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Montmorillonite K10-Catalyzed Solvent-Free Conversion of Furfural into Cyclopentenones

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Abstract: A simple and eco-friendly montmorillonite K10 (MK10)-catalyzed method for the synthesis of cyclopentenone derivatives from biomass-produced furfural has been developed. The versatility of this protocol is that the reactions were performed under solvent-free conditions and in a short reaction time under heterogeneous catalysis. Montmorillonite K10 is mostly explored as a heterogeneous catalyst since it is inexpensive and environmentally friendly.

Keywords: heterogeneous catalysis; montmorillonite; furfural; cyclopentenones

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1. Introduction

In the last few decades, the use of heterogeneous catalysis has become a promising field in chemical synthesis, especially in industrial applications [1]. From an economic point of view, the tendency to use heterogeneous acid catalysis in the industrial field derives from their intrinsic stability, ease of recovery, separation and recycling minimizing waste contamination. On the other hand, the use of volatile and dangerous solvents in the chemical industry represents a risk for the environment and human health [2–6], so that the necessity for clean processes, in which energy, waste and costs are reduced, is of general concern [7].

Different studies have encouraged the use of unconventional methods or "green" solvents [8], principally water [8–15], ionic liquids [16–20], deep eutectic solvents [21–24], or bio-solvents [25–30], but the use of solvent-free conditions [31–36] is certainly the best choice to conduct eco-sustainable chemical procedures. A solvent-free reaction can be performed by using the reactants alone, or incorporating them in solid supports simplifying the experimental and work-up procedures, and considerably lowering the environmental impact. These would be particularly important in industrial manufacturing, where, in the last few decades, the use of microwave heating among others [37–40], was proposed in solvent-free chemical processes catalyzed by solid Lewis acids as a useful method for increasing the reaction rate, simplifying the work and improving the yield [41–44].

The Pollution Prevention Act of 1990 was endorsed to raise interest in pollution prevention, and to encourage the design of environmentally benign processes and products.

Lowering the environmental impact of industrial activities is particularly important for the pharmaceutical industry, as it is very often indicated as the principal source of environmental pollution [45]. In recent years, the use of renewable sources or waste materials as starting products has become very important for obtaining useful pharmaceutical synthons [46–48]. In this context, furfural is an important biomass compound that is derived and used to synthesize different bio-products [49]. The cyclopentenone derivatives in fact represent a vast variety of bioactive molecules. Particularly, the chiral 2,4-disubstituted cyclopentenones as prostaglandins have anti-inflammatory [50], anticancer [51], and antiviral activities [52,53], and the presence of an α,β-unsaturated carbonyl group is important for the biological activity of these compounds. The cyclization rearrangement can be realized by different Lewis acids as metallic compounds [54], triflate [55–57], and metal chloride [58] in ionic liquids [59], or by using green media as water [60] or deep eutectic solvents [61].

Solid supports have gained interest in organic synthesis for their extremely versatile properties, thermal stability, and low cost.

Recyclable heterogeneous catalysts have been extensively experimented, but their activities are generally lower with respect to those of homogeneous catalysts, as the exposure degree of the active site to the reactants is lower. Lanthanide chloride immobilized on silica as $ErCl_3 \cdot 6H_2O$ [62,63] was proposed for the preparation of diaminocyclopent-2-enones from furfural, but the procedure involved the use of organic solvents to obtain a selectivity of above 83%. Recently, a metal-organic framework (MOF) showed a higher activity than the homogeneous catalyst, but the system conditions under which the reaction occurred, such as the use of organic solvents under an N_2 atmosphere, were crucial in determining the course of the performance [64].

MK10 is considered to be a very interesting clay catalyst [65,66] because it offers several advantages compared to other solid supports [67]. It might act as a general Brønsted or Lewis acid, and it is considered to be an inexpensive green catalyst [68] since it prevents waste, and it is reusable and safe to handle. In fact, MK10 can be simply recovered by filtration and used in a one-pot process under solvent-free conditions and microwave or ultrasound irradiation [69].

Taking into account the stability and catalytic activity of MK10, and considering our knowledge in developing eco-friendly reactions for the synthesis of pharmaceutical compounds [70–78], we decided to test the MK10 as catalyst in the cyclization of the furfural for the synthesis of bifunctionalized cyclopentenones. The catalytic process showed high conversion and selectivity under MW irradiation. It is scalable and can be considered a promising renewable method for the production of bio-derived compounds in the pharmaceutical industry. In particular, these diamino derivatives are successfully used for the synthesis of a diaminated product, such as the marine sponge pyrrole-2-aminoimidazole alkaloid (±)-agelastatin A. [79] These diamino cyclopentenone adducts can also be important intermediates if they are treated with different nucleophiles to achieve a second rearrangement, yielding 4-substituted 2-amino-cyclopentenones. Sequential reactions including these rearrangements could produce novel molecular structures with a high degree of complexity, and they seem to be of increasing interest, in the context of biomass valorisation, to generate chemicals from bio-based furan derivatives under industrially relevant reaction conditions [80].

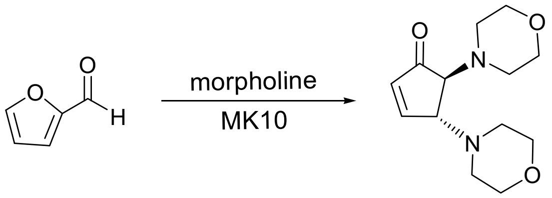
2. Results

In our initial experiment, we choose morpholine as an amine substrate to be added to 2-furaldehyde to selectively obtain *trans*-4,5-dimorpholinocyclopent-2-enone. The studies conducted for the development and optimization of the cyclization rearrangement of furfural and morpholine are presented in Table 1.

The influence of MK10 on the furfural/morpholine system was investigated, and it accomplished the reaction at room temperature (Table 1, entries 1) using 10 wt % of MK10 with respect to furfural. The corresponding *trans*-4, 5-dimorpholinocyclopent-2-enone was produced at 55% yield in 2 hr. The gas chromatograpy-mass spectrometry (GC-MS) analysis showed the presence of 2,4-dimorpholinecyclopen-2-enone as a by-product (45% yield).

Although the complete conversion of furfural at room temperature was observed, the confirmation that the procedure could work better was recorded when the same reaction was conducted at higher temperatures, observing a total conversion with better selectivity in only 35 minutes (Table 1, entries 2 and 3).

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



Entry	MK10 wt (%) [b]	Temp (°C)	Time (min)	Conversion (%) [c]	Selectivity (%) [d]
1	10	rt	120	99.9	55.0
2	10	60	35	99.9	61.1
3	10	80	35	99.9	65.3
4	20	80	35	99.9	75.0
5	20	100	20	99.9	78.3
6	-	100	20	60.0	49.0
7 [e]	20	80	5	99.9	99.9
8 [e]	**20**	**60**	**5**	**99.9**	**99.9**
9 [e]	20	60	10	99.9	99.9

[a] General reaction conditions: 1 mmol furfural and 2 mmol morpholine were stirred for 5–120 min at different temperatures and different wt (%) of MK10. [b] wt % respect to furfural. [c] Percentage conversion calculated from the GC-MS data for the conversion of furfural. [d] Yield (%) of *trans*-4,5-dimorpholinocyclopent-2-enone obtained, calculated from GC-MS. The by-product obtained is constituted by 2,4-dimorpholinocyclopent-2-enone. [e] Reaction mixture under MW irradiation.

We observed a better conversion with higher selectivity toward the desired product when the amount of catalyst was increased at 20 wt % when performing the reaction at 80 °C (Table 1, Entry 4); comparable selectivity was achieved by increasing the temperature (Table 1, Entry 5). Under the same reaction conditions, but in the absence of a catalyst, no complete conversion of furfural, and poor selectivity were observed (Table 1, entry 6). Based on our skills in the development of eco-friendly and selective procedures [54,55], we tested the microwave activation of the reaction, finding that the microwave irradiation at 60 °C gave the best results in terms of reaction rate and product yield (Table 1, entries 7–9). Surprisingly, we obtained the desired product at 99% yield in only 5 min at 60 °C (Table 1, entry 8).

Furthermore, we have evaluated the recyclability of the heterogeneous catalyst in the model reaction. The final reaction mixture, including MK10 and the product, was treated with a green solvent such as ethyl acetate [81]; the catalyst was separated from the solution by filtration, washed with ethyl acetate (3 mL) four times, and dried in an oven (80 °C) to remove traces of the solvent. Afterwards, the combined organic phases were concentrated under a vacuum, and the crude product was analyzed by GC-MS. The recovered catalyst was used directly for the next run, with the addition of fresh reagents. Thus, the second reaction mixture was subjected again to the above-described procedure, and further reaction cycles were repeated by using the previously recycled MK10.

To demonstrate the efficiency of the catalyst recycled: the MK10 can be recovered and recycled for three sequential cycles in the synthesis of *trans*-4,5-dimorpholinocyclopent-2-enone, furnishing high yields in every single cycle (Figure 1). The recycling showed the real heterogeneous catalytic nature for the rearrangement reaction, and the stable structure of MK10.

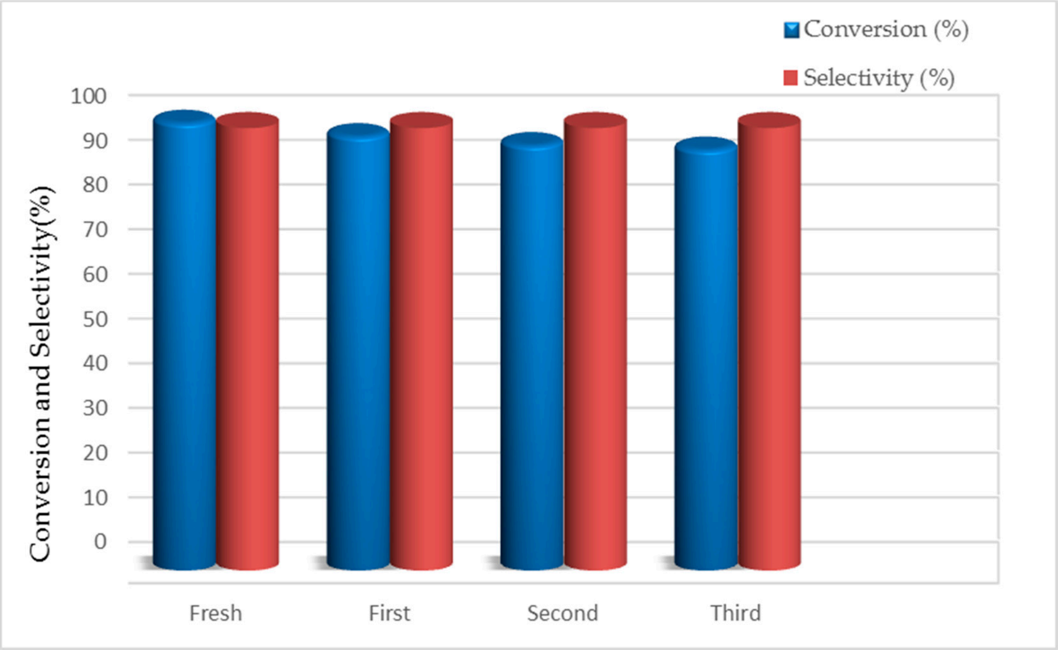
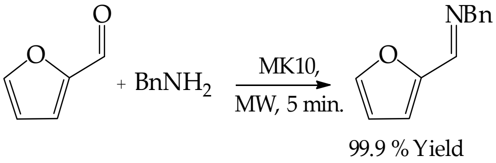


Figure 1. Cycling performance of MK10 in the synthesis of *trans*-4,5-dimorpholinocyclopen-2-enone under MW irradiation.

Then, to prove the applicability of this eco-friendly process, the model reaction was performed on a scale of 10 mmol of furfural and 20 mmol of morpholine, using the respective amount of MK10. The reaction was accomplished in 10 min with 98% isolated yield after simple extraction with ethyl acetate.

At this point, the experimental procedure was applied to different amines to obtain the desired 4,5-diaminocyclopenten-2-enones, and quantitative yields superior to 90% were obtained in all cases (Table 2). The reaction gave excellent results after the above reported simple workup with the alicyclic (Table 2, Entries 2–4), aliphatic (Table 2, Entries 5–7), and with the aromatic secondary amines (Table 2, entries 8–9); this reaction takes place especially with secondary amines, by the formation of an enamine intermediate as proposed by a previously reported mechanism of reaction [60,61]. In the case of primary aliphatic amines, the corresponding imine was observed as the only product (Scheme 1).



Scheme 1. Reaction of furfural with $BnNH_2$.

Table 2. Synthesis of bifunctionalized cyclopentenones. [a]

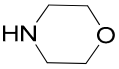
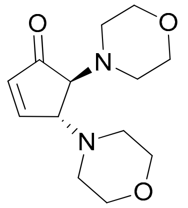
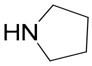
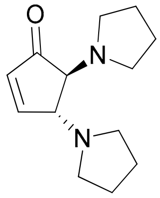
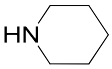
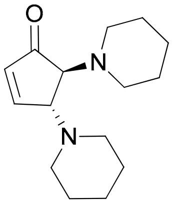
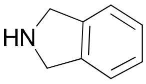
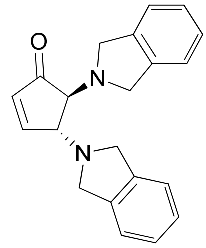
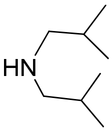
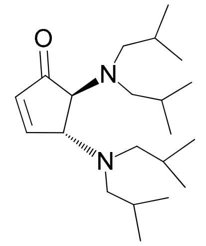
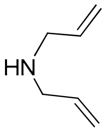
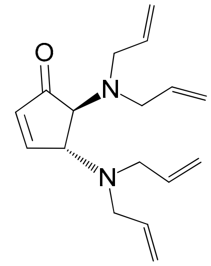
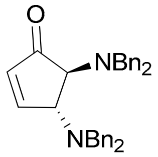
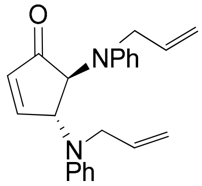
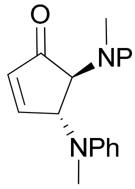
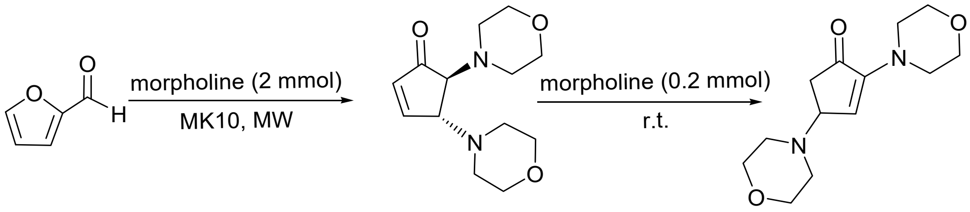
Entry	Amine	Product	Conversion (%)	Selectivity (%)	Yield (%) [b]
1			99.9	99.9	95.0
2			95.9	99.7	96.6
3			99.9	99.7	99.6
4			91.0	99.3	90.8
5			97.8	99.0	94.8
6			96.8	99.0	94.1
7	$HNBn_2$		90.6	99.0	98.3

Table 2. *Cont.*

Entry	Amine	Product	Conversion (%)	Selectivity (%)	Yield (%) [b]
8	AllylNHPh		99.7	99.8	97.8
9	CH_3NHPh		99.9	99.6	95.6

[a] General reaction conditions: 1 mmol of furfural and 2 mmol of amine are added to a final concentration of 20 mol % to furfural of MK10. The reaction was conducted in a Syntos 3000 microwave oven (Anton-Paar) at 60°C for 5 min.
[b] Percentage yield, estimated from GC-MS data.

2,4-Diamino cyclopent-2-enone, a by-product observed in the cyclization, was obtained at room temperature or in the absence of a catalyst (Table 1, entries 1 and 6) after a long reaction time. As previously observed [57,60], the conversion of 4,5-diamino cyclopentenone to 2,4-diamino cyclopentenone was performed in the presence of an excess of amine. To investigate the catalytic activity of MK10 and its selectivity, we tested the performance of *trans*-4,5-dimorpholinocyclopent-2-enone in the presence of a small amount of morpholine, to obtain 2,4-dimorpholinocyclopent-2-enone (Scheme 2).



Scheme 2. Synthesis of 2,4-dimorpholinocyclopenten-2-one.

Adding the amine (0.2 mmol) to the reaction mixture at room temperature without microwave irradiation, we observed that the 4,5-dimorpholino cyclopentenone was converted into the respective 2,4-cyclopentenone derivative after only one hour. In fact, the presence of excess amines leads to the formation of an enolic intermediate that successively yields the respective 2,4-cyclopentenone derivative. The mechanism of this reaction was proposed by Lewis and Mulquiney [82].

3. Materials and Methods

3.1. General Methods

All chemicals and solvents were purchased from common commercial sources, and were used as received without any further purification. Montmorillonite K10 clay (SBET ($m^2 \cdot g^{-1}$): 64.16. Vtotal ($cm^3 \cdot g^{-1}$): 0.108) obtained from Sigma-Aldrich, has the following chemical composition (wt %) SiO_2: 67.6; Al_2O_3: 14.6; Fe_2O_3: 2.9; MgO: 1.8.

All reactions were monitored by GC-MS. The GC-MS Shimadzu workstation was constituted by a GC 2010 equipped with a QUADREX 007-5MS (30 m × 0.25 mm, 0.25 µm) capillary column, operating in "split" mode with 1 $mL \cdot min^{-1}$ flow of He as the carrier gas.

^{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 the 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). ^{13}C-NMR spectra were recorded on a Brüker spectrometer 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 (Graz, Austria), equipped with a 4 × 24MG5 rotor, with an IR probe used for external temperature control.

3.2. General Experimental Procedure for the Microwave-Assisted Cyclical Rearrangement of Furfural and Amines

Morpholine (2 mmol) was added to a stirred solution of furfural (1 mmol) and MK10 (20 mg). The resulting mixture was reacted for 5 min in a Synthos 3000 microwave instrument, fixed at a temperature value of 60 °C (IR limit).

After completion of the reaction (monitored by GC-MS), the MK10 was separated from the reaction mixture by filtration, and washed with ethyl acetate (3 mL) four times. The products were isolated after evaporation of the solvent to yield compounds at an efficiency of 90–99%. Spectral data were in accordance with the literature [61].

The reaction of morpholine with furfural was scaled up to grams, using 20 mmol of furfural and 40 mmol of morpholine, with amounts corresponding to MK10. After completion of the reaction and separation of MK10, the product was obtained with a yield of 97%. All the characterization data are available in Supplementary Materials.

3.3. General Protocol for the Synthesis of 2,4-Diamorpholinecyclopent-2-enones

After the formation of *trans*-4,5-dimorpholinocyclopen-2-enone following the reported procedure, we added 0.2 mmol of morpholine to the mixture, and kept the reaction at room temperature for a further hour. After completion, ethyl acetate was added (3 mL), the catalyst was filtered, and the product was isolated after evaporation of the solvent to afford 2,4-dimorpholinecyclopent-2-enone at 99% yields. Spectral data were in agreement with the literature [61].

3.4. Catalyst Recycling

The MK10 obtained was further evaluated in the cyclization reaction of furfural and morpholine. As shown in Figure 1, after four runs, the selectivity still remained above 99%, and the conversion was only slightly reduced.

4. Conclusions

An effective procedure for the synthesis of *trans*-4,5-diamino-cyclopent-2-enones has been developed. The reaction showed a high degree of conversion and selectivity.

The use of MK10 under MW irradiation is a valuable method of for the use of a heterogeneous catalyst, as compared to previously reported procedures: the performance does not allow for the use of a solvent, the reaction times are very short, and a greater degree of selectivity in the rearrangement process occurs, thus avoiding the formation of by-products.

Additional advantages of this method are the use of a recyclable heterogeneous catalyst that is stable for the next run. MK10 was reused for three consecutive cycles without any significant loss in catalytic activity for the synthesis of *trans*-4,5-dimorpholine-cyclopent-2-enones.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/3/301/s1, General Experimental Procedure for Microwave-Assisted Cyclitation rearrangement of furfural and amines.

Author Contributions: M.N. and A.P. conceived and designed the experiments; S.B. and P.C. performed the experiments; A.D.N., M.L.D.G., and M.O. analyzed the data; A.D.N. and A.P. contributed reagents/materials/analysis tools; M.N., M.L.D.G. and A.P. wrote the paper.

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

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