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A facile tandem construction of C–O and C–C bonds: a novel one-pot transformation of Baylis–Hillman adducts into 2-benzoxepines

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Abstract—A facile and one-pot synthesis of 2-benzoxepines, from Baylis–Hillman adducts that is, alkyl 3-aryl-3-hydroxy-2-methylenepropanoates, via treatment with HCHO in the presence of concd H_2SO_4, involving tandem construction of C–O and C–C bonds via Prins-type and Friedel–Crafts reactions, is described.

The 2-benzoxepine moiety is an important structural unit present in many biologically important molecules such as doxaminol (vasodilator and β-sympathomimetic agent),[1a,b] isoxepac (antiinflammatory agent),[1c–e] oxepinac (antiinflammatory, analgesic, antipyretic agent),[1d,f,g] pinoxepin (neuroleptic agent, tranquilliser used for treatment of schizophrenia),[1h,i] spiroxepin (antidepressant, spasmolytic agent)[1j,k] and natural products[1l–n] such as cassialactone, psorolactone, *seco*-furanoeremophilane. Also synthetic 2-benzoxepine derivatives are found to possess antianaphylactic, oral hypotensive and antiulcer activities.[1o–q] Due to their interesting and important biological properties, development of simple and convenient methodologies for the synthesis of 2-benzoxepine derivatives represents an attractive and interesting endeavour in synthetic organic chemistry and medicinal chemistry.[1d,n–q,2] In continuation of our interest in the synthesis of heterocyclic molecules using Baylis–Hillman chemistry,[3] we herein describe a facile, one-pot synthesis of 2-benzoxepine derivatives via the treatment of Baylis–Hillman adducts with HCHO, in the presence of concd H_2SO_4.

In recent years, the Baylis–Hillman reaction has attracted the attention of organic chemists because it is atom economical and provides a unique class of attractive densely functionalized molecules, which are of high synthetic potential.[3–5] During our ongoing research program on heterocyclic chemistry,[3] we required various 2-benzoxepine derivatives. Recently, we developed a simple and convenient methodology for the synthesis of 2-benzazepines from Baylis–Hillman alcohols via the tandem construction of C–N and C–C bonds involving simultaneous Ritter and Houben–Hoesch reactions.[3a] Based on the above methodology, we envisioned that Baylis–Hillman adducts could be transformed directly to 2-benzoxepine derivatives via the construction of a C–O bond followed by the simultaneous construction of a C–C bond. We also envisaged that the C–O bond could be constructed through a Prins-type reaction on Baylis–Hillman adducts and the C–C bond could be constructed simultaneously through a Friedel–Crafts reaction via a carbocation (oxonium ion), according to the retro-synthetic pathway as described in Scheme 1. Accordingly, we first selected methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**), as a substrate for performing Prins-type and Friedel–Crafts reactions with HCHO in the presence of concd H_2SO_4 under various conditions. The best results were obtained when the Baylis–Hillman adduct (**1a**) (2 mmol) was treated with HCHO (2 mmol) in CH_2Cl_2 (4 mL) in the presence of concd H_2SO_4 (2 mmol) at room temperature for 1 h, thus providing 4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (**2a**) in 60% isolated yield after the usual work-up followed by column chromatography (Eq. 1 and Table 1).[6]

This was indeed an encouraging result in the sense that this strategy constructs C–O and C–C bonds

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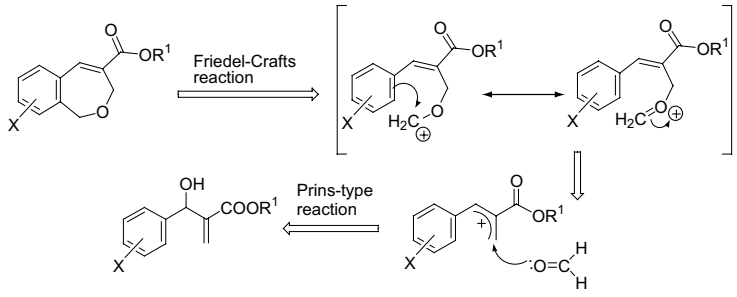
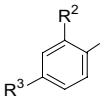
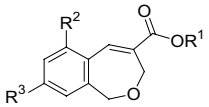


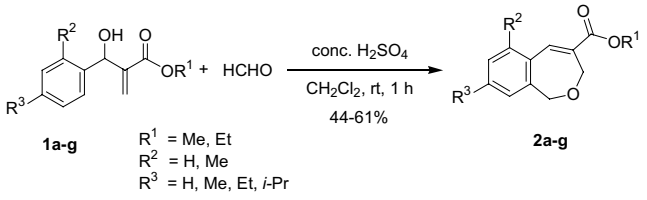
Scheme 1. Retrosynthetic pathway for the synthesis of 2-benzoxepine derivatives.

Table 1. Synthesis of 2-benzoxepine derivatives[a]

Alcohol		R^1	 Product[b,c]	Yield (%)[d]	Mp (°C)
1a	Phenyl	Me	**2a**[e]	60	46–48
1b	4-Methylphenyl	Me	**2b**[e]	51	58–60
1c	4-Ethylphenyl	Me	**2c**	56	Viscous liquid
1d	4-Isopropylphenyl	Me	**2d**	44	57–59
1e	2-Methylphenyl	Me	**2e**[e]	48	59–60
1f	Phenyl	Et	**2f**	61	36–39
1g	4-Methylphenyl	Et	**2g**	56	Viscous liquid
3a	Phenyl	Me	**2a**	59	46–48

[a] All reactions were carried out on a 2 mmol of Baylis–Hillman alcohols (**1a**–**g**) [or rearranged alcohol (**3a**)] with HCHO (2 mmol) in 4 mL of CH_2Cl_2 in the presence of concd H_2SO_4 (2 mmol) at room temperature for 1 h.
[b] The compounds **2a**,**b**,**d**–**f** were obtained as colourless solids and the compounds **2c** and **2g** were obtained as colourless viscous liquids.
[c] All the products gave satisfactory IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.
[d] Yields of the pure products obtained after column chromatography (silica gel, 4% EtOAc in hexanes).
[e] These compounds were also characterised by mass spectral analyses.

simultaneously leading to the synthesis of the 2-benzoxepine derivative **2a** from an easily accessible starting material. With a view to understanding the generality of this reaction we successfully subjected representative Baylis–Hillman adducts (**1b**–**g**), to this strategy to provide the desired 2-benzoxepine derivatives (**2b**–**g**) in moderate to good yields (Eq. 1 and Table 1).

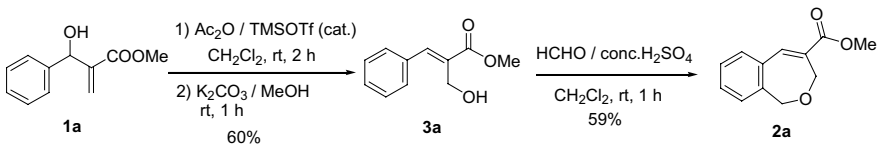


A facile one-pot synthesis of 2-benzoxepine derivatives.

(1)

With a view to understanding the reaction mechanism and also to increase the yield of the 2-benzoxepine derivatives, we examined the reaction of the rearranged alcohol, methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate (**3a**)[7] [obtained from methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) (Scheme 2)] with *para*-formaldehyde in the presence of H_2SO_4 following a similar procedure described for **2a**. Thus the reaction of **3a** (2 mmol) with HCHO (2 mmol) in CH_2Cl_2 (4 mL) in the presence of concd H_2SO_4 (2 mmol) at room temperature for 1 h, provided 4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (**2a**) in 59% isolated yield (Scheme 2 and Table 1).

In conclusion, we have successfully developed a simple one-pot methodology for the synthesis of 2-benzoxepine derivatives involving a tandem construction of C–O and C–C bonds through Prins-type and Friedel–Crafts



Scheme 2. Transformation of methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate (**3a**) into 2-benzoxepine derivative **2a**.

reactions via the treatment of Baylis–Hillman adducts with HCHO under the influence of H_2SO_4.

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6. *Typical experimental procedure*: *4-Methoxycarbonyl-1,3-dihydro-2-benzoxepine* (**2a**): To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) (2 mmol, 0.384 g) and *para*-formaldehyde (0.06 g) [HCHO, 2 mmol] in CH_2Cl_2 (4 mL), was added dropwise concd H_2SO_4 (2 mmol, 0.196 g) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was diluted with water (4 mL) and extracted with ether (3×10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to afford 4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (**2a**), as a colourless solid, in 60% (0.245 g) yield. Mp: 46–48 °C; IR (KBr): 1714, 1633 cm^{-1}; ^1H NMR: δ 3.81 (s, 3H), 4.69 (s, 2H), 4.80 (d, 2H, $J = 1.4$ Hz), 7.11–7.48 (m, 4H), 7.72 (t, 1H, $J = 1.4$ Hz); ^{13}C NMR: δ 51.82, 72.85, 73.88, 127.17, 127.88, 129.10, 132.45, 133.06, 133.35, 138.68, 141.13, 166.72. MS (m/z): 204 (M^+). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.45; H, 5.94.
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