Notes

An Efficient Synthesis of 4-(Phenylsulfonyl)-4*H*-furo[3,4-*b*]indoles

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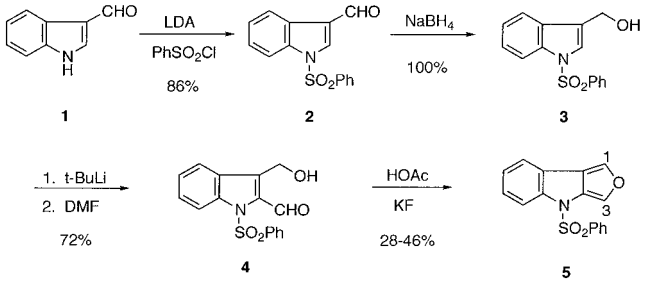
Abstract: The fused heterocycle 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole, which is an indole-2,3-quinodimethane synthetic analogue, is prepared in five steps from indole in 46% yield. A similar sequence is used to synthesize C-3 derivatives (3-methyl, 3-phenyl, and 3-heptyl). Thus, indole-3-carbaldehyde (**1**) is protected as the *N*-phenylsulfonyl derivative **2** and converted to the ethylene acetal **6**. Lithiation at C-2 followed by treatment with an aldehyde affords the expected hydroxy acetals **7** and **8**. Exposure to acid effects cyclization to the furoindoles **5** and **9**. Furthermore, C-1 lithiation of furo[3,4-*b*]indole **9c** followed by treatment with methyl iodide affords disubstituted furo[3,4-*b*]indole **10**.

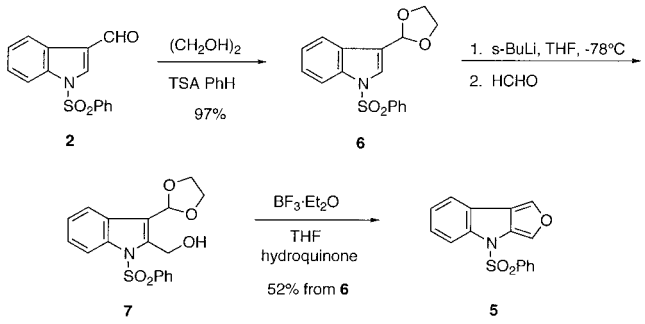
The fused heterocycle 4*H*-furo[3,4-*b*]indole has served admirably over the past 20 years as an indole-2,3-quinodimethane synthetic analogue in Diels−Alder reactions.[1,2] We have employed this ring system in syntheses of isomeric benzocarbazoles,[1a,b,f] bis(benzo[*b*]carbazoles),[1c] and pyridocarbazoles, including the antitumor alkaloid ellipticine.[1d,e,2h]

Unfortunately, our original method[1a] of ring construction (Scheme 1) was plagued by a low-yielding and erratic final cyclization step, particularly in the case of the parent compound **5**. Moreover, the lithiation of 3-(hydroxyalkyl)indoles such as **3** and quenching with formyl (or acyl) equivalents were not conducive to a general synthesis of C-3 substituted furo[3,4-*b*]indoles. Likewise, our attempts to prepare 2-hydroxymethyl-1-(phenylsulfonyl)indole-3-carbaldehyde, which is isomeric with **4**, were unsuccessful. Although some improvement was later found in the conversion of **3** to **4** by using methyl formate in place of DMF (82 vs 72%),[1e] and the yields of furan-ring substituted derivatives are invariably higher than that of **5** (Thorpe-Ingold effect[3]), we now describe a shorter and more efficient route to this fused heterocycle and to C-3 alkyl- and aryl-substituted analogues of this ring system.

Scheme 1



Scheme 2



Indole-3-carbaldehyde **1**[4] was protected using a phase-transfer method to give the *N*-phenylsulfonyl derivative **2** (Scheme 2). This method is higher-yielding than our original method of N-protection (LDA/$PhSO_2Cl$).[1a] Acetalization under typical conditions gave acetal **6** (97% yield). Lithiation of **6** at C-2 with *sec*-BuLi followed by treatment with gaseous formaldehyde gave hydroxy acetal **7** (not isolated). The reaction mixture was treated with $BF_3{\cdot}Et_2O$ and hydroquinone to afford furoindole **5** in 52% yield from acetal **6**. This route to **5** represents a significant improvement over our original synthesis[1a] (48 vs 28%).

Given the facility with which aldehydes serve as electrophiles in lithiation reactions, this furoindole syn-

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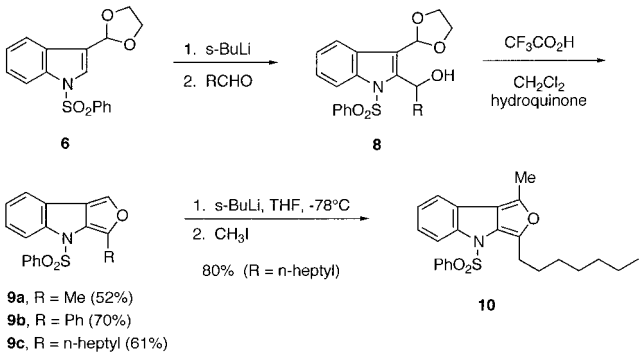
Scheme 3



thesis is readily applicable to C-3 substituted derivatives (Scheme 3). Thus, lithiation of acetal **6** followed by reactions with aldehydes gave hydroxy acetals **8**. Flash chromatography of **8** and exposure to trifluoroacetic acid and hydroquinone in dichloromethane at room temperature afforded furoindoles **9** in 52−70% yields from acetal **6**. By comparison, our previous syntheses of **9a** and **9b** involved six steps from 3-methyl-1-(phenylsulfonyl)indole (24−30% overall yields).

Finally, lithiation of these C-3 substituted furoindoles affords a route to C-1,C-3 disubstituted furoindoles. Thus, treatment of **9c** with *sec*-BuLi followed by the addition of methyl iodide gave furoindole **10** (80% yield). This complements our earlier selective C-3 lithiation of the parent furoindole **5**.[1e]

In summary, we have improved the synthesis of furoindoles **5** and **9** from indole-3-carbaldehyde. The parent furoindole **5** is now available from **1** in three operations and in an overall yield of 48%. The overall yields of **5** and **9** from indole are 46−63%.

Experimental Section

General Procedures. Melting points are uncorrected. Elemental analyses were done by Atlantic Microlab, Inc. High-resolution mass spectrometry (HRMS) was carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign. Tetrahydrofuran (THF) was distilled from sodium/benzophenone.

Indole-3-carbaldehyde (1). This was prepared from indole in 96% yield according to a known procedure:[4] mp 190−192 °C (lit.[4] 196−197 °C).

1-(Phenylsulfonyl)indole-3-carbaldehyde (2). To an ice-cooled, stirred mixture of indole-3-carbaldehyde (**1**) (11.95 g, 0.0823 mol), crushed sodium hydroxide pellets (9.65 g, 0.241 mol), and tetra-*n*-butylammonium hydrogen sulfate (1.09 g, 3.21 mmol) in dichloromethane (100 mL) was added dropwise via an addition funnel over 10 min benzenesulfonyl chloride (17.16 g, 0.0972 mol). The mixture was stirred at room temperature for 2 h. Water was added, and the organic layer was separated, washed with water, and dried ($MgSO_4$). Rotary evaporation of the organic layer gave 22.6 g (96%) of **2** as a colorless solid: mp 156−157 °C (lit.[5] 158−158.8 °C); ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 8.22−8.17 (m, 2H), 7.94−7.89 (m, 3H), 7.58−7.32 (m, 5H).

1-(Phenylsulfonyl)indole-3-carbaldehyde Ethylene Acetal (6). A suspension of 1-(phenylsulfonyl)indole-3-carbaldehyde (**2**) (8.0 g, 28 mmol), ethylene glycol (40 mL, 0.7 mol), and *p*-toluenesulfonic acid (0.30 g, 1.6 mmol) in benzene (100 mL) was heated at reflux with a Dean−Stark trap for 16 h. The mixture was allowed to cool to room temperature, and the benzene layer was separated and evaporated in vacuo to give an oil. Trituration with cold ethyl acetate/hexane (3:7) gave 4.1 g of **6** as colorless needles. Concentration of the mother liquor afforded an additional 4.8 g for a total yield of 8.9 g (97%), mp 87−90 °C. The analytical sample was prepared by recrystallization from ether/hexane: mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.94−7.83 (m, 3H), 7.63−7.17 (m, 7H), 6.03 (s, 1H), 4.11−3.98 (m, 4H). Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.74. Found: C, 61.75; H, 4.63; N, 4.36; S, 9.85.

4-(Phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (5). To a −70 °C stirred solution of 1-(phenylsulfonyl)indole-3-carbaldehyde ethylene acetal (**6**) (0.66 g, 2.0 mmol) dissolved in dry THF (50 mL) under nitrogen was added a solution of *sec*-butyllithium (1.3 M in cyclohexane, 2.4 mmol) dropwise via syringe. The reaction mixture was stirred at −70 °C for 2 h and allowed to warm to room temperature for 2 h. The dark brown reaction mixture was recooled to 0 °C; then, gaseous formaldehyde generated by cracking paraformaldehyde (0.12 g, 4.0 mmol) was bubbled in, and the mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with THF (100 mL), and hydroquinone (0.1 g) and boron trifluoride etherate (2.6 mL, 20 mmol) were added successively; the mixture was stirred at room temperature for 15 min. The mixture was basified by triethylamine (4 mL) and quenched with saturated aqueous sodium bicarbonate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by flash chromatography (10% ethyl acetate in hexanes) to give 0.31 g (52%) of **5** as white crystals, mp 146−147 °C (lit.[1e] 145 °C). The ^{1}H and ^{13}C NMR spectra matched literature reports.[1e]

General Procedure for 3-Substituted-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indoles 9. 3-Heptyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (9c). To a −70 °C stirred solution of 1-(phenylsulfonyl)indole-3-carbaldehyde ethylene acetal (**6**) (0.66 g, 2.0 mmol) in dry THF (50 mL) under nitrogen was added a solution of *sec*-butyllithium (1.3 M in cyclohexane, 2.4 mmol) dropwise via syringe. The reaction mixture was stirred at −70 °C for 2 h and allowed to warm to room temperature for 2 h. The dark brown reaction mixture was recooled to −70 °C; then, octyl aldehyde (0.48 mL, 3.0 mmol) was added, and the mixture was stirred for 16 h. The mixture was quenched by aqueous ammonium chloride (100 mL). The organic layer was separated; the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by flash chromatography (30% ethyl acetate in hexanes) to give crude hydroxy acetal **8** as a syrup, which was dissolved in CH_2Cl_2 (125 mL). Hydroquinone (0.1 g) and TFA (0.1 mL) were added, and the mixture was stirred at room temperature for 2 h. The mixture was basified with triethylamine (0.5 mL), and the solvent was removed in vacuo. The resulting oil was purified by flash chromatography (10% ethyl acetate in hexanes) over basic alumina to give 0.48 g (61%) of **9c** as white crystals. Recrystallization from ether/hexane gave the analytical sample: mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 8.05−8.10 (d, 1H, 8.7), 7.59−7.65 (d, 2H, 8.7), 7.45−7.50 (m, 3H), 7.18−7.39 (m, 4H), 3.17 (t, 2H, 7.5), 1.73−1.85 (m, 2H); 1.23−1.47 (m, 8H), 0.86−0.93 (t, 3H, 6.9); ^{13}C NMR ($CDCl_3$) δ 146.3, 140.8, 137.4, 134.3, 129.7, 129.4, 128.4, 128.2, 127.9, 125.8, 124.1, 123.7, 123.1, 117.9, 32.8, 30.4, 30.1, 29.5, 28.0, 23.6, 15.1; IR (KBr) ν_{max} 2926, 2856, 1451, 1370, 1176, 751, 724 cm^{-1}; MS *m*/*z* 395 (M^+, 100%), 310, 254, 226, 170, 128, 77; HRMS calcd for M^+ *m*/*z* 395.1555, found 395.1546. Anal. Calcd for $C_{23}H_{25}NO_3S$: C, 69.84; H, 6.37; N, 3.54; S, 8.11. Found: C, 69.60; H, 6.19; N, 3.60; S, 8.08.

3-Methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (9a). This was prepared from **6** and acetaldehyde in 52% yield by the general method. The product is a white solid, mp 145−146 °C (lit.[1e] 146−148 °C). The ^{1}H and ^{13}C NMR spectra matched literature reports.[1e]

3-Phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (9b). This was prepared from **6** and benzaldehyde in 70% yield by the general method. The product is a white solid, mp 148−149 °C (lit.[1e] 148.5−149.5 °C). The ^{1}H and ^{13}C NMR spectra matched literature reports.[1e]

1-Methyl-3-heptyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (10). To a −70 °C stirred solution of 3-heptyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**9c**) (198 mg, 0.50 mmol) dissolved in dry THF (5 mL) under nitrogen was added a solution of *sec*-butyllithium (1.3 M in cyclohexane, 0.60 mmol) dropwise via

(5) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757−761.

syringe. The reaction mixture was stirred at −70 °C for 2 h and allowed to warm to room temperature for 2 h. The yellow reaction mixture was recooled to −70 °C; then, iodomethane (0.05 mL, 0.7 mmol) was added, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by flash chromatography (5% ethyl acetate in hexanes) to give 164 mg (80%) of **10**. Recrystallization from ether/hexane gave the analytical sample as white crystals: mp 78−79 °C; ^{1}H NMR ($CDCl_3$) δ 8.03−8.07 (m, 1H), 7.63−7.69 (m, 2H), 7.38−7.47 (m, 2H), 7.25−7.34 (m, 3H), 7.16−7.22 (m, 1H), 3.12 (t, 2H, 7.5), 2.45 (s, 3H), 1.72−1.83 (m, 2H), 1.25−1.49 (m, 8H), 0.91 (t, 3H, 6.9); ^{13}C NMR ($CDCl_2$) δ 146.0, 139.2, 138.3, 137.7, 134.4, 129.7, 128.5, 128.0, 127.3, 125.7, 124.7, 122.0, 119.6, 117.7, 32.8, 30.4, 30.1, 29.8, 27.9, 23.7, 15.1, 14.5; IR (KBr) ν_{max} 2921, 2849, 1675, 1449, 1363, 1173, 1091, 964, 751, 684 cm^{-1}; MS *m*/*z* 410 ($M^+ + 1$), 408, 286, 270 (100%), 268, 228, 184, 137; HRMS calcd for $M^+ + 1$ *m*/*z* 410.1791, found 410.1774. Anal. Calcd for $C_{24}H_{27}NO_3S$: C, 70.39; H, 6.64; N, 3.42; S, 7.83. Found: C, 70.24; H, 6.50; N, 3.48; S, 7.80.

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