Synthesis of 2-(2-Arylethyl)-indoles

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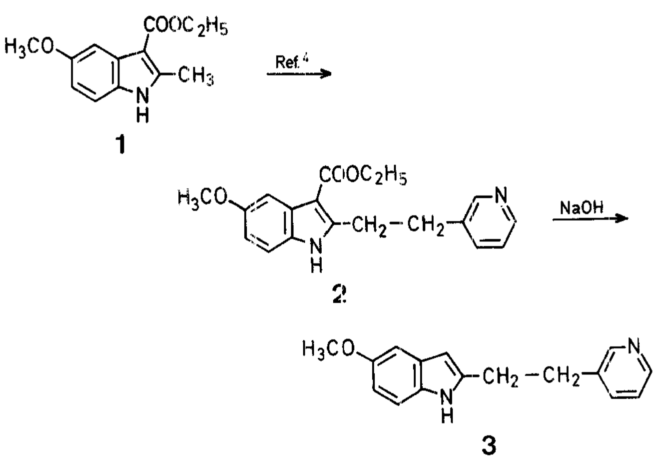
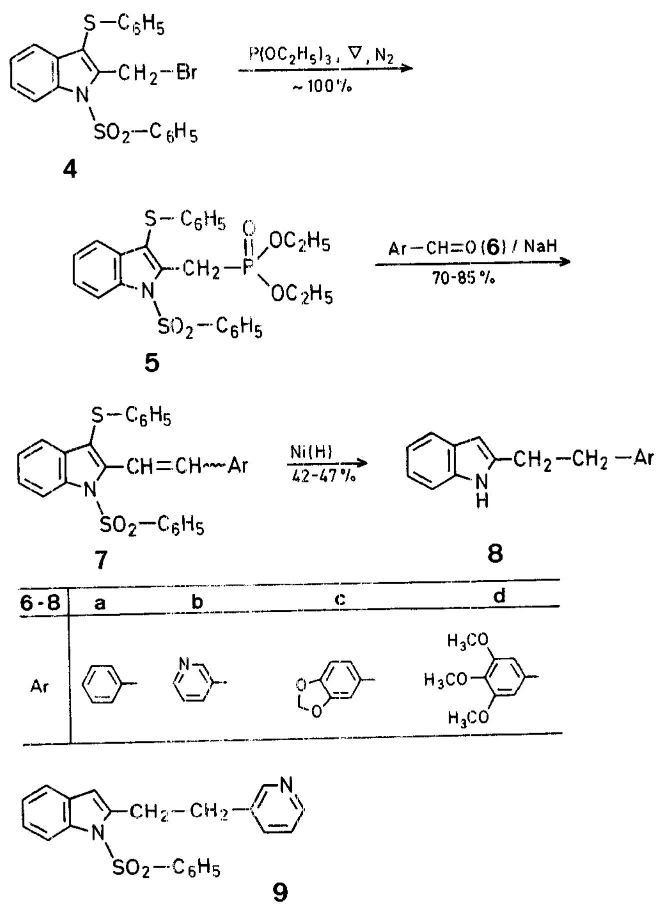
In continuation of our interest in 2-substituted indoles, we report here a synthesis of 2-(2-arylethyl)-indoles which may serve as precursors for a variety of medicinally important alkaloids and their analogs[1,2,3]. Initially we carried out the deethoxycarbonylation of ethyl 5-methoxy-2-[2-(3-pyridyl)-ethyl]-indole-3-carboxylate (2)[4] under basic conditions to give 5-methoxy-2-[2-(3-pyridyl)-ethyl]-indole (3) in 54% yield. We find that this is not a preferred route for the synthesis of 2-(2-arylethyl)-indoles as the available methods for the preparation of esters of 2-methylindole-3-carboxylic acids of the type 1 suffer from low to poor yields[5,6].

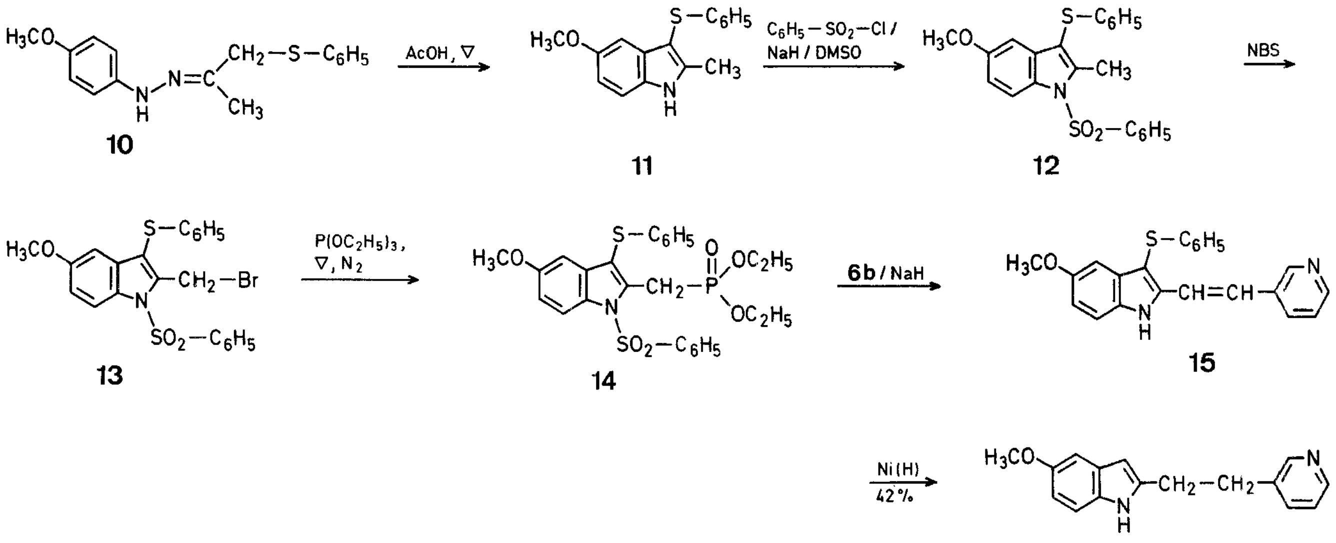


Hence, we chose the bromo compound 4, which has served[7,8] as a precursor for various 2-substituted indoles, as the starting material for our work. Compound 4 was converted to the 2-(2-arylvinyl)-indoles 7 using our reported procedure for the preparation of analogous indole derivatives[4] as shown in Scheme A. The title compounds 8 were prepared by treating 7 with Raney nickel contaminated with a trace of alkali, which effected not only the expected desulfurization but also reduction of the vinyl double bond and removal of the *N*-benzenesulfonyl group. Our attempts to isolate the intermediate *N*-benzenesulfonyl-2-(2-arylethyl)-indoles by performing the reaction with Raney nickel completely free from alkali were unsuccessful, except in the case of 7b where 9 was isolated in poor yield when shorter reaction times were used.



Scheme A

Extension of the Wittig-Horner reaction to the 5-methoxyindole derivative **14**, easily prepared from **10** (Scheme **B**), with pyridine-3-carboxaldehyde (**6b**) furnished directly the de-*N*-protected indole **15**. Similar cleavage of *N*-benzenesulfonyl group has been observed[4] in Wittig-Horner reactions of 5-methoxyindoles. The vinylindole **15** on treatment with Raney Nickel yielded **3** in 42% yield, identical with an authentic sample obtained from **2**.



Scheme **B**

Table. Indoles **3**, **5**, **7a**–**d**, **8a**–**d**, **9**, **11**–**15** prepared

Product No.	Yield [%][a]	m.p. [°C] (solvent)	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CCl_4/CDCl_3$) δ [ppm]
3	54	140–142° (C_2H_5OAc)	$C_{16}H_{16}N_2O$ (252.3)	3420 (NH)	2.93 (s, 4H); 3.80 (s, 3H); 6.1 (s, 1H); 6.63–7.5 (m, 5H); 8.3–8.9 (m, 3H)
5	98	96° (CCl_4)	$C_{25}H_{26}NO_5PS_2$ (575.3)	1340, 1100 (SO_2)	1.2 (t, 6H, $J = 7$ Hz); 4.00 (q, 4H, $J = 7$ Hz); 4.03 (d, 2H, $J_{HP} = 17$ Hz); 6.8–8.16 (m, 14H)
7a	85	146–147° (C_2H_5OH)	$C_{28}H_{21}NO_2S_2$ (467.5)	1360, 1100 (SO_2)	6.70–8.33 (m)
7b	82	200° (CH_3OH)	$C_{27}H_{20}N_2O_2S_2$ (468.5)	1370, 1100 (SO_2)	6.73–8.6 (m)
7c	70	131° (C_6H_6)	$C_{29}H_{21}NO_4S_2$[c] (511.5)	1370, 1100 (SO_2)	5.86 (s, 2H); 6.6–8.2 (m, 19H)
7d	72	Oil	$C_{31}H_{27}NO_5S_2$ (557.7)	1370 1135 (SO_2)[d]	3.85 (s, 9H); 6.65–8.3 (m, 18H)
8a	42	95° (hexane/C_6H_6)	$C_{16}H_{15}N$ (221.3)	3445 (NH)	3.00 (s, 4H); 6.15 (s, 1H); 6.8–7.4 (m, 10H)
8b	40	142° (C_6H_6)	$C_{15}H_{14}N_2$[e] (222.3)	3250 (NH)	3.00 (s, 4H); 6.28 (s, 1H); 7.05–7.65 (m, 6H); 8.5–8.7 (m, 3H)
8c	47	92° (hexane/C_6H_6)	$C_{17}H_{15}NO_2$ (265.3)	3460 (NH)	3.00 (s, 4H); 5.93 (s, 2H); 6.23 (s, 1H); 6.53–7.7 (m, 8H)
8d	45	118° (hexane/C_6H_6)	$C_{19}H_{21}NO_3$[f] (314.4)	3385 (NH)	2.96 (s, 4H); 3.65 (s, 6H); 3.73 (s, 3H); 6.15 (s, 1H); 6.23 (s, 2H); 6.9–7.45 (m, 4H); 8.02 (br. s, 1H)
9	12	97° (C_6H_6)	$C_{21}H_{18}N_2O_2S$ (362.4)	1370, 1100 (SO_2)	2.9–3.32 (m, 4H); 6.28 (s, 1H); 7.03–8.04 (m, 13H)
11	70	125–126° (C_2H_5OAc)	$C_{16}H_{15}NOS$ (269.3)	3400 (NH)	2.43 (s, 3H); 3.76 (s, 3H); 6.7–7.3 (m, 8H); 8.03 (br. s, 1H)
12	85	98° (CH_3OH)	$C_{22}H_{19}NO_3S_2$ (409.4)	1340, 1105 (SO_2)	2.67 (s, 3H); 3.76 (s, 3H); 6.7–8.23 (m, 13H)
13	94	97° (CCl_4)	$C_{22}H_{18}BrNO_3S_2$ (488.3)	1360, 1100 (SO_2)	3.83 (s, 3H); 5.03 (s, 2H); 6.73–8.3 (m, 13H)
14	95	62° (CCl_4/hexane)	$C_{26}H_{28}NO_6PS_2$ (545.6)	1340, 1110 (SO_2)	1.15 (t, 6H, $J = 7$ Hz); 3.55 (s, 3H); 4.00 (q, 4H, $J = 7$ Hz); 4.15 (d, 2H, $J_{HP} = 17$ Hz); 6.5–8 (m, 13H)
15	65	134–136° ($CHCl_3$)	$C_{22}H_{18}N_2OS$ (326.4)	3400 (NH)	3.83 (s, 3H); 7.1–8.6 (m, 15H)

[a] Yield of pure isolated product.

[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.15, N ±0.23.

[c] M.S.: $m/e = 511$ (M^+, 61%); 261 (100%).

[d] Measured in $CHCl_3$.

[e] M.S.: $m/e = 222$ (M^+, 32%); 130 (100%).

[f] M.S. (C.I): $m/e = 312$ (M + 1, 100%).

The 2-(2-arylethyl)-indoles **8a–d** and **3** prepared exhibited in their ^{1}H-N.M.R. spectra, a singlet around $\delta = 3.0$ ppm for 4 protons of the two methylenic groups arising from an accidental equivalence. However, proton decoupled and coupled[13] C-N.M.R. spectra of **8b** and **8c** exhibited two singlets and triplets around $\delta = 29–35$ ppm for two methylenic carbons respectively, thus unambiguously confirming their structure.

Thus we have demonstrated the utility of the bromo compounds **4** and **13** for the preparation of a variety of 2-(2-arylethyl)-indoles. The main advantage of this method lies in the removal of phenylthio and benzenesulfonyl groups with concurrent reduction of the vinyl double bond in one step. This method might be extended for the synthesis of title compounds substituted in the phenyl ring starting from the appropriate 2-methyl-3-phenylthioindoles.

5-Methoxy-2-[2-(3-pyridyl)-ethyl]indole (3):
A mixture of **2**[4] (324 mg, 1 mmol), sodium hydroxide (600 mg, 15 mmol) and ethanol (3 ml) is heated on a steam bath for 8 h. The ethanol is then distilled off and the residue is diluted with water (10 ml). The mixture is extracted with ethyl acetate (5 × 10 ml), the organic phase is dried over potassium carbonate and concentrated. The residue is chromatographed on a silica gel column using benzene/ethyl acetate (3 : 1) as eluent to furnish pure **3**; yield: 136 mg (54 %).

5-Methoxy-2-methyl-3-phenylthioindole (11):
Prepared by a modification of the reported[9] general procedure for 3-phenylthioindoles by cyclizing the phenylhydrazone **10** in boiling glacial acetic acid (6 h).

1-Benzenesulfonyl-2-bromomethyl-5-methoxy-3-phenylthioindole (13):
Prepared from methoxyindole according to Ref.[7].

Phosphonate Esters 5 and 14:
Prepared in nearly quantitative yield according to Ref.[4].

2-(2-Arylvinyl)-indoles 7a–d and 15:
Prepared by Wittig-Horner reaction of the phosphonate esters **5** and **14** respectively with the appropriate aryl aldehyde **6** according to Ref.[4].

2-(2-Arylethyl)-indoles 8a–d or 3; General Procedure:
A solution of **7a–d** or **15** (2 mmol) in ethanol (150 ml) is refluxed with an excess of Raney nickel (10 g) for 6–8 h. Then 5 % aqueous sodium hydroxide (2 ml, except for **15**) is added and the resulting mixture is refluxed for 2 h. The catalyst is filtered off, the residue obtained after removal of the solvent is taken up in ether (25 ml), the ether phase is washed with water (15 ml) and dried with sodium sulfate. The solvent is removed and the residue is chromatographed over silica gel, eluting with benzene/ethyl acetate, to afford **8a–d** or **3** (Table).

1-Benzenesulfonyl-2-(3-pyridylethyl)-indole (**9**): This compound is isolated from the reaction of **7b** with alkali free Raney nickel using shorter reaction (1.5 h) time.

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