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New oxidative reactions of 1,2,3,6-tetrahydropyridines: imination, lactamination and decyclisation in the presence of potassium permanganate

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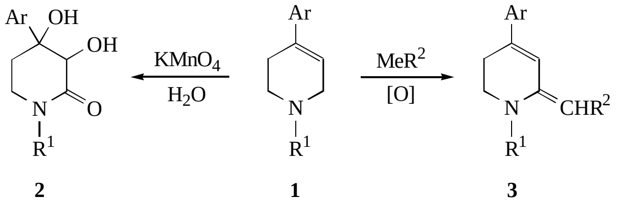
A novel oxidative imination reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **1a** by 4-nitroaniline/potassium permanganate has been found to occur yielding 2-(4-nitrophenyl)imino-1,2,5,6-tetrahydropyridine **4**; in the absence of nitroaniline the shorter reaction time allows the reaction to be stopped at the unsaturated lactam **5** formation stage; the oxidation of **1a** hydrochloride leads to 1-(*N*-formyl-*N*-methyl)amino-3-phenylpropan-2-one **6** *via* decyclisation–elimination steps, providing a new method for *N*-formyl-substituted aminoketone synthesis.

Very recently we reported two new oxidative reactions of 4-aryl-substituted 1,2,3,6-tetrahydropyridines (THP) **1** under the action of potassium permanganate: their ketodihydroxylation[1–3] and coupling with compounds possessing an activated methyl group (methyl ketones and nitromethane).[4–7] The allylamino moiety of the THP is involved in the reactions, which are both regioselective and stereoselective thus providing us with a convenient ‘one-pot’ method of preparation of two potentially important sets of substances: 4-aryl-3,4-dihydroxy-2-oxopiperidines **2** and 4-aryl-2-R-methylene-1,2,5,6-tetrahydropyridines **3** (Scheme 1).

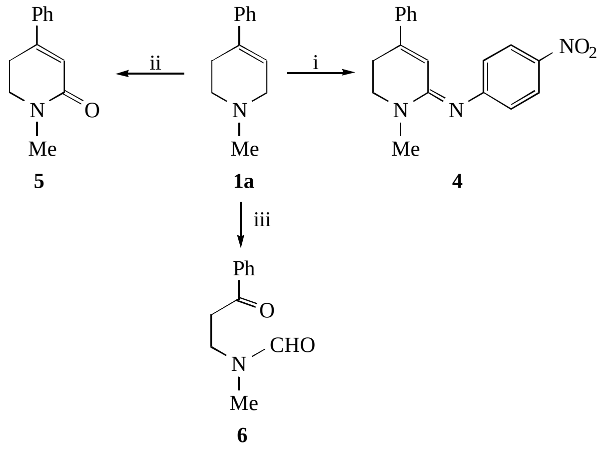


R^1 = Me, Et, CH_2Ph
R^2 = COMe, COPh, NO_2
Ar = Ph, 4-Py, 4-paracyclophane

Scheme 1

In a continuation of our studies dealing with the oxidation of THP we now report three new routes to the oxidative structure modification of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **1a**. The reactions were carried out in acetonitrile at room temperature with potassium permanganate as oxidising agent, and the structure of the final products depends on the structure of the initial reactants and the reaction time.

It was found that in the presence of 4-nitroaniline oxidation of **1a** for 2 h afforded the imination product: 2-(4-nitrophenyl)-imino-1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine **4** (Scheme 2). This oxidative reaction is unknown in tetrahydropyridine chemistry, and thus it can be useful as a new method for the synthesis of 2-imino derivatives of tetrahydropyridines.



Scheme 2 *Reagents and conditions*: i, **1a**:$NH_2C_6H_4NO_2$-*p*:$KMnO_4$ = 1:1:1, room temperature, 2 h; ii, **1a**:$KMnO_4$ = 1:1, room temperature, 30–50 min; iii, **1a**·HCl:$KMnO_4$ = 1:1.5, room temperature, 2 h.

As we found previously,[1] oxidation of **1a** by $KMnO_4$ in acetonitrile media for 2 h yields the diol lactam **2**. Here we demonstrate that decreasing the reaction period to *ca.* 1 h allows us to stop the oxidative transformation at the intermediate compound stage: 1-methyl-2-oxo-4-phenyl-1,2,5,6-tetrahydropyridine **5**. The yield of the unsaturated lactam **5** is 65%. This means that the time variation of the reaction now allows us to effectively lactamise tetrahydropyridines. In the case of **1a** used in the form of hydrochloride the reaction proceeded further, since the final product has the structure of 1-(*N*-formyl-*N*-methyl)-3-phenylpropan-3-one **6**. The presence of the quaternised piperidine **1a** thus sharply enhances the oxidising ability of the permanganate anion (as in the case of phase transfer catalysts). This new reaction seems to proceed *via* initial formation of the lactam **5** and diol lactam **2**, the latter being then oxidatively decyclised with elimination of CO_2. The 85% yield of **6** speaks in favour of the new method of preparative synthesis for *N*-formyl substituted β-aminoketones. The structures of **4**–**6** were confirmed spectroscopically.[†]

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[†] NMR spectra were recorded at 300 MHz (^1H) and 75.5 MHz (^{13}C), standard TMS, $CDCl_3$, δ/ppm. Compounds **4**–**6** gave satisfactory elemental analyses.

Compound **4**: yield 33%, mp 92–94 °C; ^1H NMR: 2.87 (t, 2H, 5-CH_2, $^2J = {}^3J$ = 6.61 Hz), 3.16 (s, 3H, Me), 3.53 (t, 2H, 6-CH_2, $^2J = {}^3J$ = 6.61 Hz), 6.27 (s, 1H, 3-H), 6.88 and 8.15 (d, 2×2H, AA′BB′, J = 9.0 Hz), 7.36 (br. s, 5H, Ph); MS (EI, 70 eV, 140 °C), m/z (%): 307 (100) [M^+], 306 (44), 259 (27), 250 (33), 187 (35), 166 (37), 149 (60); IR (KBr, ν/cm^{-1}): 1640 (C=N), 1627 (C=C), 1550 and 1339 (NO_2).

Compound **5**: yield 65%, mp 78–80 °C; ^1H NMR: 2.73 and 3.48 (t, 2×2H, 5-CH_2 and 6-CH_2, $^2J = {}^3J$ = 7.02 Hz), 3.00 (s, 3H, Me), 6.24 (s, 1H, 3-H), 7.25–7.5 (m, 5H, Ph); ^{13}C NMR: 26.31 (5-C), 34.02 (Me), 47.36 (6-C), 119.73 (3-C), 125.56, 128.60, 129.25 and 148.87 (6×C Ph), 137.45 (4-C), 165.46 (C=O); MS (100 °C), m/z (%): 187 (100) [M^+]; IR (KBr, ν/cm^{-1}): 1657 (NC=O), 1600 (C=O).

Compound **6**: yield 85%, colourless oil (purified by chromatography on silica gel column, eluent ether, R_f 0.73 in acetone). In the ^1H NMR and ^{13}C NMR spectra of the amide **6** double sets of signals are observed. ^1H NMR: 2.88 and 3.03 (s, 2×1.5H, Me), 3.23 and 3.30 (t, 2×1H, 2-CH_2, $^2J = {}^3J$ = 6.64 Hz), 3.74 (t, 2H, 1-CH_2, $^2J = {}^3J$ = 6.64 Hz), 7.48, 7.59 and 7.94 (m, 5H, Ph), 8.02 and 8.18 (s, 2×0.5H, NCHO); ^{13}C NMR: 29.43 and 35.39 (Me), 36.05 and 36.58 (2-C), 40.38 and 44.36 (1-C), 127.80, 128.5, 133.4 and 136.45 (6×C Ph), 162.72 and 163.03 (NC=O), 197.20 and 198.25 (C=O). MS (70 °C), m/z (%): 191 (100) [M^+]; IR (paraffin oil, ν/cm^{-1}): 1675 and 1645 (C=O).

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