Non-biomimetic oxidation of 1,4-dihydropyridines†

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The reaction between *N*-alkyl-1,4-dihydropyridines and dimethyldioxirane leads to dimeric tetrahydropyridines having oxygen atoms at the 2- and 3-positions in good yields and with good stereocontrol; these compounds are useful iminium ion precursors, and are satisfactorily transformed into 2-substituted 3-hydroxy-1,2,3,4-tetrahydropyridines.

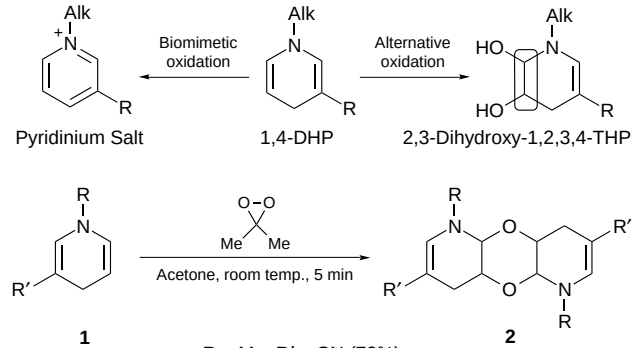
1,4-Dihydropyridines are interesting compounds and play an important role in synthetic, therapeutic and bioorganic chemistry.[1] New methods for their preparation[2] and transformations have been the subject of research in our laboratory: selective reductions,[3] electrophilic additions[4] and total syntheses of alkaloids[5] have been developed.

Here we report an efficient, mild and selective non-biomimetic oxidation of *N*-alkyl-1,4-dihydropyridines.‡ Although the conversion of these compounds to the corresponding pyridinium salts is a well-established process that has relevant significance in cell metabolism [NAD(P)H is commonly oxidized to $NAD(P)^+$ in many enzyme-assisted reductions], very little is known about 'alternative' dihydropyridine oxidations (*i.e.* epoxidations or dihydroxylations).[6,7] To our knowledge, no synthetically useful reports dealing with this subject have been published. After several unsuccessful attempts to oxidize *N*-alkyl-1,4-dihydropyridines with MCPBA or OsO_4, we turned our attention to the use of dimethyldioxirane (DMD), a reagent used in a wide range of functional group transformations,[8] including the oxidation of enamines.[9] It should be mentioned that a chemically related dioxetane was involved in the 'normal' oxidation of a NADH analogue.[10]

The required *N*-methyl-1,4-dihydropyridines **1** were prepared by sodium dithionite reduction of the corresponding pyridinium salts, following published procedures.[11] When dihydropyridines **1** were treated at room temperature with DMD for 5 min, the tricyclic dioxanes **2** were obtained in good yields.§¶ This process can be rationalized by considering the initial epoxidation of the enamine double bond with subsequent ring opening of the oxirane ring to give an iminium ion that undergoes dimerization.

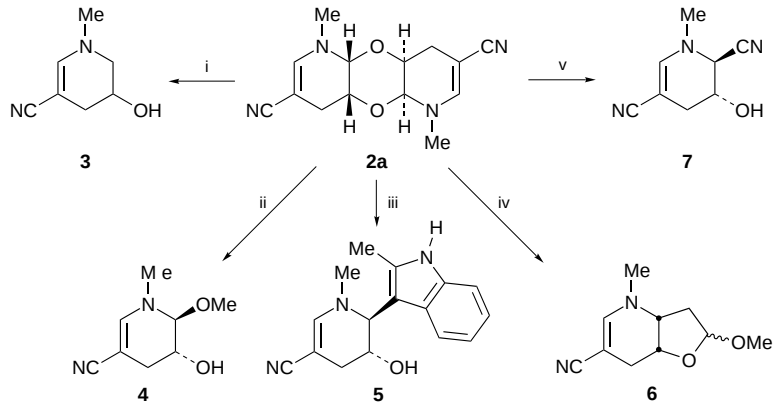
This transformation constitutes the first general, non-biomimetic oxidation of 1,4-dihydropyridines, avoiding the natural oxidation pathway to pyridinium salts. In contrast, the use of dioxiranes generated *in situ* from 2-chlorocyclohexanone or 1,1,1-trifluoroacetone in the presence of stochiometric amounts of Oxone®[12] was not satisfactory, showing the incompatibility of dihydropyridines with strong oxidants like peroxyacids. The major stereoisomers **2** have a centre of symmetry,[13] showing a *cis* stereochemistry for the oxygens at C_2–C_3 and a *anti* relationship between the two tetrahydropyridine moieties; minor amounts of other isomers were isolated, probably having a *syn* stereochemistry. The stereochemical assignments were based on the coupling constants in the ^1H NMR spectra and on ^1H-^1H COSY, HMQC and NOESY experiments. Dioxanes **2** were stable enough to be chromatographed, spectroscopically characterized and stored indefinitely in the freezer under an inert atmosphere. An additional interest of dimers **2** lies in the fact that they are highly functionalized iminium ion precursors.

A preliminary study of this type of reactivity was undertaken, including the generation of iminium ions under different conditions and their subsequent interaction with nucleophiles. Thus, reduction of **2a** with triethylsilane in the presence of



a R = Me, R′ = CN (72%)
b R = Me, R′ = CO_2Me (76%)
c R = Bn, R′ = CN (69%)
d R = Bn, R′ = CO_2Me (60%)

Scheme 1



Scheme 2 *Reagents and conditions*: i, Et_3SiH, $TiCl_4$, THF, −60 °C, 5 min (95%); ii, MeOH, TFA, 0 °C, 5 min (72%; *cis* isomer 24%); iii, 2-methylindole, TFA, 20 °C, 5 min (60%; *cis* isomer 24%); iv, 1-methoxyethene, $BF_3{\cdot}Et_2O$, THF–CH_2Cl_2, −60 °C, 5 min (60%, mixture of isomers at the acetalic carbon); v, Me_3SiCN, $TiCl_4$, CH_2Cl_2, 0 °C, 5 min (40%; *cis* isomer 27%)

titanium tetrachloride afforded tetrahydropyridinol **3**, whereas TFA-induced addition of methanol gave the 'protected' α-alcoxy tetrahydropyridine **4**. On the other hand, addition of 2-methylindole was achieved under acid catalysis, affording adduct **5** with moderate stereoselectivity. In the latter two reactions, minor amounts of the *cis* isomers were isolated. Addition of methoxyethylene was achieved in the presence of boron trifluoride. In this case, the intramolecular trapping of the resulting carbonium ion by the hydroxy group allowed the formation of the partially reduced furopyridine **6** (ring fusion *cis*) in a one-pot transformation. Finally, Me_3SiCN was added to give α-amino nitrile **7** (epimeric mixture at C-2) in good yield.‖

In conclusion, a useful, mild and selective method for the formal epoxidation of 1,4-dihydropyridines has been developed, and some relevant reactions of the resulting compounds, which act as iminium ion precursors, are reported. These results present interesting possibilities in the study of the chemical reactivity of dihydropyridines, a class of compounds with a significant role in biochemistry and in natural product synthesis (*e.g.* alkaloids and azasugars).

This work was supported by the Dirección General de Investigación Científica y Técnica, Spain, (PB94-0214) and by the Comissionat per Universitats i Recerca (Generalitat de Catalunya, Grant SGR95-00428).

Footnotes

† Presented in part at the Eigth FECHEM Conference on Heterocycles in Bio-Organic Chemistry, September 1–4, 1996, Villa Olmo, Italy.

‡ The term non-biomimetic is used in a broad sense, meaning that the process involves an oxygen transfer rather than the usual two-electron oxidation observed in nature.

§ All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, UV, MS and HRMS.

¶ *Typical procedure*: A 1.1 fold excess of DMD (0.07 m) in acetone[14] was added to a solution of the dihydropyridine **1a** (1 mmol) in acetone (20 ml) at 0 °C. The progress of the reaction was monitored by TLC. When all the starting material had been consumed (*ca.* 5 min), the solvent was removed under reduced pressure and the residue was chromatographed through neutral alumina (CH_2Cl_2–MeOH) to give the corresponding dioxane **2a** (72%). ^{1}H NMR (300 MHz, CD_3OD) 2.16 (ddd, 1 H, *J* 16.3, 2.7 and 1.5 Hz, H-4), 2.53 (ddd, 1 H, *J* 16.3, 3.7 and 1.9 Hz, H-4), 3.15 (s, 3 H, CH_3), 3.83 (m, 1 H, H-3), 4.41 (dd, 1 H, *J* 2.6 and 1.5 Hz, H-2), 6.74 (d, 1 H, *J* 1.9 Hz, H-6); ^{13}C NMR (75.4 MHz, CD_3OD) 24.4 (C-4), 39.3 (CH_3), 63.9 (C-3), 70.3 (C-5), 80.4 (C-2), 122.7 (CN), 146.0 (C-6). HRMS (e.i.) *m/z*: calc. 272.1273, found 272.1272.

‖ *Selected spectral data* for **3**: ^{1}H NMR (300 MHz, $CDCl_3$) 2.20 (br s, 2 H, H-4 and OH), 2.49 (br d, 1 H, *J* 15.8 Hz, H-4), 2.95 (s, 3 H, CH_3), 3.01 (m, 1 H, *J* 12.6, 5.6, 2.5 and 0.9 Hz, H-2), 3.17 (ddd, 1 H, *J* 12.6, 2.6 and 1.1 Hz, H-2), 4.19 (br s, 1 H, H-3), 6.79 (d, 1 H, *J* 0.9 Hz, H-6); ^{13}C NMR (75.4 MHz, $CDCl_3$): 30.0 (C-4), 42.9 (CH_3), 52.9 (C-2), 61.9 (C-3), 69.5 (C-5), 123.0 (CN), 147.5 (C-6). For **4** (major stereoisomer, *trans*): ^{1}H NMR (300 MHz, $CDCl_3$) 2.12 (ddd, 1 H, *J* 16.6, 2.2 and 1.3 Hz, H-4), 2.40 (ddd, 1 H, *J* 16.6, 3.8 and 1.9 Hz, H-4), 3.09 (s, 3 H, NCH_3), 3.38 (s, 3 H, OCH_3), 3.93 (m, 1 H, H-3), 4.07 (dd, 1 H, *J* 3.2 and 1.2 Hz, H-2), 6.77 (dd, 1 H, *J* 2.0 and 1.0 Hz, H-6); ^{13}C NMR (75.4 MHz, $CDCl_3$): 25.6 (C-4), 42.6 (NCH_3), 56.4 (OCH_3), 61.8 (C-3), 73.1 (C-5), 89.4 (C-2), 122.1 (CN), 145.2 (C-6). HRMS (e.i.) *m/z*: calc. 168.0899, found 168.0902. For **5** (major stereoisomer, *trans*): ^{1}H NMR (300 MHz, $CDCl_3$) 2.33 (dd, 1 H, *J* 15.6 and 6.7 Hz, H-4), 2.43 (s, 3 H, CH_3), 2.50 (dd, 1 H, *J* 15.6 and 4.0 Hz, H-4), 2.81 (s, 3 H, NCH_3), 4.20 (ddd, 1 H, *J* 6.7, 5.4 and 4.0 Hz, H-3), 4.30 (d, 1 H, *J* 5.4 Hz, H-2), 7.02 (s, 1 H, H-6), 7.07–7.20 (m, 2 H, H-5 and H-6 indole), 7.33 (d, 1 H, *J* 8.0 Hz, H-7 indole), 7.47 (d, 1 H, *J* 7.7 Hz, H-4 indole), 8.10 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) 11.8 (CH_3), 28.3 (C-4), 40.9 (NCH_3), 60.6 (C-2), 66.4 (C-3), 69.2 (C-5), 108.0 (C-3 indole), 110.6 (C-7 indole), 117.8 (C-4 indole), 119.8 (C-6 indole), 120.0 (CN), 121.6 (C-5 indole), 122.2 (C-3a indole), 134.5 (C-2 indole), 136.1 (C-7a indole), 148.5 (C-6). HRMS (e.i.) *m/z*: calc. 267.1372, found 267.1381. For **6** (major stereoisomer): ^{1}H NMR (300 MHz, $CDCl_3$): 1.97 (ddd, 1 H, *J* 13.7, 7.5 and 2.9 Hz, H-3), 2.40 (m, 1 H, H-3), 2.47 (m, 2 H, H-7), 2.92 (s, 3 H, NCH_3), 3.35 (s, 3 H, OCH_3), 3.55 (m, 1 H, H-3a), 4.25 (m, 1 H, H-7a), 5.02 (dd, 1 H, *J* 5.9 and 2.9 Hz, H-2), 6.72 (s, 1 H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) 25.5 (C-7), 36.6 (C-3), 40.8 (NCH_3), 55.4 (OCH_3), 57.1 (C-3a), 73.5 (C-7a), 79.9 (C-6), 104.0 (C-2), 123.1 (CN), 147.1 (C-5). HRMS (e.i.) *m/z*: calc. 194.1055, found 194.1060. For **7** (major stereoisomer, *trans*): ^{1}H NMR (300 MHz, $CDCl_3$) 2.30 (ddd, 1 H, *J* 16.8, 2.6 and 2.3 Hz, H-4), 2.75 (ddd, 1 H, *J* 16.8, 3.6 and 2.0 Hz, H-4), 3.08 (s, 3 H, NCH_3), 3.98 (dd, 1 H, *J* 2.6 and 2.3 Hz, H-2), 4.39 (m, 1 H, H-3), 6.77 (d, 1 H, *J* 2.0 Hz, H-6); ^{13}C NMR (75.4 MHz, $CDCl_3$) 27.2 (C-4), 41.3 (NCH_3), 52.7 (C-2), 63.2 (C-3), 76.3 (C-5), 115.4 (CN), 120.7 (CN), 145.9 (C-6). HRMS (e.i.) *m/z*: calc. 163.0746, found 163.0746.

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Received, 9th October 1996; Com. 6/06919C