



Indium-mediated alkylation of Baylis–Hillman acetates: a novel route to 1,4-enynes

Jhillu S. Yadav*, Basi V. Subba Reddy, Nagendra Nath Yadav, Ashutosh Pratap Singh, Madavi Choudhary, Ajit C. Kunwar

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

Baylis–Hillman acetates undergo smooth alkylation with aryl-substituted iodoalkynes in the presence of indium metal in refluxing dichloromethane to furnish 1,4-enynes in high yields with (*E*)-stereoselectivity. In the absence of Lewis acid, the reaction follows both S_N2 and S_N2' pathways affording 1:1 mixtures of 1,4-enynes. Upon addition of 10 mol % of InBr_3 , the reaction proceeds preferably in the S_N2' manner. In the case of adducts derived from acrylonitrile, the corresponding products are obtained in fairly good yields and with (*Z*)-stereoselectivity.

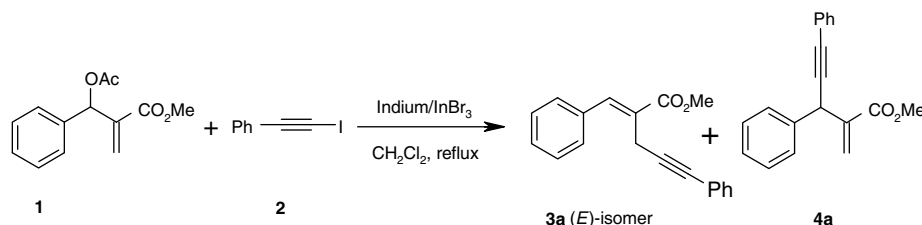
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Baylis–Hillman adducts and their acetates are well known carbon electrophiles capable of reacting with various nucleophiles. Their ability to undergo S_N2' allylic substitution reactions contributes largely to their synthetic value.¹ The ready availability and versatility of Morita–Baylis–Hillman adducts makes them valuable synthetic intermediates 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, frontaline, trimethoprim, sarkomycin, ilmofosine, nuciferol and many others.^{1,2} Consequently, various nucleophiles such as allylzinc reagents, metal hydrides, halides, azides, cyanides, alcohols, amines, arenes, indoles and active methylene compounds have been used to prepare a wide range of synthetic intermedi-

ates.^{3–7} However, there have been no reports on the allylic substitution of Baylis–Hillman acetates with alkynylindium reagents to produce 1,4-enynes.

Indium has emerged as a very useful metal in organic synthesis as it possesses certain unique properties. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. In addition, indium exhibits low heterophilicity in organic reactions, and thus oxygen- and nitrogen-containing functional groups are usually well tolerated by organoindium reagents.⁸ Moreover, indium-assisted reactions display low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity.⁹

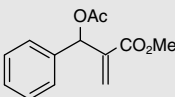
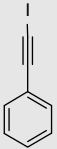
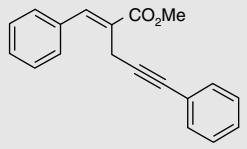
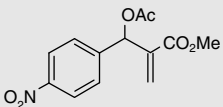

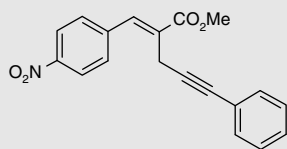
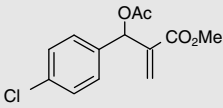
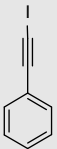
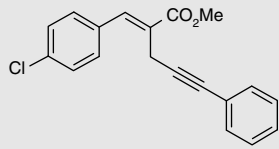
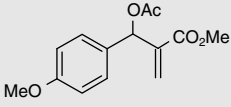
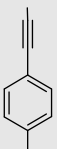
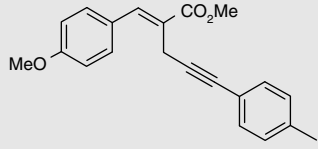
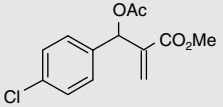
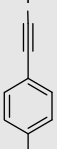
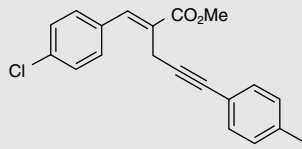
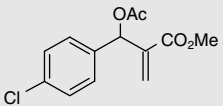
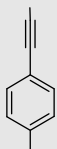
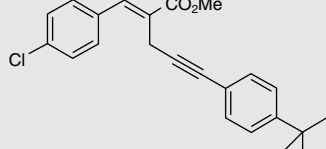
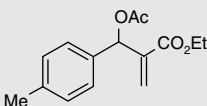
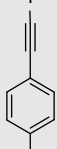
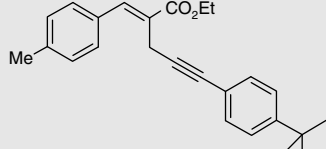
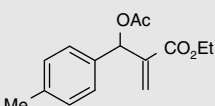

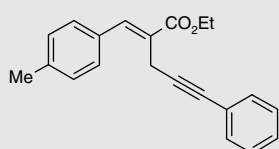
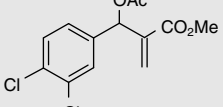
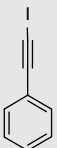
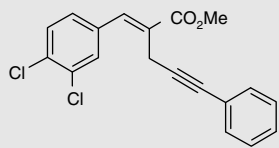
In this Letter, we report a versatile approach for the preparation of 1,4-enynes by means of allylic nucleophilic substitution of Baylis–Hillman acetates with iodophenyl acetylenes using the



Scheme 1. Preparation of 3a/4a.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J. S. Yadav).

Table 1
Indium/InBr₃-promoted alkylation of Baylis–Hillman acetates with iodophenylacetylenes

Entry	Acetate 1	Iodoalkyne 2	Product ^a 3	Time (h)	Yield ^b (%)	Ratio (3:4) ^c
a				7.0	85	80:20
b				6.0	91	90:10
c				8.0	92	90:10
d				7.5	83	80:20
e				10.0	86	75:25
f				5.0	91	65:35
g				4.5	93	70:30
h				8.5	87	80:20
i				7.5	96	95:5

(continued on next page)

Table 1 (continued)

Entry	Acetate 1	Iodoalkyne 2	Product ^a 3	Time (h)	Yield ^b (%)	Ratio (3:4) ^c
j				5.0	90	80:20
k				8.0	87	85:15
l				10.0	72	65:35
m				12.0	70	60:40
n				9.0	82	90:10
o				13.0	70	60:40

^a The products were characterized by NMR, IR and mass spectrometry.

^b Yield refers to pure products after chromatography.

^c Ratio of products **3** and **4** was determined from the NMR spectra of the crude products.

In/InBr₃ reagent system. Thus, treatment of the Baylis–Hillman acetate derived from benzaldehyde and methyl acrylate, methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1**) with 2 equiv of iodophenylacetylene (**2**) and 2 equiv of indium metal in the presence of 10 mol % InBr₃ in refluxing dichloromethane gave the corresponding enyne product in 85% yield as a mixture of **3a** and **4a** in an 8:2 ratio favouring **3a** (Scheme 1).

The products **3a** and **4a** could be separated easily by column chromatography. In the absence of InBr₃, **3a** and **4a** were obtained in a 1:1 ratio. The ratio was determined by ¹H NMR spectroscopy of the crude product. Thus, the addition of 10 mol % of InBr₃ is crucial to achieve the desired product **3a** predominantly. Other indium(III) halides such as InCl₃ and InI₃ can also be used for this conversion. Similarly, various aryl-substituted Baylis–Hillman acetates reacted smoothly with iodophenylacetylene to provide (*E*)-methyl 2-benzylidene-5-phenylpent-4-ynoate derivatives in good to excellent yields and with complete (*E*)-selectivity (entries **b**, **c** and **i**, Table 1). The (*E*)-stereochemistry of the product **3a** was assigned on the basis of the chemical shift value of the olefinic proton in the

¹H NMR spectrum.¹⁰ The structure of **3f** was established by two-dimensional nuclear Overhauser effect spectroscopy (NOESY, Fig. 1).

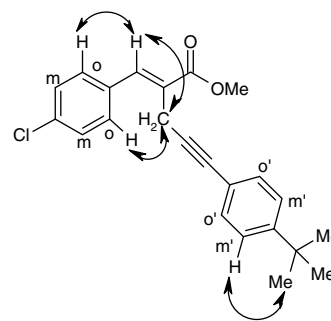
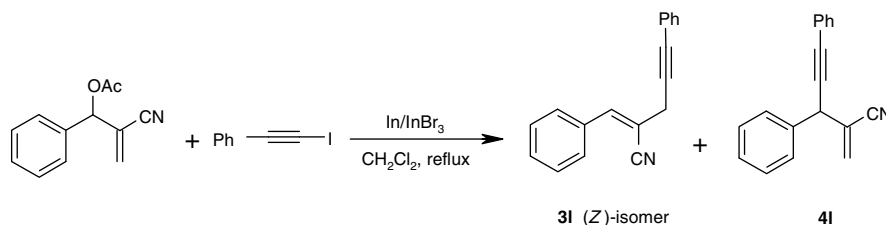


Figure 1. Characteristic nOe's of **3f**.



Scheme 2. Preparation of 3I/4I.

The nOe correlations, CH- H_{ortho} and t -butyl- H_{meta} , were sufficient for assigning the aromatic resonances. The *cis* orientation of the two aromatic substituents across the double bond was inferred from a strong nOe cross peak between CH_2 and H_{ortho} . Additional support for the proposed structure came from a weak nOe correlation between CH_2 and CH, being *trans* to each other. This result provided incentive for an extensive study. Interestingly, various aryl-substituted iodophenylacetylenes also participated in this reaction (entries **d**, **e**, **f** and **g**, Table 1). However, reaction of the Baylis–Hillman acetates derived from acrylonitrile, that is, 3-acetoxy-2-methylene-3-phenylpropionitrile, with iodophenylacetylene gave the product as a mixture of **3I** and **4I** favouring **3I** (Scheme 2).

In the case of 3-acetoxy-2-methylene-3-aryl propionitriles, the products were obtained with (*Z*)-stereoselectivity. The (*Z*)-stereochemistry of the products was assigned on the basis of the chemical shift value of the olefinic proton in the 1H NMR spectrum.¹⁰ The structure of **3m** was established by nOe experiments (Fig. 2).

The resonance assignments of the aromatic groups were facilitated by the nOes between Me- H_{meta} and CH- H_{ortho} . The presence of a strong nOe correlation between the CH and CH_2 protons implies that they are *cis* to each other. In this geometry, unlike **3f**, the CH_2 and the H_{ortho} distance is large and no nOe cross peak is observed between CH_2 and H_{ortho} . The reactions were clean and highly stereoselective affording the products in good yields. The products were characterized by 1H NMR, IR and mass spectrometry.

Furthermore, the reactions were carried out with Baylis–Hillman adducts (hydroxy compounds) instead of acetates. Even though the reactions succeeded with hydroxy compounds, low conversions (20–45%) were obtained even after long reaction times. The best results were obtained with Baylis–Hillman acetates. As solvent, dichloromethane gave the best results. In the absence of indium metal, no nucleophilic substitution occurred even after long reaction times (9–12 h) under reflux conditions. The scope of this method was investigated with respect to various allylic acetates, and the results are presented in Table 1.¹¹ The observation of (*E*)-selectivity with esters and (*Z*)-selectivity with nitriles is consistent with earlier reports.¹² The reversal of stereochemistry may be attributed to the chelated structure, in the case of ester leading to (*E*)-product and to non-chelated structure, in the case of nitriles leading to (*Z*)-product (Scheme 3).

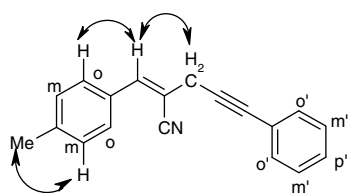
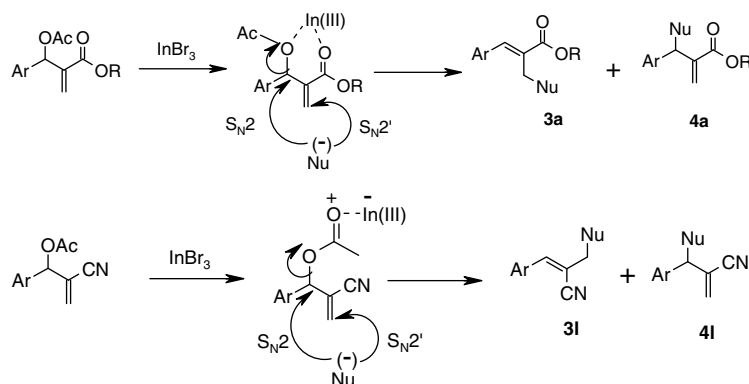
In conclusion, we have described a novel method for the preparation of 1,4-enynes from Baylis–Hillman acetates and iodophenylacetylenes via S_N2' type allylic substitution. The method has several advantages such as operational simplicity, mild reaction conditions, clean reaction profiles and simple experimental and work-up procedures which makes it a useful and attractive process for the preparation of 1,4-enynes.

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Figure 2. Characteristic nOe's of **3m**.

Scheme 3. A plausible reaction mechanism.

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11. *General procedure*: To a stirred suspension of indium metal (2.0 mmol) in dichloromethane was added a solution of Baylis–Hillman acetate (1 mmol), iodophenylacetylene (2.0 mmol) and InBr_3 (10 mol %) in dichloromethane at room temperature. The resulting mixture was stirred at room temperature for 2 h and then at reflux for 6–12 h. After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:50) to afford pure product. Spectroscopic data for selected products: **Compound 3b**: Yellow viscous liquid IR (KBr): ν 2925, 2853, 1717, 1597, 1519, 1490, 1439, 1345, 1297, 1268, 1219, 1087, 917, 853, 756, 693, 527 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.32 (d, $J = 8.3$ Hz, 2H), 7.78 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.40–7.26 (m, 5H), 3.91 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 166.8, 141.3, 137.9, 134.3, 131.6, 130.3, 129.0, 128.0, 126.0, 123.7, 123.2, 85.8, 81.8, 52.6, 18.7; LCMS: m/z : 322 ($\text{M}+\text{H}^+$), 279, 258, 161, 133, 102; HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{NO}_4\text{Na}$: 344.0898, Found: 344.0912. **Compound 3f**: Viscous liquid, IR (KBr): ν 2957, 2924, 2853, 1717, 1633, 1491, 1462, 1436, 1274, 1213, 1088, 834, 762, 562 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.73 (s, 1H, CH), 7.53 (d, $J = 8.6$ Hz, 2H, *ortho*), 7.40 (d, $J = 8.6$ Hz, 2H, *meta*), 7.33 (d, $J = 8.5$ Hz, 2H, *ortho'*), 7.30 (d, $J = 8.5$ Hz, 2H, *meta'*), 3.87 (s, 3H, CO_2Me), 3.56 (s, 2H, CH_2), 1.30 (s, 9H, $3 \times \text{Me}$); ^{13}C NMR (75 MHz, CDCl_3): δ 167.5, 151.1, 139.2, 135.0, 133.4, 131.3, 131.0, 128.8, 128.5, 125.1, 120.4, 85.8, 81.3, 52.3, 34.6, 31.1, 18.7; LCMS: m/z : 367 ($\text{M}+\text{H}^+$). HRMS calcd for $\text{C}_{23}\text{H}_{23}\text{O}_2\text{ClNa}$: 389.1284, Found: 389.1298. **Compound 3j**: Viscous liquid, IR (KBr): ν 2923, 2853, 1715, 1638, 1508, 1438, 1270, 1225, 1160, 1083, 836, 756, 692, 523 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.73 (s, 1H), 7.58 (dd, $J = 5.2, 8.3$ Hz, 2H), 7.41–7.23 (m, 5H), 7.12 (t, $J = 8.3$ Hz, 2H), 3.87 (s, 3H), 3.56 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 167.5, 164.6, 161.3, 139.5, 131.7, 131.6, 128.1, 127.8, 123.6, 115.8, 115.6, 86.7, 81.1, 52.3, 22.6, 18.6; LCMS: m/z : 317 ($\text{M}+\text{Na}$), 295, 232; HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{FO}_2\text{Na}$: 317.0953, Found: 317.0938. **Compound 3m**: Viscous liquid; IR (KBr): ν 3028, 2923, 2854, 2210, 1726, 1604, 1510, 1490, 1446, 1416, 1378, 1261, 1183, 1067, 1027, 912, 813, 757, 693, 528 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.67 (d, $J = 8.2$ Hz, 2H, *ortho*), 7.47 (m, 2H, *ortho'*), 7.40 (m, 3H, *meta'*, *para'*), 7.31 (t, $J = 1.7$ Hz, 1H, CH), 7.23 (d, $J = 8.2$ Hz, 2H, *meta*), 3.56 (d, $J = 1.7$ Hz, 2H, CH_2), 2.39 (s, 3H, Me); ^{13}C NMR (75 MHz, CDCl_3): δ 144.2, 140.7, 131.7, 130.5, 129.5, 128.7, 128.5, 128.3, 122.7, 118.4, 104.9, 85.6, 83.0, 26.2, 21.4; LCMS: m/z : 258 ($\text{M}+\text{H}^+$), 221, 102; HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{NNa}$: 280.1102, Found: 280.1104.
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