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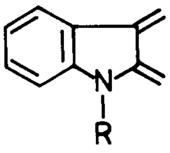
4-(PHENYLSULFONYL)-4H-FURO[3,4-b]INDOLE - A STABLE SYNTHETIC ANALOGUE OF INDOLE-2,3-QUINODIMETHANE

Mark G. Saulnier and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Summary: The N-phenylsulfonyl derivative (2) of the previously unknown fused heterocycle 4H-furo[3,4-b]indole is synthesized from indole-3-carboxaldehyde (3) in 28% yield and undergoes a Diels-Alder reaction with benzyne to give 5H-benzo[b]carbazole (11) in 33% yield after deoxygenation and deprotection.

Indole-2,3-quinodimethanes (1) have been the focus of recent synthetic interest[1] and, somewhat earlier, were implicated as intermediates in alkaloid synthesis[2] and rearrangement.[3] Although not isolable, derivatives of 1 undergo inter-[1a] and intramolecular[1b,c] Diels-Alder reactions leading to carbazoles and the indole alkaloid aspidospermidine, respectively. Due to the reported[1a] lability of 1 (R=Me, t-BOC) this methodology presumably cannot be used with highly reactive dienophiles, such as arynes.



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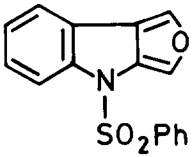
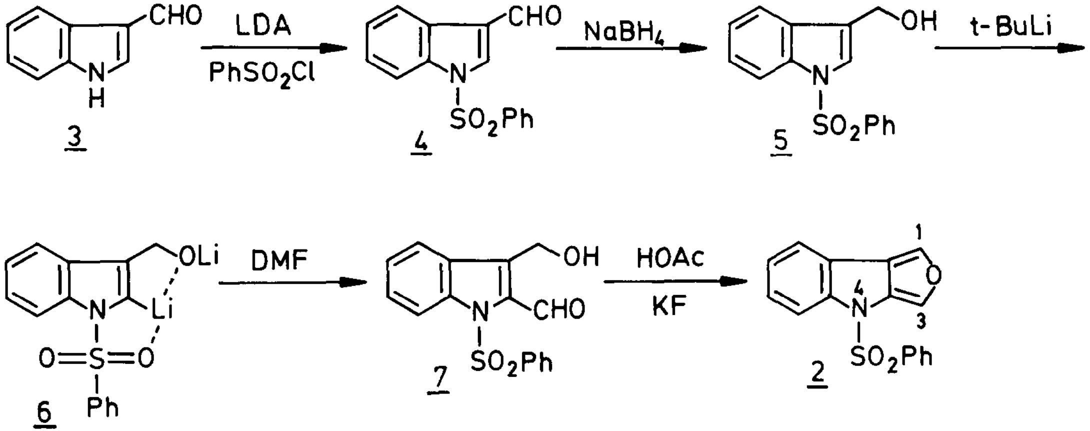


2

To circumvent this potential obstacle and to extend to the synthesis of carbazoles our aryne Diels-Alder/bridge-extrusion methodology,[4] we sought to prepare a stabilized functional analogue of 1. We chose the previously unknown 4H-furo[3,4-b]indole (protected as the N-phenylsulfonyl derivative 2) as our target molecule, since the only known examples of related fused heterocycles are either highly labile (pyrrolo[3,4-b]indole[5]) or are presumed to be poorer dienes than 2 in Diels-Alder reactions (thieno- and selenolo[3,4-b]indole[6]).

Our synthesis of 2 is shown in Scheme I. Commercially available indole-3-carboxaldehyde (3) was protected as the N-phenylsulfonyl derivative 4 (mp 157.5-158.5°C; lit.[7] mp 158-158.5°C) in 86% yield [lithium diisopropylamide (LDA) and benzenesulfonyl chloride, tetrahydrofuran (THF), -70°C]. Reduction of 4 with sodium borohydride (aqueous THF-ethanol, 0-5°C) gave alcohol 5[8] (mp 82-83°C) in quantitative yield. Regioselective dilithiation of 5 was achieved using 2.1 equiv. of tert-butyllithium (THF, -40°→23°C) to give a deep-red colored solution due to anion 6, which is presumably coordinated to both the the alkoxide[9] and the sulfonyl[10] groups as shown. Quenching this solution with D_2O afforded the C-2 deuterated alcohol in 77% purified yield (95% deuterium incorporation by mass spectrometry and disappearance of a single line at 123.5 ppm in the ^{13}C NMR spectrum). Treatment of a solution of 6 (THF, -70°C) with dimethylformamide (DMF) gave aldehyde 7[8,11] (mp 125.5-126°C) in 72% yield. After some experimentation we found that ring closure to the desired furo[3,4-b]indole 2 could be effected by heating 7 in glacial acetic acid in the presence of potassium fluoride and hydroquinone (100°C, 3 h). After column chromatography (Florisil) the yield of 2[8,12] (mp 145°C dec), a moderately stable colorless solid, was 46%.

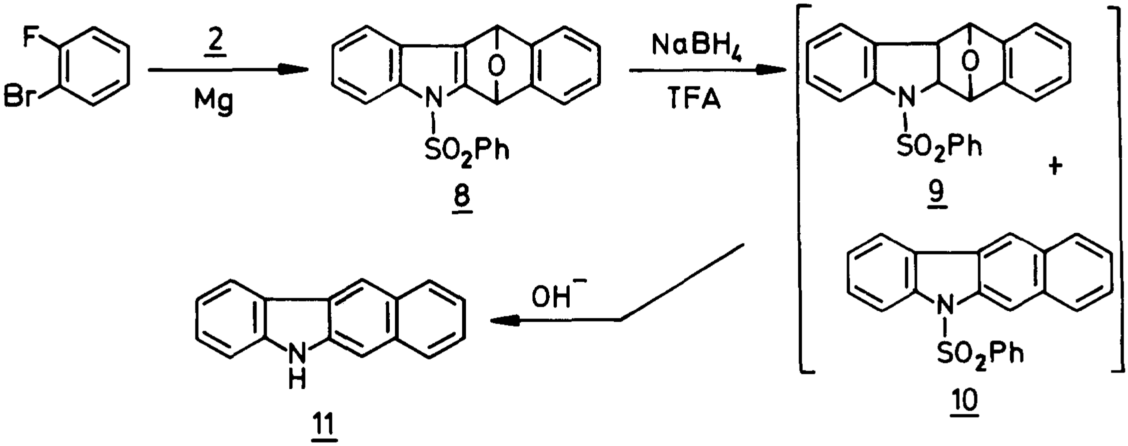
Scheme I



The structure of 2 is supported by elemental analysis, mass spectroscopy, and the 360 MHz ^1H NMR spectrum which displays H-1 and H-3 as doublets (J=1.3 Hz)[13] at 7.77 and 7.61 ppm, respectively. The ^{13}C-NMR spectrum is also consistent with the assigned structure.

Reaction of 2 with benzyne[14] gave the anticipated Diels-Alder adduct 8[8,15] (mp 165.5°C) in 38% yield[16] after flash chromatography (Scheme II). Deoxygenation of 8 ($NaBH_4/CF_3CO_2H$[17]) gave a mixture of what is proposed to be 9 and 10 (mass spectrometry). In any event, treatment of this mixture with base (aqueous methanolic sodium hydroxide, THF, reflux, 48 h) afforded 5H-benzo[b]carbazole (11)[18] (mp 332-333°C; lit.,[19] mp 330-331°C) in 88% purified yield from 8.

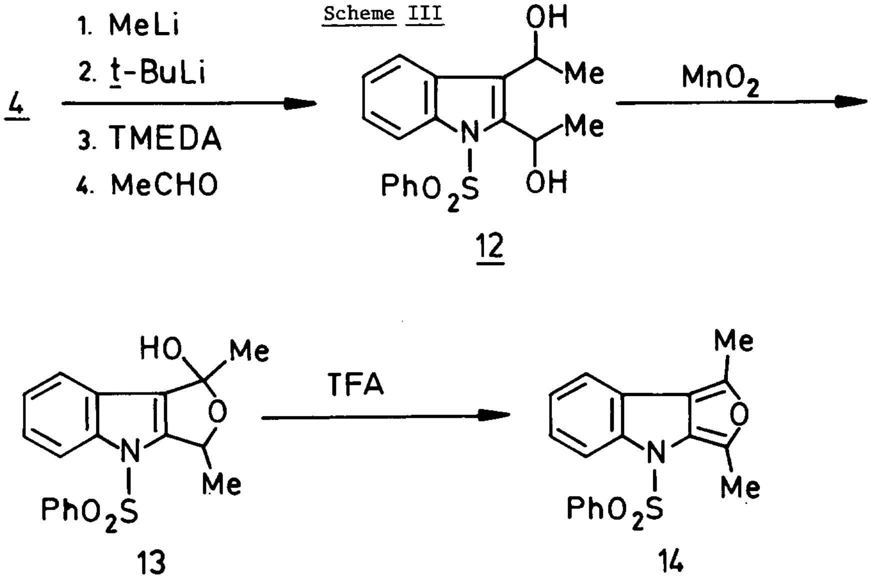
Scheme II



Attempts to prepare the parent 4H-furo[3,4-b]indole by base cleavage of 2 (aqueous methanolic sodium hydroxide or potassium tert-butoxide in THF) gave only polymeric material.

We have extended this methodology to the synthesis of 1,3-dialkyl-substituted derivatives of 2. For example, 4-(phenylsulfonyl)-1,3-dimethyl-4H-furo[3,4-b]indole (14) is readily constructed from 4 in 24% overall yield (Scheme III), without purification of intermediates. Thus, 4 was transformed in one flask into diol 12 as a mixture of diastereomers in 81% yield. Oxidation of 12 with activated manganese dioxide ($CHCl_3$, reflux, 26 h) gave lactol 13[20], which was directly converted to 14[8,21] (mp 167-170°C dec) with a catalytic amount of TFA (CH_2Cl_2, reflux, 55 min) in 30% yield from 12. The related oxidation of (Z)-2-butene-1,4-diols to furans has been reported recently.[22]

Scheme III



12

13

14

In summary, we have described a convenient and general synthesis of 4-(phenylsulfonyl)-4H-furo[3,4-b]indoles, a ring system which functions as a indole-2,3-quinodimethane synthon and which should find use in the synthesis of carbazoles and related heterocyclic systems. We will report further on the chemistry of these 4H-furo[3,4-b]indoles in due course.

Acknowledgment. This investigation was supported by Grant CH-200 from the American Cancer Society and in part by PHS Grant GM-30761 awarded by the National Institutes of Health. We also thank Merck Sharp and Dohme Research Laboratories for partial support, Dr. Catherine E. Costello (Massachusetts Institute of Technology) for the high-resolution mass spectra (NIH Resource Grant FR00317 from the Division of Research Facilities and Resources), and the Colorado State University Regional NMR Center, funded by NSF Grant No. CHE-8208821, for high-resolution NMR spectra.

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8. This new compound gave an elemental analysis within the following limits: C, ±0.08%; H, ±0.04%; N, ±0.15%; S, ±0.10%.

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11. 7: IR (KBr) 3420, 1648, 1527, 1449 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.60 (br s, 1H), 4.76 (s, 2H), 7.0-7.9 (m, 8H), 8.2 (m, 1H), 10.72 (s, 1H); mass spectrum m/e 315.0539 (M$^+$, calcd. 315.0565).

12. 2: IR (KBr) 1450, 1369, 1179, 1092 cm^{-1}; 360 MHz ^{1}H NMR (CDCl$_3$) δ 7.23 (m, 1H), 7.33-7.40 (m, 3H), 7.48-7.58 (m, 2H), 7.61 (d, 1H, J=1.3 Hz), 7.77 (d, 1H, J=1.3 Hz), 7.81-7.85 (m, 2H), 7.98 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 115.1, 121.4, 121.8, 122.5, 124.3, 124.4, 126.8, 127.4, 128.9, 131.0, 133.2, 133.7, 136.9, 144.2; UV (EtOH) λ_{max} 245 sh, 256 sh, 274, 293 nm (log ε 4.13, 4.08, 3.71, 3.69); mass spectrum, m/e 297 (M$^+$), 204, 156, 128 (100%), 101, 77, 51.

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15. 8: IR (KBr) 1480, 1449, 1441, 1368, 1183 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.13 (s, 1H), 6.31 (s, 1H), 6.75-7.55 (m, 10H), 7.57-8.05 (m, 3H); mass spectrum, m/e 373 (M$^+$), 232 (100%), 216, 204, 203, 176, 77; m/e 373.0744 (M$^+$, calcd. 373.0773).

16. We believe that the low yield is due to competing exchange metalation at C-3 (or C-1) in 2 since the same reaction with the dimethyl derivative 14 proceeds in 91% yield.

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18. The UV spectrum of 11 is identical to that reported by G.R. Clemo and D.G.I. Felton, J. Chem. Soc., 1658 (1952).

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20. 13: IR (KBr) 3425 cm^{-1}; mass spectrum, m/e 343 (M$^+$), 286, 202, 184, 160, 77, 43 (100%); the structure of 13 is as shown, rather than the isomeric lactol, since we have prepared the latter by another route.[5b]

21. 14: IR (KBr) 1458, 1368, 1182, 1000 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.42 (s, 3H), 2.69 (s, 3H), 7.15-7.90 (m, 8H), 8.15 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 12.8, 13.3, 116.5, 118.4, 120.9, 123.5, 124.5, 126.2, 126.9, 127.8, 128.6, 132.4, 133.3, 136.6, 138.0, 144.8; UV (EtOH) λ_{max} 240 sh, 266 sh, 305 nm (log ε 4.21, 3.82, 3.81); mass spectrum, m/e 325 (M$^+$), 184, 142, 115, 77, 43 (100%).

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