Applications of the Baylis–Hillman Reaction 2: a Simple Stereoselective Synthesis of (*E*)- and (*Z*)-Trisubstituted Alkenes

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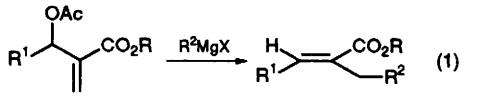
Reaction of Grignard reagents with methyl 3-acetoxy-2-methylenealkanoates produces (2*E*)-2-substituted alk-2-enoates, whereas a similar reaction with 3-acetoxy-2-methylenealkanenitriles provides (2*Z*)-2-substituted alk-2-enenitriles in high (*Z*)-stereoselectivity.

The Baylis–Hillman reaction[1] is a novel carbon–carbon bond forming reaction at the α-position of activated vinylic systems producing synthetically useful multifunctional molecules.[2–14] There has been increasing interest in this fascinating reaction and several papers have appeared in recent years. Here, we report a simple stereoselective synthesis of (2*E*)-2-substituted alk-2-enoates and (2*Z*)-2-substituted alk-2-enenitriles *via* the reaction of Grignard reagents on 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles, respectively. The simplicity and high stereoselectivity of this reaction render it a useful and attractive alternative to the classical Horner–Wadsworth–Emmons reaction, particularly for esters.

Recently, we have reported a general synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles *via* the reaction of LAH:EtOH (1:1) reagent with 3-acetoxy-2-methylenealkanoates **1** and 3-acetoxy-2-methylenealkanenitriles **2** respectively.[1] This reaction involves the attack of hydride nucleophile on the allyl acetates **1** and **2**. Though this procedure represents a novel stereoselective synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles, this methodology is limited to the preparation of 2-methyl-substituted products only. We have therefore examined the attack of carbon nucleophiles on the allyl acetates **1** and **2**, in order to provide a more general synthesis of trisubstituted alkenes of defined stereochemistry. We have found that 3-acetoxy-2-methylenealkanoates† react with a variety of Grignard reagents providing pure (2*E*)-2-substituted alk-2-enoates in high yields [eqn. (1)] (Table 1).



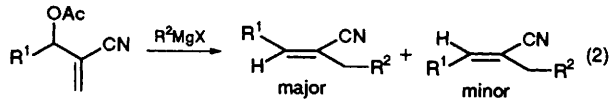
(1)

1a–f R = Me, Et

3a–f R^1,R^2 = alkyl, aryl

	a	b	c	d	e	f
R	= Me	Me	Me	Me	Et	Et
R^1	= Me	Me	n-C_6H_{13}	Ph	n-C_6H_{13}	Ph
R^2	= Bu^n	Ph	Bu^n	Bu^n	n-C_7H_{15}	Me

A similar reaction of 3-acetoxy-2-methylenealkanenitriles‡ with Grignard reagents provides (2*Z*)-2-substituted alk-2-enenitriles in high (*Z*)-selectivity and high yields [eqn. (2)], (Table 2).



(2)

2a–f **4a–f**

R^1, R^2 = alkyl, aryl

	a	b	c	d	e	f
R^1	= Pr^n	Bu^n	Bu^n	Ph	Ph	Ph
R^2	= Pr^n	Bu^n	Ph	Me	Ph	*p*-MeC_6H_4

This observation of (*E*)-selectivity with esters and (*Z*)-selectivity with nitriles is consistent with our earlier observation, *i.e.* reversal of stereochemistry of the products formed in the reactions of 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles with the reagent LAH:EtOH.[1] This reversal of stereochemistry may be attributed to the chelated structure **A** (in the case of esters) leading to (*E*)-product and to nonchelated structure **B** (in the case of nitriles) leading to (*Z*)-product.

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Table 1 Stereoselective synthesis of (2*E*)-2-substituted alk-2-enoates[a,b,c]

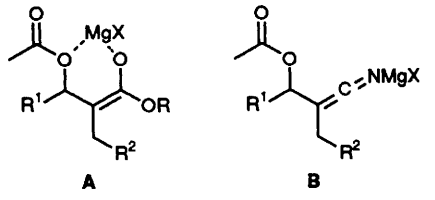
R	R^1	R^2	Product[d]	Yield (%)[e]
Me	Me	Bu^n	**3a**	68
Me	Me	Ph	**3b**	75
Me	n-C_6H_{13}	Bu^n	**3c**	62
Me	Ph	Bu^n	**3d**	70
Et	n-C_6H_{13}	n-C_7H_{15}	**3e**	68
Et	Ph	Me	**3f**	64

[a] All reactions were carried out on 5 mmol scale using 7.5 mmol of the Grignard reagent in THF at reflux temperature for 5 h. [b] All products were characterised by IR, ^1H (200 MHz) and ^{13}C (25 or 50 MHz) NMR spectra. [c] ^1H NMR indicates the absence of any (*Z*)-isomer.[15–17,§] [d] All products are obtained as colourless liquids. [e] Yields of the column chromatography purified products. [f] This reaction was carried out in refluxing diethyl ether for 6 h.

Table 2 Stereoselective synthesis of (2*Z*)-2-substituted alk-2-enenitriles[a,b]

R^1	R^2	Product[c]	Yield(%)[d]	*Z*/*E*[e]
Pr^n	Pr^n	**4a**[f]	79	88:12
Bu^n	Bu^n	**4b**	73	82:18
Bu^n	Ph	**4c**	76	91:09
Ph	Me	**4d**[f]	75	80:20
Ph	Ph	**4e**	72	(*Z*)-Isomer[g]
Ph	*p*-MeC_6H_4	**4f**	81	(*Z*)-Isomer[g]

[a] All reactions were carried out on 5 mmol scale using 7.5 mmol of the Grignard reagent, in refluxing THF for 4 h. [b] All products were characterized by IR, ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra. [c] All products are obtained as colourless liquids. [d] Yields of *Z*/*E* mixtures, isolated by column chromatography or distillation. [e] *Z*/*E* ratio was determined by ^1H NMR.[18–21,¶] [f] These reactions were carried out in refluxing diethyl ether for 5 h. [g] ^1H and ^{13}C NMR spectra show the absence of other isomer.



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Footnotes

† 3-Acetoxy-2-methylenealkanoates are obtained by the action of acetyl chloride on 3-hydroxy-2-methylenealkanoates.[3]

‡ 3-Acetoxy-2-methylenealkanenitriles are obtained by the action of acetyl chloride on 3-hydroxy-2-methylenealkanenitriles.[13]

§ In ^{1}H NMR spectrum, β-vinylic proton *cis* to the ester group [(*E*)-isomer] appears at δ 6.8 while β-vinylic proton *trans* to the ester group [(*Z*)-isomer] appears at δ 5.7 when R^1 is alkyl.[15,16] Similarly, the β-vinylic proton of (*E*)-isomer appears at δ 7.52 while that of (*Z*)-isomer appears at δ 6.48 when R^1 is aryl.[17] Spectral data for **3f**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J* 7.4 Hz), 1.35 (t, 3H, *J* 7 Hz), 2.55 (q, 2H, *J* 7.4 Hz), 4.29 (q, 2H, *J* 7 Hz), 7.24–7.43 (m, 5H), 7.65 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92, 14.39, 20.90, 60.72, 128.31, 128.52, 129.24, 135.21, 136.00, 138.34, 168.29; IR: ν_{max}/cm^{-1} (neat) 1710, 1620.

¶ In ^{1}H NMR spectrum, the β-vinylic proton *cis* to the nitrile [(*E*)-isomer] appears at δ 6.33 (downfield) while β-vinylic proton *trans* to the nitrile group [(*Z*)-isomer] appears at δ 6.13, (upfield) when R^1 is alkyl.[18,19] Similarly, the β-vinylic proton of (*E*)-isomer appears at δ 7.02 while that of (*Z*)-isomer appears at δ 6.79, when R^1 is aryl.[20,21] Spectral data for **4d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, 3H, *J* 7.5 Hz), 2.35–2.59 (m, 2H), 6.92 [s, vinylic H, (*Z*)-isomer], 7.18 [s, vinylic H, (*E*)-isomer], 7.25–7.76 (m, 5H); IR: ν_{max}/cm^{-1} (neat) 2210, 1620. Pure (*Z*)-isomer was obtained by purification of *Z*/*E* mixture on column chromatography (silica gel, 1% ethyl acetate in hexane). ^{13}C NMR (50 MHz, $CDCl_3$) for pure (*Z*)-isomer **4d**: δ 12.87, 29.51, 112.94, 118.60, 128.46, 128.68, 129.71, 133.82, 142.37.

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