Ruthenium Catalyzed Oxidation of 3-Amino-β-Lactams

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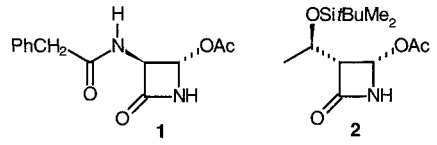
Abstract: 3-Aminoazetidin-2-ones were converted into the corresponding 4-acetoxy derivatives by treatment with AcOOH and ruthenium on carbon as catalyst.

Azetidin-2-ones possessing a C-4 substituent replaceable with a variety of nucleophiles are recognised as synthetically useful in β-lactam chemistry.[1] In this field, 4-acetoxyazetidin-2-ones derivatives **1** and **2** have been demonstrated to be versatile building blocks.[2]

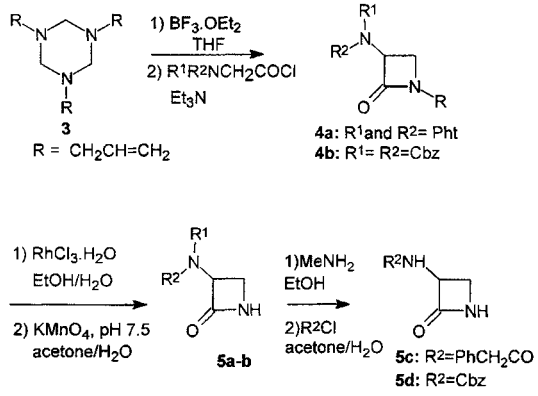


The azetidin-2-one **2** is nowadays commercially available and even though compound **1** appears to be an interesting intermediate, it can only be prepared in a multistep procedure starting from a derivative of methyl penicillanate 1-oxide[3] or from the *N*-trimethylsilylimine of (2*S*)-lactal.[4]

In a general program related to the design, synthesis and study of novel β-lactams, we became interested in developing a short synthetic methodology for optically active monocyclic 3-amino-4-acetoxy-azetidin-2-ones that could provide versatile intermediates for the synthesis of monolactams, cephem and multicycle β-lactams. In the strategy envisaged for the preparation of **1**, the key step would be accomplished by a C-4 oxidation of a 3-aminoazetidin-2-one. Despite many methods that provided acetoxylation of 3-hydroxyethylazetidin-2-one[5], the same derivatization on 3-amino-β-lactams has been less investigated[6].

Here we describe a method for the synthesis of 3-amino-4-acetoxy-azetidin-2-one through a ruthenium-catalyzed oxidation of C-4.

The β-lactams used in this work were obtained as shown in Scheme 1.

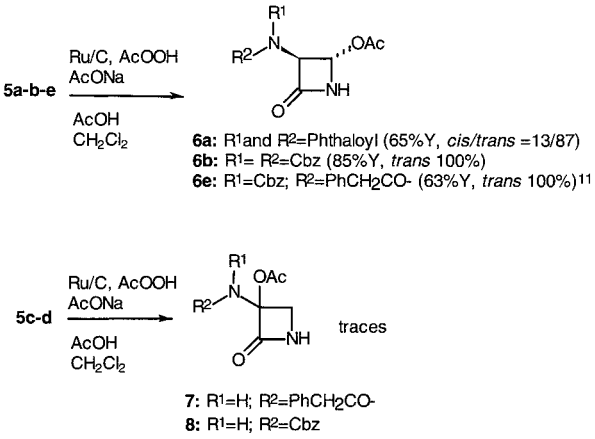


Scheme 1

The *N*-allylhexahydrotriazine **3** was converted, according to a modified Kamiya procedure[7] into β-lactams **4a-b** using phthalimidoacetyl chloride or *N,N*-dicarbobenzyloxyglycyl chloride,[8] respectively. Isomerization and hydrolysis of the *N*-allyl group afforded **5a-b** in good yield. Compound **5a** was converted into **5c-d** *via* deprotection of the phthalimido group with $MeNH_2$ and treatment under Schotten-Baumann conditions using phenylacetyl chloride or CbzCl and aqueous sodium carbonate.[9]

The catalytic activity of various metal complexes was examined for the oxidation of **5a** with AcOOH. Ruthenium catalyst such as $RuCl_3.nH_2O$ and $RuCl_2(PPh_3)_3$ were effective (57% and 40% yield, respectively), but Ru on carbon gave better results (65% yield). The diastereoselectivity of the reaction was in favour of the more stable *trans* isomer.

Representative results on the formation of 4-acetoxy β-lactams are reported in Scheme 2.[10]



Scheme 2

It is noteworthy that the acetoxylation did not take place when this reaction was carried out on N-1 substituted compounds such as **4a**. Moreover, the substituent on the C-3 amino group plays an important role: when it is a mono substituted amide **5c-d**, we observed a sluggish reaction leading to a complex mixture where traces of the 3-acetoxy derivative (**7-8**) could be recovered.

The stereochemistry of the acetate **6a** was assigned on the basis of ^1H NMR spectral data. The major isomer exhibited a coupling constant of 1.5 Hz for interaction between the vicinal lactam protons, while the minor component showed a vicinal coupling constant of 4.0 Hz consistent with the assignment of these compounds as the *trans*- and *cis*-isomers, respectively. The reaction of ruthenium with peracetic acid leads to oxoruthenium species, which abstracts the H atom from C-4 of the β-lactam and subsequent electron transfer gives a four membered acyliminium ion.[12] Nucleophilic reaction of this intermediate with AcOH gives 4-acyloxyazetidinones.[13] The substituent on C-3 drove the stereochemistry towards extremely high levels, in fact in the case of **6b-c** the only products observed have *trans* arrangement of C-3 and C-4 .

In conclusion, the methodology described above provides an efficient route for the synthesis of 3-amino-4-acyloxy-substituted azetidinones that are suitable for elaboration by nucleophilic substitution of the acyloxy group. This oxidation requires two conditions: a N-1 unsubstituted position and a fully protected C-3 amino group.

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References and Notes

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(6) To our knowledge, the only example reported in the literature concerns to the oxidation of **5a** to give the corresponding 4-acetyloxy and benzoyloxy derivative: Easton, C. J.; Love, S.G.; Wang, P. *J. Chem. Soc. Perkin Trans. I* **1990**, 277.

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(8) *N,N*-dicarbobenzyloxy-glycylchloride was formed *in situ* by adding oxalyl chloride to the corresponding *N,N*-dicarbobenzyloxy-glycine (1.5 eq., CH_2Cl_2, rt, 3h). The glycine derivative was obtained in a 60% overall yield through alkylation of Dibenzyl Iminodicarboxylate Potassium Salt (cfr. *J. Chem. Soc: Perkin Trans. I* **1991**, 49) with tert-butyl bromoacetate and subsequent deprotection of tert-butyl group with $TiCl_4$ (1.5eq., CH_2Cl_2, 0°C, 1 min) (cfr. *J. Am. Chem. Soc.* **1982**, *104*, 1116).

(9) All new compounds gave correct analytical data (^{1}H NMR, ^{13}C NMR, IR).

(10) Typically, the oxidation of **5a** is as follows: a mixture of Ru 5% on carbon (80 mg, 0.04 mmol), anhydrous sodium acetate (82 mg, 1 mmol), acetic acid (1mL), β-lactam **5a** (1 mmol) and CH_2Cl_2 (3mL) was charged in a 25 ml flask at room temperature. To the above mixture was added a 32% solution of AcOOH in AcOH (0.46 ml, 2.2 mmol) dropwise at room temperature over a period of 1h and the resulting solution was stirred for 2 h. The reaction mixture was poured into cold water, filtered and extracted with CH_2Cl_2 (3x15mL). The organic solution was washed with 10% aqueous solution of sodium sulfite (20mL), with brine and dried over sodium sulfate. Evaporation followed by column chromatography on silica gel (cyclohexane/ethyl acetate=6/4) gave **6a** (177 mg, 0.65 mmol, 65%) in a 13/87 *cis/trans* ratio.

(11) The starting material of **6e** (**5e**) has been obtained from **4a** in good yield through a different sequence of the same steps reported in Scheme 1 and precisely: deprotection of phthalimido group with $MeNH_2$/EtOH, refunctionalization as 3-phenylacetamido-azetidin-2-one under Schotten-Baumann conditions, protection of the amidic hydrogen with NaH/CbzCl in THF and final deprotection of the *N*-allyl group.

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(13) **6a** *trans*: m.p. 197-198°C; IR (nujol): 3250, 1790, 1745, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H); 5.4 (d, 1H, *J*=1,5 Hz); 6.18 (d, 1H, *J*=1.5 Hz); 6,75 (bs, 1H); 7.8 (m, 2H); 7.9 (m, 2H). ^{13}C NMR (75.5 MHz, d-DMSO): δ 170.2; 166.7; 162.5; 135.1; 131.1; 123.7; 76.6; 60.2; 20.6 . **6a** *cis*: ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H); 5.57 (dd, 1H, *J*=1,34 Hz, *J*=4 Hz); 6.05 (d, 1H, *J*=4 Hz); 6.88 (bs, 1H); 7.85 (m, 4H). **6b**: IR (CH_2Cl_2): 3350, 1805, 1720, 1700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H); 5.26 (s, 4H); 5.52 (d, 1H, J=1Hz); 5.93 (s, 1H); 6.5 (bs, 1H); 7.3 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.3; 163.2; 152.2; 128; 134; 78; 67; 43.1; 20.5. **6c**: IR ($CHCl_3$): 3300, 1800, 1750, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H); 4.26 (AB, 2H); 5.25 (s, 2H); 5.6 (s, 1H); 5.9 (s, 1H); 6.42 (b, 1H); 7.2-7.5 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.7; 171; 163; 152 ; 127; 133; 78; 69.8; 65.6; 44.3; 20.6.