Tetrahedron Letters 51 (2010) 2291–2294

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The allylic nucleophilic substitution of Morita–Baylis–Hillman acetates with isocyanides: a facile synthesis of trisubstituted olefins

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ARTICLE INFO

Article history:
Received 23 October 2009
Revised 15 February 2010
Accepted 20 February 2010
Available online 24 February 2010

Keywords:
Morita–Baylis–Hillman acetates
S_N2' substitution
TosMIC
Alkylation

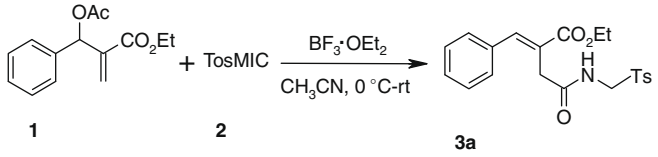
ABSTRACT

Morita–Baylis–Hillman acetates undergo smooth allylic nucleophilic substitution (S_N2') with tosylmethyl isocyanide (TosMIC) in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ under mild conditions to furnish trisubstituted olefins in high yields with (*E*)-stereoselectivity.

The ready availability and versatility of Morita–Baylis–Hillman acetates make 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, frontalin, trimethoprim, sarkomycin, ilmofosine nuciferol and many others.[1,2] Consequently, various nucleophiles such as allyl–zinc reagents, metal hydrides, halides, azides, cyanides, alcohols, amines, arenes, indoles and active methylene compounds have been used to prepare a wide range of synthetic intermediates.[3–7] However, there have been no reports on the allylic substitution of Baylis–Hillman acetates with TosMIC to produce trisubstituted olefins. Lewis acid-catalyzed carbon–carbon bond-forming reactions are of great significance in organic synthesis because of their high reactivity, selectivity and mild reaction conditions.[8]

In this Letter, we report a versatile approach for the preparation of trisubstituted olefins by means of allylic nucleophilic substitution of Baylis–Hillman acetates with tosylmethyl isocyanide using a catalytic amount of $BF_3{\cdot}OEt_2$. Thus, treatment of the Baylis–Hillman acetate derived from benzaldehyde and ethyl acrylate, ethyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1**) with TosMIC (**2**) in the presence of 10 mol % $BF_3{\cdot}OEt_2$ in dry acetonitrile gave the corresponding trisubstituted olefin **3a** in 90% yield (Scheme 1).

The product was obtained as a mixture of *E*- and *Z*-isomers in 9:1 ratio favouring *E*-isomer. The ratio of (*E*) and (*Z*) isomers was determined on the basis of integration ratios of isomeric olefinic proton and allylic methylene protons in ^{1}H NMR spectra of products. The (*E*)-stereochemistry of the products was assigned on the basis of the chemical shift values of vinyl and allylic protons in the ^{1}H NMR spectra of the products and also by the comparison of the spectral data with authentic samples.[9] In the ^{13}C NMR spectra of trisubstituted olefins, allylic carbon cis- to aryl group appears up field while the same carbon trans to aryl group appears down field.[10] The structure of **3a** was also established by two-dimensional nuclear Overhauser effect spectroscopy (NOESY, Fig. 1).



Scheme 1. Preparation of **3a** from allylic acetate (**1**) and isocyanide (**2**).

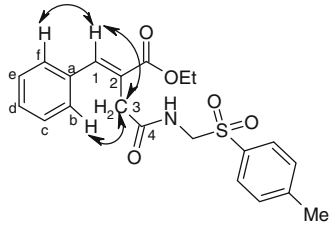


Figure 1. Characteristic NOEs' of product **3a**.

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0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.130

The cis orientation of the two aromatic substituents across the double bond was inferred from a strong NOE cross peak between CH_2 (C-3) and H_b. Additional support for the proposed structure came from a weak NOE correlation between CH_2 (C-3) and CH (C-1), being trans to each other.

These results encouraged us to examine the reactivity of various substituted Baylis–Hillman acetates. Interestingly, Baylis–Hillman acetates derived from both aliphatic and aromatic aldehydes participated well in this reaction (Table 1). In all cases, the reactions were clean and stereoselective affording the trisubstituted olefins in good yields with complete (*E*)-selectivity. In case of cinnamaldehyde, the corresponding product was obtained in 85% yield with (2*E*,4*E*)-selectivity (Table 1, entry h). Allylic acetates derived from heteroaromatic aldehydes were also equally effective for this transformation (Table 1, entries k and l). The reaction conditions were compatible with various functionalities such as olefins, halides, aryl methyl ethers and esters (Table 1). The products were characterized by ^{1}H NMR, IR and mass spectroscopy. In the absence of $BF_3{\cdot}OEt_2$, no allylic substitution occurred even after long reaction times (6–12 h) under reflux conditions. Various Lewis acids such as $InCl_3$, $FeCl_3$ and $CeCl_3{\cdot}7H_2O$ were screened and none gave desired product. Furthermore, metal triflates such as $Sc(OTf)_3$,

Table 1
Allylic nucleophilic substitution of Baylis–Hillman acetates with isocyanides using $BF_3{\cdot}OET_2$

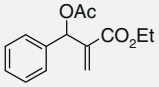
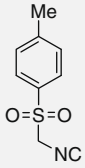
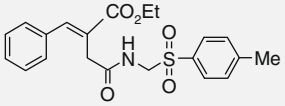
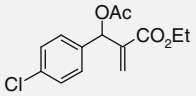
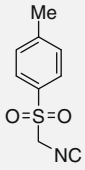
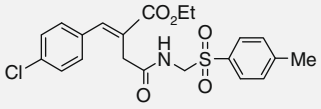
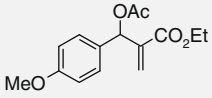
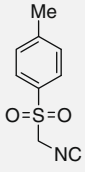
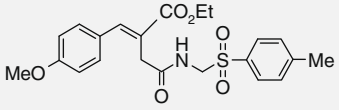
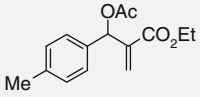
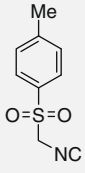
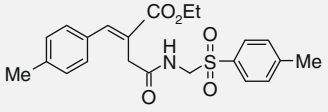
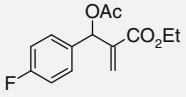
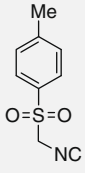
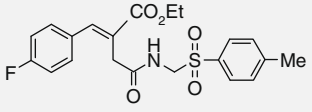
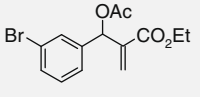
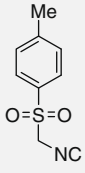
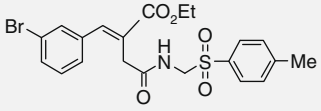
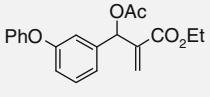
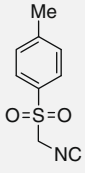
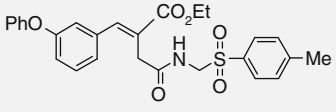
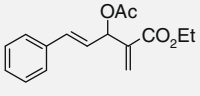
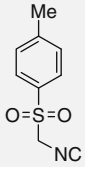
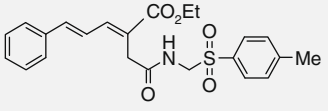
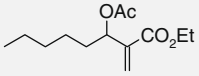
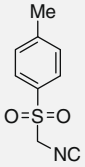
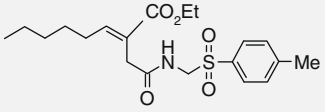
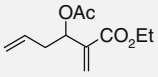
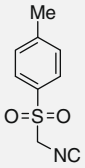
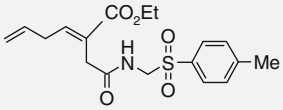
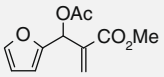
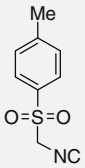
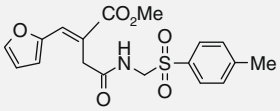
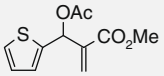
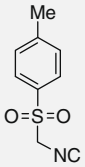
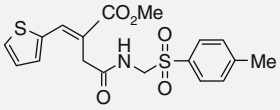
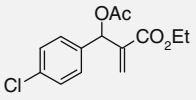
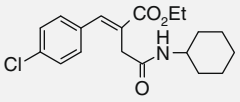
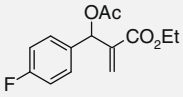
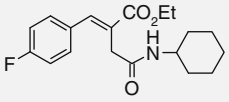
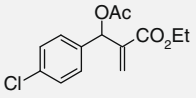
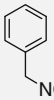
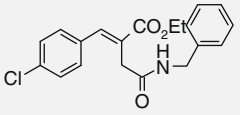
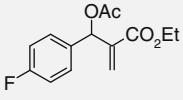
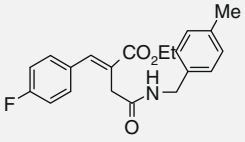
Entry	Substrate	Isocyanide	Product (**3**)[a]	Reaction time (h)	Yield[b] (%)
a				2.0	90
b				3.0	95
c				2.0	92
d				4.0	85
e				3.0	88
f				5.0	78
g				4.0	84
h				4.0	85

Table 1 (*continued*)

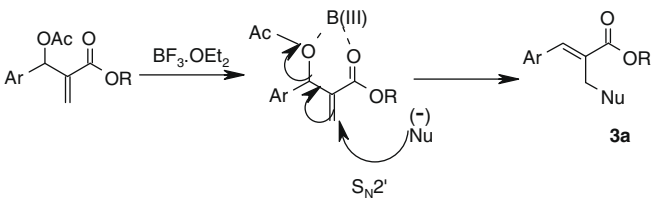
Entry	Substrate	Isocyanide	Product (**3**)[a]	Reaction time (h)	Yield[b] (%)
i				3.0	78
j				4.0	77
k				5.0	84
l				3.0	88
m				4.0	74
n				3.0	76
o				3.5	72
p				3.5	70

[a] The product was characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

$Yb(OTf)_3$ and $In(OTf)_3$ also failed to give the desired product under similar conditions. Interestingly, various isonitriles such as cyclohexyl, benzyl and *p*-methylbenzyl isocyanides also participated in this reaction (Table 1, entries m–p). As a solvent, acetonitrile gave the best results. The scope of the $BF_3.OEt_2$-promoted allylic substitution was investigated with respect to various Baylis–Hillman acetates and the results are presented in Table 1.[11] 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. High conversions were obtained only with Baylis–Hillman acetates. Though the reaction was successful with cyclohexyl isocyanide, the yields were low compared to those of TosMIC (Table 1, entries m and n).

The reaction may proceed via the activation of allylic acetate by the Lewis acid. A preferential attack of isonitrile across the olefin gave the trisubstituted olefin. The stereochemistry may be attributed to the formation of chelated structure, in the case of ester, leading to (*E*)-product (Scheme 2).[12]

In conclusion, we have described a novel method for the preparation of trisubstituted olefins from Morita–Baylis–Hillman acetates and tosylmethyl isocyanide via S_N2' type allylic substitution. The method has several advantages such as operational simplicity, mild reaction conditions, clean reaction profiles, simple experimental



Scheme 2. A plausible reaction mechanism.

and work-up procedures and the use of inexpensive and readily available reagents which makes it a useful and attractive process for the preparation of trisubstituted olefins.

Acknowledgement

A.P.S. and N.M. thank CSIR, New Delhi for the award of fellowships.

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11. *General procedure*: A mixture of Baylis–Hillman acetate (1.0 mmol), TosMic (1.2 mmol) and $BF_3{\cdot}OEt_2$ (0.1 mmol) in dry acetonitrile (5 mL) was stirred at 0 °C until complete reaction took place. The mixture was then diluted with saturated $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (2×10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent was followed by purification by silica gel column chromatography eluting with hexane/ethyl acetate (6:4) gave the pure product. *Spectral data* (**3b**): white solid, mp 87–89 °C; IR (neat): ν 3288, 3089, 2982, 2934, 1711, 1644, 1557, 1490, 1442, 1370, 1287, 1232, 1088, 1012, 924, 846, 816, 765, 721 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, 3H, J = 7.5 Hz), 1.97 (s, 3H), 2.04 (d, 2H, J = 6.7 Hz), 4.05–4.17 (m, 2H), 4.25–4.32 (m, 2H), 6.19 (s, 1H, NH), 7.18 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 7.40 (d, 2H, J = 8.3 Hz), 7.51 (d, 2H, J = 9.0 Hz), 7.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 185.6, 169.5, 167.5, 140.5, 135.2, 132.5, 130.9, 128.8, 128.5, 127.6, 127.5, 61.2, 61.0, 60.3, 54.2, 36.6, 29.5, 23.2, 20.9, 14.1, 13.9; ESIMS: m/z: 436.3 (M^+H); HRMS calcd for $C_{21}H_{22}ClNO_5SNa$: 458.0805, found: 458.0807. *Compound* **3d**: colourless solid, mp 85–87 °C. IR (neat): ν 3275, 2982, 2926, 1706, 1653, 1540, 1447, 1369, 1288, 1229, 1185, 1109, 1025, 815, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, 3H, J = 7.5 Hz), 1.96 (s, 3H), 2.01 (d, 2H, J = 5.2 Hz), 2.36 (s, 3H), 4.04–4.12 (m, 2H), 4.23–4.31 (m, 2H), 6.20 (s, 1H, NH), 7.20 (d, 4H, J = 7.5 Hz), 7.39 (d, 4H, J = 7.5 Hz), 7.69 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 188.3, 177.2, 166.5, 155.8, 144.0, 143.4, 133.7, 129.6, 127.9, 106.7, 95.5, 92.8, 90.6, 73.1, 69.2, 48.3, 47.1, 29.6, 24.5, 21.3, 14.0; ESIMS: m/z: 438 (M^+Na); HRMS calcd for $C_{22}H_{25}NO_5SNa$: 438.1351, found: 438.1354. *Compound* **3e**: white solid, mp 84–86 °C; IR (neat): ν 3282, 3067, 2984, 2925, 1708, 1651, 1601, 1510, 1371, 1288, 1229, 1110, 1023, 837, 761, 517 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.36 (dt, 3H, J = 9.0 Hz), 1.96 (d, 3H, J = 1.5 Hz), 2.01 (s, 2H), 4.07–4.16 (m, 2H), 4.26 (dq, 2H, J = 6.7, 8.3 Hz), 6.35 (s, 1H, NH), 6.94 (dt, 1H, J = 8.3 Hz), 7.08 (dt, 3H, J = 9.8 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.56 (t, 3H, J = 6.7 Hz), 7.66 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 164.6, 140.7, 131.7, 131.6, 128.1, 128.0, 127.8, 127.1, 115.8, 115.5, 115.4, 115.1, 61.1, 60.9, 54.1, 36.6, 29.5, 23.2, 14.2, 13.8; ESIMS: m/z: 420; HRMS calcd for $C_{21}H_{22}ClNO_5SNa$: 442.1100, found: 442.1103.
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