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First example of the C-alkylation of indoles with Baylis–Hillman acetates[☆]

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Abstract—Baylis–Hillman acetates undergo S_N2' allylic substitution with indoles in the presence of 20 mol% of indium tribromide under mild conditions to afford a new class of substituted indoles in high yields with (*E*)-stereoselectivity. The stereochemistry of the products was assigned by various NMR experiments.

The Baylis–Hillman reaction is an important carbon–carbon bond forming reaction.[1] The coupling of activated vinylic systems with aldehydes or imines in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO), known as the Baylis–Hillman reaction,[2] is widely used for the direct synthesis of α-hydroxy or α-aminoalkyl or aryl–vinyl systems. The versatility of functionalities present have made Baylis–Hillman adducts valuable synthetic intermediates.[5] 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, azetidinone, 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, there are no precedents for the allylic substitution of Baylis–Hillman acetates with indoles. In recent years, indium halides have been used as mild and water-tolerant Lewis acids imparting high regio-, stereo- and chemoselectivity in various organic transformations.[8] Compared to conventional Lewis acids, indium halides have the advantages of water stability, recyclability and operational simplicity. Indium tribromide in particular, is a useful Lewis acid catalyst in promoting various organic transformations.[9,10]

In this letter, we report our results on the nucleophilic allylic substitution of Baylis–Hillman acetates with indoles using catalytic indium bromide. Thus treatment of ethyl 3-acetoxy-3-phenyl-2-methylenepropanoate **1** with indole **2** in the presence of 20% $InBr_3$ in dichloromethane afforded ethyl 2-(-3-indolylmethyl)-3-phenyl-(*E*)-2-propenoate **3a** in 85% yield (Scheme 1).[11]

The assignment of structure and stereochemistry of the product **3a** was achieved by detailed NMR studies including DQCOSY, NOESY and HSQC experiments. The HSQC and ^{13}C spectra clearly showed the presence of 20 carbons with 1 methyl, 2 methylene, 11 methine and 6 quaternary carbons. The structure of **3a** was supported by NOE cross peaks between H10 and H14. The ^{13}C chemical shifts of C-12 and C-11 at 140.1 and 130.0 ppm, respectively, are close to the values expected for the *E*-geometry, which was shown to be an energetically most favourable isomer by molecular mechanics calculations (Fig. 1).[12]

Various substituted indoles also reacted smoothly with 3-acetoxy-2-methylene alkanoates to give the corresponding 3-substituted indoles in good yields (entries **b**–**i**, Table 1). Further, the reaction of 3-acetoxy-2-methylene-3-phenylpropionitrile **4** with indole afforded the

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Keywords: Indium compounds; Allylic substitution; Heteroaromatics.

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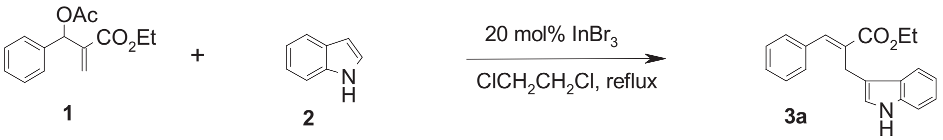


Scheme 1.

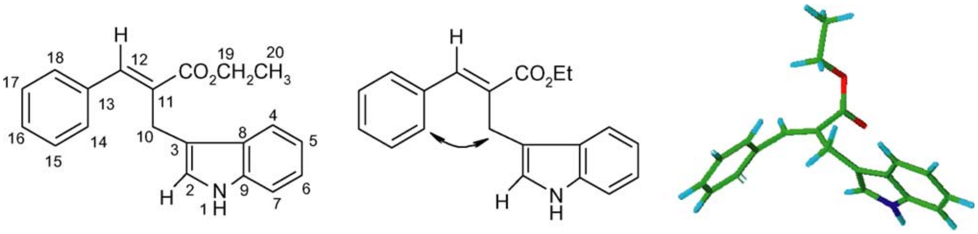
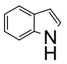
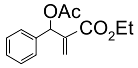
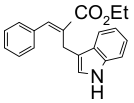
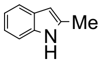
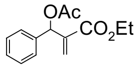
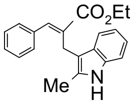
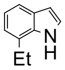
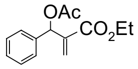
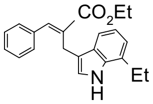
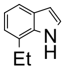
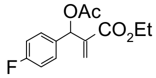
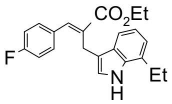
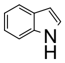
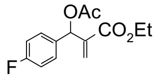
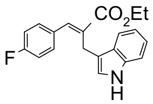
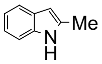
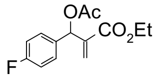
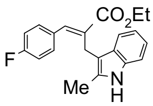
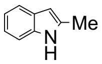
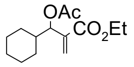
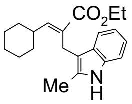
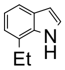
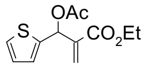
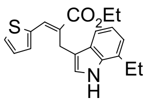
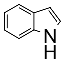
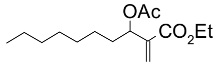
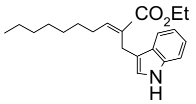
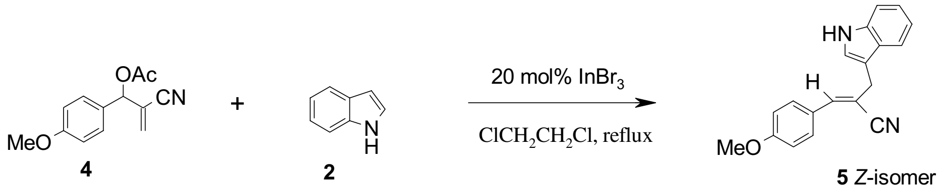


Figure 1. Important NOEs and the energy-minimised structure of product **3a**.

Table 1. Indium(III) bromide-promoted alkylation of indoles with Baylis–Hillman acetates

Entry	Indole	Allylic acetate	Product[a]		Time (h)	Yield (%)[b]
a				**3a**	3.5	85
b				**3b**	3.0	87
c				**3c**	4.0	81
d				**3d**	3.5	79
e				**3e**	4.0	82
f				**3f**	3.0	86
g				**3g**	3.0	90
h				**3h**	2.5	85
i				**3i**	3.5	82

[a] All products were characterised by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimised yields.



Scheme 2.

corresponding trisubstituted alkene **5** in 82% yield after 4 h (Scheme 2).

The product **5** was obtained with (*Z*)-stereoselectivity. The (*Z*)-stereochemistry of the product **5** was assigned on the basis of the H^1 chemical shifts of the vinyl and allylic protons. Metal triflates such as $Bi(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ were also found to catalyse the reaction but in only moderate yields. Best results were obtained when indium tribromide was used as the catalyst. In the absence of any catalyst, the reactions did not proceed even after long reaction times (8–12 h) under reflux. As a solvent, 1,2-dichloroethane yielded the best results compared to other solvents such as $CHCl_3$, CH_3CN, THF. The scope of indium tribromide catalysed alkylations of indoles was investigated with respect to various heteroaromatics and allylic acetates[7b] and the results are presented in Table 1.

In conclusion, we have described an efficient protocol for the alkylation of indoles with Baylis–Hillman acetates via S_N2' type allylic substitution using indium tribromide as the catalyst. This is a new approach for the functionalisation of indoles with allylic acetates.

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11. *Experimental procedure*: a mixture of indole (2 mmol), Baylis–Hillman acetate (2.5 mmol) and indium(III) bromide (20 mol%) in 1,2-dichloroethane (10 mL) was stirred at reflux for the appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure 3-substituted indole. Spectral data for selected products: **3a**: IR (Neat): ν 3389, 3056, 2931, 2874, 1713, 1631, 1602, 1508, 1441, 1369, 1293, 1226, 1160, 1097, 958, 833, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (br d, 1H, $J = 2.0$ Hz), 7.86 (br s, 1H, NH), 6.93 (br s, 1H, H-2), 7.63–7.10 (aromatic, 9H), 4.22 (q, 2H, $J = 7.1$ Hz, H-19), 4.02 (br s, 2H, H-10), 1.25 (t, 3H, $J = 7.1$ Hz, H-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (*C*=O), 140.1 (C-12), 135.6 (C-8), 133.0 (C-13), 130.0 (C-11), 129.4 (C-14), 129.3 (C-18), 128.5 (C-16), 128.3 (C-17), 128.1 (C-6), 126.9 (C-9), 122.2 (C-15), 121.7 (C-2), 119.4 (C-5), 119.0 (C-4), 111.1 (C-7), 109.0 (C-3), 60.9 (C-10), 23.4 (C-19), 14.1 (C-20). EIMS: *m*/*z*: 305 (M^+, 10), 276 (19), 232 (53), 130 (20), 102 (30), 91 (100), 77 (88), 51 (45). **5**: IR (Neat): ν 3372, 3066, 2965, 2841, 2210, 1743, 1605, 1511, 1438, 1305, 1258, 1180, 1029, 929, 830, 759 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (br d, $J = 2.0$ Hz, 1H, NH), 7.60–7.09 (m, 8H, aromatic), 7.23 (m, 1H), 6.95 (m, 1H), 3.83 (m, 2H), 3.81 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (C-16), 143.0 (C-12), 137.0 (C-8), 129.5 (C-14), 128.4 (C-6), 128.16 (C-18), 128.0 (C-2), 127.7 (C-17), 127.0 (C-13), 122.1 (C-2), 124.1 (C-15), 119.9 (C-5), 119.3 (C-4), 118.0 (–*C*≡N), 116.9 (C-11), 111.0 (C-7), 111.0 (C-3), 55.3 (C-10). EIMS: *m*/*z*: 288 (M^+, 44), 236 (19), 130 (53), 105 (100), 77 (78), 51 (35).
12. Molecular mechanics calculations were carried out using the Sybyl 6.8 programme on a Silicon Graphics O2 workstation.