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Benzannulation of 3-Substituted Pyrroles to Indoles

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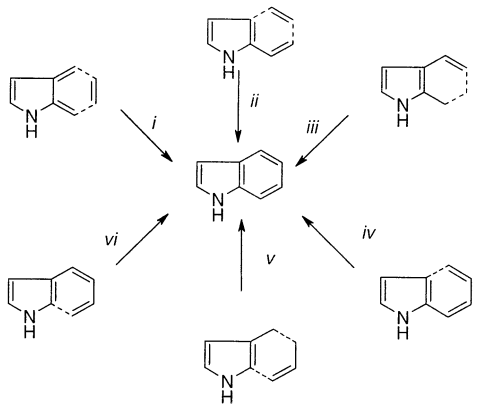
Abstract: In a new general indole synthesis, the anion derived from benzotriazolyl derivative **5b** underwent regioselective 1,4-addition to various α,β−unsaturated ketones; subsequent acid-catalyzed cyclization formed the corresponding indoles **1a**−**f**.

Despite the elegant and efficient methods accumulated for indole synthesis over a century, new routes continue to appear, stimulated by the presence of indole subunits in numerous biologically active compounds, natural and artificial.[1] Most indole syntheses are based on the construction of a pyrrole ring onto a functionalized benzene precursor. Reported syntheses starting from pyrroles include (Scheme 1) the following: (i) Diels−Alder cycloadditions of pyrrol-2,3-quinodimethanes, or their precursors or analogue,[2,3] (ii) a similar route from vinyl pyrroles,[4] (iii) cycloadditions of pyrrole−carbene chromium complexes with alkynes,[5] (iv) palladium-catalyzed cyclocarbonylation of 2-pyrrolylallyl acetate[6] and our own synthesis using benzotriazole methodology, and C2-substitued pyrrole,[7] (v) Junjappa's intramolecular electrophilic cyclization using α-oxoketene dithioacetals of C2 activated pyrroles;[8] and (vi) Natsume's method[9] using C2 and C3 substitued pyrroles in intramolecular electrophilic ring closures. We now report that an approach similar to (v) can be used from a C3 functionalized pyrrole (Scheme 1).

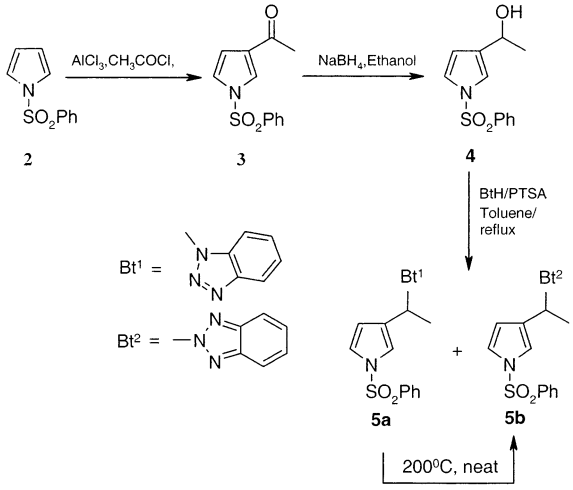
1-(1-Benzenesulfonyl-1*H*-pyrrol-3-yl)ethanol **4**, now utilized as the pyrrole fragment precursor, is readily available.[10a,b] Thus, **4** was made in 90% yield starting from *N*-phenylsulfonylpyrrole by acetylation followed by reduction. Compound **5** was obtained by refluxing **4** in toluene with benzotriazole and a catalytic amount of *p*-toluenesulfonic acid (Scheme 2).

SCHEME 1. Benzannulation To Give Indoles[a]



[a] For definitions of i−vi, see text.

SCHEME 2



The benzotriazole-functionalized pyrrole derivative **5** was obtained as a 30:70 mixture of Bt^1 and Bt^2 isomers, **5a** and **5b**, respectively, which were separated and characterized. Heating neat to 200 °C converts **5a** into the thermodynamically more stable **5b**. Usually in benzotriazole chemistry, the Bt^1 and Bt^2 isomers exhibit the same reactivity.[11] However, in the present case, **5a** and **5b** reacted differently: unexpectedly, the *n*-BuLi derived anion from **5a** did not react with the chalcone; unreacted starting materials were recovered after workup. But the anion generated from **5b** reacted smoothly with chalcones. Such an unusual difference of reactivity was previously observed and explained by the formation of an unstable radical anion intermediate.[12]

Consequently **5b** was deprotonated with *n*-butyllithium, in THF at −78 °C, and allowed to react with chalcone **9a** to afford a mixture of **7** and **8**, which without separation was refluxed in 2-propanol−10% H_2SO_4 to give the corresponding indole **1a** (Scheme 3). Other

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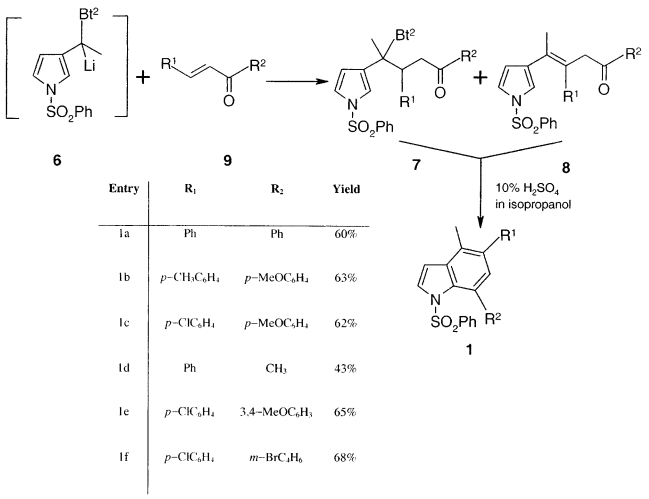
SCHEME 3



Entry	R_1	R_2	Yield
1a	Ph	Ph	60%
1b	*p*-$CH_3C_6H_4$	*p*-$MeOC_6H_4$	63%
1c	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	62%
1d	Ph	CH_3	43%
1e	*p*-ClC_6H_4	3,4-$MeOC_6H_3$	65%
1f	*p*-ClC_6H_4	*m*-BrC_4H_6	68%

substituted chalcones **9b**−**f** also reacted similarly and the respective indoles **1b**−**f** were isolated in yields of 40 to 65%.

The reactions proceeded through the selective 1,4-addition of **6** to the enones. We expected that the interconvertible mixture of **7** and **8** thus formed would spontaneously cyclize, followed by aromatization to the indole. However, mild acid treatment was required to facilitate the cyclization. In the case of **1b,** intermediate **7b** was isolated. In the case of **1d**, **8d** was isolated. For the other indoles prepared, the intermediate addition products were subjected to acid treatment without isolation. Attempts to generalize this methology with use of α,*β*-unsaturated esters failed.

In conclusion we have described a novel route to substituted indoles proceeding under mild conditions. The procedure utilizes three characteristics of benzotriazole chemistry: its easy introduction (**4** to **5**), its ability to stabilize an adjacent negative charge (**5** to **6**), and its ability to act as a leaving group (**7** to **8**).

Experimental Section

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300-MHz NMR spectrometer in chloroform-*d* solution. Column chromatography was performed on silica gel. THF was distilled from sodium−benzophenone ketal prior to use. All the reactions were performed under a nitrogen atmosphere and in flame-dried glasswares.

Preparation of 1-(1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl))-ethanone (3).[10b] To a suspension of anhydrous $AlCl_3$ (4 g, 0.03 mol) in 40 mL of 1,2-dichloroethane at room temperature was added slowly acetyl chloride (1.57 g 0.02 mol). The resulting solution was stirred for 20 min, then a solution of 1-*H*-phenylsulfonyl-pyrrole (2 g, 0.01 mol) in 15 mL of 1,2-dichloroethane was added slowly and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into ice and water, and the product was extracted with dichloromethane. After concentration the solid obtained was recrystallized from diethyl ether. White needles (92%): mp 97 °C (lit.[10b] mp 97−99 °C); ^{1}H NMR δ 2.41 (s, 3H), 6.67 (dd, J = 1.5, 3.5 Hz, 1H), 7.19 (dd, J = 2.5, 3.5 Hz, 1H), 7.42−7.72 (m, 3H), 7.76 (dd, J = 2.5, 3.5 Hz, 1H), 7.95−7.99 (m, 2H); ^{13}C NMR δ 27.3, 112.5, 121.7;124.6, 127.2, 129.8, 134,6, 139.2, 196.2.

Preparation of 1-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]-ethyl-2*H*-1,2,3-benzotriazole (5b). To a solution of 5 g (0.020 mol) of **3** in 200 mL of ethanol was added $NaBH_4$ (0.76 g 0.02 mol). The mixture was stirred for 2 h, and then 1 M HCl was added slowly. Ethanol was evaporated; the resulting oil was taken into dichloromethane and washed with water. The organic layer was dried over Na_2SO_4, and then evaporated to give **4**[10a] in quantitative yield (5.02 g). Without further purification, this was dissolved in toluene (150 mL), and benzotriazole (3.57 g, 0.03 mol) was added followed by a catalytic amount of *p*-TSA, (250 mg, 0.0015 mol). The mixture was refluxed under Dean−Stark apparatus for 10 h. Then the mixture was washed with 10% Na_2CO_3 solution (100 mL) and water (100 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded an oil, which is a mixture of **5b** and **5a** (70/30); the two isomers were separated on silica gel chromatography (hexane/ethyl acetate:3/1), and the minor isomer **5a** was converted to **5b** by heating neat at 200 °C for 1 h. White microcrystals (70%): mp 95 °C; ^{1}H NMR δ 2.06 (d, J = 7 Hz, 3H), 6.04 (q, J = 7.0 Hz, 1H), 6.37 (br, 1H), 7.15 (t, J = 2.7 Hz, 1H), 7.29 (s, 1H), 7.34−7.42 (m, 2H), 7.49−7.55 (m, 2H), 7.60−7.65 (m, 1H), 7.88−7.90 (m, 4H); ^{13}C NMR δ 21.0, 59.7, 112.6, 118.0, 118.1, 121.3, 126.2, 126.9, 128.4, 129.4, 134.0, 138.6, 144.1. Anal. Calcd for $C_{18}H_{16}O_2N_4S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.53; H, 4.56; N, 15.79.

General Procedure for the Preparation of Indoles 1a−f. To a solution of 2-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethyl-2*H*-1,2,3-benzotriazole **(5b)** (2 mmol) in THF (30 mL) at −78 °C was added *n*-butyllithium (1.58 M in cyclohexane, 1.43 mL, 2.2 mmol). The solution, which turned brown, was stirred for 10 min followed by the addition of appropriate chalcone (2.2 mmol) in one portion. The solution was kept at −78 °C for an hour, then the temperature was allowed to rise to room temperature and the mixture was stirred overnight. Saturated NH_4Cl solution (10 mL) was added and the organic layer was extracted with ethyl acetate. The combined ethyl acetate layer was washed with water and concentrated. The residue was refluxed with 50 mL of 10% H_2SO_4 2-propanol solution. After 24 h, the solution was cooled and neutralized with Na_2CO_3 solution. The organic phase was extracted with ethyl acetate and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum and the oil was purified by column chromatography over silica gel (hexane/ethyl acetate 4/1) to give the pure product.

4-Methyl-5,7-diphenyl-1-(phenylsulfonyl)-1*H*-indole (1a). Yellow prisms (60%): mp 153 °C; ^{1}H NMR δ 2.52 (s, 3H), 6.93 (d, J = 4.0 Hz, 1H), 7.08 (s, 1H), 7.20−7.70 (m, 15H), 7,87 (d, J = 4.5 Hz, 1H); ^{13}C NMR δ 16.3, 108.6, 126.4, 126.7, 126.8, 126.8, 127.3, 127.9, 128.0, 128.7, 129.5, 129.7, 130.2, 130.8, 132.1, 133.1, 133.4, 137.0, 138.3, 140.5, 141.0. Anal. Calcd for $C_{27}H_{21}NO_2S$: C, 76.57; H, 5.00; N, 3.31. Found: C, 76.78; H, 5.12; N, 3.15.

7-(4-Methoxyphenyl)-4-methyl-5-(4-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole (1b). Pale yellow prisms (63%): mp 153 °C; ^{1}H NMR δ 2.43 (s, 3H), 2.49 (s, 3H), 3.90 (s, 3H), 6.77 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 3.5 Hz, 1H), 7.00 (s, 1H), 7.13 (d, J = 8.7 Hz, 2H), 7.21−7.44 (m, 8H), 7.44−7.59 (m, 1H), 7.84 (d, J = 4.0 Hz, 1H); ^{13}C NMR δ 16.3, 21.1, 55.2, 108.5 112.7, 126.4, 126.6, 127.5, 128.7, 129.5, 130.2, 130.9, 131.0, 132.4, 132.8, 133.0, 133.3, 136.4, 137.0, 138.1, 138.5, 158.6. Anal. Calcd for $C_{29}H_{25}NO_3S$: C, 74.49; H, 5.39; N, 3.00. Found: C, 74.36; H, 5.43; N, 2.84.

5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-4-methyl-1-(phenylsulfonyl)-1*H*-indole (1c). Gray needles (62%): mp 157 °C ^{1}H NMR δ 2.41 (s, 3H), 3.84 (s, 3H), 6.71 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 4.0 Hz, 1H), 6.90 (s, 1H), 7.05 (d, J = 8.5 Hz, 2H), 7.20−7.39 (m, 8H), 7.43−7.55 (m, 1H), 7.80 (d, J = 4 Hz, 1H); ^{13}C NMR δ 16.2, 55.2, 108.2, 112.7, 126.4, 126.6, 127.6, 128.2, 128.7, 130.4, 130.7, 130.9, 130.9, 132.6, 132.6, 132.8, 133.1, 133.9, 135.7, 138.6, 139.5, 158.7. Anal. Calcd for $C_{28}H_{22}ClNO_3S$: C, 68.91; H, 4.54; N, 2.87. Found: C, 68.72; H, 4.45; N, 2.71.

4,7-Dimethyl-5-phenyl-1-(phenylsulfonyl)-1*H*-indole (1d). Yellow prisms **(**43%): mp 102 °C; ^{1}H NMR δ 2.46 (s, 3H), 2.57 (s, 3H), 6.87 (d, J = 4 Hz, 1H), 7.02 (s, 1H), 7.36−7.65 (m, 9H), 7,79 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 4 Hz, 1H); ^{13}C NMR δ 16.1, 21.5, 107.5, 121.6, 125.4, 126.4, 126.7, 128.1, 129.4, 129.6, 129.6, 130.4, 133.1, 133.6, 133.6, 137.1, 140.2, 141.4. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.87. Found: C, 73.32; H, 5.21; N, 3.64.

5-(4-Chlorophenyl)-7-(3,4-dimethoxyphenyl)-4-methyl-1-(phenylsulfonyl)-1*H*-indole (1e). White microcrystals (65%): mp 170 °C; ^{1}H NMR δ 2.43 (s, 3H), 3.68 (s, 3H), 3.92 (s, 3H), 6.58 (br s, 1H), 6.68 (br s, 2H), 6.85 (d, J = 4 Hz, 1H), 6.92 (s, 1H), 7.20−7.52 (m, 10H), 7.85 (d, J = 4 Hz, 1H); ^{13}C NMR δ 16.2, 55.5, 55.8, 107.7, 109.9, 113.5, 122.4, 126.3, 126.7, 127.4, 128.2, 128.7, 130.3, 130.5, 130.9, 132.3, 132.5, 132.8, 133.0, 133.3, 135.5, 138.7, 139.4, 147.4, 148.1. Anal. Calcd for $C_{29}H_{24}ClNO_4S$: C, 67.24; H, 4.67; N, 2.70. Found: C, 67.53; H, 4.57; N, 2.54.

7-(3-Bromophenyl)-4-methyl-5-(4-methylphenyl)-1-(phenylsulfonyl)-1H-indole (1f). White prisms (68%): mp 161 °C; ^{1}H NMR δ 2.36 (s, 3H), 2.44 (s, 3H), 6.84 (d, J = 3.5 Hz, 1H), 6.91 (s, 1H), 7.12−7.58 (m, 13H), 7.79 (s, 1H); ^{13}C NMR δ 16.3, 21.1, 108.2, 121.2, 126.0, 126.3, 127.5, 128.7, 128.7, 129.0, 129.0, 129.4, 130.0, 130.2, 130.6, 131.6, 132.6, 133.3, 133.4, 136.5, 136.9, 137.8, 138.2, 142.4. Anal. Calcd for $C_{28}H_{22}BrNO_2S$: C, 65.12; H, 4.29; N, 2.71. Found: C, 64.80; H, 4.33; N, 2.56.

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