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Ruthenium-catalyzed glycine-selective oxidative backbone modification of peptides

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Abstract

The reaction of *N,C*-protected peptides containing glycine residues with peracetic acid in the presence of a ruthenium catalyst gives α-ketoamides derived from the oxidation at the C^{α} position of the glycine residues selectively.

Keywords: oxidation; peptide; glycine; backbone modification; ruthenium catalyst.

Oxidation of proteins and peptides is of interest in view of aging and diseases.[1,2] Oxidative modification of peptides is also a useful tool for altering chemical and biological properties.[3,4] However, there is no report on catalytic backbone modification of peptides except for the modification by the side-chain scission at the serine and the threonine residues.[3] We wish to report a novel catalytic backbone modification at the glycine residue of peptides without backbone fragmentation. Glycine selective reactions are limited to the glycine-selective N–C^{α} bond cleavage with nickel peroxide.[5]

During our study on a simulation of the enzymatic functions of cytochrome P-450,[6] we found that ruthenium-catalyzed oxidation of amines[7] and amides[8] with peroxides proceeds highly efficiently. We wanted to apply this method to the oxidation of peptides, and found that the ruthenium-catalyzed oxidation of *N,C*-protected peptides with peracetic acid gives α-ketoamide derivatives which are formed by the selective oxidation at the C^{α} position of the glycine residue. This is the first example of transition metal-catalyzed oxidative backbone modification of peptides and also of the selective oxidation at the C^{α} position of glycine.

The catalytic oxidation of Ac–Gly–Ala–OEt (**1**) with peracetic acid in the presence of $RuCl_3$ catalyst (20 mol%) in acetic acid gave Ac–NHCOCO–Ala–OEt (**2**) (81% yield, based on the converted substrate), which was obtained by the oxidation at the C^{α} position of the glycine

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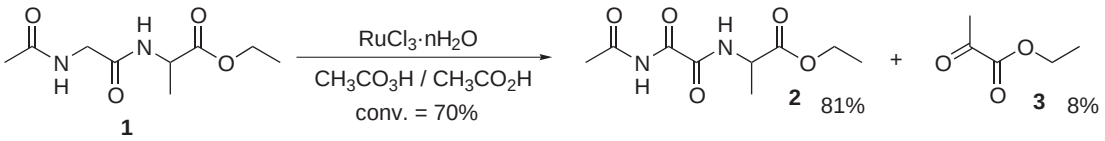
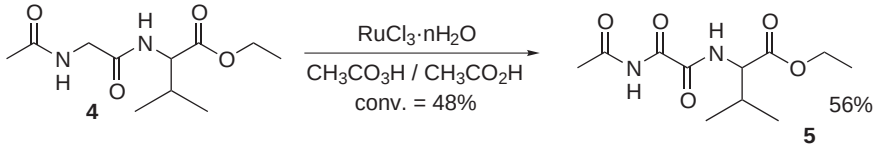
residue, and ethyl pyruvate (**3**) (8%), obtained by the oxidation at the C^{α} position of the alanine residue followed by hydrolysis, along with the recovered substrate (70% conversion) (Scheme 1). The product ratio of the oxidation of the glycine residue and the alanine residue is 10 to 1. The ruthenium-catalyzed glycine selective backbone modification thus occurs. The catalytic activity of various ruthenium catalysts was examined for the oxidation of **1** with peracetic acid. $RuCl_3{\cdot}nH_2O$ gave the best result. Ruthenium on charcoal also showed high catalytic activity; however, other ruthenium complexes such as $RuCl_2(PPh_3)_3$, $[RuCl_2(CO)_3]_2$, $RuCl_2(bpy)_2$, $Ru_3(CO)_{12}$, $Ru(acac)_3$, and RuO_2 gave unsatisfactory results.



Scheme 1.

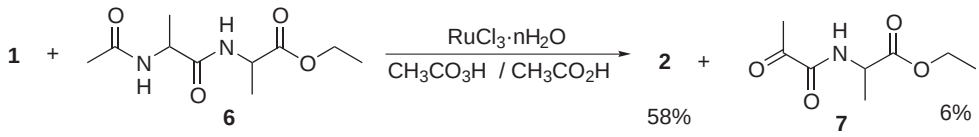
Typical procedure of the ruthenium-catalyzed oxidation of **1** is as follows. To a solution of $RuCl_3{\cdot}nH_2O$ (0.1 mmol) and **1** (0.5 mmol) in acetic acid (1.0 mL) was added a 30% ethyl acetate solution of peracetic acid (2.0 mmol) dropwise at room temperature over a period of 2 h. After additional stirring for 2 h, acetophenone was added as an internal standard, and the conversion of **1** (70%) and the yields of **2** (81%) and **3** (8%) were determined by HPLC and GLC analyses. Isolation of **2** was carried out as follows. To the reaction mixture was added a saturated aqueous solution of Na_2SO_3 (0.5 mL). The resulting solution was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. Column chromatography on silica gel gave **2** (48 mg, 60% yield) as a colorless solid.

The oxidation of Ac–Gly–Val–OEt (**4**) under the present reaction conditions gave the corresponding α-ketoamide derivative (**5**) (48% conversion, 56% yield) (Scheme 2). Again, the glycine residue was oxidized selectively, although the reactivity of **4** was decreased because of the steric effect of the isopropyl group.



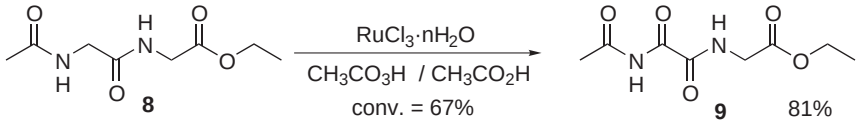
Scheme 2.

The oxidation of a mixture of **1** and Ac–Ala–Ala–OEt (**6**) (1:1) under the present reaction conditions resulted in selective modification of the glycine residue of **1** (Scheme 3). Thus, the relative reactivity towards the oxidation of the glycine residue of **1** and the acetyl protected alanine residue of **6** is 10 to 1. This was calculated based on the yields of **2** (58%, based on **1**) and MeCOCO–Ala–OEt (**7**) (6%, based on **6**) that were obtained by the oxidation at the C^{α} position of the acetyl-protected alanine residue followed by hydrolysis. The low reactivity of **6** is ascribed to the steric effect of the methyl group at the alanine residue towards the oxoruthenium species.[8]



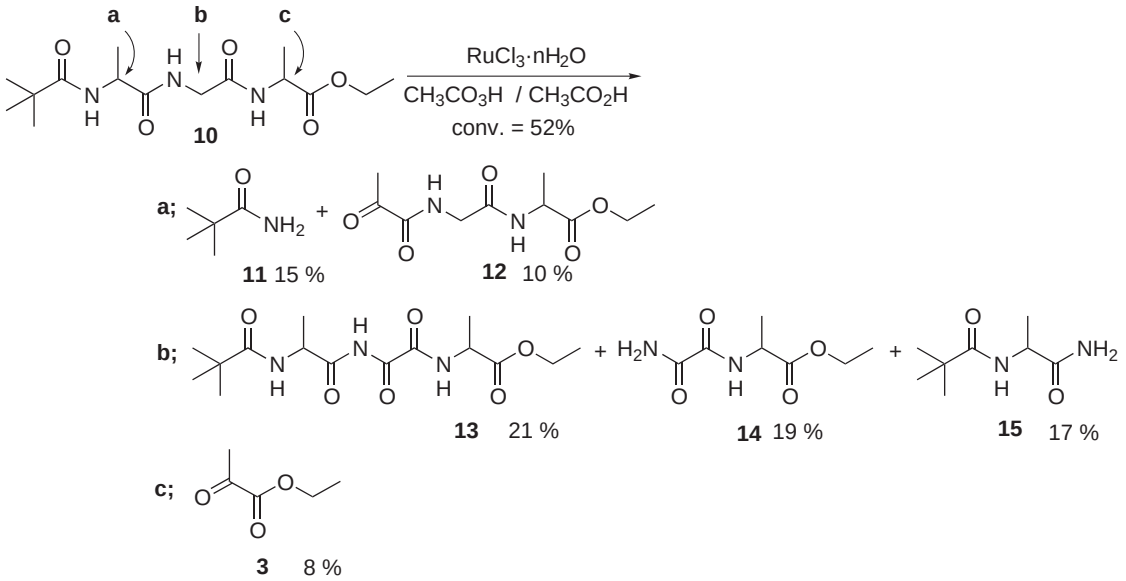
Scheme 3.

Next, we examined the oxidation of the dipeptide Ac–Gly–Gly–OEt (**8**) bearing two glycine residues (Scheme 4). The C^{α} position of the N-terminal glycine of **8** was oxidized to give the corresponding α-ketoamide derivative **9**[9] (81% yield); however, the C^{α} position of the C-terminal glycine of **8** was not modified (67% conversion). The protecting groups of the glycine residues are a crucial factor, and the glycine residues that are protected with two amide groups are readily oxidized.



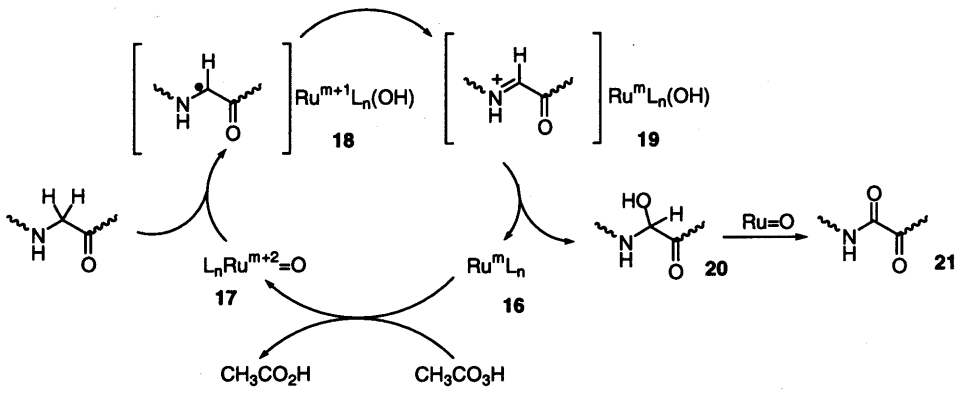
Scheme 4.

Accordingly, one can expect that inner glycine residues can be modified readily. Indeed, the catalytic oxidation of Piv–Ala–Gly–Ala–OEt (**10**) gave the products, Piv–NH_2 (**11**) (15%), MeCOCO–Gly–Ala–OEt (**12**) (10%), Piv–Ala–NHCOCO–Ala–OEt (**13**) (21%), NH_2COCO–Ala–OEt (**14**) (19%), Piv–Ala–NH_2 (**15**) (17%), and **3** (8%) (52% conversion) (Scheme 5). The products derived from the oxidation at the glycine residue (b) were obtained predominantly (**13**+**14**+**15** = 57%). Selective backbone modification at the glycine residues can be carried out not only at the terminal position of peptides but also at the inner position of peptides.



Scheme 5.

The oxidation can be rationalized by assuming the cytochrome P-450 type mechanism as shown in Scheme 6.[6] The reaction of low-valent ruthenium complex L_nRu^m ($m=2$ or 3) (**16**) with peracetic acid gives oxoruthenium species $L_nRu^{m+2}=O$ (**17**).[7] Abstraction of hydrogen from the C^α position of the glycine residue and subsequent single electron transfer would afford an iminium ion complex **19**. Rebounding of the hydroxyl ligand would afford α-hydroxyglycine (**20**) and **16** to complete the catalytic cycle. The hydroxy compound **20** can be converted to α-ketoamide derivative (**21**) under the reaction conditions. Iodosylbenzene, which is used for generation of an oxo-metal species,[10] was also effective for the oxidation at the glycine residue of **1**, although the conversion and the yield were low in comparison with peracetic acid. It is noteworthy that the oxidation of glycine residues with RuO_4 does not occur.[3] Glycine selective modification is due to the abstraction of hydrogen with the oxoruthenium species at the C^α position of the glycine residues, which have a less sterically hindered secondary carbon–hydrogen bond.[8]



Scheme 6.

In summary, glycine-selective backbone modification of peptides can be performed by the ruthenium-catalyzed reaction with peracetic acid.

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