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Reductive dehydroxylation of Baylis–Hillman adducts with low-valent titanium reagent: syntheses of stereoselective trisubstituted alkenes

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Abstract—The Baylis–Hillman adducts prepared from aromatic aldehydes and methyl acrylate underwent smooth dehydroxylation with concomitant olefin isomerisation with low-valent titanium reagent to provide the trisubstituted alkenes with high (*E*)-selectivity. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

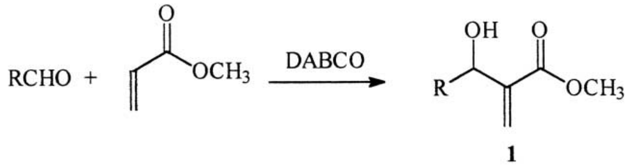
Low-valent titanium (LVT) reagents are rich sources of electrons and highly oxophilic in nature. These attributes of LVT reagents have been extensively used in organic synthesis ranging from the preparation of simple symmetrical alkenes from carbonyl compounds[1] to the strategic construction of an eight membered ring of the anticancer drug ®taxol.[2] Beside carbon–carbon bond formation, LVT reagents were also successfully used for carbon–heteroatom bond cleavage reactions (by SET mechanism) in our laboratory. This has led to the development of new approaches for the reductive deprotection of various propargyl/allyl/benzyl ethers and amines.[3]

Herein, we report a LVT mediated protocol for reductive dehydroxylation of Baylis–Hillman (B–H) adducts with concomitant isomerisation leading to the stereoselective formation of trisubstituted alkenes (Schemes 1 and 2).

2. Results and discussion

Stereoselective construction of the trisubstituted alkene moiety is an important organic transformation especially in the syntheses of various terpenoids and insect pheromones.[4] The tertiary amine catalysed coupling of an activated vinyl system with an electrophile (usually an aldehyde) is commonly termed as Baylis–Hillman (B–H) reaction which is operationally simple and often high yielding.[5] The B–H adducts are synthetically useful intermediates due to the presence of three functionalities, viz. the allylic hydroxyl group, the double bond and the olefin activating group. Dehydroxylation of allylic alcohols to corresponding 1,5-dienes by LVT is known in the literature.[6] We envisioned that LVT mediated reductive dehydroxylation of the allylic alcohol in the B–H adduct (**1**) could lead to the formation of a trisubstituted alkene.

With this, we synthesised[5a] **1a** as the model substrate and



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a: R = C_6H_5 (93 %)
b: R = 2-$OMeC_6H_4$ (92 %)
c: R = 4-$OMeC_6H_4$ (90 %)
d: R = 4-ClC_6H_4 (95 %)
e: R = 3,4-(-CH_2-O-)C_6H_3 (87 %)
f: R = 2-BrC_6H_4 (90 %)
g: R = 2- furfuryl (83 %)
h: R = $CH_3(CH_2)_9$ (65 %)

Scheme 1. The Baylis–Hillman reaction (% yield).

Keywords: Baylis–Hillman; low-valent titanium; dehydroxylation; trisubstituted alkene.

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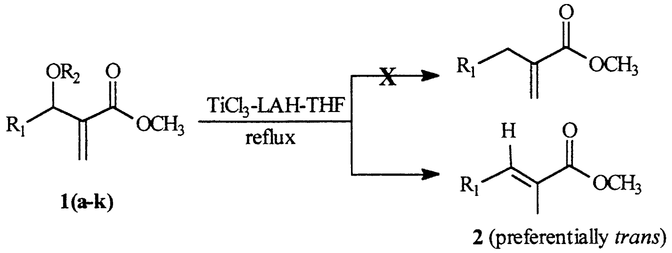


i: $R_1 = C_6H_5$; $R_2 = Ac$

j: $R_1 = 2\text{-}OMeC_6H_4$; $R_2 = Ac$

k: $R_1 = 4\text{-}OMeC_6H_4$; $R_2 = Ac$

Scheme 2.

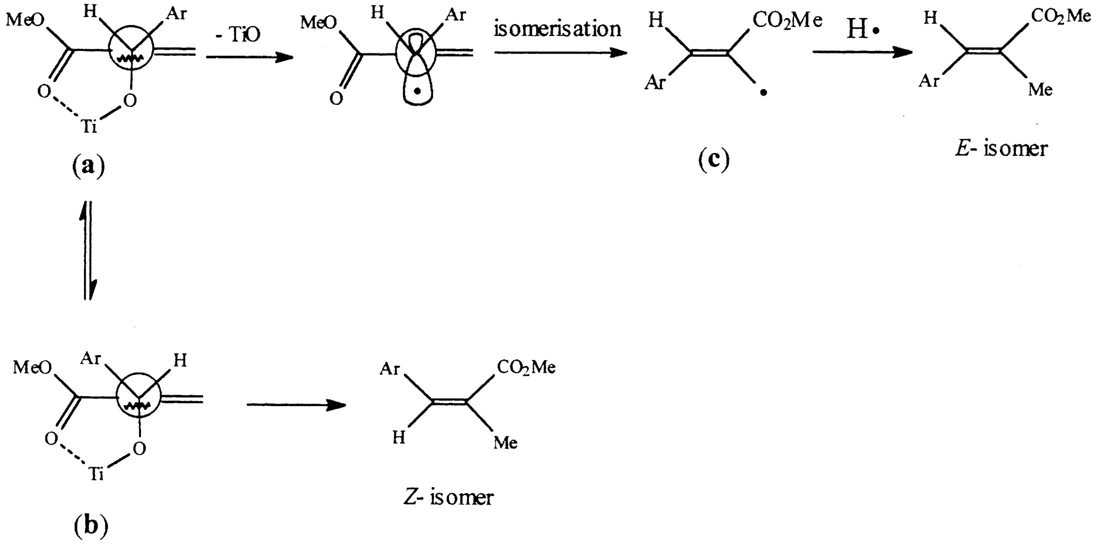
attempted its LVT mediated dehydroxylation. To our satisfaction, exposure of **1a** to the LVT reagent ($TiCl_3$–LAH–THF) under reflux (1 h) yielded the corresponding trisubstituted alkenes **2a** albeit in modest yield (Table 1, entry 1). Besides being regioselective, the reaction proceeded with appreciable stereoselectivity, providing (*E*)-olefin as the major isomer (*E*:*Z*=88:12). Formation of **2a** suggests reductive dehydroxylation followed by isomerisation of the allyl radical to form the thermodynamically more stable alkene. Tentatively, the *E*-stereoselectivity in the product may be explained by invoking a model in which the transition state **b** is less preferred over **a** (which leads to the formation of *E*-alkene) as **b** involves larger steric crowding between aryl and carbomethoxy function (Scheme 3). The preferential formation of *E*-alkenes further suggests that the rate of H-capture of the radical **c** is faster than the alkene isomerisation. A similar type of isomerisation has also been observed earlier during the Friedel–Crafts reaction of B–H adducts with alcohols/phenols.[7]

Table 1. Reductive dehydroxylation of allylic alcohol of Baylis–Hillman adduct **1a** to trisubstituted alkene **2a** with LVT: Influence of reducing agents and solvents

Entry	Substrate	Reaction conditions	Product (% yield)[a]	*E*:*Z*[b]
1	**1a**	$TiCl_3$–LAH–THF (reflux, 1 h)	**2a** (46%)	88:12
2	**1a**	$TiCl_3$–LAH–DME (reflux, 22 h)	**2a** (35%)	92:8
3	**1a**	$TiCl_3$–LAH–NEt_3-THF (reflux, 1.5 h)	**2a** (47%)	86:14
4	**1a**	$TiCl_3$–Mg–THF (reflux, 5 h)	**2a** (40%)	92:8
5	**1a**	$TiCl_3$–Li–THF (reflux, 4 h)	**2a** (35%)	68:32
6	**1a**	$TiCl_3$–LAH–THF (25°C, 6 h)	**2a** (10%)	86:14

[a] After column chromatography.

[b] The ratio of *E* and *Z*-isomers was determined by GC and the ^1H NMR shift of the methyl protons CH_3–C=CH; the methyl protons of the *trans* isomer were always at lower field than those of the *cis* isomers.[9]



Scheme 3.

Table 2. Reductive dehydroxylation of allylic alcohol of Baylis–Hillman adducts to stereoselective trisubstituted alkenes with $TiCl_3$–LAH–THF

Entry	Substrate	Reaction conditions (time)	Product (% yield)[a]	*E*:*Z*[b]
1	**1b**	reflux (22 h)	**2b** (38)	88:12
2	**1c**	reflux (4 h)	**2c** (46)	87:13
3	**1d**	reflux (16 h)	**2d** (48)	82:18
4	**1e**	reflux (20 h)	**2e** (41)	92:8
5	**1f**	reflux (22 h)	**2f** (41)	92:8
6	**1g**	reflux (2 h)	**2g** (50)	96:4
7	**1h**	reflux (4.5 h)	intractable mixture	–
8	**1i**	reflux (1 h)	**2a** (65)	88:12
9	**1j**	reflux (22 h)	**2b** (50)	92:8
10	**1k**	reflux (4 h)	**2c** (55)	83:17

[a] After column chromatography.

[b] The ratio of *E* and *Z*-isomers was determined by GC and the ^{1}H NMR shift of the methyl protons CH_3–C=CH; the methyl protons of the *trans* isomer were always at lower field than those of the *cis* isomers.[9]

The yield and stereoselectivity of LVT induced reactions are known to be considerably influenced by its mode of generation, viz. the source of the reducing metal, solvent, ligand, additives etc.[8] In view of the modest yield of the reaction, other LVT reagents were also explored and the results are summarised in Table 1.

It is evident from the result that the LVT reagent prepared from $TiCl_3$–LAH–THF was the best choice for the designated transformation and was chosen for all subsequent studies.

In order to see the generality of this reaction, a variety of B–H adducts were prepared and used as the substrates. Thus, the B–H adducts prepared from the aromatic and heteroaromatic aldehydes **1b**–**g** underwent smooth deoxygenation with the LVT reagent. In all the cases, the corresponding trisubstituted alkenes **2b**–**g** were formed with a high degree of (*E*)-selectivity (Table 2, entries 1–6). However, deoxygenation reaction of the aliphatic aldehyde derived B–H adduct **1h** yielded an intractable mixture of products (entry 7) which could not be analysed. When the dehydroxylation was carried out with the acetates of the B–H adducts (**1i**–**k**) marginal improvement in the yields of the trisubstituted alkenes (**2a**–**c**) was observed (Table 2, entries 8–10).

3. Conclusion

The LVT mediated transformation of the B–H adducts (prepared from aromatic aldehyde and methyl acrylate in high yields) furnished the *E*-selective α-methylcinnamates. The reaction proceeded via dehydroxylation and concomitant olefin isomerisation. The yields of α-methylcinnamates are marginally low (38–65%) as compared to that obtained by the conventional methods (50–70%).[9] However, the stereoselectivity in the product obtained by the present method is superior to that obtained by other procedures.

4. Experimental

The FT–IR spectra were scanned with a Nicolet spectrophotometer (model 410). The ^{1}H NMR were recorded with a Bruker AC 200 (200 MHz) spectrometer. All reactions were carried out under argon atmosphere. $TiCl_3$ was obtained from Aldrich Chemical Co., USA. THF was distilled freshly from sodium-benzophenone ketyl prior to use. The Baylis–Hillman adducts and their acetates were prepared according to the literature procedure.[5b]

4.1. Typical procedure for the dehydroxylation: synthesis of methyl 2-methyl-3-phenyl-2-propenoate (2a)

To a slurry of $TiCl_3$ (617 mg, 4 mmol) in dry THF (25 mL) at 0°C, LAH (76 mg, 2 mmol) was added cautiously in portions. The mixture was refluxed for 0.5 h at 65°C. The LVT reagent thus prepared, was cooled to ambient temperature (25°C) and a solution of the B–H adduct **1a** (192 mg, 1 mmol) in THF (2 mL) was added to it. The reaction was complete after refluxing for 1 h (cf. tlc). The black mixture was diluted with hexane, passed through Celite and washed with ether. The collected extract was dried (Na_2SO_4), the solvent was evaporated in vacuo and the crude product purified by preparative tlc (5% EtOAc/hexane) to yield **2a**[10a] (81 mg, 46%), a thick oil, R_f (5% EtOAc/hexane) 0.77; ν_{max} (liquid film) 1713, 1634, 1447, 1257 cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.1 (d, 0.36 H, *J* 1.4 Hz, C=C(*CH₃*) for *Z*-isomer), 2.13 (d, 2.64 H, *J* 1.3 Hz, C=C(CH_3) for *E*-isomer), 3.65 (s, 0.36 H, CO_2CH_3 for *Z*-isomer), 3.83 (s, 2.64 H, CO_2CH_3 for *E*-isomer), 7.25–7.40 (m, 5.12 H, Ar*H* and (*Z*)-Ar*CH*=), 7.71 (d, 0.88 H, *J* 1.28 Hz, (*E*)-Ar*CH*=); *m/z* (EI) 176 (15, M$^+$), 145 (8), 133 (9), 115 (100), 91 (50), 77 (8), 51 (4.5).

The following compounds were prepared in a similar way.

4.2. Methyl 3-(2-methoxyphenyl)-2-methyl-2-propenoate (2b)

(78 mg, 38%), a thick oil, [Found: C, 69.98; H, 6.92. $C_{12}H_{14}O_3$ requires C, 69.90; H, 6.79 %]; R_f (5% EtOAc/hexane) 0.74; ν_{max} (liquid film) 1704, 1605, 1435 cm^{-1}; δ_H (200 MHz $CDCl_3$) 2.06 (d, 0.36 H, *J* 1.4 Hz, C=C(CH_3) for *Z*-isomer), 2.12 (d, 2.64 H, *J* 1.3 Hz, C=C(CH_3) for *E*-isomer), 3.6 (s, 0.36 H, Ar–OCH_3 for *Z*-isomer), 3.75 (s, 0.36 H, CO_2CH_3 for *Z*-isomer), 3.79 (s, 2.64 H, Ar–OCH_3 for *E*-isomer), 3.85 (s, 2.64 H, CO_2CH_3 for *E*-isomer), 6.88–7.36 (m, 4.12 H, Ar*H* and (*Z*)–Ar*CH*=), 7.84 (s, 0.88 H, (*E*)-Ar*CH*=); *m/z* (EI) 206 (18, M$^+$), 175 (65), 146 (20), 131 (100), 115 (32), 91 (69), 77 (9).

4.3. Methyl 3-(4-methoxyphenyl)-2-methyl-2-propenoate (2c)[10b]

(94 mg, 46%), a thick oil, R_f (5% EtOAc/hexane) 0.75; ν_{max} (liquid film) 1704, 1605, 1435 cm^{-1}; δ_H (200 MHz CDCl$_3$) 2.06 (d, 0.39 H, *J* 1.4 Hz, C=C(CH_3) for *Z*-isomer), 2.13 (d, 2.61 H, *J* 1.3 Hz, C=C(CH_3) for *E*-isomer), 3.6 (s, 0.39 H, ArOCH_3 for *Z*-isomer), 3.7 (s, 0.39 H, CO$_2$$CH_3$ for *Z*-isomer), 3.79 (s, 2.61 H, ArOCH_3 for *E*-isomer), 3.81 (s, 2.61 H, CO$_2$$CH_3$ for *E*-isomer), 6.89–7.39 (m, 4.13 H, Ar*H*+(*Z*)–ArC*H*=), 7.68 (s, 0.87 H, (*E*)-ArC*H*=); *m/z* (EI) 206 (84, M$^+$), 175 (40), 146 (100), 131 (70), 115 (75), 91 (93), 77 (10).

4.4. Methyl 3-(4-chlorophenyl)-2-methyl-2-propenoate (2d)

(100 mg, 48%), a thick oil, [Found: C, 62.95; H, 5.30. $C_{11}H_{11}ClO_2$ requires C, 62.85; H, 5.22%]; R_f (5% EtOAc/hexane) 0.73; ν_{max} (liquid film) 1713, 1650, 1436 cm^{-1}; δ_H (200 MHz CDCl$_3$) 2.08 (d, 0.54 H, *J* 1.2 Hz, C=C(CH_3) for *Z*-isomer), 2.09 (d, 2.46 H, *J* 1.2 Hz, C=C(CH_3) for *E*-isomer), 3.72 (s, 0.54H, CO$_2$$CH_3$ for *Z*-isomer), 3.78 (s, 2.46 H, CO$_2$$CH_3$ for *E*-isomer), 7.14–7.38 (m, 4.18 H, Ar*H* and (*Z*)-ArC*H*=), 7.62 (s, 0.82 H, (*E*)-ArC*H*=); *m/z* (EI) 210 (27, M$^+$), 150 (53), 115 (100), 91 (57), 77 (68).

4.5. Methyl 3-(3,4-methylenedioxyphenyl)-2-methyl-2-propenoate (2e)

(90 mg, 41%), a thick oil, [Found: C, 65.53; H, 5.39. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.45%]; R_f (5% EtOAc–hexane) 0.69; ν_{max} (liquid film) 1704, 1630, 1435 cm^{-1}; δ_H (200 MHz CDCl$_3$) 2.06 (d, 0.24 H, *J* 1.4 Hz, C=C(CH_3) for *Z*-isomer), 2.12 (d, 2.76 H, *J* 1.3 Hz, C=C(CH_3) for *E*-isomer), 3.7 (s, 0.24 H, CO$_2$$CH_3$ for *Z*-isomer), 3.8 (s, 2.76 H, CO$_2$$CH_3$ for *E*-isomer), 5.99 (s, 2 H, –OCH_2O–), 6.85–6.93 (m, 3.08 H, Ar*H* and (*Z*)-ArC*H*=), 7.26 (s, 0.92 H, (*E*)-ArC*H*=); *m/z* (EI) 220 (23, M$^+$), 160 (42), 131 (28), 103 (100), 91 (10), 77 (10), 58 (4).

4.6. Methyl 3-(2-bromophenyl)-2-methyl-2-propenoate (2f)[10b]

(105 mg, 41%), a thick oil, R_f (5% EtOAc/hexane) 0.75; ν_{max} (liquid film) 1712, 1634, 1436 cm^{-1}; δ_H (200 MHz CDCl$_3$) 1.67 (d, 0.24 H, *J* 1.3 Hz, C=C(CH_3) for *Z*-isomer), 1.97 (d, 2.76 H, *J* 1.22 Hz, C=C(CH_3) for *E*-isomer), 3.77 (s, 0.24 H, CO$_2$$CH_3$ for *Z*-isomer), 3.83 (s, 2.76 H, CO$_2$$CH_3$ for *E*-isomer), 7.22–7.59 (m, 4.08 H, Ar*H* and (*Z*)-ArC*H*=), 7.69 (s, 0.92 H, (*E*)-ArC*H*=); *m/z* (EI) 255 (15, M$^+$), 221 (10), 174 (12), 162 (10), 115 (100), 91 (20), 77 (10), 59 (5).

4.7. Methyl 3-(2-furfuryl)-2-methyl-2-propenoate (2g)[10c]

(83 mg, 50%), a thick oil, R_f (5% EtOAc/hexane) 0.77; ν_{max} (liquid film) 1724, 1436, 1215 cm^{-1}; δ_H (200 MHz CDCl$_3$) 2.1 (d, 0.12 H, *J* 1.4 Hz, C=C(CH_3) for *Z*-isomer), 2.26 (d, 2.88 H, *J* 1.6 Hz, C=C(CH_3) for *E*-isomer), 3.80 (s, 0.12 H, CO$_2$$CH_3$ for *Z*-isomer), 3.82 (s, 2.88 H, CO$_2$$CH_3$ for *E*-isomer), 6.52–6.54 (m, 1 H), 6.65 (d, 1 H, *J* 3.4 Hz), 7.44 (d, 1 H, *J* 1.2 Hz), 7.57 (d, 0.96 H, *J* 1.6 Hz, (*E*)-furfuryl–C*H*=); *m/z* (EI) 166 (100, M$^+$), 151 (10), 135 (55), 106 (62), 95 (12), 79 (67), 77 (95), 51 (48).

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