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Regioselective oxidation of *N*-alkylpyrrolidines to pyrrolidin-5-ones by $RuCl_3/NaIO_4$ ☆

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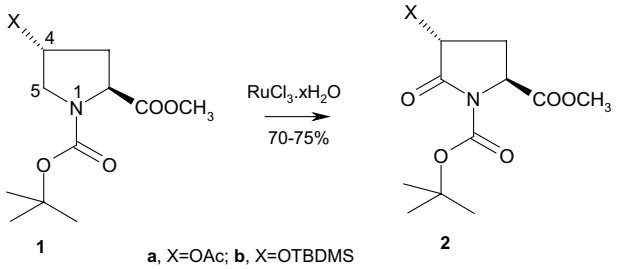
Abstract—$RuCl_3/NaIO_4$ under EtOAc/H_2O biphasic conditions, selectively oxidizes the Nα-*endo*-methylene group of pyrrolidine derivatives, without affecting the *exo*-methylene group adjacent to the N-heteroatom.

Functionalized pyrrolidinone derivatives are key intermediates for the synthesis of many biologically active compounds.[1] Pyroglutamic acids are known to introduce unique structural constraints into peptide chains[2] and derivatives functionalized at C4 have important biological activities.[3,4] Most reported methods to obtain C4-functionalized pyroglutamates involve asymmetric 1,3-dipolar cycloadditions[5] or N-alkylation using lithium enolates derived from pyroglutamic esters.[6] In a recent report, C4-substituted *N*-Boc pyrrolidin-5-one derivatives were synthesized from 4-(*R*)-hydroxy-L-proline through oxidation of 4-substituted-*N*-Boc proline[7,8] using the versatile oxidizing agent RuO_4 generated in situ from $RuO_2/NaIO_4$ in a biphasic solvent system.[9] Our intention was to prepare C4-functionalized N-alkylated pyroglutamate derivatives **5** (Scheme 2) as intermediates for the synthesis of modified peptide nucleic acids (PNA). This can be achieved by N-alkylation of suitable pyroglutamates; however, the use of strong bases in N-alkylation is accompanied by a facile opening of the pyrrolidine ring. To overcome this, we attempted a hitherto unknown direct oxidation of various N-alkylated C4-substituted pyrrolidine derivatives **4** (Scheme 2) using the oxidizing agent $RuCl_3/NaIO_4$. Herein we report the interesting results observed on regioselective oxidation of the endocyclic Nα-methylene (C5), in preference to oxidation of other Nα-methylenes such as the exocyclic N-CH_2 or CH_2-NHBoc, which yield the desired monomers for *aepone*-PNA synthesis.[10]

To test the efficiency of $RuCl_3/NaIO_4$, *N*-Boc-4-acetoxy and 4-*O*-TBDMS proline methyl esters **1** were treated with the reagent in two different biphasic solvent systems $CCl_4/CH_3CN/H_2O$ (1:1:1.5) and EtOAc/H_2O (1:1) (Scheme 1). The reaction gave the corresponding C5-one products **2** in 70–75% yield. The structures of the compounds were confirmed from the spectral data. Thus $RuCl_3/NaIO_4$ is as efficient as $RuO_2/NaIO_4$ for oxidation of the present substrates.

Various *N*-(Boc-aminoethyl)-4-(*R*/*S*)-substituted proline methyl esters **4** (Scheme 2) prepared from 4-(*R*)-hydroxyproline derivative **3** directly or via a Mitsunobu reaction,[11] at C4 were then subjected to oxidation using $RuCl_3/NaIO_4$ in either $CCl_4/CH_3CN/H_2O$ (1:1:1.5) or EtOAc/H_2O (1:1) at room temperature and, as followed by TLC analysis, the starting materials disappeared with the appearance of a major product during a 30 min to 1 h period. Isolation of the product after aqueous



Scheme 1.

Keywords: $RuCl_3/NaIO_4$; Oxidation; *N*-Alkyl pyrrolidinones.
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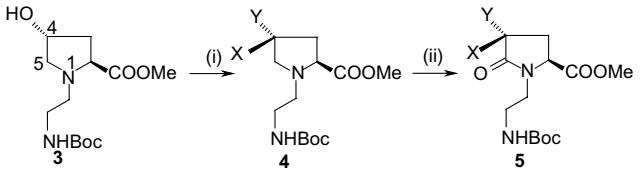

Scheme 2. Reagents and conditions: (i) Ac_2O, Py, rt, 5 h for **4b**, 80%; TBDMSCl, DMF, imidazole 6 h for **4c**, 70%; Ph_3P, DIAD, PhCOOH for **4d**, THF, 5 h, 80%; Ph_3P, DIAD, methyl tosylate for **4e**, THF, 8 h, 65%; Ph_3P, DIAD, 4-nitrobenzoic acid for **4f**, THF, 10 h, 70%; (ii) $NaIO_4/RuCl_3{\cdot}xH_2O$, AcOEt/$H_2O$, rt, 30 min to 1 h, yields 30–45%. Details of **a**–**f** are given in the footnote of Table 1.

work-up and characterization indicated the structures to be **5**, with oxidation occurring at C5. The isolated yields of the products were in the range 30–45% and the solvent system EtOAc/H_2O (1:1) gave the best yield (Table 1). There was no particular dependence of the yields on the stereochemistry of the C4-substituents, with *R* and *S* isomers behaving similarly. Among the different C4-substituents OMs, OBz, OAc, TBDMS, OTs and OPNB, the reaction gave the best yield with the 4-OMs derivative. A comparable C5-one product was obtained even with the proline substrate **4g** lacking any C4-substituents.[5] The reactions of *N*-alkyl substrates **4** were also found to be faster than those of *N*-Boc analogues **1**. All products were characterized by appropriate spectral data.

RuO_4 generated in situ from $RuCl_3/NaIO_4$ is well known to oxidize methylene groups α to N or O heteroatoms into carbonyl groups.[12] In the case of tertiary amines present as a part of polycyclic systems with *N*-benzyl substitution, the first oxidation occurs at the exocyclic benzylic methylene followed by the endocyclic methylene.[13] In the substrates used here (**4a**–**4g**), there are three Nα-methylene groups—endocyclic C5, exocyclic N-CH_2 and NHBoc-CH_2. Of the different possible oxidation products including N-oxide formation, it was found that the major products (**5a**–**5g**) obtained from a regioselective oxidation of the endocyclic CH_2 resulted at C5 of the pyrrolidine ring to give the lactam derivatives. The identity of the oxidation product was unambiguously confirmed by single crystal X-ray data for **5a**[10] and **5d** (Fig. 1). The present approach is therefore convenient as it gave intermediates for transformation into other C4-substituted pyrrolidin-5-ones, particularly the *aepone*-PNA analogues.[10]

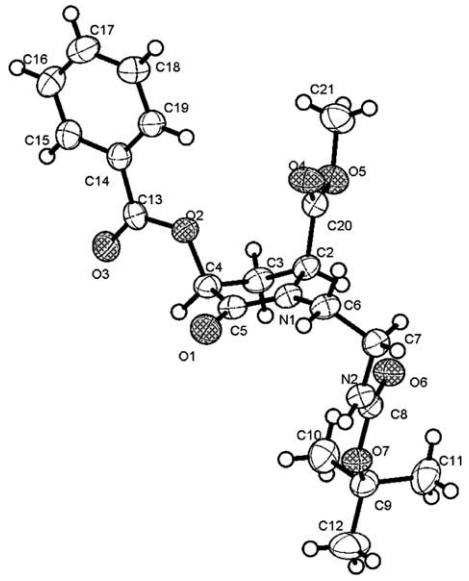

Figure 1. ORTEP diagram of the crystal structure[15] of **5d**.

Spectroscopic characterization. In the absence of any crystallographic data, it is necessary to unambiguously identify the site of oxidation and this was done using ^1H and ^{13}C NMR data (Table 2). In view of the similar chemical shifts of different Nα-methylene protons, the ^1H NMR was completely assigned using ^1H–^1H DQF COSY. While assignment of H5 is straightforward due to coupling with H4, assignment of βH′H″ were done via the connectivity with NH followed by assignment of αH′H″. The different carbons were assigned from the ^1H–^{13}C HETCOR experiment.

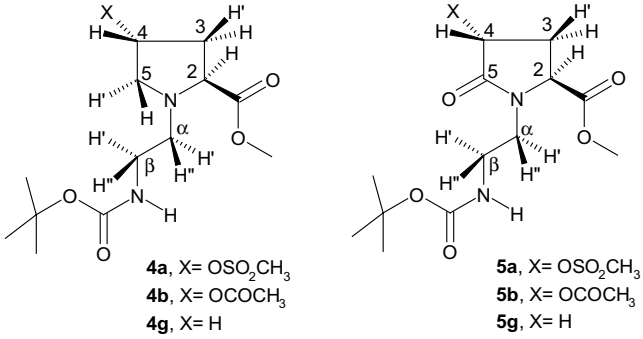

Table 1. Reaction yields for $RuCl_3/NaIO_4$ oxidation of substrates **4**[a]

Entry	Substrate	Product	EtOAc/H_2O (% yield)	$CH_3CN/CCl_4/H_2O$ (1:1:1.5)	Time (min)
1	**4a**	**5a**	45	45	60
2	**4b**	**5b**	38	30	30
3	**4c**	**5c**	39	32	45
4	**4d**	**5d**	45	36	30
5	**4e**	**5e**	35	30	75
6	**4f**	**5f**	40	37	45
7	**4g**	**5g**	35	41	45

[a] For **a**–**c**, X = H; **d**–**f**, Y = H; **a**, Y = OMs; **b**, Y = OAc; **c**, Y = OTBDMS; **d**, X = OBz; **e**, X = OTs; **f**, X = OPNB; **g**, X = H; Y = H. For a typical reaction procedure, see Ref. 14.

Table 2. Selected ^{1}H and ^{13}C chemical shifts (δ ppm)[a]

Compound	4a	5a	4b	5b	4g	5g
H4	5.2	5.3	5.3	5.4	1.8, 1.9	2.1
H5′	2.8	—	2.6	—	2.4	—
H5″	3.4	—	3.5	—	3.1	—
αH′	2.6	3.0	2.6	3.1	2.6	3.1
αH″	2.7	3.1	2.7	3.1	2.7	3.2
βH′	3.1	3.5	3.1	3.5	3.1	3.1
βH″	3.1	3.7	3.2	3.7	3.1	3.4
NH	5.1	4.8	5.2	4.9	5.2	4.9
C4	79.0	75.6	73.0	69.6	23.3	23.0
C5	58.4	169.8	58.6	171.2	53.4	172.4
Cα	53.5	42.0	53.2	42.9	54.8	42.1
Cβ	39.0	37.4	39.0	37.5	39.0	38.2

[a] All spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C in $CDCl_3$.

The oxidized products **5** exhibited characteristic similarities in their ^{1}H and ^{13}C NMR data compared to the reaction substrates **4** as seen from the selected data shown in Table 2. In the ^{13}C NMR, the signal around 68.0 ppm due to C5 in substrates **4** disappeared after oxidation giving rise to a new signal at around 170.0 ppm characteristic of C=O. The C4-signal was shifted upfield by 3.4 ppm in **5a**–**5b** upon oxidation, while that of Cα was shifted upfield by 10–12 ppm. In contrast, the chemical shift of Cβ was not affected much. In the ^{1}H NMR of **4**, the multiplets arising from the nonequivalent H5′5″ protons around 2.6 and 3.4 ppm disappeared in product **5**, while signals due to αH and βH were retained with a downfield shift of ca. 0.3 ppm perhaps due to anisotropic effects of the C5-carbonyl. Interestingly, no significant changes were seen for H4, except for a change of the multiplet to a triplet. The spectral data shown in Table 2 are for **5a** whose crystal structure is known[10] along with **5b** and **5g** whose crystal structures are not available. All three compounds showed similar patterns in NMR, strongly supporting the regiospecificity of the reaction.

In summary, we have observed that the endocyclic methylene group at C5 of pyrrolidine derivatives is more susceptible to oxidation with $RuCl_3/NaIO_4$ than the other two exocyclic methylene groups α to heteroatom N. These derivatives could be useful for synthesis of N-alkylated pyrrolidinones and unnatural amino acids.

Supplementary material

Experimental procedures, NMR (^{1}H–^{1}H COSY and ^{13}C–^{1}H HETCOR) and mass spectra of **5a**, **5d**, **5e** and **5g** are available in the supplementary material.

Acknowledgements

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References and notes

1. (a) Najera, C.; Miguel, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303, and references cited therein; (b) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Guarneri, M.; Gandolfi, C.; Ceserani, R.; Longiave, D. *J. Med. Chem.* **1981**, *24*, 625–628.
2. Bernardi, F.; Garavelli, M.; Scatizzi, M.; Tomasini, C.; Trigari, V.; Crisma, M.; Formaggio, F.; Peggion, C.; Toniolo, C. *Chem. Eur. J.* **2002**, *8*, 2516–2525.
3. Hon, Y.-S.; Chang, Y.-C.; Gong, M. I. *Heterocycles* **1990**, *31*, 191–195.
4. (a) Dinsmore, A.; Doyle, P. M.; Steger, M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 613–621; (b) Bourry, A.; Pitard, F.; Rigo, B.; Sanz, G.; Camus, F.; Norberg, B.; Durant, F.; Couturier, D. *J. Heterocycl. Chem.* **2002**, *39*, 109–114; (c) Goswami, L. N.; Srivastava, S.; Panday, S. K.; Dikshit, D. K. *Tetrahedron Lett.* **2001**, *42*, 7891–7892; (d) Tomasini, C.; Villa, M. *Tetrahedron Lett.* **2001**, *42*, 5211–5214; (e) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411–3414; (f) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353–6359; (g) Konas, D. W.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 8831–8842.
5. Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167–172.
6. (a) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Ferrando, S. S. *Tetrahedron* **1993**, *49*, 8665–8678; (b) Ezquerra, J.; Pedregal, C.; Rubio, A. *J. Org. Chem.* **1994**, *59*, 4327–4331; (c) Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920–1924.
7. Zhang, X.; Schmitt, A. C.; Jiang, W. *Tetrahedron Lett.* **2001**, *42*, 5335–5338.
8. Qiu, X. L.; Qing, F. L. *J. Org. Chem.* **2003**, *68*, 3614–3617.
9. Nakata, H. *Tetrahedron* **1963**, *19*, 1959–1963.
10. Sharma, N. K.; Ganesh, K. N. *Chem. Commun.* **2003**, *19*, 2484–2485.
11. (a) D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *Org. Lett.* **1999**, *1*, 1513–1516; (b) Vidal, J. A. G.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2481–2484.
12. Sheehan, J. C.; Tulis, R. W. *J. Org. Chem.* **1974**, *39*, 2264–2267.
13. Bettoni, G.; Carbonara, G.; Franchini, C.; Tortorella, V. *Tetrahedron* **1981**, *37*, 4159–4164.
14. Typical general procedure: To a vigorously stirred solution of compound **4** (2.3 mmol) in AcOEt (20 mL), an aqueous solution (20 mL) of $NaIO_4$ (9.08 mmol) and $RuCl_3{\cdot}xH_2O$ (catalytic amount, 0.02 mmol) was added. After 30 min, the reaction was quenched by the addition of isopropyl alcohol and stirred for another 20 min and then the reaction mixture was concentrated in vacuo. The residue was taken into ethyl acetate (20 mL) and washed with water, the organic extract dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography to give **5** as a white foam. Yield 30–45%.
15. Single crystals of the compound **5d** were obtained from a mixture of CH_2Cl_2 and CH_3OH and a good quality crystal was selected using a Leica Polarizing Microscope. X-ray intensity data were collected on a Bruker SMART APEX

CCD diffractometer at room temperature. Crystal data: $C_{20}H_{26}N_2O_7$, $M = 406.43$, crystal dimensions $0.61 \times 0.59 \times 0.14$ mm, crystal system monoclinic, space group $P2_1$, $a = 9.2779(15)$, $b = 8.9289(14)$, $c = 13.239(2)$ Å, $\beta = 96.512(3)°$, $V = 1089.7(3)$ Å^3, $Z = 2$, $D_c = 1.239$ g cm^{-3}, μ(Mo-K$_\alpha$) $= 0.094$ mm^{-1}, $T = 293(2)$ K, $F(000) = 432$, 5493 reflections collected, 3634 unique [$I > 2\sigma(I)$], S = 1.053, R value 0.0393, $wR2 = 0.1116$ (all data $R = 0.0416$, $wR2 = 0.1135$). CCDC no 221794: *cis*-1-(*N*-Boc-amino-ethyl)-4(*S*)-*O*-benzoyl-5-one-2(*S*)-proline methyl **5d**. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.