176–2180. [CrossRef]

32. Procopio, A.; Cravotto, G.; Oliverio, M.; Costanzo, P.; Nardi, M.; Paonessa, R. An Eco-Sustainable Erbium(III)-Catalysed Method for Formation/Cleavage of O-tert-butoxy carbonates. *Green Chem.* **2011**, *13*, 436–443. [CrossRef]

33. Oliverio, M.; Costanzo, P.; Macario, A.; De Luca, G.; Nardi, M.; Procopio, A. A Bifunctional Heterogeneous Catalyst Erbium-Based: A Cooperative Route Towards C-C Bond Formation. *Molecules* **2014**, *19*, 10218–10229. [CrossRef] [PubMed]

34. Procopio, A.; Das, G.; Nardi, M.; Oliverio, M.; Pasqua, L. A Mesoporous Er(III)-MCM-41 Catalyst for the Cyanosilylation of Aldehydes and Ketones under Solvent-free Conditions. *ChemSusChem* **2008**, *1*, 916–919. [CrossRef] [PubMed]

35. Procopio, A.; Costanzo, P.; Curini, M.; Nardi, M.; Oliverio, M.; Sindona, G. Erbium(III) Chloride in Ethyl Lactate as a Smart Ecofriendly System for Efficient and Rapid Stereoselective Synthesis of trans-4,5-Diaminocyclopent-2-enones. *ACS Sustain. Chem. Eng.* **2013**, *1*, 541–544. [CrossRef]

36. Viro, M.; Tomao, V.; Ginies, C.; Chemat, F. Total lipid extraction of food using d-limonene as an alternative to n-hexane. *Chromatographia* **2008**, *68*, 311–313. [CrossRef]

37. Lapkin, A.; Plucinski, P.K.; Cutler, M. Comparative assessment of technologies for extraction of artemisinin. *J. Nat. Prod.* **2006**, *69*, 1653–1664. [CrossRef]

38. Pereira, C.S.M.; Silva, V.M.T.M.; Rodrigues, A.E. Ethyl lactate as a solvent: Properties, applications and production processes. *Green Chem.* **2011**, *13*, 2658–2671. [CrossRef]

39. Garcia, J.I.; Garcia-Marín, H.; Pires, E. Glycerol based solvents: Synthesis, properties and applications. *Green Chem.* **2014**, *16*, 1007–1033. [CrossRef]

40. Nardi, M.; Oliverio, M.; Costanzo, P.; Sindona, G.; Procopio, A. Eco-friendly stereoselective reduction of α,β-unsaturated carbonyl compounds by Er(OTf)₃/NaBH₄ in 2-MeTHF. *Tetrahedron* **2015**, *71*, 1132–1135. [CrossRef]

41. Nardi, M.; Herrera Cano, N.; De Nino, A.; Di Gioia, M.L.; Maiuolo, L.; Oliverio, M.; Santiago, A.; Sorrentino, D.; Procopio, A. An eco-friendly tandem tosylation/Ferrier N-glycosylation of amines catalyzed by Er(OTf)₃ in 2-MeTHF. *Tetrahedron Lett.* **2017**, *58*, 1721–1726. [CrossRef]

42. Weishi Miao, W.; Chan, T.H. Ionic-Liquid-Supported Synthesis: A Novel Liquid-Phase Strategy for Organic Synthesis. *Acc. Chem. Res.* **2006**, *39*, 897–908.

43. Abbott, A.P.; Davies, D.L.; Capper, G.; Rasheed, R.K.; Tambryrajah, V. Ionic Liquids and Their Use As solvents. U.S. Patent 7,183,433, 27 February 2007.

44. Di Gioia, M.L.; Costanzo, P.; De Nino, A.; Maiuolo, L.; Nardi, M.; Olivito, F.; Procopio, A. Simple and efficient Fmoc removal in ionic liquid. *RSC Adv.* **2017**, *7*, 36482–36491. [CrossRef]
45. De Nino, A.; Maiuolo, L.; Merino, P.; Nardi, M.; Procopio, A.; Roca-López, D.; Russo, B.; Algieri, V. Efficient organocatalyst supported on a simple ionic liquid as a recoverable system for the asymmetric diels-alder reaction in the presence of water. *ChemCatChem* 2015, 7, 830–835. [CrossRef]

46. Abbott, A.P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambaryajah, V. Novel solvent properties of choline chloride/water mixtures. *Chem. Commun.* 2003, 1, 70–71. [CrossRef] [PubMed]

47. Gorke, J.T.; Srie, F.; Kazlauskas, R.J. Hydrolase-catalyzed biotransformations in deep eutectic solvents. *Chem. Commun.* 2008, 10, 1235–1237. [CrossRef]

48. Smith, E.L.; Abbott, A.P.; Ryder, K.S. Deep Eutectic Solvents (DESs) and their applications. *Chem. Rev.* 2014, 114, 11060–11082. [CrossRef] [PubMed]

49. Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R.L.; Duarte, A.R.C. Natural deep eutectic solvents—Solvents for the 21st century. *ACS Sustain. Chem. Eng.* 2014, 2, 1063–1071. [CrossRef]

50. Gravito, G.; Cintas, P.; Costanzo, P.; Herrera Cano, N.; Maiuolo, L.; Nardi, M.; Nicoletta, E.P.; Oliverio, M.; Procopio, A. Green Synthesis of Privileged Benzimidazole Scaffolds Using Active Deep Eutectic Solvent. *Molecules* 2019, 24, 2885. [CrossRef] [PubMed]

51. Bonacci, S.; Di Gioia, M.L.; Costanzo, P.; Maiuolo, L.; Tallarico, S.; Nardi, M. Natural Deep Eutectic Solvent as Extraction Media for the Main Phenolic Compounds from Olive Oil Processing Wastes. *Antioxidants* 2020, 9, 513. [CrossRef]

52. Leitner, W.; Poljakoff, M. Supercritical fluids in green chemistry. *Green Chem.* 2008, 10, 730.

53. Carlès, P. A brief review of the thermophysical properties of supercritical fluids. *J. Supercrit. Fluids* 2010, 53, 2–11. [CrossRef]

54. Lindström, U.M. Stereoselective Organic Reactions in Water. *Chem. Rev.* 2002, 10, 2751–2772. [CrossRef] [PubMed]

55. Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Tagarelli, A.; Sindona, G. Simple and efficient MW-assisted cleavage of acetics and ketals in pure water. *Tetrahedron Lett.* 2007, 48, 8623–8627. [CrossRef]

56. Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Rosati, O. Highly efficient and versatile chemoselective addition of amines to epoxides in water catalyzed by erbium(III) triflate. *Tetrahedron Lett.* 2008, 49, 2289–2293. [CrossRef]

57. Simon, M.O.; Li, C.J. Green chemistry oriented organic synthesis in water. *Chem. Soc. Rev.* 2012, 41, 1415–1427. [CrossRef] [PubMed]

58. Oliverio, M.; Costanzo, P.; Paonessa, R.; Nardi, M.; Procopio, A. Catalyst-free tosylation of lipophilic alcohols in water. *RSC Adv.* 2013, 3, 2548–2552. [CrossRef]

59. Nardi, M.; Herrera Cano, N.; Costanzo, P.; Oliverio, M.; Sindona, G.; Procopio, A. Aqueous MW eco-friendly protocol for amino group protection. *RSC Adv.* 2015, 5, 18751–18760. [CrossRef]

60. Nardi, M.; Di Gioia, M.L.; Costanzo, P.; De Nino, A.; Maiuolo, L.; Oliverio, M.; Olivito, F.; Procopio, A. Selective acetylation of small biomolecules and their derivatives catalyzed by Er(OTf)3. *Catalysts* 2017, 7, 269. [CrossRef]

61. Nardi, M.; Costanzo, P.; De Nino, A.; Di Gioia, M.L.; Olivito, F.; Sindona, G.; Procopio, A. Water excellent solvent for the synthesis of bifunctionalized cyclopentenones from furfural. *Green Chem.* 2017, 19, 5403–5411. [CrossRef]

62. Olivito, F.; Costanzo, P.; Di Gioia, M.L.; Nardi, M.; Oliverio, M.; Procopio, A. Efficient synthesis of organic thioacetate in water. *Org. Biomol. Chem.* 2018, 16, 7753–7759. [CrossRef]

63. Procopio, A.; De Luca, G.; Nardi, M.; Oliverio, M.; Paonessa, R. General MW-assisted grafting of MCM-41: Study of the dependence on time dielectric heating and solvent. *Green Chem.* 2009, 11, 770–773. [CrossRef]

64. Esteve, M.S.; Afonso, C.A.M. Synthesis of trans-4,5-diaminocyclopent-2-ones from furfural catalyzed by Er(III) immobilized on silica. *Tetrahedron Lett.* 2017, 58, 302–304. [CrossRef]

65. Senthilkumar, S.; Maru, M.S.; Somani, R.S.; Bajaj, H.C.; Neogi, S. Unprecedented NH2-MIL-101(Al)/n-Bu4NBr system as solvent-free heterogeneous catalyst for efficient synthesis of cyclic carbonates via CO2 cycloaddition. *Dalton Trans.* 2018, 47, 418–428. [CrossRef] [PubMed]

66. Mason, T.J. Sonochemistry: Current uses and future prospects in the chemistries and processing industries. *Philos. Trans. R. Soc. Lond. A* 1999, 357, 355–369. [CrossRef]

67. Cravotto, G.; Cintas, P. The combined use of microwaves and ultrasound: Improved tools in process chemistry and organic synthesis. *Chem. Eur. J.* 2007, 13, 1902–1909. [CrossRef] [PubMed]

68. Je’selnik, M.; Varma, R.S.; Polanca, S.; Kocevar, M. Catalyst-free reactions under solvent-free conditions: Microwave-assisted synthesis of heterocyclic hydrazones below the melting points of neat reactants. *Chem. Commun.* 2001, 18, 1716–1717. [CrossRef]
69. Kappe, O. Controlled microwave heating in modern organic synthesis. Angew. Chem. Int. Ed. 2004, 43, 6250–6284. [CrossRef]

70. Desai, K.R. Green Chemistry Microwave Synthesis, 1st ed.; Himalaya Publication House: New Delhi, India, 2005; p. 20.

71. Horikoshi, S.; Serpone, N. Role of microwaves in heterogeneous catalytic systems. Catal. Sci. Technol. 2014, 4, 1197–1210.

72. Procopio, A.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Nardi, M.; Romeo, G. Mild and efficient method for the cleavage of benzylidene acetal by using erbium (III) triflate. Org. Biomol. Chem. 2005, 3, 4129–4133. [CrossRef]

73. Oliverio, M.; Costanzo, P.; Nardi, M.; Calandrucio, C.; Salerno, R.; Procopio, A. Tunable microwave-assisted method for the solvent-free and catalyst-free peracetylation of natural products. Beilstein J. Org. Chem. 2016, 12, 2222–2233. [CrossRef]

74. Maiuolo, L.; Merino, P.; Algieri, V.; Nardi, M.; Di Gioia, M.L.; Russo, B.; Delso, I.; Tallarida, M.A.; De Nino, A. Nitrones and nucleobase-containing spiro-isoxazolidines derived from isatin and indanone: Solvent-free microwave-assisted stereoselective synthesis and theoretical calculations. RSC Adv. 2017, 7, 48980–48988. [CrossRef]

75. Bortolini, O.; D’Agostino, M.; De Nino, A.; Maiuolo, L.; Nardi, M.; Sindona, G. Solvent-free, microwave assisted 1,3-cycloaddition of nitrones with vinyl nucleobases for the synthesis of N,O-nucleosides. Tetrahedron 2008, 64, 8078–8081. [CrossRef]

76. Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Romeo, R. MW-assisted Er(OTf)3-catalyzed mild cleavage of isopropylidene acetals in Tricky substrates. Tetrahedron Lett. 2008, 49, 1961–1964. [CrossRef]

77. Nardi, M.; Bonacci, S.; De Luca, G.; Maiuolo, J.; Oliverio, M.; Sindona, G.; Procopio, A. Biomimetic synthesis and antioxidant evaluation of 3,4-DHPEA-EDA [2-(3,4-hydroxyphenyl) ethyl (3S,4E)-4-formyl-3-(2-oxoethyl)hex-4-enoate]. Food Chem. 2014, 162, 89–93. [CrossRef] [PubMed]

78. Oliverio, M.; Nardi, M.; Cariati, L.; Vitale, E.; Bonacci, S.; Procopio, A. “on Water” MW-Assisted Synthesis of Hydroxytyrosol Fatty Esters. ACS Sustain. Chem. Eng. 2016, 4, 661–665. [CrossRef]

79. Maiuolo, L.; De Nino, A.; Algieri, V.; Nardi, M. Microwave-assisted 1,3-dipolar cyclo-addition: Recent advances in synthesis of isoxazolidines. Mini-Rev. Org. Chem. 2017, 14, 136–142. [CrossRef]

80. Nardi, M.; Bonacci, S.; Cariati, L.; Costanzo, P.; Oliverio, M.; Sindona, G.; Procopio, A. Synthesis and antioxidant evaluation of lipophilic oleuropein aglycone derivatives. Food Funct. 2017, 8, 4684–4692. [CrossRef]

81. Costanzo, P.; Calandrucio, C.; Di Gioia, M.L.; Nardi, M.; Oliverio, M.; Procopio, A. First multicomponent reaction exploiting glycerol carbonate synthesis. J. Clean. Prod. 2018, 202, 504–509. [CrossRef]

82. Costanzo, P.; Bonacci, S.; Cariati, L.; Maiuolo, J.; Oliverio, M.; Procopio, A. Simple and efficient sustainable semi-synthesis of oleic acid [2-(3,4-hydroxyphenyl) ethyl (3S,4E)-4-formyl-3-(2-oxoethyl)hex-4-enoate] as potential additive for edible oils. Food Chem. 2018, 245, 410–414. [CrossRef]

83. Paonessa, R.; Nardi, M.; Di Gioia, M.L.; Olivito, F.; Oliverio, M.; Procopio, A. Eco-friendly synthesis of lipophilic EGCG derivatives and antitumor and antioxidant evaluation. Nat. Prod. Commun. 2018, 9, 1117–1122. [CrossRef]

84. Li, J.-T.; Xing, C.-Y.; Li, T.-S. An efficient and environmentally friendly method for synthesis of arylmethylenemalononitrile catalyzed by Montmorillonite K10–ZnCl2 under ultrasound irradiation. J. Chem. Technol. Biotechnol. 2004, 79, 1275–1278. [CrossRef]

85. Bhattacharyya, K.G.; Gupta, S.S. Adsorption of a few heavy metals on natural and modified kaolinite and montmorillonite: A review. Adv. Colloid Interface Sci. 2008, 140, 114–131. [CrossRef] [PubMed]

86. Kaur, N.; Kishore, D. Montmorillonite: An efficient, heterogeneous and green catalyst for organic synthesis. J. Chem. Pharm. Res. 2012, 4, 991–1015.

87. Kumar, B.S.; Dhakshinamoorthy, A.; Pitchumani, K. K10 montmorillonite clays as environmentally benign catalysts for organic reactions. Catal. Sci. Technol. 2014, 4, 2378–2396. [CrossRef]

88. Hechelski, M.; Ghinet, A.; Brice Louvel, B.; Dufrenoy, P.; Rigo, B.; Daich, A.; Waterlot, C. From Conventional Lewis Acids to Heterogeneous Montmorillonite K10: Eco-Friendly Plant-Based Catalysts Used as Green Lewis Acids. ChemSusChem 2018, 11, 1249–1277. [CrossRef] [PubMed]

89. Rostamizadeh, S.; Amani, A.M.; Aryan, R.; Ghaeni, H.R.; Norouzi, L. Very fast and efficient synthesis of some novel substituted 2-arylbenzimidazoles in water using ZrOCl2·nH2O on montmorillonite K10 as catalyst. Mon. Chem. 2009, 140, 547–552. [CrossRef]
90. Hashemi, M.M.; Eftekhari-Sis, B.; Abdollahifar, A.; Khalili, B. ZrOCl₂·8H₂O on montmorillonite K10 accelerated conjugate addition of amines to α,β-unsaturated alkenes under solvent-free conditions. *Tetrahedron* 2006, 62, 672–677. [CrossRef]

91. Borah, S.J.; Das, D.K. Modified Montmorillonite: An Active Heterogeneous Catalyst for the Synthesis of Benzimidazoles. *J. Chem. Pharm. Res.* 2018, 10, 118–123.

92. Bonacci, S.; Nardi, M.; Costanzo, P.; De Nino, A.; Di Gioia, M.L.; Oliverio, M.; Procopio, A. Montmorillonite K10-Catalyzed Solvent-Free Conversion of Furfural into Cyclopentenones. *Catalysts* 2019, 9, 301. [CrossRef]

93. Hegedüs, A.; Hell, Z.; Potor, A. Zeolite-Catalyzed Environmentally Friendly Synthesis of Benzimidazole Derivatives. *Synth. Commun.* 2009, 36, 3625–3630. [CrossRef]

94. Khanday, W.A.; Tomar, R. Conversion of zeolite—A in to various ion-exchanged catalytic forms and their catalytic efficiency for the synthesis of benzimidazole. *Catal. Commun.* 2014, 43, 141–145. [CrossRef]

95. Saberi, A. Efficient synthesis of Benzimidazoles using zeolite, alumina and silica gel under microwave irradiation. *Iran. J. Sci. Technol.* 2015, 39, 7–10.

96. Nardi, M.; Cozza, A.; Maiuolo, L.; Oliverio, M.; Procopio, A. 1,5-Benzoheteroazepines through eco-friendly general condensation reactions. *Tetrahedron Lett.* 2011, 52, 4827–4834. [CrossRef]

97. Nardi, M.; Cozza, A.; De Nino, A.; Oliverio, M.; Procopio, A. One-pot synthesis of dibenzo[b,e][1,4]diazepin-1-ones. *Synthesis* 2012, 44, 800–804. [CrossRef]

98. Oliverio, M.; Costanzo, P.; Nardi, M.; Rivalta, I.; Procopio, A. Facile ecofriendly synthesis of monastrol and its structural isomers via biginelli reaction. *ACS Sustain. Chem. Eng.* 2014, 2, 1228–1233. [CrossRef]

99. Herrera Cano, N.; Uranga, J.G.; Nardi, M.; Procopio, A.; Wunderlin, D.A.; Santiago, A.N. Selective and eco-friendly procedures for the synthesis of benzimidazole derivatives. The role of the Er(OTf)₃ catalyst in the reaction selectivity. *Beilstein J. Org. Chem.* 2016, 12, 2410–2419. [CrossRef] [PubMed]

100. De Nino, A.; Maiuolo, L.; Nardi, M.; Pasceri, R.; Procopio, A.; Russo, B. Development of one-pot three component reaction for the synthesis of N’-aryl-N-cyanoformamidines, essential precursors of formamidine pesticides family. *Arab. J. Chem.* 2016, 9, 32–37. [CrossRef]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).