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Prins reaction under manganese dioxide control: the synthesis of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones from tetrahydropyridines and formaldehyde

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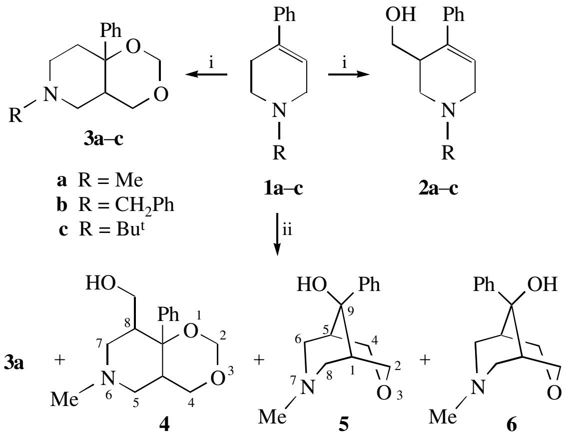
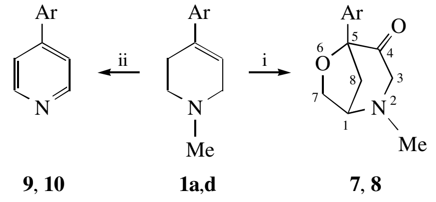
The course of the acid-catalysed Prins reaction of tetrahydropyridines **1** with formaldehyde, leading to derivatives of piperidinodioxane **4** and 3-oxa-7-azabicyclononanes **5** and **6**, is dramatically changed in the presence of manganese dioxide to give new products, 6-oxa-2-azabicyclo[3.2.1]octan-4-ones **7** and **8**.

The previous studies of acid-catalysed condensation of 4-aryl-substituted terahydropyridines (THPs) **1** with an excess of formaldehyde and sulfuric acid have shown that this Prins reaction gave 3-hydroxymethyl THPs **2**[1] or, in the case of a tenfold molar excess of formaldehyde, corresponding piperidinodioxanes **3**[2] (Scheme 1). In repeating an analogous reaction of THP **1a** with a fourfold excess of formaldehyde, we separated not only known 1,3-dioxane **3a** but also three new products: 8-hydroxymethyl derivative of piperidinodioxane **4** and 3-oxa-7-azabicyclo[3.3.1]nonanes **5** and **6**, the last two being isomers by the position of 9-hydroxyl in respect to the ring nitrogen atom (*cis* N/9-OH and *trans* N/9-OH, respectively). The X-ray diffraction data suggest that piperidine and tetrahydropyrane rings in the crystalline form of *cis*-isomer **5** (Figure 1 shows the general view and numeration of atoms in a molecule of **5**) exhibit a chair conformation; the hydroxyl group of one molecule forms an intermolecular hydrogen bond with the nitrogen atom of another molecule. In solution, the piperidine ring of the same isomer (^{1}H NMR spectra in $CDCl_3$) has a boat conformation fixed by an intramolecular hydrogen bond.



Scheme 1 *Reagents and conditions*: i, CH_2O, H^+; ii, **1a**:CH_2O = 1:4, boiling in aqueous H_2SO_4, 7 h, then 20 °C, 18 h.

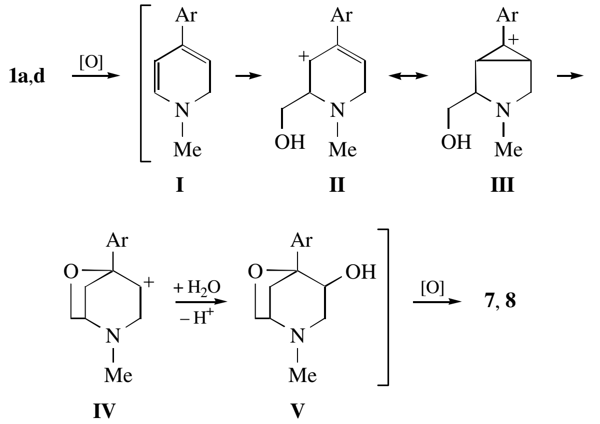
As a continuation of our work on the new oxidative reactions of hydropyridines initiated by manganese compounds,[3–5] we report the reaction of THPs **1a**,**d** with an excess of formaldehyde in the presence of manganese dioxide with an emphasis on the modification of the Prins method to prepare an oxidatively new heterocyclic system (Scheme 2, conditions i). A conventional chromatographic procedure gave product **7** in an isolated yield of 31% (from THP **1a**) and a product **8** in 35% yield (from **1d**). The structures of these compounds were different from those of compounds obtained by the Prins reaction previously[1,2,6] or in this work (Scheme 1, conditions ii). Compounds **7** and **8** showed spectroscopic data consistent with the structure of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones, indicating an unexpected addition of formaldehyde at the α-position of a THP heterocycle and unusual oxidation of the latter into a β-piperidone fragment.



7, **9** Ar = Ph
1d, **8**, **10** Ar = *p*-MeC_6H_4

Scheme 2 *Reagents and conditions*: i, **1**:CH_2O:MnO_2:H_2SO_4 = 1:3:5:6, boiling in an aqueous solution, 7 h; ii, **1**:MnO_2 = 1:10, boiling in toluene, 3 h.

The key step in the mechanism of the formation of bicyclooctanes **7**, **8** may be the oxidative dehyrogenation of the initial THPs to form intermediate 1,2-dihydropyridines. It is clear that analogous dihydropyridines should be formed as intermediates in other experiments (Scheme 2, conditions ii), which demonstrated the readiness of THPs **1a**,**d** to transformation into pyridines **9**, **10** on boiling in toluene in the presence of MnO_2. The data thus obtained allow us to propose the following sequence for the synthesis of bicyclooctanones **7**, **8** (Scheme 3).



Scheme 3

Dihydropyridines **I** formed at the initial oxidative step are then selectively attacked by protonated formaldehyde at the α-position (C-6) to give carbocations **II** stabilised by species **III**. The intramolecular cycloaddition yields bicyclic cation **IV**, which leads to final products **7** and **8** *via* hydroxylation followed by the oxidative dehydrogenation of intermediate alcohol **V**. The trasformation of secondary alcohols into ketones under the action of MnO_2 is well documented.[7] The ^{1}H and ^{13}C NMR spectral data together with the Dreiding modelling and molecular mechanic calculations of conformer energies are consistent with a distorted (flatted) boat conformation of a piperidine ring *cis*-1,3-diaxially condensed with a tetrahydrofuranic ring, which has a rigid envelope confomation.

Thus, the series of conversions demonstrates a new useful method for an effective control of the Prins reaction by man-

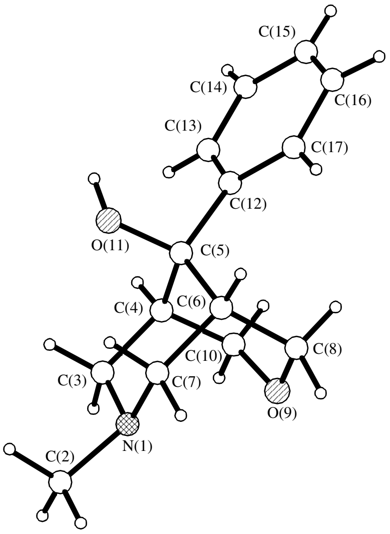


Figure 1 General view and numeration of atoms in a molecule of **5** (X-ray diffraction data).

ganese dioxide, which dramatically changes the course of condensation of tetrahydropyridines with formaldehyde leading to a new group of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones.

The structures of compounds **3a** and **4–10** were confirmed spectroscopically.†

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† NMR spectra were recorded at 300 MHz (^{1}H) and 75.5 MHz (^{13}C), standard TMS, $CDCl_3$. Compounds **3a** and **4–10** gave satisfactory elemental analyses.

For **3a**: yield 15%, mp 60–62 °C (lit.,[2] **3a**·HCl, mp 320 °C). ^{1}H NMR, δ: 1.8 (m, 2H, 8-CH_2), 2.37 (s, 3H, Me), 2.5–3.2 (m, 5H, 5-CH_2 and 7-CH_2 and 4-H_a), 3.6 (d, 1H, 4-CH_2, ^2J 11.5 Hz), 3.8 (dd, 1H, 4-CH_2, ^2J 11.5 Hz, ^3J 2.5 Hz), 4.77 and 4.83 (2d, 1H each, 2-CH_2, ^2J 6.5 Hz), 7.3 (m, 5H, Ph). MS (EI, 70 eV), *m/z* (%): 233 (7) [M$^+$], 174 (38), 128 (5), 105 (11), 77 (12), 57 (13), 44 (100).

For **4**: yield 6%, mp 88–90 °C. ^{1}H NMR, δ: 1.57 (br. s, 1H, 8-H), 2.34 (s, 3H, Me), 2.83–3.05 (m, 6H, 5-CH_2 and 7-CH_2 and CH_2OH), 3.53 (d, 1H, 4-CH_2, ^2J 11.6 Hz), 3.61 (dd, 1H, 4-CH_2, ^2J 11.6 Hz, ^3J 2.6 Hz), 3.9 (dd, 1H, 4-H_a, ^3J 11.7 Hz, ^4J 2.0 Hz), 4.75 and 4.83 (2d, 1H each, ^2J 6.1 Hz), 7.28–7.5 (m, 5H, Ph). ^{13}C NMR, δ: 35.1 (8-C), 46.1 (Me), 47.1 (4a-C), 55.2 (5-C), 57.2 (7-C), 65.8 (COH), 66.2 (4-C), 77.7 (C_{quat}–O), 89.4 (2-C), 126.5, 127.5, 128.4, 129.3 and 140.7 (6C, Ph); MS, *m/z*: 263 [M$^+$]. IR (KBr, ν/cm^{-1}): 3310 (OH). Found (%): C, 68.21; H, 8.16; N, 5.28. Calc. for $C_{15}H_{21}NO_3$ (%): C, 68.44; H, 7.99; N, 5.32.

For **5**: yield 14%, mp 176 °C. ^{1}H NMR, δ: 2.38 (s, 3H, Me), 2.68 (m, 2H, 1-H and 5-H), 2.84 (dd, 2H, 6-H and 8-H, ^2J 11.1 Hz, ^3J 2.5 Hz), 3.25 (dd, 2H, 6-H and 8-H, ^2J 11.1 Hz, ^3J 7.3 Hz), 3.64 (d, 2H, 2-H and 4-H, ^2J 11.4 Hz), 3.75 (d, 2H, 2-H and 4-H, ^2J 11.4 Hz), 7.3–7.5 (m, 5H, Ph). ^{13}C NMR, δ: 37.9 (1-C and 5-C), 45.1 (Me), 55.9 (6-C and 8-C), 69.8 (2-C and 4-C), 71.8 (9-C), 126.1, 127.8, 128.9 and 141.6 (6C, Ph). MS, *m/z* (%): 233 (100) [M$^+$], 232 (38), 216 (27), 190 (20), 184 (8), 170 (10), 133 (34), 128 (35), 105 (38), 91 (15), 77 (16). IR (KBr, ν/cm^{-1}): 3220 and 3410 (br. OH). Found (%): C, 71.92; H, 8.27; N, 5.85. Calc. for $C_{14}H_{19}NO_2$ (%): C, 72.10; H, 8.27; N, 6.01.

For **6**: yield 7%, mp 180 °C. ^{1}H NMR, δ: 2.12 (s, 3H, Me), 2.37 (m, 2H, 1-H and 5-H), 2.42 (d, 2H, 6-H and 8-H, ^2J 11.4 Hz), 3.0 (d, 2H, 6-H and 8-H, ^2J 11.4 Hz), 4.02 (dd, 2H, 2-H and 4-H, ^2J 10.9 Hz, ^3J 2.3 Hz), 4.54 (dd, 2H, 2-H and 4-H, ^2J 10.9 Hz, ^3J 2.3 Hz), 7.3–7.5 (m, 5H, Ph). ^{13}C NMR, δ: 38.3 (1-C and 5-C), 46.5 (Me), 58.3 (6-C and 8-C), 67.4 (2-C and 4-C), 71.3 (9-C), 125.4, 128.0, 129.1, 142.4, (6C, Ph). MS, *m/z* (%): 233 (100) [M$^+$]. IR (KBr, ν/cm^{-1}): 3200 and 3420 (br. OH). Found (%): C, 72.2; H, 8.23; N, 5.91. Calc. for $C_{14}H_{19}NO_2$ (%): C, 72.10; H, 8.27; N, 6.01.

For **7**: yield 31%, colourless oil (purified by chromatography on a silica gel column; eluent, acetone; R_f 0.7). ^{1}H NMR, δ: 2.51 (s, 3H, Me), 3.0 (t, 1H, 8-H_a, $^2J \approx {}^3J$ 12.6 Hz), 3.16 (br. d, 1H, 8-H_e, ^2J 12.6 Hz), 3.73 (t, 1H, 7-H_a, ^2J 10.7 Hz), 4.0 (m, 1H, 1-H_e), 4.12 (d, 1H, 3-H_a, ^2J 9.5 Hz), 4.23 (br. d, 1H, 7-H_e, $^2J \approx {}^3J$ 10.7 Hz), 4.42 (br. d, 1H, 3-H_e, ^2J 9.5 Hz), 7.3–7.5 (m, 5H, Ph). MS, *m/z* (%): 217 (16) [M$^+$], 202 (43), 187 (15), 131 (12), 105 (100), 77 (37). IR (paraffin oil, ν/cm^{-1}): 1680 (C=O), 3360 (br. OH). Found (%): C, 71.7; H, 7.03; N, 6.52. Calc. for $C_{13}H_{15}NO_2$ (%): C, 71.89; H, 6.91; N, 6.45.

For **8**: yield 35%, colourless oil (purified by chromatography on a silica gel column; eluent, acetone; R_f 0.7). ^{1}H NMR, δ: 2.39 (s, 3H, Me), 2.51 (s, 3H, Me), 2.98 (t, 1H, 8-H_a, $^2J \approx {}^3J$ 12.9 Hz), 3.16 (br. d, 1H, 8-H_a, ^2J 12.9 Hz), 3.76 (t, 1H, 7-H_a, ^2J 10.9 Hz), 4.07 (m, 1H, 1-H_e), 4.10 (d, 1H, 3-H_a, ^2J 9.4 Hz), 4.20 (br. d, 1H, 7-H_e, ^2J 10.9 Hz), 4.40 (br. d, 1H, 3-H_e, $^2J \approx {}^3J$ 9.4 Hz), 7.27 and 7.86 (AA′BB′ system, 4H, Ar, ^3J 7.2 Hz, ^4J 1.1 Hz). ^{13}C NMR, δ: 22.6 (*C*Me), 40.3 (1-C), 40.8 (NMe), 55.8 (8-C), 70.2 (7-C), 86.7 (3-C), 129.7 (5-C), 129.3, 130.5, 144.3, 145.4 ($C_{arom.}$), 200.0 (C=C). MS, *m/z* (%): 231 (7) [M$^+$], 216 (36), 203 (6), 188 (28), 172 (34), 160 (38), 145 (12), 119 (100), 91 (45). IR (paraffin oil, ν/cm^{-1}): 1675 (C=O), 3350 (br. OH). Found (%): C, 73.01; H, 7.49; N, 5.90. Calc. for $C_{14}H_{17}NO_2$ (%): C, 72.72; H, 7.36; N, 6.06.

For **9**: yield 45%, mp 76–78 °C (lit.,[8] mp 76–78 °C). ^{1}H NMR and mass spectra are identical to those given in ref. 3.

For **10**: yield 42%, mp 43–45 °C. ^{1}H NMR, δ: 2.4 (s, 3H, Me), 7.25 and 7.5 (AA′BB′ system, 4H, Ar, ^3J 7.1 Hz, ^4J 1.1 Hz), 7.61 and 8.63 (AA′XX′ system, 4H, Py, ^3J 5.4 Hz, ^4J 2.0 Hz). MS, *m/z* (%): 169 (100) [M$^+$], 168 (43), 155 (95), 91 (20). Found (%): C, 84.98; H, 6.67; N, 8.01. Calc. for $C_{12}H_{11}N$ (%): C, 85.21; H, 6.51; N, 8.28.