Reductive Cyclization of 1-(2-Nitroaryl)isoquinoline Derivatives

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Isoquinoline derivatives **3b** and **3c** were prepared and their triethyl phosphite mediated reductive cyclization reactions investigated. Only the indazolo[3,2-*a*]isoquinolines **4b** and **4c** were formed.

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The triethyl phosphite mediated reductive cyclization [1-3] of nitroaryl compounds is an established method for preparing nitrogen containing heterocycles and we have previously reported [4] that compound **3a** yielded only indazolo[3,2-*a*]isoquinoline **4a** in this reaction. Compound **2a** undergoes a similar cyclization giving the corresponding dihydro derivative of compound **4a** from which compound **4a** has also been obtained [5].

We were interested to discover whether compounds **3b** and **3c** would also give the corresponding indazolo-[3,2-*a*]isoquinolines **4b** and **4c** even though steric interactions between the 1-aryl group and either the C-8 hydrogen atom of compound **4b** or the C-8 methyl group of compound **4c** might preclude this mode of cyclization and other products might therefore be formed.

Cyclization of amides **1b** and **1c** gave the corresponding 3,4-dihydroisoquinoline derivatives **2b** and **2c**. The four protons associated with the isoquinoline ring C-3 and C-4 positions in compound **2c** showed non-equivalence in its proton-nmr spectrum as a consequence of the restricted rotation of the 1-aryl substituent. Treatment of compounds **2b** and **2c** with *N*-bromosuccinimde (NBS) gave isoquinolines **3b** and **3c** respectively. Reductive cyclization of compounds **3b** and **3c** was achieved by heating with triethyl phosphite and the proton-nmr spectra of the reaction products indicated that cyclization had occurred yielding only the indazolo[3,2-*a*]isoquinolines **4b** and **4c**. No other products could be isolated from these reactions after chromatography indicating a strong preference for nitrogen-nitrogen bond formation.

EXPERIMENTAL

Infra-red spectra were recorded as potassium bromide discs. Proton-nmr spectra were determined in deuteriochloroform solution at either 90 or 300 MHz using tetramethylsilane as an internal standard.

N-(2-Methyl-6-nitrobenzoyl)-2-phenylethylamine **1b**.

To a solution of 2-methyl-6-nitrobenzoyl chloride [prepared by heating (2 hours) 2-methyl-6-nitrobenzoic acid (4.81 g) and thionyl chloride (9.7 ml) in boiling toluene (30 ml)] and triethylamine (2.73 g) in dichloromethane (20 ml) was added 2-phenylethylamine (3.30 g) dropwise. The exothermic reaction caused the mixture to boil and after 1 hour the mixture solidified. Dichloromethane (40 ml) was then added, the solution was stirred at room temperature for 1 hour, poured into water and the organic layer separated, washed with water and dried (magnesium sulfate). The solvent was evaporated giving compound **1b** as white needles, 5.3 g (70%), mp 144-145° (from ethanol); ir: ν 3400, 1640, 1520 and 1340 cm^{-1}; ^1H nmr: δ 7.95 (1H, dd, J = 7 and 2 Hz), 7.49 (2H, m), 7.49 (5H, s), 5.79 (1H, broad s), 3.75 (2H, t, J = 6 Hz), 2.99 (2H, t, J = 6 Hz) and 2.35 (3H, s) ppm.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.7; N, 9.9. Found: C, 67.8; H, 5.65; N, 9.85.

N-(2-Methyl-6-nitrobenzoyl)-2-(2,5-dimethylphenyl)ethylamine **1c**.

Compound **1c** (73%) was prepared as colorless needles, mp 165-166° (from ethanol) from 2-(2,5-dimethylphenyl)ethylamine [obtained by lithium aluminium hydride reduction of 2-(2,5-dimethylphenyl)nitroethene] in a similar manner to that described above for compound **1b**. Compound **1c** had; ir: ν 3250, 2900, 1640, 1560, 1530, 1460, 1350, 1290 and 800 cm^{-1}; ^1H nmr: δ 7.95 (1H, dd, J = 8 and 2 Hz), 7.50 (2H, m), 7.04 (3H, m), 5.85 (1H, broad s), 3.69 (2H, t, J = 8 Hz), 2.92 (2H, t, J = 8 Hz), 2.41 (3H, s), 2.34 (3H, s) and 2.33 (3H, s) ppm.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.45; N, 8.9. Found: C, 69.2; H, 6.25; N, 9.05.

1-(2-Methyl-6-nitrophenyl)-3,4-dihydroisoquinoline **2b**.

To a mixture of compound **1b** (2.3 g) and phosphorus pentoxide (3.44 g) in xylene (50 ml) was added phosphorus oxychloride (2.3 ml). The mixture was heated (3 hours) at 130-140°, allowed to cool to room temperature and poured into iced-water. The organic layer was separated and the aqueous layer was basified by the addition of 30% sodium hydroxide solution. The basic layer was extracted twice with ether and the combined organic extracts were washed with water, dried (magnesium sulfate) and evaporated yielding compound **2b** as a dark oil, 2.0 g (97%); ir: ν 2920, 1525, 1360 and 1065 cm^{-1}; ^1H nmr: δ 7.91 (1H, d, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 7.45 (1H, t, J = 8 Hz), 7.37 (1H, t, J = 8 Hz), 7.28 (1H, d, J = 8 Hz), 7.08 (1H, t, J = 8 Hz), 6.75 (1H, d, J = 8 Hz), 3.85-3.75 (2H, m), 2.95-2.70 (2H, m) and 2.11 (3H, s) ppm. Compound **2b** gave a perchlorate as colorless plates, mp 188-189° (from ethanol).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_6$: C, 52.4; H, 4.1; N, 7.6. Found: C, 52.45; H, 4.0; N, 7.6.

1-(2-Methyl-6-nitrophenyl)-3,4-dihydro-5,8-dimethylisoquinoline **2c**.

In a similar manner to that described above, compound **1c** yielded a waxy solid which was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 4:6 changing to 2:8) giving compound **2c** (30%) as buff colored prisms, mp 158-159° (from ethanol); ir: ν 2900, 1605, 1580, 1530, 1360, 1285, 1165, 820 and 800 cm^{-1}; ^1H nmr: δ 7.81 (1H, t, J = 4 Hz), 7.40 (2H, m), 7.15 (1H, d, J = 6 Hz), 6.95 (1H, d, J = 6 Hz), 4.10-3.80 (1H, dt, J = 11 and 6 Hz), 3.60-3.30 (1H, dt, J = 14 and 6 Hz), 3.00-2.55 (2H, m), 2.30 (3H, s), 2.00 (3H, s) and 1.80 (3H, s) ppm.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.2; N, 9.5. Found: C, 73.6; H, 6.05; N, 9.45.

1-(2-Methyl-6-nitrophenyl)isoquinoline **3b**.

Compound **2b** (2.18 g), NBS (0.39 g) and a few crystals of dibenzoyl peroxide were heated at reflux (4.5 hours) in 1,2-dichloroethane (50 ml). The mixture was allowed to cool to room temperature, washed with dilute sodium hydroxide solution and then with water, dried (magnesium sulfate) and evaporated giving a dark, viscous oil (1.55 g). This oil was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 9:1) giving compound **3b** as a pale yellow oil, 0.30 g (15%) which was used directly without further characterization; ^1H nmr: δ 8.70 (1H, d, J 8 Hz), 8.00-7.30 (8H, m) and 2.00 (3H, s) ppm.

1-(2-Methyl-6-nitrophenyl)-5,8-dimethylisoquinoline **3c**.

Compound **2c** (0.70 g), NBS (0.47 g) and a few crystals of dibenzoyl peroxide were heated (4 hours) at reflux in carbon tetrachloride (20 ml). The mixture was allowed to cool to room temperature, washed with dilute sodium hydroxide solution and then with water, dried (magnesium sulfate) and evaporated giving a dark, viscous oil (0.58 g). This oil was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 1:1) giving compound **3c** as a yellow oil, 0.25 g (36%) which was used directly without further characterization; ^1H nmr: δ 8.50 (1H, d, J = 6 Hz), 8.00 (1H, m), 7.80 (1H, d, J = 6 Hz), 7.50-7.30 (3H, m), 7.25 (1H, d, J = 6 Hz), 2.65 (3H, s), 2.00 (3H, s) and 1.85 (3H, s) ppm.

5-Methylindazolo[3,2-*a*]isoquinoline **4b**.

Compound **3b** (0.30 g) and triethyl phosphite (5 ml) were heated at reflux (4 hours) under a nitrogen atmosphere. The mixture was allowed to cool to room temperature, evaporated and the residual brown oil was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 3:1) giving compound **4b** as a yellow oil, 0.1 g (36%); ^1H nmr: δ 9.00 (1H, d, J = 7 Hz), 8.54 (1H, d, J = 7 Hz), 7.44-7.90 (4H, m), 7.35 (1H, d, J = 9 Hz), 7.30 (1H, d, J = 9 Hz), 7.05 (1H, d, J = 7 Hz) and 3.32 (3H, s) ppm. Compound **4b** gave a perchlorate as colorless needles, mp >250° (decomp.) (from ethanol).

Anal. Calcd. for $C_{16}H_{13}ClN_2O_4$: N, 8.4. Found: N, 8.4.

5,6,9-Trimethylindazolo[3,2-*a*]isoquinoline **4c**.

Compound **3c** (0.25 g) and triethyl phosphite (5 ml) were heated at reflux (2 hours) under an atmosphere of nitrogen. The mixture was allowed to cool to room temperature, evaporated and the residue was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 3:1) giving compound **4c** as a pale yellow oil, 0.2 g (89%); ^1H nmr: δ 8.45 (1H, d, J = 8 Hz), 7.45 (1H, dd, J = 8 and 2 Hz), 7.40 (4H, m), 7.00 (1H, dd, J = 8 and 2 Hz), 2.53 (6H, s) and 2.52 (3H, s). Compound **4c** gave a methiodide, mp 164-166° (from ethanol).

Anal. Calcd. for $C_{19}H_{19}IN_2.H_2O$: C, 54.3; H, 5.0; N, 6.7. Found. C, 54.5; H, 4.7; N, 6.55.

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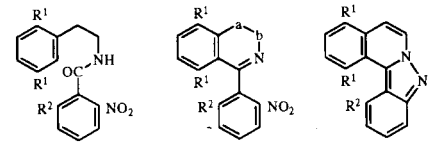

1 **2**, a-b = CH_2CH_2; **3**, a-b = CHCH **4**

Informulae **1-4**: **a**, $R^1 = R^2 = H$; **b**, $R^1 = H$, $R^2 = Me$; **c**, $R^1 = R^2 = Me$