Abstract

We report a green synthetic approach for the synthesis of amino carbonyl scaffolds via four component coupling of aromatic aldehydes, ketones and nitriles in presence of acetyl chloride by using bentonite clay as catalyst under solvent free conditions. Our interest is in developing this methodology as a novel route to access highly functionalized carbonyl scaffolds via green synthetic approach.

I. INTRODUCTION

The increasing rates of petrochemicals and increase of energy and raw material utilization is forcing the traditional chemistry to gain a greener look. As a consequence, chemical industry demands the development of green reaction methodologies to obtain novel structural scaffolds in a fast, clean and efficient way\textsuperscript{1-11}. The same thing is happening in the area of multicomponent reactions (MCRs) and scientists practicing MCRs are constantly engaged in the search for new catalysts and processes. The chemistry of amido carbonyl compounds is also subjected to such a change and consequently, large numbers of new catalysts are available for this process\textsuperscript{12-18}. This includes SnCl\textsubscript{4}/SiO\textsubscript{2} \textsuperscript{19a}, Cu (OTf)\textsubscript{2} and Sc(OTf)\textsubscript{3} \textsuperscript{19b}, Mn(bpdo)\textsubscript{2}Cl\textsubscript{2}/MCM-41 \textsuperscript{19c}, CeCl\textsubscript{3}/H\textsubscript{2}O \textsuperscript{19d}, iron (III) chloride \textsuperscript{19e} SiCl\textsubscript{4}-ZnCl\textsubscript{2} \textsuperscript{19f} etc. Even though these chiral Lewis acids have proven to be efficient for many
reactions, a major drawback is that most Lewis acids are unstable in presence of water and some of them are even moisture sensitive and also the multi-step program demands high synthetic skill. On regarding the new methodologies, some are efficient and provide the practical means for the synthesis of acetamido ketones, but some of the reported methods suffer drawbacks such as longer reaction times, tedious work up, higher temperatures, expensive catalysts, lower yields and feasible only under an inert atmosphere.

Until recently, the scope of this four component process was limited to the synthesis of amido carbonyl compounds. Recent developments in this area, particularly from our laboratory, revealed the potential of this protocol as an economic way for the synthesis of highly functionalized organic intermediates. Therefore, the introduction of new and efficient methods is still necessary for this reaction. Towards this goal, and in continuation of our investigations on the synthesis of highly functionalized structural scaffolds in a cost-effective, environmentally friendly and more importantly, for the development of a process which requires less operational skill and infrastructure, we were prompted to explore new methods for the incorporation of a large variety of substrates in mild conditions. For this, we decided to explore the possibility of Bentonite Clay Catalysis (BCC) in this reaction.

II. EXPERIMENTAL PROCEDURE

General: All solvents and reagents were of reagent grade quality from Aldrich Chemical Company, Fluka, or Merck and used without any further purification. Fourier transform infrared (FT-IR) spectra were recorded on a Jasco FTIR-4100 spectrometer. The $^1$H-nuclear magnetic resonance (NMR) spectra operating at the frequencies of 400, respectively, were measured with Varian NMR (VNMRS-400) spectrometer in dimethylsulphoxide-d (DMSO-d$_6$). Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard (d=0ppm) for $^1$H NMR. The coupling constants are reported in hertz (Hz). Reactions were monitored by thin-layer chromatography (TLC) using plates prepared with Merck silica gel G by irradiation with UV light and/or treatment with iodine. Column chromatography was performed on Merck silica (100 to 200 meshes) eluting with the indicated solvent system. Stereochemistry of the compounds were assigned by comparing the coupling constant (J value) of the methine proton with reported data.

Typical Experimental Procedure for the Stereoselective One Pot Three Component Coupling Reaction of Aldehydes, Ketones and Acetonitrile with bentonite as catalyst.

A 100 mL Rb flask was charged with a solution of the aryl aldehyde (1.25 mmol), aryl ketone (1.25 mmol), acetyl chloride (3 mL) and acetonitrile (5 mL) in the presence of bentonite clay (10wt%). The resulting mixture was then set to stir continuously for 4 hours at70°C. After the completion of the reaction as indicated by TLC, the reaction mixture was diluted with distilled water and stirred well. The obtained precipitate was collected by filtration, washed with distilled water (3 x 20 mL) and dried under vacuum. Column chromatography was performed on Merck silica (100 to 200 mesh) . The product was identified by comparing its NMR and IR values.
III. RESULTS AND DISCUSSION

We have initiated our studies with the synthesis of the amino carbonyl compound 2a (Table 2). The sequential addition of benzaldehyde, ethyl methyl ketone and acetyl chloride in the presence of bentonite clay in acetonitrile resulted in the rapid formation of 2a. With a very low amount of the clay, the reaction reached 55% conversion (with respect to the consumption of aldehyde and ketone) within 4 hour. Here the nitrile source acted as both reagent and solvent. Many nitriles are expensive and their uses in quantities at solvent level are not affordable. In order to overcome this problem, we then examined the synthesis of 2a in solvents like chloroform and dichloromethane with stoichiometric amount of aldehyde, enolizable ketone, nitrile source and acid chloride and successfully isolated the desired amino acid derivatives in comparable yield corresponding to that obtained from reactions carried out with excess amount of nitriles.

Table 1: Activity of bentonite clay for the multicomponent synthesis of amino carbonyl scaffolds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of the catalyst (wt %)</th>
<th>Reaction time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt; Reaction at 70 °C</th>
<th>Reaction at rt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bentonite</td>
<td>10</td>
<td>1.0</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Bentonite</td>
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<td>1.5</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
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<td>10</td>
<td>2.0</td>
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<td>22</td>
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<tr>
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<td>23</td>
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<tr>
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<td>Bentonite</td>
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<td>3.0</td>
<td>46</td>
<td>23</td>
</tr>
<tr>
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<td>Bentonite</td>
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<td>3.5</td>
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<td>24</td>
</tr>
<tr>
<td>7</td>
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<td>55</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>Nil</td>
<td>-</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on the weight of the isolated pure products.

The reaction can be readily followed by FT-IR spectroscopy by recording the disappearance of the aldehyde peak followed by the appearance of amide peak at 1654 cm<sup>-1</sup>. The structure of the product was confirmed via <sup>1</sup>H NMR and FT-IR studies. Stereochemistry was assigned by comparing the J values of the methine proton with reported data.
The substrate scope of the reaction was demonstrated with various aldehydes and ketones (Tables 2). The reactions were generally conducted with 2g of bentonite clay. In general, variations in the substitution patterns on aldehyde and ketone units were well tolerated (Table 2).
Table 2: Bentonite clay catalyzed stereoselective four component reactions of aldehydes, substituted ketones, acetonitrile and acetyl chloride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Bentonite as catalyst % Yield</th>
<th>Components</th>
</tr>
</thead>
<tbody>
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<td><img src="2a.png" alt="Image" /></td>
<td>55</td>
<td><img src="A.png" alt="Image" /> <img src="B.png" alt="Image" /> <img src="C.png" alt="Image" /> <img src="D.png" alt="Image" /></td>
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<tr>
<td>2</td>
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<td>57</td>
<td><img src="A.png" alt="Image" /> <img src="B.png" alt="Image" /> <img src="C.png" alt="Image" /> <img src="D.png" alt="Image" /></td>
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<td>3</td>
<td><img src="2c.png" alt="Image" /></td>
<td>56</td>
<td><img src="A.png" alt="Image" /> <img src="B.png" alt="Image" /> <img src="C.png" alt="Image" /> <img src="D.png" alt="Image" /></td>
</tr>
</tbody>
</table>

&superscript;All reactions were carried out at room temperature.
&superscript;bIsolated yield, all products were identified by comparing their NMR and IR values with those for authentic samples.
&superscript;cAssigned based on comparison with literature value for the coupling constants of methine proton.

The reaction is initiated by the complexation of the carbonyl oxygen of the ketone to the catalyst to produce a more sterically hindered enolate anion with a more nucleophilic carbon. Subsequent reactions of this enolate with aldehyde and acid chloride resulted in the carbon-carbon bond formation to produce an acyloxy ketone derivative. The steric interaction between the acyloxy group present in the aldehyde carbon and the more hindered substituted enolate anion restricts the addition to takes place through the less hindered face to produce an intermediate in the anti form. The acyloxy group in the intermediate then displaced by nucleophilic nitrogen of the nitrile to produce a stable cation intermediate. Addition of water or other reactive species like HOCl formed during the reaction leads to the formation of the anti-diastereomer.

IV. CONCLUSION
Conclusively, we have reported the efficiency of bentonite clay catalysts for the synthesis of amido carbonyl compounds (Mannich type products) via a four component coupling reaction. Under the described catalytic conditions, a diverse array of functional groups, present in aldehydes, ketones and nitriles are tolerated. The reusability of the catalyst and increased anti-diastereoselectivity makes it as a green alternative to the rapid generation of Mannich-type products. To our knowledge, this report describes the first example of the use of bentonite clay in a stereoselective multicomponent process.
V. REFERENCES


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