Synthesis of Indoles and Benzisoxazolines from Baylis-Hillman Adducts of 2-Nitrobenzaldehydes

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Recently a variety of interesting chemical transformations involving the use of Baylis-Hillman adducts have been reported.[1-4] Among them the use of Baylis-Hillman adducts of 2-nitrobenzaldehydes have been investigated extensively for the synthesis of quinoline-*N*-oxides,[2a,d,e,3b] quinolines,[2a,e] quinolones,[2b,c,3a] benzisoxazolines,[2b] and indoles.[4] Although there have been reported numerous methods for the synthesis of indole derivatives,[4-6] a development of new synthetic method of indole scaffold is required due to their biological importance and usefulness as synthetic intermediates.[4]

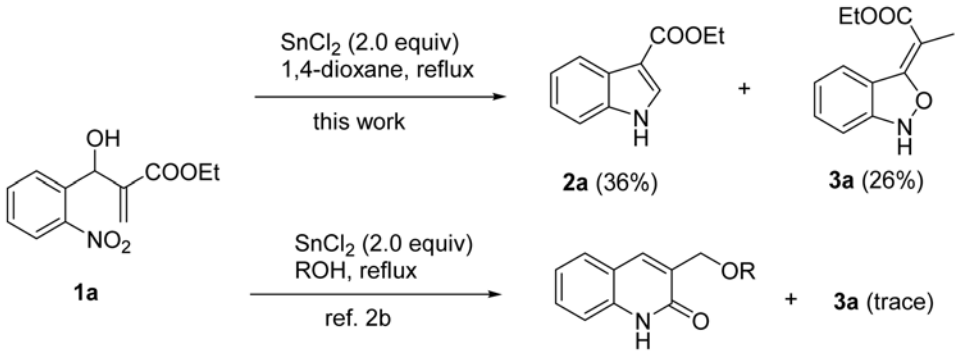
A few years ago we reported the synthesis of 3-alkoxymethyl 2(*1H*)-quinolones from the $SnCl_2$-mediated reduction of the Baylis-Hillman adducts **1a** in alcohol solvent (Scheme 1).[2b] In the reaction, the nitro group of **1a** was reduced to amino group and we obtained 3-alkoxymethyl 2(*1H*)-quinolones as the major products.[2b] In some cases we obtained benzisoxazoline compounds (5-10%) like **3a** as the side products, which might be formed *via* the hydroxylamine intermediate.[2b] At that time we also observed the formation of trace amounts of indole derivatives in some cases, especially when we used alcohols having high boiling point.[7]

Encouraged by recent publications on the synthesis of indoles from Baylis-Hillman adducts,[4] we reinvestigated the $SnCl_2$-mediated reduction of **1a** in order to obtain the benzisoxazoline or indole derivatives in improved yields. To our delight, we found an efficient condition for the formation of 3-substituted indoles and benzisoxazolines and wish to report herein the results (Scheme 1).

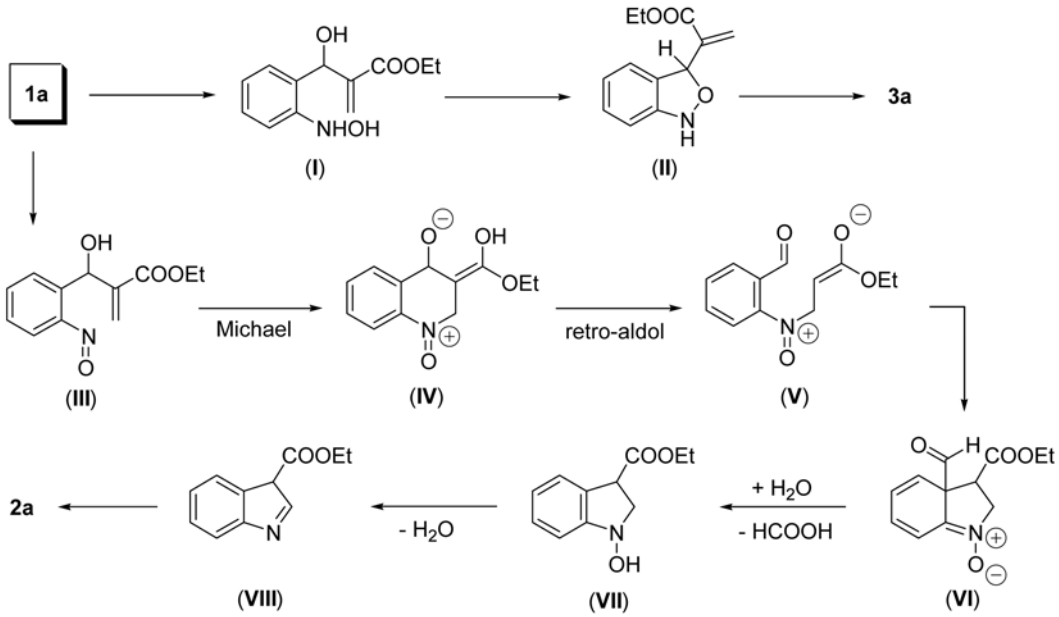
As shown in Scheme 1, the reaction of Baylis-Hillman adduct **1a** of 2-nitrobenzaldehyde and $SnCl_2$ in 1,4-dioxane at refluxing temperature gave the indole **2a** and benzisoxazoline **3a** in moderate yields.[8] As described above the formation of benzisoxazoline compound was already reported in part in our previous paper[2b] and the reaction mechanism could be regarded involving the hydroxylamine intermediate (**I**) and the cyclized intermediate (**II**) as in Scheme 2.

Although the reaction mechanism for the formation of indole **2a** was not clear at this stage we could tentatively propose a plausible mechanism as shown in Scheme 2: (i) formation of nitroso intermediate (**III**), (ii) Michael addition to form (**IV**), (iii) reversible retro-aldol type ring-opening to form (**V**), (iv) cyclization to (**VI**), (v) water-assisted elimination of formic acid to give indoline derivative (**VII**), (vi) dehydration to (**VIII**) and the final isomerization to indole **2a**.

Based on the experimental results and the proposed mechanism there must be formed hydroxylamine intermediate (**I**) and nitroso intermediate (**III**) under $SnCl_2$/dioxane conditions in a variable ratios. In order for the selective formation of either (**I**) or (**III**), we examined the reaction conditions including solvent, temperature, the equivalents of $SnCl_2$, but all failed to improve the yields or selectivity. The nitro group is readily converted to a series of functions of various degrees of reduction: very exceptionally to a nitroso group, more often to a hydroxylamino group and most frequently to the amino group.[2e,9] Nitroso compounds are usually not obtained directly but rather by reoxidation of hydroxylamino compounds,[9] which can be prepared from nitro compounds by $SnCl_2$.[2e,9] Moreover there have been few instances in

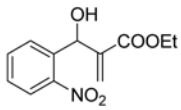
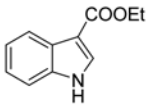
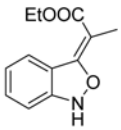
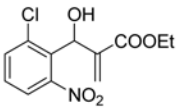
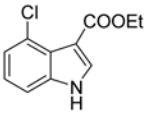
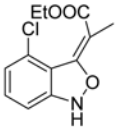
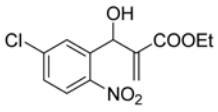
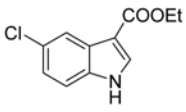
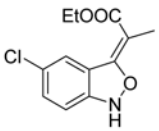
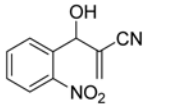
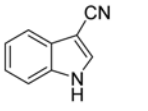
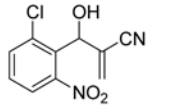
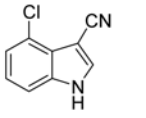
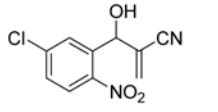
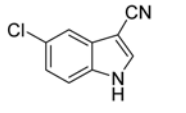


Scheme 1



Scheme 2

Table 1. Synthesis of indoles and benzisoxazolines[a]

Entry	B-H adduct	Time (h)	Product (%)	
1	 **1a**	10	 **2a** (36%)	 **3a** (26%)
2	 **1b**	2	 **2b** (41%)	 **3b** (25%)
3	 **1c**	4	 **2c** (38%)	 **3c** (26%)
4	 **1d**	10	 **2d** (48%)	– [b]
5	 **1e**	2	 **2e** (48%)	– [b]
6	 **1f**	2	 **2f** (44%)	– [b]

[a]Conditions: **1** (1.0 equiv), dioxane, $SnCl_2$ (2.0 equiv), reflux. [b]Not formed.

which nitroso compounds have been isolated as intermediates in reductions of nitro compounds. It is interesting to compare the results with our previous paper.[2e] In our pervious paper we also proposed the involvement of nitroso intermediate, which was converted into quinoline *N*-oxides *via* Michael addition followed by dehydration.[2e] Dehydration occurred efficiently in the acidic conditions. However, when we used $SnCl_2$/dioxane conditions, retro-aldol type ring-opening reaction of the zwitterinoic intermediate (**IV**) proceeded as in Scheme 2 instead of dehydration. Similarly, Baylis-Hillman adducts **1b** and **1c** gave similar results as shown in Table 1. We also prepared indole derivatives **2d-f** from the reactions of **1d-f** in moderate yields (44-48%). However, we could not observe the corresponding benzisoxazline derivatives **3d-f** in these cases on TLC, unexpectedly.

Whatever the details of the mechanism, the reaction represents an unprecendented, reproducible, and useful method for the preparation of interesting indoles and benzisoxazolines starting from the readily available Baylis-Hillman adducts.

Experimental Section

Typical procedure for the synthesis of 2a and 3a: To a stirred mixture of **1a** (251 mg, 1.0 mmol) in dioxane (4 mL) was added tin (II) chloride dihydrate (451 mg, 2.0 mmol) and the reaction mixture was heated to reflux for 10 h. The reaction mixture was cooled to room temperature and poured into cold saturated NH_4Cl solution. After extraction with EtOAc, washing with aq K_2CO_3 solution, and column chromatographic purification process (hexanes/EtOAc, 5:1) we obtained **2a** (68 mg, 36%) and **3a** (57 mg, 26%) as white solids. The representative spectroscopic data of prepared compounds are as follows.

Compound 2a:[5a,b] 36%; white solid, mp 125-126 °C; IR (KBr) 3271, 1668, 1531, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H), 4.41 (q, J = 7.2 Hz, 2H), 7.25-7.31 (m, 2H), 7.40-7.44 (m, 1H), 7.93 (d, J = 3.0 Hz, 1H), 8.18-8.21 (m, 1H), 8.68 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.56, 59.85, 109.07, 111.54, 121.54, 121.99, 123.14, 125.83, 131.06, 136.16, 165.43. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.58; H, 5.92; N, 7.32.

Compound 3a: 26%; white solid, mp 187-188 °C; IR (KBr) 3305, 1662, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 2.75 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.18-7.32 (m, 3H), 8.08-8.12 (m, 1H), 8.31 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.23, 14.59, 59.47, 104.71, 110.40, 121.34, 121.67, 122.33, 127.16, 134.41, 143.82, 166.06. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.65; H, 5.91; N, 6.27.

Compound 2b: 41%; white solid, mp 126-127 °C; IR (KBr) 3288, 1695, 1419, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.40 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.13-7.33 (m, 3H), 7.92 (d, J = 3.0 Hz, 1H), 8.84 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 14.43, 60.32, 109.80, 110.31, 122.99, 123.77, 123.81, 126.85, 132.23, 137.96, 164.08. Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.22; H, 4.63; N, 6.08.

Compound 3b: 25%; white solid, mp 147-148 °C; IR (KBr) 3298, 1693, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.42 (t, J = 7.2 Hz, 3H), 2.62 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.03-7.23 (m, 3H), 9.60 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 13.78, 14.42, 60.22, 109.46, 122.43, 122.51, 122.91, 124.02, 125.65, 136.53, 142.42, 165.67. Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.49; H, 4.48; N, 5.39.

Compound 2c:[5a] 38%; white solid, mp 186-187 °C; IR (KBr) 3228, 1666, 1446, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.32 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 7.08-7.31 (m, 2H), 7.85 (d, J = 3.0 Hz, 1H), 8.00 (s, 1H), 11.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 13.89, 58.83, 106.77, 112.58, 119.79, 121.99, 126.29, 126.40, 132.14, 134.36, 164.13.

Compound 3c:[2b] 26%; white solid, mp 168-169 °C; IR (KBr) 3277, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.45 (t, J = 7.2 Hz, 3H), 2.74 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.14 (dd, J = 8.4 and 1.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 8.46 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 14.12, 14.62, 59.32, 103.50, 111.95, 120.40, 121.81, 126.70, 128.43, 133.41, 145.99, 165.75.

Compound 2d:[6] 48%; white solid, mp 177-178 °C; IR (KBr) 3251, 2226, 1431 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.20-7.31 (m, 2H), 7.56-7.65 (m, 2H), 8.24 (s, 1H), 12.21 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 84.33, 113.04, 116.46, 118.51, 121.78, 123.47, 126.85, 134.57, 135.33; Mass (70 eV) *m/z* (rel. intensity) 88 (7), 115 (30), 142 (M^+, 100).

Compound 2e: 48%; white solid, mp 223-225 °C (dec.); IR (KBr) 3263, 2224 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.26-7.28 (m, 2H), 7.50-7.56 (m, 1H), 8.39 (s, 1H), 12.52 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 83.56, 112.11, 116.13, 121.78, 123.40, 124.14, 124.24, 136.36, 136.59.

Compound 2f: 44%; white solid, mp 198-199 °C; IR (KBr) 3273, 2224, 1415, 1304 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.30 (dd, J = 8.7 and 2.1 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 8.30 (s, 1H), 12.38 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 84.03, 114.52, 115.59, 117.61, 123.50, 126.41, 127.70, 133.64, 135.95.

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