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A novel radical cyclization of 2-bromoindoles. Synthesis of hexahydropyrrolo[3,4-*b*]indoles

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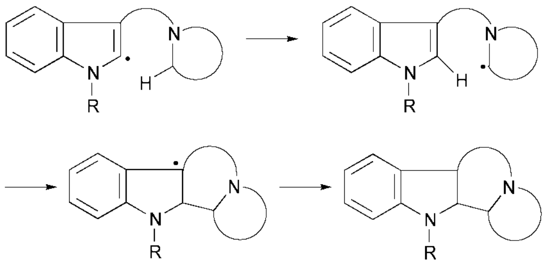
Hexahydropyrrolo[3,4-*b*]indoles 6, 10, and 13 are obtained from 2-bromo-3-carboxamides 5, 9, and 12, respectively, by a 1,5-radical translocation process followed by 5-*endo-trig* cyclization to the indole C-2 position.

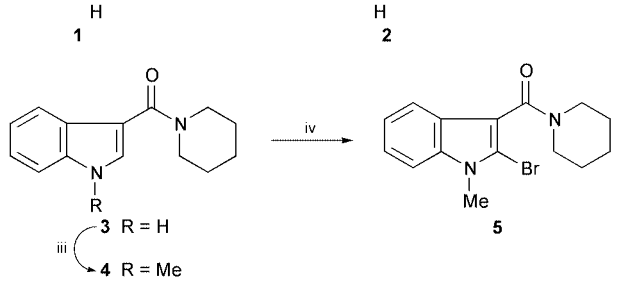
We wish to describe a new synthesis of hexahydropyrrolo[3,4-*b*]indoles from 2-bromoindole-3-carboxamides involving sequential indole C-2 radical generation, 1,5-hydrogen atom abstraction, and 5-*endo-trig* cyclization to the indole C-2 position. In connection with our interest in pyrrolo[3,4-*b*]indoles[1] and indolo[2,3-*a*]quinolizidines,[2] we envisioned the free radical sequence shown in Scheme 1 as an attractive route to these ring systems.



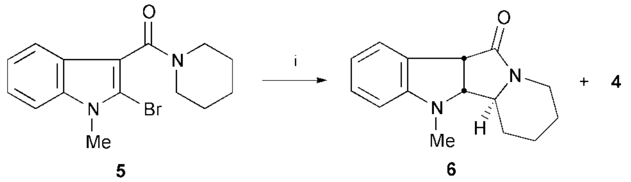
Scheme 1

We herein report the viability of this sequence for the synthesis of hexahydropyrrolo[3,4-*b*]indoles. The radical precursor 2-bromoindole **5** was prepared as shown in Scheme 2. Indole (**1**) was converted to amide **3** in two steps as previously described.[3] Subsequent *N*-methylation and C-2 bromination using the conditions described by Bergman[4] for *N*-carboxyindole afforded **5**† in excellent overall yield. An X-ray crystal structure determination confirmed the structure of **5**.[5]

The radical cyclization was performed by the slow addition over 36 h of a degassed solution of tri-*n*-butyltin hydride and catalytic AIBN in toluene to a refluxing solution of bromoindole **5** in toluene. This resulted in the formation of the desired dihydroindole **6**† (54%), along with the reduction product **4** (42%) (Scheme 3). The structure of **6** is fully supported by spectral and analytical data, including an X-ray crystal structure determination.[5]

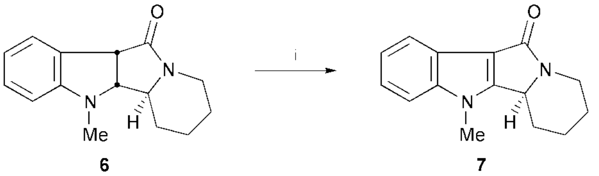


Scheme 2 *Reagents and conditions*: i, $(CF_3CO)_2O$, Et_2O, 0 °C (87%); ii, BuLi, piperidine, THF, 0 °C (97%); iii, NaOH, EtOH, MeI, acetone, rt (99%); iv, Bu^{t}Li, THF, $BrCl_2CCCl_2Br$, −78 °C to rt (88%).



Scheme 3 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 36 h (**6**, 54%; **4**, 42%).

We believe that this reaction involves the sequence (1) generation of the expected C-2 radical, (2) 1,5-H atom abstraction to give the α-amidoyl radical, (3) 5-*endo-trig* cyclization to the indole double bond, and (4) hydrogen abstraction to give indoline **6**. The first two steps in this process have been termed ‘radical translocation’ by Snieckus and Curran.[6] Attempts to improve the yield of **6** relative to reduction product **4** using other radical generation methods have not been successful. Treatment of indoline **6** with DDQ (CH_2Cl_2, rt) gave indole **7** in 50% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: DDQ, CH_2Cl_2, rt, 18 h (50%).

As summarized in Scheme 5 we have applied this radical cyclization to several other substrates (**9**, **12**, **15**) and two of these afforded the expected cyclized pyrrolo[3,4-*b*]indoles **10** and **13**. However, only reduction product **14** was obtained from **15**.

Amides **8**,† **11**,† and **14**,† were synthesized by *N*-methylation of the corresponding indole-3-carboxamides[3] in 97, 77, and 80% yields, respectively, as illustrated in Scheme 2 for **4**. The usual bromination procedure afforded the 2-bromoindoles **9**,† **12**,† and **15**† in excellent yields. The structures of **9**, **12**, and **15** were confirmed by X-ray crystallography.[5]

Although radical cyclizations to the indole C-2 position are precedented[7] and the generation of indole C-2 radicals has been described by Jones,[8,9] our work is the first example of a 1,5-hydrogen atom transfer reaction of a 2-bromoindole-3-carboxamide and subsequent 5-*endo-trig* cyclization to the indole double bond. Following the completion of our initial work, Jones reported[9] a similar 1,5-H atom abstraction from the radical derived from 2-bromo-3-formyl-*N*-(4-phenylbutyl)indole and subsequent radical translocation and 5-*exo-trig* cyclization to the indole C-2 position. Jones has also recently described[10] a radical translocation sequence leading to indole C-3 5-*exo-trig* cyclization. Some other hydrogen atom abstrac-

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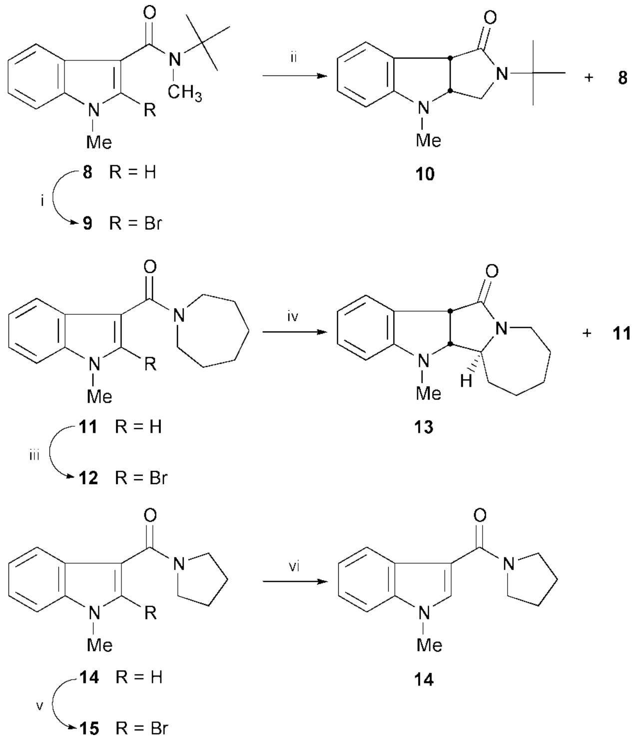

Scheme 5 *Reagents and conditions*: i, Bu^{t}Li, THF, $BrCl_2CCCl_2Br$, −78 °C to rt (86%); ii, Bu_3SnH, AIBN, toluene, reflux, 48 h (**10**, 51%; **8**, 22%); iii, Bu^{t}Li, THF, $BrCl_2CCCl_2Br$, −78 °C to rt (90%); iv, Bu_3SnH, AIBN, toluene, reflux, 72 h (**13**, 51%; **11**, 30%); v, Bu^{t}Li, THF, $BrCl_2CCCl_2Br$, −78 °C to rt (94%); vi, Bu_3SnH, AIBN, toluene, reflux, 72 h.

tion–translocation of α-amidoyl radical schemes not involving indoles have been reported.[6,11] While we favor the direct 5-*endo-trig* radical cyclization pathway shown in Scheme 1, of which there are precedents,[12,13] a 4-*exo-trig* cyclization to a spiro β-lactam intermediate followed by a 1,2-alkyl migration (ring expansion), as suggested by a referee, cannot be ruled out. However, such 1,2-alkyl shifts for radicals are rare[14] and the migration terminus is a nucleophilic carbon-centered radical. Moreover, based on the work of Ikeda,[13] we would have expected to isolate spiro β-lactams if a 4-*exo-trig* radical cyclization pathway was operating.

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Notes and references

† *Selected physical and spectroscopic data*: **4**: mp 103–104 ^{0}C; δ_H (300 MHz, $CDCl_3$) 7.59–7.63 (m, 2H), 7.33–7.36 (m, 1H), 6.98–7.13 (m, 2H), 3.78 (s, 3H), 3.53–3.57 (t, 4H, J = 5.4 Hz), 1.38–1.61 (m, 6H); δ_C (500 MHz, $CDCl_3$, −50 °C) 166.3, 135.7, 131.6, 125.3, 121.9, 120.4, 120.2, 110.2, 109.7, 48.8, 43.2, 33.3, 26.6, 25.4, 24.4; IR ν(KBr)/cm^{-1} 2934, 2850, 1611; *m*/*z* 242 (M$^+$), 228, 158 (100%), 131, 103, 77 (Calc. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.23; H, 7.51; N, 11.50%). **5**: mp 105–107 °C; δ_H (300 MHz, $CDCl_3$) 7.46–7.49 (m, 1H), 7.07–7.26 (m, 3H), 3.73 (br s, 5H), 1.59 (m, 8H); δ_C (500 MHz, $CDCl_3$, −50 °C) 164.5, 135.6, 125.0, 122.1, 120.6, 118.6, 113.9, 110.7, 109.5, 48.2, 42.7, 31.4, 26.6, 25.4, 24.1; IR ν(KBr)/cm^{-1} 2934, 2845, 1622, 1522, 1428; *m*/*z* 320 (M$^+$), 236 (100%), 209, 158, 129; HRMS: calc. *m*/*z* 320.0524, found *m*/*z* 306.0517. **6**: mp 120–121 °C; δ_H (300 MHz, $CDCl_3$) 7.40 (d, 1H, J = 7.3 Hz), 7.13 (t, 1H, J = 8.0 Hz), 6.70 (td, 1H, J' = 1.0 Hz, J'' = 7.3 Hz), 6.42 (d, 1H, J = 7.7 Hz), 4.14 (dd, 2H, J' = 4.5 Hz, J'' = 13.2 Hz), 4.08 (d, 1H, J = 9.4 Hz), 3.84 (dd, 1H, J' = 2.1 Hz, J'' = 9.4 Hz), 2.86 (s, 3H), 2.64 (td, 1H, J' = 3.4 Hz, J'' = 12.8 Hz), 1.95 (m, 2H), 1.48 (m, 3H); δ_C ($CDCl_3$) 170.6, 151.0, 128.6, 125.1, 124.9, 118.0, 106.1, 69.2, 62.9, 48.9, 40.6, 33.4, 26.7, 24.6, 23.9; IR ν(film)/cm^{-1} 2922, 2856, 2344, 1678, 1606, 1489; *m*/*z* 242 (M$^+$), 158, 131 (100%), 103, 77; HRMS: calc. *m*/*z* 242.1420, found *m*/*z* 242.1421; (Calc. for $C_{15}H_{18}N_2O$: C, 74.34; H, 7.49; N, 11.57. Found: C, 74.12; H, 7.41; N, 11.54%). **8**: mp 165–166 °C; δ_H (300 MHz, $CDCl_3$) 7.68–7.71 (dd, 1H, J' = 1.39 Hz, J'' = 7.31 Hz), 7.46 (s, 1H), 7.19–7.35 (m, 3H), 3.81 (s, 3H), 3.06 (s, 3H), 1.57 (s, 9H); δ_C ($CDCl_3$) 169.4, 136.8, 132.4, 126.1, 122.4, 121.2, 121.0, 114.4, 109.9, 56.4, 35.5, 33.4, 28.1; IR ν(KBr)/cm^{-1} 3458, 3113, 2975, 1627 (Calc. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.67; H, 8.30; N, 11.44%). **9**: mp 105–106 °C; δ_H (300 MHz, $CDCl_3$) 7.57–7.71 (dt, 1H, J' = 1.2 Hz, J'' = 8.0 Hz), 7.14–7.34 (m, 3H), 3.76 (s, 3H), 2.96 (s, 3H), 1.57 (s, 9H); δ_C ($CDCl_3$) 167.1, 136.4, 125.8, 122.5, 121.0, 119.6, 114.7, 114.2, 109.5, 56.5, 34.2, 31.5, 28.0; IR ν(film)/cm^{-1} 3456, 3052, 2979, 1627 (Calc. for $C_{15}H_{19}BrN_2O$: C, 55.74; H, 5.92; N, 8.67; Br, 24.72. Found: C, 56.13; H, 5.94; N, 8.64; Br, 24.42%). **11**: mp 111–112 °C; δ_H (300 MHz, $CDCl_3$) 7.80–7.83 (dt, 1H, J' = 1.1 Hz, J'' = 7.0 Hz), 7.13–7.28 (m, 4H), 3.70 (s, 3H), 3.63–3.67 (t, 4H, J = 5.9 Hz), 1.57–1.74 (m, 8H); δ_C (500 MHz, $CDCl_3$, −45 ^{0}C) 166.9, 135.7, 129.8, 126.2, 121.8, 120.8, 120.1, 110.1, 109.3, 49.0, 45.6, 33.0, 29.3, 28.2, 27.2, 26.0; IR ν(film)/cm^{-1} 3053, 2932, 1605 (Calc. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.90; H, 7.93; N, 10.79%). **12**: mp 125–126 °C; δ_H (300 MHz, $CDCl_3$) 7.46 (d, 1H, J' = 7.1 Hz), 7.10–7.27 (m, 4H), 3.73 (s, 3H), 3.40–3.70 (m, 4H), 1.52–1.87 (m, 8H); δ_C ($CDCl_3$) 166.0, 136.3, 125.6, 122.5, 120.8, 119.0, 113.0, 112.9, 109.5, 49.4, 45.9, 31.4, 29.5, 27.9, 27.4, 26.4; IR ν(film)/cm^{-1} 3053, 2933, 1618; *m*/*z* 334 (M$^+$), 255, 236 (100%), 130, 103, 77 (Calc. for $C_{16}H_{19}BrN_2O$: C, 57.32; H, 5.71; N, 8.36; Br, 23.83. Found: C, 57.57; H, 5.69; N, 8.35; Br, 23.54%). **14**: mp 110–113 °C; δ_H (300 MHz, $CDCl_3$) 8.15 (d, 1H, J' = 7.5 Hz), 7.38 (s, 1H), 7.34–7.21 (m, 3H), 3.81 (s, 3H), 3.69 (m, 2H), 1.95 (m, 2H); δ_C (500 MHz, $CDCl_3$, −40 °C) 165.0, 135.9, 130.7, 127.0, 122.3, 121.8, 120.8, 110.2, 109.2, 48.9, 46.3, 33.3, 26.4, 24.2; IR ν(film)/cm^{-1} 2942, 2872, 1590; *m*/*z* 228 (M$^+$), 158 (100%), 130, 103, 77. **15**: mp 100–105 °C; δ_H (300 MHz, $CDCl_3$) 7.54 (d, 1H, J = 8.1 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.23 (td, 1H, J' = 7.6 Hz, J'' = 1.0 Hz), 7.15 (td, 1H, J' = 7.6 Hz, J'' = 1.2 Hz), 3.76 (s, 3H), 3.74 (t, 2H, J = 6.6 Hz), 3.41 (t, 2H, J = 6.6 Hz), 2.00 (m, 2H), 1.87 (m, 2H); δ_C ($CDCl_3$) 164.7, 136.2, 125.1, 122.5, 121.0, 120.8, 119.7, 119.4, 109.6, 48.3, 45.8, 31.5, 25.9, 24.6; IR ν(KBr)/cm^{-1} 3456, 2922, 2856, 1733, 1622; *m*/*z* 308 (M$^+$), 262, 236, 192 (100%), 158, 129; HRMS: calc. *m*/*z* 306.0368, found *m*/*z* 306.0367.

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