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Synthetic Applications of the Baylis–Hillman Adducts: A Simple Stereoselective Synthesis of (*E*)-3-(Nitroxymethyl)alk-3-en-2-ones†

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Abstract—First simple, stereoselective synthesis of (*E*)-3-(nitroxymethyl)alk-3-en-2-ones from Baylis–Hillman adducts (4-hydroxy-3-methylenealkan-2-ones) is described.

Certain classes of nitrate esters ($RONO_2$) are well known for their therapeutic importance as drugs for the treatment of heart and vascular diseases.[1,2] As part of our research program in nitrate esters we have recently reported a simple and convenient methodology for the synthesis of (1*R*,2*R*) and (1*S*,2*S*)-2-nitroxycyclohexan-1-ols in enantiomerically pure form.[3] In recent years the Baylis–Hillman reaction[4–6] has attracted the attention of organic chemists as it provides synthetically useful multifunctional molecules which have been successfully employed in various stereoselective processes.[4–11] To the best of our knowledge, there is no report in the literature for the conversion of the Baylis–Hillman adducts into the corresponding allyl nitrates stereoselectively. With a view that these allyl nitrates may be of interest as potential drugs for vascular and heart diseases and in continuation of our research program[12–15] on the development of the Baylis–Hillman reaction as a source for stereoselective processes we herein report the first simple stereoselective synthesis of (*E*)-3-(nitroxymethyl)-alk-3-en-2-ones via the reaction of 4-hydroxy-3-methylenealkan-2-ones with concentrated nitric acid (69%).

Recently we have successfully transformed the Baylis–Hillman adducts, i.e. 4-hydroxy-3-methylenealkan-2-ones (**1**), obtained from a reactive activated alkene, methyl vinyl ketone, into functionalized trisubstituted olefins i.e. (3*Z*)-3-(bromomethyl)alk-3-en-2-ones and (3*Z*)-3-(chloromethyl)-alk-3-en-2-ones[16] via the treatment with aqueous HBr and HCl respectively. With an objective of utilizing the 4-hydroxy-3-methylenealkan-2-ones (**1**), in various other useful stereoselective transformations we have directed our studies to the transformation of these molecules into 3-(nitroxymethyl)alk-3-en-2-ones (**2**) with defined stereochemistry. Accordingly we first treated 4-hydroxy-3-methylene-4-phenylbutan-2-one (**1a**) (1 mmol) with 1 mL of conc. HNO_3 (69%) at room temperature. This reaction is instantaneous and provided the desired (*E*)-3-(nitroxymethyl)-4-phenylbut-3-en-2-one (**2a**) in 72% yield after usual work up followed by column chromatography. The (*E*)-stereochemistry was established on the basis of ^{1}H NMR spectral analysis in comparison with that of (3*Z*)-3-(halomethyl)alk-3-en-2-ones.[16] This success led us to transform representative 4-hydroxy-3-methylenealkan-2-ones (**1b–i**) into stereochemically pure (*E*)-3-(nitroxymethyl)alk-3-en-2-ones (**2b–i**) under similar reaction conditions (Eq. (1); Table 1).

Table 1. Synthesis of (3*E*)-3-(nitroxymethyl)alk-3-en-2-ones (all reactions were carried out on a 1 mmol scale (alcohols **1a–i**) with 1 mL of conc. HNO_3 (69%) at room temperature. Satisfactory spectral [IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz)] data and elemental analyses were obtained for all molecules (**2a–i**). ^{1}H and ^{13}C NMR indicate the absence of any (*Z*)-isomer. (*E*)-Stereochemistry was established by ^{1}H NMR spectral analysis.[17])

Substrate	R	Product	Yield (%)[a]
1a	phenyl	**2a**	72
1b	*p*-tolyl	**2b**	79
1c	*p*-isopropylphenyl	**2c**	77
1d	*p*-methoxyphenyl	**2d**	80
1e	*p*-chlorophenyl	**2e**	76
1f	*o*-methoxyphenyl	**2f**	78
1g	*o*-chlorophenyl	**2g**	79
1h	*n*-propyl	**2h**	58
1I	*n*-heptyl	**2i**	70

[a] Isolated yields of the products after column chromatography (silica gel, 4% ethyl acetate in hexanes).

† Preliminary results were presented at the American Chemical Society 218th national meeting in New Orleans, USA, August 22–26, 1999 as a poster (poster no. 510).

Keywords: Baylis–Hillman reaction; methyl vinyl ketone; stereoselectivity; (*E*)-3-(nitroxymethyl)alk-3-en-2-ones.

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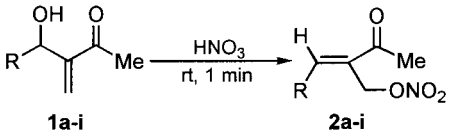
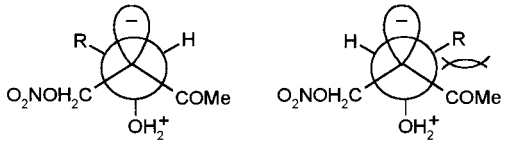


(1)

The (*E*)-selectivity in the formation of (3*E*)-3-(nitroxymethyl)alk-3-en-2-ones (**2a–i**) can be explained through the transition state models **A** and **B**. The transition state model **A** is more favored than **B** due to the COMe group having a larger steric effect than the CH_2ONO_2 group.



In conclusion, this methodology describes the first simple stereoselective synthesis of (*E*)-3-(nitroxymethyl)alk-3-en-2-ones thus demonstrating the synthetic potential of the Baylis–Hillman adducts.

Experimental

Melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT-IR model 5300 or Perkin–Elmer model 1310 spectrometer using samples as neat liquids or in KBr. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker-AC-200 spectrometer using tetramethylsilane (TMS, δ=0) as internal standard. Elemental analyses were recorded on a Perkin–Elmer 240C-CHN analyzer. Mass spectra were recorded on a micromass VG 7070H instrument. All the required Baylis–Hillman adducts (starting materials) 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.[18,19]

General procedure for the preparation of (*E*)-3-(nitroxymethyl)alk-3-en-2-ones

Conc. HNO_3 (69%) (1 mL) was added to the Baylis–Hillman adduct (1 mmol) at room temperature and swirled thoroughly for one minute (monitored by TLC). The reaction mixture was immediately diluted with water (5 mL) and extracted with ether (2×5 mL). Combined organic layer was washed with aqueous potassium carbonate solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to afford the pure (*E*)-3-(nitroxymethyl)alk-3-en-2-ones.

(3*E*)-3-(Nitroxymethyl)-4-phenylbut-3-en-2-one (2a). Colorless liquid. Yield: 72%; IR (neat): 1674, 1631 cm^{-1}; ^{1}H NMR: δ 2.48 (s, 3H), 5.28 (s, 2H), 7.42 (m, 5H), 7.95 (s, 1H); ^{13}C NMR: δ 25.41, 66.60, 128.91, 129.24, 130.28, 131.32, 133.47, 148.23, 197.36; MS (*m*/*z*): 221 (M^+); Analysis calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33; found: C, 60.00; H, 4.99; N, 6.35.

(3*E*)-4-(4-Methylphenyl)-3-(nitroxymethyl)but-3-en-2-one (2b). Colorless liquid. Yield: 79%; IR (neat): 1670, 1622 cm^{-1}; ^{1}H NMR: δ 2.40 (s, 3H), 2.48 (s, 3H), 5.31 (s, 2H), 7.29 (m, 4H), 7.92 (s, 1H); ^{13}C NMR: δ 21.42, 25.54, 66.80, 129.60, 129.86, 130.62, 130.73, 141.24, 148.76, 197.87; Analysis calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; found: C, 61.50; H, 5.54; N, 5.93.

(3*E*)-4-(4-Isopropylphenyl)-3-(nitroxymethyl)but-3-en-2-one (2c). Colorless liquid. Yield: 77%; IR (neat): 1670, 1620 cm^{-1}; ^{1}H NMR: δ 1.25 (d, 6H, *J*=6.8 Hz), 2.46 (s, 3H), 2.92 (sept, 1H, *J*=6.8 Hz), 5.29 (s, 2H), 7.19–7.41 (m, 4H), 7.88 (s, 1H); ^{13}C NMR: δ 23.69, 25.58, 34.08, 66.88, 127.24, 129.72, 130.61, 131.12, 148.40, 151.93, 197.24; Analysis calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; found: C, 63.91; H, 6.53; N, 5.29.

(3*E*)-4-(4-Methoxyphenyl)-3-(nitroxymethyl)but-3-en-2-one (2d). Colorless solid. Yield: 80%; mp: 70–72°C; IR (KBr): 1661, 1622 cm^{-1}; ^{1}H NMR: δ 2.48 (s, 3H), 3.86 (s, 3H), 5.33 (s, 2H), 6.98 (d, 2H, *J*=8.0 Hz), 7.40 (d, 2H, *J*=8.0 Hz), 7.87 (s, 1H); ^{13}C NMR: δ 25.60, 55.53, 67.05, 114.77, 126.16, 129.47, 131.69, 148.07, 161.76,197.12; Analysis calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58; found: C, 57.03; H, 5.21; N, 5.58.

(3*E*)-4-(4-Chlorophenyl)-3-(nitroxymethyl)but-3-en-2-one (2e). Colorless liquid. Yield: 76%; IR (neat): 1674, 1626 cm^{-1}; ^{1}H NMR: δ 2.48 (s, 3H), 5.25 (s, 2H), 7.33 (d, 2H, *J*=8.8 Hz), 7.44 (d, 2H, *J*=8.8 Hz), 7.85 (s, 1H); ^{13}C NMR: δ 25.59, 66.39, 129.37, 130.63, 132.07, 136.63, 146.54, 196.91; Analysis calcd for $C_{11}H_{10}ClNO_4$: C, 51.68; H, 3.94; N, 5.48; found: C, 51.35; H, 3.96; N, 5.50.

(3*E*)-4-(2-Methoxyphenyl)-3-(nitroxymethyl)but-3-en-2-one (2f). Colorless liquid. Yield: 78%; IR (neat): 1660, 1621 cm^{-1}; ^{1}H NMR: δ 2.50 (s, 3H), 3.89 (s, 3H), 5.27 (s, 2H), 6.92–7.11 (m, 2H), 7.25–7.37 (m, 1H), 7.44 (m, 1H), 8.12 (s, 1H); ^{13}C NMR: δ 25.61, 55.63, 67.29, 110.98, 120.87, 122.85, 129.85, 131.53, 132.06, 144.22, 157.80, 197.30; Analysis calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58; found: C, 57.61; H, 5.22; N, 5.56.

(3*E*)-4-(2-Chlorophenyl)-3-(nitroxymethyl)but-3-en-2-one (2g). Colorless liquid. Yield: 79%; IR (neat): 1672, 1620 cm^{-1}; ^{1}H NMR: δ 2.50 (s, 3H), 5.19 (s, 2H), 7.34–7.52 (m, 4H), 8.03 (s, 1H); ^{13}C NMR: δ 25.74, 66.50, 127.28, 129.97, 130.05, 131.35, 132.28, 133.25, 134.17, 144.66, 196.92; Analysis calcd for $C_{11}H_{10}ClNO_4$: C, 51.68; H, 3.94; N, 5.48; found: C, 51.45; H, 3.92; N, 5.49.

(3*E*)-3-(Nitroxymethyl)hept-3-en-2-one (2h). Colorless liquid. Yield: 58%; IR (neat): 1678, 1630 cm^{-1}; ^{1}H NMR: δ 0.99 (t, 3H, *J*=7.0 Hz), 1.48–1.70 (m, 2H), 2.29–2.50 (m, 5H), 5.23 (s, 2H), 7.03 (t, 1H, *J*=7.2 Hz); ^{13}C NMR: δ 13.72, 21.86, 25.24, 31.34, 65.34, 132.89, 152.47, 196.88; Analysis calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; found: C, 51.28; H, 6.96; N, 7.52.

(3*E*)-3-(Nitroxymethyl)undec-3-en-2-one (2i). Colorless liquid. Yield: 70%; IR (neat): 1676, 1631 cm^{-1}; ^1H NMR: δ 0.87 (t, 3H, J=6.3 Hz), 1.15–1.61 (m, 10H), 2.31–2.51 (m, 5H), 5.23 (s, 2H), 7.02 (t, 1H, J=7.6 Hz); ^{13}C NMR: δ 13.94, 22.54, 25.21, 28.61, 28.94, 29.26, 29.46, 31.62, 65.38, 132.91, 152.36, 196.70; Analysis calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76; found: C, 59.62; H, 8.72; N, 5.73.

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17. In the ^1H NMR spectrum of trisubstituted alkenes with ketone group, the vinylic proton *cis* to the carbonyl group appears downfield in comparison with that of the vinylic proton *trans* to the carbonyl group.[20,21] In the ^1H NMR spectrum of (3*Z*)-3-(halomethyl)alk-3-en-2-ones[16] (R=aryl) the vinylic proton *cis* to the carbonyl group appears at $\approx$ δ 7.60–7.90 as a singlet. In the case of compounds **2a**–**2g** (R=aryl) the vinylic proton appears at $\approx$ δ 7.85–8.12 as a singlet. Therefore we have assigned (*E*)-stereochemistry to the compounds **2a**–**2g**. The vinylic proton *cis* to the carbonyl group in the case of (3*Z*)-3-(halomethyl)alk-3-en-2-ones[16] (R=alkyl) appears at $\approx$ δ 6.80 as a triplet. In the case of compounds **2h**–**2i** (R=alkyl) the vinylic proton appears at $\approx$ δ 7.00 as a triplet. Therefore we assigned (*E*)-stereochemistry to the molecule **2h**–**2i**.
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