Dehydrogenation of tetrahydrospiro[3*H*-2-benzazepines] under mild conditions as a new route to dihydro derivatives

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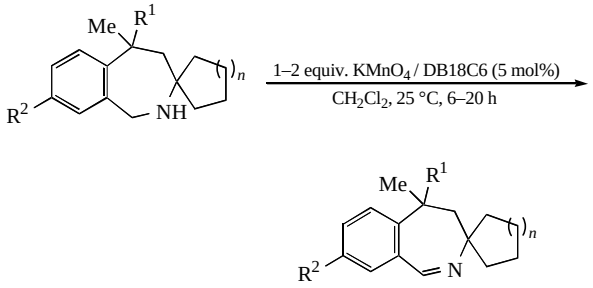
The oxidation of 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1′-cycloalkanes] by $KMnO_4$ under phase-transfer conditions gives the corresponding substituted cyclic imines in high yields.

Although the methods for imine synthesis are well documented,[1] the preparation of cyclic imines,[2–5] which are important intermediates in alkaloid synthesis, was developed insufficiently. Only three examples of 4,5-dihydro-3*H*-2-benzazepine synthesis were reported.[6] On the other hand, the synthesis of such cyclic Schiff's bases is very important because they are useful precursors for the synthesis of homoberberine alkaloids[7–9] and analogues of alkaloids from the 1,2,3,4-tetrahydroisoquinoline series.

We found that the oxidation of substituted 2-benzazepines[10] by the H_2O_2–Na_2WO_4 system resulted in the corresponding cyclic nitrones in good yields.[11,12] We also found that the interaction of spiro[3*H*-2-benzazepine-3,1′-cycloalkanes] with $KMnO_4$ under phase-transfer conditions gave the corresponding imines in excellent yields.



1–**5**

	R^1	R^2	*n*	Yield (%)
1	H	H	1	94
2	H	H	2	95
3	H	H	3	92
4	Me	H	2	90
5	H	NO_2	2	92

Scheme 1

The oxidation was carried out with 1–2 equiv. of $KMnO_4$ in dichloromethane at room temperature in the presence of 5 mol% dibenzo-18-crown-6 (DB18C6).† The removal of the solvent after the separation of MnO_2 and the crown ether gave pure aldimines **1**–**5** in 90–95% yields (Scheme 1). The 4,5-dihydrospiro-3*H*-2-benzazepines **1**–**4** are colourless viscous liquids (compound **5** is a yellow solid) relatively stable on standing.

An attempt to oxidise 1,2,4,5-tetrahydro-1,5-dimethylspiro-[3*H*-2-benzazepine-3,1′-cyclohexane] containing an additional methyl group at C-1 under the same reaction conditions was unsuccessful. The reaction mixture was stirred for 50 h at 40 °C and ~20 equiv. of $KMnO_4$ was added (TLC monitoring). After the standard work-up an inseparable mixture of products was obtained. This difficulty may be explained by the presence of a methyl group at C-1 which, in the product, is allylic and therefore is susceptible to further oxidation.

The structures of the synthesised aldimines **1**–**5** were confirmed by IR and NMR spectroscopy.‡ The characteristic C=N absorption at 1630–1640 cm^{-1} was observed in the IR spectra. The characteristic singlet due to H-1 of the aldimine group, typically present in compounds of this class, was observed in ^1H NMR spectra of cyclic imines **1**–**5** at 8.41–8.31 ppm.

Thus, a simple and efficient method for the synthesis of 3-substituted 4,5-dihydro-3*H*-2-benzazepines has been demonstrated.

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† The synthesis of 4,5-dihydrospiro[3*H*-2-benzazepine-3,1′-cyclohexane] **2** is a typical example of the reaction. $KMnO_4$ (6.90 g, 43.70 mmol) was added in three portions to a solution of 1,2,4,5-tetrahydro-5-methylspiro[3*H*-2-benzazepine-3,1′-cyclohexane] (10.00 g, 43.70 mmol) and dibenzo-18-crown-6 (0.78 g, 2.18 mmol) in CH_2Cl_2 (100 ml) with stirring for 30 min. The reaction mixture was stirred at room temperature for 6 h. Next, an additional $KMnO_4$ amount (6.90 g) was added in the same manner, and the reaction mixture was stirred for 12 h. The residue of MnO_2 was filtered off and washed with 500 ml of dichloromethane. The combined filtrate was concentrated *in vacuo* and dissolved in 20 ml of diethyl ether–hexane (1:1). The crown ether precipitate was filtered off and washed with hexane (2×10 ml). The evaporation of the solvent *in vacuo* yielded pure **2** (9.41 g, 41.50 mmol) as a pale yellow oil.

‡ All new compounds gave satisfactory analytical and spectral data.

For **1**: ^1H NMR (200 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 7.40–7.20 (m, 4H), 3.07 (m, 1H, *J* 7.0, 9.8 and 4.0 Hz), 2.09 (dd, 1H, *J* 14.0 and 4.0 Hz), 1.97 (dd, 1H, *J* 14.0 and 9.8 Hz), 1.90–1.30 (m, 8H), 1.35 (d, 3H, *J* 7.0 Hz). MS, *m*/*z* (rel. intensity): 213 (M^+, 40), 198 (31), 184 (22), 170 (30), 168 (70), 131 (100), 117 (19), 115 (20), 98 (9), 91 (41), 77 (34). IR (film, ν/cm^{-1}): 1635 (C=N).

For **2**: ^1H NMR (200 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 7.35–7.20 (m, 4H), 3.12 (m, 1H, *J* 6.7, 11.1 and 3.7 Hz), 2.07 (dd, 1H, *J* 14.4 and 3.7 Hz), 1.73 (dd, 1H, *J* 14.4 and 11.1 Hz), 1.80–1.30 (m, 10H), 1.34 (d, 3H, *J* 6.7 Hz). MS, *m*/*z* (rel. intensity): 227 (M^+, 20), 212 (13), 198 (24), 186 (36), 184 (100), 131 (50), 117 (12), 115 (9), 98 (17), 91 (56), 77 (22). IR (film, ν/cm^{-1}): 1633 (C=N).

For **3**: ^1H NMR (200 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 7.45–7.20 (m, 4H), 3.07 (m, 1H, *J* 7.0, 10.7 and 3.1 Hz), 2.04 (dd, 1H, *J* 14.3 and 3.1 Hz), 1.76 (dd, 1H, *J* 14.3 and 10.7 Hz), 2.00–1.20 (m, 12H), 1.36 (d, 3H, *J* 7.0 Hz). MS, *m*/*z* (rel. intensity): 241 (M^+, 31), 226 (19), 212 (23), 198 (55), 184 (18), 172 (47), 131 (100), 117 (22), 115 (46), 103 (23), 91 (47), 77 (24). IR (film, ν/cm^{-1}): 1636 (C=N).

For **4**: ^1H NMR (200 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 7.45–7.15 (m, 4H), 2.08 (s, 2H), 1.37 (s, 6H), 1.80–1.15 (m, 10H). MS, *m*/*z* (rel. intensity): 241 (M^+, 70), 226 (36), 212 (20), 198 (30), 186 (36), 145 (100), 129 (54), 117 (20), 115 (38), 105 (2), 102 (12), 98 (10), 91 (36), 77 (26). IR (film, ν/cm^{-1}): 1638 (C=N).

For **5**: mp 78–80 °C. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 8.26 (d, 1H, *J* 2.4 Hz), 8.16 (d, 1H, *J* 2.4 and 8.5 Hz), 7.47 (d, 1H, *J* 8.5 Hz), 3.17 (m, 1H, *J* 7.0, 3.4 and 10.7 Hz), 2.13 (dd, 1H, *J* 14.7 and 3.4 Hz), 1.76 (dd, *J* 14.7 and 10.7 Hz), 1.41 (d, 3H, *J* 7.0 Hz), 1.80–1.30 (m, 10H). MS, *m*/*z* (rel. intensity): 272 (M^+, 9), 267 (90), 253 (48), 239 (65), 228 (35), 217 (52), 203 (100), 200 (78). IR (KBr, ν/cm^{-1}): 1636 (C=N), 1519 (NO_2), 1352 (NO_2).

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