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Tetrahedron Letters 46 (2005) 2761–2763

Tetrahedron Letters

# Nucleophilic displacement by azide and cyanide on Baylis–Hillman acetates in water☆

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Received 2 September 2004; revised 14 February 2005; accepted 25 February 2005

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**Abstract**—Baylis–Hillman acetates undergo smooth nucleophilic displacement with sodium azide and sodium cyanide in water under mild conditions to afford the corresponding ethyl 2-azidomethyl-3-phenylpropenoate, 2-azidomethyl-3-phenylacrylonitrile and 2-(phenylmethylidene)succinonitrile in excellent yields.

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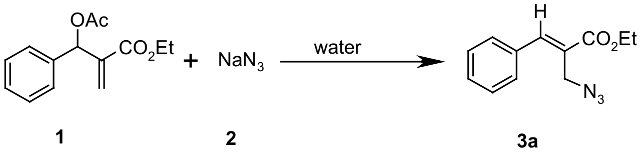
The Baylis–Hillman reaction is an important carbon–carbon bond forming reaction in organic synthesis.[1] The coupling of activated vinylic systems with aldehydes or imines in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO), a procedure known as the Baylis–Hillman reaction,[2] is widely used for the direct synthesis of α-hydroxy- or α-amino alkyl- or aryl–vinyl systems. Baylis–Hillman adducts and their acetates are useful precursors for the synthesis of a variety of heterocycles such as quinolines, pyrimidones, isoxazolines, pyrazolones, pyrrolidines, indolizines, azetidinones, diazacyclophanes and chromanones as well as biologically active natural products including α-alkylidene-β-lactams, α-methylene-γ-butyrolactones and mikanecic acids, frontalin, trimethoprim, sarkomycin, ilmofosine nuciferol and many others.[3–6] Nucleophilic displacement of Baylis–Hillman acetates is one of the most straightforward reactions in organic chemistry, however, only a few methods have been developed for the nucleophilic displacement by azide and cyanide.[3,7,8] Recently, there has been great interest in the development of carbon–carbon bond forming reaction in aqueous medium.[9,10] It was thus important to develop a mild, efficient and convenient protocol for the nucleophilic displacement by azide and cyanide on Baylis–Hillman acetates in water and our results are reported herein.

Treatment of ethyl 2-(acetoxyphenylmethyl)acrylate **1** with sodium azide **2** in water afforded ethyl (*E*)-2-azidomethyl-3-phenylpropenoate **3a**, exclusively, in 90% yield (Scheme 1).

Similarly, various other aryl- and alkyl-substituted Baylis–Hillman acetates reacted smoothly with sodium azide to give the corresponding products in good yields with (*E*)-stereoselectivity (Table 1, entries a–f). The (*E*)-stereochemistry (Table 1, entries 3a–f) was assigned on the basis of NMR experiments, which clearly showed NOEs between the methylene protons and aromatic protons and the absence of an effect between these protons and the vinylic proton. Further, the reactions of Baylis–Hillman acetates derived from acrylonitriles that is 3-acetoxy-2-methylene-3-phenylacrylonitrile with



**Scheme 1.**

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*Keywords*: Baylis–Hillman acetate; Nucleophilic displacement; Sodium azide; Sodium cyanide; Water.

☆ IICT Communication No = 041212.

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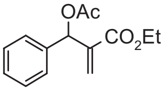
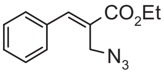
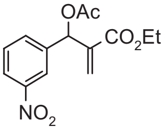
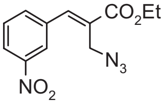
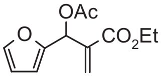
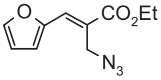
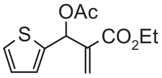
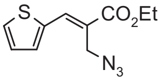
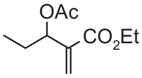
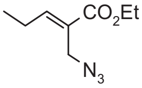
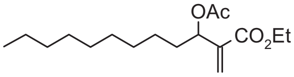
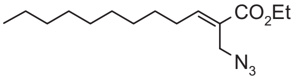
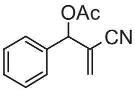
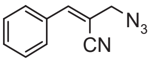
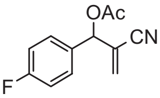
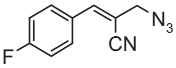
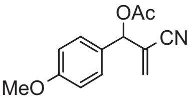
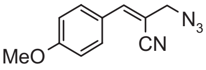
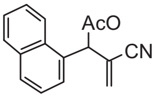
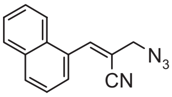
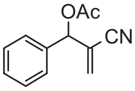
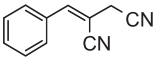
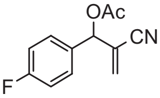
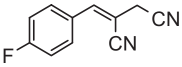
doi:10.1016/j.tetlet.2005.02.157

**Table 1.** Nucleophilic displacement by azide and cyanide on Baylis–Hillman acetates in water

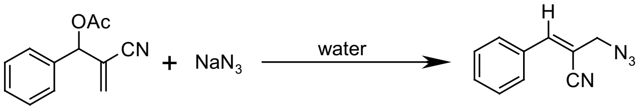
| Entry | Acetate | Azide/cyanide | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| a |  | $NaN_3$ |  | 4.0 | 90 |
| b |  | $NaN_3$ |  | 4.5 | 91 |
| c |  | $NaN_3$ |  | 4.5 | 84 |
| d |  | $NaN_3$ |  | 5.0 | 81 |
| e |  | $NaN_3$ |  | 5.5 | 78 |
| f |  | $NaN_3$ |  | 6.0 | 76 |
| g |  | $NaN_3$ |  | 3.5 | 92 |
| h |  | $NaN_3$ |  | 3.5 | 89 |
| i |  | $NaN_3$ |  | 3.0 | 87 |
| j |  | $NaN_3$ |  | 4.5 | 83 |
| k |  | NaCN |  | 3.0 | 95 |
| l |  | NaCN |  | 3.5 | 88 |

[a] All products were characterized by $^1H$ NMR and IR spectroscopy and mass spectrometry.

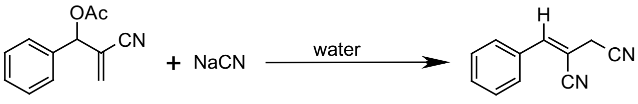
[b] Yield refers to the isolated pure products after column chromatography.

sodium azide produced the corresponding products in good yields having (*Z*)-stereochemistry (Table 1, entries g–j, Scheme 2).

Encouraged by these results, we turned our attention to the reaction with cyanide. Treatment of two examples of 3-acetoxy-2-methylene-3-arylacrylonitriles with sodium cyanide in water afforded 2-(arnylmethylidene)succinonitriles in excellent yield with (*Z*)-stereochemistry (Scheme 3, Table 1, entries k and l). The (*Z*)-stereochemistry of the products (Table 1, entries k and l) was confirmed by NOE experiments, which clearly showed the presence of diagnostic NOEs between the vinylic proton and the methylene protons.



**Scheme 2.**



**Scheme 3.**

All products were confirmed by $^1$H NMR, IR spectroscopy and mass spectrometry and also by comparison with reported spectral data.[7] It should be noted that aryl-substituted Baylis–Hillman acetates gave higher yields compared to alkyl-substituted Baylis–Hillman acetates. The scope and generality of this process is illustrated with respect to various Baylis–Hillman acetates and the results are presented in Table 1.

In summary, we have described a simple, convenient and efficient protocol for the nucleophilic displacement by azide and cyanide on Baylis–Hillman acetates in water.[11]

## Acknowledgements

M.K.G., S.K.P. and B.V.S.R. thank CSIR New Delhi for the award of fellowships.

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11. *General procedure*: A mixture of Baylis–Hillman acetate (1 mmol), sodium azide or sodium cyanide (1.2 mmol) in water (10 mL) was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated in vacuo and purified on column chromatography by silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure product. Spectroscopic data for selected product: Ethyl (*E*)-2-azidomethyl-3-phenylpropenoate **3a**: Liquid. IR (KBr): $\nu$ 3061, 2983, 2938, 2104, 1708, 1630, 1575, 1494, 1448, 1369, 1263, 1220, 1202, 1103, 1023, 770, 699 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.91 (s, 1 H), 7.39 (s, 5H), 4.34 (q, $J = 6.5$ Hz, 2H), 4.13 (s, 2H), 1.39 (t, $J = 6.5$ Hz, 3H). EIMS: $m/z$ (%): 231 ($M^+$, 5), 174 (45), 130 (100), 115 (48), 77 (30), 50 (10). Ethyl (*E*)-2-azidomethyl-2-dodecenoate **3f**: Liquid. IR (KBr): $\nu$ 2927, 2855, 2104, 1712, 1647, 1464, 1370, 1259, 1218, 1175, 1095, 864, 771, 666 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.03 (t, $J = 7.3$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.01 (s, 2H), 2.27 (q, $J = 7.5$ Hz, 2H), 1.48–1.27 (m, 17H), 0.88 (t, $J = 7.5$ Hz, 3H). EIMS: $m/z$ (%): 281 ($M^+$, 10), 237 (15), 225 (5), 154 (60), 136 (90), 118 (90), 91 (100), 44 (95). (*Z*)-2-(4-Fluorophenylmethylidene)succinonitrile **3l**: Creamy solid, m.p. = 79–82 °C. IR (KBr): $\nu$ 2924, 2216, 1599, 1508, 1413, 1235, 1162, 833, 529 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82–7.79 (m, 2H), 7.29 (s, 1H), 7.18–7.12 (m, 2H), 3.52 (s, 2H). EIMS: $m/z$ (%): 186 ($M^+$, 100), 160 (80), 132 (10), 110 (35), 69 (8), 57 (30).