A Convenient Synthesis of 2-(2-Arylethyl)-3-ethoxycarbonyl-5-methoxyindoles via the Wittig-Horner Reaction

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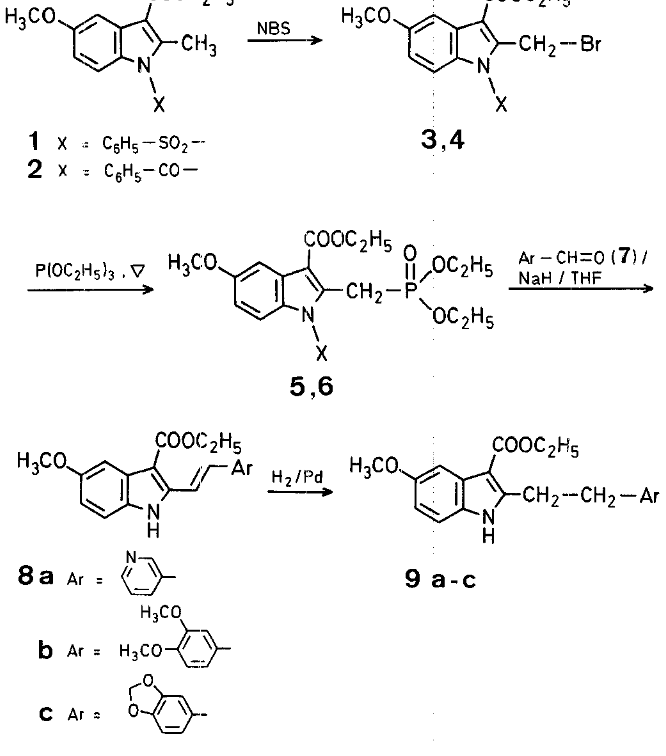
Recently, 2-substituted indoles have been used as intermediates for the synthesis of many alkaloids and their analogs[1,2,3]. The thermolysis of azirines[4] is reported to give 2-(2-arylvinyl)-indoles. Similarly the Wittig reaction[5] of arylaldehydes with 2-indolylmethyltriphenylphosphonium bromide also furnishes 2-(2-arylvinyl)-indoles. The latter compounds have been prepared in many steps from indole-2-carboxylic acid[5,6].

Here we report a facile side-chain bromination of *N*-benzenesulfonyl or *N*-benzoyl derivatives of ethyl 5-methoxy-2-methylindole-3-carboxylate (**1**[7] or **2**) by *N*-bromosuccinimide in boiling carbon tetrachloride to give **3** or **4**. Bromination of 2-methylindole derivatives usually gives only ring brominated products[8,9]. Compounds **3** or **4** then react smoothly with triethyl phosphite to give the phosphonate esters **5** or **6**, respectively, which upon reaction with aryl aldehydes **7** in the presence of sodium hydride in dry tetrahydrofuran at 5–10 °C afford the 2-(2-arylvinyl)-indoles **8a–c** in 45–50% yield with concomitant loss of the *N*-protective group during work-up. Based on previous observations[5], we have assigned *trans*-geometry to the olefinic double bond in compounds **8a–c**. Indoles **8a–c** are smoothly hydrogenated in ethanol in the presence of 10% palladium on charcoal to give the title compounds **9a–c** in excellent yields.



We have noted that deprotonation of the phosphonate ester by sodium hydride occurs only in the presence of aryl aldehydes, while in their absence the phosphonate ester is unaffected by sodium hydride even in refluxing tetrahydrofuran, in accordance with previous reports[10].

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Table. Indoles **3**, **4**, **5**, **6**, **8a–c**, and **9a–c** prepared

Product	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	95	151–152° (CCl_4)	$C_{19}H_{18}BrNO_5S$ (452.3)	1685 (C=O); 1350, 1180 (SO_2)	1.50 (t, 3H); 3.73 (s, 3H); 4.40 (q, 2H); 5.40 (s, 2H); 6.7–8.0 (m, 8H)
4	90	106° (CCl_4)	$C_{20}H_{18}BrNO_4$ (416.3)	1680–1665 (C=O)	1.47 (t, 3H); 3.80 (s, 3H); 4.47 (q, 2H); 5.36 (s, 2H); 6.4–8.0 (m, 8H)
5	98	130° (n-C_6H_{14})	$C_{23}H_{28}NO_8PS$ (509.4)	1690 (C=O); 1360, 1160 (SO_2)	1.30 (t, 6H); 1.46 (t, 3H); 3.50 (s, 3H); 4.10 (q, 4H); 4.30 (q, 2H); 4.36 (d, 2H, $J_{HP}=16$ Hz); 6.7–8.1 (m, 8H)
6	98	oil	$C_{24}H_{28}NO_7P$ (473.4)	1710–1700 (C=O)[c]	1.30 (t, 6H); 1.60 (t, 3H); 4.00 (s, 3H); 4.10 (q, 4H); 4.50 (d, 2H, $J_{HP}=16$ Hz); 4.60 (q, 2H); 6.4–8.1 (m, 8H)
8a	45	215° (C_2H_5OAc)	$C_{19}H_{18}N_2O_3$ (322.4)	3350 (NH); 1685 (C=O)	1.48 (t, 3H); 3.90 (s, 3H); 4.20 (q, 2H); 7.0–9.0 (m, 9H); 9.40 (s, 1H)
8b	48	188° (C_2H_5OAc)	$C_{22}H_{23}NO_5$ (381.4)	3300 (NH); 1680 (C=O)	1.50 (t, 3H); 3.80 (s, 3H); 3.83 (s, 3H); 3.85 (s, 3H); 4.50 (q, 2H); 6.6–8.2 (m, 8H); 9.40 (s, 1H)
8c	50	178° (C_2H_5OAc)	$C_{21}H_{19}NO_5$ (365.4)	3340 (NH); 1680 (C=O)	1.45 (t, 3H); 3.90 (s, 3H); 4.40 (q, 2H); 5.93 (s, 2H); 6.6–8.1 (m, 8H); 9.30 (s, 1H)
9a	95	177–178° (C_2H_5OH)	$C_{19}H_{20}N_2O_3$ (324.4)	3340 (NH); 1690 (C=O)	1.40 (t, 3H); 2.90–3.20 (t, 2H); 3.20–3.50 (t, 2H); 3.93 (s, 3H); 4.50 (q, 2H); 6.8–7.7 (m, 7H); 10.13 (s, 1H)
9b	95	137° (C_2H_5OH)	$C_{22}H_{25}NO_5$ (383.4)	3340 (NH); 1690 (C=O)	1.40 (t, 3H); 2.70–3.10 (t, 2H); 3.10–3.43 (t, 2H); 3.53 (s, 3H); 3.66 (s, 3H); 3.80 (s, 3H); 4.30 (q, 2H); 6.6–7.7 (m, 6H); 10.13 (s, 1H)
9c	95	116° (C_2H_5OH)	$C_{21}H_{21}NO_5$ (367.4)	3330 (NH); 1695 (C=O)	1.40 (t, 3H); 2.70–3.00 (t, 2H); 3.10–3.40 (t, 2H); 3.73 (s, 3H); 4.30 (q, 2H); 5.80 (s, 2H); 6.4–7.6 (m, 6H); 9.60 (s, 1H)

[a] Yield of pure, isolated product.

[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.09, N ±0.22.

[c] $CHCl_3$ solution.

Ethyl 1-Benzoyl-5-methoxy-2-methylindole-3-carboxylate (2):

The experimental procedure is the same as that reported earlier for 1[7]. The crude product is purified by passing through a column of silica gel using petroleum ether (b.p. 60–80 °C)/benzene (1 : 1) as eluent. Recrystallisation from carbon tetrachloride/petroleum ether (b.p. 60–80 °C) gives **2** as white needles; yield: 85%; m.p. 74 °C.

$C_{20}H_{19}NO_4$	calc.	C 71.20	H 5.68	N 4.15
(337.4)	found	71.32	5.70	4.04

I.R. (KBr): $\nu = 1680-1660$ cm^{-1} (C=O).

^{1}H-N.M.R. (CCl_4/$CDCl_3$): $\delta = 1.23$ (t, 3H); 3.50 (s, 3H); 3.66 (s, 3H); 4.18 (q, 2H); 6.3–7.7 ppm (m, 8H).

Bromination of Indoles 1 or 2:

A finely powdered mixture of **1** or **2** (0.003 mol) and *N*-bromosuccinimide (0.003 mol) in dry carbon tetrachloride (200 ml) containing benzoyl peroxide (10 mg) is refluxed for 4 h. Succinimide is filtered off and concentration of the filtrate affords the crystalline bromo compounds **3** or **4**; yield: 90–95%.

Phosphonate Esters 5 or 6:

A mixture of the bromomethylindole **3** or **4** (0.003 mol) and triethyl phosphite (0.0033 mol) is heated at 155–160 °C for 3 h under nitrogen and the excess triethyl phosphite is removed under vacuum to leave the phosphonate ester **5** or **6** as a single product; yield: 98%.

2-(2-Arylvinyl)-3-ethoxycarbonyl-5-methoxyindoles 8a–c; General Procedure:

To a well-stirred solution of the phosphonate ester **5** or **6** (2.5 mmol) and aryl aldehyde **7** (3 mmol) in dry tetrahydrofuran (25 ml) under nitrogen at 5 °C sodium hydride (0.12 g, 5 mmol) is added slowly, so that the evolution of hydrogen is not too vigorous. The resulting bright yellow solution is stirred for 24 h at room temperature. Then the solvent is distilled off, the residue is decomposed with ice/water (15 ml), and extracted with ethyl acetate (3 × 20 ml). The dried (sodium sulphate) extract affords **8a–c** upon concentration and cooling; yield: 45–50%.

Catalytic Recuction of 8a–c; General Procedure:

A solution of **8a–c** (0.20 g) in ethanol (10 ml) is hydrogenated over 10% palladium on charcoal (25 mg) at 50 psi for 20 h. Filtration of the catalyst and concentration of the filtrate gives the *2-(2-arylethyl)-3-ethoxycarbonyl-5-methoxyindoles* **9a–c** as white crystals; yield: 95%.

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