Pergamon

Tetrahedron Letters 42 (2001) 2949–2951

TETRAHEDRON
LETTERS

Generation and reactions of 2,3-dilithio-*N*-methylindole. Synthesis of 2,3-disubstituted indoles

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Received 6 February 2001; revised 14 February 2001; accepted 16 February 2001

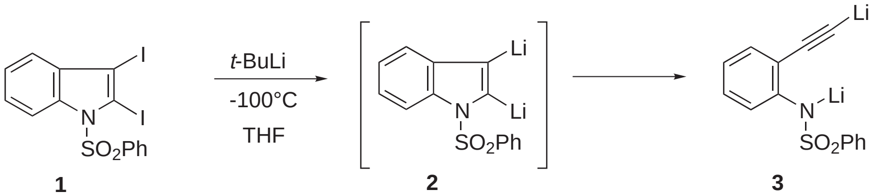
Abstract—Generation of 2,3-dilithio-*N*-methylindole (**7**) from 2,3-diiodo-*N*-methylindole (**6**) and subsequent reaction with various electrophiles (NH_4Cl, DMF, $ClCO_2Me$, CO_2, phthalic anhydride) affords the corresponding 2,3-disubstituted indoles in good to excellent yields (41–99%). © 2001 Elsevier Science Ltd. All rights reserved.

The metallation and subsequent reaction of heterocycles is a powerful tactic in synthesis,[1] and the generation and utility of lithioindoles has been used by many investigators to elaborate indoles.[2,3] Several years ago we attempted to generate 2,3-dilithio-*N*-(phenylsulfonyl)indole (**2**).[4] Surprisingly, this species underwent facile indole ring fragmentation at temperatures down to and even below −100°C, to afford the stable lithium 2-(*N*-lithiophenylsulfonamido)phenylacetylide (**3**). Subsequent trapping of **3** with electrophiles (aq. NH_4Cl, TMSCl, $ClCO_2Et$) afforded the corresponding products in good yields (66–82%).[4] Products with an intact indole ring were obtained in low yield (<20%).

We now report that the *N*-methyl analogue of **2** is stable at low temperatures and can be trapped with electrophiles to give 2,3-disubstituted indoles. This chemistry is summarized in Scheme 1. We synthesized 2,3-diiodo-*N*-methylindole (**6**) in two steps from indole (**4**). Thus, the Bergman procedure[5] gave 2-iodoindole (**5**)[6] in 90% yield. Treatment of **5** with I_2/KOH/DMF followed by methyl iodide in the presence of tetra-*n*-butylammonium hydrogen sulfate gave **6**[7,8] in 91% yield. The dilithio species **7** was generated with excess *tert*-butyllithium (5–10 equiv.) at −78°C (THF, 20 min). Quenching the resulting bright yellow solution at −78°C with saturated aqueous NH_4Cl afforded *N*-methylindole (**8**)[9] in 99% yield. Evidence for the formation of dilithioindole **7**, rather than monolithiated iodinated intermediates, was revealed by direct injection of the lithiated reaction mixture into a gas chromatograph. This showed the presence of only **8** and no iodinated *N*-methylindoles. Quenching dilithioindole **7** with DMF (10 equiv.) gave 2,3-diformyl-*N*-methylindole (**9**)[10] in 82% yield. A similar reaction with methyl chloroformate gave 2,3-bis(methoxycarbonyl)-*N*-methylindole (**10**)[12] in 75% yield. Likewise, reaction of **7** with gaseous CO_2 gave *N*-methyl-2,3-indole dicarboxylic acid (**11**)[14] in 66% yield.

In view of our long interest in employing lithiated indoles as a synthetic route to the anticancer ellipticine alkaloid family and related benzo[*b*]carbazoles,[3,16] we quenched dilithioindole **7** with phthalic anhydride. This afforded 5-methyl-5*H*-benzo[*b*]carbazole-6,11-dione (**12**)[17] in 41% yield. Work is currently underway to adapt this latter reaction to a synthesis of pyridocarbazolequinones and pyridocarbazoles such as ellipticine.

Unfortunately, attempts to achieve bis-electrophilic reactions with TMSCl and methyl iodide have led to



Keywords: 2,3-dilithio-*N*-methylindole; 2,3-diiodo-*N*-methylindole; lithiation; benzo[*b*]carbazole-6,11-dione.

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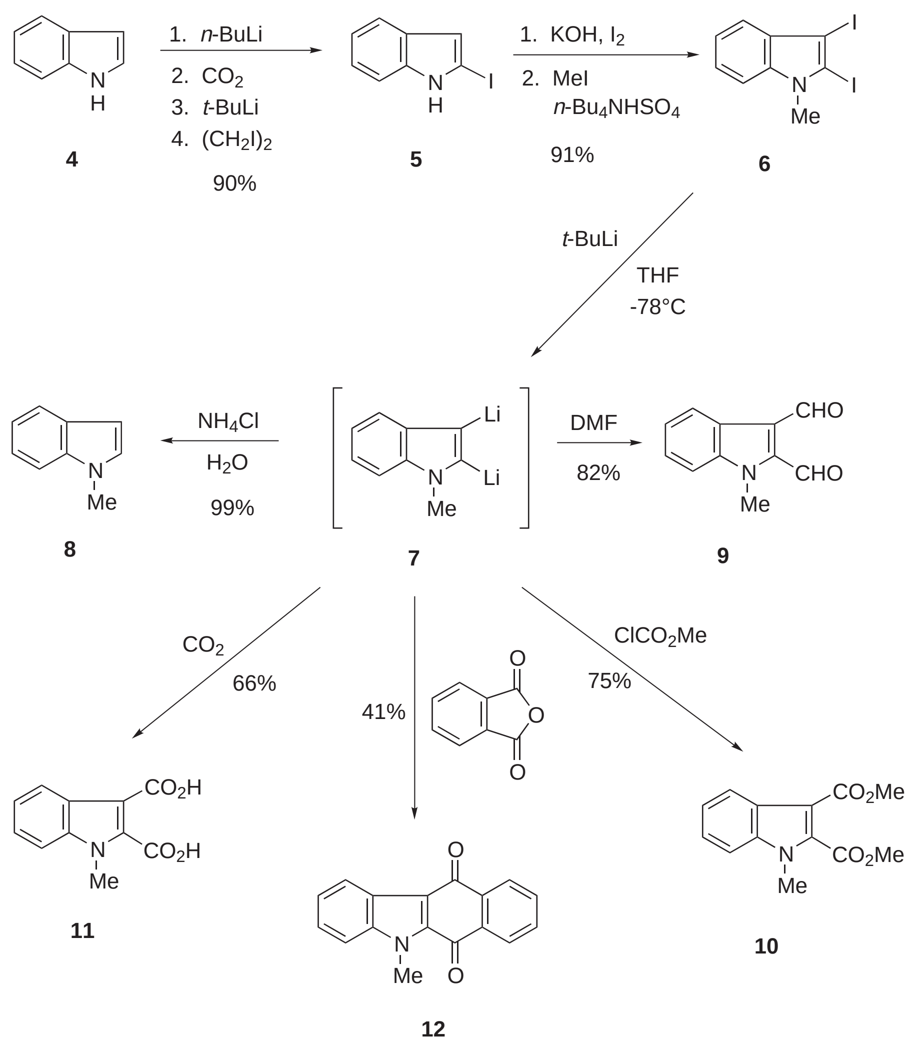
PII: S0040-4039(01)00332-X



Scheme 1.

mixtures of products. For example, reaction of **7** with excess methyl iodide afforded a 60:40 (GC–MS) mixture of 1,2,3-trimethylindole and a dimethylindole. Reaction of **7** with α,α′-dibromo-*o*-xylene and 1,4-dibromobutane led to complex reaction mixtures and the apparent formation of an unidentified indole dimer.

In conclusion, the substitution of the electron-donating methyl group for the electron-withdrawing phenylsulfonyl group prevents indole ring fragmentation of 2,3-dilithioindole and allows for bis-electrophilic reactions of this novel species.[19,20] Finally, it should be noted that Winter has described the synthesis of a stable dimeric 2,3-dialuminated indole.[21]

Acknowledgements

This work was supported by the National Institutes of Health (GM58601), for whose support we are grateful.

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6. Compound **5** (90%): Mp 77°C (decomposed into tar) (lit.[5] mp 98–99°C); ^{1}H NMR (CDCl$_3$) δ 8.1 (s, br, 1H), 7.55 (m, 1H), 7.34 (m, 1H), 7.16–7.08 (m, 2H), 6.74 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 138.9, 129.8, 122.5, 120.5, 119.4, 112.9, 110.3, 74.9. HRMS m/z calcd for C_8H_6IN (M$^+$): 242.9545; found: 242.9542.
7. Compound **6** (91%): Mp 64–65°C (lit.[8] mp 76–78°C); ^{1}H NMR (CDCl$_3$) δ 7.41 (m, 1H), 7.29 (m, 1H), 7.23–7.14 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 137.9, 130.9, 122.5, 120.6, 120.3, 110.9, 99.7, 71.6, 35.9.
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9. Compound **8** (99%): Oil; IR (film) ν_{max} 3056, 2933, 1611, 1506, 1456, 1422, 1317, 1239, 1150, 1072, 1006, 741 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 7.65 (m, 1H), 7.35 (d, 1H, $J=8.5$ Hz), 7.27–7.21 (m, 1H), 7.15–7.11 (m, 1H), 7.07 (d, 1H, $J=3.0$ Hz), 6.50 (d, 1H, $J=3.0$ Hz), 3.81 (s, 3H). This material was identical to a commercial sample of *N*-methylindole by NMR and TLC.
10. Compound **9** (82%): Mp 161°C (lit.[11] mp 158°C); IR (film) ν_{max} 2920, 2848, 2365, 1679, 1653, 1478, 1386, 1345, 1134, 1015, 898, 749 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 10.77 (s, 1H), 10.74 (s, 1H), 8.39 (d, 1H, $J=8.1$ Hz), 7.72 (d, 1H, $J=8.7$ Hz), 7.58–7.53 (t of d, 1H, $J=0.6$, 8.1 Hz), 7.43–7.38 (t, 1H, $J=8.1$ Hz), 4.22, (s, 3H).
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12. Compound **10** (75%): Oil (lit.[13] mp 35°C); IR (film) ν_{max} 2956, 2356, 1706, 1528, 1472, 1439, 1400, 1372, 1250, 1217, 1156, 1106, 1028 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.08 (d, 1H, $J=8.5$ Hz), 7.59 (d, 1H, $J=8.5$ Hz), 7.39 (m, 1H), 7.30 (m, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H).
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14. Compound **11** (66%): Mp 205–207°C (dec.) (lit.[15] mp 208–209°C (dec.)); IR (film) ν_{max} 3144, 2356, 1700, 1600, 1550, 1500, 1461, 1344, 1228 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.33 (d, 1H, $J=8.0$ Hz), 7.76 (d, 1H, $J=8.5$ Hz), 7.51 (m, 1H), 7.40 (m, 1H), 4.25 (s, 3H).
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17. Compound **12** (41%): Mp 207–208°C (lit.[18] mp 206–208°C); IR (film) ν_{max} 2922, 2856, 1656, 1594, 1517, 1394, 1233 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.49 (d, 1H, $J=8.0$ Hz), 8.24 (d, 1H, $J=7.5$ Hz), 8.20 (d, 1H, $J=7.5$ Hz), 7.75–7.71 (m, 2H), 7.51 (m, 2H), 7.43 (m, 1H), 4.29 (s, 3H).
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19. General procedure: A solution of **6** (0.050 g, 0.13 mmol) in dry THF (10 mL) was cooled to −78°C and treated dropwise with *tert*-butyllithium (5–10 equiv. of 1.7 M pentane solution). The resulting bright yellow solution was stirred for 20 min at −78°C and then treated with the electrophile (1.3 mmol; in the case of phthalic anhydride, 0.13 mol). The reaction was allowed to warm to room temperature, poured into water, and extracted with ethyl acetate. The organic phase was dried (MgSO$_4$), and concentrated in vacuo to afford the crude product. Flash chromatography over silica gel gave the purified products in the yields indicated.
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