

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

Erin T. Pelkey, Louis Chang and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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.

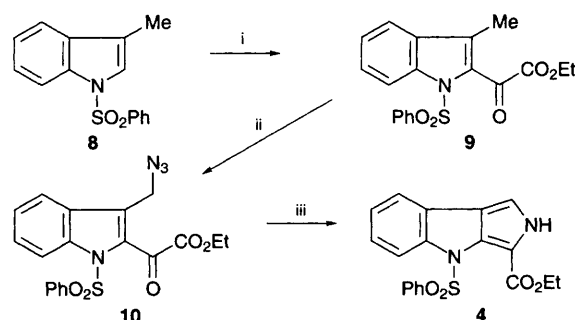
However, attempts both to convert **4** to a known compound and to synthesize **4** by an independent method clearly revealed that **4** is not the product of this reaction. Thus, using Sha's method,⁵ we synthesized 3-methyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole **7** from the known bromo ketone **5**¹⁰ and azide **6** (Scheme 2). A Staudinger reaction of **6** with Ph₃P gave the expected **7**. Vigorous LiAlH₄ reduction¹¹ 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

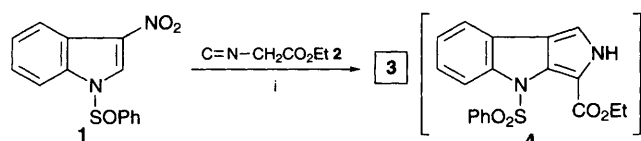
material **3** obtained from the reaction between **1** and **2** (Scheme 1). Therefore, **3** must be an isomer of **4**.

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 NIOSY 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.

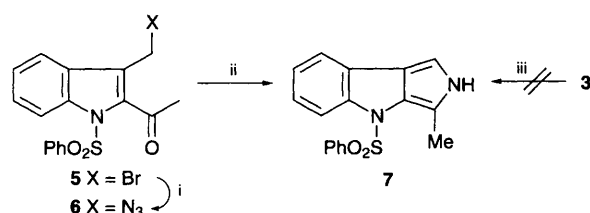
Finally, the structure of **3** was confirmed by the independent synthesis shown in Scheme 5. Thus, using Moody's general procedure for the synthesis of the pyrrolo[2,3-*b*]indole ring system,¹³ we transformed azide **11** into **3**, identical in all



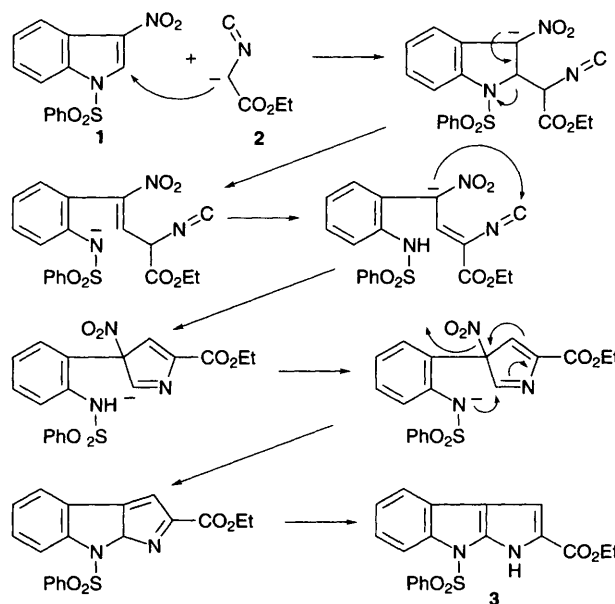
Scheme 3 Reagents and conditions: i, Bu^tLi, THF, –78 °C to room temp., then COCICO₂Et, –78 °C to room temp. (31%); ii, NBS, CCl₄, AIBN, 3 h (88%), then NaN₃, aq. THF, 12 h (87%); iii, Ph₃P, THF, reflux, 20 min, then room temp., 14 h (94%)



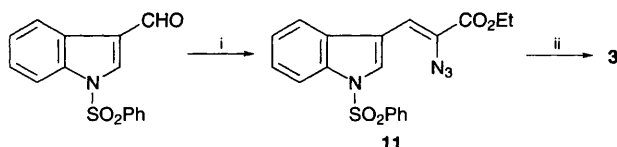
Scheme 1 Reagents and conditions: i, DBU, THF, room temp., 20 h (85%)



Scheme 2 Reagents and conditions: i, NaN₃, aq. THF, room temp., 2 h, 89% (**6**); ii, Ph₃P, THF, room temp., 20 h, 84% (**7**); iii, LiAlH₄, THF, reflux, 1 h



Scheme 4



Scheme 5 Reagents and conditions: i, $\text{N}_3\text{CH}_2\text{CO}_2\text{Et}$, NaOEt , EtOH , $-10\text{ }^\circ\text{C}$, 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 $165\text{--}168\text{ }^\circ\text{C}$; 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 $122\text{--}126\text{ }^\circ\text{C}$; 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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