Stereoselective Transformation of Baylis-Hillman Adducts into (3*E*)-3-(Alkoxymethyl)alk-3-en-2-ones[#]

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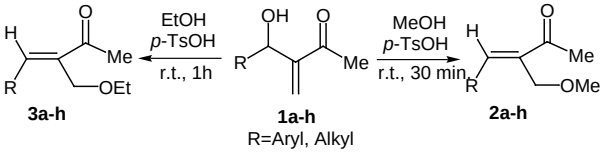
Abstract: The pure (3*E*)-3-(methoxymethyl)alk-3-en-2-ones and (3*E*)-3-(ethoxymethyl)alk-3-en-2-ones are formed in the acid induced reaction of 4-hydroxy-3-methylenealkan-2-ones with methanol and ethanol, respectively.

Key words: Baylis–Hillman reaction, stereoselectivity, (3*E*)-3-(alkoxymethyl)alk-3-en-2-ones, trisubstituted alkenes, alcoholysis



Scheme

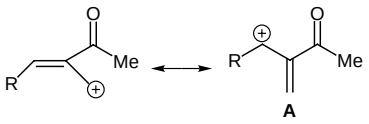
The trisubstituted alkene moiety is an integral part of a variety of natural products,[1-7] however, stereoselective construction of trisubstituted alkenes has been and continues to be one of the major problems in synthetic organic chemistry. Many methods for the synthesis of functionalized alkenes with stereo-defined trisubstituted double bonds have been devised.[8-13] In continuation of our work in the stereo-defined synthesis of trisubstituted alkenes,[14-18] we herein report a stereoselective synthesis of (3*E*)-3-(alkoxymethyl)alk-3-en-2-ones via the methanolysis and ethanolysis of 4-hydroxy-3-methylenealkan-2-ones under acidic conditions.

The Baylis–Hillman reaction involves the coupling of the α-position of activated alkenes with carbon electrophiles under the catalytic influence of a tertiary amine, particularly 1,4-diazabicyclo[2.2.2.]octane (DABCO), producing a synthetically useful class of multifunctional compounds which have been used in a variety of stereoselective transformations.[19-24] Recently we have successfully transformed 4-hydroxy-3-methylenealkan-2-ones into (3*Z*)-3-(bromomethyl)alk-3-en-2-ones and (3*Z*)-3-(chloromethyl)alk-3-en-2-ones.[25]

With a view to transform the Baylis–Hillman adducts **1**, obtained from methyl vinyl ketone, into (3*E*)-3-(methoxymethyl)alk-3-en-2-ones, we first carried out the reaction between 4-hydroxy-3-methylene-4-phenylbutan-2-one (**1a**) and methanol under various conditions. The best results were obtained when **1a** was treated with excess methanol in the presence of *p*-toluenesulfonic acid at room temperature to provide after usual workup and column chromatography, pure (3*E*)-3-(methoxymethyl)-4-phenylbut-3-en-2-one (**2a**) in 75% yield (Scheme). The (*E*)-configuration was assigned by the chemical shift value (^{1}H NMR) of the vinylic proton[26,27] in analogy with that of (3*Z*)-3-(halomethyl)alk-3-en-2-ones.[25] The (*E*)-configuration was further confirmed by a 2D NOESY experiment. The Baylis–Hillman adducts **1b-h** under similar reaction conditions provided (3*E*)-3-(methoxymethyl)alk-3-en-2-ones **2b-h** in good yields (Scheme, Table 1).

We have also treated the Baylis–Hillman adducts **1a-h** with excess ethanol, in the presence of *p*-toluenesulfonic acid to provide (3*E*)-3-(ethoxymethyl)alk-3-en-2-ones **3a-h** in 54–76% yields (Scheme, Table 1). It is worth mentioning here that alcoholysis of allyl alcohols was earlier carried out under the catalytic influence of $PdCl_2$[28] or $RuCl_3$.[29]

The (*E*)-selectivity in the alcoholysis of 4-hydroxy-3-methylenealkan-2-ones **1** can be possibly explained through the formation of the stable allylic carbocation **A** followed by nucleophilic attack by the alcohols leading to the thermodynamically more stable products **2** and **3**.



In conclusion our study describes a simple and convenient stereoselective synthesis of (3*E*)-3-(alkoxymethyl)alk-3-en-2-ones from easily available Baylis–Hillman adducts.

Table 1 Synthesis of (3*E*)-3-(Alkoxymethyl)alk-3-en-2-ones

Alcohol	R	Product	Yield (%)	Product	Yield (%)
1a	phenyl	**2a**	75	**3a**	72
1b	*p*-tolyl	**2b**	70	**3b**	73
1c	*p*-chlorophenyl	**2c**	82	**3c**	76
1d	*p*-isopropylphenyl	**2d**	73	**3d**	74
1e	*o*-chlorophenyl	**2e**	75	**3e**	71
1f	*o*-methoxyphenyl	**2f**	71	**3f**	72
1g	n-heptyl	**2g**	60	**3g**	56
1h	n-propyl	**2h**	55	**3h**	54

Table 2 Data for Products **2a–h**[a]

Product	R_f[b]	IR (Neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS, 200 MHz); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS, 50 MHz); δ
2a[c]	0.48	1668, 1624	2.46 (s, 3 H), 3.41 (s, 3 H), 4.22 (s, 2 H), 7.38–7.62 (m, 5 H), 7.72 (s, 1 H)	26.10, 58.32, 65.55, 128.60, 129.48, 129.85, 134.83, 137.45, 144.10, 199.04
2b	0.50	1668, 1620	2.38 (s, 3 H), 2.45 (s, 3 H), 3.41 (s, 3 H), 4.23 (s, 2 H), 7.22 (d, 2 H, *J* = 7.8), 7.42 (d, 2 H, *J* = 7.8), 7.69 (s, 1 H)	21.39, 26.05, 58.29, 65.57, 129.40, 130.02, 132.03, 136.71, 139.92, 144.42, 199.08
2c	0.46	1670, 1624	2.45 (s, 3 H), 3.40 (s, 3 H), 4.19 (s, 2 H), 7.39 (d, 2 H, *J* = 8.4), 7.48 (d, 2 H, *J* = 8.4), 7.64 (s, 1 H)	26.03, 58.32, 65.36, 128.84, 131.16, 133.27, 135.60, 137.83, 142.57, 198.65
2d	0.53	1668, 1620	1.27 (d, 6 H, *J* = 6.8), 2.46 (s, 3 H), 2.93 (sept. 1 H, *J* = 6.8), 3.45 (s, 3 H), 4.25 (s, 2 H), 7.29 (d, 2 H, *J* = 8.0), 7.48 (d, 2 H, *J* = 8.0), 7.71(s, 1 H)	23.83, 26.11, 34.10, 58.34, 65.64, 126.83, 130.22, 132.44, 136.78, 144.43, 150.84, 199.12
2e	0.54	1670, 1620	2.49 (s, 3 H), 3.37 (s, 3 H), 4.12 (s, 2 H), 7.24–7.50 (m, 3 H), 7.55–7.68 (m, 1 H), 7.86 (s, 1 H)	26.29, 58.51, 65.78, 126.89, 129.56, 130.54, 131.04, 133.40, 134.35, 138.74, 140.50, 198.87
2f	0.46	1666, 1624	2.47 (s, 3 H), 3.40 (s, 3 H), 3.87 (s, 3 H), 4.17 (s, 2 H), 6.85–7.09 (m, 2 H), 7.30–7.45 (m, 1 H), 7.60 (m, 1 H), 7.98 (s, 1 H)	25.96, 55.32, 58.15, 65.74, 110.20, 120.39, 123.68, 130.54, 131.05, 136.75, 139.95, 157.56, 198.99
2g	0.54	1672, 1637	0.87 (t, 3 H, *J* = 7.0), 1.20-1.61 (m, 10 H), 2.25–2.48 (m, 5 H), 3.32 (s, 3 H), 4.16 (s, 2 H), 6.84 (t, 1 H, *J* = 7.8)	14.03, 22.62, 25.76, 28.87, 29.04, 29.36, 31.73, 58.24, 64.83, 138.05, 148.38, 198.65
2h	0.52	1675, 1630	0.91 (t, 3 H, *J* = 7.6), 1.46 (m, 2 H), 2.15–2.40 (m, 5 H), 3.25 (s, 3 H), 4.11 (s, 2 H), 6.78 (t, 1 H, *J* = 7.2)	13.84, 22.11, 25.76, 30.94, 58.22, 64.79, 138.20, 148.10, 198.66

[a] Satisfactory elemental analysis was obtained for all compounds **2a-h** C ± 0.46%; H ± 0.46%.
[b] Eluent = 10% EtOAc in hexanes**.**
[c] MS (*m/z*): 190 (M^+).

IR spectra were recorded on JASCO-FT-IR model 5300 spectrometer using samples as neat liquids. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ on Bruker-AC-200 spectrometer using TMS as internal standard. Elemental analyses were recorded on Perkin–Elmer 240C-CHN analyzer. Mass spectra were recorded on micromass VG 7070H instrument. All the required Baylis–Hillman adducts **1** were prepared by the reaction of the corresponding aldehydes with methyl vinyl ketone in presence of a catalytic amount of DABCO according to the literature procedure.[30,31]

(3E)-3-(Alkoxymethyl)alk-3-en-2-ones 2(a-h), 3(a-h); General Procedure

To a stirred solution of the Baylis–Hillman adduct (1 mmol) in dry MeOH (2 mL) or EtOH (2 mL) was added *p*-toluenesulfonic acid (p-TsOH.H_2O) (100 mg) at r.t. After 0.5 h (in the case of MeOH) or 1 h (in the case of EtOH), the excess solvent (MeOH or EtOH) was removed under reduced pressure and the reaction mixture was diluted with Et_2O (10 mL) and washed successively with sat. K_2CO_3 (5 mL) and H_2O (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel, 2% EtOAc in hexanes) to afford the pure (3*E*)-3-(alkoxymethyl)alk-3-en-2-ones as colorless oils. The isolated yields of the products **2** and **3** are mentioned in Table 1. The spectral data of the products **2** and **3** (along with the elemental analyses and R_f values) are given in Tables 2 and 3 respectively.

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Table 3 Data for Products **3a–h**[a]

Product	R_f[b]	IR (Neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS, 200 MHz); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS, 50 MHz); δ
3a[c]	0.57	1668, 1624	1.26 (t, 3 H, *J* = 7.0), 2.47 (s, 3 H), 3.61 (q, 2 H, *J* = 7.0), 4.27 (s, 2 H), 7.30–7.62 (m, 5 H), 7.72 (s, 1 H)	15.18, 26.09, 63.52, 66.03, 128.46, 129.32, 129.80, 134.82, 137.51, 143.74, 198.95
3b	0.60	1688, 1621	1.25 (t, 3 H, *J* = 6.8), 2.39 (s, 3 H), 2.46 (s, 3 H), 3.58 (q, 2 H, *J* = 6.8), 4.28 (s, 2 H), 7.23 (d, 2 H, *J* = 8.0), 7.46 (d, 2 H, *J* = 8.0), 7.69 (s, 1 H)	15.32, 21.43, 26.17, 63.64, 66.11, 129.37, 130.08, 132.11, 136.86, 139.86, 144.25, 199.16
3c	0.51	1670, 1626	1.24 (t, 3 H, *J* = 7.0), 2.46 (s, 3 H), 3.55 (q, 2 H, *J* = 7.0), 4.23 (s, 2 H), 7.38 (d, 2 H, *J* = 8.4), 7.50 (d, 2 H, *J* = 8.4), 7.64 (s, 1 H)	15.15, 26.05, 63.44, 66.12, 128.75, 131.17, 133.40, 135.48, 138.12, 142.07, 198.61
3d	0.62	1668, 1622	1.28 (m, 9 H), 2.49 (s, 3 H), 2.97 (sept. 1 H, *J* = 6.8), 3.63 (q, 2 H, *J* = 6.9), 4.32 (s, 2 H), 7.31 (d, 2 H, *J* = 8.2), 7.54 (d, 2 H, *J* = 8.2), 7.73 (s, 1 H)	15.24, 23.71, 26.04, 33.94, 63.51, 65.97, 126.63, 130.12, 132.33, 136.62, 144.27, 150.60, 199.01
3e	0.58	1688, 1622	1.22 (t, 3 H, *J* = 7.2), 2.48 (s, 3 H), 3.52 (q, 2 H, *J* = 7.2), 4.17 (s, 2 H), 7.25–7.45 (m, 3 H), 7.60–7.71 (m, 1 H), 7.83 (s, 1 H)	15.11, 26.18, 63.64, 66.10, 126.67, 129.35, 130.33, 130.92,133.29, 134.15, 138.73, 139.95, 198.61
3f	0.51	1670, 1622	1.23 (t, 3 H, *J* = 6.8), 2.47 (s, 3 H), 3.59 (q, 2 H, *J* = 6.8), 3.86 (s, 3 H), 4.22 (s, 2 H), 6.88–7.09 (m, 2 H), 7.30–7.45 (m, 1 H), 7.64 (m, 1 H), 7.96 (s, 1 H)	15.21, 26.15, 55.43, 63.91, 66.01, 110.31, 120.44, 123.93, 130.73, 131.03, 137.11, 139.68, 157.69, 199.11
3g	0.66	1672, 1620	0.88 (t, 3 H, *J* = 6.8), 1.17 (t, 3 H, *J* = 7.0), 1.20–1.55 (m, 10 H), 2.25–2.44 (m, 5 H), 3.47 (q, 2 H, *J* = 7.0), 4.19 (s, 2 H), 6.81 (t, 1 H, *J* = 7.6)	13.98, 15.16, 22.56, 25.75, 28.81, 29.00, 29.33, 31.68, 62.78, 65.90, 138.23, 148.27, 198.69
3h	0.60	1672, 1620	0.97 (t, 3 H, *J* = 7.2), 1.19 (t, 3 H, *J* = 7.0), 1.51 (m, 2 H), 2.30–2.45 (m, 5 H), 3.49 (q, 2 H, *J* = 7.0), 4.21 (s, 2 H), 6.84 (t, 1 H, *J* = 7.6)	13.86, 15.19, 22.11, 25.80, 30.96, 62.83, 65.93, 138.46, 147.94, 198.71

[a] Satisfactory elemental analysis was obtained for **3a–g** C ± 0.41%; H ± 0.48% and for **3h** C +0.34%; H –0.56%).
[b] Eluent = 10% EtOAc in hexanes.
[c] MS (*m/z*): 204 (M^+).

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