An Efficient Synthesis of 2-Benzoxepines from Morita–Baylis–Hillman Adducts Using Heterogeneous Recyclable Catalysts[1)]

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2-Benzoxepines have efficiently been synthesized from Morita–Baylis–Hillman adducts, alkyl 3-aryl-3-hydroxy-2-methylenepropanoates by treatment with HCHO catalyzed by silica supported perchloric acid ($HClO_4 \cdot SiO_2$) or Amberlyst-15 in CH_2Cl_2 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.

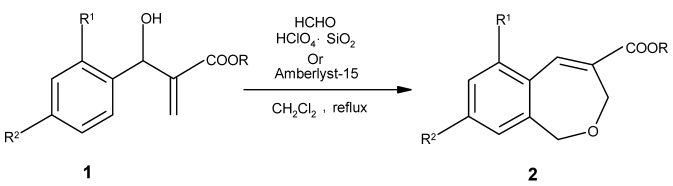
Key words 2-benzoxepine; Morita–Baylis–Hillman adduct; formaldehyde; silica supported perchloric acid; Amberlyst-15; antibacterial activity

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 utilized[11—14)] by us for the synthesis of various bioactive molecules. We have observed that treatment of Morita–Baylis–Hillman adducts **1** with HCHO in the presence of silica supported perchloric acid ($HClO_4 \cdot SiO_2$) or Amberlyst-15 in CH_2Cl_2 under reflux afforded the corresponding 2-benzoxepines **2** in good yields (Chart 1).

Previously, only one method was developed[15)] for the conversion of **1** into **2** using concentrated H_2SO_4 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 $HClO_4 \cdot SiO_2$ 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** ($R^1=R^2=H$, R=Et) (1 mmol) with HCHO (1 mmol) in the presence of different solid acid catalysts (100 mg each) in CH_2Cl_2 under reflux for 2 h (Table 1). $HClO_4 \cdot SiO_2$ and Amberlyst-15 were only found to be effective but $HClO_4 \cdot SiO_2$ was better and within 1.5 h it afforded an yield of 80% of the product. When the reaction was carried out with Amberlyst-15 at room temperature a conversion of only 48% was observed after 3 h and the yield was not increased even after overnight treatment. On the other hand, $HClO_4 \cdot SiO_2$ afforded no product at room temperature. To make a series of 2-benzoxepines (Table 2) $HClO_4 \cdot SiO_2$ was utilized for a time of 1.5—2 h under reflux to form the products with the yields of 66—82% while under the similar conditions the other catalyst Amberlyst-15 required somewhat more time (0.5 h) and the yields were also somewhat low



1
R = Me, Et
R^1 = H, Et
R^2 = H, Me, Et, *i*-Pr

2

Chart 1

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

Entry	Catalyst	Isolated yield (%)
a	KSF clay	0
b	Mont K-10	0
c	HY-Zeolite	0
d	$NaHSO_4 \cdot SiO_2$	22
e	Amberlyst-15	79
f	$HClO_4 \cdot SiO_2$	82

Table 2. Conversion of Baylis–Hillman Adducts **1** into 2-Benzoxepines **2** Using $HClO_4 \cdot SiO_2$[a)]

Entry	R^1	R^2	R	Time (h)	Isolated yield (%)
a	H	H	Me	1.5	82
b	H	Me	Me	1.5	75
c	H	Et	Me	1.5	77
d	H	*i*-Pr	Me	2	66
e	Et	H	Me	1.5	73
f	H	H	Et	1.5	80
g	H	Me	Et	1.5	68
h	H	Et	Et	1.5	78
i	H	*i*-Pr	Et	2	70
j	Et	H	Et	1.5	76

a) The structures of the products were established from their spectral (IR, ^{1}H-, ^{13}C-NMR, MS) and analytical data. Compounds **1a**—**d**, **f** and **g** are known.[5)]

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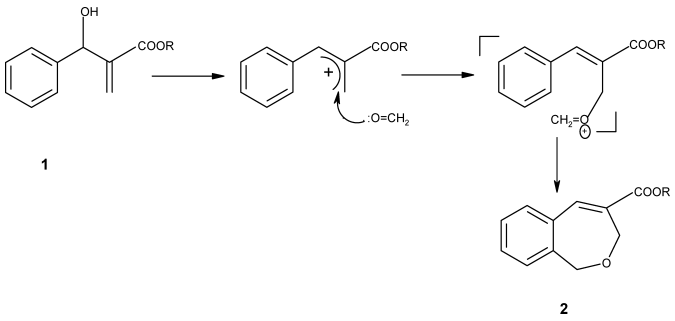

Chart 2

Table 3. Reaction of **1f** (R^1=R^2=H, R=Et) with HCHO under Reflux Using Fresh and Recovered Catalysts[a)]

Entry	Catalyst	Run	Time (h)	Isolated yield (%)
a	$HClO_4 \cdot SiO_2$	1	2	82
		2	2	78
		3	2.5	75
		4	2.5	70
b	Amberlyst-15	1	2	79
		2	2	76
		3	2.5	71
		4	2.5	66

a) Reaction of **1f** (1 mmol) with HCHO (1 mmol) was conducted with a catalyst (100 mg) under reflux in CH_2Cl_2. The recovered $HClO_4 \cdot SiO_2$ and Amberlyst-15 were activated by heating at 80 °C under vacuum for 2 and 5 h respectively. The fresh catalyst was used only in 1st run and then the recovered catalyst, after activation, was used for consecutive three times.

(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[16—18)] 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[15)] 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, ^{1}H-, ^{13}C-NMR, MS) and analytical data.

The catalyst $HClO_4 \cdot SiO_2$ and Amberlyst-15 work under heterogeneous conditions. The first catalyst can easily be prepared[19)] from $HClO_4$ and silica gel while the second catalyst is commercially available. They can recovered from the reaction mixture and reused. They were recycled for consecutive three times with a minimum variation of the yields of the products (Table 3).

The antibacterial activity of the new benzoxepines (**2e**, **h**—**j**) was studied[20)] against different gram-positive [*Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus*] and gram-negative [*Pseudomonas aeruginosa*, *Klebsiella aerogenes* and *Chromobacterium violaceum*] microorganisms using ciprofloxacin as standard. No compound was found to show the activity.

In conclusion, we developed a convenient and efficient method for direct conversion of Morita–Baylis–Hillman adducts into the corresponding 2-benzoxepines using heterogeneous 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-benzoxepines that can be utilized for their known activities and also to explore their new bio-properties.

Experimental

The spectra were recorded with the following instruments: IR: Perkin Elmer RX 1 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 GF_{254}.

General Experimental Procedure for the Preparation of Benzoxepines To a solution of Morita–Baylis–Hillman adduct (1 mmol) (prepared by reported method[21)]) and *para*-formaldehyde (1 mmol) in CH_2Cl_2 (5 ml) $HClO_4 \cdot SiO_2$ 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 Et_2O (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-benzoxepine.

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

2e: IR (KBr): ν_{max} 1713, 1626, 1438, 1264 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.01 (1H, s), 7.28—7.19 (2H, m), 7.08 (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); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 167.2, 145.1, 140.8, 137.0, 132.0, 131.9, 129.5, 128.9, 126.1, 72.0, 70.0, 52.1, 26.9, 15.6; EI-MS: *m*/*z* 232 ($M^{+\cdot}$), 203, 174, 129, 115; *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90%. Found: C, 72.36; H, 6.82%.

2h: IR (KBr): ν_{max} 1712, 1612, 1455, 1264 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): 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); ^{13}C-NMR (50 MHz, $CDCl_3$): 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 ($M^{+\cdot}$), 203, 174, 129, 115; *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32%. Found: C, 73.28; H, 7.25%.

2i: IR (KBr): ν_{max} 1702, 1631, 1463, 1259 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): 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 ($M^{+\cdot}$), 214, 187, 145, 117; *Anal.* Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69%. Found: C, 73.72; H, 7.73%.

2j: IR (KBr): ν_{max} 1712, 1624, 1458, 1262 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): 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 ($M^{+\cdot}$), 216, 173, 145; *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32%. Found: C, 73.23; H, 7.27%.

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