A RAPID AND GREEN METHOD FOR SYNTHESIS OF β-AMINO KETONES (MANNICH REACTION) USING AN ACID CATALYST NANO- SiO₂

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ABSTRACT
In this work we have reported a simple new catalytic method for the synthesis of β-amino carbonyl compounds by one-pot three-component Mannich reaction of cetophenone, aromatic aldehydes and aromatic amines using an nano-SiO₂ acidic catalyst as an efficient and reusable, catalyst. High yields, relatively short reaction times and easy work up are just a few of the advantages of this procedure.

Keywords: β-amino Ketones; Catalyst; Mannich Reaction; Nano-SiO₂; Synthesis

INTRODUCTION
One of the important goals in organic chemistry is the development of new methodologies for the synthesis of functionalized biologically active compounds with structural diversity from simple and readily available precursor molecules.

β-Amino carbonyl compounds are important intermediates for various pharmaceutical and natural product syntheses including β-amino alcohols, β-amino acids, and lactams (Simplício et al., 2007), (Mandloi et al., 2005).

Therefore, the development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention. However, the classic Mannich reaction has limited applications. But the preferred route is to use a one-pot three-component strategy that gives a wide range of structural variations.

Recently, some one-pot Mannich reactions on the use of ketones, aldehydes and amines have been catalyzed by organic or mineral acids likes- proline (List et al., 2002), CeCl₃•7H₂O (Dai et al., 2010), p-dodecyl benzene sulfonic acid (DBSA) (Manabe and Kobayashi, 1999), L-proline (List, 2000), urea derivatives (Wenzel and Jacobsen 2002), Zn(BF₄)₂ (Brindaban et al., 2002), Yb(OTf)₃ (Komoto and Kobayashi, 2004), Cu(OTf)₂ (Wolfgang et al., 2001), TiCl₄ (Periasamy et al., 2005), ZrOCl₂•8H₂O (Knüppel, 2005), Bi(OTf)₃•4H₂O (Ollevier et al., 2006), Zn(OTf)₂ (Salter et al., 2006), H₃PW₁₂O₄₀ (Azizi et al., 2006), NbCl₅ (Wang et al., 2007), guanidine hydrochloride (GuHCl) (Heravi et al., 2011), rare earth per fluoro octanoate (Wang et al., 2005), silica supported aluminum chloride (Li et al., 2007), and a few others.

However, these methods have some drawbacks such as long reaction time, use of costly and non-recoverable catalysts, use of toxic reagents, and requirement of special effort for catalyst preparation. Nano SiO₂ sulfuric acid is an excellent acidic catalyst, which is frequently used to promote some important reactions (Salehi et al., 2005), (Khodaei et al., 2005), (Wu et al., 2006).

We report herein full details of a novel, convenient, and simple procedure to realize a one-pot three-component reaction of aldehydes, amines, and ketones, catalyzed by using an nano-SiO₂ acid catalyst, for the preparation of β-amino carbonyl compounds in EtOH (Scheme 1).
Scheme 1: Mannich reaction catalyzed by Experimental

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by comparing of their physical data with those of known samples or by their spectral data.

The catalyst was synthesized according to the known literature. Melting points were recorded on an electro thermal type 9100 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The $^1$H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer.

General Procedure for the Synthesis of β-amino Carbonyl Compounds by nano SiO$_2$ Catalyzed Mannich Reaction. To a mixture of acetophenone (2 mmol), aromatic aldehyde (2 mmol) and aromatic amine (2 mmol) in ethanol (7 ml), nano-SiO$_2$ acid catalyst (0.10 g) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. Upon completion, the mixture was heated up to boiling. The catalyst was dissolved in hot ethanol and centrifugation at 2000–3000 rpm. The product was collected from the centrifugation after cooling to room temperature and recrystallized from ethanol to give compounds 4a-l in high yields.
RESULTS AND DISCUSSION

Nano-SiO$_2$ acid catalyst is a dry, non volatile, odourless and white crystalline solid with outstanding physical property and stability. The crystals can be kept in the laboratory for many years without change. It is commercially available and is very cheap, highly reactive and eco-friendly.

Initially, the synthesis of compound 4a was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by stirring a mixture of acetophenone (2 mmol), benzaldehyde (2 mmol) and 4-chloroaniline (2 mmol) in ethanol in the presence of various amount of nano-SiO$_2$ acidic as a catalyst. The efficiency of the reaction is affected mainly by the amount of nano-SiO$_2$ acid catalyst (Table 1).

Table 1: Effect of the amounts of nano-SiO$_2$ acid catalyst on the model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
<td>5.30</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>4.30</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>4.30</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>0.15</td>
<td>5</td>
<td>94</td>
</tr>
</tbody>
</table>

No products were produced in the absence of the catalyst (entry 1). To give the product, the catalyst is necessary for the reaction. Increasing the amount of the catalyst increased the yield of the product 4a. The optimal amount of nano-SiO$_2$ acid catalyst was 0.10 g (entry 5); increasing the amount of the catalyst beyond this value did not increase the yield noticeably (entries 6-7).

In order to evaluate the generality of this model reaction, other aldehydes and amines were tested for the Mannich reactions with acetophenone in ethanol at room temperature. The type of aldehydes and amines had no significant effect on the reaction. The results are summarised in (Table 2).

Table 2: Nano-SiO$_2$ acid catalyzed Mannich reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Aŕ</th>
<th>Products$^b$</th>
<th>Time (h)</th>
<th>Yield (%)$^c$</th>
<th>mp (°C) Found</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="path/to/image1.png" alt="Image" /></td>
<td><img src="path/to/image2.png" alt="Image" /></td>
<td><img src="path/to/image3.png" alt="Image" /></td>
<td>4:30</td>
<td>90</td>
<td>174-176</td>
<td>170-171</td>
</tr>
<tr>
<td>2</td>
<td><img src="path/to/image4.png" alt="Image" /></td>
<td><img src="path/to/image5.png" alt="Image" /></td>
<td><img src="path/to/image6.png" alt="Image" /></td>
<td>4:00</td>
<td>81</td>
<td>146-148</td>
<td>138-139</td>
</tr>
<tr>
<td>3</td>
<td><img src="path/to/image7.png" alt="Image" /></td>
<td><img src="path/to/image8.png" alt="Image" /></td>
<td><img src="path/to/image9.png" alt="Image" /></td>
<td>6:30</td>
<td>87</td>
<td>117-118</td>
<td>114-115</td>
</tr>
<tr>
<td>4</td>
<td><img src="path/to/image10.png" alt="Image" /></td>
<td><img src="path/to/image11.png" alt="Image" /></td>
<td><img src="path/to/image12.png" alt="Image" /></td>
<td>4:20</td>
<td>85</td>
<td>124-126</td>
<td>118-119</td>
</tr>
</tbody>
</table>
Acetophenone (2 mmol), aromatic aldehyde (2 mmol), aromatic amine (2 mmol) in ethanol at rt.
All the products were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also, the structures of some products were confirmed by $^1$H NMR spectral data.

Isolated yields.

**Conclusion**

In conclusion, we have described herein an efficient methodology for the Mannich reaction among acetophenone, aromatic aldehydes and aromatic amines at room temperature. The catalyst can be recovered and reused, thus making this procedure more environmentally acceptable. In addition, our method does not use expensive reagents or high temperatures. Further investigations on the synthetic applications of SiO$_2$-nanoparticles are in progress and will be reported in due course.

**REFERENCES**


Research Article


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