A Simple Synthesis of 2-Substituted Indoles

Dhanapalan Nagarathnam

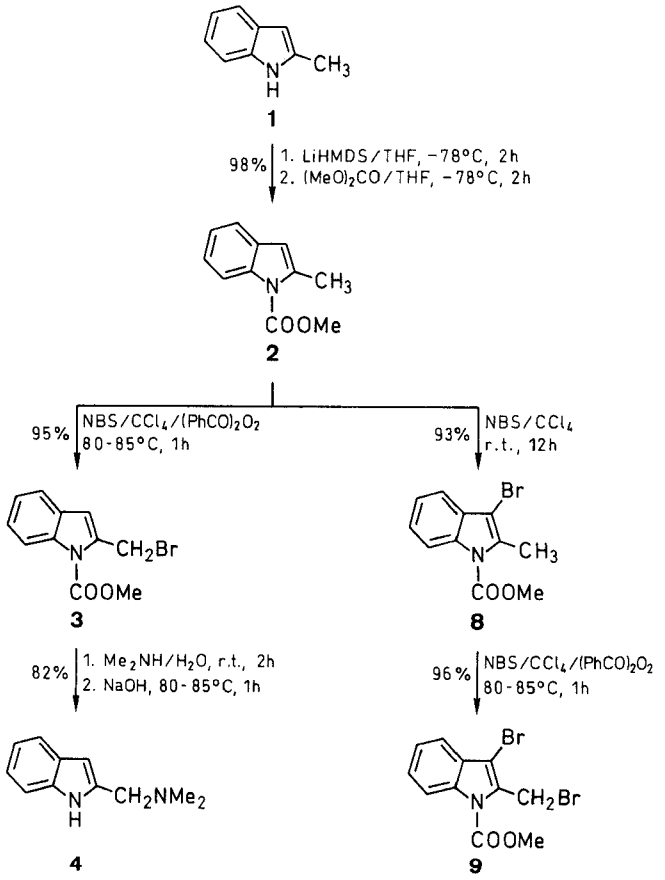
Department of Medicinal Chemistry and Pharmacognosy, (M/C 781), University of Illinois at Chicago, PO Box 6998, Chicago, Illinois 60680, USA

Received 9 August 1991; revised 27 November 1991

A simple preparation of 2-(dimethylaminomethyl)indole, indole-2-acetonitrile and 2-(2-arylvinyl)indoles from 2-methylindole is described.

2-Substituted indoles are potential intermediates for many alkaloids and pharmacologically important substances,[1-7] and 2-vinylindoles are used in Diels–Alder reactions.[8,9] While the methods for the preparation of 3-substituted indoles are well established, there is a need for yet easier access to 2-substituted indoles.[6-8] Recently, 2-methylindoles have been elaborated into many 2-substituted indole derivatives using an allylic bromination reaction.[10-12] All these methods involve protection of the indole 3-position with an ester, phenylthio or benzoyl group and masking the indole nitrogen as a benzenesulfonamide or benzamide during bromination.[10-12]

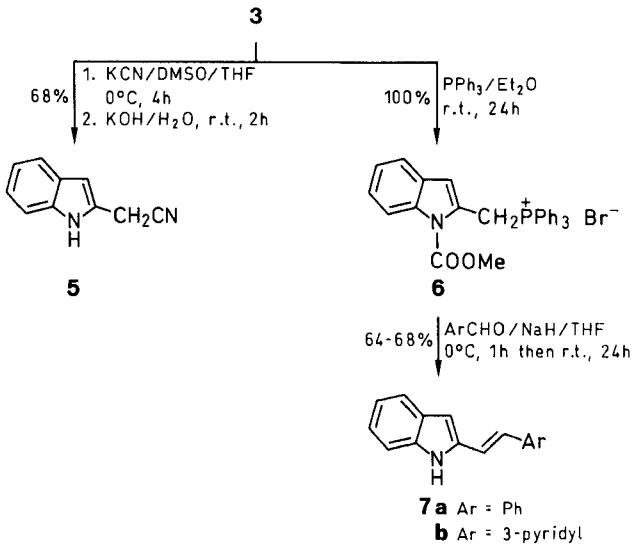
The present study describes a more convenient, improved method over procedures described earlier.[10-12] This method effectively avoids the complications of introducing and removing the protecting groups for the indole 3-position, and proves such protection not to be essential during *N*-bromosuccinimide (NBS) bromination. Reaction of 1.1 equiv of butyllithium with 2-methylindole (**1**), followed by treatment with dimethyl carbonate, gives methyl 2-methyl-1-indolecarboxylate (**2**) in 82% yield. The same reaction using lithium bis(trimethylsilyl)amide (LiHMDS) as the base gives **2** in nearly quantitative yield. Reaction of **2** with one equivalent of NBS in boiling tetrachloromethane in the presence of a catalytic amount of benzoyl peroxide for 1 hour affords the desired 2-bro-



Scheme 1

momethylindole **3** in 95% yield. Compound **3** on treatment with dimethylamine followed by sodium hydroxide hydrolysis gives 2-(dimethylaminomethyl)indole (**4**), another useful intermediate for the synthetic elaboration of indoles,[5-7] in 82% yield (Scheme 1).

Reaction of **3** with potassium cyanide and subsequent hydrolysis affords indole-2-acetonitrile (**5**). Bromomethylindole **3** reacts with triphenylphosphine to give the phosphonium bromide **6** in quantitative yield and this, on treatment with benzaldehyde and pyridine-3-carbaldehyde in the presence of sodium hydride followed by sodium hydroxide hydrolysis, affords the 2-(2-arylvinyl)indoles **7a** and **7b** in 68% and 64% yields, respectively (Scheme 2). The trans geometry of compounds **7a** and **7b** is confirmed by the ^{1}H NMR spectra and physical characteristics.[5]



Scheme 2

When the NBS bromination of **2** is repeated, it sometimes forms a small amount of methyl 3-bromo-2-methyl-1-indolecarboxylate (**8**) and methyl 3-bromo-2-bromomethyl-1-indolecarboxylate (**9**) as byproducts, as shown by the ^{1}H NMR spectra. Close observation of this reaction has shown that **2** reacts with NBS at room temperature, to give **8** in 93% yield. The optimum condition for the formation of **3** as the exclusive product was to set the reaction mixture refluxing, in a preheated oil-bath, immediately after mixing the reagents. This completely avoids the formation of both **8** and **9**. Reaction of **8** with 1 equivalent of NBS in boiling tetrachloromethane in the presence of benzoyl peroxide gives **9** in excellent yield, which can also be used as a potential intermediate for many 2-substituted indoles.

In summary, a short, simple and general method for the preparation of 2-substituted indoles has been developed using a methoxycarbonyl group to protect the nitrogen of 2-methylindole followed by NBS bromination of the methyl group. Work is in progress to utilize this method for the preparation of many indole derivatives to be screened as antitumor and antisickling agents.

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Chemical Ionization (CI) mass spectra were obtained on a Finnegan 4000 spectrometer. ^{1}H NMR spectra were run on a Varian VXR-500S spectrometer. IR spectra were obtained on a Beckman IR-33 spectrophotometer.

Methyl 2-Methyl-1-indolecarboxylate (2):
LiHMDS in THF (1 M, 55 mL, 55 mmol) was added to a solution of 2-methylindole (**1**, 6.55 g, 50 mmol) in THF (150 mL) under argon at −78 °C over 20 min and the mixture was allowed to warm to r.t. over a period of 2 h. It was cooled again to −78 °C and a solution of dimethyl carbonate (4.95 g, 55 mmol) in THF (10 mL) was added over 10 min. The stirring was continued for 2 h at −78 °C and then 6 h at r.t., and the mixture was poured into ice–water (250 mL) containing HCl (5 M, 10 mL). The mixture was extracted with Et_2O (2 × 75 mL) and the combined extracts were washed with brine (2 × 40 mL). The solvents were evaporated from the dried (Na_2SO_4) ether layer and the crude product was purified by passing it through a bed of silica gel (10 g) using 10% $CHCl_3$ in hexane as the eluent to afford **2** as a colorless oil; yield: 9.27 g (98%). An analytical sample was obtained by preparative TLC using hexane as the eluent.

$C_{11}H_{11}NO_2$ calc. C 69.82 H 5.86
(189.2) found 70.12 5.99

CIMS (isobutane): m/z = 190 (MH^+, 100%).

CIMS (neat): ν = 1750 cm^{-1} (CO_2Me).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.60 (s, 3H), 4.04 (s, 3H), 6.34 (s, 1H), 7.19–7.25 (m, 2H), 7.43 (dd, 1H), 8.08 (dd, 1H).

Methyl 2-Bromomethyl-1-indolecarboxylate (3):
Powdered NBS (1.78 g, 10 mmol) and benzoyl peroxide (20 mg) were added to a solution of **2** (1.89 g, 10 mmol) in CCl_4 (100 mL) and the mixture was stirred and heated at 80–85 °C for 1 h. The succinimide formed was filtered off and the solvent was evaporated from the filtrate under reduced pressure. The oily residue was triturated with hexane, yielding a pale yellow crystalline powder; yield: 2.55 g (95%); mp 104–106 °C.

$C_{11}H_{10}BrNO_2$ calc. C 49.28 H 3.76
(268.1) found 49.40 3.57

CIMS (isobutane): m/z = 268 (MH^+, 4.18%), 188 (100%).

IR (KBr): ν = 1740 cm^{-1} (CO_2Me).

^{1}H NMR ($CDCl_3$/TMS): δ = 4.09 (s, 3H), 4.88 (s, 2H), 7.17–7.19 (dt, 1H), 7.26–7.28 (dt, 1H), 7.43–7.45 (dd, 1H), 8.05–8.06 (dd, 1H).

2-(Dimethylaminomethyl)indole (4):
A mixture of **3** (2.68 g, 10 mmol) and 40% aqueous dimethylamine (10 mL) was stirred at r.t. for 2 h. NaOH (1 g) was added, the mixture was heated at 80–85 °C for 1 h, cooled and extracted with Et_2O (3 × 20 mL). The solvent was evaporated from the dried (K_2CO_3) ether extract to give the product as a viscous oil which was crystallized from hexane; yield: 1.43 g (82%); mp 59–61 °C (Lit.[13,14] 60–61 °C).

Indole-2-acetonitrile (5):
2-Bromomethylindole **3** (2.68 g, 10 mmol) was added to a well-stirred suspension of KCN (0.975 g, 15 mmol) in DMSO (25 mL) and THF (10 mL) at 0 °C, and the mixture was stirred for 4 h. KOH solution (40%, 10 mL) was added and the reaction mixture was allowed to warm to r.t. After 2 h, ice–water (200 mL) was added and the mixture was extracted with Et_2O (4 × 30 mL). The combined ether extracts were washed with saturated brine (3 × 50 mL), dried (Na_2SO_4), and the solvents were evaporated. The crude product was purified by flash chromatography on silica gel using 20% $CHCl_3$ in hexane as the eluent; yield: 1.06 g (68%); mp 97–98 °C (Lit.[14] 96–98 °C).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.95 (s, 2H), 6.50 (s, 1H), 7.12–7.15 (dt, 1H), 7.21–7.23 (dt, 1H), 7.35–7.37 (d, 1H), 7.56–7.58 (dd, 1H), 8.15 (br s, 1H, NH).

(1-Methoxycarbonylindol-2-yl)methyl(triphenyl)phosphonium Bromide (6):
Triphenylphosphine (1.44 g, 5.5 mmol) was added to a solution of **3** (1.34 g, 5 mmol) in dry Et_2O (100 mL), and the mixture was stirred for 24 h at r. t. The white crystalline product that formed was filtered and dried at reduced pressure; yield: 2.55 g (100%); mp 129–130°C.

$C_{29}H_{25}BrNO_2P$ (530.4) calc. C 65.67 H 4.75
found 65.89 5.01

IR (KBr): ν = 1730 cm^{-1} (CO_2Me).

^1H NMR (DMSO-d_6/TMS): δ = 3.61 (s, 3H), 6.19 (d, J = 14 Hz, 2H), 7.26–7.76 (m, 20H).

2-(2-Arylvinyl)indoles 7a and 7b; General Procedure:
Sodium hydride (0.24 g, 10 mmol) was added to a well-stirred suspension of **6** (2.06 g, 4 mmol) and benzaldehyde (0.53 g, 5 mmol) or pyridine-3-carbaldehyde (0.54 g, 5 mmol) in dry THF (50 mL) under argon at 0°C, and the stirring was continued at 0°C for 1 h and at r. t. for 24 h. Water (5 mL) was added cautiously and the resultant mixture was stirred and heated at 60°C for 2 h. Solvents were distilled and the residue was poured into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4) and the solvents were evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, 25 g) and eluted with 10% EtOAc in $CHCl_3$ to give products.

2-(Phenylvinyl)indole (**7a**): Yield: 0.68 g (68%); mp 211–212°C (Lit.[5] 210°C).

2-[2-(3-Pyridyl)vinyl]indole (**7b**): Yield: 0.56 g (64%); mp 193–4°C (Lit.[5] 194°C).

CIMS (isobutane): m/z = 221 (MH^+, 100%).

^1H NMR ($CDCl_3$/TMS): δ = 6.67 (s, 1H), 6.87 (d, J = 17 Hz, 1H), 7.09–7.13 (m, 1H), 7.18 (d, J = 17 Hz, 1H), 7.21–7.24 (m, 1H), 7.29–7.32 (dd, 1H), 7.35–7.37 (dd, 1H), 7.59–7.61 (d, 1H), 7.82–7.84 (m, 1H), 8.49–8.51 (m, 2H), 8.71 (d, 1H).

Methyl 3-Bromo-2-methyl-1-indolecarboxylate (8):
Powdered NBS (3.56 g, 20 mmol) was added to a solution of **2** (3.78 g, 20 mmol) in CCl_4 (200 mL) and the mixture was stirred at r. t. for 12 h. The succinimide that formed was filtered off and the filtrate was passed through a bed of silica gel (10 g). The solvents were evaporated and the residue was triturated with hexane to give **8** as a white crystalline powder. An analytical sample was prepared by recrystallization from Et_2O–hexane; yield: 5.0 g (93%); mp 75–76°C.

$C_{11}H_{10}BrNO_2$ (268.1) calc. C 49.28 H 3.76
found 49.61 3.78

CIMS (isobutane): m/z = 268 (MH^+, 100%), 190 (80%).

IR (KBr): ν = 1735 cm^{-1} (CO_2Me).

^1H NMR ($CDCl_3$/TMS): δ = 2.65 (s, 3H), 4.09 (s, 3H), 7.28–7.34 (m, 2H), 7.43 (dd, 1H), 8.08 (dd, 1H).

Methyl 3-Bromo-2-bromomethyl-1-indolecarboxylate (9):
Prepared from **8** (2.67 g, 10 mmol), NBS (1.78 g, 10 mmol) and benzoyl peroxide (20 mg) using the procedure described for **3**. An analytical sample was prepared by recrystallization from $CHCl_3$-hexane; yield: 3.33 g (96%); mp 118–119°C.

$C_{11}H_9Br_2NO_2$ (347.0) calc. C 38.07 H 2.61
found 38.31 2.82

CIMS (isobutane): m/z = 346 (MH^+, 6.12%), 266 (100%).

IR (KBr): ν = 1740 cm^{-1} (CO_2Me).

^1H NMR ($CDCl_3$/TMS): δ = 4.11 (s, 3H), 5.05 (s, 2H), 7.30–7.35 (m, 1H), 7.37–7.44 (m, 1H), 7.50–7.53 (dd, 1H), 8.08–8.11 (dd, 1H).

Financial support by the National Heart, Lung, and Blood Institute, Grant No. HL45977 and the interest of Prof. Michael E. Johnson in this project are gratefully acknowledged.

(1) Kuehne, M.E.; Podhorez, D.E.; Mulamba, T.; Bornmann, W.G. *J. Org. Chem.* **1987**, *52*, 347.
(2) Hashimoto, C.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 4563.
(3) Leon, P.; Garbay-Jaureguiberry, C.; Barsi, M.C.; Le Pecq, J.B.; Roques, B.P. *J. Med. Chem.* **1987**, *30*, 2074.
(4) Modi, S.P.; Zayed, A.-H.; Archer, S. *J. Org. Chem.* **1989**, *54*, 3084.
(5) Eenkhoorn, J.A.; De Silva, O.S.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1970**, 1095.
(6) Sundberg, R.J. In *The Chemistry of Indoles*; Blomquist, A.T., Ed.; Academic Press: New York, 1970.
(7) Brown, R.K. In *Heterocyclic Compounds*; Houlihan, W.J., Ed.; Wiley-Interscience: New York, 1972, Vol. 25.
(8) Macor, J.E.; Newman, M.E.; Ryan, K. *Tetrahedron Lett.* **1989**, *30*, 2509.
(9) Pindur, U. *Heterocyles* **1988**, *27*, 1253, and references cited within.
(10) Nagarathnam, D.; Srinivasan, P.C. *Synthesis* **1982**, 926.
(11) Mohan, B.; Nagarathnam, D.; Vedachalam, M.; Srinivasan, P.C. *Synthesis* **1985**, 188, and references cited therein.
(12) Nagarathnam, D. *Tetrahedron* (submitted).
(13) Yoneda, F.; Miyamae, T.; Nitta, Y. *Chem. Pharm. Bull.* **1967**, *15*, 8.
(14) Schindler, W. *Helv. Chim. Acta*, **1957**, *40*, 2156.