OSMIUM-CATALYZED OXIDATION OF β -LACTAMS WITH PEROXIDES

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Summary. Osmium-catalyzed oxidation of β -lactams with peroxides in acetic acid gives the corresponding 4-acetoxy β -lactams, which are versatile synthetic intermediate of carbapenem antibiotics, in good to excellent yields.

Oxidation of β -lactams is of importance in view of synthesis of carbapenem and thiopenem antibiotics.¹ We wish to report that osmium-catalyzed oxidation of β -lactams with peroxides gives 4-acctoxy β -lactams highly efficiently (eq. 1). This is the first example of the osmium-catalyzed oxidation of C-H bonds, although some osmium-catalyzed reactions have been reported.²

The osmium trichloride catalyzed oxidation of β -lactams with peracetic acid in acetic acid proceeds highly efficiently under mild conditions. The oxidation of azetidin-2-one (1) is the representative result. To a mixture of 1 (0.20 g, 2.8 mmol), anhydrous sodium acetate (0.23 g, 2.8 mmol), OsCl₃ (17 mg, 2 mol%) in acetic acid (2 ml) was added a 30% solution of peracetic acid in ethyl acetate (1.56 g, 6.2 mmol) dropwise with stirring at room temperature over a period of 2 h. After stirring for 3 h, the reaction mixture was poured into water and extracted with ethyl acetate (100 ml x 2). To decompose excess peracetic acid, the combined organic layer was washed with aqueous 5% sodium sulfite solution (20 ml) and dried over magnesium sulfate. Evaporation followed by column chromatography on silica gel (hexane:ethyl acetate, 1:1) gave 4-acetoxyazetidin-2-one (2) (0.28 g, 2.2 mmol, 78%).

The representative results of the formation of 4-acetoxyazetidin-2-ones are shown in Table 1. Various azetidin-2-ones (entries 1-6) can be converted into the corresponding 4-acetoxyazetidin-2-ones in good yields. The oxidation of (4S)-4-carboxyazetidin-2-one (3) gave racemic 2 accompanied by decarboxylation (entry 3). It is noteworthy that Kolbe type electrolysis of 4-carboxyazetidin-2-one gives 2.³ Importantly, (1'R, 3S)-3-(1'-t)-butyldimethylsiloxy)ethylazetidin-2-one (4)⁴ can be readily converted

entry	substrate	products ^b	yield, ^c %
1	NH 1	OAc NH 2	78
2	O CH3		76
3	NH 3	OAc NH 2	77
4	CO ₂ CH ₃	OAC CO ₂ CH ₃	48
5	t-Bu(CH ₃)₂SiO	t-Bu(CH ₃)₂SiO M. OAc NH 5	92
6		HO HO HO AC HO NH OAC NH 7 8	43 ^d

Table 1. Conversion of Azetidin-2-ones into 4-Acetoxyazetidin-2-ones^a

^aThe reaction was carried out as described in the text. ^bThe structure of the product has been determined on the basis of analytical and IR, NMR, and mass spectral data. ^cIsolated yield. ^dA mixture of two diastereomers (7:8, 4:1)

into (1'R,3R,4R)-4-acetoxy-3-(1'-t-butyldimethylsiloxy)ethylazetidin-2-one (5) (entry 5), which is a versatile key intermediate for synthesis of thienamycin and other important carbapenem antibiotics.⁵ The ¹H NMR and HPLC analyses show that the diastereometric excess of 5 is over 99%. The preferential formation of trans-isomer is due to the steric interaction between acetoxy group and the substituent at C-3 position. Actually, the oxidation of (1'R, 3S)-3-(1'-hydroxy)ethylazetidin-2-one (6) afforded a mixture of *trans*-7 and *cis*-8 (ca. 4:1).

The osmium trichloride has proved to be the most effective catalyst, although other osmium complexes such as $Os_3(CO)_{12}$, $Os(NH_4)_2Cl_2$, and OsH_2Cl_6 are ineffective. It is noteworthy that no reaction takes place upon treatment with peracetic acid in the presence of catalytic amount and stoichiometric of OsO4. The effect of oxidants has been examined for the oxidation of 4. As shown in Table 2, peracetic acid was found to be the most effective oxidant among those examined, and other oxidants such as methyl ethyl ketone peroxide, *m*-chloroperbenzoic acid, PhIO, and PhI(OAc)₂ gave good results. Oxidants such as *t*-BuOOH, H₂O₂, NaOCl, PhCO₃-*t*-Bu, and *N*-methylmorpholin *N*-oxide are ineffective for the present oxidation reaction. It is noteworthy that cobalt complexes such as CoCl₂, Co(OAc)₂, and Co(acac)₂ can be utilized as catalysts, although their catalytic activity is not so high.⁶

entry	oxidant ^b	yield, [°] %
1	CH ₃ CO ₃ H	92
2	mCPBAd	73
3	MEKP ^e	70
4	PhI(OAc) ₂	70
5	PhIO	67

Table 2. Various Oxidants for the Oxidation of Azetidinone 4^a.

^aTo a mixture of 4 (200 mg, 0.87 mmol), $OsCl_3$ (1~3 mol %), anhydrous sodium acetate (72 mg, 0.87 mmol), and acetic acid (2 ml) was added an oxidant (1.91 mmol) dropwise with stirring at room temperature over a period of 2 h. ^b2.2 equivalents were used. ^cIsolated yield. ^dMEKP; methyl ethyl ketone peroxide. ^cmCPBA; m-chloroperbenzoic acid

The present oxidation is different from the OsO4 catalyzed oxidation², and can be rationalized by assuming an intermediacy of oxoosmium (V) species, which may have a similar function to oxoruthenium (IV) complexes.^{7,8} Thus, osmium (III) complex seems to be oxidized with peracetic acid to give oxoosmium (V) complex, which undergoes hydrogen abstraction and subsequent electron transfer to give four-menbered acyliminium ions. Reaction with acetic acid gives the corresponding 4-acetoxyazetidin-2-ones.⁹

Further mechanistic study is actively in progress in comparison with cytochrome P-450 type oxidation reactions.¹⁰

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References and Notes

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