Oxidative coupling and unusual hydroxymethylation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the presence of dicyanomethane

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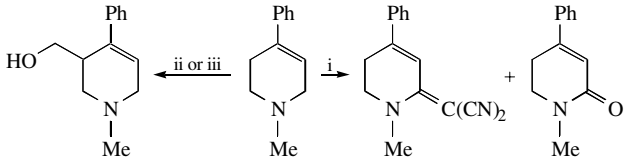
Potassium permanganate oxidizes a mixture of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (THP) 1 and dicyanomethane to 2-dicyanomethylidenetetrahydropyridine 2, but using manganese dioxide leads to the unusual oxidative hydroxymethylation of 1; subsequent treatment of the 3-hydroxymethyltetrahydropyridine 4 formed with aqueous potassium permanganate results in lactamination, accompanied by aromatization or oxodihydroxylation.

In our recent work[1,2] on the oxidative transformation of the notorious neurotoxin THP **1**[3] and its analogues we have discovered a novel C_{sp^3}–C_{sp^3} coupling reaction between tetrahydropyridines and compounds containing an activated methyl group such as acetone, methyl aryl ketones and nitromethane. In the presence of potassium permanganate the THP nucleus in this unusual reaction is attacked by the CH acid at the allylamine position 2 leading to the formation of 2-R-methylideneTHP.

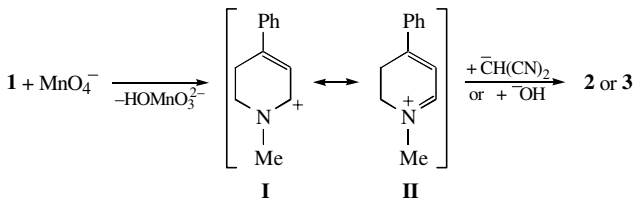


4 **1** **2** **3**

Scheme 1 *Reagents and conditions*: i, **1**:$CH_2(CN)_2$:$KMnO_4$ = 1:1:1 in aqueous MeCN, 0–5 °C, 1.5 h; ii, **1**:$CH_2(CN)_2$:MnO_2 = 1:1:10 in aqueous benzene, 20 °C, 1.5 h; iii, **1**:CH_2O:MnO_2 = 1:1:10 in aqueous benzene, 20–50 °C, 1.5 h.

In order to widen the scope of this important reaction it is of interest to utilise other CH acid groups containing, for example, an active methylene grouping. Described here is a study of the oxidation of a mixture of THP **1** with dicyanomethane in the presence of potassium permanganate or manganese dioxide. It is found that oxidation of the mixture is initiated by the permanganate at 0–5 °C, affording the expected 2-dicyanomethylideneTHP **2** (Scheme 1). The low yield of **2** (11.5%) can in part be explained by the fact that a significant amount of the oxidizing equivalent was consumed to yield 2-oxotetrahydropyridine **3** (29%) and some intractable material. The formation of the structures **2** and **3** can be rationalised on the basis of the transformations indicated in Scheme 2. The key step in the most likely mechanism may be confirmed by the known hydride transfer from the methyl group of toluene to a permanganate anion.[4] The *tert*-amino group in the THP is in a proximate position with one of the allylic positions and can therefore serve as an internal nucleophile stabilising the carbocation **I** by the iminium ion form **II**. These intermediates dictate the regioselectivity (at the C-6 position of the THP) of the intermolecular attack by the nucleophilic $^-CH(CN)_2$ or ^-OH species from solution.

With the aim of increasing the yield of the target compound **2** it was decided to carry out oxidation of the same substrate



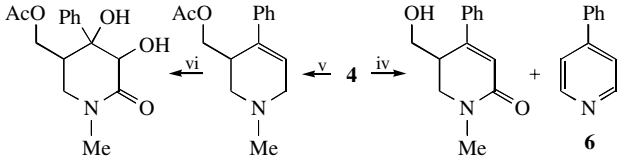
I **II**

Scheme 2

mixture using a milder oxidant: activated manganese dioxide in aqueous benzene (conditions ii). We were surprised, however, to find that in this case the reaction proceeded by a completely different pathway and instead of the expected product **2** separation of the reaction mixture gave a sole identified product in an isolated yield of 36.5%, which had spectroscopic and X-ray data (the latter will be reported elsewhere) consistent with the structure of 3-hydroxymethylTHP **4**. The unusual oxidative hydroxy-methylation reaction of THP with dicyanomethane has presumably occurred due to oxidative degradation of the latter forming formaldehyde (*via* its imine) in the presence of water. The instability of the cyano groups in the presence of high valent manganese compounds is well documented.[5] To probe this possibility we have performed an analogous experiment involving oxidation of **1** in aqueous formaldehyde. Indeed, this example yielded evidence for the possible participation of formaldehyde in the oxidative (in the absence of the oxidant no reaction takes place) hydroxymethylation: compound **4** has been shown to be formed as well, although with an achieved maximum yield of 22%. In contrast to the oxidative coupling, the hydroxymethylation is directed at the C-3 position which can be connected with steric hindrance created at the C-6 carbon by complexation of the vicinal basic N atom with manganese dioxide consumed in great excess (conditions iii).

The presence of the double bond in the hydroxymethyl derivative **4** raises the possibility of oxodihydroxylating this THP system using a one-pot protocol recently elaborated in our laboratory.[6] However, the attempted polyfunctionalization of **4** yielded only an intermediate 2-oxo-5-hydroxymethylTHP **5** (50%) and 4-phenylpyridine **6** (10%) (Scheme 3). The formation of the latter presents, to our knowledge, the first example of the oxidative elimination of two groups (methyl and hydroxymethyl) from the THP ring, thus achieving total aromatization under such mild conditions.

The repetition of the same oxidation using THP **7** which has an acetyl-protected hydroxyl grouping (compound **7** was obtained by acetylation of **4** with Ac_2O in a yield of 75%) led to the targetted polyfunctionalized piperidine **8** in an isolated yield of 37.5%. Its stereochemistry should be analogous to that of 4-aryl-substituted 2-oxo-3,4-dihydroxypiperidines whose stereo structures were established by X-ray analysis. So, the piperidine ring in **8** should have a distorted (flatted) chair conformation with phenyl and acyloxy groups oriented equatorially and two



8 **7** **5**

Scheme 3 *Reagents and conditions*: iv, **4**:$KMnO_4$ = 1:1.5 in aqueous MeCN, 20 °C, 1.5 h; v, **4**:Ac_2O = 1:1 in pyridine at 20 °C, 48 h; vi, **7**:$KMnO_4$ = 1:2 in aqueous MeCN, 20 °C, 2.25 h.

vicinal hydroxyls in a mutual *cis* position. Thus, the observed series of conversions from THP **1** to amino sugar analogue **8** paves a new synthetic way to structural analogues of polyhydroxypiperidine alkaloids such as nojirimicin and others which have important chemoterapeutic potential.[7]

The structures of compounds **2**, **4**, **5**, **7** and **8** were confirmed spectroscopically.†

† NMR spectra were recorded at 300 MHz (^{1}H) and 75.5 MHz (^{13}C), standard TMS, $CDCl_3$. Compounds **2**, **4**, **5**, **7** and **8** gave satisfactory elemental analyses.

Compound **2**: yield 11.5%, mp 166–168 °C; ^{1}H NMR δ: 2.88 and 3.59 (t, 2×2H, 5-CH_2 and 6-CH_2, ^2J 7.16 Hz, ^3J 7.16 Hz), 3.55 (s, 3H, Me), 6.9 (s, 1H, 3-H), 7.43 and 7.55 (m, 3H and 2H, Ph); ^{13}C NMR δ: 26.08 (5-C), 42.41 (Me), 51.26 (6-C), 116.81 (3-C), 117.54 (2′-C), 125.95, 129.06, 130.55 and 141.8 (6C, Ph), 136.29 (4-C), 148.34 (2×CN), 160.73 (2-C); MS (EI, 70 eV, 220 °C), *m*/*z* (%): 235 (100) [M$^+$]; IR (KBr, ν/cm^{-1}): 2187, 2207 (CN), 1625, 1567 (C=C).

Compound **3**: yield 29%, mp 78–80 °C.[8]

Compound **4**: yield 36.5%, mp 82-8 4 °C; ^{1}H NMR δ: 2.4 (s, 3H, Me), 2.67 (dd, 1H, 2-H, ^2J 11.5 Hz, ^3J 8.1 Hz), 2.83 (m, 2H, 3-H and 6-H), 3.1 (dd, 1H, 2-H), 3.44 (dd, 1H, 6-H, ^2J 13.5 Hz, ^3J 3.5 Hz), 3.65 and 3.89 (dd, 2×1H, 3-CH_2O, ^2J 10.5 Hz, ^3J 7.0 Hz), 4.6 (br. s, 1H, OH), 6.03 (dd, 1H, 5-H, ^3J 3.5 Hz, ^4J 1.6 Hz), 7.3 (m, 5H, Ph); MS (120 °C), *m*/*z* (%): 203 (55) [M$^+$], 202 (17), 184 (6), 173 (19), 172 (100), 170 (54), 144 (23), 142 (16), 128 (21), 117 (19), 115 (28); IR (KBr, ν/cm^{-1}): 3153 (br., OH), 1640, 1570 (C=C).

Compound **5**: yield 50%, colourless oil (purified by chromatography on silica gel colomn, eluent diethyl ether, R_f 0.65 in acetone). ^{1}H NMR δ: 3.0 (s, 3H, Me), 3.05 (m, 1H, 5-H), 3.55 (m, 2H, 6-H), 3.67 (m, 2H, 5-CH_2O), 4.21 (s, 1H, OH), 6.23 (s, 1H, 3-H), 7.32 and 7.5 (m, 3H and 2H, Ph); ^{13}C NMR δ: 34.33 (5-C), 39.22 (Me), 48.35 (C–OH), 60.47 (6-C), 119.89 (3-C), 126.07, 128.78, 129.6 and 150.09 (6C, Ph), 136.0 (4-C), 165.19 (2-C=O); MS (120 °C), *m*/*z* (%): 217 (60) [M$^+$], 186 (50), 185 (100); IR (paraffin oil, ν/cm^{-1}): 3370 (OH), 1642 and 1592 (NC=O and C=C).

Compound **6**: yield 10%, mp 76-7 8 °C;[9] ^{1}H NMR δ: 7.36-7 .70 (m, 5H, Ph), 7.44 and 8.58 (AA′BB′ system, 2×2H, Py, ^3J 5.8 Hz, ^4J 1.6 Hz); MS (35 °C), *m*/*z* (%): 155 (100) [M$^+$], 128 (74), 127 (67), 115 (70), 102 (78).

Compound **7**: yield 75%, colourless oil (purified by chromatography on silica gel colomn, eluent diethyl ether, R_f 0.57 in acetone); ^{1}H NMR δ: 1.98 (s, 3H, CMe), 2.4 (s, 3H, NMe), 2.7 (dd, 2H, 2-H, ^2J 11.8 Hz, ^3J 2.9 Hz), 3.0 (m, 1H, 3-H), 3.1 (dd, 2H, 6-H, ^2J 12.6 Hz, ^3J 2.5 Hz), 4.03 (dd, 2H, 3-CH_2O, ^2J 10.0 Hz, ^3J 1.5 Hz), 5.95 (t, 1H, 5-H, ^3J 2.5 Hz), 7.25 (m, 5H, Ph); MS (60 °C), *m*/*z* (%): 245 (100) [M$^+$], 184 (76), 172 (99), 170 (30), 91 (35), 77 (19); IR (paraffin oil, ν/cm^{-1}): 1730 (C=O), 1640, 1596 (C=C).

Compound **8**: yield 37.5%, mp 154–156 °C; ^{1}H NMR δ: 1.98 (s, 1H, CMe), 2.5 (m, 1H, 5-H), 3.0 (s, 3H, NMe), 3.22 (dd, 1H, 6-H, ^2J 12.1 Hz, ^3J 2.5 Hz), 3.32 (br. s, 1H, OH), 3.8 (s, 1H, 3-H), 3.85 (m, 2H, 5-CH_2O), 4.6 (s, 1H, OH), 7.3–7.5 (m, 5H, Ph); MS (120 °C), *m*/*z* (%): 293 (13) [M$^+$], 203 (17), 174 (75), 144 (33), 105 (100); IR (KBr, ν/cm^{-1}): 3550 narrow and 3355 broad (OH), 1716 (C=O), 1644 and 1626 (NC=O).

We are grateful to the Russian Foundation for Basic Research (grant nos. 96-03-33432a and 97-03-33783a) for financial support of this work.

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Received: Moscow, 30th June 1998
Cambridge, 23rd July 1998; Com. 8/05564E