Cyclodehydration of *N*-(2-Nitroaryl)-1,2,3,4-tetrahydroisoquinoline Derivatives

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Compounds **1a-1g** gave the corresponding *N*-oxide derivatives **3a-3g** when heated with acetic or propionic acid.

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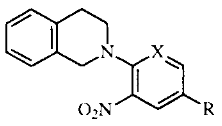
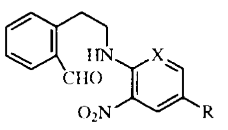
We have previously shown that treatment of 1,2,3,4-tetrahydroisoquinoline derivatives **1** with *N*-bromosuccinimide (NBS) followed by basic work-up afforded excellent yields of the aminoaldehyde derivatives **2** [1]. Prior to this work, we observed that heating compound **1a** in dimethyl sulfoxide (DMSO) in the presence of air gave the aminoaldehyde **2a** in low yield [2]. We subsequently sought a method to improve the yield of compound **2a** and the NBS method described above was therefore developed. We also investigated the effect of replacing DMSO with other solvents on the yield of the aldehyde **2a** and found that in boiling acetic acid compound **1a** yielded the *N*-oxide derivative **3a** (86% yield) after basification. Compounds **3b-3g** were similarly cyclised (74-87% yield) in either boiling acetic or propionic acid. The rate of cyclisation in some cases was slow in acetic acid and propionic acid was therefore used to increase the reaction rate. The products **3** had spectral data consistent with the proposed structure and showed two characteristic low field signals at 9.42-9.50 ppm and 7.71-8.93 ppm in their proton nmr spectra which were attributed to the protons located at the 1- and 11-positions respectively. Analytical data on the products indicated that in several cases hydrates or partial hydrates were formed.

The benzimidazo[2,1-*a*]isoquinoline ring-system has scarcely been reported [2-5] and this method provides an expedient synthesis of *N*-oxide derivatives **3** (X = CH) of this ring-system. Related cyclodehydration reactions (the *t*-amino effect) of nitroaryl compound are known [6] for which a mechanism has been proposed.



1



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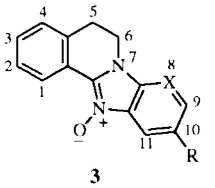

3

	R	X
a	Me	CH
b	CF_3	CH
c	F	CH
d	CN	CH
e	COPh	CH
f	NO_2	CH
g	H	N

EXPERIMENTAL

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

Compounds **3**. General Method.

Compounds **1** in either acetic or propionic acid were heated at reflux, allowed to cool to room temperature and poured into water. The mixture was basified by addition of dilute sodium hydroxide solution and the products **3** (with the exception of product **3c**) collected by filtration and dried. Compound **3c** was isolated by extraction into dichloromethane. The organic extracts were washed with water, dried (magnesium sulfate) and evaporated to give the product.

10-Methyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-Oxide **3a**.

Compound **1a** (1.0 g) in acetic acid (50 ml) for 6 hours gave compound **3a**, 0.80 g (86%) as fawn needles, mp 241-243° (from ethanol). Compound **3a** had; ir: ν 3600-3100 (broad), 1500-1620, 1450, 1440, 1380, 1345, 1300, 1280, 1270, 1210, 1200, 1190, 820, and 765 cm^{-1}; ^1H nmr: δ 9.50 (1H, m, ArH), 7.80 (1H, s, ArH), 7.52-7.19 (5H, m, ArH), 4.28 (2H, t, J = 6 Hz, $-CH_2CH_2-$), 3.27 (2H, t, J = 6 Hz, $-CH_2CH_2-$) and 2.49 (3H, s, -Me) ppm.

Anal. Calcd. for $C_{16}H_{14}N_2O{\bullet}0.25H_2O$: C, 75.4; H, 5.7; N, 11.0. Found: C, 75.7; H, 5.55; N, 10.95.

10-Trifluoromethyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-Oxide **3b**.

Compound **1b** (0.5 g) in propionic acid (50 ml) for 10 hours gave compound **3b**, 0.35 g (75%) as green needles, mp 247-250° dec (from ethanol). Compound **3c** had; ir: ν 1450, 1350, 1325, 1275, 1250, 1170, 1105, 880, 815 and 765 cm^{-1}; ^1H nmr: δ 9.42 (1H, m, ArH), 8.27 (1H, s, ArH), 7.56-7.30 (5H, m, ArH), 4.31 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.26 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{16}H_{11}F_3N_2O$: C, 63.1; H, 3.65; N, 9.2. Found: C, 63.25; H, 3.5; N, 9.25.

10-Fluoro-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **3c**.

Compound **1c** (0.25 g) in propionic acid (20 ml) for 8 hours gave compound **3c**, 0.18 g (78%) as cream needles, mp 237-238° (from dichloromethane). Compound **3c** had; ir: ν 3600-3100, 1490, 1450, 1300, 1270, 1220, 1205, 1170, 770 and 755 cm^{-1}; ^1H nmr: δ 9.50 (1H, m, ArH), 7.71 (1H, dd, J = 3 and 1 Hz, ArH), 7.55-7.11 (5H, m, ArH), 4.33 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.33 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{15}H_{11}FN_2O{\bullet}2.5H_2O$: C, 60.2; H, 5.3; N, 9.4. Found: C, 60.5; H, 4.9; N, 9.35.

10-Cyano-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **3d**.

Compound **1d** (0.5 g) in propionic acid (50 ml) for 10 hours gave compound **3d**, 0.39 g (85%) as green needles, mp 264-265° dec (from ethanol). Compound **3a** had; ir: ν 2200, 1500, 1450, 1350, 1275, 1190, 815 and 755 cm^{-1}; ^1H nmr: δ 9.43 (1H, m, ArH), 8.29 (1H, s, ArH), 7.77-7.80 (5H, m, ArH), 4.42 (2H, t, J = 6 Hz, $-CH_2CH_2-$) and 3.32 (2H, t, J = 6 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.2; N, 16.1. Found: C, 73.6; H, 4.2; N, 15.9.

10-Benzoyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-Oxide **3e**.

Compound **1e** (0.5 g) in propionic acid (50 ml) for 9 hours gave compound **3e**, 0.33 g (78%) as green needles, mp 276-277° dec (from ethanol). Compound **3e** had; ir: ν 1655, 1610, 1450, 1380, 1305, 1270, 1220, 1195, 770, 750 and 695 cm^{-1}; ^1H nmr: δ 9.43 (1H, m, ArH), 8.32 (1H, s, ArH), 8.01 (1H, dd, J = 10 and 2 Hz, ArH), 7.82-7.34 (9H, m, ArH), 4.34 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.28 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7; N, 8.2. Found: C, 77.9; H, 4.75; N, 8.2.

10-Nitro-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-Oxide **3f**.

Compound **1f** (0.25 g) in propionic acid (20 ml) for 8 hours gave compound **3f**, 0.17 g (74%) as pale green needles, mp 273-274° dec (from acetone). Compound **3f** had; ir: ν 1520, 1500, 1450, 1375, 1335, 1275, 1265, 1190, 745, 730 and 690 cm^{-1}; ^1H nmr: δ 9.48 (1H, m, ArH), 8.93 (1H, d, J = 2 Hz, ArH), 8.34 (1H, dd, J = 10 and 2 Hz, ArH), 7.58-7.31 (4H, m, ArH), 4.43 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.36 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.9; N, 14.9. Found: C, 64.25; H, 3.9; N, 14.8.

5,6-Dihydropyrido[2',3':5,4]imidazo[2,1-*a*]isoquinoline 12-Oxide **3g**.

Compound **1g** (0.75 g) in propionic acid (30 ml) for 7 hours gave compound **3g**, 0.60 g (87%) as green needles, mp 236-239° dec (from ethanol). Compound **3g** had; ν 1605, 1580, 1485, 1450, 1430, 1310, 1280, 1190, 1050, 795 and 760 cm^{-1}; ^1H nmr δ 9.45 (1H, m, ArH), 8.50 (1H, dd, J = 8 and 2 Hz, ArH), 8.31 (1H, dd, J = 10 and 2 Hz, ArH), 7.58-7.20 (4H, m, ArH), 4.57 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.32 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O{\bullet}2H_2O$: C, 61.5; H, 5.5; N, 15.5. Found: C, 61.6; H, 5.4; N, 15.25.

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REFERENCES AND NOTES

[1] K. A. Hedley and S. P. Stanforth, *Tetrahedron*, **48**, 743 (1992).

[2] A. P. Shawcross and S. P. Stanforth, *J. Heterocyclic Chem.*, **27**, 367 (1990).

[3] R. Barik, K. Bhattacharyya, P. K. Das and M. V. George, *J. Org. Chem.*, **51**, 3420 (1986).

[4] T. Kametani, *Japan Kokai* 77 12,197; *Chem. Abstr.*, **87**, P68354v (1977).

[5] T. Kametani, *Japan Kokai* 77 91,894; *Chem. Abstr.*, **88**, P74390r (1978).

[6] O. Meth-Cohn and H. Suschitzky, *Adv. Heterocyclic Chem.*, **14**, 211 (1972).