Nucleophilic Tele-substitution in 2-Chloro-3-formylindoles *via* Ring Opening–Ring Closure

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2-Chloro-3-formylindoles give 5-azido-3-cyanoindoles on reaction with an excess of sodium azide in dimethylsulphoxide, as a result of a ring opening–ring closure with concomitant nucleophilic substitution at the 5-position in the indole ring; the *X*-ray crystal structure of the new 5-azidoindole has been determined.

We have recently described[1] a new ring opening–ring closure reaction of 5-azido-4-formyl-1-methylpyrazoles in which a thermally formed nitrene or ylide intermediate in the presence of excess sodium azide rearranges to the corresponding 1-azidomethyl-4-cyanopyrazoles. Here we report that the reaction of 1-substituted-2-chloro-3-formylindoles with an excess of sodium azide in dimethylsulphoxide in a very fast reaction leads to a related ring opening–ring closure reaction, concomitantly followed by a nucleophilic tele-substitution at the indole 5-position.

Reaction of 2-chloro-3-formyl-1-methylindole (**2a**)[2] [(5 mmol) with an excess of sodium azide in dimethylsulphoxide (DMSO) (15 ml), reaction temp. 97—105 °C, reaction time 5 min] resulted in the evolution of one equivalent of N_2 whereupon the reaction mixture was immediately quenched with water. The reaction product (**3a**) separated as pale yellow crystals, crude yield 51%. Recrystallization from petroleum ether afforded nearly colourless crystals of (**3a**),† m.p. 133.5—134.5 °C (41%). The i.r. spectrum (KBr) showed the presence of a CN group (ν 2220 cm^{-1}) as well as a N_3 group (ν 2120 cm^{-1}). The ^1H n.m.r. spectrum ($CDCl_3$) showed one *N*-methyl δ 3.90 (s) one aryl H at 7.52 (s), and three aryl H 6.98 (H-6, dd, $J_{6,7}$ 8.9, $J_{4,6}$ 2.0 Hz); 7.29 (H-4, dd, $J_{4,6}$ 2.0, $J_{4,7}$ 0.6 Hz) and 7.33 (H-7, dd, $J_{6,7}$ 8.9, $J_{4,7}$ 0.6 Hz) indicating that substitution had taken place in the benzene ring at the 5-position. An *X*-ray structure determination‡ confirmed the structure shown in Figure 1.

The same reaction of 2-chloro-3-formyl-1-phenylindole (**2b**)[7] with sodium azide in DMSO (5 mmol, 15 ml DMSO, reaction temperature 92—98 °C, reaction time 5 min) resulted in formation of the corresponding 5-azido-3-cyano-1-phenylindole (**3b**) in 34% yield (crude 54%) [m.p. 170—171 °C (ethanol)]. When 2-chloro-3-formyl-1-methylindole (**2a**) was treated with sodium azide in DMSO at 20 °C (12 h) 2-azido-3-formyl-1-methylindole (**4a**) [m.p. 122—123 °C (methylene chloride)] was isolated in almost quantitative yield. Heating of (**4a**) in DMSO with an excess of sodium azide also gave compound (**3a**) and it can therefore be concluded that the 2-azido-3-formylindole is an intermediate in the reaction. At

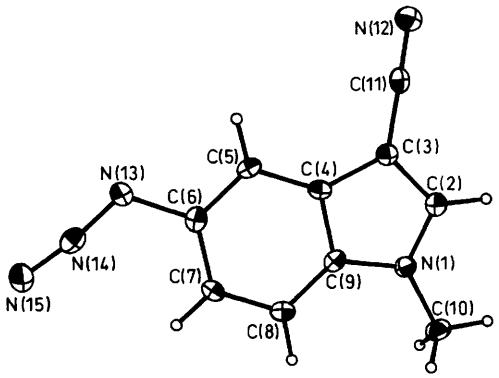
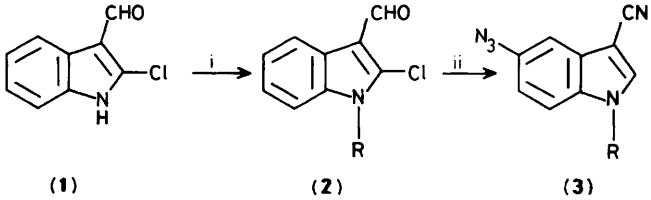


Figure 1. ORTEP drawing of (**3a**) (50% probability ellipsoids). Selected bond lengths (Å) and angles (°): N(1)–C(2) 1.357(2), N(1)–C(9) 1.383(2), N(1)–C(10) 1.460(2), C(2)–C(3) 1.376(2), C(3)–C(4) 1.439(2), C(3)–C(11) 1.422(3), C(4)–C(5) 1.394(2), C(4)–C(9) 1.412(2), C(5)–C(6) 1.379(2), C(6)–C(7) 1.408(2), C(6)–N(13) 1.433(2), C(7)–C(8) 1.381(2), C(8)–C(9) 1.391(2), C(11)–N(12) 1.149(2), N(13)–N(14) 1.238(2), N(14)–N(15) 1.142(2); C(2)–N(1)–C(9) 109.1(1), C(2)–N(1)–C(10) 126.3(2), C(9)–N(1)–C(10) 124.4(1), N(1)–C(2)–C(3) 109.6(1), C(2)–C(3)–C(4) 107.5(1), C(2)–C(3)–C(11) 125.7(2), C(4)–C(3)–C(11) 126.7(2), C(3)–C(4)–C(5) 134.8(2), C(3)–C(4)–C(9) 105.6(1), C(5)–C(4)–C(9) 119.6(2), C(4)–C(5)–C(6) 118.0(2), C(5)–C(6)–C(7) 122.1(2), C(5)–C(6)–N(13) 115.9(2), C(7)–C(6)–N(13) 122.1(2), C(6)–C(7)–C(8) 120.6(2), C(7)–C(8)–C(9) 117.5(2), N(1)–C(9)–C(4) 108.2(1), N(1)–C(9)–C(8) 129.5(2), C(4)–C(9)–C(8) 122.2(2), C(3)–C(11)–N(12) 178.8(2), C(6)–N(13)–N(14) 116.8(2), N(13)–N(14)–N(15) 172.5(2).

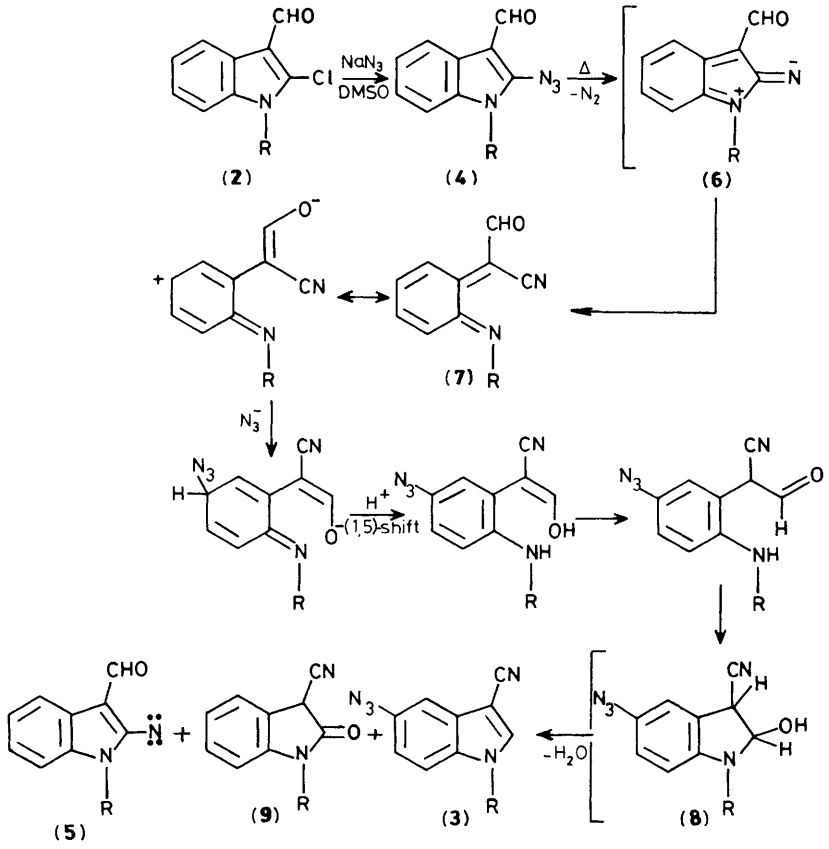


a; R = Me
b; R = Ph
c; R = $CH_2(CH_2)_2CH{=}CH_2$
d; R = CH_2Ph

Scheme 1. *Reagents and conditions:* i, see ref. 2 and 7; ii, sodium azide (3 equiv.) and dimethyl sulphoxide as solvent (15 ml DMSO for 5 mmol (**2**), reaction time less than 5 min, the reaction is quenched with water after the evolution of one equivalent of N_2; (**3a**), reaction temp. 97—105 °C, m.p. 133.5—134.5 °C (petroleum ether); (**3b**), reaction temp. 92—108 °C, m.p. 170—171 °C (ethanol); (**3c**), reaction temp. 80—93 °C, oil; (**3d**), reaction temp. 88—93 °C, m.p. 111—112 °C (ethanol).

† All new compounds gave satisfactory elementary analysis (±0.4% in C, H, and N), compounds (**3**) were found to be photochemically unstable in accordance with ref. 6.

‡ *Crystal data* for (**3a**): $C_{10}H_7N_5$, M = 197.20, monoclinic, space group $P2_1/c$, a = 13.369(4), b = 9.255(1), c = 7.458(4) Å, β = 93.38(3)°, U = 921.1(9) Å^3, Z = 4, D_c = 1.42 g cm^{-3}, R = 0.037, R_w = 0.042 for 1342 observed reflections, $1^0 < \theta < 28^0$, $I > 2\sigma(I)$. Crystal size 0.08 × 0.20 × 0.50 mm^3, CAD4 diffractometer, Mo-K_α radiation, λ = 0.71073 Å, T = 105 K. The structure was solved by Patterson search using PATSEE,[3] with the ring system from ref. 4 as search fragment. Remaining atoms (non-hydrogen and hydrogen) found in ΔF map. Full-matrix least-squares refinement. Where all non-hydrogen atoms had anisotropic temperature factors, and hydrogen atoms had isotropic temperature factors was performed using the SDP-system.[5] Maximum and minimum Δρ in final map 0.25 e/Å^3 and −0.24 e/Å^3. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



ca. 95 °C the reaction is very fast and exothermic and one equivalent of nitrogen is evolved in five minutes or less. As shown by Abramovitch and Cue[8] such relatively mild reaction conditions indicate a concerted process, probably involving nitrogen evolution followed by ring opening *via* an ylide intermediate (**6**) without formation of a nitrene intermediate (**5**) (Scheme 1). DMSO seems to be the solvent of choice for this reaction although the reaction also takes place in, for example, dimethylformamide (DMF), however in this case the rearranged product (**3**) is accompanied by many by-products. This effect of DMSO may be due to stabilization of an intermediate such as (**6**) by complexation with the solvent. However in all cases the reaction also gives by-products as the modest yields of the main products (**3**) clearly shows. For example for substrate (**2b**) a by-product was isolated after column chromatography (chloroform, silica) and characterized as 3-cyano-1-phenyl-2(3*H*)-indolone (**9b**) [yield 25%, m.p. 138—139.5 °C (ethanol)], i.r. 1736 (CO) and 2228 cm^{-1} (CN), mass spectroscopy: 234 (M^+, 100), 205 (M^+-29, 95%). Compound (**9b**) may be formed by oxidation of intermediate (**8**) by DMSO, in fact the use of less sodium azide and a longer reaction time seems to give improved yield of the indolone product.

Direct nucleophilic substitution in the indole arene ring is very rare and only possible using indole chromium tricarbonyl complexes.[9] However the surprising result of the formation of the 5-azidoindole products (**3**) reported may in fact be due to a nucleophilic reaction taking place on a ring opened *o*-quinoid species and not in the indole itself as suggested in Scheme 2. Theoretical considerations based on frontier orbital theory and semi-empirical AM1 calculations[10] support the suggested mechanism in that nucleophilic attack should be easier on the *o*-quinoid structure (**7**) than on indole (**4**), and furthermore that attack should occur preferentially at the 5-position in compound (**7**).

A Danish Natural Science Research Council postdoctoral grant (to K. P., on leave from The Silesian School of Medicine, Sosnowiec, Poland) is gratefully acknowledged, as well as a helpful suggestion concerning the reaction mechanism from Prof. R. A. Abramowitch.

Received, 27th June 1988; Com. 8/02554A

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