A Benzyne Route to Indoles from *o*- or *m*-Bromoaryl Ketones †

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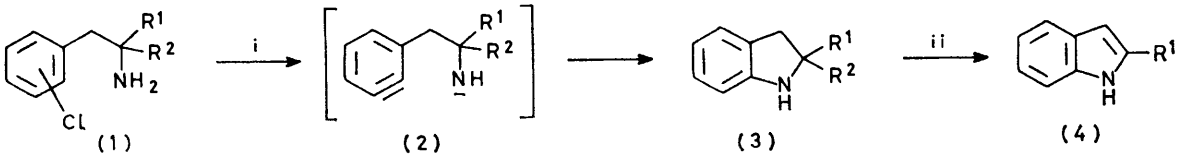
Indoles (11) or (14) are formed directly when 2-amino-1-*o*- (or *m*-)bromoaryl-ethanols (8) or (13) are treated with potassamide in liquid ammonia.

MOST indole syntheses avoid making the bond between the benzene ring and the nitrogen atom in the critical step. One that does use this disconnection is the benzyne route of Huisgen [1] (1a) ⟶ (2a) ⟶ (3a) ⟶ (4a). However, to make the indole (4) from the indoline



(1) (2) (3) (4)

a; $R^1 = R^2 = H$
b; R^1 = Me, R^2 = OH

Reagents: i, $NaNH_2$–NH_3; ii, Pd–C for ($R^1 = R^2 = H$) or spontaneously for (R^1 = Me, R^2 = OH)

(3), an oxidation, which is not always high yielding, has to be performed. This route was used by Julia [2] to prepare 4-, 5-, and 6-methoxyindole. One way of avoiding the oxidation is to use an amine (1b) already raised to a higher oxidation level by having R^2 as a hydroxy-group.[3] (Other formulations, of the mechanism of this sequence, differing in detail, are possible, but need not concern us here.) The final step (3b) ⟶ (4b) is then spontaneous, and indoles are obtained directly on work-up. The amino-alcohol (1b) is not isolated: it is a probable intermediate when the corresponding ketone is treated directly with amide ion in liquid ammonia, and the whole sequence [*o*- or *m*-chlorophenylacetone ⟶ (4b)] is carried out in one pot.

We now report that an alternative placement of the hydroxy-group is also successful. The amino-alcohols (8) are available from the epoxides (6) or from the cyanohydrin silyl ethers (7),[4] and on treatment with potassamide in liquid ammonia give the indoles (11) directly. A 3-hydroxyindoline (10) is probably an intermediate but, as expected, it loses the elements of water even with the mildest work-up. We have used this route to make skatole (11a) (55%), 5-methoxyskatole (11b) (64%), and 3-ethyl-5-methoxyindole (11c) (67%). We were less successful in making indoles unsubstituted in the 3-position: the yields were low, but we did prepare 5-methoxyindole (11d) (11%) and indole itself (11e) (22%) this way. As in earlier routes,[1] the bromine can be *meta* to the side-chain, because the benzyne is selectively formed towards that side-chain. We used this route (12) ⟶ (14) to prepare 6-methoxyskatole (14a) (57%) and 6-methoxyindole (14b) (12%), but the reaction failed when attempting to prepare 4-methoxyskatole from the amino-alcohol (13c).

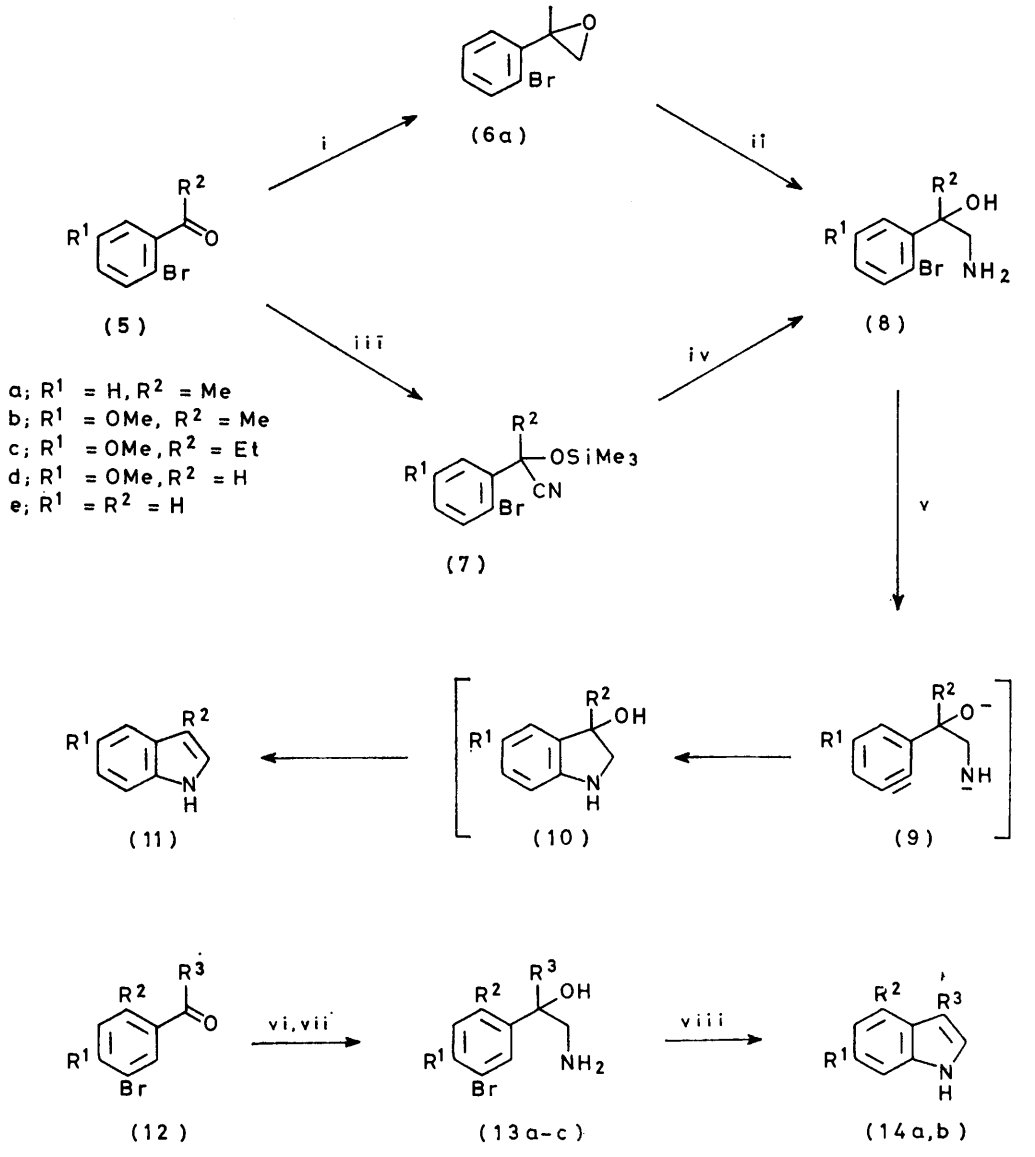
† There are no reprints of this paper.

EXPERIMENTAL

The syntheses of the starting materials (5), (6), (7), (8), (12), and (13) are described in the following paper.[4]

3-Methylindole (11a).—A solution of 1-amino-2-(2-bromophenyl)propan-2-ol (8a) (900 mg, 3.9 mmol) in dry THF (10 ml) was added under nitrogen to a solution of potassium amide (from 0.9 g of potassium) in dry ammonia (35 ml) and kept under reflux for 9.5 h. It was then cooled to −78 °C and ammonium chloride (2.0 g) added. The solvent was allowed to evaporate overnight and the dark brown residue partitioned between ether (50 ml) and hydrochloric acid (2M; 20 ml). The aqueous layer was separated, washed with ether (2 × 25 ml) and the organic extract dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallisation from ether gave 3-methylindole (0.22 g, 55%) as plates, m.p. 95 °C (lit.,[5] m.p. 95 °C), identical (m.p., mixed m.p., i.r., and n.m.r.) with an authentic sample. A closely similar reaction using 1-amino-2-(2-chlorophenyl)propan-2-ol (900 mg, 4.8 mmol) also gave 3-methylindole (262 mg, 42%), identical with an authentic sample.

The following indoles were prepared by a similar procedure. (a) 5-Methoxy-3-methylindole (11b) (64%), plates, m.p. 66 °C (from MeOH) (lit.,[6] m.p. 66 °C), $\nu_{max.}(CHCl_3)$ 3 470m cm^{-1} (NH); τ($CHCl_3$) 2.34br (1 H, disappears with D_2O), 2.90 (1 H, d, *J* 9.0 Hz), 3.00 (1 H, d, *J* 2.5 Hz), 3.18br (1 H), 3.19 (1 H, dd, *J* 2.5 and 9.0 Hz), 6.16 (3 H, s), and 7.72 (3 H, s); *m/e* 161 (100%, M^+), and 146 (66%, $M - CH_3$). (b) 3-Ethyl-5-methoxyindole (11c) (67%), plates, m.p. 27—28 °C (from ether) (lit.,[7] m.p. 27 °C), $\nu_{max.}(CHCl_3)$ 3 490m cm^{-1} (NH); τ($CDCl_3$) 2.30br (1 H, disappears with D_2O), 2.72 (1 H, d, *J* 9.0 Hz), 2.95 (1 H, d, *J* 2.5 Hz), 3.11 (1 H, s), 3.17 (1 H, dd, *J* 2.5 and 9.0 Hz), 6.14 (3 H, s), 7.24 (2 H, q, *J* 7.0 Hz), and 8.68 (3 H, t, *J* 7.0 Hz); *m/e* 175 (61%, M^+) and 160 (100%, $M - CH_3$). (c) 5-Methoxyindole (11d) (11%), needles, m.p. 53—54 °C (from EtOH) (lit.,[8] m.p. 55 °C, $\nu_{max.}(CHCl_3)$ 3 490 m cm^{-1} (NH); τ($CDCl_3$) 2.34br (1 H, disappears with D_2O), 2.90 (1 H, d, *J* 9.0 Hz), 3.00 (1 H, d, *J* 2.5 Hz), 3.18 br (1 H), 3.19 (1 H, dd, *J* 2.5 and 9.00 Hz), 6.16 (3 H, s), and 7.72 (3 H, s); *m/e* 147 (86%, M^+) and 132 (100%, $M^+ - CH_3$). (d) Indole (11e) (22%) from 2-amino-1-(2-bromophenyl)-ethanol (8e) (14%) from 2-amino-1-(2-chlorophenyl)ethanol, identical (mixed m.p., t.l.c., i.r., n.m.r., and mass spectrum) with an authentic sample. (e) 6-Methoxy-3-methylindole



Reagents: i, $Me_2SO{:}CH_2$; ii, NH_3–MeOH; iii, Me_3SiCN; iv, $LiAlH_4$; v, KNH_2–NH_3, vi, Me_3SiCN; vii, $LiAlH_4$; viii, KNH_2–NH_3

(14a) from (13a) (57%), plates, m.p. 127 °C (from EtOH) (lit.,[9] m.p. 125 °C), $\nu_{max.}(CHCl_3)$ 3 490m cm^{-1} (NH); $\tau(CHCl_3)$ 2.15br (1 H, disappears with D_2O), 2.60 (1 H, d, J 9.0 Hz), 3.16—3.40 (3 H, m), 6.19 (3 H, s) and 7.71 (3 H, s); *m/e* 161 (100%, M^+) and 146 (56%, $M^+ - CH_3$). (f) 6-Methoxyindole (14b) (12%), plates, m.p. 91 °C (from ether) (lit.,[10] m.p. 91—92 °C), identical (t.l.c., mixed m.p., i.r., and mass spectrum) with an authentic sample.

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