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Synthesis of Tetracyclic Oxindoles from Isatin Containing Baylis-Hillman Adducts *via* Pd-Catalyzed Aryl-Aryl Coupling and Reduction with $NaBH_4$

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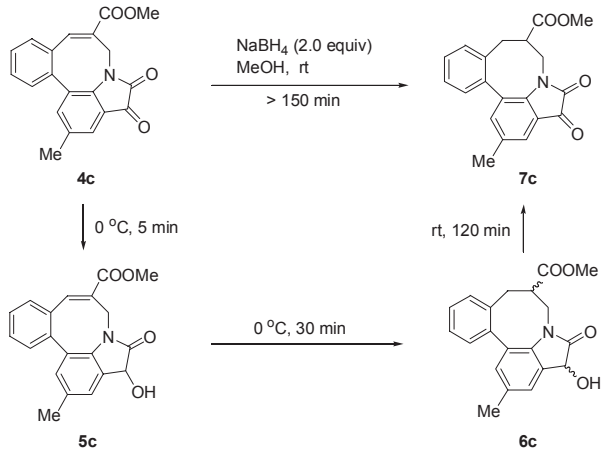
Numerous poly-fused heterocyclic compounds having a medium-sized ring were known to possess many interesting biological activities.[1,2] As an example, various indole moiety-containing tetracyclic compounds showed hepatitis C virus (HCV) NS5B polymerase inhibitory activity.[2] Palladium-catalyzed direct aryl-aryl bond-forming protocols have been used extensively for the synthesis of poly-fused heterocyclic compounds.[3,4] Recently we reported the synthesis of tetracyclic compounds having a heterocyclic moiety such as indole, imidazole, benzimidazole and isatin, starting from the Baylis-Hillman adduct.[4a,b]

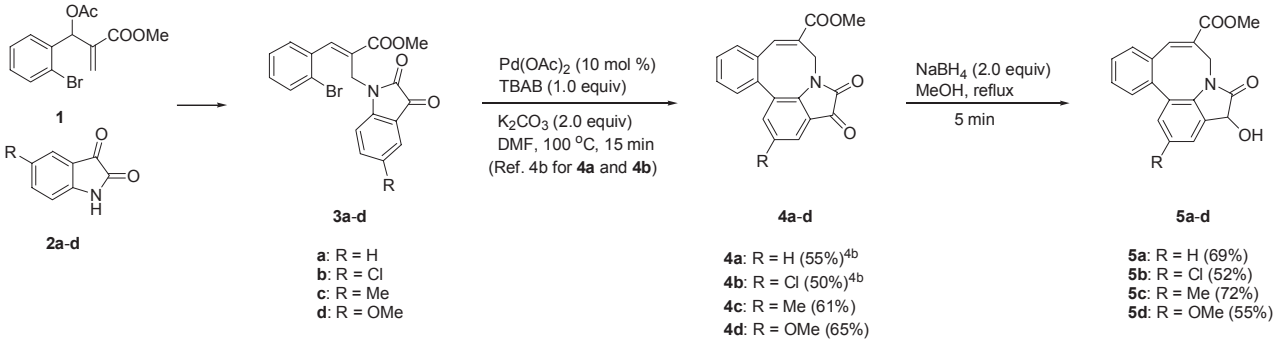
Many 3-hydroxyoxindole moiety-containing compounds showed interesting biological activities,[5] thus development of a synthetic methodology and derivatization of 3-hydroxyoxindoles is very important. In these contexts, we decided to examine the synthesis of tetracyclic hydroxyoxindole derivatives. Our synthetic strategy of a tetracyclic 3-hydroxyoxindoles **5a-d** is depicted in Scheme 1. The required starting materials **4a-d** were prepared in 50 - 65% yields from **3a-d**, prepared by the reaction of Baylis-Hillman acetate **1** and isatin derivatives **2a-d**, under the influence of $Pd(OAc)_2$/TBAB (tetrabutylammonium bromide)/K_2CO_3 in DMF (100 °C, 15 min), by following the previous method.[4b]

Initially we ran the reduction of **4a** with $NaBH_4$ at room temperature; however, TLC showed the formation of many spots. Literature survey stated that the reduction of isatin derivatives with $NaBH_4$ was somewhat complex.[6] Based on the reported method,[6a] in which described the reduction of isatin at high temperature in short time produced the best result, we carried out the reduction of **4a** with $NaBH_4$ (2.0 equiv) in MeOH at refluxing temperature (5 min) and obtained 3-hydroxyoxindole derivative **5a** in a reasonable yield (69%). However, the yield was quite dependent on the reaction time. Depending on time progress formations of other compounds were observed on TLC. Thus the reaction mixture has to be quenched instantaneously after 4 - 5 min by pouring into cold water, and the crude product has to be separated with organic solvent. Otherwise the yield of product was dramatically decreased. By using this method we carried out the reductions of **4b-d** at refluxing temperature in short time, and obtained **5b-d** in moderate yields (52 - 72%), as shown in Scheme 1.

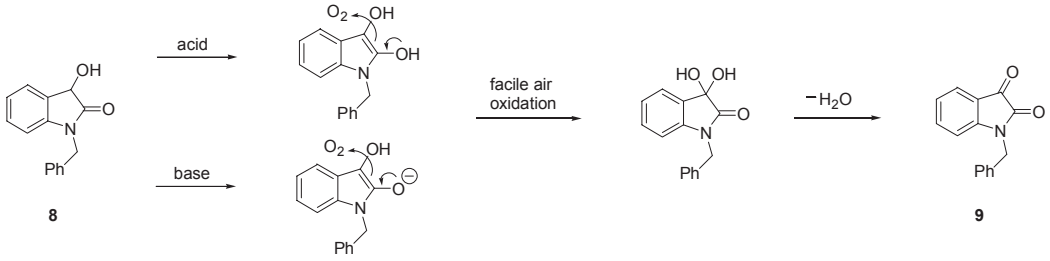
In order to understand the unusual observations during the reductions of **4a-d**, we examined the reduction of **4c** at low temperature with $NaBH_4$ (2.0 equiv), as shown in Scheme 2. When we ran the reaction of **4c** at 0 °C, compound **5c** was observed as the major component in short time (5 min). However,



Scheme 2



Scheme 1



Scheme 3

compound **5c** was gradually converted to **6c** *via* the conjugate addition of a hydride,[7] and **6c** was the major component after around 30 min. Unexpectedly, however, compound **6c** was again changed to another compound **7c** slowly. Thus we carried out the reduction of **4c** three times in order to identify the structures of these compounds, **6c** and **7c**. First run was carried out at 0 °C and the reaction mixture was quenched after 5 min, and compound **5c** was isolated in 60%. When we ran the reaction at 0 °C for 30 min, compound **6c** was isolated in 51%. Finally, the reaction of **4c** at room temperature for 2 h afforded **7c** in 58%. A facile conjugate reduction[7] of **5c** to **6c** and unusual oxidation of **6c** to **7c** in the presence of a reducing agent $NaBH_4$ were interesting.

The unusual oxidation was observed with 3-hydroxyoxindole **8**, as shown in Scheme 3. Complete oxidation of **8** to **9** was observed in MeOH at room temperature within 30 min in the presence of $NaBH_4$. Without $NaBH_4$, compound **8** was stable in MeOH and we could not observe the formation of **9** up to 24 h. The reaction of **8** in AcOH (100 °C, 3 h) produced **9** quantitatively.[8c] In addition, treatment of **8** with K_2CO_3 or NaOMe in MeOH readily produced **9** within 30 min at room temperature almost quantitatively. From the results we tentatively assume that aerobic oxidation of **8** can occur easily in the presence of an acid or base catalyst *via* the corresponding enol or enolate intermediates.[8] Some basic species such as $[BH_3(OMe)]^-$ anion,[9] produced by the decomposition of $NaBH_4$ in MeOH, might be the reason for the facile air oxidation of compound **8** (Scheme 3) and compound **6c** (Scheme 2).

In summary, tetracyclic hydroxyoxindole derivatives were synthesized *via* a Pd-catalyzed aryl-aryl coupling and the following reduction with $NaBH_4$ from isatin moiety-containing Baylis-Hillman adducts. The screening of biological activities of prepared compounds is underway and will be reported in due course.

Experimental Section

Typical experimental procedure of 5a. The syntheses of **4a** and **4b** were already reported by us,[4b] and the starting materials **4c** (61%) and **4d** (65%) were prepared similarly.[4b] A stirred solution of **4a** (160 mg, 0.5 mmol) and $NaBH_4$ (39 mg, 1.0 mmol) in MeOH (3 mL) was heated to reflux for 5 min. The reaction mixture was poured into cold water. After the usual aqueous extractive workup with CH_2Cl_2 and column chromatographic purification process (hexanes/EtOAc, 1:4) compound **5a** was obtained as a pale yellow solid, 111 mg (69%). The selected spectroscopic data of unknown compounds **4c**, **4d**, **5a-d**, **6c**, and **7c** are as follows.

Compound 4c: 61%; orange solid, mp 203 - 205 °C; IR (KBr) 1741, 1719, 1275, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.80 (s, 3H), 3.90 (d, *J* = 13.8 Hz, 1H), 5.32 (d, *J* = 13.8 Hz, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.44-7.55 (m, 3H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.43, 37.82, 52.52, 118.98, 125.46, 126.70, 128.17, 128.35, 129.22, 130.02, 132.49, 134.03, 134.49, 136.61, 143.48, 144.19, 146.15, 157.82, 165.82, 184.13; ESIMS *m/z* 356 (M^++Na). Anal. Calcd For $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.37; H, 4.81; N, 4.08.

Compound 4d: 65%; orange solid, mp 151 - 153 °C (decomp); IR (KBr) 1738, 1720, 1488, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H), 3.80 (s, 3H), 3.87 (d, *J* = 13.8 Hz, 1H), 5.31 (d, *J* = 13.8 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.45-7.55 (m, 2H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.79, 52.48, 55.94, 109.31, 119.42, 128.13, 128.17, 128.52, 129.03, 129.16, 130.01, 132.40, 134.44, 136.17, 140.24, 146.03, 156.41, 157.83, 165.74, 184.20; ESIMS *m/z* 372 (M^++Na).

Compound 5a (1:1 mixture of rotamers): 69%; pale yellow solid, mp 134 - 136 °C; IR (KBr) 3324, 1717, 1700, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H*0.5), 3.79 (s, 3H*0.5), 3.88 (d, *J* = 13.8 Hz, 1H*0.5), 3.92 (d, *J* = 13.5 Hz, 1H*0.5), 3.96 (br s, 1H*0.5), 4.07 (br s, 1H*0.5), 5.05 (s, 1H*0.5), 5.20 (s, 1H*0.5), 5.25 (d, *J* = 13.8 Hz, 1H*0.5), 5.31 (d, *J* = 13.5 Hz, 1H*0.5), 7.02 (d, *J* = 7.2 Hz, 2H*0.5), 7.13 (dd, *J* = 7.5 and 7.2 Hz, 2H*0.5), 7.21 (d, *J* = 7.5 Hz, 2H*0.5), 7.28 (d, *J* = 7.5 Hz, 2H*0.5), 7.36-7.51 (m, 6H*0.5), 8.14 (s, 2H*0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.49, 37.81, 52.36, 52.38, 69.73, 70.28, 123.41, 123.62, 124.74, 124.86, 125.23, 125.51, 127.31, 127.61, 127.66, 127.74, 127.89, 128.00, 129.47, 129.58, 129.80, 129.89, 132.88, 133.18, 134.56, 134.65, 134.78, 134.90, 137.88, 137.95, 138.99, 139.60, 145.75, 146.10, 166.10, 166.15, 175.22, 175.93; ESIMS *m/z* 344 (M^++Na). Anal. Calcd For $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.35; H, 4.64; N, 4.11.

Compound 5b (1:1 mixture of rotamers): 52%; pale yellow solid; IR (KBr) 3412, 1731, 1459, 1436, 1291 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H*0.5), 3.79 (s, 3H*0.5), 3.85 (d, *J* = 13.5 Hz, 1H*0.5), 3.89 (d, *J* = 13.5 Hz, 1H*0.5), 4.53 (br s, 2H*0.5), 5.06 (s, 1H*0.5), 5.21 (s, 1H*0.5), 5.22 (d, *J* = 13.5 Hz, 1H*0.5), 5.29 (d, *J* = 13.5 Hz, 1H*0.5), 7.01-7.03 (m, 2H*0.5), 7.20-7.30 (m, 4H*0.5), 7.37-7.52 (m, 6H*0.5), 8.12 (s, 2H*0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.55, 37.83, 52.41, 52.42, 69.55, 70.06, 125.04, 125.23, 126.43, 126.65, 128.02,

128.13 (2C), 28.20, 128.83, 129.00, 129.32, 129.34, 129.64, 129.69, 129.95, 130.05, 132.66, 132.95, 133.89, 133.93, 134.48, 134.57, 136.51, 136.62, 137.45, 138.08, 145.49, 145.91, 165.95, 165.97, 175.44, 176.10; ESIMS *m*/*z* 378 (M^++Na), 380 (M^++2+Na).

Compound 5c (1:1 mixture of rotamers): 72%; pale yellow solid, mp 182 - 184 °C; IR (KBr) 3400, 1724, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H*0.5), 2.32 (s, 3H*0.5), 3.77 (s, 3H*0.5), 3.78 (s, 3H*0.5), 3.85(d, *J* = 13.8 Hz, 1H*0.5), 3.89 (d, *J* = 13.8 Hz, 1H*0.5), 4.54 (br s, 1H*0.5), 4.69 (br s, 1H*0.5), 5.05 (s, 1H*0.5), 5.20 (s, 1H*0.5), 5.23 (d, *J* = 13.8 Hz, 1H*0.5), 5.29 (d, *J* = 13.8 Hz, 1H*0.5), 6.81-6.83 (m, 2H*0.5), 7.17-7.21 (m, 2H*0.5), 7.27-7.29 (m, 4H*0.5), 7.37-7.49 (m, 4H*0.5), 8.12 (s, 2H*0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.69, 20.72, 37.43, 37.72, 52.27, 52.29, 69.74, 70.28, 124.84, 125.06, 125.58, 125.78, 127.48, 127.56, 127.75, 127.79, 127.89, 127.99, 129.45, 129.62, 129.71, 129.77, 132.72, 132.98, 133.01, 133.24, 134.47, 134.57, 134.77, 134.80, 136.32, 136.93, 137.94, 138.01, 145.62, 145.98, 166.08, 166.11, 175.79, 176.47; ESIMS *m*/*z* 358 (M^++Na). Anal. Calcd For $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.57; H, 5.42; N, 4.34.

Compound 5d (1:1 mixture of rotamers): 55%; pale yellow solid; IR (KBr) 3368, 1724, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.72-3.89 (m, 2H*0.5), 3.77 (s, 3H*0.5), 3.78 (s, 3H*0.5), 3.79 (s, 3H*0.5), 3.80 (s, 3H*0.5), 4.46 (br s, 1H*0.5), 4.61 (br s, 1H*0.5), 5.05 (s, 1H*0.5), 5.20 (s, 1H*0.5), 5.22 (d, *J* = 14.1 Hz, 1H*0.5), 5.28 (d, *J* = 13.8 Hz, 1H*0.5), 6.55 (s, 1H*0.5), 6.56 (s, 1H*0.5), 7.08-7.51 (m, 10H*0.5), 8.13 (s, 2H*0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.49, 37.78, 52.33, 52.35, 55.78, 55.79, 70.07, 70.58, 111.53, 111.82, 119.24, 119.35, 125.91, 126.13, 127.71, 127.79, 127.87, 127.98, 128.97, 129.23, 129.50, 129.69, 129.77, 129.83, 132.04, 132.61, 132.67, 132.97, 134.51, 134.60, 137.63, 137.73, 145.51, 145.89, 156.21, 156.39, 166.08, 166.11, 175.58, 176.27; ESIMS *m*/*z* 374 (M^++Na).

Compound 6c (1:1 mixture of rotamers and the relative stereochemistry between OH and COOMe was not confirmed): 51%; pale yellow solid, mp 120 - 122 °C; IR (KBr) 3400, 1732, 1489, 1275, 764, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H*0.5), 2.37 (s, 3H*0.5), 2.96-3.37 (m, 8H*0.5), 3.73 (s, 3H*0.5), 3.74 (s, 3H*0.5), 3.77 (d, *J* = 4.5 Hz, 1H*0.5), 3.97 (d, *J* = 4.2 Hz, 1H*0.5), 4.28-4.40 (m, 2H*0.5), 5.06 (d, *J* = 4.2 Hz, 1H*0.5), 5.12 (d, *J* = 4.5 Hz, 1H*0.5), 6.98-7.20 (m, 2H), 7.29-7.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.80, 20.82, 32.40, 32.54, 37.71, 37.76, 41.30, 41.71, 51.82 (2C), 69.19, 69.21, 123.46, 123.61, 125.34 (2C), 126.76, 127.04, 127.81, 127.85, 128.39, 128.41, 129.37, 129.44, 130.05, 130.22, 133.16, 133.26, 133.70, 133.99, 134.18, 134.30, 138.47, 138.52, 138.71, 138.73, 172.00, 172.16, 176.35, 176.66; ESIMS *m*/*z* 360 (M^++Na). Anal. Calcd For $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, C, 71.55; H, 5.62; N, 4.01.

Compound 7c (1:1 mixture of rotamers): 58%; orange solid, mp 154 - 156 °C; IR (KBr) 1732, 1618, 1597, 1482, 764, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H*0.5), 2.36 (s, 3H*0.5), 2.97-3.41 (m, 8H*0.5), 3.74 (s, 3H*0.5), 3.75 (s, 3H*0.5), 4.37-4.44 (m, 2H*0.5), 7.08-7.46 (m, 12H*0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.44 (2C), 31.93, 32.46, 37.73, 39.29, 41.56, 43.70, 51.90, 52.44, 117.73, 117.81, 124.98, 125.03, 125.07, 125.14, 127.77, 128.02, 129.11, 129.25, 129.29, 129.61, 129.85, 130.02, 133.80, 133.92, 134.05, 135.95, 137.11, 137.24, 142.55, 142.96, 145.91, 146.29, 158.23, 158.33, 171.63, 172.95, 183.15, 183.41; ESIMS *m*/*z* 358 (M^++Na). Anal. Calcd For $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.46; H, 5.46; N, 3.97.

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