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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4169–4172

The first one-pot oxidative Michael reaction of Baylis–Hillman adducts with indoles promoted by iodoxybenzoic acid

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Received 21 March 2007; revised 6 April 2007; accepted 18 April 2007
Available online 22 April 2007

Abstract—Baylis–Hillman adducts undergo smooth, one-pot oxidative conjugate addition with indoles in the presence of 2-iodoxybenzoic acid (IBX) under neutral conditions to afford a new class of substituted indoles in good yields.

The Baylis–Hillman reaction is an important carbon–carbon bond forming reaction and involves coupling of activated vinylic systems with aldehydes or imines in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO).[1,2] It is widely used for the direct synthesis of α-hydroxy or α-amino alkyl- or aryl–vinyl systems. The versatility of the functionality in such Baylis–Hillman adducts and their acetates makes them valuable synthetic intermediates[3] 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.[4–6] Consequently, various nucleophiles such as metal hydrides, halides, azides, cyanides, alcohols, amines, arenes and active methylene compounds have been used to prepare a wide range of synthetic intermediates.[1,3,7] However, oxidative Michael reaction of Baylis–Hillman adducts with indoles has not been reported.

The indole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activities, and thus considerable attention has been directed towards general, flexible and selective methods for the synthesis of highly functionalized indole derivatives.[8] Recently, the use of hypervalent iodine reagents has attracted increasing interest as oxidants in organic synthesis due to their mild, selective and environmentally benign oxidizing properties.[9] Among various hypervalent iodine reagents, iodoxybenzoic acid (IBX) is versatile because of its high efficiency, easy availability, mild reaction conditions and its stability to moisture and air.[10] Wide functional group tolerance and high-yielding reactions, without over-oxidation have made IBX very familiar for the oxidation of alcohols even in the presence of olefins, thioethers and amino groups,[11] and in other elegant oxidative transformations.[12]

In this Letter, we report a novel and efficient oxidative Michael reaction of Baylis–Hillman adducts with indoles using 2-iodoxybenzoic acid (IBX) under neutral conditions. Initially, we examined the oxidative Michael reaction of ethyl 2-[hydroxyl(phenyl)methyl] acrylate (**1**) with indole (**2**) in the presence of 1.2 equiv of IBX in acetonitrile. The reaction went to completion in 8 h and the product, ethyl 2-((1*H*-indol-3-yl)methyl)-3-oxo-3-phenylpropanoate (**3a**) was obtained in 80% yield (Scheme 1).

Thus encouraged, we examined other substituted Baylis–Hillman adducts and indoles (Table 1). This method worked well with both substrates derived from aliphatic and aromatic aldehydes. In all cases, the reactions were clean and afforded the Michael adducts in good yields.

Keywords: Baylis–Hillman adducts; Hypervalent iodine; Indoles; Conjugate addition.
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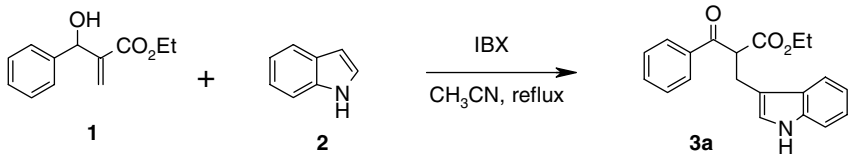
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.04.086



Scheme 1.

Table 1. One-pot oxidative Michael addition of indoles to Baylis–Hillman adducts

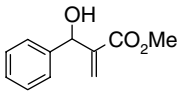
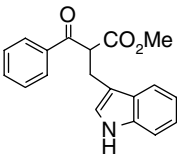
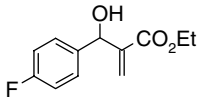
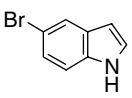
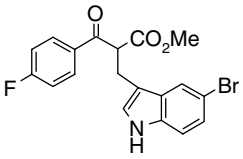
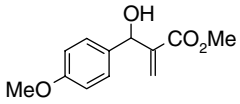
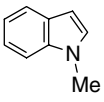
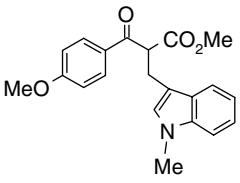
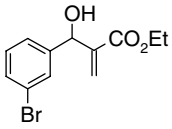
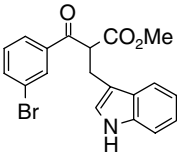
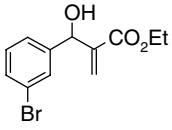
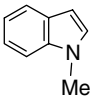
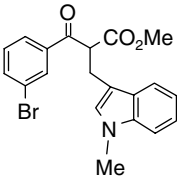
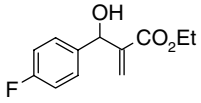
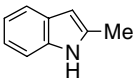
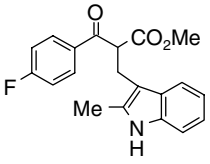
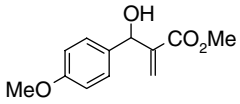
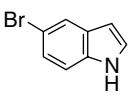
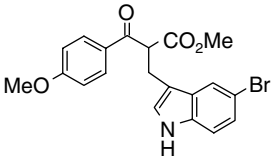
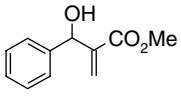
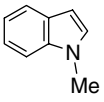
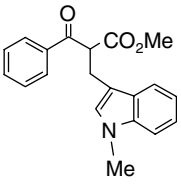
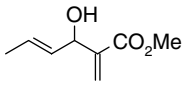
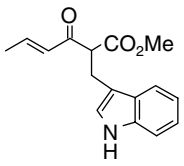
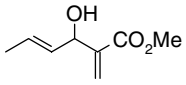
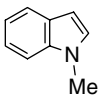
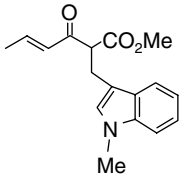
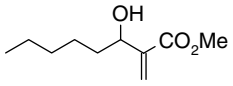
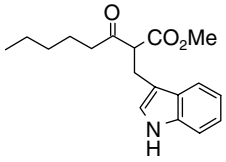
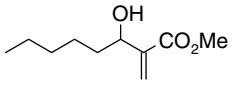
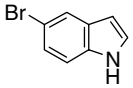
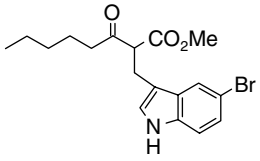
Entry	Substrate	Indole	Product[a]		Reaction time (h)	Yield[b] (%)
a				**3a**	8	80
b				**3b**	7	76
c				**3c**	10	80
d				**3d**	8	79
e				**3e**	7	85
f				**3f**	6	82
g				**3g**	9	83
h				**3h**	7	86

Table 1 (*continued*)

Entry	Substrate	Indole	Product[a]		Reaction time (h)	Yield[b] (%)
i				**3i**	10	78
j				**3j**	11	75
k				**3k**	12	81
l				**3l**	12	82

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers 1δ pure products after column chromatography.

The reaction conditions were compatible with various functionalities such as halides, aryl methyl ethers, esters and alkenes (Table 1). The products were characterized by ^{1}H NMR, IR and mass spectroscopy. Of various hypervalent iodine reagents examined, including iodosobenzene (PhIO), iodobenzene diacetate ($PhI(OAc)_2$) and Dess–Martin periodinane (DMP), 2-iodoxybenzoic acid (IBX) was found to be the best in terms of conversion. Other oxidants such as Oxone® and *m*-CPBA failed to produce the desired product. In the absence of IBX, no reaction occurred even after long reaction times (8–12 h) under reflux. As a solvent, acetonitrile appeared to give the best results. The byproduct, iodosobenzoic acid, was separated by simple filtration. The recovered iodosobenzoic acid (IBA) could be reoxidized to IBX. The scope of the IBX promoted alkylation of indoles was investigated with respect to various Baylis–Hillman adducts and the results are presented in Table 1.[13]

In conclusion, we have described a novel method for the alkylation of indoles with Baylis–Hillman adducts via an oxidative Michael addition using IBX. The method has several advantages such as operational simplicity, mild reaction conditions, clean reaction profiles, a simple work-up procedure and the use of inexpensive and readily available IBX.

Acknowledgement

A.P.S. and A.K.B. thank the CSIR, New Delhi, for the award of fellowships.

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13. *Experimental procedure*: A mixture of Baylis–Hillman adduct (1 mmol), indole (1 mmol) and IBX (1.2 mmol) in acetonitrile (5 mL) was stirred at reflux for a specified amount of time (Table 1). After complete conversion as indicated by TLC, the obtained solid was filtered and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography using a gradient mixture of ethyl acetate/hexane (1:9) as eluent to afford a pure adduct. Spectral data for selected compounds: **3e**: brown oil, IR (neat): ν 2924, 2854, 1735, 1688, 1470, 1324, 1227, 1024, 724 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, 3H, $J = 6.8$ Hz), 3.41 (d, 2H, $J = 6.7$ Hz), 3.67 (s, 3H), 4.10 (q, 2H, $J = 6.8$ Hz), 4.58 (t, 1H, $J = 6.7$ Hz), 6.81 (s, 1H), 7.02–7.30 (m, 4H), 7.54 (d, 1H, $J = 7.5$ Hz), 7.60 (d, 1H, $J = 8.3$ Hz), 7.80 (d, 1H, $J = 7.5$ Hz), 8.02 (s, 1H). LCMS: m/z: 436 (M+Na). HRMS calcd for $C_{21}H_{20}NO_3NaBr$: 436.0524; found, 436.0511. Compound **3h**: Brown oil, IR (neat): ν 2926, 2101, 1739, 1685, 1596, 1448, 1326, 1233, 1020, 741 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.42 (d, 2H, $J = 6.8$ Hz), 3.63 (s, 3H), 3.69 (s, 3H), 4.66 (t, 1H, $J = 7.5$ Hz), 6.88 (s, 1H), 7.02–7.20 (m, 3H), 7.40 (d, 1H, $J = 7.5$ Hz), 7.49 (d, 1H, $J = 7.5$ Hz), 7.56 (d, 1H, $J = 8.3$ Hz), 7.92 (d, 1H, $J = 7.5$ Hz). LCMS: m/z: 344 (M+Na). HRMS calcd for $C_{20}H_{19}NO_3Na$: 344.1262; found, 344.1272. Compound **3l**: Brown oil, IR (neat) ν 3389, 2954, 2929, 2863, 1740, 1711, 1459, 1278, 1213, 1098, 795 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.83 (t, 3H, $J = 6.6$ Hz), 1.08–1.30 (m, 5H), 1.39–1.58 (m, 1H), 2.20–2.60 (m, 2H), 3.22 (d, 2H, $J = 7.3$ Hz), 3.68 (s, 3H), 3.84 (t, 1H, $J = 7.3$ Hz), 6.91 (d, 1H, $J = 2.1$ Hz), 7.20 (t, 2H, $J = 3.6$ and 1.4 Hz), 7.64 (s, 1H), 8.39 (br s, 1H, NH). LCMS: m/z: 402 (M+Na). HRMS calcd for $C_{18}H_{22}NO_3NaBr$: 402.0680; found, 402.0686.