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The Baylis−Hillman Reaction: One-Pot Facile Synthesis of 2,4-Functionalized 1,4-Pentadienes

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Abstract: The Baylis−Hillman coupling between activated alkenes and alkyl 2-(bromomethyl)prop-2-enoates in the presence of DABCO (or DBU) leading to the formation of 2,4-functionalized 1,4-pentadienes, has been described.

The Baylis−Hillman reaction is a three-component reaction involving the construction of the carbon−carbon bond between the α-position of activated alkene and a carbon electrophile under the influence of a catalyst (most commonly tertiary amines, particularly, DABCO), leading to the formation of interesting densely functionalized molecules whose applications in a variety of synthetic transformation methodologies have been well documented in the literature.[1−3] In continuation of our research program on the development of Baylis−Hillman chemistry,[3] we herein report a simple synthesis of 2,4-functionalized 1,4-pentadienes via the Baylis−Hillman coupling between alkyl 2-(bromomethyl)prop-2-enoates and various activated alkenes in the presence of appropriate tertiary amine (DABCO or DBU).

During the last 15 years, the Baylis−Hillman reaction has seen a tremendous growth in terms of all the three essential components, i.e., activated alkene, electrophile, and the catalyst. Although a variety of electrophiles, such as aldehydes, α-keto esters, aldimine derivatives, fluoro ketones, etc., have been extensively used in this fascinating reaction, the application of allyl halides, another highly important class of carbon electrophiles, in the Baylis−Hillman reaction has not been well explored. We have recently described, for the first time, the application of (*Z*)-allyl halides, **1** and **2**, obtained from Baylis−Hillman adducts, as suitable electrophiles in the Baylis−Hillman coupling reaction, thus providing a simple synthesis of 3-substituted 2,4-functionalized 1,4-pentadienes[3c] (**3** and **4**) (Scheme 1). Literature survey reveals that the 1,4-diene framework constitutes an important structural assembly owing to the presence of this structural unit in various molecules of biological importance,[4] and in fact, the 1,4-pentadiene skeleton occupies a special place in 1,4-diene framework due to the high degree of applicability of this moiety in various aspects of organic synthesis.[5] Hence the development of new, simple, and efficient methodologies for the synthesis of the 1,4-pentadiene framework represents an important and attractive objective in the area of synthetic organic chemistry.[5b,e,6] Since we have already developed a simple methodology for synthesis of 3-substituted 2,4-functionalized 1,4-pentadienes[3c] using Baylis−Hillman chemistry (Scheme 1), it occurred to us that if we can also utilize Baylis−Hillman chemistry for generating simple procedures for synthesis of 2,4-functionalized 1,4-pentadienes without any substitution at the 3-position, this methodology will not only compliment our earlier procedure but also demonstrate the importance of Baylis−Hillman chemistry in organic synthesis.

In this direction, it appeared to us that the Baylis−Hillman reaction between alkyl 2-(bromomethyl)prop-2-enoates and the activated alkenes would provide the desired 1,4-pentadiene framework with appropriate functionalities at 2- and 4-positions. Accordingly, we have first selected methyl 2-(bromomethyl)prop-2-enoate, the allyl bromide derived from methyl 2-(hydroxymethyl)prop-2-enoate, as a carbon electrophile and methyl vinyl ketone (MVK) as an activated alkene for performing the Baylis−Hillman reaction. The best results were achieved when methyl 2-(bromomethyl)prop-2-enoate (**5a**) (1 mM) was treated with MVK (1 mL) in the presence of DABCO (2 mM) at room temperature for 15 min, thus providing 4-acetyl-2-methoxycarbonylpenta-1,4-diene (**6**) in 82% yield, after usual workup followed by column chromatography (silica gel, 4% EtOAc in hexanes). Encouraged by this result, we have synthesized representative class of 4-alkanoyl-2-alkoxycarbonylpenta-1,4-dienes (**7**−**9**) via the reaction between various alkyl 2-(bromomethyl)prop-2-enoates (**5b**,**c**) with methyl vinyl ketone/ethyl vinyl

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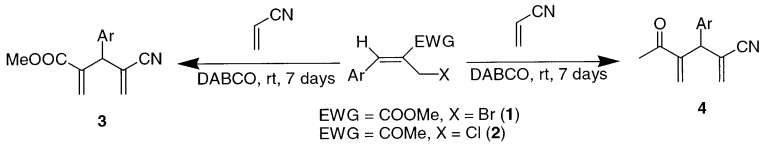
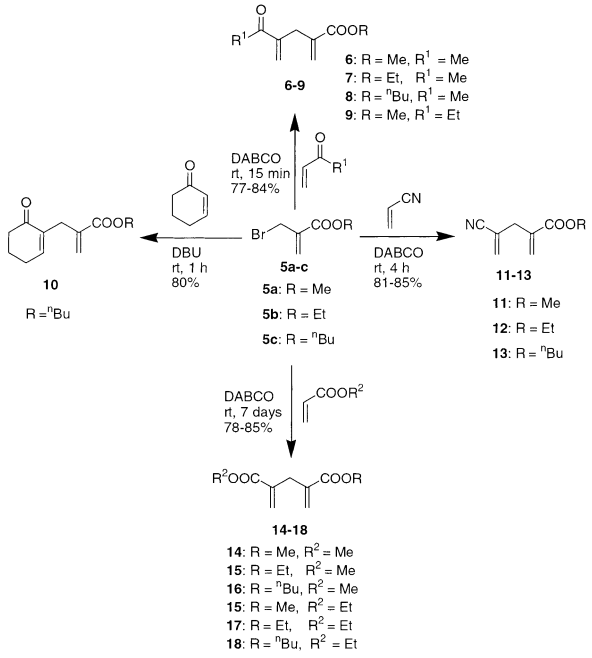
SCHEME 1



SCHEME 2



ketone (Scheme 2, Table 1). With a view to understanding the application of the cyclic enones in this strategy, we have performed the Baylis−Hillman reaction between cyclohex-2-en-1-one with *n*-butyl 2-(bromomethyl)prop-2-enoate (**5c**) in the presence of DBU (this reaction is not clean in the presence of DABCO) at room temperature for 1 h, to provide 2-[2-(*n*-butoxycarbonyl)prop-2-en-1-yl]-cyclohex-2-en-1-one (**10**), in 80% yield, after usual workup followed by column chromatography (silica gel, 4% EtOAc in hexanes) (Scheme 2).

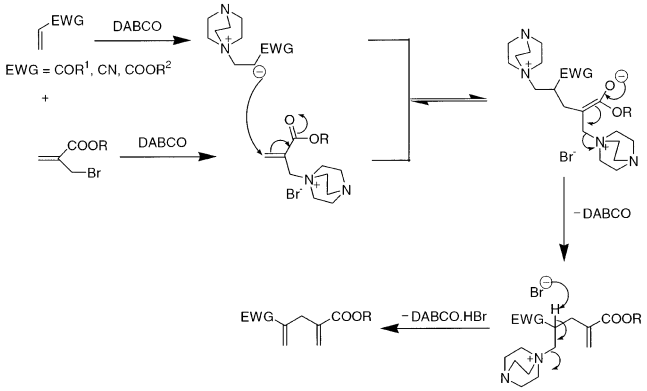
With a view to expanding the scope of this methodology, we have also employed acrylonitrile as an activated alkene for Baylis−Hillman coupling with alkyl 2-(bromomethyl)prop-2-enoates (**5a**−**c**) in the presence of DABCO (2 mM) at room temperature, for 4 h, to provide 4-cyano-2-alkoxycarbonylpenta-1,4-dienes (**11**−**13**) in good yields (Scheme 2, Table 1). We have then used alkyl acrylates as activated alkenes for coupling with alkyl 2-(bromomethyl)prop-2-enoates in the presence of DABCO (2 mM) at room temperature for 7 days to afford 2,4-dialkoxycarbonylpenta-1,4-dienes (**14**−**18**) (Scheme 2). A plausible mechanism for the formation of 1,4-pentadienes in all these reactions is presented in Scheme 3.[7]

TABLE 1. Synthesis of Functionalized 1,4-Pentadienes[a−d]

no.	allyl bromide	activated alkene	product[e]	yield (%)[f]
1	**5a**	methyl vinyl ketone	**6**[a,g]	82
2	**5b**	methyl vinyl ketone	**7**[a]	78
3	**5c**	methyl vinyl ketone	**8**[a]	84
4	**5a**	ethyl vinyl ketone	**9**[a]	77
5	**5c**	cyclohex-2-en-1-one	**10**[b,g]	80
6	**5a**	acrylonitrile	**11**[c]	81
7	**5b**	acrylonitrile	**12**[c]	83
8	**5c**	acrylonitrile	**13**[c,g]	85
9	**5a**	methyl acrylate	**14**[d,h]	80
10	**5b**	methyl acrylate	**15**[d]	84
11	**5c**	methyl acrylate	**16**[d,g]	85
12	**5a**	ethyl acrylate	**15**[d]	81
13	**5b**	ethyl acrylate	**17**[d,h]	82
14	**5c**	ethyl acrylate	**18**[d]	78

[a] All the reactions were carried out on 1 mM scale of allyl bromides (**5a**−**c**) with alkyl vinyl ketone (1 mL) in the presence of DABCO (2 mM) at room temperature for 15 min. [b]The reaction was carried out on 1 mM scale of allyl bromide (**5c**) with cyclohex-2-en-1-one (1 mL) in the presence of DBU (2 mM) at room temperature for 1 h. [c]All the reactions were carried out on 1 mM scale of allyl bromides (**5a**−**c**) with acrylonitrile (1 mL) in the presence of DABCO (2 mM) at room temperature for 4 h. [d]All the reactions were carried out on 1 mM scale of allyl bromides (**5a**−**c**) with alkyl acrylate (1 mL) in the presence of DABCO (2 mM) at room temperature for 7 days. [e]All the products were obtained as colorless liquids and gave satisfactory IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data, and elemental analyses. [f]Isolated yields of the pure products (based on allyl bromides) after column chromatography (silica gel, 4% EtOAc in hexanes). [g] These products were also characterized by mass spectral analysis. [h]These molecules are known in the literature.[5b] ^{1}H NMR spectral data of molecule **17** is reported[5b] and our data is in agreement with that of the literature.

SCHEME 3



In conclusion, we have successfully developed a one-pot convenient simple methodology for synthesis of 2,4-functionalized 1,4-pentadienes, via the Baylis−Hillman reaction between activated alkenes and alkyl 2-(bromomethyl)prop-2-enoates in the presence of DABCO or

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(7) We have proposed a similar mechanism in the formation of 3-substituted 2,4-functionalized 1,4-pentadienes.[3c]

DBU, thus demonstrating the application of the Baylis–Hillman chemistry in organic synthesis.

Experimental Section

IR spectra were recorded on a FT-IR spectrometer using samples as neat liquids. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS, $\delta = 0$) as internal standard. Mass spectra were recorded on a micromass instrument. Elemental analyses were recorded on a CHN analyzer. All the required allyl bromides, i.e., alkyl 2-(bromomethyl)prop-2-enoates were obtained via the reaction of the corresponding Baylis–Hillman adducts[1a–c] with PBr_3 according to the literature procedure.[8]

General Procedure for the Preparation of 4-Alkanoyl-2-alkoxycarbonylpenta-1,4-dienes. Methyl 2,4-Dimethylidene-5-oxohexanoate (6). A solution of methyl 2-(bromomethyl)prop-2-enoate (**5a**) (1 mM, 0.179 g) and DABCO (2 mM, 0.224 g) in methyl vinyl ketone (1 mL) was kept at room temperature for 15 min. The reaction mixture was diluted with ether (15 mL) and washed successively with 2 N HCl solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product, thus obtained, was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to provide pure methyl 2,4-dimethylidene-5-oxohexanoate (**6**) in 82% yield (0.138 g), as a colorless liquid. IR (neat): 1722, 1680, 1631 cm^{-1}; ^{1}H NMR: δ 2.35 (s, 3H), 3.29 (s, 2H), 3.74 (s, 3H), 5.57 (s, 1H), 5.81 (s, 1H), 6.10 (s, 1H), 6.24 (s, 1H); ^{13}C NMR: δ 25.49, 32.35, 51.56, 126.28, 126.62, 137.91, 146.15, 166.84, 198.34; MS (*m*/*z*): 168 (M^+). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19; found: C, 64.42; H, 7.21.

2-[2-(*n*-Butoxycarbonyl)prop-2-en-1-yl]cyclohex-2-en-1-one (10). A solution of *n*-butyl 2-(bromomethyl)prop-2-enoate (**5c**) (1 mM, 0.221 g) and DBU (2 mM, 0.304 g) in cyclohex-2-en-1-one (1 mL) was kept at room temperature for 1 h. The reaction mixture was diluted with ether (15 mL) and washed successively with 2 N HCl solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to provide the pure 2-[2-(*n*-butoxycarbonyl)prop-2-en-1-yl]cyclohex-2-en-1-one (**10**) in 80% yield (0.189 g), as colorless liquid. IR (neat): 1718, 1676, 1631 cm^{-1}; ^{1}H NMR: δ 0.93 (t, 3H, J = 7.2 Hz), 1.24–1.52 (m, 2H), 1.54–1.75 (m, 2H), 1.90–2.10 (m, 2H), 2.28–2.51 (m, 4H), 3.22 (s, 2H), 4.13 (t, 2H, J = 6.5 Hz), 5.55 (s, 1H), 6.21 (s, 1H), 6.75 (t, 1H, J = 4.2 Hz); ^{13}C NMR: δ 13.48, 19.01, 22.88, 25.93, 30.50, 31.15, 38.25, 64.31, 126.20, 136.95, 138.38, 146.46, 166.68, 198.12; MS (*m*/*z*): 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 71.30; H, 8.50.

General Procedure for the Preparation of 4-Cyano-2-alkoxycarbonylpenta-1,4-dienes. Methyl 2-Methylidene-4-cyanopent-4-enoate (11). A solution of methyl 2-(bromomethyl)prop-2-enoate (**5a**) (1 mM, 0.179 g) and DABCO (2 mM, 0.224 g) in acrylonitrile (1 mL) was kept at room temperature for 4 h. The reaction mixture was diluted with ether (15 mL) and washed successively with 2 N HCl solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to provide the pure methyl 2-methylidene-4-cyanopent-4-enoate (**11**) in 81% yield (0.122 g), as a colorless liquid. IR (neat): 2226, 1722, 1635 cm^{-1}; ^{1}H NMR: δ 3.25 (s, 2H), 3.77 (s, 3H), 5.77 (s, 1H), 5.83 (s, 1H), 5.96 (s, 1H), 6.39 (s, 1H); ^{13}C NMR: δ 36.47, 51.85, 117.84, 120.31, 128.21, 132.07, 135.28, 165.97. Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27; found: C, 63.78; H, 6.05; N, 9.31.

General Procedure for the Preparation of 2,4-Dialkoxycarbonylpenta-1,4-dienes. 2,4-Dimethoxycarbonylpenta-1,4-diene (14). A solution of methyl 2-(bromomethyl)prop-2-enoate (**5a**) (1 mM, 0.179 g) and DABCO (2 mM, 0.224 g) in methyl acrylate (1 mL) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (15 mL) and washed successively with 2 N HCl solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to provide pure 2,4-dimethoxycarbonylpenta-1,4-diene (**14**) in 80% yield (0.147 g), as colorless liquid. IR (neat): 1724, 1631 cm^{-1}; ^{1}H NMR: δ 3.33 (s, 2H), 3.74 (s, 6H), 5.60 (s, 2H), 6.25 (s, 2H); ^{13}C NMR: δ 33.65, 51.69, 126.61, 137.69, 166.85. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.88; H, 6.50.

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Supporting Information Available: Characterization data for compounds **7**–**9**, **12**, **13**, **15**–**18** and ^{13}C NMR spectra for all the compounds **6**–**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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