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Selective lithiation of 2,3-dibromo-1-methylindole. A synthesis of 2,3-disubstituted indoles

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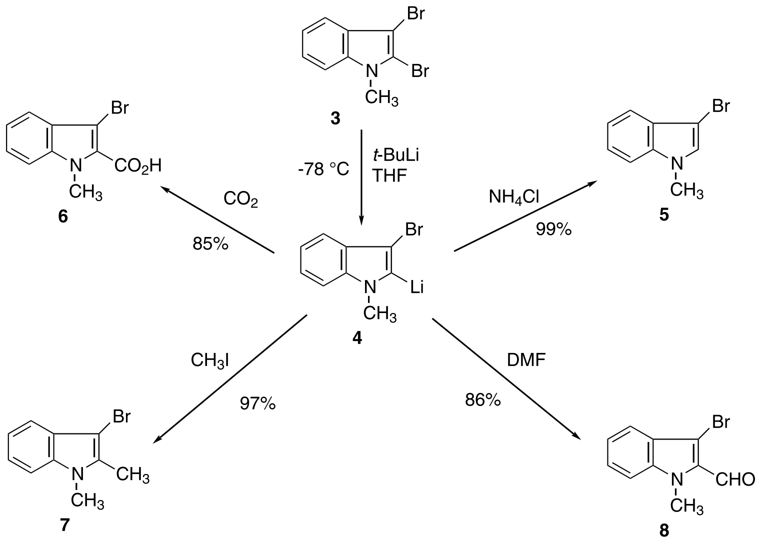
Abstract—Indole (**1**) can be converted to 2,3-dibromo-1-methylindole (**3**) in two operations (92% yield). Treatment of **3** with *tert*-butyllithium effects clean monolithiation to 3-bromo-2-lithio-1-methylindole (**4**), which can be trapped with various electrophiles to afford the 3-bromo-2-substituted indoles (**5**–**8**) in 85–99% yield. A second bromine–lithium exchange reaction and quenching with electrophiles yields the 2,3-disubstituted indoles (**9**–**10**) in 88–95% yield. © 2002 Published by Elsevier Science Ltd.

Although polyhalogenated indoles are ubiquitous in nature,[1] only recently have these compounds been employed in synthesis. For example, we have employed 2,3-diiodoindoles, which are readily synthesized from indole,[2] in bis-Suzuki reactions,[3] to generate and trap 2,3-dilithio-1-methylindole,[4] to effect (inadvertently) an unusual indole ring fragmentation;[5] and in a synthesis of isatins.[6] Others have recently used monohaloindoles in synthesis.[7] We recently described a highly efficient preparation of 2,3-dibromo-1-methylindole (**3**) from indole (**1**) en route to syntheses of the naturally occurring 2,3,6-tribromo-1-methylindole and 2,3,5,6-tetrabromo-1-methylindole.[8] This sequence makes use of the excellent Katritzky indole C-2 lithiation protocol[9] followed by Bergman's indole C-2 bromination method to give 2-bromoindole (**2**).[10] Subsequent bromination and



Scheme 1.

Keywords: 2,3-dibromo-1-methylindole; 2,3-disubstituted indoles; lithiation; lithioindoles.

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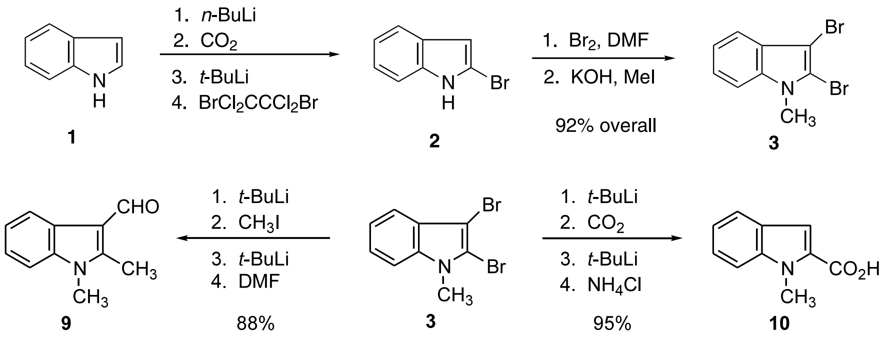

methylation of **2** in one-pot affords 2,3-dibromo-1-methylindole (**3**) in excellent overall yield (92% from indole).

Whereas our earlier attempts to effect selective monolithiation of 2,3-diiodoindoles and 2,3-bromoiodoindoles were unsuccessful,[11] we now report that selective monolithiation of 2,3-dibromo-1-methylindole (**3**) at −78°C is a clean process, even with a large excess of *tert*-butyllithium, to generate the relatively stable 3-bromo-2-lithio-1-methylindole (**4**).[12] Subsequent reaction of **4** with various electrophiles affords the corresponding 3-bromo-2-substituted indoles (**5**–**8**) in 85–99% yield as summarized in Scheme 1. Presumably, the inductive electron withdrawing effect of the indole nitrogen is responsible for the observed selective bromine–lithium exchange at C-2. Also, the greater electron density at C-3 may destabilize an anion at this position. These new 3-bromoindoles (**5**–**8**) exhibited satisfactory spectral and elemental analytical data,[13] and a general procedure is given.[14]

In a one-pot operation we have also found that both bromines of **3** can be sequentially replaced by electrophiles. Thus, treatment of **3** with *tert*-butyllithium followed by methyl iodide affords **7**, which, without isolation, is further treated with *tert*-butyllithium and then DMF to afford 1,2-dimethyl-3-formylindole (**9**)[15,16] in 88% yield. A similar protocol with carbon dioxide and ammonium chloride as the two electrophiles gave 2-carboxy-1-methylindole (**10**)[17,18] in 95% yield. Both **9** and **10** are known compounds, and the synthesis of **9** is representative of our procedure.[19] For the synthesis of **10** it is necessary to remove the excess carbon dioxide in vacuo before adding the second equivalent of *tert*-butyllithium.

In summary, we have shown that 2,3-dibromo-1-methylindole (**3**) can be selectively converted to 3-bromo-2-lithio-1-methylindole (**4**) by bromine-lithium exchange with *tert*-butyllithium at −78°C. The resulting species **4** can be trapped with electrophiles to give **5**–**8**. Furthermore, in one-pot sequential bromine–lithium exchange reactions, **3** can be converted to 2,3-disubstituted indoles, e.g. **9**, **10**.

Acknowledgements

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12. For example, allowing **4** to warm to room temperature in the presence of 2,5-dimethylfuran (to trap 1-methyl-2,3-indolyne, if formed) for 3 days returned only 3-bromo-1-methylindole (**5**) upon workup. In a similar experiment (in the absence of 2,5-dimethylfuran), although the THF solution of **4** changed from bright yellow to bluish upon warming to room temperature, upon workup with water **5** was obtained in 89% yield. In one reaction with a large excess of *tert*-butyllithium and quenching with DMF, some 2,3-diformyl and 3-formyl products were detected by NMR in the crude product, but **8** was the major product.
13. 3-Bromo-1-methylindole (**5**) (99%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 1H), 7.34–7.27 (m, 2H), 7.23–7.19 (m, 1H), 7.09 (s, 1H), 3.80 (s, 3H); MS m/z 211, 209 (M^+, 100%), 131, 130, 115, 103, 88, 77. HRMS m/z calcd for C_9H_8NBr (M^+) 208.9840, found 208.9840. 3-Bromo-2-carboxy-1-methylindole (**6**) (85%): mp 180°C (dec.) (recrystallized from aqueous acetone to afford a colorless solid); ^{1}H NMR (DMSO-d_6) δ 7.61 (d, 1H, $J=8.5$ Hz), 7.53 (d, 1H, $J=8.0$ Hz), 7.39 (t, 1H, $J=8.0$ Hz), 7.22 (t, 1H, $J=8.0$ Hz), 3.99 (s, 3H); MS m/z 255, 253 (M^+, 100%), 221, 208, 194, 167, 146, 128, 115, 102, 91, 77. HRMS m/z calcd for $C_{10}H_8NO_2Br$ (M^+) 252.9738, found 252.9737. Anal. calcd for $C_{10}H_8NO_2Br$: C, 47.44; H, 3.19; N, 5.54. Found: C, 47.27; H, 3.25; N, 5.36%. 3-Bromo-1,2-dimethylindole (**7**) (97%): mp 60°C (dec.) (off-white solid); ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 1H), 7.27 (m, 1H), 7.23–7.15 (m, 2H), 3.72 (s, 3H), 2.46 (s, 3H); MS m/z 225, 223 (M^+), 144 (100%), 128, 115, 102, 89, 77. HRMS m/z calcd for $C_{10}H_{10}NBr$ (M^+) 222.9997, found 222.9997. 3-Bromo-2-formyl-1-methylindole (**8**) (86%): mp 91–92°C (dec.) (yellowish solid); ^{1}H NMR (DMSO-d_6) δ 10.05 (s, 1H), 7.70 (d, 1H, $J=8.5$ Hz), 7.65 (d, 1H, $J=8.0$ Hz), 7.54–7.51 (m, 1H), 7.30–7.27 (m, 1H), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.3, 138.9, 129.8, 128.0, 125.3, 121.9, 120.7, 111.7, 103.7, 31.8; MS m/z 239, 237 (M^+, 100%), 210, 208, 196, 194, 169, 167, 144, 130, 115, 103, 89, 77, 63. HRMS m/z calcd for $C_{10}H_8NOBr$ (M^+) 236.9789, found 236.9789.
14. General procedure: To a solution of 2,3-dibromo-1-methylindole (**3**) (0.100 g, 0.346 mmol) in THF (10 mL) cooled to −78°C under N_2 was added *tert*-butyllithium (0.45 mL, 0.765 mmol, 1.7 M solution in hexanes). The resulting yellow solution was stirred at −78°C for 5 min and then treated with an electrophile. The reaction mixture was allowed to warm to rt, poured into water, and extracted with ethyl acetate (2×10 mL). The organic extract was washed with water (3×20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude product. Flash chromatography (silica gel; EtOAc/hexanes) gave **5**–**8**.[13] Except for **6**, these new 3-bromoindoles were too labile to obtain elemental analyses but correct HRMS data were obtained. In general one must use 2 equiv. of *tert*-butyllithium for each bromine in order to decompose the so-formed *tert*-butyl bromide; and normally we use the electrophile in excess of the *tert*-butyllithium. For example, even with a 12-fold excess of *tert*-butyllithium and quenching **4** with 12.5 equiv. of DMF the yield of **8** is 72%, along with 16% of 2,3-diformyl-1-methylindole and 12% of 3-formyl-1-methylindole.
15. 1,2-Dimethyl-3-formylindole (**9**) (88%): mp 129–130°C (white solid) (lit.[16] mp 131–132°C); ^{1}H NMR (DMSO-d_6) δ 10.08 (s, 1H), 8.10 (m, 1H), 7.55 (d, 1H, $J=8.1$ Hz), 7.29–7.18 (m, 2H), 3.75 (s, 3H), 2.71 (s, 3H); MS m/z 173 (M^+), 172 (100%), 144, 128, 115, 102, 77. HRMS m/z calcd for $C_{11}H_{11}NO$ (M^+) 173.0841, found 173.0842. Anal. calcd for $C_{11}H_{11}NO$: C, 76.26; H, 6.41; N, 8.09. Found: C, 76.28; H, 6.42; N, 8.10.%
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17. 2-Carboxy-1-methylindole (**10**) (96%): mp 209–210°C (recrystallized from aqueous acetone to give a colorless solid) (lit.[18] mp 209–210°C); ^{1}H NMR (DMSO-d_6) δ 12.9 (bs, 1H), 7.67 (d, 1H, $J=8.0$ Hz), 7.56 (d, 1H, $J=8.0$ Hz), 7.33 (m, 1H), 7.21 (s, 1H), 7.12 (t, 1H, $J=7.5$ Hz), 4.02 (s, 3H); MS m/z 175 (M^+, 100%), 158, 144, 130, 102, 89, 75, 63. HRMS m/z calcd for $C_{10}H_9NO_2$ (M^+) 175.0633, found 175.0631. Anal. calcd for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 8.00. Found: C, 68.11; H, 5.21; N, 7.86.
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19. 1,2-Dimethyl-3-formylindole (**9**). To a solution of 2,3-dibromo-1-methylindole (**3**) (0.100 g, 0.346 mmol) in THF (10 mL) cooled to −78°C under N_2 was added *tert*-butyllithium (0.450 mL, 0.765 mmol, 1.7 M solution in hexanes). The resulting yellow solution was stirred for 5 min and then treated at −78°C with methyl iodide (50 μL, 0.796 mmol). The solution was warmed to rt, stirred at rt for 10 min, and recooled to −78°C. A second batch of *tert*-butyllithium (0.610 mL, 1.04 mmol, 1.7 M solution in hexanes) was added and, after 5 min of stirring, DMF (100 μL, 1.3 mmol) was added. The reaction mixture was allowed to warm to rt, poured into water, and extracted with ethyl acetate (2×10 mL). The organic extract was washed with water (3×20 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was flash chromatographed on silica gel (EtOAc/hexane, 1:1) to give 52 mg (88%) of **9** as a colorless solid.[15]