An abnormal Barton–Zard reaction leading to the pyrrolo[2,3-*b*]indole ring system

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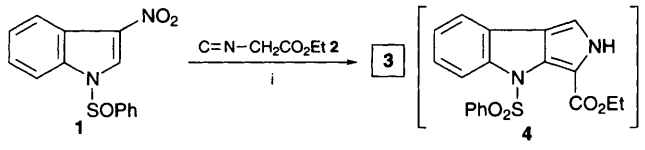
The reaction of 3-nitro-*N*-(phenylsulfonyl)indole 1 with ethyl isocyanoacetate 2 under the Barton–Zard pyrrole synthesis conditions gives ethyl 8-(phenylsulfonyl)-1,8-dihydropyrrolo[2,3-*b*]indole-2-carboxylate 3 rather than the anticipated ethyl 4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole-3-carboxylate 4.

In continuation of our interest in the furo[3,4-*b*]indole ring system and related fused heterocycles,[1] we examined the Barton–Zard pyrrole synthesis[2,3] as a possible new route to the pyrrolo[3,4-*b*]indole ring system, which is of considerable interest as a stable analogue of indole-2,3-quinodimethane.[4–7]

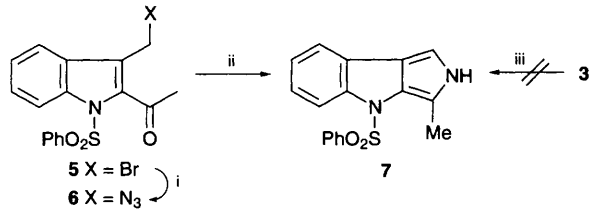
Indeed, treatment of 3-nitro-*N*-(phenylsulfonyl)indole **1**[8] with ethyl isocyanoacetate **2**[9] in the presence of DBU gave a product **3**,† in 85% yield, the properties of which were consistent with that expected for the anticipated product ethyl 4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole-3-carboxylate **4**. (Scheme 1). This material gave satisfactory analytical and spectral data for the desired compound,† except for the fact that the coupling constant between the pyrrole ring proton and the NH was slightly smaller than generally seen (1.8 Hz *vs.* the expected *ca.* 3 Hz). Nevertheless, we remained confident that **4** was the product of this reaction.

However, attempts both to convert **4** to a known compound and to synthesize **4** by an independent method clearly revealed that **4** is not the product of this reaction. Thus, using Sha's method,[5] we synthesized 3-methyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole **7** from the known bromo ketone **5**[10] and azide **6** (Scheme 2). A Staudinger reaction of **6** with Ph_3P gave the expected **7**. Vigorous $LiAlH_4$ reduction[11] of **3** did not yield **7**, but rather gave a different compound.

Again using the general Sha methodology, we carried out an independent synthesis of **4** as shown in Scheme 3. Thus, conversion of **8** into glyoxylate **9** was followed by elaboration of the methyl group to give azide **10**. A Staudinger reaction yielded the product **4**,† which was definitely not the same material **3** obtained from the reaction between **1** and **2** (Scheme 1). Therefore, **3** must be an isomer of **4**.



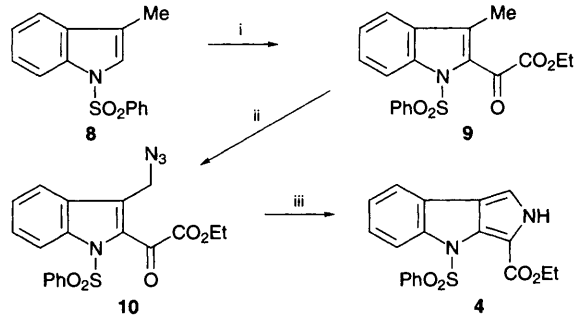
Scheme 1 *Reagents and conditions*: i, DBU, THF, room temp., 20 h (85%)



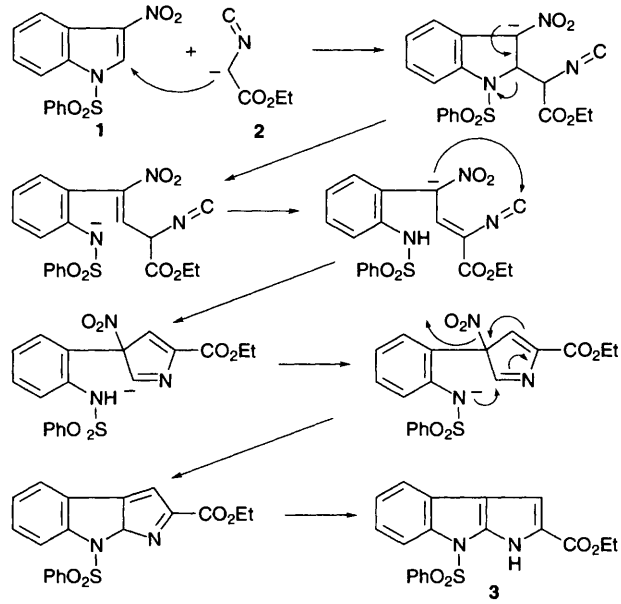
Scheme 2 *Reagents and conditions*: i, NaN_3, aq. THF, room temp., 2 h, 89% (**6**); ii, Ph_3P, THF, room temp., 20 h, 84% (**7**); iii, $LiAlH_4$, THF, reflux, 1 h

Since our earlier work had uncovered the facile fragmentation of 3-lithioindoles to alkynes,[12] we considered that **3** might be ethyl 8-(phenylsulfonyl)-1,8-dihydropyrrolo[2,3-*b*]indole-2-carboxylate formed possibly as depicted in Scheme 4. This structure is consistent with all of the spectral and analytical data, including a NOSY cross peak between H-3 and H-4, as well as being consistent with the smaller observed coupling constant between H-3 and the NH.

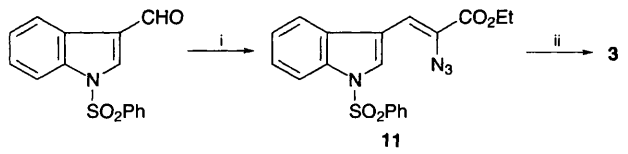
Finally, the structure of **3** was confirmed by the independent synthesis shown in Scheme 5. Thus, using Moody's general procedure for the synthesis of the pyrrolo[2,3-*b*]indole ring system,[13] we transformed azide **11** into **3**, identical in all



Scheme 3 *Reagents and conditions*: i, Bu^{s}Li, THF, −78 °C to room temp., then $COClCO_2Et$, −78 °C to room temp. (31%); ii, NBS, CCl_4, AIBN, 3 h (88%), then NaN_3, aq. THF, 12 h (87%); iii, Ph_3P, THF, reflux, 20 min, then room temp., 14 h (94%)



Scheme 4



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Scheme 5 *Reagents and conditions*: i, $N_3CH_2CO_2Et$, NaOEt, EtOH, −10 °C, 3.5 h (30%); ii, *p*-xylene, reflux, 2 h (43%)

respects (IR, TLC, UV, ^1H and ^{13}C NMR) with that obtained in Scheme 1.

We are currently attempting to modify the nitroindole substrate so as to preclude this abnormal pathway and to obtain the desired pyrrolo[3,4-*b*]indole ring system.

Interestingly, the 1,8-dihydropyrrolo[2,3-*b*]indole-2-carboxylate ring system embodied in **3** is present in the newly discovered antibiotics pyrroindomycins A and B produced by *Streptomyces rugosporus*.[14]

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Footnote

† *Selected physical and spectroscopic data* for **3**: mp 165–168 °C; IR (KBr) ν/cm^{-1} 3333 and 1685; UV–VIS (EtOH) λ_{max} 208, 226, 247 (sh) and 306 nm; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (br s, 1 H), 7.96 (m, 1 H), 7.80 (d, 2 H, *J* 8.4 Hz), 7.57 (m, 1 H), 7.51 (m, 1 H), 7.37 (m, 2 H), 7.26–7.30 (m, 2 H), 7.16 (d, 1 H, *J* 1.8 Hz), 4.43 (q, 2 H, *J* 7.2 Hz) and 1.44 (t, 3 H, *J* 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.5, 138.8, 137.3,136.7, 134.5, 129.5, 126.9, 124.9, 124.8, 124.0, 123.5, 120.0, 114.8, 113.3, 107.0, 60.9 and 14.7; mass spectrum, *m/z* 368 (M^+), 227 (100%), 199, 181, 153, 127 and 77; HRMS Calc. for M^+ *m/z* 368.0831, found 368.0826. For **4**: mp 122–126 °C; IR (KBr) ν/cm^{-1} 3266 and 1685; UV–VIS (EtOH) λ_{max} 206, 224, 238 (sh), 252, 287 (sh) and 299 (sh) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (br s, 1 H), 8.08 (d, 1 H, *J* 8.4 Hz), 7.63 (m, 2 H), 7.48 (d, 1 H, *J* 7.5 Hz), 7.41 (m, 1 H), 7.20–7.33 (m, 4 H), 7.12 (d, *J* 3.3 Hz), 4.44 (q, 2 H, *J* 7.2 Hz) and 1.41 (t, 3 H, *J* 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.2, 144.7, 137.3, 133.4, 132.6, 128.5, 127.1, 125.4, 125.04, 125.00, 121.2, 120.2, 118.1, 111.2, 108.7, 61.2 and 14.5; mass spectrum, *m/z* 368 (M^+), 322, 227 (100%), 181, 155, 153, 127, 101 and 77; HRMS Calc. for M^+ *m/z* 368.0831, found 368.0833.

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