PART – B

CHAPTER-VI

Synthesis of 1,3-benzodioxoles
6.1 Introduction and literature

The 1,3-benzodioxoles are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties. Their derivatives can act as inhibitors of mono-oxygenase enzymes [1], pesticide intermediates [2-5], herbicides [6], antioxidants [7-8], antimicrobials [9] and other medicines [10-11]. The formation of 1,3-benzodioxole derivatives on the other hand, serves as the method for the protection of catechol as well as carbonyl compounds [12]. 1,3-Benzodioxoles with various substituents at 2-position have received more and more attention, because this ring system is an integral part of many natural products, such as sesamol and piperine [12-15]. Therefore, their synthesis assumed great importance in both biological chemistry and organic synthesis. The commonly used catalysts for the synthesis of 1,3-benzodioxoles are phosphorus pentoxide [16], trimethylsilyl chloride [17], phosphorus trichloride [18], super acids [19], montmorillonite KSF or K-10 [20] and p-toluenesulfonic acid [21]. Most of these catalysts are corrosive and are not environment-friendly. In addition to tedious work-up processes, trimethylsilyl chloride and phosphorus trichloride are poisonous, expensive and unstable. Moreover, most of them could not be recycled due to the difficulty in purification methods. Consequently, there is a genuine need for an efficient catalytic procedure for the synthesis of 1,3-benzodioxoles and therefore, it is desirable to use solid acid catalysts that are free from the above disadvantages. In the present work the interest has been focused on Cu(II) impregnated sulfated MCM-41 as green catalyst for the efficient synthesis of 1,3-benzodioxoles. A series of 2-substituted 1,3-benzodioxoles have been synthesized by the reaction of catechol with corresponding aldehydes and ketones using Cu(II) impregnated sulfated MCM-41 as catalyst.
6.2. Results and discussion

6.2.1 Characterization of catalyst

The powder X-ray diffraction patterns of MCM-41 and sulfated MCM-41 are shown in Fig. 6.1. The XRD figures showed a very strong peak at $2\theta = 2.2^\circ$ due to (1 0 0) index. Other weak peaks below 5° suggest the hexagonal symmetry [22-23]. The modification with sulfate considerably reduces the intensities of the XRD peaks; however, the lattice parameters ($a_0$) are not affected by functionalization. So the structure of sulfated MCM-41 is still mesoporous and similar to that of MCM-41, but poorly crystallized.

![XRD patterns](image)

**Fig. 6.1** XRD patterns of MCM-41; sulfated MCM-41 (5% sulfate content) and sulfated MCM-41 (10% sulfate content)

6.2.2 Effect of different catalysts on ketalization of catechol

Investigation of effect of different catalysts for the ketalization of catechol with cyclohexanone is listed in Table 6.1. No reaction was observed over ZSM-5, SiO₂, Al₂O₃; HX was found to be slightly active, whereas NaX was also inactive.
From the Table 6.1, it is clear that the sulfated Cu(II)-MCM-41 (A) showed the highest catalytic activity for the reaction with the conversion over 98% within 1 h, while (B) and (D) [the similar catalysts with Ni(II) and Co(II)] were not so efficient with the conversion below 20% even after 4 h. Although, the Fe(III)-MCM-41 (C) gave a preferable result with the conversion of around 90%, it is having difficulties of product separation and catalyst instability. The observed results may be due to the acidity order of the catalyst as follows [21];

$$\text{Cu(III)} > \text{Fe(II)} > \text{Co(II)} > \text{Ni(II)}$$

Table 6.1: Effect of catalyst on ketalization of cyclohexanone with catechol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(II)-MCM-41 (A)</td>
<td>1.0</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Ni(II)-MCM-41 (B)</td>
<td>4.0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Fe(III)-MCM-41 (C)</td>
<td>1.0</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Co(II)-MCM-41 (D)</td>
<td>5.0</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Montmorillonite K-10</td>
<td>2.7</td>
<td>93[20]</td>
</tr>
<tr>
<td>6</td>
<td>HY-Zeolite</td>
<td>6.0</td>
<td>81[23]</td>
</tr>
<tr>
<td>7</td>
<td>Cu(II)-p-Toluenesulfonate</td>
<td>1.5</td>
<td>97[24]</td>
</tr>
</tbody>
</table>

Reaction conditions: weight of the catalyst = 0.10 g; mole ratio = 1:1.8 (Catechol: Cyclohexanone).

6.2.3 Influence of molar ratio

The influence of various mole ratios of the reactants (Catechol: Cyclohexanone) in the condensation reaction was studied over Cu(II)-MCM-41 with constant reaction period (2 h) under dean-stark conditions. Of the examined mole ratios of the range 1:1 to 1:2 (Catechol: Cyclohexanone), the 1,3-
benzodioxoles formation increases from 1:1 to 1:1.8 and then decreases. The results from the Fig 6.3 showed that conversion increased with addition of cyclohexanone due to effective collision of cyclohexanone with catechol. The conversion reached the peak when the molar ratio was 1:1.8 and decreased steeply beyond this. Product analysis showed a considerable amount of adipic acid leading to the conclusion that, oxidation of cyclohexanone predominates over the condensation at higher concentrations.

![Graph](image)

**Fig 6.3** Influence of molar ratio on the ketalization of catechol over Cu(II)-MCM-41

### 6.2.4 Influence of catalyst loading

The way in which the reactivity of sulfated-MCM-41 varies with cupric nitrate loading is shown in Fig. 6.4. Reactivity increases up to the cupric nitrate loading of 3.0 mmol g\(^{-1}\). Above this, the reactivity falls, as the support appears to be overloaded with the salt.
Fig 6.4 Influence of support on the ketalization of catechol over Cu(II)-MCM-41.

6.2.5 Reusability of the catalyst

Reusability of the catalyst was studied for the reaction of catechol with cyclohexanone as the model substrates. The reaction was carried out under optimized reaction conditions using Cu(II)-MCM-41 as the catalyst. After completion of the reaction, the reaction mixture was centrifuged for 10min, and the deposited catalyst was washed with acetone three times to confirm the complete removal of any residual material. The recovered catalysts were activated at 400 °C in the muffle furnace and used for further catalytic reaction cycle. The yield of the reaction decreased from 93-78 % (Fig.6.5) in the subsequent cycles. The results showed that the Cu(II)-MCM-41 could be reused at least four times without considerable lowering of the catalytic activity.
Fig 6.5 Reusability of the catalyst on the ketalization of catechol over Cu(II)-MCM-41. Reaction conditions: weight of the catalyst = 0.10g; mole ratio = 1:1.8 (Catechol: Cyclohexanone).

6.2.6 Catalytic synthesis of 2-substituted and 2,2-disubstituted 1,3-benzodioxoles

Since Cu(II)-MCM-41 is found to be an optimum catalyst, the condensation of catechol with various aldehydes and ketones were performed with this catalyst and the results are presented in Table 6.2. Sulfated MCM-41 worked better than an ordinary MCM-41 for the protection of catechol and this may be due to the structure that retains more acidic sites after treatment with 0.25N H₂SO₄. As we expected, Cu(II)-MCM-41 showed high activities for the reaction with the average conversion. For almost all the aliphatic acyclic ketone compounds (Entry 2-3), the yields were around 80% but decreased in the case of acetone. This might be due to the high miscibility of acetone with water, which made difficult to remove water from the reaction system (Entry 1). We have also investigated the condensation of
catechol with benzil and benzoin where the yields were very poor due to ring strains (entry 12 and 13).

**Table 6.2** Preparation of 1,3-benzodioxoles catalysed by Cu(II) impregnated sulfated MCM-41

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbonyl compound</th>
<th>Product</th>
<th>Time (h)</th>
<th>Conversion%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>1.5</td>
<td>27.0</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>2.0</td>
<td>82.4</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>5.5</td>
<td>89.7</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>1.0</td>
<td>98.1</td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>1.5</td>
<td>76.5</td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>0.5</td>
<td>88.2</td>
</tr>
<tr>
<td>7</td>
<td>O</td>
<td><img src="image" alt="Image" /></td>
<td>3.5</td>
<td>61.9</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td><img src="image" alt="Image" /></td>
<td>2.0</td>
<td>77.0</td>
</tr>
</tbody>
</table>
The reaction was acid catalyzed and the probable mechanism is shown below. It can be concluded from the mechanism that the determining factor for the reaction is the acidity, while our catalyst suffices that. Meanwhile, as the reaction is reversible, simultaneously removing the water from the reaction system using dean-stark conditions could improve the yield significantly.
Scheme 6.2 Plausible mechanism for the condensation of catechol and carbonyl compounds
6.3. Experimental

6.3.1 Synthesis of MCM-41

The original method of preparation of MCM-41 first proposed by Beck and co-workers has been adopted [10]. In a typical synthesis, 1.988 g of cetyl trimethyl ammonium bromide (CTAB, 98%, LOBA Chem.) was dissolved in 120 g of water at room temperature. After complete dissolution, 8 ml of aqueous NH₃ (32% in water, Merck) was added to the above solution. Then 10 ml of tetraethyl orthosilicate (TEOS, 99%, Merck) was added to the solution under vigorous stirring (300 rpm). The hydrolysis of TEOS takes place during the first 2 min at room temperature (the solution becomes milky and slurry forms) whereas the condensation of the meso-structured hybrid material is achieved after 1 h of reaction. The material was then filtered and allowed to dry under static air at 80 °C for 12 h. The mesoporous material was finally obtained by calcination of the hybrid structure at 550 °C for 5 h.

6.3.2 Synthesis of sulfated MCM-41

A series of sulfated MCM-41 samples was prepared by wet impregnation method. The sulfate ion was impregnated in the form of H₂SO₄. About 1 g of calcined sample (MCM-41) was treated with required amount of 0.25M H₂SO₄ (98%, 5 ml) at room temperature for 2 h and heated at 70 °C until complete dryness. The sample was dried at 110 °C for 10 h, in an oven and subsequently calcined at 550 °C for 5 h in a muffle furnace.

6.3.3 Synthesis of metal impregnated sulfated MCM-41

The mixture of metal nitrate (3 mmol), sulfated MCM-41 (1 g) and acetone (100 ml) were stirred at room temperature for 4 h. After filtration, the catalyst was activated at 400 °C for 2 h in a muffle furnace.
6.3.4 Preparation of 1,3-benzodioxoles

A mixture of carbonyl compound (1.8 mmol), catechol (1 mmol), 10 ml of toluene and the catalyst (100 mg) were mixed in a two necked round bottom flask equipped with thermometer, and a Dean-Stark apparatus was used to remove the water continuously from the reaction mixture. The mixture was refluxed with stirring for the specified periods. TLC was used to monitor the progress of the reaction. On completion, the catalyst was recycled by filtering and washing with acetone, then dried in a muffle furnace at 400 °C for about 6-8 h. The quantitative analysis of the reaction mixture was carried out on a temperature-programmed Younglin (GC- 6000 series) gas chromatograph. A 15m long capillary column, AT-wax (Alltech) and nitrogen as a carrier gas were used. $^1$H NMR spectra were recorded as DMSO-d$_6$ solutions on a Bruker Spectro Spin DRX-300 MHz using TMS as an internal standard.

2-(3-Nitrophenyl)benzo[d][1,3]dioxole

![Chemical structure of 2-(3-Nitrophenyl)benzo[d][1,3]dioxole]

Light yellow needles; Mp 88–89 °C, $\delta_H$ (300 MHz) 6.90 (4H, s.), 7.045 (1H, s), 7.64 (1H, t), 7.93 (1H, d), 8.31 (1H, dd) and 8.46 (1H, t); m/z 243 (M$^+$, 62%), 224 (5), 197 (11), 168 (1), 150 (5), 139 (4), 121 (100), 115 (14) and 104 (6).

2-Methyl-2-phenylbenzo[d][1,3]dioxole

![Chemical structure of 2-Methyl-2-phenylbenzo[d][1,3]dioxole]
Yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.61-7.58 (m, 2H), 7.38-7.32 (m, 3H), 6.80-6.76 (m, 4H), 1.98 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.3, 141.3, 129.0, 128.5, 125.1, 121.5, 116.7, 108.8, 27.2; GCMS m/z (% rel intensity) 212 (M+, 68%), 197 (100), 166 (2), 151 (3), 135 (12), 110 (67), 103 (69), 91 (4), 77 (27).

Fig 6.6 $^1$H-NMR spectra of 2-methyl-2-phenylbenzo[\textit{d}][1,3]dioxole

Fig 6.7 $^{13}$C-NMR spectra of 2-methyl-2-phenylbenzo[\textit{d}][1,3]dioxole
6.3.5 One pot synthesis of 2-methyl-5-nitro-2-phenylbenzo[d][1,3]dioxole:

A mixture of acetophenone (180mg, 1.5mmol), 10 mL toluene, catechol (110 mg, 1 mmol), and Cu(NO₃)₂ loaded sulfated MCM-41 (without activation) were mixed together in a three-necked round-bottom flask equipped with magnetic stirrer, thermometer, and a Dean-Stark apparatus used to remove the water continuously from the reaction mixture. The mixture was refluxed for the specified periods. The reaction process was monitored by GC analysis of the small aliquots withdrawn at regular intervals.

![Chemical structure](image)

**Fig 6.8** GC analysis for the synthesis of 2-methyl-5-nitro-2-phenylbenzo[d][1,3]dioxole using Cu(NO₃)₂ loaded sulfated MCM-41
Fig 6.9 GC analysis for the synthesis of 2-methyl 2-phenylbenzo[d][1,3]dioxole using Cu(II)-sulfated MCM-41 (after activation).

Fig 6.10 $^1$H-NMR spectra of 2-methyl-5-nitro-2-phenylbenzo[d][1,3]dioxole
Fig 6.11 $^{13}$C-NMR spectra of 2-methyl-5-nitro-2-phenylbenzo[\textit{d}][1,3]dioxole

Yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.84 (dd, 1H), 7.64 (d, 1H), 7.54-7.57 (m, 2H), 7.37-7.42 (m, 3H), 6.82 (d, 1H), 2.03 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.8, 147.9, 142.8, 139.7, 129.6, 128.6, 124.8, 120.4, 119.7, 107.6, 104.6, 21.2; GCMS $m/z$ (% relative intensity): 257 (M+, 20%), 242 (34), 196 (8), 180 (5), 134 (4), 103 (100), 91(3), 77 (25).
6.4. Conclusion

In this chapter, we have studied an alternative method for the preparation of a variety of 2-substituted and 2,2-disubstituted 1,3-benzodioxoles using Cu(II)-sulfated MCM-41 as catalyst. Aldehydes gave moderate yields while ketones gave good yields. Dicarbonyl compounds can selectively provide mono-benzodioxole compounds by using an excess of the ketone. Highly sterically hindered ketones and diaryl ketones fail to react in this reaction. In case of un-activated catalyst, nitration was also observed due to the generation of NO$_3^-$ and NO$^+$ ions. The present method has the additional advantages of mild conditions, easy set-up and work-up and non-corrosive, inexpensive, reusable and environmentally friendly catalysts.
6.5 Reference


