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Ruthenium-Catalyzed Oxidation of β-Lactams with Molecular Oxygen and Aldehydes

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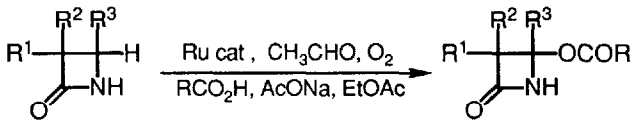
Key Words Oxidation of β-lactams, 4-Acyloxy β-lactams, Ruthenium Catalyst, Aerobic oxidation, Oxoruthenium species

Abstract The $RuCl_3$ catalyzed reaction of β-lactams in the presence of acetaldehyde and molecular oxygen in an acid and ethyl acetate under buffer conditions gives the corresponding 4-acyloxy β-lactams highly efficiently

During the course of our study on the simulation of enzymatic function with metal complex catalysts, we have found that the ruthenium-catalyzed oxidations of amines[1] and amides[2] with peroxides give the corresponding oxygenated compounds at α-position of nitrogen For the oxidation of β-lactams, peroxides such as peracetic acid and methyl ethyl ketone peroxide have been used However, these peroxides are not always available and sometimes contain undesirable materials, therefore we have examined the formation of peracids *in situ* from aldehydes with molecular oxygen in the presence of catalysts It is well known that peracetic acid, for example, can be prepared upon treatment of acetaldehyde with molecular oxygen in the presence of cobalt salts [3] We have found that ruthenium-catalyzed transformation of β-lactams into the corresponding 4-acyloxy β-lactams can be performed readily upon treatment with molecular oxygen in the presence of acetaldehyde and acids (eq 1)

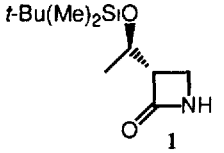
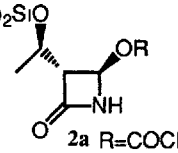
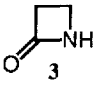
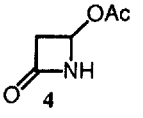
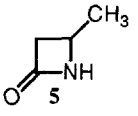
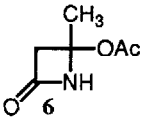
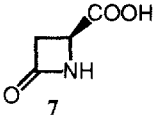
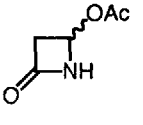
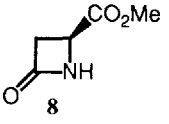
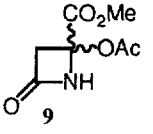


(1)

Acetoxylation of β-lactams at C-4 position can be performed by the ruthenium trichloride catalyzed oxidation in the presence of acetaldehyde and acetic acid with molecular oxygen in ethyl acetate at 40 °C In particular, the oxidation of (1'*R*, 3*S*)-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (**1**)[4] gives (1'*R*, 3*R*, 4*R*)-4-acetoxy-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (**2a**) (91%), which is a versatile key intermediate for the synthesis of carbapenem antibiotics [5] Under the present reaction conditions the

catalytic activity of various ruthenium complexes has been examined for the oxidation of **1** $RuCl_3$ gives the best results, and the catalytic activity is in the order of $RuCl_3$>$RuBr_3$>$Ru(OAc)_3$>1% Ru-graphite >$Ru_3(CO)_{12}$ $OsCl_3$ shows the similar catalytic activity to $RuCl_3$ The effect of an aldehyde was also examined for the oxidation of **1** Acetaldehyde gave the best results, and the other aliphatic aldehydes such as propanal, 2-methylpropanal, and hexanal gave good to excellent yields [6] The solvent effect is remarkable Ethyl acetate was found to be the best solvent for the present oxidation Acetonitrile can be used, but solvents such as DMF and DMSO could not be used because of their strong coordination ability to the ruthenium catalyst Sodium acetate was added as buffer in order to avoid ring opening of β-lactams and desilylation reaction

Table 1. Conversion of β-Lactams into 4-Acyloxy β-Lactams[a]

entry	substrate	product	yield, %[b]
	 **1**		
1		**2a** R=$COCH_3$	91
2		**2b** R=COC_2H_5	83[c]
3		**2c** R=$COCH_2OCH_3$	74
4		**2d** R=$COCH_2C_6H_5$	83
5		**2e** R=$COCH_2CN$	81
6		**2f** R=$COCH_2Cl$	92
7		**2g** R=$COCHCl_2$	70
8	 **3**	 **4**	88
9	 **5**	 **6**	72
10	 **7**		87
11	 **8**	 **9**	63

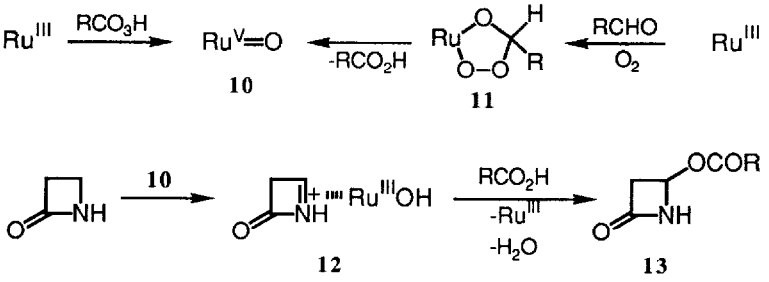
[a]The reaction was carried out as described in the text. [b]Isolated yield [c]Propanal was used in place of acetaldehyde

Typically, the oxidation of β-lactam **1** is as follows A mixture of $RuCl_3 \cdot 3H_2O$ (130 mg, 0 5 mmol, 5 mol%), anhydrous sodium acetate (205 mg, 2 5 mmol), β-lactam **1** (2 29 g, 10 mmol), acetic acid (5 mL), and ethyl acetate (100 mL) was charged to a side-armed round-bottomed flask, and atmosphere was replaced with molecular oxygen Keeping the temperature at 40 °C, acetaldehyde (1 1 mL, 20 mmol) was added to the mixture all at once, and the resulting mixture was stirred under oxygen atmosphere for 3 h The reaction mixture was poured into 10% aqueous solution of sodium sulfite (400 mL) and extracted with two 500 mL portions of hexane The hexane solution was washed with brine (200 mL) and dried over anhydrous magnesium sulfate Evaporation followed by column chromatography on silica gel (hexane/ethyl acetate, 5 1) gave **2a** (2 61 g, 9 1 mmol, 91%)

The representative results of the formation of 4-acetoxy β-lactams are listed in Table 1 Various acyloxy substituents can be introduced at the C-4 position of β-lactams Thus, the ruthenium-catalyzed oxidation of **1** in the presence of propanal and propionic acid under the same reaction conditions gave (1'*R*, 3*R*, 4*R*)-3-[1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-ethylcarbonyloxyazetidin-2-one (**2b**) in 83% yield Furthermore, the present reaction provides various 4-acyloxy β-lactams such as 4-methoxyacetoxy- (**2c**), 4-phenylacetoxy- (**2d**), 4-cyanoacetoxy- (**2e**), 4-chloroacetoxy- (**2f**), and 4-dichloroacetoxy- (**2g**) in good to excellent yields These 4-acyloxy β-lactams are useful intermediates for the synthesis of carbapenem antibiotics, because these compounds have highly reactive leaving groups [7]

Kaneda *et al* reported that the cleavage of carbon-carbon double bonds occurs upon treatment of alkenes with $RuCl_3$ catalyst in the presence of molecular oxygen and acetaldehyde, and claimed that ruthenium tetroxide is formed as a key intermediate [8] However, neither ruthenium dioxide (IV) nor ruthenium tetroxide (VIII) show catalytic activity for the oxidation of β-lactams Therefore, the active species of the present oxidation seems to be oxoruthenium species, as we have already shown as the key intermediate for the ruthenium-catalyzed oxidation with peracetic acid [2]

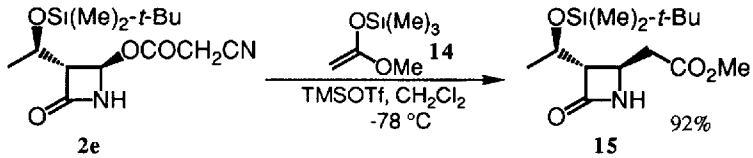
Two pathways can be considered to generate oxoruthenium species The reaction of acetaldehyde with molecular oxygen promoted by ruthenium catalysts would give peracetic acid likewise cobalt-promoted formation of peracetic acid [3] Subsequent reaction of peracetic acid thus formed with ruthenium trichloride gives oxoruthenium species (**10**) [2] An altanative process involves the formation of metalacyclic intermediate (**11**) as observed for platinum and other complexes [9] Protonolysis of **11** give oxoruthenium species (**10**) along with acetic acid



It is noteworthy that the acetoxylation did not take place, when this reaction was carried out without a proton source such as acetic acid, and N-acylated products were obtained Hydrogen abstraction of C_4-H of

β-lactams with **10**, followed by electron transfer would give four-membered acyliminium ion intermediate **12** Nucleophilic reaction of acids would give 4-acyloxy β-lactams The intermediacy of the four-membered acyliminium ion is supported by the exclusive formation of 4-dichloroacetoxy β-lactam upon oxidation of **1** in a mixture of acetic acid and dichloroacetic acid (1 1)

The present reaction provides an efficient method for the synthesis of 4-acyloxy β-lactams, which will be superior key intermediates for the synthesis of various carbapenem antibiotics Actually, TMSOTf promoted reaction of 4-cyanoacetoxy β-lactam **2e** with ketene silyl acetal **14** in CH_2Cl_2 at -78 °C gave 4-methoxycarbonylmethyl β-lactam (**15**) stereoselectively in 92% isolated yield, while the same reaction with **2a** gave **15** in 60% yield



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REFERENCES AND NOTES

1 Murahashi, S -I , Naota, T , Yonemura, K *J Am Chem Soc* **1988**, *110*, 8256-8258

2 Murahashi, S -I , Naota, T , Kuwabara, T , Saito, T , Kumobayashi, H , Akutagawa, S *J Am Chem Soc* **1990**, *112*, 7820-7822

3 (a) Phillips, B , Frostick, F C , Jr , Starcher, P S *J Am Chem Soc* **1957**, *79*, 5982-5986 (b) Boullion, G , Lick, C , Schank, K In *The Chemistry of Peroxides*, Patai, S Ed , John Wiley & Sons New York, 1983, pp 297–309

4 (a) Noyori, R , Ikeda, T , Ohkuma, T , Widhalm, M , Kitamura, M , Takaya, H , Akutagawa, S , Sayo, N , Saito, T , Taketomi, T , Kumobayashi, H *J Am Chem Soc* **1989**, *111*, 9134-9135 (b) Mashima, K , Matsumura, Y , Kusano, K , Kumobayashi, H , Sayo, N , Hori, Y , Ishizaki, T , Akutagawa, S , Takaya, H *J Chem Soc , Chem Commun* **1991**, 609-610

5 (a) Fuentes, L M , Shinkai, I , Salzmann, T N *J Am Chem Soc* **1986**, *108*, 4675-4676 (b) Shirai, F , Nakai, T *J Org Chem* **1987**, *52*, 5491-5492 (c) Ito, Y , Terashima, S *Tetrahedron Lett* **1987**, *28*, 6625-6628 (d) Sowin, T J , Meyers, A I *J Org Chem* **1988**, *53*, 4154-4156 (e) Déziel, R , Favreau, D *Tetrahedron Lett* **1989**, *30*, 1345-1348 (f) Nagao, Y , Abe, T , Shimizu, H, Kumagai, T, Inoue, Y *J Chem Soc , Chem Commun* **1989**, 821-823

6 The effect of aldehydes for the ruthenium-catalyzed oxidation of **1** with molecular oxygen is as follows β-Lactam **2a** was obtained by using propanal, 2-methylpropanal, and hexanal in 88%, 86%, and 90% yields, respectively

7 Speckamp, W N , Hiemstra, H *Tetrahedron* **1985**, *41*, 4367-4416

8 Kaneda, K , Haruna, S , Imanaka, T , Kawamoto, K *J Chem Soc , Chem Commun* **1990**, 1467-1468 See also for Ni catalyzed epoxidation Yamada, T , Takai, T , Rhode, O , Mukaiyama, T *Chem Lett* **1991**, 1-4

9 Ugo, R , Zanderighi, G M , Fusi, A , Carreri, D *J Am Chem Soc* **1980**, *102*, 3745-3751

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