Mendeleev Commun., 1998, 8(4), 137–138

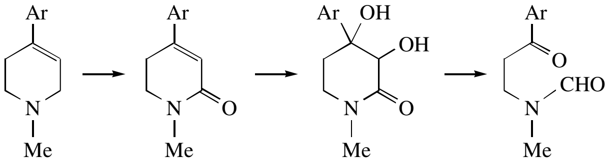
Cascade and stepwise oxidation of 4-phenyl- and 4-(-pyridyl)tetrahydropyridines

Anatoly T. Soldatenkov,* Ayalew W. Temesgen, Ives A. Bekro, Svetlana A. Soldatova and Boris N. Anissimov

Peoples' Friendship University of Russia, 117198 Moscow, Russian Federation. Fax: + 7 095 433 1511

A general cascade and stepwise oxidation scheme for 4-aryl-substituted 1,2,3,6-tetrahydropyridines with $KMnO_4$ is described, which includes the consecutive oxidative transformation of the carbon triad in the substrate allylamine fragment, yielding tetrahydropyridin-2-ones, 3,4-dihydroxypiperidin-2-ones and, finally, 1-formylamino-3-arylpropan-3-ones.

The ability of 1,2,3,6-tetrahydropyridines (THP) to react with aqueous $KMnO_4$ was reported[1] to depend considerably on the nature of the substituent present at the 4-position of the pyridine ring. For example, the 4-methyl-substituted THPs are easily hydroxylated under the classical conditions of the Vagner reaction (cooling, water–alcohol solution), whereas their 4-phenyl analogues appeared to be completely inert.[1] This latter fact appears to be connected with the coplanarity of the phenyl and tetrahydropyridine moities which increases steric hindrance to permanganate anion attack on the double bond. Nevertheless, we have recently found[2,3] that 4-phenylTHP **1a** and 4-(-pyridyl)THP **1b** can be readily polyfunctionalised by a one-pot oxidation protocol, making available a high-yield synthetic method for the preparation of 3,4-dihydroxypiperidin-2-ones **3a**,**b** under slightly modified conditions (20–35 °C, water–acetonitrile solution). Our subsequent investigation[4] of the one-pot oxidations has demonstrated the possibility of 2-oxo-4-phenylTHP **2a** and 1-formylamino-3-phenylpropan-3-one **4a** formation starting in each case from **1a**. The data thus obtained have prompted us to pose two important questions: are the compounds **2a**–**4a** recovered in the different experiments formed as a result of a gradual elevation of the degree of oxidation in one reaction sequence; and, if so, can this cascade reaction be considered as a general one, at least for the 4-aryl-substituted THP series?



1a,**b** **2a**,**b** **3a**,**b** **4a**,**b**

a Ar = Ph
b Ar = 4-Py

Scheme 1

In order to answer these questions it was decided to use the same one-pot procedures[4] to afford new 2-oxo-THP **2b** and aminopropanone **4b** from **1b**. Their successful repetition together with the separate oxidation of the lactam **2a** into the lactamdiol **3a**, the separate oxidative conversion of the latter through ring cleavage into the aminoketone **4a**, and repeating the same experimental sequence with **2b** and **3b**, would provide supporting evidence for generalising both the cascade and the stepwise routes for the THP oxidative transformations. All the reactions were carried out in the presence of $KMnO_4$ in water–acetonitrile solutions and afforded unambiguously the expected results. It was therefore established that oxidation of 4-pyridyl-THP **1b** into **2b** and **4b** proceeded well, though with lower yields (27% and 58%, respectively) in comparison with the analogous reactions of 4-phenylTHP.[2,4] The lactams **2a**,**b** were readily hydroxylated at < 0 °C (in contrast to the inert 4-aryl THP **1**[1]) into the *cis*-diol lactams **3a**,**b** with yields 54% and 45%, respectively. However, at room temperature the yield of **3a** was increased to 76%. Apart from the importance of the **1** → **2** → **3** conversions, it is worth pointing out the decisive role of the amide group in the **2** → **3** reaction. The presence of the electron-accepting amide group seems likely to significantly polarize the C=C bond in lactams **2** thus leading (even < 0 °C) to successful dihydroxylation of the 4-aryl THP system.

The final stage in the oxidative transformation study consisted of proving the fact that the lactam diols **3** were intermediate products in the formation of amidoketones **4**. On treatment of **3** with $KMnO_4$ under elevated temperatures (up to 50 °C), TLC showed complete conversion to compounds **4**. On work-up a colourless, thick oil of **4** was obtained in 34% to 58% yield. In the case of one-pot oxidation of **1b** hydrochloride at room temperature the amide **4b** was chromatographically separated in 43% yield. The structures of new compounds **2b** and **4b** were confirmed spectroscopically.†

The data thus obtained allow us to conclude that a general cascade and stepwise scheme for the transformation of 4-aryl-substituted THP can be elaborated, based on the gradual elevation of the degree of oxidation of the triad of carbon atoms present in the allylamine moiety of the initial THP. These schemes can be useful in understanding certain azine oxidation mechanisms and can also serve as new, effective laboratory methods for the synthesis of three important groups of compounds.

We thank the Russian Foundation for Basic Research (grant no. 96-03-33432a) for supporting the investigation.

---

† ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$, standard TMS.

Compound **2b** was prepared by oxidation of **1b** with $KMnO_4$ (**1a**:$KMnO_4$ = 1:1.5) in MeCN at 20 °C, 1.5 h; yield 27%, mp 84–85 °C. ^{1}H NMR, δ: 2.78 and 3.58 (t, 2×2H, 5-CH_2 and 6-CH_2, ^2J 7.0 Hz, ^3J 7.0 Hz), 3.03 (s, 3H, Me), 6.43 (s, 1H, 3-H), 7.37 and 8.64 (dd, 2×2H, AA′BB′, ^2J 5.0 Hz, ^3J 1.5 Hz); MS (EI, 70 eV, 80 °C), m/z (%): 188 (100) [M$^+$]; IR (KBr, ν/cm^{-1}): 1650 (NC=O), 1600 (C=C). Found (%): C, 69.86; H, 6.83; N, 14.82. Calc. for $C_{11}H_{12}N_2O$ (%): C,70.21; H, 6.38; N, 14.89.

Compound **2a** was obtained similarly from **1a** (**1a**:$KMnO_4$ = 1:1.5, 0.75 h); yield 65%, mp 78–80 °C.[4]

Compound **3a** was obtained by hydroxylation of **2a** in aqueous MeCN (**2a**:$KMnO_4$ = 1:1.5) at 0 °C, 1.5 h; yield 54%, mp 117 °C.[2] The yield of **3a** was increased to 76% at 20 °C, 2 h. One-pot oxodihydroxylation of **1a** in aqueous MeCN (**1a**:$KMnO_4$ = 1:1.5) at 20 °C, 2 h gave **3a** in 76% yield.[2]

Compound **3b** was prepared by hydroxylation of **2b** in aqueous MeCN (**2b**:$KMnO_4$ = 1:1.5) at 0 °C, 2 h; yield 45%, mp 220–222 °C.[3] One-pot oxodihydroxylation of **1b** in aqueous MeCN (**1b**:$KMnO_4$ = 1:1.5) at 20 °C yielded 65% of **3b** in 2 h.[3]

Compound **4a** was obtained from one-pot oxidation of **1a**·HCl in acetone (**1a**·HCl:$KMnO_4$ = 1:1.5) at 20 °C, 2 h; yield 85%, colourless oil, R_f 0.73 in acetone.[4] **4a** was also obtained from oxidation of **3a** in MeCN (**3a**:$KMnO_4$ = 1:1.5) at 50 °C, 0.5 h; yield 34%.

Compound **4b** was prepared by oxidation of **3b** in MeCN (**3b**:$KMnO_4$ = 1:1.5) at 50 °C, 0.5 h; yield 58%, colourless thick oil (purified by chromatography on silica gel column, eluent diethyl ether, R_f 0.41 in acetone). Compound **4b** was also prepared by one-pot **1b**·HCl oxidation (**1b**·HCl:$KMnO_4$ = 1:1.5) in acetone at 20 °C, 2 h; yield 43%. In the ^{1}H NMR spectrum of the amide **4b** a double set of N(Me)CHO group signals are observed. ^{1}H NMR, δ: 2.92 and 3.12 (s, 2×1.5H, Me), 3.3 (t, 2H, 1-CH_2, ^2J 6.0 Hz, ^3J 6.0 Hz), 3.8 (t, 2H, ^2J 6.0 Hz, ^3J 6.0 Hz), 7.75 and 8.85 (dd, 2×2H, AA′BB′, ^2J 4.5 Hz, ^3J 1.5 Hz), 8.01 and 8.2 (s, 2×0.5H, NCHO); MS (100 °C), m/z (%): 192 (80) [M$^+$], 107 (36), 106 (81), 86 (100), 78 (74), 72 (59), 58 (44); IR (paraffin oil, ν/cm^{-1}): 1676 and 1646 (C=O). Found (%): C, 61.96; H, 6.47; N, 14.21. Calc. for $C_{10}H_{12}N_2O_2$ (%): C, 62.50; H, 6.25; N, 14.58.

References

1 T. N. Maksimova, V. B. Mochalin and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 1980, 783 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1980, 604].

2 A. T. Soldatenkov, I. A. Bekro, J. A. Mamyrbekova, S. A. Soldatova, A. W. Temesgen, N. D. Sergeeva, L. N. Kuleshova and V. N. Khrustalev, *Khim. Geterotsikl. Soedin.*, 1996, 222 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1996, 197].

3 A. T. Soldatenkov, I. A. Bekro, S. A. Soldatova, E. Glover, A. Temesgen, L. N. Kuleshova, V. N. Khrustalev and N. D. Sergeeva, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 2020 (*Russ. Chem. Bull.*, 1997, **46**, 1916).

4 A. T. Soldatenkov, A. W. Temesgen, I. A. Bekro, T. P. Khristoforova, S. A. Soldatova and B. N. Anissimov, *Mendeleev Commun.*, 1997, 243.

Received: Moscow, 14th May 1998
Cambridge, 23rd June 1998; Com. 8/03650K