An Efficient Synthesis of 2-Benzoxepines from Morita–Baylis–Hillman Adducts Using Heterogeneous Recyclable Catalysts

Biswa Nath Das,* Anjoy Majhi, Joydeep Banerjee, Nikhil Chowdhury, Harish Holla, Kankipati Harakishore, and Upadhyula Suryanarayana Murty

Organic Chemistry Division–I, Indian Institute of Chemical Technology; Hyderabad–500 007, India.
Received November 5, 2005; accepted December 15, 2005

2-Benzoxepines belong to a class of medicinally important compounds. They exhibit antianaphylactic, oral hypotensive and antiulcer properties.2—4) 2-Benzoxepine moiety is present in many useful neuroleptic (pinoxepin),5,6) antidepressant (spiroxepin)7,8) and anti-inflammatory agents (isoxepac and oxepinac).7,9,10) The synthesis of 2-benzoxepines having different functionalities is thus necessary.

As a part of our program related to the discovery of novel bioactive compounds we recently required to prepare some 2-benzoxepines (as they are reputed for their bioactivity) and to study their antibacterial property. We connected the program with our on-going endeavor on Morita–Baylis–Hillman chemistry which has already been utilized11—14) by us for the synthesis of various bioactive molecules. We have observed that treatment of Morita–Baylis–Hillman adducts 

![Diagram](image-url)  

**Chart 1**

with HCHO in the presence of silica supported perchloric acid (HClO₄ · SiO₂) or Amberlyst-15 in CH₂Cl₂ under reflux for a short period of time (1.5—2.5 h). The catalyst can be recovered and recycled. The antibacterial properties of the new 2-benzoxepines were studied but no activity was found.

Key words 2-benzoxepine; Morita–Baylis–Hillman adduct; formaldehyde; silica supported perchloric acid; Amberlyst-15; antibacterial activity

Previously, only one method was developed15) for the conversion of 1 into 2 using concentrated H₂SO₄ which is not ecologically acceptable. The reagent may also cause charring of the reaction mixture. The yields of the products were reported to be in the range of 44—61%.

In recent year, economic and environmental concerns encourage the application of heterogeneous catalysts in organic transformations. These catalysts make the processes clean, safe, high-yielding and inexpensive. We have discovered that HClO₄ · SiO₂ and Amberlyst-15 are two efficient catalysts for conversion of the Morita–Baylis–Hillman adducts 1 into the corresponding 2-benzoxepines 2 by treatment with HCHO.

Initially we treated 1f (R¹=H, R²= Et) (1 mmol) with HCHO (1 mmol) in the presence of different solid acid catalysts (100 mg each) in CH₂Cl₂ under reflux for 2 h (Table 1). The yields of the products were reported to be in the range of 44—61%.

In recent year, economic and environmental concerns encourage the application of heterogeneous catalysts in organic transformations. These catalysts make the processes clean, safe, high-yielding and inexpensive. We have discovered that HClO₄ · SiO₂ and Amberlyst-15 are two efficient catalysts for conversion of the Morita–Baylis–Hillman adducts 1 into the corresponding 2-benzoxepines 2 by treatment with HCHO.}

Table 1. Treatment of 1f (R¹=R²=H, R=Et) with HCHO under Reflux for 2 h Using Heterogeneous Solid Acid Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>KSF clay</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>Mont K-10</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>HY-Zeolite</td>
<td>0</td>
</tr>
<tr>
<td>d</td>
<td>NaHSO₄ · SiO₂</td>
<td>22</td>
</tr>
<tr>
<td>e</td>
<td>Amberlyst-15</td>
<td>79</td>
</tr>
<tr>
<td>f</td>
<td>HClO₄ · SiO₂</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 2. Conversion of Baylis–Hillman Adducts 1 into 2-Benzoxepines 2 Using HClO₄ · SiO₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>1.5</td>
<td>82</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>1.5</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Et</td>
<td>Me</td>
<td>1.5</td>
<td>77</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>i-Pr</td>
<td>Me</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>e</td>
<td>Et</td>
<td>H</td>
<td>Me</td>
<td>1.5</td>
<td>73</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>1.5</td>
<td>80</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>1.5</td>
<td>68</td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>Et</td>
<td>Et</td>
<td>1.5</td>
<td>78</td>
</tr>
<tr>
<td>i</td>
<td>H</td>
<td>i-Pr</td>
<td>Et</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>j</td>
<td>Et</td>
<td>H</td>
<td>Et</td>
<td>1.5</td>
<td>76</td>
</tr>
</tbody>
</table>

a) The structures of the products were established from their spectral (IR, ¹H-, ¹³C-NMR, MS) and analytical data. Compounds 1a–d, f and g are known.31
(3—12%). The conversion of 1 into 2 was also tried with Yb(OTf)₃ at room temperature and under reflux for 2 h but no product could be observed. Previously several acid-catalyzed conversions were successfully carried out under mild conditions with Yb(OTf)₃ which is also a reusable catalyst. However, in the present case it was found to be unsuitable.

The mechanism of the present conversion involves a Prins-type reaction (for the formation of C–O bond) followed by a Friedel–Crafts reaction (for the formation of C–C bond) (Chart 2). The structures of the products were settled from their spectra (IR, ¹H-, ¹³C-NMR, MS) and analytical data.

The catalyst HClO₄·SiO₂ and Amberlyst-15 work under heterogeneous conditions. The first catalyst can easily be prepared from HClO₄ and silica gel while the second catalyst was used only in 1st run and then the recovered catalyst, after activation, was used for consecutive three times.

Using Fresh and Recovered Catalysts

The operational simplicity, high yields of the products and reusability of the catalysts are the advantages of the method. The prepared new compounds did not show antibacterial activity. However, the present method can be utilized for easy preparation of different 2-benzoazepines that can be utilized for their known activities and also to explore their new bio-activities.

Experimental

The spectra were recorded with the following instruments: IR: Perkin Elmer RX I FT-IR spectrophotometer, NMR: Varian Gemini 200 MHz spectrometer and EI-MS: VG micromass 7070 H (70 eV). Column chromatography was performed with silica gel (BDH, 60—120 mesh) and TLC with silica gel GF₃₄₉.

General Experimental Procedure for the Preparation of Benoxepines

To a solution of Morita–Baylis–Hillman adduct (1 mmol) in CH₂Cl₂ (5 ml) HClO₄·SiO₂ or Amberlyst-15 (100 mg) was added. The mixture was heated under reflux and the reaction was monitored by TLC. After completion the reaction mixture was diluted with EtOAc (10 ml) and filtered. The catalyst was recovered from the residue by washing with Et₂O (3 × 5 ml). The filtrate was concentrated. The residue was subjected to column chromatography over silica gel using 5% EtOAc in hexane as eluent to afford pure 2-benzoazepine.

The spectral and analytical data of the unknown compounds are given below.

1e: IR (KBr): v_max 1713, 1626, 1438, 1264 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃); δ 7.72 (1H, s), 7.25—7.19 (2H, m), 7.03 (1H, dd, J=8.0, 2.0 Hz), 4.63 (2H, s), 4.52 (2H, s), 3.84 (3H, s), 2.83 (2H, q, J=7.0 Hz), 1.25 (3H, t, J=7.0 Hz); ¹³C-NMR (50 MHz, CDCl₃); δ 168.2, 145.1, 140.8, 137.0, 131.4, 131.9, 129.5, 128.9, 126.1, 72.0, 70.0, 52.1, 26.9, 15.6, 14.2; EI-MS: m/z 232 (M⁺), 203, 174, 129, 115; Anal. Caled for C₁₅H₁₈O₃: C, 72.41; H, 7.27%; Found: C, 72.36; H, 6.82%.

1f: IR (KBr): v_max 1612, 1455, 1264 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃); δ 7.72 (1H, s), 7.32 (1H, d, J=8.0 Hz), 7.17 (1H, dd, J=8.0, 2.0 Hz), 6.92 (1H, d, J=2.0 Hz), 4.72 (2H, s), 4.63 (2H, s), 4.22 (2H, q, J=7.0 Hz), 2.61 (2H, q, J=7.0 Hz), 1.32 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.0 Hz); ¹³C-NMR (50 MHz, CDCl₃); δ 166.4, 145.8, 141.1, 138.5, 133.6, 131.6, 130.7, 127.3, 126.9, 74.2, 73.0, 60.8, 28.6, 15.2, 14.2; EI-MS: m/z 246 (M⁺), 203, 174, 129, 115; Anal. Caled for C₁₅H₁₈O₃: C, 73.17; H, 7.32%; Found: C, 73.28; H, 7.25%.

2e: IR (KBr): v_max 1713, 1626, 1438, 1264 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃); δ 7.62 (1H, s), 7.32 (1H, d, J=8.0 Hz), 7.09 (1H, dd, J=8.0, 2.0 Hz), 6.92 (1H, d, J=2.0 Hz), 4.72 (2H, s), 4.63 (2H, s), 4.22 (2H, q, J=7.0 Hz), 2.61 (2H, q, J=7.0 Hz), 1.32 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.0 Hz); ¹³C-NMR (50 MHz, CDCl₃); δ 166.6, 145.8, 141.1, 138.5, 133.6, 131.6, 130.7, 127.3, 126.9, 74.2, 73.0, 60.8, 28.6, 15.2, 14.2; EI-MS: m/z 246 (M⁺), 203, 174, 129, 115; Anal. Caled for C₁₅H₁₈O₃: C, 73.17; H, 7.32%; Found: C, 73.23; H, 7.27%.

2f: IR (KBr): v_max 1713, 1626, 1438, 1264 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃); δ 7.64 (1H, s), 7.32 (1H, d, J=8.0 Hz), 7.14 (1H, dd, J=8.0, 2.0 Hz), 6.98 (1H, d, J=2.0 Hz), 4.74 (2H, s), 4.63 (2H, s), 4.22 (2H, q, J=7.0 Hz), 2.89 (1H, m), 1.37 (3H, t, J=7.0 Hz), 1.25 (6H, d, J=7.0 Hz); EI-MS: m/z 260 (M⁺), 214, 187, 145, 117; Anal. Caled for C₁₅H₂₀O₃: C, 73.85; H, 7.69%; Found: C, 73.72; H, 7.73%.

3a: IR (KBr): v_max 1713, 1624, 1458, 1262 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃); δ 8.05 (1H, s), 7.25—7.12 (2H, m), 7.02 (1H, dd, J=8.0, 2.0 Hz), 4.61 (2H, s), 4.48 (2H, s), 4.28 (2H, q, J=7.0 Hz), 2.82 (2H, q, J=7.0 Hz), 1.39 (3H, t, J=7.0 Hz), 1.25 (3H, t, J=7.0 Hz); EI-MS: m/z 246 (M⁺), 216, 173, 145; Anal. Caled for C₁₅H₁₈O₃: C, 73.17; H, 7.32%; Found: C, 73.23; H, 7.27%.

Acknowledgement

The authors thank UGC and CSIR, New Delhi for financial assistance.

References and Notes


9) Ueno K., Kubo S., Tagawa H., Yoshioka T., Tsukada W., Tsubokawa