One-step syntheses of the pyrrolo[3,4-*b*]indole and pyrrolo[2,3-*b*]indole ring systems from 3-nitroindoles

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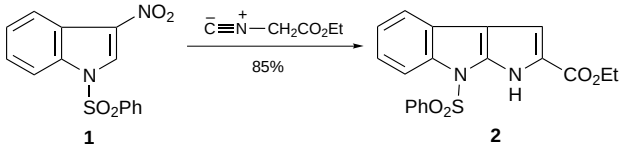
The reaction of 1-ethoxycarbonyl-3-nitroindole with ethyl isocyanoacetate in the presence of DBU gives ethyl 4-ethoxycarbonyl-2,4-dihydropyrrolo[3,4-*b*]indole-3-carboxylate, averting a novel rearrangement that we previously reported with 3-nitro-1-phenylsulfonylindole that yielded ethyl 8-phenylsulfonyl-1,8-dihydropyrrolo[2,3-*b*]indole-2-carboxylate.

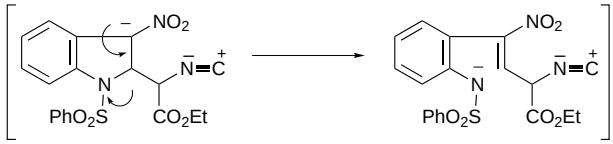
We recently reported a remarkable rearrangement which led to an expeditious synthesis of the pyrrolo[2,3-*b*]indole ring system.[1] Thus, treatment of 3-nitro-1-phenylsulfonylindole **1** with ethyl isocyanoacetate[2] and DBU gave pyrrolo[2,3-*b*]indole **2** in 85% yield (Scheme 1).[1] We anticipated that this application of the Barton–Zard pyrrole synthesis[3] would give a pyrrolo[3,4-*b*]indole[4–7] which could be utilized as a fused stable analogue of indole-2,3-quinodimethane,[8] in continuation of our interest in a related fused ring system, the furo[3,4-*b*]indoles.[9]



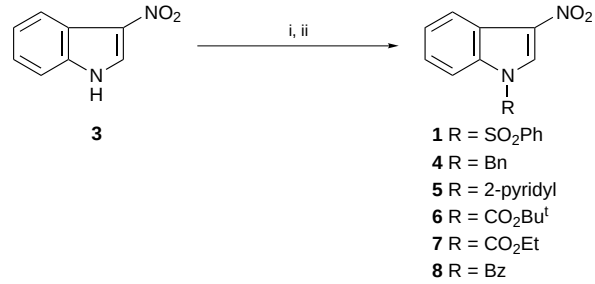
Scheme 1 *Reagents and conditions*: i, DBU, THF, room temp., 20 h, 85%

To explain the outcome of this abnormal Barton–Zard reaction leading to the rearranged product **2**, we proposed a mechanism which involved a fragmentation of the indole ring system (Scheme 2),[1] which can be rationalized by the presence of a good leaving group, the aryl sulfonamide anion [*N*-(phenylsulfonyl)benzenesulfonamide has a pK_a of 11.8[10]].

To circumvent this fragmentation and subsequent rearrangement in order to develop a succinct route to the pyrrolo[3,4-*b*]indole ring system, which was our original goal, we have investigated this reaction with 3-nitroindole substrates containing *N*-protecting groups that are less electron-withdrawing than *N*-phenylsulfonyl but which will still activate the indole double bond to the initial C-2 Michael addition. The requisite protected 3-nitroindoles were synthesized from 3-nitroindole **3**[11] utilizing sodium hydride as the base in DMF. For example, treatment of **3** with sodium hydride in DMF followed by benzenesulfonyl chloride gave **1**[12] in 86% yield. Likewise, 3-nitroindoles **4**–**8** were synthesized in variable yields utilizing benzyl bromide (79% yield), 2-fluoropyridine (19% yield),[13] *tert*-butyl phenyl carbonate (40% yield),[14] ethyl chloroformate (50% yield)[15] and benzoyl chloride (31% yield),[15] respectively (Scheme 3).



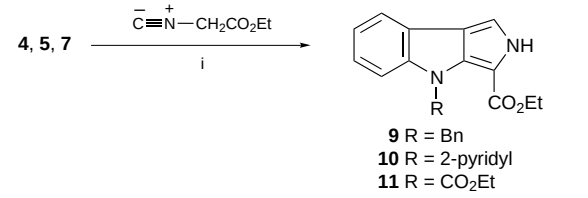
Scheme 2



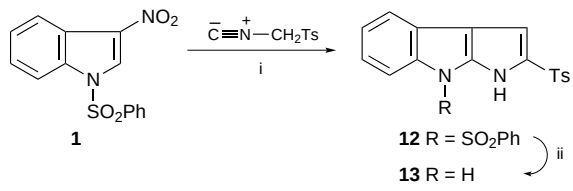
Scheme 3 *Reagents and conditions*: i, NaH, DMF, 0 °C, 0.5–2 h; ii, (for **1**) $PhSO_2Cl$, 86%; (for **4**) $PhCH_2Br$ (79%); (for **5**) 2-fluoropyridine, 100 °C, 10 h, 19%; (for **6**) $PhOCO_2Bu^t$, 40%; (for **7**) $ClCO_2Et$, 50%; (for **8**) BzCl, 31%

The abatement of the rearrangement was first observed when *N*-benzylindole **4** was subjected to the Barton–Zard pyrrole synthesis conditions (Scheme 4). In the event, treatment of **4** with ethyl isocyanoacetate and DBU in THF at room temperature resulted in no reaction, but after being heated at reflux for 9 h, pyrrolo[3,4-*b*]indole **9**† was obtained in 30% yield. The low yield is most likely due to the decreased degree of electrophilicity associated with **4** as compared to **1**. To confirm the structure of this product, we synthesized the corresponding known isomer, ethyl 8-benzyl-1,8-dihydropyrrolo[2,3-*b*]indole-2-carboxylate,[16] which was clearly different from **9** in all respects (IR, TLC, UV, and ^{1}H NMR). An increase in yield utilizing milder reaction conditions was observed with the more electrophilic *N*-(2-pyridyl)indole **5**, which, upon treatment with ethyl isocyanoacetate and DBU in THF at room temperature, gave pyrrolo[3,4-*b*]indole **10** in 72% yield. A simple and reliable method for determining the regiochemistry of these Barton–Zard reactions is to determine the pyrrole ring C-1 proton–NH coupling constant. For the pyrrolo[2,3-*b*]indole systems, the resulting four bond coupling is usually 1.5 Hz, while for pyrrolo[3,4-*b*]indole systems the resulting three bond coupling is usually 3.0 Hz. Indeed, the coupling constant observed for the pyrrole ring proton of **10** is 3.3 Hz.

Although the synthesis of **10** in good yield accomplished the initial goal of precluding the rearrangement, a more practical protecting group was sought which could provide a similar result. Treatment of *N*-benzoylindole **8** under the usual conditions resulted in deprotection, and similar treatment of *N*-butoxycarbonylindole **6** resulted in no reaction even after prolonged reflux. Finally, to our delight, treatment of



Scheme 4 *Reagents and conditions*: i, (for **9**) DBU, THF, reflux, 9 h, 30%; (for **10**) DBU, THF, room temp., 12 h, 72%; (for **11**) DBU, THF, room temp., 18 h, 91%

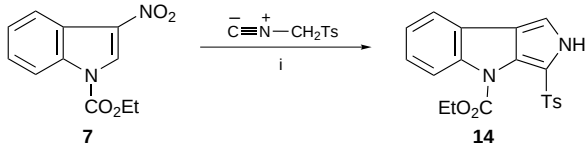


Scheme 5 *Reagents and conditions*: i, DBU, THF, room temp., 22 h, 63%; ii, 6% Na/Hg, THF, MeOH, −40 °C, 73%

N-ethoxycarbonylindole **7** with ethyl isocyanoacetate in DBU at room temperature gave the desired pyrrolo[3,4-*b*]indole **11**† in 91% yield.

We have also found that the fragmentation–rearrangement pathway occurs with tosylmethyl isocyanide (TsMIC).[17] Treatment of **1** with TsMIC and DBU in THF gave pyrrolo[2,3-*b*]indole **12**† in 63% yield, which was subsequently deprotected with sodium amalgam[18] to afford pyrrolo[2,3-*b*]indole **13** in 73% yield (Scheme 5). In accord with the structural assignment, the coupling constants for the pyrrole ring protons of **12** and **13** are 1.8 and 1.5 Hz, respectively.

In contrast, treatment of **7** under the same conditions gave the corresponding pyrrolo[3,4-*b*]indole **14**† in 41% yield (Scheme 6). Support for the structural assignment of **14** can again be found with the observed pyrrole ring proton coupling constant of 3.3 Hz.



Scheme 6 *Reagents and conditions*: i, DBU, THF, room temp., 20 h, 41%

In conclusion, we have shown that both pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles can be synthesized from 3-nitroindole substrates depending on the *N*-indole protecting group in one step *via* the Barton–Zard pyrrole synthesis.

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Footnotes and References

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† *Selected data* for **9**: mp 202–204 °C; ν(KBr)/cm^{-1} 3250, 1658; λ_{max}(EtOH)/nm 210, 238, 278, 302, 330; δ_H (300 MHz, [$^2H_6$]DMSO) 11.80 (br s, 1 H), 7.75 (d, 1 H, *J* 7.5), 7.46 (d, 1 H, *J* 3.6), 7.13–7.32 (m, 7 H), 7.05 (m, 1 H), 5.83 (s, 2 H), 4.22 (q, 2 H, *J* 7.2), 1.19 (t, 3 H, *J* 7.2); δ_C ([$^2H_6$]DMSO) (one quaternary carbon missing) 159.8, 144.7, 139.0, 128.3, 126.8, 126.5, 123.5, 120.1, 120.0, 119.0, 116.2, 113.6, 109.9, 99.6, 59.2, 47.6, 14.4; *m/z* 319 (M^+ + 1), 273, 246, 195, 155, 119; Calc. for $C_{20}H_{18}N_2O_2$ (M^+); 318.1638. Found: 318.1637. For **11**: mp 143–145 °C; δ_H (300 MHz, $CDCl_3$) 9.34 (br s, 1 H), 8.20 (d, 1 H, *J* 8.4), 7.67 (m, 1 H), 7.35 (m, 1 H), 7.27 (m, 1 H), 7.19 (d, 1 H, *J* 3.0), 4.50 (q, 2 H, *J* 6.9), 4.38 (q, 2 H, *J* 7.2), 1.43 (t, 3 H, *J* 6.9), 1.40 (t, 3 H, *J* 7.2); δ_C ($CDCl_3$) 159.9, 151.9, 143.7, 132.7, 125.5, 123.5, 123.0, 120.2, 119.6, 116.3, 110.8, 106.4, 63.3, 60.7, 14.8, 14.6; *m/z* 323.1 (M + Na^+); Calc. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.73; H, 5.38; N, 9.31%. For **12**: mp 236–238 °C (decomp.); ν(KBr)/cm^{-1} 3256; λ_{max}(EtOH)/nm 210, 274 (sh), 300, 346 (sh); δ_H (300 MHz, $CDCl_3$) 9.78 (br s, 1 H), 7.89 (m, 3 H), 7.76 (m, 2 H), 7.52 (m, 2 H), 7.37 (m, 4 H), 7.26 (m, 2 H), 7.11 (d, 1 H, *J* 1.8), 2.41 (s, 3 H); δ_C ($CDCl_3$) 144.3, 139.6, 138.5, 137.6, 136.4, 134.8, 130.2, 129.6, 128.8, 127.2, 126.9, 125.0, 124.6, 124.3, 120.1, 114.8, 113.4, 107.6, 21.8; *m/z* 473.1 (M + Na^+); Calc. for $C_{23}H_{18}N_2O_4S_2$: C, 61.32; H, 4.03; N, 6.22; S, 14.23. Found: C, 61.35; H, 4.04; N, 6.23; S, 14.23%. For **14**: mp 121–123 °C (decomp.); δ_H (300 MHz, $CDCl_3$) 9.97 (br s, 1 H), 8.17 (d, 1 H, *J* 7.8), 7.66–7.73 (m, 3 H), 7.33 (d, 1 H, *J* 3.3), 7.24–7.37 (m, 4 H), 4.27 (q, 2 H, *J* 7.2), 2.39 (s, 3 H), 1.17 (t, 3 H, *J* 7.2); δ_C ($CDCl_3$) 150.9, 143.4, 142.0, 141.3, 130.1, 129.5, 126.2, 126.0, 123.7, 122.4, 120.3, 120.2, 116.6, 111.7, 108.5, 63.2, 21.7, 14.4; *m/z* 405.0 (M + Na^+).

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