Peer-reviewed version available at *Catalysts* **2020**, *10*, 845; doi:10.3390/catal10080845

Article

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

Sonia Bonacci [1], Giuseppe Iriti [1], Stefano Mancuso [1], Paolo Novelli [1], Rosina Paonessa [1], Sofia Tallarico[1] and Monica Nardi [1,*]

[1] Dipartimento di Scienze della Salute, Università Magna Græcia, Viale Europa, Germaneto, 88100 Catanzaro CZ, Italia; 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.); monica.nardi@unicz.it (M.N.)

* Correspondence: monica.nardi@unicz.it (M.N.);
Tel. of M.N.: +39-0961-3694116

Abstract: The use of alternative synthetic methods, in the face of traditional processes that do not conform to the principles of Green Chemistry, represent a problem in the pharmaceutical industry. The procedures for the synthesis of benzimidazole derivatives have become a focus in synthetic organic chemistry, as they are building blocks of strong interest for the synthesis of compounds with pharmacological activity. Various benzimidazole derivatives have found very strong application in medicine and their synthesis is reported in the literature. A simple and environmental Montmorillonite K10 (MK10) catalyzed method for the synthesis of benzimidazole derivatives has been developed. The use of MK10 as heterogeneous catalysis provides various advantages in terms of yields, in the work up procedure of the reaction, selectivity and the possible recycle of catalyst without waste formation. The reactions were carried out in solvent free condition and in short reaction time using an inexpensive and environmentally friendly heterogeneous catalysis and it has been shown that the reaction process is applicable in the industrial field.

Keywords: heterogeneous catalysis; montmorillonite; benzimidazoles

1. Introduction

The use of the heterogeneous catalysis has become a talented field in organic chemical synthesis. Their use especially in pharmaceutical industry [1] is favored by their easy recovery, their stability and the ability to minimize waste. Montmorillonite is non-corrosive, environmental friendly, cheap, easy of handling. Such as clay catalysts, is very available and have a high surface area containing two types of catalytic sites: Brønsted and Lewis sites catalyzing organic reactions.

Benzimidazole is a hetero bicyclic aromatic organic compound consisting in the fusion of benzene and imidazole. The benzimidazole ring is one of the most known systems in Nature thanks to its various therapeutic applications. Its "nucleus" is present in many important molecules as, for example, the vitamin B_{12} [2].

In the early nineties, various benzimidazole derivatives were synthesized obtaining fluorine, propylene and tetrahydroquinoline derivatives with greater stability and biological activity [3,4] while derivatives with electron donating group have proven to have good antiulcer activity [5,6], for example the Omeoprazole.

Recently, the therapeutic activity of benzimidazole derivatives in diseases such as ischemia-reperfusion injury or hypertension has been demonstrated [7].

Thanks to their various pharmacological activities, various synthetic methodologies have been developed in the field of organic synthesis. The reaction between o-phenylenediamines and carboxylic acids or their derivatives has been used [8,9] in classic synthetic methods.

The most common procedure used for the synthesis of the benzimidazoles derivatives is the condensation of o-phenylenediamine with differently substituted aldehydes obtaining 2-substituted and 1,2-substituted benzimidazoles derivatives. These protocols, however, present several problems that make the methods less convenient for long reaction times, the use of expensive reagents and toxic organic solvents. Furthermore, non-recoverable, difficult to prepare and poorly selective catalysts are often used [10-15].

The use of toxic and hazardous solvents in the pharmaceutical industry is considered a risk for the environment and human health, but in the last years, Green Chemistry principles influenced the activities drug industries introducing less use of toxic organic solvents [16-18], cuts in waste production with the use the recyclable reagents [19-23] and enviromental organic synthetic methods.

Various research studies have been conducted on the use of "green" solvents [24], principally bio-solvents [25-30], ionic liquids [31-33], deep eutectic solvents [34-40], supercritical fluids [41,42], or water [43-51]. Certainly adopting methods experimental tests based on solvent-free or solid state reaction conditions reduces pollution. These reactions may be carried out using the reactants alone. Often the same reactions involve use of solid supports (clays, zeolites, silica, alumina or other matrices) making it easier the experimental and work-up procedures improving yield, increasing the reaction rate and lowering considerably environmental impact [52-54]. In this context , therefore, solid Lewis acid catalysts are widely used and thermal process [55,56] can be employed to bring about the reaction. In the last decades, the use of microwave in solvent free reactions [57-60] , is been particularly important for industrial production.

Since the development of new synthetic methods to produce potential drug compounds has always an important research area, in recent years, very important has become the use of recyclable heterogeneous catalysts for their extremely versatile properties, thermal stability and their low cost.

In addition, the reaction products catalyzed by solid supports or in solid state provide better selectivity in the products, compared to the solution phase reactions.

Recently, various heterogeneous catalyst showed higher activity than homogeneous catalyst [61, 62]. MK10 is an interesting clay heterogeneous catalysts [63-66] because act as a general Brønsted or Lewis acid and it is recoverable by filtration and employed in one-pot synthesis under solvent-free conditions and microwaves (MW) or ultrasound irradiation [67] prevents waste. The use of irradiation MW increase the rate of chemical reactions and have great potential for use in innovative chemical reaction processes [68]. Chemical reactions induced by MW radiation in heterogeneous catalytic systems, have demonstrated that acceleration of chemical reactions using microwave method cannot be achieved and compared with conventional heating under identical temperature conditions, due, probably, to interaction(s) between the MW radiation fields and the catalyst. Recently, this has given rise, over the years, to a strong interest in the field of the synthesis of pharmaceutical compounds [69-79].

Considering the stability, catalytic activity and selectivity of MK10 shown to us in the synthesis reactions of bifunctionalized cyclopentenones [80] and our experience in developing environmental reactions for the synthesis of pharmaceutical azo-compounds [81-85], we present a new and selective synthetic route to

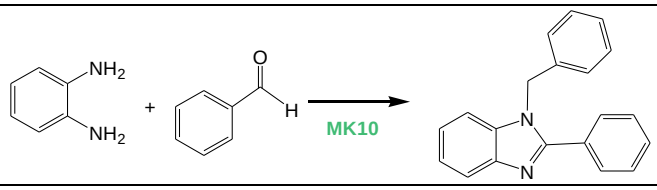
benzimidazole derivatives in solvent free condition reaction testing the MK10 as heterogeneous catalyst.

2. Results

In initial experiment, we choose *o*-phenylenediamine (1 mmol) and benzaldehyde start material to obtain selectively 1,2-disubstituted benzimidazole derivative **1b**. The results for development and optimization of the model reaction are displayed in Table 1. The effect of MK10 on the model reaction was investigated performing the reaction at room temperature (entries 1, Table 1,) using 10 wt% of MK10 respect to *o*-phenylendiamine. The reaction mixture was left under magnetic stirring at room temperature using the diamine and benzaldehyde in a 1:1 and 1:2 molar ratio and monitored by thin layer chromatography (TLC) and gas chromatography/mass spectrometry (GC/MS) analysis (entries 1 and 2 in Table 1).

The GC/MS analysis showed the low conversion of the reagents within 10 minutes affording and low selectivity even when using 2 mmol benzaldehyde (entry 2 in Table 1). At the higher temperature, 60°C, the 2-substituted benzimidazole derivative **1a** and the 1,2-disubstituted benzimidazole derivative **1a** in 34.9 and 65.1 % yields respectively obtained (entry 3 in Table 1) not improving selectivity that has worsened using 1 mmol benzaldehyde at 80°C (entry 4, Table 1). The GC-MS analysis showed the presence of the corresponding 2-phenyl-benzimidazole by-product (66.7% yield) in 2 h.

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*-phenylendiamine (1 mmol) and benzaldehyde (1 or 2 mmol) were stirred for 5-120 min at different temperatures and different wt (%) of MK10. [b] wt % respect to *o*-phenylendiamine. [c] Percent conversion of the reagents calculated from GC/MS data of conversion of *o*-phenylendiamine. [d] By-product obtained is constituted by 2-phenyl-benzimidazole (**1b**). [e] Reaction mixture under MW irradiation.

The model reaction showed the complete conversion of *o*-phenilendiammine when the same reaction was performed higher temperatures (100°C) (entries 5 and 6,

Table 1) in 1 h. Improving the molar ratio of benzaldeide (2 mmol) at the same temperature in the same reaction time (60 minutes), was observed a better selectivity (entry 6, Table 1). In the same reaction conditions, but in the absence of catalyst and in longer reaction time (90 minutes), no complete conversion of *o*-phenilendiammine and a poor selectivity was observed (Table 1, entry 7).

We observed the complete conversion when the amount of catalyst was improved at 20 wt% of MK10 at 60 °C under MW irradiation (Table 1, entry 8), obtaining 2-phenyl-benzimidazole as principal product (81.2% yield) and using 1 mmol of benzaldehyde. The microwave irradiation at 60 °C gave the best results in terms of reaction rate (only 5 minutes) and product yield. Surprisingly, we obtained the desiderated product, 1-benzyl-2-phenyl-benzimidazole **1b** in 98.5% yield and in only 5 minutes at 60° C (Table 1, entry 9) using 2 mmol of benzaldehyde.

To demonstrate the eco-sustainability of the method, we have evaluated the recyclability of the MK10 in the reaction model system using the reaction condition of entry 9, Table 1. The final reaction mixture, including MK10 and product, was treated with ethyl acetate; the catalyst was separated from the organic solution by filtration, washed with ethyl acetate (3 mL) for four times and dried in oven (40°C). The combined organic phases were concentrated under vacuum and analyzed by GCMS. The recovered catalyst was used directly for the next run adding new fresh reagents following the procedures reported in the literature [80] (Figure 1).

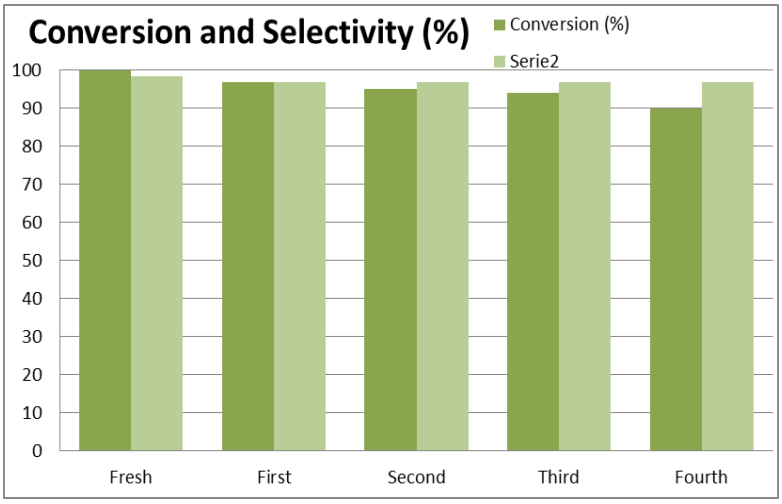
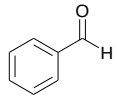
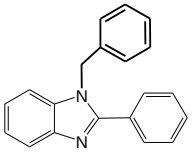
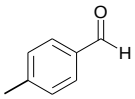
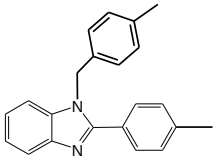
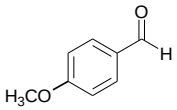
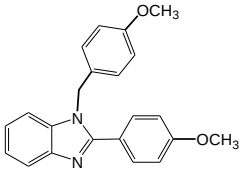
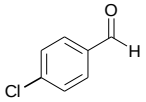
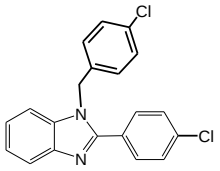
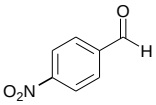
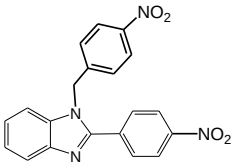
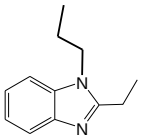
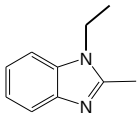
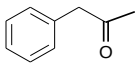
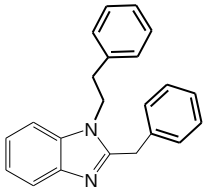


Figure 1. Cycling performance of MK10 in synthesis of 1-benzyl-2-phenyl-benzimidazole **1b** under MW irradiation.

In the same time, the model reaction was carried out in a scale of 10 mmol of *o*-phenilendiammine and 20 mmol of benzaldehyde using the respective amount of MK10 to demonstrate the potential industrial applicability of this green procedure. The reaction was completed in 25 min with 95% isolated yield after simple extraction with ethyl acetate.

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**	90.6	0
5[c]		 **5a**	90.6	0
6		 **6a**	91.0	90.8
7		 **7a**	97.8	95.1
8		 **8a**	96.8	93.8

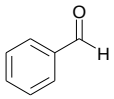
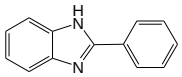
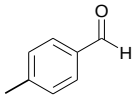
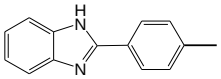
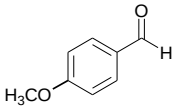
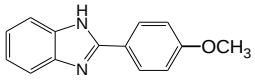
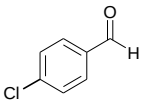
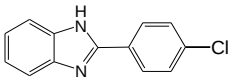
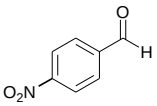
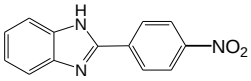
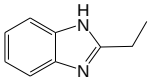
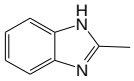
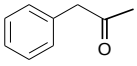
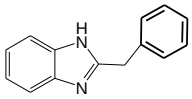
[a] General reaction conditions: 1 mmol of *o*-phenylendiamine and 2 mmol of aldehyde are added t to 20% mw to *o*-phenylendiamine of MK10. The mixture conducted in a Syntos 3000 microwave oven (Anton-Paar) at 60°C for 5 min. The reaction mixture was then treated with AcOEt (3 x 2 mL) and filtered to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

The experimental procedure was applied to different aldehydes to obtain the desired 1,2-disubstituted benzimidazole derivatives and the quantitative yields superior to 90% were obtained in all cases of aldehydes containing electron donor groups (entries 1-3 and entries 6 and 7, Table 2).

The reactions performed with aldehydes containing electron withdrawing groups such as *p*-chloro or *p*-nitro benzaldehyde (entries 4 and 5, Table 2) afforded the corresponding 2-monosubstituted benzimidazoles (**4b** and **5b**) in good yields without observing the formation of disubstituted derivative.

The reactions performed with 1 molar amount of aldehydes afforded the corresponding 2-monosubstituted benzimidazoles (**1b-8b**) in good yields without observing the formation of disubstituted derivative. This result is in accordance with the data reported in the literature [39,84].

Table 3. Synthesis of monofunctionalized cyclopentenones.[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**	90.6	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*-phenylendiamine and 2 mmol of aldehyde are added t to 20% mw to *o*-phenylendiamine of MK10. The mixture conducted in a Syntos 3000 microwave oven (Anton-Paar) at 60°C for 5 min. [b] Percent yield calculated from GC/MS data. The corresponding monosubstituted benzimidazole derivative was recovered as the sole product.

All reactions performed in short reaction times (5 minutes). The reaction yields related to the formation of the disubstituted benzimidazoles derivative were between

90% and 99%. The reaction yields related to the formation of the 2-substituted benzimidazoles derivative ranged from 90% to 99%.

In the development of a green procedure, the recyclability of the heterogeneous catalyst MK10 is an essential feature.

Unlike the procedures reaction reported in the literature, the method described does not provide for the use of solvents (84) or the synthesis of deep eutectic solvents (39) essential to perform the reaction.

3. Materials and Methods

3.1. General Methods

Montmorillonite K10 clay obtained from Aldrich, has the following chemical composition (wt%) SiO2: 67.6; Al2O3: 14.6; Fe2O3: 2.9; MgO: 1.8.

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification.

All reactions were monitored by GC-MS. The GC-MS Shimadzu workstation was 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).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Brüker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with tretramethylsilane (TMS) as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Brüker at 75 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0).

MW-assisted reactions were performed on a Synthos 3000 instrument from Anton Paar, equipped with a 4 × 24MG5 Rotor and an IR probe used for external temperature control.

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

The aldehyde (2 mmol) was added to a solution of *o*-phenilendiammine (1 mmol) and MK10 (20 mg). The resulting mixture was reacted for 5 min in a Synthos 3000 microwave instrument, fixed on the temperature value of 60 °C (IR Limit).

After completion of the reaction (monitored by GCMS), the MK10 was separated from the reaction mixture by filtration and washed with ethyl acetate (3 mL) for four times. The products were isolated after evaporation of the solvent to afford compounds in 90-99 % yields. Spectral data were in accordance with the literature [39].

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

The aldehyde (1 mmol) was added to a solution of *o*-phenilendiammine (1 mmol) and MK10 (20 mg). The resulting mixture was reacted for 5 min in a Synthos 3000 microwave instrument, fixed on the temperature value of 60 °C (IR Limit).

After completion of the reaction (monitored by GCMS), the products were isolated as previously described. Spectral data were in accordance with the literature [39].

3.4. Catalyst recycling

After completion of the reaction (monitored by GCMS), the MK10 was separated from the reaction mixture by a rapid filtration and washed with ethyl acetate (3 mL) for four times and dried in a oven (50 °C). The MK10 recycled is further evaluated in the reaction for 4 runs (Fig. 1)

4. Conclusions

An effective procedure for the synthesis of 1,2-substituted and 2-substituted benzimidazoles has been developed. The reactions showed high conversion and selectivity.

The use of the heterogeneous catalyst MK10 under MW irradiation is a valuable method respect to the previously reported procedure: the performance don't allows the use of solvent, the reaction times are very short and a greater selectivity, thus avoiding the formation of by-products.

Moreover, other advantages of this method are the use of a heterogeneous catalysts recycling and stable after next run. MK10 was reused for three consecutive cycles without any significant loss in catalytic activity, as previously demonstrated (80).

Supplementary Materials: The following are available online at www.mdpi.com/link.

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.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thomas, J. M.; Raja, R.; Lewis, D. W. Single-site heterogeneous catalysts. *Angew. Chem. Int. Ed*. **2005**, *44*, 6456. DOI:10.1002/ANIE.200462473.
2. Emerson, G.; Brink, N. G.; Holly, F. W.; Koniuszy, F.; Heyl, D.; Folker, K. Vitamin B_{12} . VIII. Vitamin B_{12} -Like Activity of 5,6-Dimethylbenzimidazole and Tests on related compounds. *J. Am. Chem. Soc.*, **1950**, 72, 3084-3085
3. Kubo, K.; Oda, K.; Kaneko, T.; Satoh, H.; Nohara, A. Synthesis of 2-(4-Fluoroalkoxy-2-pyridyl) methyl] sulfinyl]-1H-benzimidazoles as Antiulcer Agents. *Chem Pharm Bull*. **1990**, *38*(10), 2853-2858.
4. Uchida, M.; Chihiro, M.; Morita, S.; Yamashita, H.; Yamasaki, K.; Kanbe, T.; Yabuuchi, Y.; Nakagawz, K. Synthesis and Antiulcer Activity of 4- Substituted 8-[(2-Benzimidazolyl) sulfinylmethyl]-1, 2, 3, 4-tetrahydroquinolines and Related Compounds. *Chem Pharm Bull.* **1990**, *38*(6), 1575-1586.
5. 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*(2), 251-259.
6. 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*(8), 3293-3298.
7. 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 Antiallergy Agents Med Chem*. **2012;** *11*(3, 267-75.
8. Thakuria, H.; Das, G. An expeditious one-pot solvent-free synthesis of benzimidazole derivatives *ARKIVOC* **2008** (xv) 321-328
9. Rithe, S.R.; Jagtap, R.S. ; Ubarhande S.S. One Pot Synthesis Of Substituted Benzimidazole Derivatives And Their Characterization *RASAYAN J. Chem*., **2015**, *8* (2), 213-217.
10. Saberi A. Efficient synthesis of Benzimidazoles using zeolite, alumina and silica gel under microwave irradiation *Iran. J. Sci. Technol*., **2015**, 39A1, 7-10.
11. Mobinikhaledi, A.; Hamta, A.; Kalhor, M.; Shariatzadeh, M. Simple Synthesis and Biological Evaluation of Some Benzimidazoles Using Sodium Hexafluroaluminate, Na3 AlF6 , as an Efficient Catalyst *Iran. J. Pharm. Res.* **2014**, *13* (1), 95–101.
12. Birajdar, S.S.; Hatnapure, G.D.; Keche, A.P.; Kamble, V.M. Synthesis of 2-substituted-1 H-benzo[d]imidazoles through oxidative cyclization of O-phenylenediamine and substituted aldehydes using dioxanedibromide *Res. J. Pharm. Biol. Chem. Sci.* **2014**, *5* (1), 487–493.
13. Srinivasulu, R.; Kumar, K.R.; Satyanarayana, P.V.V. Facile and Efficient Method for Synthesis of Benzimidazole Derivatives Catalyzed by Zinc Triflate *Green Sustainable Chem*. **2014**, *4*, 33–37.
14. Sehyun, P.; Jaehun, J.; Eun, J.C. Visible-Light-Promoted Synthesis of Benzimidazoles *J. Org. Chem.* **2014**, 4148– 4154.

15. Vishvanath, D.P.; Ketan, P.P. Synthesis of Benzimidazole and Benzoxazole Derivatives Catalyzed by Nickel Acetate as Organometallic Catalyst *Int. J. ChemTech Res*. **2014**, *8* (11), 457–465.
16. W. M. Nelso, Green Solvents for Chemistry Perspectives and Practice, Oxford University Press, **2004**
17. K. Mikami, Green Reaction Media in Organic Synthesis, Blackwell, 2005.
18. Clark, J. H.; Tavener, S. J. Alternative Solvents: Shades of Green *Org. Process Res. Dev.* **2007**, *11*,1, 149-155
19. 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
20. 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.
21. 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.
22. Oliverio, M.; Costanzo, P.; Macario, A.; De Luca, G.; Nardi, M.; Procopio. A. A Bifuctional Heterogeneous Catalyst Erbium-Based: A Cooperative Route Towards C-C Bond Formation. *Molecules*, **2014**, *19*, 10218–10229.
23. 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.
24. W. M. Nelso, Green Solvents for Chemistry Perspectives and Practice, Oxford University Press, **2004**
25. Virot, 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.
26. Lapkin, A.; Plucinski, P.K.; Cutler, M. Comparative assessment of technologies for extraction of artemisinin. *J. Nat. Prod*. **2006**, *69*, 1653–1664.
27. 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.
28. García, J. I. ; García-Marín, H.; Pires, E. Glycerol based solvents: synthesis, properties and applications. *Green Chem*., **2014**, *16*, 1007-1033
29. Nardi, M.; Oliverio, M.; Costanzo, P.; Sindona, G.; Procopio, A. Eco-friendly stereoselective reduction of α,β-unsaturated carbonyl compounds by $Er(OTf)_3/NaBH_4$ in 2-MeTHF. *Tetrahedron* **2015**, *71*, 1132–1135.
30. 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.
31. Abbott, A.P.; Davies, D.L.; Capper, G.; Rasheed, R.K.; Tambyrajah, V. Ionic Liquids and Their Use As solvents. U.S. Patent, *7*,183,433, 27 February 2007.
32. Di Gioia, M.L.; Barattucci, A.; Bonaccorsi, P.; Leggio, A.; Minuti, L.; Romio, E.; Temperini, A.; Siciliano, C. Deprotection/reprotection of the amino group in α-amino acids and peptides. A one-pot procedure in [Bmim][BF4] ionic liquid. *RSC Adv.* **2014**, *4*, 2678–2686.
33. 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
34. De Nino, A.; Maiuolo, L.; Merino, P.; Nardi, M.; Procopio, A.; Roca-Lõpez, 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, 5, 830-835
35. Abbott, A.P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. *Chem. Commun.* **2003**, 70–71.
36. Gorke, J.T.; Srienc, F.; Kazlauskas, R.J. Hydrolase-catalyzed biotransformations in deep eutectic solvents. *Chem. Commun.* **2008**, *10*, 1235–1237.
37. Smith, E.L.; Abbott, A.P.; Ryder, K.S. Deep Eutectic Solvents (DESs) and their applications *Chem. Rev.* **2014**, *114*, 11060–11082.
38. 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 Sustainable Chem. Eng*. **2014**, *2*, 1063–1071.

39. Di Gioia, M.L.; Cassano, R.; Costanzo, P.; Herrera Cano, N.; Maiuolo, L.; Nardi, M.; Nicoletta, F. P.; Oliverio, M.; Procopio, A. Green Synthesis of Privileged Benzimidazole Scaffolds Using Active Deep Eutectic Solvent *Molecules* **2019**, *24*(16), 2885

40. 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*(6), 513;

41.

42. Leitner, W.; Poliakoff, M. Supercritical fluids in green chemistry *Green Chem.*, **2008**, *10*, 730-730

43. Carlès P. A brief review of the thermophysical properties of supercritical fluids *J. of Supercritical Fluids* **2010**, 53, 2–11

44. Lindström, U.M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *10*, 2751–2772.

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

46. 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.

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

48. Oliverio, M., Costanzo, P., Paonessa, R., Nardi, M., Procopio, A. Catalyst-free tosylation of lipophilic alcohols in water *RSC Advances*, **2013**, *3*(8), 2548-2552

49. 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.

50. 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*, 269–282.

51. 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.

52. 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.

53. 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.

54. Estevão, M.S.; Afonso, C.A.M. Synthesis of trans-4,5-diaminocyclopent-2-enones from furfural catalyzed by Er(III) immobilized on silica, *Tetrahedron Letters* **2017**, *58*, 302–304

55. Senthilkumar, S.; Maru M. S.; Somani, R. S.; Bajaj, H. C.; Neogi. S. Unprecedented NH_2-MIL-101(Al)/*n*-Bu_4NBr system as solvent-free heterogeneous catalyst for efficient synthesis of cyclic carbonates *via* CO_2 cycloaddition *Dalton Trans.*, **2018**,*47*, 418-428.

56. T. J. Mason Sonochemistry: current uses and future prospects in the chemical and processing industries *Phil. Trans. R. Soc. Lond. A* , **1999**, *357*, 355–369

57. 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

58. Jeˇselnik, M.; S. Varma, R.; 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**, 1716–1717

59. Kappe, O. Controlled microwave heating in modern organic synthesis. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284;

60. Desai, KR. *Green Chemistry Microwave Synthesis 1st ed.*; Himalaya Publication House: New Delhi, India, **2005**; 20.

61. 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.

62. Deng, Q.; Wang, R. Heterogeneous MOF catalysts for the synthesis of trans-4,5-diaminocyclopent-2-enones from furfural and secondary amines *Catalysis Communication*, **2019**, *120*, 11-16.
63. 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.
64. Kaur, N.; Kishore, D. Montmorillonite: an efficient, heterogeneous and green catalyst for organic synthesis. *J. Chem. Pharm. Res*. **2012**, *4*, 991–1015.
65. Kumar, B.S.; Dhakshinamoorthy, A.; Pitchumani, K. K10 montmorillonite clays as environmentally benign catalysts for organic reactions. *Catal. Sci. Technol*., **2014**, *4*, 2378–2396.
66. Hechelski, M.; Ghinet, A.; Brice Louvel, B.; Dufrenoy, P.; Rigo,B.; Dai¨ch, 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
67. Li, J.-T., Xing, C.-Y., Li, T.-S., An efficient and environmentally friendly method for synthesis of arylmethylenemalononitrile catalyzed by Montmorillonite K10–$ZnCl_2$ under ultrasound irradiation. *J. Chem. Technol. Biotechnol*. **2004**, *79*, 1275–1278.
68. Horikoshi, S.; Serpone, N. Role of microwaves in heterogeneous catalytic systems *Catal. Sci. Technol*., **2014**,*4*, 1197-1210.
69. Oliverio, M.; Costanzo, P.; Nardi, M.; Calandruccio, 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.
70. 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.
71. 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*(35), 8078-8081
72. 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 Letters*, **2008**, *49*(12), 1961-1964.
73. 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 Chemistry*, **2014**, *162*, 89-93.
74. Oliverio, M.; Nardi, M.; Cariati, L.; Vitale, E.; Bonacci, S.; Procopio, A. "on Water" MW-Assisted Synthesis of Hydroxytyrosol Fatty Esters *ACS Sustainable Chem. Eng.* **2016**, *4*, 661-665
75. Maiuolo, L.; De Nino, A.; Algieri, V.; Nardi, M. Microwave-assisted 1,3-dipolar cyclo-addition: Recent advances in synthesis of isoxazolidines *Mini-Reviews in Organic Chemistry* **2017,** *14(2)***,** 136-142.
76. Nardi, M.; Bonacci, S.; Cariati, L.; Costanzo, P.; Oliverio, M.; Sindona, G.; Procopio, A. Synthesis and antioxidant evaluation of lipophilic oleuropein aglycone derivatives *Food and Function*, **2017**, *8*, 12, 4684-4692
77. Costanzo, P.; Calandruccio, C.; Di Gioia, M.L.; Nardi, M.; Oliverio, M.; Procopio, A. First multicomponent reaction exploiting glycerol carbonate synthesis, *Journal of Cleaner Production*, **2018**, 202, 504-509
78. Costanzo, P.; Bonacci, S.; Cariati, L.; Nardi, M.; Oliverio, M.; Procopio, A. Simple and efficient sustainable semi-synthesis of oleacein [2-(3,4-hydroxyphenyl) ethyl (3S,4E)-4-formyl-3-(2-oxoethyl)hex-4-enoate] as potential additive for edible oils *Food Chemistry*, **2018**, *245*, 410-414.
79. 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 *Natural product communications*, **2018**, *9*, 1117-1122
80. 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*, 301-311.
81. Nardi, M.; Cozza, A.; Maiuolo, L.; Oliverio, M.; Procopio, A. 1,5-Benzoheteroazepines through eco-friendly general condensation reactions *Tetrahedron Letters*, **2011**, *52* (38), 4827-4834.

82. 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.
83. 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
84. 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.
85. 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 *Arabian Journal of Chemistry*, **2016**, *9*, 1, 32-37