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Synthesis of 2-Nitroindoles via the Sundberg Indole Synthesis

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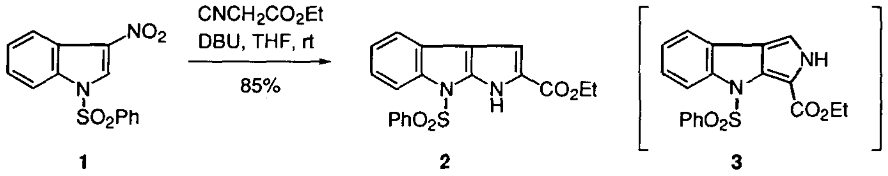
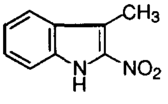
Abstract: A three-step sequence has been developed for converting *o*-nitrobenzaldehydes into 2-nitroindoles. The key step involves the thermolysis of 2-(*o*-azidophenyl)nitroethylene (**10**) in xylenes which gives 2-nitroindole (**4**) in 54% yield, akin to the classic Sundberg indole synthesis. This procedure has also been utilized to synthesize 5,6-dimethoxy-2-nitroindole (**14**).

We recently discovered a novel rearrangement leading to pyrrolo[2,3-*b*]indole **2**, which occurs upon treatment of 3-nitro-1-(phenylsulfonyl)indole (**1**) with ethyl isocyanoacetate and DBU.[1] We anticipated that this reaction would instead give pyrrolo[3,4-*b*]indole **3**, a fused indole which potentially could be elaborated into novel carbazoles utilizing cycloaddition chemistry. In order to preclude this rearrangement and develop a succinct route to the pyrrolo[3,4-*b*]indole ring system, we decided to investigate this reaction with a 2-nitroindole substrate.



To our surprise, 2-nitroindole (**4**) is an unknown compound. Indeed, although the other five possible simple nitroindole compounds are all known compounds,[2-6] only two simple 2-nitroindoles have been synthesized, 3-methyl-2-nitroindole (**5**)[2] and 3-phenyl-2-nitroindole (**6**).[7] Both were obtained in low yield with undesirable 3-substitution. One of the most useful methods of elaborating the indole moiety at the 2-position is directed metalation.[8] Unfortunately, this technique is incompatible with nitro functionalization, due to the apparent lack of an NO_2^+ equivalent capable of adding to a localized carbanion.[9] We now wish to report a general synthesis of 2-nitroindoles based on the classic Sundberg indole synthesis,[10] which involves the thermolysis of *β*-substituted-*o*-azidostyrenes.



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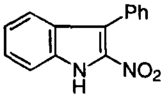

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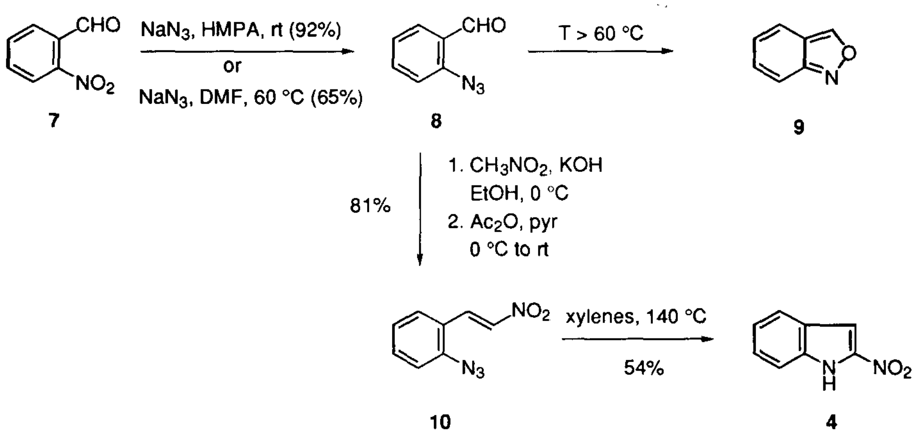
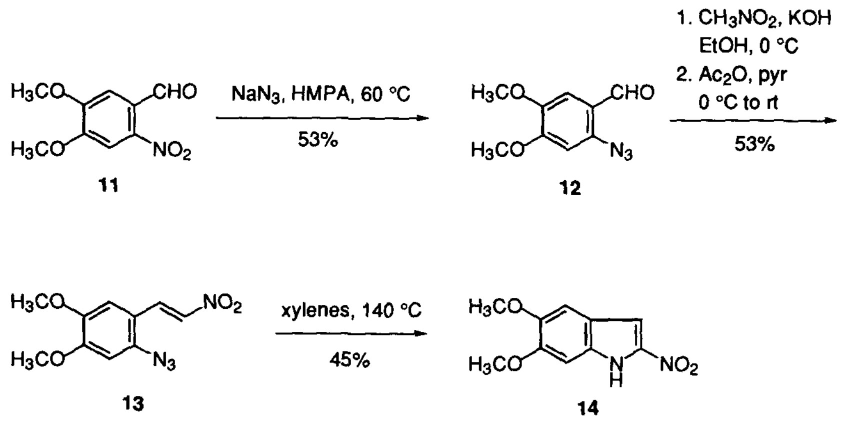
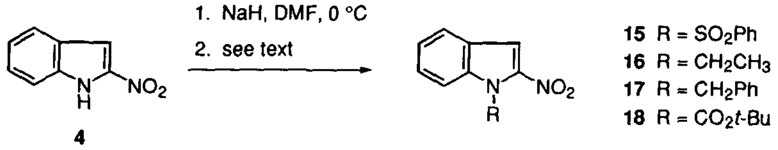
The synthesis of **4** was achieved in three steps from 2-nitrobenzaldehyde (**7**) in 40% overall yield. Conversion of **7** into 2-azidobenzaldehyde (**8**) was accomplished in 92% yield with sodium azide in HMPA at ambient temperature following the procedure of Spagnolo.[11] The use of the carcinogenic solvent HMPA can be avoided by heating **7** and sodium azide in DMF for 20 hours at 60 °C to give **8** in 65% yield. Higher reaction temperatures lead to the formation of the undesirable side product anthranil (**9**).[12] Using the procedure of Molina,[13] **8** was converted into the known nitrostyrene **10** in an improved 81% yield.[14] Finally, thermolysis of **10** in xylenes at 140 °C for 12 hours gave 2-nitroindole (**4**) in 54% yield.[15]



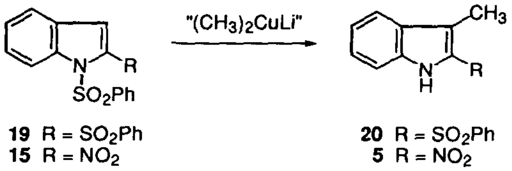
The three-step sequence was also utilized to synthesize 5,6-dimethoxy-2-nitroindole (**14**). Attempts to synthesize azide **12** from *o*-nitrobenzaldehyde **11** by heating in DMF failed, which was probably due to the decreased electrophilicity of the ring resulting from the presence of electron-rich methoxy groups. This conversion was finally realized by heating **12**[16] and sodium azide in HMPA at 60 °C for 9 hours to give **12** in 53% yield. No reaction was observed in the absence of heating. A Henry reaction on **12** gave styrene **13** in 53% yield. Finally, thermolysis of **13** in xylenes at 125 °C for 16 hours gave **14** in 45% yield.[17]



Protection of **4** can be cleanly accomplished utilizing sodium hydride as the base in DMF. A few *N*-protected 2-nitroindoles have been synthesized by this method. For example, treatment of **4** with sodium hydride in DMF followed by benzenesulfonyl chloride gave 2-nitro-1-(phenylsulfonyl)indole (**15**) in 57% yield.[18] Likewise, 2-nitroindoles **16-18** were synthesized in good yields utilizing iodoethane (88% yield), benzyl bromide (72% yield), and *tert*-butyl phenyl carbonate (89% yield), respectively.



A few years back, we discovered that 1,2-bis(phenylsulfonyl)indole (**19**) was capable of undergoing conjugate addition by lithium dimethylcuprate.[19] Treatment of **19** with lithium dimethylcuprate in ether gave indole **20** in 67% yield by conjugate addition and ejection of the phenylsulfonyl protecting group. Likewise, we now report that treatment of **15** with lithium dimethylcuprate gave known indole **5**[2] in 30% yield. These reactions represent one of the very few known examples of formal nucleophilic addition to the indole 3-position.[20] We are continuing to study the reactions of these novel 2-nitroindoles.



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14. **Caution**: azidostyrene **10** is a strong skin and eye irritant.
15. **4**: Mp 116-118 °C; IR (KBr) υ_{max} 3275 (NH), 3133, 3067, 1624 (C=C), 1526, 1489, 1452, 1394, 1340, 1284, 1232, 1151, 1100, 822, 734 cm^{-1}; UV (EtOH) λ_{max} 214, 242, 350 nm; ^{1}H NMR (CDCl$_3$) δ 9.27 (bs, 1 H), 7.75 (m, 1 H), 7.44-7.52 (m, 3 H), 7.26 (m, 1 H) ppm; ^{13}C NMR (CDCl$_3$) δ 143.7, 135.2, 128.4, 126.1, 124.0, 122.7, 112.6, 104.4 ppm; MS *m/z* 263 (M$^+$+1), 262, (M$^+$), 146, 132, 115, 104, 89, 77, 63, 51, 39, 30. Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.36; H, 3.79; N, 17.21.
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17. **14**: Mp 186-188 °C; IR (Nujol) υ_{max} 3289 (NH), 1627 (C=C) cm^{-1}; UV (EtOH) λ_{max} 210, 256 (sh), 274 (sh), 294 (sh), 396 nm; ^{1}H NMR (CDCl$_3$) δ 9.27 (bs, 1 H), 7.35 (d, 1 H, J = 1.5 Hz), 7.03 (s, 1 H), 6.82 (s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H) ppm; ^{13}C NMR (CDCl$_3$) δ 152.8, 147.7, 139.8, 131.5, 119.6, 105.1, 102.8, 93.9, 56.4, 56.3 ppm; MS *m/z* 222 (M$^+$), 207, 192, 176, 161, 149, 133, 119, 106, 89, 76, 63, 30. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.56; N, 12.45. Found: C, 53.95; H, 4.54; N, 12.61.
18. **15**: Mp 157-160 °C; IR (KBr) υ_{max} 3111, 1606 (C=C), 1549, 1507, 1476, 1450, 1363, 1238, 1171, 1122, 1088, 1035, 914, 841, 725, 566 cm^{-1}; UV (EtOH) λ_{max} 212, 270 (sh), 276 (sh), 324 nm; ^{1}H NMR (CDCl$_3$) δ 8.18 (m, 1 H), 8.08 (m, 2 H), 7.54-7.68 (m, 5 H), 7.45 (s, 1 H), 7.39 (m, 1 H) ppm; ^{13}C NMR (CDCl$_3$) δ 138.3, 137.8, 134.7, 129.7, 129.4, 127.7, 125.6, 125.5, 124.1, 116.2, 113.8 ppm; MS *m/z* 302 (M$^+$), 272, 191, 165, 141, 115, 103, 77, 51, 30. Anal. Calcd for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27; S, 10.61. Found: C, 55.58; H, 3.35; N, 9.22; S, 10.70.
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