Synthesis of 2-Alkylindoles via Sulfones

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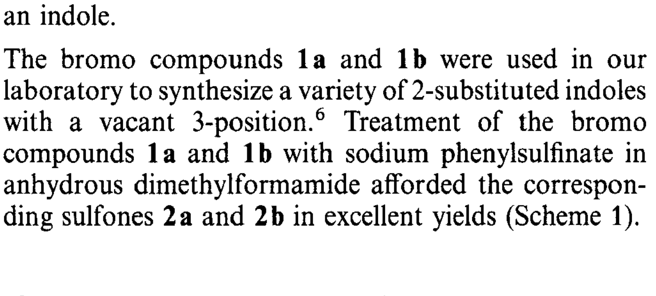
Elaboration of carbanions generated from 1-phenylsulfonyl-2-(phenylsulfonylmethyl)indole derivatives followed by removal of the *C*-phenylsulfonyl group by Raney nickel affords 2-alkylindoles.

Deprotonation of the side chain alkyl group of a π-electron rich indole has been achieved only recently and the resulting carbanion has been further investigated.[1-5] The synthetic elaboration of the side chain at the indole 2-position has been employed as a key step in the synthesis of indole alkaloids. We report here a simple route for the synthesis of 2-alkylindoles via a sulfone stabilized carbanion generated at the 2-methyl carbon of an indole.

The bromo compounds **1a** and **1b** were used in our laboratory to synthesize a variety of 2-substituted indoles with a vacant 3-position.[6] Treatment of the bromo compounds **1a** and **1b** with sodium phenylsulfinate in anhydrous dimethylformamide afforded the corresponding sulfones **2a** and **2b** in excellent yields (Scheme 1).



1,2	R^1	R^2	3	R^1	R^2
a	SPh	H	a	H	H
b	CO$_2$Et	OMe	b	CO$_2$Et	OMe

Scheme 1

Treatment of the sulfones **2a** and **2b** with Raney nickel in boiling ethanol afforded **3a** and **3b**, respectively, indicating that facile removal of the *C*-phenylsulfonyl group along with *N*-phenylsulfonyl and 3-phenylthio groups is possible after the elaboration of the active methylene group.[6]

Reaction of the sulfones **2a** and **2b** with sodium hydride and alkyl halides in tetrahydrofuran or dimethyl sulfoxide gave the alkylated sulfones **4a–e** in 71–84% yields. Raney nickel treatment of **4a–e** in boiling ethanol followed by treatment with 10% sodium hydroxide afforded 2-alkylindoles[6,7] **5a–e** in 71–91% yields. The sulfone **2a** was condensed with aromatic aldehydes in presence of sodium hydride in tetrahydrofuran to give the vinyl sulfones **6a–c** in 62–71% yields. Raney nickel treatment of these vinyl sulfones in boiling ethanol gave the corresponding 2-(2-arylethyl)indoles[6] **7a**, **7b** and **5c** in 79–89% yields (Scheme 2).

The 3-phenylthio group of the sulfone **2a** was selectively removed by Raney nickel in boiling acetone to afford the sulfone **8** in 65% yield. The sulfone **8** also could be methylated under similar conditions to give **9** as a gum which upon boiling with Raney nickel in ethanol gave 2-ethylindole (**5a**) in 50% overall yield. The sulfone **8** also condensed with *N*,*N*-dimethylformamide dimethylacetal to give the vinyl sulfone **10** in 63% yield. Attempted Diels–Alder reaction of **10** with dimethyl acetylenedicarboxylate in boiling benzene or toluene was unsuccessful. However, Raney desulfurization of **10** in ethanol gave only 2-ethylindole (**5a**) instead of the expected *N*,*N*-dimethylisotryptamine (Scheme 2).

In summary, we have presented a simple method to make 2-alkylindoles with easily available reagents. This method is also applicable to indoles with a methoxy group in the benzene ring in which case the lithiation is known to be nonregioselective.[8] Further work is in progress to use these sulfones to synthesize medicinally important indole alkaloids.

Meltings are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer and ^{1}H NMR on a Varian EM-390 spectrometer.

Commercial NaH (50% dispersion in oil) was washed with petroleum ether (bp 60–80°C) before use.

1-Phenylsulfonyl-2-phenylsulfonylmethyl-3-(phenylthio)indole (2a) and 3-Ethoxycarbonyl-5-methoxy-1-phenylsulfonyl-2-(phenylsulfonylmethyl)indole (2b):

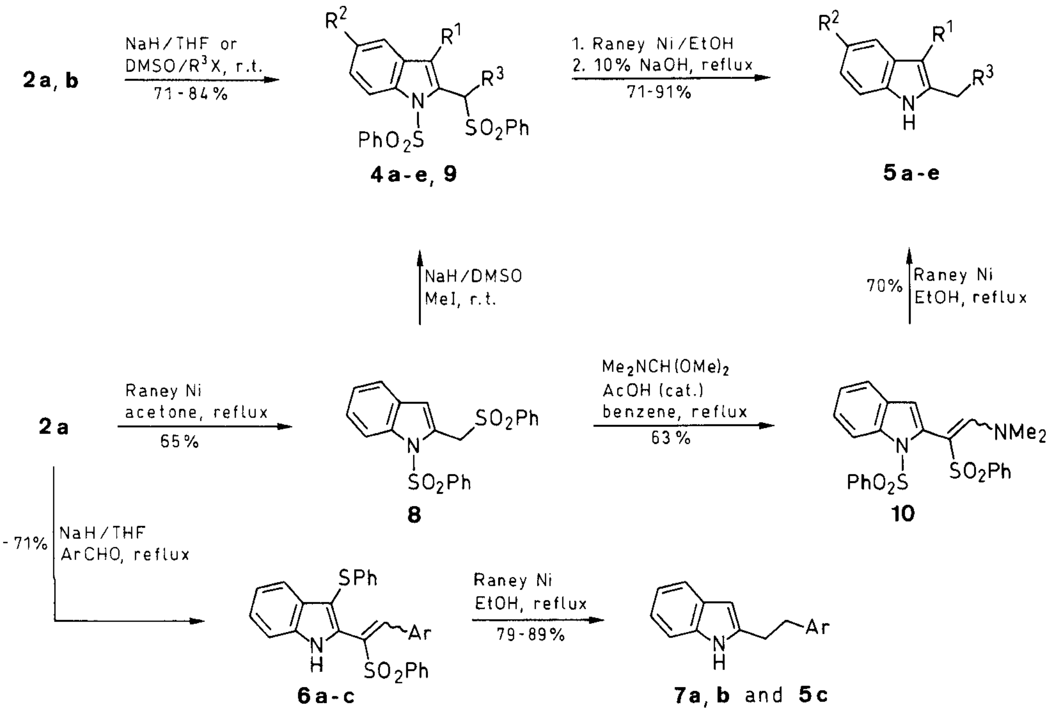
To a solution of the bromo compound **1a** or **1b** (20 mmol) in anhydrous DMF (40 mL) sodium phenylsulfinate (3.3 g, 20 mmol) was added and stirred at r.t. for 12 h. The solution was poured over crushed ice and the precipitated solid was filtered off and washed with water. The solid was dried in a desiccator ($CaCl_2$) and crystallized from acetone to afford the sulfones **2a** or **2b** in 95% yield.

2-Methylindole (3a) and 3-Ethoxycarbonyl-5-methoxy-2-methylindole (3b):

A suspension of the sulfone **2a** or **2b** (2 mmol) and Raney nickel[9] (W-2, 9 g) in EtOH (25 mL) was refluxed for 20 h. The catalyst was filtered and the filtrate evaporated to leave the crude product. This is taken up in Et_2O (25 mL) and the Et_2O solution was washed with water (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed and the crude product chromatographed over a column of silica gel (15 cm x 2 cm, 100–200 mesh) using benzene hexane as eluent (1 : 3) to give **3a** or **3b**; yield: 75–80% (Table).

Alkylation of Sulfones 2a,b and 8; General Procedure:

A solution of the sulfone **2a,b** or **8** (2 mmol) in anhydrous THF or DMSO (30 mL) was added to NaH (50 mg, 2 mmol) under N_2 and the mixture stirred for 15 min. The alkyl halide (2.5 mmol) dissolved in the same solvent was added slowly and the resulting mixture



	R^1	R^2	R^3		Ar
4a	SPh	H	Me	**6a**	3,4-$OCH_2OC_6H_3$
4b	SPh	H	Et	**6b**	3-pyridyl
4c	SPh	H	CH_2Ph	**6c**	Ph
4d	CO_2Et	OMe	Et	**7a**	3,4-$OCH_2OC_6H_3$
4e	CO_2Et	OMe	CH_2Ph	**7b**	3-pyridyl
5a	H	H	Me		
5b	H	H	Et		
5c	H	H	CH_2Ph		
5d	CO_2Et	OMe	Et		
5e	CO_2Et	OMe	CH_2Ph		
9	H	H	Me		

Scheme 2

stirred for 12 h at r. t. The solvent was distilled off in the case of THF and the residue poured over crushed ice. In the case of DMSO the reaction mixture as such was poured over crushed ice. Extraction with $CHCl_3$ (3 x 30 mL) and removal of solvent from the dried (Na_2SO_4) extract gave a residue. This was chromatographed over a column of silica gel (15 cm x 2 cm, 100–200 mesh) using benzene/hexane (4:1) as eluent. The product was crystallized from benzene/hexane to afford the alkylated products **4a–e** or **9**, respectively; yield: 71–84% (Table).

Compound **9** was obtained as a gum and used as such in the next step.

2-Alkylindoles 5a–e; General Procedure:

To a solution of the appropriate alkylated sulfone **4a–e** or **9** (2 mmol) in EtOH (30 mL) was added Raney nickel (W-2, 9 g) and the resulting mixture refluxed for 10 h. 10% NaOH solution (10 mL) was added and the refluxing continued for another 6 h. The catalyst was filtered and the solvent removed. The residue obtained was taken up in Et_2O (25 mL) and washed with water (3 x 15 mL). The Et_2O layer was separated, dried (Na_2SO_4) and the solvent removed. The crude product was chromatographed over a column of silica gel (15 cm x 2 cm, 100–200 mesh) using benzene/hexane (1:1) as eluent to afford 2-alkylindoles **5a–e** yield: 71–91% (Table).

2-(2-Aryl-1-phenylsulfonylethenyl)-3-(phenylthio)indoles 6a–c; General Procedure:

A solution of the sulfone **2a** (1 g, 2 mmol) in anhydrous THF (30 mL) was added to NaH (100 mg, 4 mmol) under N_2 and stirred for 15 min. A solution of the appropriate aldehyde (2.5 mmol) in the same solvent was slowly added and the stirring continued at r. t. for 4 h. The resulting solution was refluxed for 6 h under N_2. The solvent was distilled, and the residue poured over crushed ice. The product was extracted with $CHCl_3$ (3 x 30 mL), dried (Na_2SO_4) and the solvent removed. The crude product was chromatographed over a column of silica gel (15 cm x 2 cm, 100–200 mesh) using benzene/EtOAc as eluent to give the vinyl sulfones **6a–c**, which were crystallized from benzene hexane; yield: 62–71% (Table).

2-(2-Arylethyl)indoles 7a, 7b and 5c; General Procedure:

To a solution of the appropriate vinyl sulfone **6** (2 mmol) in EtOH (30 mL) was added Raney nickel (W-2, 9 g) and the resulting mixture refluxed for 8 h. The catalyst was filtered and the solvent removed. The residue was taken up in Et_2O (30 mL) and washed with water (3 x 10 mL). The Et_2O layer was separated, dried (Na_2SO_4) and the solvent removed to give the products **7a,b** and **5c**, which were crystallized from benzene hexane; yield: 79–89%.

1-Phenylsulfonyl-2-(phenylsulfonylmethyl)indole (8):

To a solution of **2a** (1.0 g, 2 mmol) in acetone was added Raney nickel (W-2, 10 g) and the resulting mixture refluxed for 20 h. The catalyst was filtered and the filtrate was evaporated to give the crude product. Recrystallization from benzene/hexane afforded pure **8**; yield: 0.53 g (65%), mp 164–165 °C (Table).

2-(2-Dimethylamino-1-phenylsulfonylethenyl)-1-phenylsulfonylindole (10):

A solution of sulfone **8** (0.82 g, 2 mmol), *N*,*N*-dimethylformamide dimethylacetal (0.48 g, 4 mmol) and AcOH (3 drops) in benzene (20 mL) was refluxed for 8 h. The solvent was removed and the residue poured over crushed ice. This was extracted with $CHCl_3$ (3 x 20 mL) and dried (Na_2SO_4). The solvent was removed and the crude product crystallized from acetone to afford the vinyl sulfone **10**; yield: 0.59 g (63%); mp 236–237 °C (Table).

Table. 2-Alkylindoles **2**, **4**–**8** and **10** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr/ $CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	95	154–155 (acetone)	$C_{27}H_{21}NO_4S_3$ (519.6)	–	5.3 (s, 2H, CH_2), 6.66–8.2 (m, 19H_{arom})
2b	95	140–141 (acetone)	$C_{25}H_{23}NO_7S_2$ (513.6)	1700 (CO)	1.33 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 3.76 (s, 3H, OCH_3), 4.2 (q, 2H, $J = 7$, $C\underline{H}_2CH_3$), 5.76 (s, 2H, CH_2), 6.8–7.96 (m, 13H_{arom})
4a	71	140–141 (benzene/hexane)	$C_{28}H_{23}NO_4S_3$ (533.7)	–	1.93 (d, 3H, $J = 7$, $CHC\underline{H}_3$), 5.96 (q, 1H, $J = 7$, $C\underline{H}CH_3$), 6.5–8.0 (m, 19H_{arom})
4b	76	126–127 (benzene/hexane)	$C_{29}H_{25}NO_4S_3$ (547.7)	–	0.80 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 2.1–3.1 (m, 2H, $C\underline{H}_2CH_3$), 5.73–5.93 (m, 1H, $CHSO_2$), 6.66–7.8 (m, 19H_{arom})
4c	80	172–173 (benzene)	$C_{34}H_{27}NO_4S_3$ (609.8)	–	3.76–4.03 (m, 2H, $C\underline{H}_2Ph$), 4.56–4.93 (m, 1H, $CHSO_2$), 6.63–8.0 (m, 24H_{arom})
4d	81	159–160 (benzene/hexane)	$C_{27}H_{27}NO_7S_2$ (541.6)	1710 (CO)	0.93 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 1.5 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 2.3–3.0 (m, 2H, $CHC\underline{H}_2CH_3$), 3.8 (s, 3H, OCH_3), 4.5 (q, 2H, $J = 7$, $OC\underline{H}_2CH_3$), 6.03 (t, 1H, $J = 7$, $C\underline{H}CH_2CH_3$), 6.8–7.86 (m, 13H_{arom})
4e	84	205–206 (benzene/hexane)	$C_{32}H_{29}NO_7S_2$ (603.7)	1710 (CO)	1.53 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 3.83 (s, 3H, OCH_3), 3.86–3.96 (m, 2H, $C\underline{H}_2Ph$), 4.2–4.5 (m, 1H, $CHSO_2$), 4.66 (q, 2H, $J = 7$, $C\underline{H}_2CH_3$), 6.5–7.8 (m, 18H_{arom})
5a	71	oil	43[7]	3440 (NH)	1.23 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 2.56 (q, 2H, $J = 7$, $C\underline{H}_2CH_3$), 6.13 (s, 1H, H-3), 6.8–7.6 (m, 5H, 4H_{arom} + NH)
5b	73	oil	34[7]	3430 (NH)	0.86 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 1.2–1.8 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.4 (t, 2H, $J = 7$, $C\underline{H}_2CH_2CH_3$), 6.1 (s, 1H, H-3), 6.8–7.7 (m, 5H, 4H_{arom} + NH)
5c	79	118–119 (benzene/hexane)	95[6]	–[6]	–[6]
5d	85	89–90 (benzene/hexane)	$C_{15}H_{19}NO_3$ (261.3)	3290 (NH), 1650 (CO)	0.95 (t, 3H, $J = 7$, $CH_2CH_2C\underline{H}_3$), 1.43 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.6–1.9 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.03 (t, 2H, $J = 7$, $C\underline{H}_2CH_2CH_3$), 3.83 (s, 3H, OCH_3), 4.43 (q, 2H, $OC\underline{H}_2CH_3$), 6.7–7.8 (m, 3H_{arom}), 9.0 (br s, 1H, NH)
5e	91	91–92 (benzene/hexane)	$C_{20}H_{21}NO_3$ (323.4)	3260 (NH), 1650 (CO)	1.46 (t, 3H, $J = 7$, $CH_2C\underline{H}_3$), 2.9–3.6 (m, 4H, CH_2CH_2), 3.86 (s, 3H, OCH_3), 4.5 (q, 2H, $J = 7$, $C\underline{H}_2CH_3$), 6.9–8.0 (m, 8H_{arom}), 9.43 (br s, 1H, NH)
6a	62	204–205 (benzene/hexane)	$C_{29}H_{21}NO_4S_2$ (511.6)	3310 (NH)	5.7 (s, 2H, OCH_2O), 6.2–7.56 (m, 17H_{arom}), 7.96 (s, 1H, $ArC\underline{H}{=}C$), 9.36 (br s, 1H, NH)
6b	71	215–216 (benzene)	$C_{27}H_{20}N_2O_2S_2$ (468.6)	3380 (NH)	6.3–8.7 (m, 19H_{arom} + $ArC\underline{H}{=}C$), 9.83 (br s, 1H, NH)
6c	67	215–216 (benzene)	$C_{28}H_{21}NO_2S_2$ (467.6)	3380 (NH)	6.1–7.9 (m, 19H_{arom}), 8.13 (s, 1H, $ArC\underline{H}{=}C$), 9.2 (br s, 1H, NH)
7a	85	93 (benzene/hexane)	92[6]	–[6]	–[6]
7b	89	142 (benzene)	142[6]	–[6]	–[6]
8	65	164–165 (benzene/hexane)	$C_{21}H_{17}NO_4S_2$ (411.5)	–	5.1 (s, 2H, CH_2), 6.9 (s, 1H, H-3), 7.2–8.06 (m, 14H_{arom})
10	63	236–237 (acetone)	$C_{24}H_{22}N_2O_4S_2$ (466.6)	–	2.83 [br s, 6H, $N(CH_3)_2$], 5.96 (s, 1H, H-3), 7.06–8.1 (m, 15H_{arom})

[a] Yield of isolated pure products.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.29, N ±0.29.

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