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 carried out in solvent free condition and in short reaction time under heterogeneous catalysis. Montmorillonite K10 is a material most explored as heterogeneous catalyst since it is inexpensive and environmentally friendly.

Keywords: heterogeneous catalysis; Montmorillonite, furfural; cyclopentenones

1. Introduction
In the last years, the use of the 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 toxic and dangerous solvents in the chemical industry is considered a major risk for the environment and human health of workers [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 promoted the use of alternative 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 condition [31-35] is certainly the best choice to conduct eco-sustainable chemical procedures. A solvent-free reaction may be carried out using the reactants alone or incorporating them in solid supports simplifying the experimental and work-up procedures lowering considerably environmental impact. These would be particularly important in the industrial manufactures where, in the last decades, the use of microwave heating among others [37-40], was proposed in solvent-free chemical processes catalyzed by solid Lewis acids as useful method for increasing the reaction rate, simplifying the work-up and improving yield [41-44].
The Pollution Prevention Act of 1990 was enacted to increase interest in source reduction or pollution prevention and encourage design of environmentally benign processes and products.

Lowering the environmental impact of the industrial activities is particularly important for the pharmaceutical industry very often indicated as the principal source of environmental pollution [46]. Anyhow, since the development of novel synthetic methods to produce potential drug compounds has always an important research area, in recent years, very important has become the use of renewable sources or waste material as start product to obtain useful pharmaceutical synthons. [47-49]. In this context, furfural is important biomass compound derived and used to synthesize different bio-products [50]. The cyclization rearrangement can be realized by different Lewis acids as metallic compounds [51], triflate [52-54], metal chloride [55] in ionic liquids [56] or using green media as water [57] or deep eutectic solvents [58].

The use of solid supports in the organic synthesis have attracted the attention of chemists for their extremely versatile properties, thermal stability and their low cost.

Recyclable heterogeneous catalysts have been extensively experimentated, but their activities are generally lower than those of homogeneous catalysts because of the lower exposure degree of active site to the reactants. Lanthanide chloride immobilized on silica as ErCl₃·6H₂O [59-60] was proposed for the synthesis of diaminocyclopent-2-enones from furfural, but the procedure involved the use of organic solvents to obtain a selectivity above 83%. Recently, metal-organic framework (MOF) showed higher activity than homogeneous catalyst, but the system condition under which the reaction occurs, such the use organic solvent under N₂ atmosphere, was crucial in determining the course of the performance [61].

MK10 is one of the most interesting clay catalysts [62-63] because over other solid support offers several advantages [64]. It may act as a general Brønsted or Lewis acid and it is considered an inexpensive green catalyst [65] since it prevents waste, it is reusable and safe to handle. In fact, MK10 can be simply recovered by filtration and employed in one-pot synthesis under solvent-free conditions and MW or ultrasound irradiation [66].

Considering the stability and catalytic activity of MK10 and our experience in developing eco-friendly reactions for the synthesis of pharmaceutical compounds [67-73], we decided to test the MK10 as catalyst in the cyclization of the furfural for synthesizing bifunctionalized cyclopentenones. The catalytic process showed high conversion and selectivity under MW irradiation. It is scalable and can be considered an environmental promising route for production of bio-compounds in pharmaceutical industry.

2. Results

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

The effect of MK10 on the system furfural/morpholine was investigated performing the reaction at room temperature (Table 1, entries 1) using 10 wt% of MK10 respect to furfural. The corresponding trans-4, 5-dimorpholinocyclopent-2-enone was produced in 55% yield in 2 h. The GC-MS analysis showed the presence of 2,4-dimorpholinecyclopen-2-enone as by-product (45% yield).

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

Table 1. Optimization of the reaction conditions. *

<table>
<thead>
<tr>
<th>Entry</th>
<th>MK10 wt (%)b</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Conversion (%)b</th>
<th>Selectivity (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>rt</td>
<td>120</td>
<td>99.9</td>
<td>55.0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>60</td>
<td>35</td>
<td>99.9</td>
<td>61.1</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>80</td>
<td>35</td>
<td>99.9</td>
<td>65.3</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>80</td>
<td>35</td>
<td>99.9</td>
<td>75.0</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>100</td>
<td>20</td>
<td>99.9</td>
<td>78.3</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>100</td>
<td>20</td>
<td>60.0</td>
<td>49.0</td>
</tr>
<tr>
<td>7s</td>
<td>20</td>
<td>80</td>
<td>5</td>
<td>99.9</td>
<td>99.9</td>
</tr>
<tr>
<td>8s</td>
<td>20</td>
<td>60</td>
<td>5</td>
<td>99.9</td>
<td>99.9</td>
</tr>
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<td>9s</td>
<td>20</td>
<td>60</td>
<td>10</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

* General reaction conditions: furfural (1 mmol) and morpholine (2 mmol) were stirred for 5-120 min at different temperatures and different wt (%) of MK10. b wt % respect to furfural. c Percent conversion calculated from GC/MS data of conversion of furfural. d Yield (%) of trans-4,5-dimorpholinocyclopent-2-enone obtained, calculated from GC/MS. 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 of desired product when the amount of catalyst was improved at 20 wt% at 80 °C (Table 1, entry 4), and comparable selectivity was achieved increasing the temperature (Table 1, entry 5). In the same reaction conditions, but in the absence of catalyst, no complete conversion of furfural and a poor selectivity was observed (Table 1, entry 6). Based on our previous experiences in developing eco-friendly and selective procedures [55,56], 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 desiderated product in 99% yield in only 5 minutes at 60 °C (Table 1, entry 8).

Furthermore, we have evaluated the recyclability of the heterogeneous catalyst in the reaction model system. The final reaction mixture, including MK10 and product, was treated with ethyl acetate; the catalyst was separated from the solution by filtration, washed with ethyl acetate (3 mL) for four times and dried in oven. Afterward, the combined organic phases were concentrated under vacuum and the crude product was analyzed by GCMS. The recovered catalyst was used directly for the next run adding new fresh reagents. Thus, the second reaction mixture was subjected again to the above-described procedure and further reaction cycle was repeated using the previously recycled MK10.
The MK10 can be recovered and reused for three consecutive cycles in the synthesis of 4,5-trans-dimorpholinocyclopent-2-enone furnishing high yields in every single cycle (Figure 1). The recycling showed the true heterogeneous catalytic nature for rearrangement reaction and the stable structure of MK10.

![Cycling performance of MK10](image)

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

Then, to demonstrate the potential applicability of this eco-friendly procedure, the model reaction was carried out in a scale of 10 mmol of furfural and 20 mmol of morpholine using the respective amount of MK10. The reaction was completed 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 the desired 4,5-diaminocyclopenten-2-enones and the quantitative yields superior to 90% were obtained in all cases (Table 2). The reaction gave those excellent results after the above reported simple workup with alicyclic (Table 2, entries 2-4), aliphatic (Table 2, entries 5-7) as well as with aromatic secondary amines (Table 2, entries 8-9); whereas, in the case of primary aliphatic amines, the corresponding imine was observed as the only product (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Reaction of furfural with BnNH₂

<p>| Table 2. Synthesis of bifunctionalized cyclopentenones. |</p>
<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HN</td>
<td><img src="image1.png" alt="Image" /></td>
<td>99.9</td>
<td>99.9</td>
<td>95.0</td>
</tr>
<tr>
<td>2</td>
<td>HN</td>
<td><img src="image2.png" alt="Image" /></td>
<td>95.9</td>
<td>99.7</td>
<td>96.6</td>
</tr>
<tr>
<td>3</td>
<td>HN</td>
<td><img src="image3.png" alt="Image" /></td>
<td>99.9</td>
<td>99.7</td>
<td>99.6</td>
</tr>
<tr>
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<td>HN</td>
<td><img src="image4.png" alt="Image" /></td>
<td>91.0</td>
<td>99.3</td>
<td>90.8</td>
</tr>
<tr>
<td>5</td>
<td>HN</td>
<td><img src="image5.png" alt="Image" /></td>
<td>97.8</td>
<td>99.0</td>
<td>94.8</td>
</tr>
<tr>
<td>6</td>
<td>HN</td>
<td><img src="image6.png" alt="Image" /></td>
<td>96.8</td>
<td>99.0</td>
<td>94.1</td>
</tr>
<tr>
<td>7</td>
<td>HNBn2</td>
<td><img src="image7.png" alt="Image" /></td>
<td>90.6</td>
<td>99.0</td>
<td>98.3</td>
</tr>
<tr>
<td>8</td>
<td>AllylNHPh</td>
<td><img src="image8.png" alt="Image" /></td>
<td>99.7</td>
<td>99.8</td>
<td>97.8</td>
</tr>
</tbody>
</table>
9 \[ \text{CH}_3\text{NHPh} \]

99.9

99.6

95.6

\(^a\) General reaction conditions: 1 mmol of furfural and 2 mmol of amine are added to 20% mw to furfural 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 2,4-diamino cyclopent-2-enone, by-product observed in the cyclization reaction of furfural, is performed at room temperature or in the absence of a catalyst (Table 1, entries 1 and 6) after long time reaction. As previously observed \([57,58]\), the conversion of 4,5-diamino cyclopentenone to 2,4-diamino cyclopentenone, performed in the presence of an excess of amine. To investigate the catalytic activity of MK10 and its selectivity, we tested the performance of 4,5-trans-dimorpholino cyclopent-2-enone in the presence of a small amount of morpholine to obtain the 2,4-dimorpholino cyclopent-2-enone (Scheme 2).

Scheme 2. Synthesis of 2, 4-dimorpholino cyclopenten-2-one.

Adding amine (0.2 mmol) to the reaction mixture at room temperature without microwave irradiation, we observed that the product 4,5-dimorpholino cyclopentenone is converted into the respective 2,4 cyclopentenone derivative after only one hour. The mechanism of reaction is proposed by Lewis and Mulquiney \([74]\).

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 obtained from Aldrich, has the following chemical composition (wt%) SiO2: 67.6; Al2O3: 14.6; Fe2O3: 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 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 tetramethylsilane (TMS) as reference (δ 0.00). All coupling constants (\(\text{J}\)) 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 CDCl₃ (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 Experimental Procedure for Microwave-Assisted Cyclitisation rearrangement of furfural and amines.

The 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 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 [57].

The reaction of morpholine with furfural was scaled up to grams using 20 mmol of furfural and 40 mmol of morpholine with amount corresponding of MK10. After completion of the reaction and separation of MK10, the product were obtained with a yield of 97%.

3.3. General protocol for the synthesis of 2,4 diamorpholinecyclopent-2-enones.

After performed the 4,5-trans-dimorpholinocyclopent-2-enone as the reported procedure, to reaction mixture we added 0.2 mmol of morpholine and kept at room temperature for further 1 hour. After completion, ethyl acetate was added (3 mL), the catalyst was filtrate and the product isolate after evaporation of the solvent to afford 2,4-dimorpholinecyclopent-2-enone in 99% yields. Spectral data were in accordance with the literature [57].

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.

The MK10 obtained is further evaluated in the cyclization reaction of furfural and morpholine. As shown in Fig. 1, after 4 runs, the selectivity still retains above 99%, and the conversion is only slightly decreased.

4. Conclusions

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

The use of MK10 under MW irradiation is a valuable method of heterogeneous catalyst 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 in the rearrangement process, 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 in the synthesis of trans-4,5-dimorpholine-cyclopent-2-enone.

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

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.

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

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