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Selenium- and Palladium-Catalyzed Oxidative Cleavage of Ene-lactams with Hydrogen Peroxide. Convenient Methods for Synthesis of Macrocyclic Ketoimides and *N*-Fused Azabicyclic Compounds

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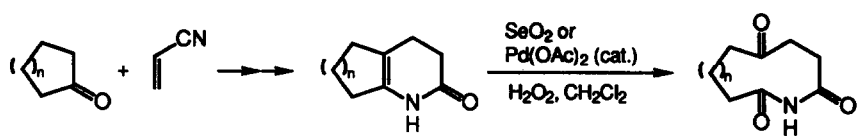
Abstract: Oxidative cleavage of ene-lactams can be performed efficiently by either SeO_2 or $Pd(OAc)_2$-catalyzed oxidation with H_2O_2 to give the corresponding ketoimides. The reaction provides convenient methods for the preparation of macrocyclic ketoimides and the construction of *N*-fused azabicyclic ring systems such as indolizidine and cephalotaxine skeletons.

Oxidative cleavage of carbon-carbon double bonds is an important and versatile method for the preparation of a variety of carbonyl compounds.[1] However, in the field of synthesis of biologically active nitrogen compounds there still remain requirements for the development of such transformations that proceed under neutral and mild conditions.

Recently we found that low valent ruthenium complex catalyzed reaction of δ-ketonitriles with water proceeds highly efficiently to give ene-lactams which are versatile synthetic intermediates.[2] We have found a convenient method for oxidative cleavage of ene-lactams affording ketoimides under mild and neutral conditions. Thus, SeO_2- or $Pd(OAc)_2$-catalyzed oxidation of ene-lactams with hydrogen peroxide proceeds at room temperature to give the corresponding ketoimides with high efficiency. Therefore, ketoimides can be obtained readily from ketones via cyanoethylation (eq 1).

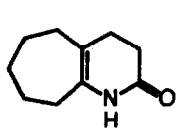
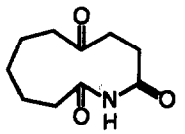
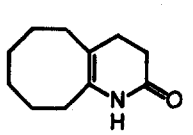
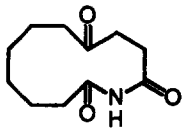
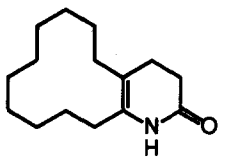
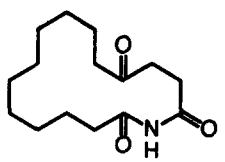
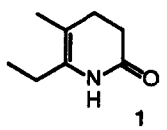
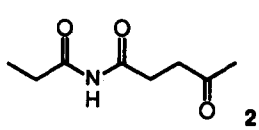
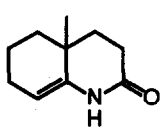
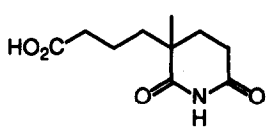


(1)

Ene-lactams have been prepared efficiently by the ruthenium-catalyzed reaction of δ-ketonitriles.[2] Typically, the treatment of 2-(2-cyanoethyl)cycloheptanone derived from cycloheptanone, with two equivalents of water in 1,2-dimethoxyethane in the presence of 3 mol% of $RuH_2(PPh_3)_4$ gave 8-azabicyclo[5.4.0]undec-1(7)-en-9-one in 65% yield. Similarly, 3,4-dihydro-6-ethyl-5-methyl-2-pyridone (**1**) can be obtained from 4-methyl-5-oxoheptanenitrile.

The catalytic activity of various metal complexes was examined for the oxidative cleavage of ene-lactam **1** with hydrogen peroxide. SeO_2 and $Pd(OAc)_2$ have proven to be effective catalysts for the formation of *N*-

Table I. Selenium- and Palladium-Catalyzed Oxidative Cleavage of Ene-lactams with H_2O_2[a]

entry	ene-lactam	product[b]	yield[c] (%)
1			73[d]
2			53[d]
3			51[d,e]
4	 1	 2	95[f]
5			82[f]

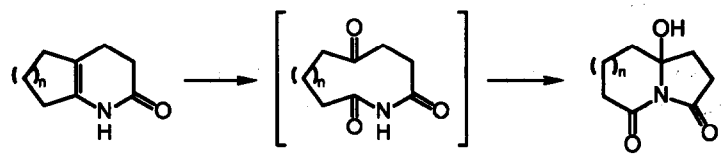
[a]To a stirred solution of ene-lactam (1.0 mmol) and catalyst (0.1 mmol) in CH_2Cl_2 (3 mL) was added a 30% H_2O_2 aqueous solution (2.2 mmol) dropwise at room temperature over a period of 3 min, and the mixtire was stirred for 2 h. [b]Satisfactory IR and NMR spectral data and elemental analysis were obtained. [c]Isolated yield. [d]$Pd(OAc)_2$ was used as a catalyst. [e]H_2O_2 (3 equiv). [f]SeO_2 was used as a catalyst.

propanoyl-4-oxopentanamide (**2**). Other metal complexes such as $CoCl_2$, $Mn(OAc)_2 \cdot 4H_2O$, $Cu(OAc)_2$, $Ni(acac)_2$, and Na_2WO_4 showed no catalytic activity. The use of aprotic solvent such as CH_2Cl_2 gave satisfactory results. Typically, to a stirred solution of ene-lactam **1** (0.140 g, 1.01 mmol) and SeO_2 (0.011 g, 0.10 mmol) in CH_2Cl_2 (3.0 mL) was added a 30% H_2O_2 aqueous solution (0.24 mL, 2.2 mmol) dropwise at room temperature over a period of 3 min. After stirring for 2 h, the mixture was poured into a saturated Na_2SO_3 solution in H_2O and extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give **2** (0.164 g, 95%) as a colorless solid.

The representative results of the oxidative cleavage of ene-lactams are listed in Table I. Various ene-lactams undergo oxidative cleavage upon treatment with H_2O_2 in the presence of SeO_2 or $Pd(OAc)_2$ catalyst. Ene-lactams derived from cyclic ketones are converted into macrocyclic ketoimides which are potent synthetic intermediatesof various azamacrocycles (entries 1-3). As for the formation of macrocyclic ketoimides $Pd(OAc)_2$ gave better results in comparison with SeO_2. Many of the conventional methods for oxidative cleavage of carbon-carbon

double bonds[1] can not be applied to the synthesis of macrocyclic ketoimides, because hydrolysis takes place giving ring opening products under the reaction conditions. Ene-lactams derived from acyclic ketones are converted into linear γ-ketoimides (entry 4). Oxidation of bicyclic ene-lactams bearing trisubstituted olefins gave imidocarboxylic acids (entry 5).

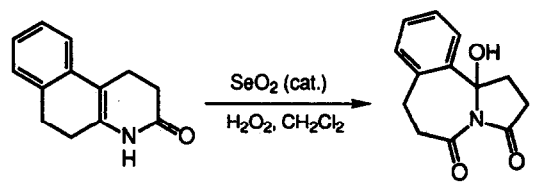
The present reaction provides a novel and efficient method for construction of *N*-fused azabicyclic ring systems such as indolizidine and cephalotaxine skeletons (eq 2).[3] Thus, the SeO_2-catalyzed oxidation of ene-lactam **3a** derived from cyclohexanone, with H_2O_2 gave 7-hydroxy-1-azabicyclo[5.3.0]decan-2,10-dione



(2)

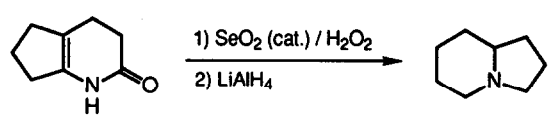
3 **a**: n = 2 **b**: n = 1 **4** **5**

(**5a**) in 95% yield. Similar treatment of ene-lactam **6** derived from β-tetralone gave 11-hydroxy-1-azatricyclo[9.3.0.$0^{5,10}$]tetradecan-5,7,9-trien-2,14-dione (**7**) in 65% yield. The reaction can be rationalized by assuming the formation of macrocyclic ketoimides **4** which undergo intramolecular nucleophilic attack of the nitrogen atom of the imide moiety to the carbonyl group. These ring opening-closure sequences are observed exclusively in the oxidation of ene-lactams bearing [4.4.0] and [4.3.0] bicyclic ring systems. This is due to conformational stability of the products in which imide moieties can keep π-conjugated planes. The present



6 **7**

method is especially useful for the synthesis of indolizidine alkaloids which have received considerable attention because of their potent enzyme inhibition properties.[3b] The reported methods for the construction of indolizidine skeletons are limited to few methods which involve annulation reactions from pyrrolidine and piperidine synthons,[3,4] intramolecular 1,3-dipolar cycloadditions of azidoolefins,[5] and intramolecular Diels-Alder reactions of 1-alkenoyl-1-azabutadienes.[6] The efficiency of the present method has been demonstrated by the short step synthesis of δ-coniceine (**8**)[7] which has been received widespread attention as model system for investigating a general synthetic strategy for the construction of indolizidine alkaloids. Thus, the SeO_2-catalyzed oxidative



3b δ-coniceine (**8**)

cleavage of ene-lactam **3b** derived from cyclopentanone, with H_2O_2 gave 6-hydroxy-1-azabicyclo[4.3.0]nonan-2,9-dione (**5b**) in 78% yield. Reduction of **5b** with $LiAlH_4$ in THF at room temperature gave **8** in 63% yield.

The present catalytic reactions can be rationalized by assuming formation of either HOSe(O)OOH[8] or Pd(OAc)(OOH)[9] intermediates which are derived from SeO_2 or $Pd(OAc)_2$ with H_2O_2. Epoxidation of ene-lactams with these intermediates and subsequent nucleophilic attack of H_2O_2 would give γ-hydroxy-δ-hydrodioxylactams which undergo ring opening to give ketoimides and water.

Work is in progress on the extension of our method to other systems and on the application to the synthesis of nitrogen containing biologically active compounds.

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