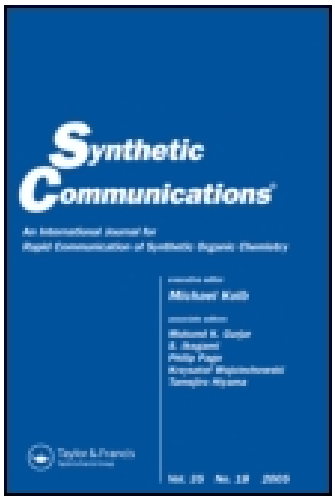

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FACILE STEREOSELECTIVE SYNTHESIS OF (E)- AND (Z)-ALLYL BROMIDES FROM THE BAYLIS-HILLMAN ADDUCTS USING $MgBr_2$

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FACILE STEREOSELECTIVE SYNTHESIS OF (*E*)- AND (*Z*)-ALLYL BROMIDES FROM THE BAYLIS-HILLMAN ADDUCTS USING $MgBr_2$

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ABSTRACT

A simple and convenient synthesis of the title compounds is described.

(2*Z*)-2-(Bromomethyl)alk-2-enoates are versatile building blocks for stereoselective synthesis of natural products such as necic acid, α-methylene-γ-butyrolactones and α-alkylidene-β-lactams. These fascinating compounds have been synthesized from Baylis-Hillman reaction products, i.e. methyl-3-hydroxy-2-methylenealkanoates using $NEt_3/MsCl$,[1] $CuBr_2$/silica gel,[2] $HBr\text{-}H_2SO_4$,[3] $NCS/NBS\text{-}Me_2S$,[4] PBr_3,[5] oxalylchloride/DMF/$CHCl_3$.[6] (HCA-PPh_3) complex[7] and by the reaction of $AlCl_3/CH_2Cl_2$[8] with the acetate derived from the corresponding alcohol.

In continuation of our research programme.[9] I herein report a convenient synthesis of methyl(2*Z*)-2-(bromomethyl)alk-2-enoates by treating methyl-3-hydroxy-2-methylenealkanoates with acetic anhydride and magnesium bromide according to the following eq. 1.

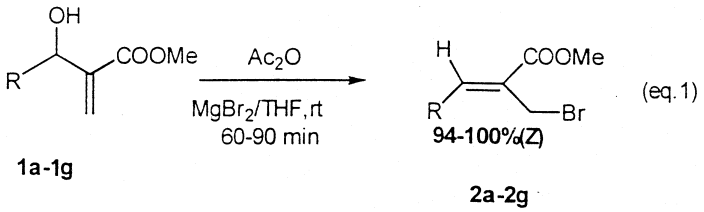

Table 1. Synthesis of Methyl(2*Z*)-2-(bromomethyl)alk-2-enoates[a,b]

Substrate	R	Time (minutes)	Product	Yield (%)[c]	Z:E[d]
1a	C_6H_5	60	2a[12]	86	100:0
1b	4-MeC_6H_4	60	2b	83	100:0
1c	4-ClC_6H_4	60	2c	81	96:04
1d	4-$^1PrC_6H_4$	60	2d	81	100:0
1e	4-MeC_6H_4	70	2e	80	95:05
1f	n-pentyl	90	2f	68	94:06
1g	n-hexyl	90	2g	71	95:05

[a]All reaction were carried out in 2 mM scale of alcohol using acetic anhydride (4 mM) and 6 mM scale of magnesium bromide in THF (5 ml) at room temperature.
[b]Satisfactory spectral data IR, ^1H (200 MHz), and ^{13}C NMR (50 MHz) were obtained.
[c]Isolated yields after column chromatography (silica gel. 1% ethyl acetate in hexane).
[d]Stereochemical assignments and isomeric purities were based on defference in chemical shifts and integration ratios of olefinic protons in ^1H NMR analysis.

In a similar fashion, 3-hydroxy-2-methylenealkane-nitriles (**3a–3g**) on reaction with acetic anhydride and magnesium bromide in THF at room temperature for 1–1.5 hours afforded the desired regiomerically pure (2*E*)-2-(bromomethyl)alk-2-enenitriles (**4a–4g**) in good yields with high (***E***)-selectivity (eq. 2) (Table 2).

From these results, it is clear that esters **1a–1g** and nitriles **4a–4g** provide allyl bromides with opposite stereochemistry. This observation is consistent with our earlier results[10] and may be explained either to the

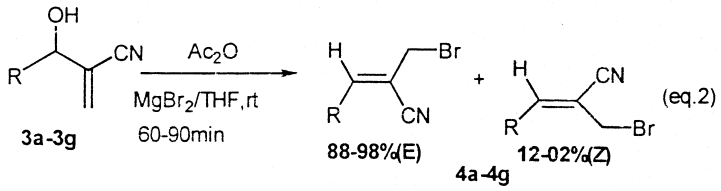

Table 2. Synthesis of (2*E*)-2-(bromomethyl)alk-2-enenitriles[a,b]

Substrate	R	Time (minutes)	Product	Yield (%)[c]	*E*:*Z*[d]
3a	Phenyl	60	4a[13]	85	93:07
3b	4-MeC_6H_4	60	4b	84	95:05
3c	4-ClC_6H_4	60	4c	83	96:04
3d	4-$^1PrC_6H_4$	75	4d	81	98:02
3e	4-MeC_6H_4	70	4e	84	94:06
3f	n-pentyl	90	4f	79	88:12
3g	n-hexyl	90	4g	77	92:08

difference in steric demands between the nitrile and ester groups or to the chelation effects.

In summary this study provides a simple stereoselective synthesis of (***Z***)- and (***E***)-allyl bromides thus demonstrating the efficiency of magnesium bromide, a very mild Lewis acid, as a stereoselective brominating reagent.

EXPERIMENTAL

All of the required Baylis-Hillman products were obtained by the reaction of the corresponding aldehydes with methyacrylate/acrylonitrile in the presence of a catalytic amount of DABCO according to the literature procedure.[11]

General Procedure

To a solution of alcohol (**1a–1g**, **3a–3g**) (2 mM) and acetic anhydride (4 mM) were added to freshly prepared magnesium bromide (6 mM) in THF (5 ml). The reaction mixture was stirred at room temperature for 1–1.5 h and monitored by TLC. On completion of the reaction, solvent was removed under reduced pressure and the residue purified by column chromatography (silicagel, 1% EtOAc in hexane) to furnish the desired product (**2a–2g**, **4a–4g**) in good yields.

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12. Spectral data for **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 4.36 (s, 2H), 7.33–7.57 (m, 5H), 7.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.62, 52.38, 128.60, 128.86, 129.55, 134.12, 143.11, 166.43; IR (neat): 1705, 1620 cm^{-1}.
13. Spectral data for **4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.19 (s, $-CH_2$ protons, (***Z***)-isomer), 4.23 (d, $-CH_2$ protons, $J = 0.8$ Hz, (***E***)-isomer) 7.23 (s, vinylic proton, (***E***)-isomer), 7.34 (s, vinylic proton, (***Z***)-isomer), 7.37–7.54 (m, 3H), 7.73–0.82 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.63, 32.70, 108.06, 117.03, 129.04, 129.23, 130.44, 131.39, 132.41, 146.47, 147.21 in these the signals at 26.63, 130.44, 147.21 are due to minor (***Z***)-isomer: IR (KBr): 2120, 1610 cm^{-1}.

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