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Isatin derivatives are reactive electrophilic components for the Baylis–Hillman reaction

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Abstract—Isatin derivatives readily react as the electrophilic component in the Baylis–Hillman reaction giving good to excellent yields of the respective adducts. It is generally accepted that ketones only take part in the Baylis–Hillman reaction under relatively extreme conditions, with a few exceptions. Isatin on the other hand readily reacts with acrylic acid derivatives in ethanol and or ethanol/THF mixtures in the presence of a catalytic quantity of DABCO. The solid state structures for these novel dioxindole derivatives were determined for two adducts by single-crystal X-ray diffraction spectroscopy, revealing an inside hydroxyl conformation.

The Baylis–Hillman reaction, also known as the Morita–Baylis–Hillman reaction, has proved to be a versatile method for the synthesis of α-hydroxy- or α-amino-alkyl activated olefins.[1,2] In spite of this versatility the reaction suffers from a number of limitations: long reaction times; poor or non-existent reactivity of activated β-substituted olefins; and the fact that ketones in general react only under high pressure and often give low yields of the respective products. However, ketone reactivity is increased by the presence of electron-withdrawing groups *alpha* to the carbonyl centre. Such groups include halogens[3–6] and carbonyls.[7–13] These substrates are often found to readily react under *normal* conditions, although in many cases reaction is limited to acrylonitrile and acrylaldehyde, or vinylketones. Whereas acrylate esters are often unreactive.[2,10]

Isatin, and a number of its derivatives, posses a reactive keto-carbonyl group that readily undergoes condensation reactions under mild conditions.[14] It was therefore speculated that isatin would be a suitable electrophilic component for the Baylis–Hillman reaction. The multifunctionalised product from such a reaction could serve as a versatile substrate for the synthesis of other heterocyclic compounds, including indoles[15,16] and quinolines.[17–21]

The Baylis–Hillman reaction has been generally performed using neat reagents. However, in the case of poor miscibility of the reagents a variety of solvents have been found to be useful.[2] Polar solvents have a beneficial effect and this has been attributed to an increase in the equilibrium constant for the formation of a zwitterionic intermediate.[22,23]

Initially, the reaction of partially solubilised *N*-methylisatin with an excess of ethyl acrylate (2 equiv.) in the presence of a catalytic quantity of DABCO (10–15 mol%) in ethanol was investigated (Fig. 1). The reaction mixture was left standing at room temperature in a stoppered sample flask.

The progress of the reaction was monitored by TLC over a period of several days, during which the formation of a polar, colourless, product and the complete

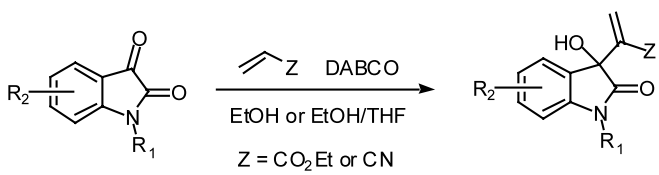

Figure 1. Synthesis of isatin Baylis–Hillman adducts. For definition of the substituents (R_1 and R_2) consult Table 1.

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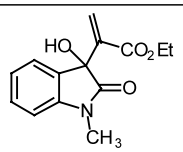
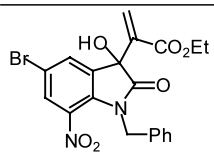
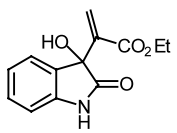
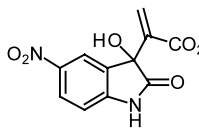
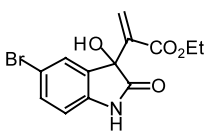
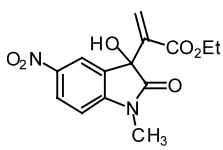
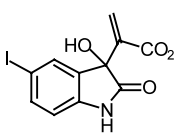
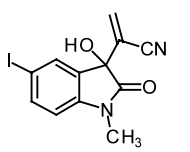
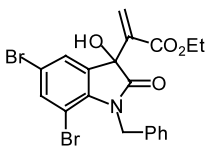
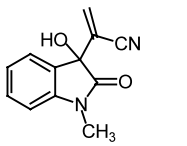
solubilisation of *N*-methylisatin was noted. After a period of 6 days the solution colouration had faded and TLC revealed only a trace of *N*-methylisatin and the presence of a sole product (Table 1, entry 1). The product was isolated by partitioning the reaction mixture between ethyl acetate and an aqueous HCl solution (0.25 M). A crude product was obtained in quantitative yield after drying the organic phase (Na_2SO_4), filtering and evaporation of the organic solvent under reduced pressure. This product was subsequently recrystallised from a mixture of hexane and ethyl acetate to give colourless plates. The spectroscopic data obtained from the analysis of the product by IR, NMR and low and high resolution mass spectrometry were consistent with that expected for the dioxindole structure of the Baylis–Hillman adduct.[24]

By analogy, various isatin derivatives were subjected to similar reaction conditions and in all cases the expected Baylis–Hillman adduct was obtained in good yield. The results are summarised in Table 1, entries 2–10, compounds **2**–**10**, respectively. From the table it can be deduced that *N*-alkylated isatins (entries 1, 5, 6 and 8–10) generally react faster than non-*N*-alkylated isatins (entries 2–4 and 7). This is attributed to the increased solubility of the former. It was also found that the presence of a nitro group resulted in shorter reaction times even though the nitro group bears a *meta* relationship with the ketone carbonyl group (entries 6–8).

On recrystallisation compounds **8** and **9** (Table 1) gave crystals suitable for single-crystal X-ray diffraction studies.[25] Fig. 2 shows an individual molecule from the respective unit cells of these compounds. Both of these structures are similar with respect to the conformation of the α-dioxindole-acrylate and -acrylonitrile fragments where the double bond (C_{10}–C_{11}) almost eclipses the carbon–hydroxyl bond, thus presenting an inside hydroxyl conformation (Fig. 3).[26] Table 2 presents some selected data with respect to the torsion angles around the C_9–C_{10} bond (crystallographic numbering). This conformation is substantially different from previous structures.[27–32] In addition, both compounds **8** and **9** present in the solid state an intermolecular hydrogen bond between the tertiary alcohol of one molecule and the amide carbonyl of a second molecule. In the case of compound **8** the chains have a 2_1 screw axis in the 010 direction, whilst in compound **9** the molecules form chains in the 001 direction via the operation of a c-glide.

Table 1. Synthesis of Baylis–Hillman adducts[24] by reaction of isatins with ethyl acrylate and acrylonitrile (see Fig. 1)[a]

Entry	Product	Reaction time (days) Yield (%); m.p. (°C)	Entry	Product	Reaction time (days) Yield (%); m.p. (°C)
1		6 >95; 142-3 (EtOAc/ hexane)	**6**		5 >95; oil, solidifies to give a waxy solid.
2		8 83-95; oil, solidifies to give a waxy solid.	**7**		2 70-82; syrup
3		11 **b** >95; 194-6 (decomp.)	**8**		3 92; 138-9 (EtOAc/ hexane)
4		14 **b** 82; 196-200 (decomp.)	**9**		3 79; 199-200 (EtOAc/ hexane)
5		4 >95; 125-6	**10**		3 83; 117-8 (EtOAc/ hexane)

a General experimental protocol: Isatin derivative (1 mmol) was suspended or solubilised in EtOH (5ml), unless otherwise indicated, in a sample flask. Ethyl acrylate, or acrylonitrile (2 mmol), was added followed by DABCO (15 mol%). The reaction mixture was sealed with a rubber septum and left stirring at room temperature. Reaction progress was followed by TLC but could also be noted by the disappearance of the colour of the respective isatin. On consumption of the isatin the reaction mixture was partitioned between dilute aqueous HCl (0.25M, 50ml) and EtOAc (2 x 30ml). The crude product was obtained after drying the organic phase over Na_2SO_4, filtering and evaporation under reduced pressure. Products were further purified by recrystallisation (as indicated) or by filtration through a short column of silica eluting with CH_2Cl_2 or CH_2Cl_2/EtOAc (4:1. V/V). **b** Use of EtOH/THF (1:1, V/V) as solvent.

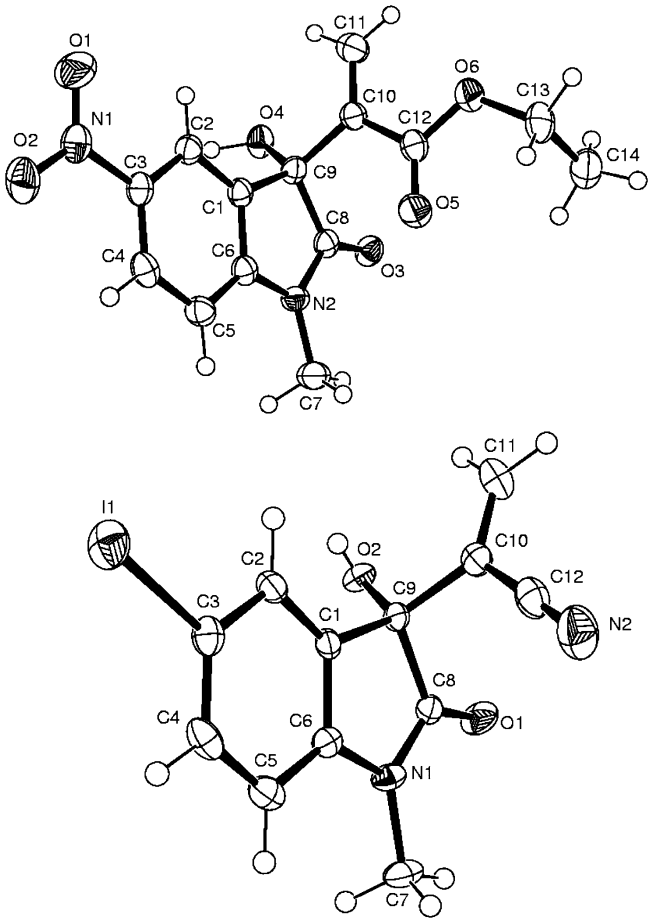


Figure 2. Single molecules from the solid state structures of compounds **8** and **9**, respectively.

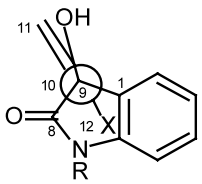


Figure 3. Newman projection of the C_9–C_{10} bond showing the inside hydroxyl conformation of compounds **8** and **9**.

Table 2. Selected data for the torsion angles around the C_9–C_{10} bond.

Compound **8**		Compound **9**	
Bonds	Angle (°)	Bonds	Angle (°)
O_4–C_9–C_{10}–C_{11}	18.9	O_2–C_9–C_{10}–C_{11}	8.2
O_4–C_9–C_{10}–C_{12}	−161.0	O_2–C_9–C_{10}–C_{12}	−175.7
C_1–C_9–C_{10}–C_{11}	−109.1	C_1–C_9–C_{10}–C_{11}	−122.5
C_1–C_9–C_{10}–C_{12}	71.0	C_1–C_9–C_{10}–C_{12}	53.5
C_8–C_9–C_{10}–C_{11}	137.5	C_8–C_9–C_{10}–C_{11}	124.9
C_8–C_9–C_{10}–C_{12}	−42.5	C_8–C_9–C_{10}–C_{12}	−59.1

In conclusion, we have found that isatin derivatives readily participate as the electrophilic component in the Baylis–Hillman reaction; this is uncommon for ketone substrates. They therefore represent an interesting new extension to the Baylis–Hillman reaction as they increase the number of known reactive ketones that could be used for the synthesis of a diverse range of highly functionalised products. The reaction times, although still on the order of days, are comparable with some of the more reactive known systems. This highlights the enhanced reactivity of these oxindolic substrates. The single-crystal structures reveal in both cases that the allylic alcohol almost eclipses the double bond and is best described as an inside hydroxyl conformation.

Acknowledgements

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24. Representative spectroscopic data for the products (Table 1). NMR data were obtained in $CDCl_3$ solutions using Bruker spectrometers (^1H recorded at 200 or 300 MHz). Compound **1**: IR (ν cm^{-1}): 3328, 1711, 1698, 1615, 1471, 1371, 1319, 1185, 1089, 1058, 771; ^1H NMR: δ 1.12 (t, J 7.2, CH_3); 3.23 (s, N-CH_3); 4.02 (s, OH); 4.02 (m, CH_2O); 6.42 (d, J 0.7, CH vinyl); 6.58 (d, J 0.7, CH vinyl); 6.85 (d, J 7.6); 7.03 (td, J 0.8, 7.6); 7.17 (dd, J 0.8, 7.6); 7.33 (td, 1.3, 7.6); ^{13}C NMR: δ 14.0; 26.6; 65.9; 76.35; 108.7; 123.2; 124.0; 127.95; 129.6; 130.35; 139.5; 144.65; 164.8; 176.5; HRMS calcd for [M+H] $C_{14}H_{16}NO_4$, 262.1079, obsd 262.1078. Compound **2**: IR (ν cm^{-1}): 3369, 3204, 1698, 1620, 1474, 1323, 1181, 1064, 944, 756, 739; ^1H NMR: δ 1.12 (t, J 7.1, CH_3); 4.06 (s, OH); 4.06 (m, CH_2O); 6.43 (s, CH vinyl); 6.58 (s, CH vinyl); 6.87 (d, J 7.5); 6.99 (t, J 7.5); 7.15 (d, J 7.5); 7.23 (td, J 1.1, 7.5); 8.70 (s, NH); ^{13}C NMR: δ 13.9; 61.3; 76.8; 110.8; 123.1; 124.25; 128.2; 128.2; 130.3; 139.1; 141.9; 164.9; 179.1. Compound **3**: IR (ν cm^{-1}): 3269, 2985, 1718, 1702, 1618, 1475, 1322, 1172, 1074, 958, 832, 691; ^1H NMR: δ 1.13 (t, J 7.1, CH_3); 4.02 (m, CH_2O); 6.13 (s, OH); 6.54 (d, J 0.9, CH vinyl); 6.60 (d, J 0.9, CH vinyl); 6.78 (d, J 8.2); 7.18 (d, J 1.9); 7.31 (dd, J 1.9, 8.2); 9.89 (s, NH); ^{13}C NMR: δ 13.5; 60.5; 75.6; 111.4; 113.85; 126.6; 127.8; 131.9; 133.4; 139.0; 141.9; 164.2; 177.4; HRMS calcd for [M+H] $C_{13}H_{13}BrNO_4$, 326.0028, obsd 326.0030. Compound **4**: IR (ν cm^{-1}): 3257, 1717, 1702, 1614, 1473, 1321, 1171, 1072, 955, 833, 690; ^1H NMR: δ 1.13 (t, J 7.1, CH_3); 4.03 (m, CH_2O); 6.29 (s, OH); 6.54 (d, J 0.7, CH vinyl); 6.59 (d, J 0.7, CH vinyl); 6.68 (d, J 8.1); 7.32 (d, J 1.5); 7.50 (dd, J 1.5, 8.1); 10.04 (s, NH); ^{13}C NMR: δ 13.3; 60.25; 75.2; 83.4; 111.8; 127.45; 131.8; 133.7; 137.6; 138.9; 142.5; 164.0; 176.9. Compound **5**: IR (ν cm^{-1}): 3369, 3068, 2991, 1717, 1708, 1453, 1317, 1179, 1142, 1060, 1027, 963, 751, 710; ^1H NMR: δ 1.19 (t, J 7.1, CH_3); 4.10 (s, OH); 4.10 (m, CH_2O); 5.35 (s, 2H, CH_2 benzyl); 6.44 (s, CH vinyl); 6.60 (s, CH vinyl); 7.21 (d, 2.0); 7.29 (m, 5H benzyl); 7.53 (d, J 2.0); ^{13}C NMR: δ 14.1; 45.1; 61.55; 75.5; 103.55; 116.2; 126.5; 126.5; 127.4; 128.8; 129.0; 134.4; 137.0; 137.9; 138.7; 140.7; 164.4; 177.4. Compound **6**: IR (ν cm^{-1}): 3322, 3096, 2981, 1747, 1713, 1617, 1581, 1541, 1469, 1357, 1328, 1165, 1098, 1061, 1028, 749, 736, 708; ^1H NMR: δ 1.23 (t, J 7.1, CH_3); 4.13 (s, OH); 4.13 (m, CH_2O); 5.01 (d, J 15.5, CH benzyl); 5.33 (d, J 15.5, CH benzyl); 6.54 (s, CH vinyl); 6.73 (s, CH vinyl); 7.13 (m, 2H benzyl); 7.24 (m, 3H benzyl); 7.45 (d, J 1.8); 7.68 (d, J 1.8); ^{13}C NMR: δ 14.05; 46.2; 61.9; 74.55; 115.0; 127.6; 128.1; 128.4; 129.1; 129.5; 131.1; 134.0; 135.3; 136.0; 136.7; 138.4; 164.2; 177.3. Compound **7**: ^1H NMR: δ (t, J 7.1, CH_3); 4.06 (q, J 7.1, CH_2O); 6.57 (s, CH vinyl); 6.69 (s, CH vinyl); 6.99 (d, J 8.6); 7.99 (d, J 2.2); 8.18 (dd, J 2.2, 8.6); 9.19 (s, NH); ^{13}C NMR: δ 14.0; 61.8; 76.0; 110.7; 120.3; 127.3; 129.3; 131.3; 138.2; 143.7; 147.9; 164.7; 178.9. Compound **8**: IR (ν cm^{-1}): 3321, 3089, 2964,1721, 1710, 1614, 1516, 1337, 1296, 1046, 982, 760, 695; ^1H NMR: δ 1.19 (t, J 7.1, CH_3); 3.32 (s, N-CH_3); 4.01 (s, OH); 4.06 (q, J 7.1, CH_2O); 6.56 (s, CH vinyl); 6.68 (s, CH vinyl); 6.96 (d, J 8.6); 8.05 (d, J 2.0); 8.32 (dd, J 8.6, 2.0); ^{13}C NMR: δ 14.1; 27.0; 61.6; 75.6; 108.5; 120.0; 127.5; 128.9; 130.5; 138.7; 143.8; 150.4; 164.4; 176.8. Compound **9**: IR (ν cm^{-1}): 3273, 2221, 1704, 1606, 1483, 1349, 1112, 953, 817, 760; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 3.22 (s, N-CH_3); 6.20 (s, CH vinyl); 6.40 (s, CH vinyl); 6.71 (d, J 8.2); 7.03 (s, OH); 7.63 (s); 7.70 (d, J 8.2); ^{13}C NMR: δ 26.2; 75.7; 85.4; 110.6; 115.5; 122.5; 130.4; 131.5; 132.9; 138.9; 143.0; 173.1. Compound **10**: ^1H NMR: δ 3.25 (s, 3H, N-CH_3); 4.30 (s, OH); 6.17 (s, CH vinyl); 6.35 (s, CH vinyl); 6.92 (d, J 7.7); 7.17 (t, J 7.7); 7.43 (m, 2H); ^{13}C NMR: δ 26.9; 76.7; 109.4; 115.7; 123.3; 124.2; 124.8; 127.3; 131.3; 131.6; 143.5; 174.5; HRMS calcd for [M+H] $C_{12}H_{11}N_2O_2$, 215.0821, obsd 215.0821.
25. X-Ray data: both structures were solved by Patterson methods. Crystal data for compound **8**: $C_{14}H_{14}N_2O_6$; $M=306.27$; monoclinic, $P21/c$; $Z=4$; $a=9.3344(9)$, $b=10.1677(8)$, $c=15.4020(10)$ Å; $\alpha=90.00$, $\beta=107.568(9)$, $\gamma=90.00°$; $V=1393.6(2)$ Å^3; $T=150(2)$ K; full-matrix least-squares refinement of 2730 unique reflections, $R=0.0482$. Crystal data for compound **9**: $C_{12}H_9IN_2O_2$; $M=340.11$; monoclinic, $P21/c$; $Z=4$; $a=10.0882(4)$, $b=12.0633(5)$, $c=11.0312(5)$ Å; $\alpha=90.00$, $\beta=116.290(3)$, $\gamma=90.00°$; $V=1203.60(9)$ Å^3; $T=150(2)$ K; full-matrix least-squares refinement of 2728 unique reflections, $R=0.0367$. These structures have been deposited with the Cambridge Crystallographic Data Centre (CCDC) and have the following deposition numbers: Compound **8** CCDC 174937 and compound **9** CCDC 174938. Sheldrick, G. M. 1997, SHELXS-97 and SHELXL-97, University of Göttingen, Germany.
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