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# Baylis–Hillman chemistry: a novel synthesis of functionalized 1,4-pentadienes

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**Abstract**—A novel synthesis of functionalized 1,4-pentadienes via the reaction of acrylonitrile with allyl halides, derived from Baylis–Hillman adducts, in the presence of DABCO has been described, demonstrating for the first time the application of allyl halides as electrophiles in the Baylis–Hillman reaction. © 2000 Elsevier Science Ltd. All rights reserved.

The Baylis–Hillman reaction continues to attract the attention of organic chemists due to its increasing importance in the development of various new synthetic methodologies often involving high levels of stereochemical control.[1–15] The 1,4-diene moiety is an important structural unit present in several biologically active molecules[16,17] and, in particular, substituted 1,4-pentadienes are versatile synthons for the synthesis of various interesting molecules.[18,19] Hence, the development of simple, convenient, and new methodologies for the synthesis of 1,4-dienes has been, and continues to be, a challenging endeavor in synthetic organic chemistry.[20–25] In continuation of our research program on the development of the Baylis–Hillman reaction,[11–15] we report a novel synthesis of functionalized 1,4-pentadienes via the reaction of acrylonitrile in the presence of DABCO with methyl (2*Z*)-2-(bromomethyl)alk-2-enoates and (3*Z*)-3-(chloromethyl)alk-3-en-2-ones, allyl halides obtained from the corresponding Baylis–Hillman adducts.

The Baylis–Hillman reaction is basically a three component reaction involving an activated alkene, a carbon electrophile and a tertiary amine catalyst (particularly DABCO) leading to the formation of a carbon–carbon bond between the α-position of the activated alkene and the carbon electrophile thus providing densely functionalized molecules. Though various electrophiles have been successfully employed in this fascinating reaction,[1–3] the application of allyl halides as electrophiles has not been reported so far in the literature. We have therefore undertaken a research program of examining the possible application of allyl halides as electrophiles in the Baylis–Hillman reaction. During our study, we directed our attention towards the application of methyl (2*Z*)-2-(bromomethyl)alk-2-enoates,[26] allyl bromides derived from Baylis–Hillman adducts (methyl 3-hydroxy-2-methylenealkanoates), as possible electrophiles in the Baylis–Hillman reaction. Accordingly, we first examined the coupling of acrylonitrile with methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) derived from methyl 3-hydroxy-2-methylene-3-phenylpropanoate, in the presence of DABCO. A fascinating result was obtained when we treated methyl

**Table 1.** Synthesis of functionalized 1,4-pentadienes[a,b]

| Substrate | Ar | Product | Yield (%)[c] |
|---|---|---|---|
| **1a** | phenyl | **2a**[d,27] | 67 |
| **1b** | 4-chlorophenyl | **2b** | 63 |
| **1c** | 4-methylphenyl | **2c** | 65 |
| **1d** | 4-ethylphenyl | **2d** | 55 |
| **1e** | 4-isopropylphenyl | **2e** | 59 |
| **1f** | 2-chlorophenyl | **2f** | 60 |
| **1g** | 2-methylphenyl | **2g** | 37 |
| **3a** | phenyl | **4a**[d,29] | 42 |
| **3b** | 4-chlorophenyl | **4b** | 36 |
| **3c** | 4-methylphenyl | **4c** | 40 |

[a] All reactions were carried out using 2 mM of the allyl halides (**1a–g**, **3a–c**) with acrylonitrile (2 mL) in the presence of DABCO (4 mM) at room temperature for 7 days.

[b] All products were obtained as colorless viscous liquids and gave satisfactory IR, $^{1}$H NMR (200 MHz), $^{13}$C NMR (50 MHz) spectral data and elemental analyses.

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

[d] These products were also characterized by mass spectral analysis.

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*Keywords*: Baylis–Hillman chemistry; acrylonitrile; DABCO; functionalized 1,4-pentadienes.

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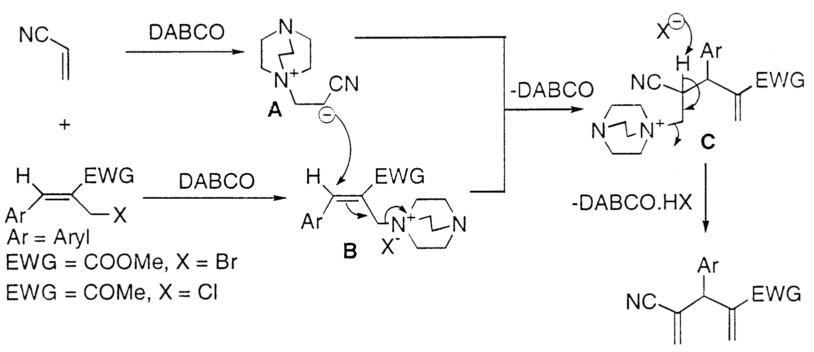
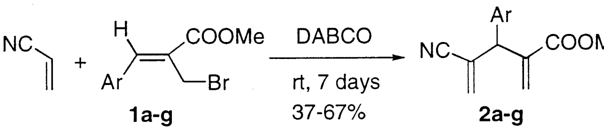


**Scheme 1.**

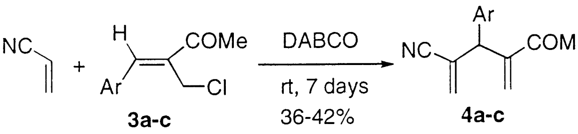
(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) (2 mM), with acrylonitrile (2 mL) in the presence of DABCO (4 mM) at room temperature for 7 days, leading to the formation of 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**2a**)[27] in 67% yield after the usual work up followed by column chromatography (silica gel, 4% ethyl acetate in hexanes). Encouraged by this result, we extended the reaction to a representative class of allyl bromides derived from methyl 3-aryl-3-hydroxy-2-methylenepropanoates to produce functionalized 1,4-pentadienes (**2b–g**) (Eq. (1), Table 1).



(1)

Ar = phenyl, 4-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 2-chlorophenyl, 2-methylphenyl

With a view to understanding the generality of this reaction, we also examined the reaction between (3*Z*)-4-aryl-3-(chloromethyl)but-3-en-2-ones[28] (**3a–c**) and acrylonitrile in the presence of DABCO at room temperature to afford 2-acetyl-3-aryl-4-cyanopenta-1,4-dienes (**4a-c**) (Eq. (2), Table 1). However, our attempts to couple acrylonitrile with methyl (2*Z*)-2-(bromomethyl)hex-2-enoate in the presence of DABCO were unsuccessful.



(2)

Ar = phenyl, 4-chlorophenyl, 4-methylphenyl

A plausible mechanism for the formation of functionalized 1,4-pentadienes in the reaction between allyl halides (derived from the Baylis–Hillman adducts) and acrylonitrile in the presence of DABCO is described in the Scheme 1.

In conclusion, our methodology describes the application of allyl halides as electrophiles in the Baylis–Hillman reaction, for the first time thus providing a novel synthesis of functionalized 1,4-pentadienes, an important class of molecules.

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26. (2*Z*)-2-(Bromomethyl)alk-2-enoates were prepared via the treatment of methyl 3-hydroxy-2-methylenealkanoates (the Baylis–Hillman adducts obtained from methyl acrylate) with $HBr/H_2SO_4$ according to the literature procedure.[30]
27. **Spectral data for 2a:** IR $\nu_{max}/cm^{-1}$ (neat): 2224, 1724, 1631. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.73 (s, 3H), 4.94 (s, 1H), 5.60 (s, 1H), 5.63 (s, 1H), 6.08 (s, 1H), 6.56 (s, 1H), 7.14–7.45 (m, 5H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 50.64, 52.24, 118.18, 124.62, 127.91, 128.56, 128.73, 128.93, 132.54, 136.88, 139.45, 166.18; *m*/*z*: 227 ($M^+$); Analysis calculated for $C_{14}H_{13}NO_2$: C, 73.99, H, 5.77, N, 6.16; found: C, 74.05, H, 5.74, N, 6.19.
28. (3*Z*)-4-Aryl-3-(chloromethyl)but-3-en-2-ones were prepared by the reaction of 4-aryl-4-hydroxy-3-methylenebutan-2-ones (the Baylis–Hillman adducts obtained from methyl vinyl ketone) with conc. HCl.[31]
29. **Spectral data for 4a:** IR $\nu_{max}/cm^{-1}$ (neat): 2224, 1680, 1630. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.38 (s, 3H), 5.06 (s, 1H), 5.58 (s, 1H), 5.88 (s, 1H), 6.06 (s, 1H), 6.43 (s, 1H), 7.13–7.46 (m, 5H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 25.87, 48.89, 118.22, 124.78, 127.70, 128.46, 128.63, 128.85, 132.61, 137.35, 147.63, 197.36; *m*/*z*: 211 ($M^+$); Analysis calculated for $C_{14}H_{13}NO$: C, 79.59, H, 6.20, N, 6.63; found: C, 79.83, H, 6.22, N, 6.60.
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