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Nucleophilic addition reactions of 2-nitro-1-(phenylsulfonyl)indole. A new synthesis of 3-substituted-2-nitroindoles

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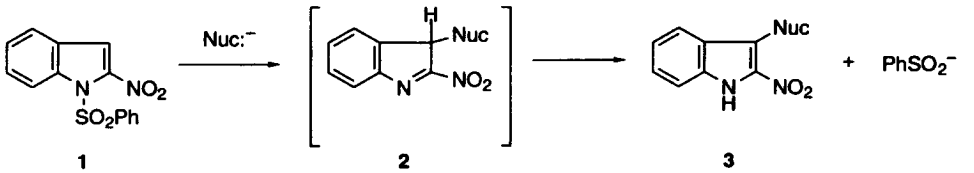
Abstract

2-Nitro-1-(phenylsulfonyl)indole (**1**) undergoes nucleophilic addition reactions with the enolates of diethyl malonate and cyclohexanone, lithium dimethylcuprate, and indole anion to afford the corresponding 3-substituted-2-nitroindoles (**4–6, 8, 9**) in low to high yields. Reaction of 1-(phenylsulfonyl)-2-(trialkylstannyl)indoles **13** and **14** with tetranitromethane affords the novel isoxazolo[5,4-*b*]indole **15** via a 1,3-dipolar cycloaddition reaction with in situ generated nitro formonitrile oxide (**19**).

Keywords: 2-nitroindoles; nucleophilic addition; 1,3-dipolar cycloaddition; isoxazolo[5,4-*b*]indole.

In continuation of our recent studies on the synthesis and reactions of 2- and 3-nitroindoles,[1] we now report that 2-nitro-1-(phenylsulfonyl)indole (**1**) undergoes a formal S_N2' nucleophilic displacement of phenylsulfinate to give the corresponding 3-substituted-2-nitroindole (**3**) in good to excellent yield. Presumably this reaction, which represents one of a growing number of such nucleophilic addition reactions to indoles,[2] involves an incipient C-2 anion that is strongly stabilized by the nitro group, leading subsequently to indolenine **2** which tautomerizes to the product **3**. Our results are summarized in Scheme 1.



1 **2** **3**

Scheme 1.

The reaction of **1** with the enolates of diethyl malonate and cyclohexanone afforded the corresponding indoles **4**[3] and **5**[4] in 88% and 72% yield, respectively (Scheme 2). Reaction of **1** with lithium

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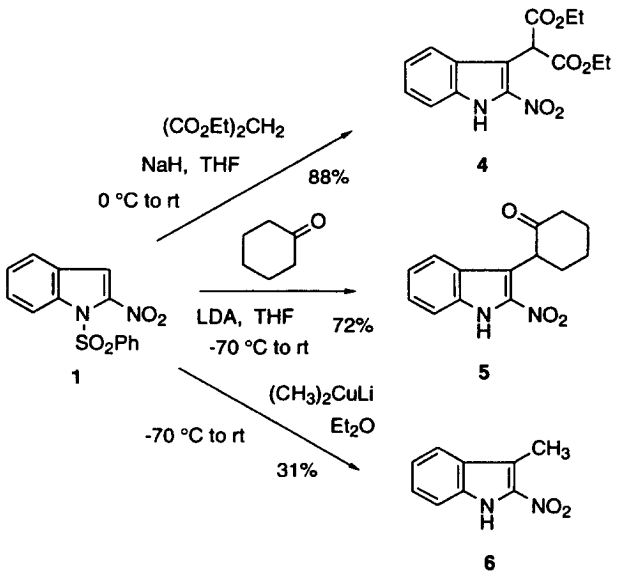
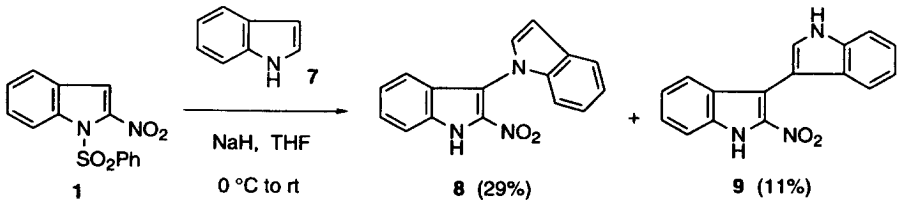
dimethylcuprate gave the known 3-methyl-2-nitroindole (**6**)[5] in fair yield (31%). The structures of these compounds are supported by spectral and analytical data.[3–5] These reactions represent the first report of the nucleophilic addition of cuprates and only the second example of the addition of enolates to the indole C-3 position.[2]



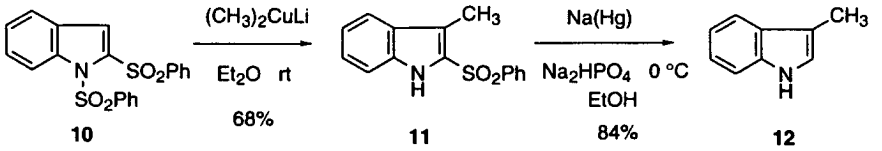
Scheme 2.

The reaction of **1** with the anion of indole (**7**) yielded a mixture of the bis-indoles **8**[6] and **9**,[7] separable by column chromatography (Scheme 3). It is interesting to note that several polybrominated examples of both ring systems are marine natural products, isolated from the blue-green alga *Rivularia firma*.[8]



Scheme 3.

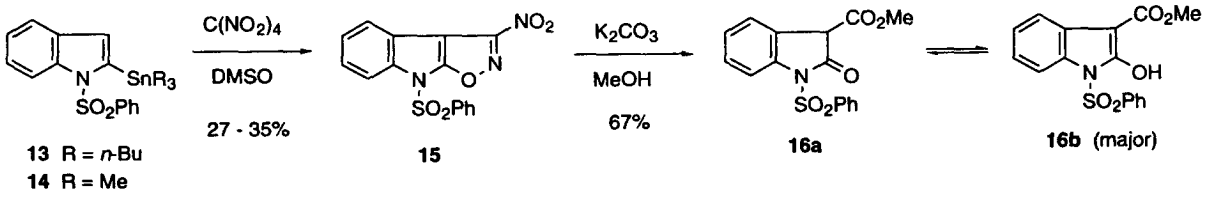
We have also found 1,2-bis(phenylsulfonyl)indole (**10**)[9] with lithium dimethylcuprate gave 3-methyl-2-(phenylsulfonyl)indole (**11**)[10] in 68% yield (Scheme 4). The structure of **11** was established by conversion to 3-methylindole (skatole) (**12**). We have been unsuccessful in our preliminary attempts to effect similar C-3 nucleophilic additions with lithium dimethylcuprate to 2-acetyl-, 2-cyano-, and 2-carbomethoxy-1-(phenylsulfonyl)indole, although small amounts of product seem to form.



Scheme 4.

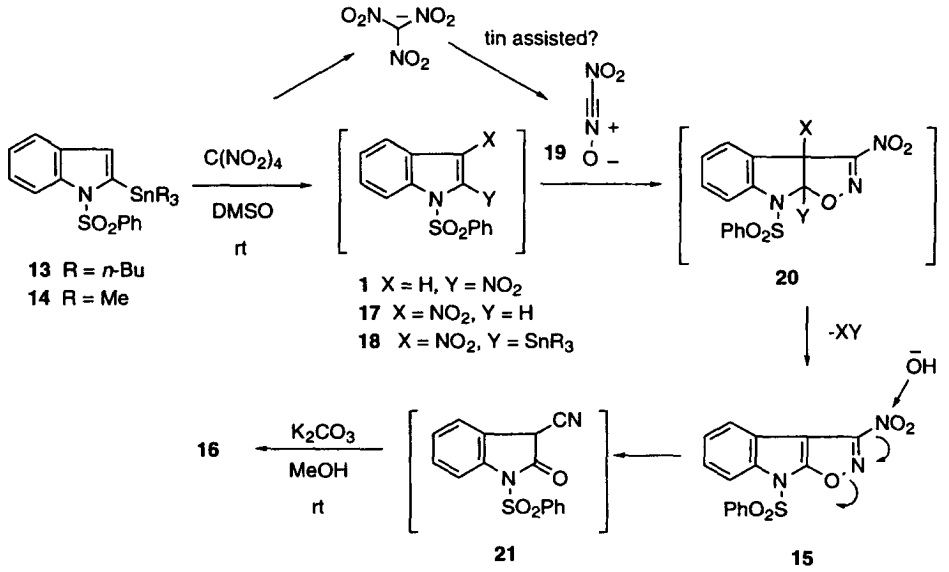
Despite the attractiveness of **1** as a potential entry to 3-substituted indoles, our current preparation of **1** involves the intermediacy of *o*-azido-β-nitrostyrene, which has toxic effects not unlike

those of the tear gas 'CS' ('pepper spray') (*o*-chlorobenzalmalononitrile).[11] Therefore, we are searching for a safer synthesis of 2-nitroindoles, and, to this end, we have examined the reaction of 1-(phenylsulfonyl)-2-(tri-*n*-butylstannyl)indole (**13**)[12] and 1-(phenylsulfonyl)-2-(trimethylstannyl)indole (**14**)[13] with tetranitromethane.[14a] However, rather than the anticipated[14b] **1**, these reactions produced the novel isoxazolo[5,4-*b*]indole (**15**),[15] which, upon treatment with base, afforded oxindole **16**[16] (Scheme 5). We are in the process of confirming the structures of **15** and **16**.



Scheme 5.

One can envision the formation of **15** via the intermediacy of the known nitro formonitrile oxide (**19**),[17] following a close literature precedent for the degradation of dinitromethyl anion to a nitrile oxide,[18] as shown in Scheme 6. Thus, a 1,3-dipolar cycloaddition between a presumed nitroindole (**1**, **17**, or **18**) and **19** would afford an intermediate **20**, which loses nitrous acid or SnR_3NO_2 to yield the product **15**. The low yields of **15** might be due to the propensity of **19** to dimerize.[17] In one experiment, 3-nitro-1-(phenylsulfonyl)indole (**17**) was isolated in low yield (<5%),[19] thus supporting the notion that a nitroindole is initially formed. Base-induced fragmentation of **15**, similar to the deprotonation-fragmentation of isoxazoles,[20] would then yield nitrile **21** (or tautomer) and finally **16** upon methanolysis. We regard the structures of **15** and **16** as tentative until confirmed by independent means. For example, **15** and **16** could be the isomeric isoxazolo[4,5-*b*]indole and carbomethoxyindoxyl, respectively.



Scheme 6.

In summary, 2-nitro-1-(phenylsulfonyl)indole (**1**) offers a potentially general, new route to 3-substituted indoles by nucleophilic addition reactions. Furthermore, subsequent manipulation of the nitro group should yield additional indole derivatives, and we are continuing our work along these lines.

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2. For an excellent review of nucleophilic addition reactions to indoles, see: Joule, J. A. *Prog. Het. Chem.* **1999**, *11*, 45–65.
3. Compound **4**: Mp 144–146°C (EtOAc/hexanes); IR (PTFE) υ_{max} 3292 (NH), 2980, 1722 (C=O), 1556, 1504, 1458, 1413, 1383, 1339, 1292, 1200, 1145, 1099, 1029 cm^{-1}; UV (EtOH) λ_{max} 212, 246, 354 nm; ^1H NMR ($CDCl_3$) δ 9.57 (br s, 1H), 7.75–7.78 (m, 1H), 7.38–7.43 (m, 1H), 7.30–7.33 (m, 1H), 7.18–7.24 (m, 1H), 5.98 (s, 1H), 4.21–4.26 (m, 4H), 1.28 (t, 6H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.5, 137.8, 133.6, 128.7, 125.9, 123.4, 122.7, 112.6, 110.1, 62.5, 49.0, 14.2; MS *m/z* 320 (M^+), 289, 274, 247, 217, 202, 172 (100%), 158, 144, 103, 75. Anal. calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.03; N, 8.75. Found: C, 56.28; H, 5.20; N, 8.64.
4. Compound **5**: Mp 196–197°C (EtOAc/hexanes); IR (PTFE) υ_{max} 3293 (NH), 2938, 1697 (C=O), 1552, 1493, 1455, 1382, 1334, 1293, 1205, 1150, 743 cm^{-1}; UV (EtOH) λ_{max} 212, 246, 356 nm; ^1H NMR (d_6-DMSO) δ 12.79 (br s, 1H), 7.72–7.75 (m, 1H), 7.40–7.47 (m, 2H), 7.12–7.18 (m, 1H), 4.55 (t, 1 H, J=9.3 Hz), 2.40–2.52 (m, 2H), 2.09–2.20 (m, 3H), 1.80–1.95 (m, 3H); ^{13}C NMR (d_6-DMSO) δ 206.6, 137.6, 134.4, 127.9, 125.6, 122.5, 121.1, 117.8, 113.0, 47.3, 41.1, 32.0, 25.4, 24.5; MS *m/z* 258 (M^+), 228, 212, 197 (100%), 169, 115, 77. Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.86; H, 5.46; N, 10.60.
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6. Compound **8**: Mp 165–167°C; IR (KBr) υ_{max} 3340 and 3259 (NH), 3060, 2948, 1621, 1574, 1501, 1464, 1449, 1407, 1382, 1336, 1310, 1272, 1210, 1175, 740 cm^{-1}; UV (EtOH) λ_{max} 208, 220, 250, 279 (sh), 290 (sh) 346 nm; ^1H NMR ($CDCl_3$) δ 9.50 (br s, 1H), 7.74–7.77 (m, 1H), 7.47–7.55 (m, 3H), 7.40 (d, 1 H, J=3.3 Hz), 7.21–7.27 (m, 3H), 7.11–7.14 (m, 1H), 6.82 (dd, 1 H, J=0.9, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 136.6, 133.2, 132.2, 129.6, 129.3, 129.2, 123.3, 123.0, 122.9, 122.4, 121.5, 121.2, 117.0, 113.0, 111.4, 105.1. HRMS *m/z* calcd for $C_{16}H_{11}N_3O_2$ (M^+) 277.0851, found 277.0855.
7. Compound **9**: red powder; IR (KBr) υ_{max} 3381 (NH), 3053, 2960, 2921, 1618, 1577, 1482, 1449, 1417, 1368, 1333, 1302, 1270, 1217, 1146, 1100, 739 cm^{-1}; UV (EtOH) λ_{max} 210, 256 (sh), 274 (sh), 294 (sh), 396 nm; ^1H NMR ($CDCl_3$) δ 9.36 (br s, 1H), 8.56 (br s, 1H), 7.73–7.76 (m, 1H), 7.69 (d, 1H, J=2.1 Hz), 7.45–7.54 (m, 4H), 7.27–7.32 (m, 1H), 7.16–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 136.8, 136.1, 134.2, 128.9, 127.1, 126.8, 126.7, 124.4, 122.8, 122.0, 121.0, 120.6, 114.3, 112.3, 111.9, 106.4. HRMS *m/z* calcd for $C_{16}H_{11}N_3O_2$ (M^+) 277.0851, found 277.0849.
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9. This was prepared from 1-(phenylsulfonyl)-2-thiophenylindole (Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761) by oxidation with *m*-CPBA to give **10** (86%): mp 177.5–178.5°C. Anal. calcd for $C_{20}H_{15}S_2O_4N$: C, 60.44; H, 3.80; N, 3.52; S, 16.13. Found: C, 60.49; H, 3.82; N, 3.49; S, 16.14. Oxidation with potassium peroxymonosulfate (oxone) afforded only the corresponding sulfoxide (91% yield), mp 191–192°C (EtOAc/hexane); MS *m/z* 381, 365, 333, 272, 240, 224, 192, 165, 141, 100, 77. Anal. calcd for $C_{20}H_{15}S_2O_3N$: C, 62.97; H, 3.96; N, 3.67; S, 16.81. Found: C, 63.06; H, 3.98; N, 3.66; S, 16.80.
10. Compound **11**: Mp 168.5–169.5°C; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.54 (s, 3H), 7.1–7.6 (m, 7H), 7.9–8.1 (m, 2H), 9.4 (br s, 1H); MS *m/z* 271 (M^+), 236, 206, 146, 129, 100, 85, 77. Anal. calcd for $C_{15}H_{13}SO_2N$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.40; H, 4.86; N, 5.16; S, 11.78. This reaction also produced a small quantity of 3-methyl-1-(phenylsulfonyl)indole, by comparison with an authentic sample.
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13. Compound **14** was prepared in 43% yield from 1-(phenylsulfonyl)indole (1. *t*-BuLi, 2. Me_3SnCl): Mp 96–97°C (MeOH); IR (KBr) υ_{max} 3070, 2988, 2917, 1446, 1434, 1357, 1294, 1266, 1225, 1166, 1122, 1086, 1011, 755, 727, 588 cm^{-1}; UV (EtOH) λ_{max} 218, 222, 260, 292 (sh) nm; ^1H NMR ($CDCl_3$) δ 7.85–7.88 (m, 1H), 7.68–7.71 (m, 2H), 7.49–7.54 (m, 2H),

7.38–7.43 (m, 2H), 7.17–7.24 (m, 2H), 6.86 (d, 1 H, J=0.9 Hz), 0.45 (s, 9H); ^{13}C NMR ($CDCl_3$ δ 143.6, 139.2, 138.4, 133.6, 132.0, 129.2, 126.5, 124.2, 123.3, 120.6, 120.5, 113.8, –6.5; MS *m/z* 406 (M^+–14, 100%), 376, 312, 281, 235, 222, 197, 165, 130, 89, 77, 51. Anal. calcd for $C_{17}H_{19}NO_2SSn$: C, 48.61; H, 4.56; N, 3.33; S, 7.63. Found: C, 48.67; H, 4.55; N, 3.35; S, 7.58.

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15. Compound **15**: Mp 168–170°C (hexanes/CH_2Cl_2); IR (KBr) υ_{max} 3099, 3028, 1678, 1600, 1535, 1517, 1448, 1386, 1356, 1314, 1224, 1174, 1118, 1088, 951 cm^{-1}; UV (EtOH) λ_{max} 210, 246 (sh), 270 (sh), 276 (sh), 334 nm; ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 2H), 8.10 (m, 2H), 7.69 (m, 2H), 7.45–7.59 (m, 3H) ppm; ^{13}C NMR (d_6-DMSO) δ 164.2, 154.6, 144.9, 135.9, 135.5, 132.5, 130.3, 127.2, 126.2, 125.7, 115.4, 114.8, 108.9 ppm; MS *m/z* 344 (M^++1, 100%), 316, 298, 288, 233, 199, 159, 143. Anal. calcd for $C_{15}H_9N_3O_5S$: C, 52.48; H, 2.64; N, 12.24; S, 9.34. Found: C, 52.73; H, 2.64; N, 12.07; S, 9.30.
16. Compound **16**: Mp 141–143°C (amorphous); IR (KBr) υ_{max} 3455 (OH), 3067, 3015, 2954, 1659 (C=O), 1600, 1584, 1550, 1481, 1457, 1400, 1378, 1280, 1176, 1125, 1079, 1038, 994, 951, 875, 763, 686, 597, 568 cm^{-1}; UV (EtOH) λ_{max} 206, 224, 262, 291 (sh), 301 (sh) nm; ^{1}H NMR ($CDCl_3$) δ 8.01–8.08 (m, 3H), 7.57–7.62 (m, 1H), 7.44–7.50 (m, 3H), 7.31–7.36 (m, 1H), 7.21–7.26 (m, 1H), 4.29 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.8, 163.6, 142.7, 137.5, 134.6, 129.5, 127.5, 126.5, 124.9, 121.5, 119.6, 114.8, 88.8, 59.4 ppm; MS *m/z* 331 (M^+), 330 (M^+–1), 299, 260, 232, 204, 189 (M^+–1–SO_2Ph), 157 (M^+–1–SO_2Ph–MeOH: 100%), 130, 102, 77.
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