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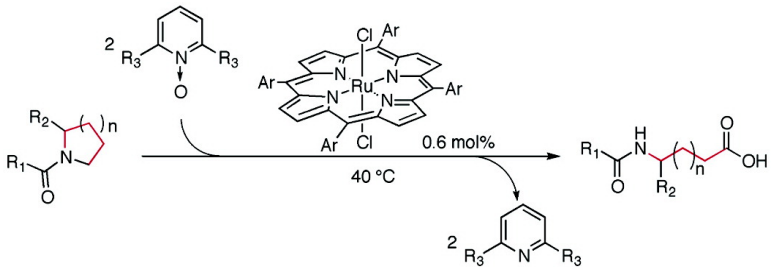
J. Am. Chem. Soc., **2005**, 127 (3), 834-835• DOI: 10.1021/ja045603f • Publication Date (Web): 29 December 2004



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Unique Oxidation Reaction of Amides with Pyridine-*N*-oxide Catalyzed by Ruthenium Porphyrin: Direct Oxidative Conversion of *N*-Acyl-L-proline to *N*-Acyl-L-glutamate

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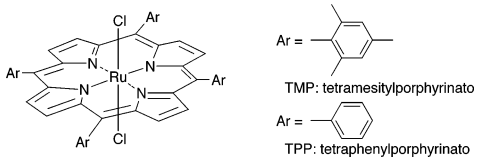
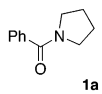
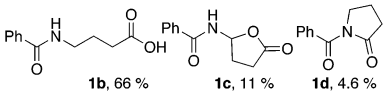
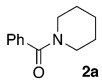
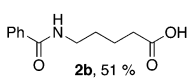
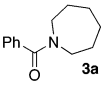
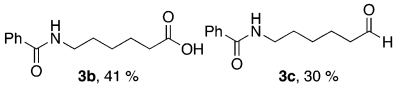
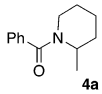
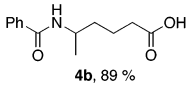
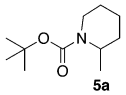
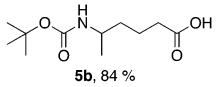
Cytochrome P450 plays a central role in drug metabolism. The exceptionally potent reactivity of P450 enables oxidative modification of unactivated alkanes and aromatic compounds. Consequently, the development of small-molecule catalysts with similar activity has been the subject of extensive research efforts, and various metalloporphyrins have been reported that oxidize alkanes and alkenes similarly to P450.[1] However, very few examples of amide oxidation have been reported, and all of them involve oxidative conversion to imides with highly active oxidants (e.g., RuO_4,[2] Co(II),[3] Mn(II, III),[4] Fe(II) salts,[5] photooxidation,[6] and anodic oxidation[7]). We have shown that the oxidation of alkanes, alkenes, and arenes is efficiently catalyzed by ruthenium porphyrins with pyridine *N*-oxides as oxidants.[8] In the presence of HCl or HBr, this catalytic system efficiently oxidizes even unactivated alkanes to alcohols and/or ketones in high yields with extremely high turnover numbers (up to 10^5 times).[8f,g] We have also reported the first examples of catalytic hydroxylation of unactivated alkanes by stable Ru(TMP)Cl_2 even in the absence of HCl or HBr.[8g] We now report that this highly reactive Ru porphyrin/pyridine *N*-oxide system shows unique reactivity for the oxidation of various amides, including the direct oxidative conversion of *N*-acyl-L-proline to *N*-acyl-L-glutamate.



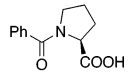
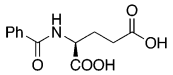
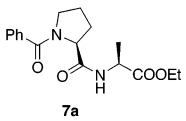
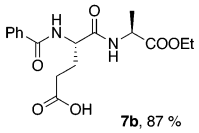
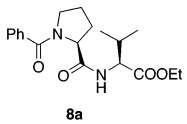
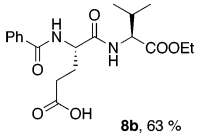
Oxidation of various *N*-acyl cyclic amines was performed with the 2,6-dichloropyridine *N*-oxide−Ru^{IV}(TMP)Cl_2 system. This system worked quite well; *N*-acyl cyclic amines were oxidized to *N*-acyl amino acids as main products in modest to good yields (Table 1). Replacement of the catalyst or the oxidant with Ru(TPP)Cl_2 or 2,6-lutidine *N*-oxide caused a drop in yield (see Supporting Information). The oxidation of *N*-acyl cyclic amines under conventional conditions is known to afford lactams such as **1d**.[2−5] In contrast, our system mainly gave ring-opened products (**1b** and **1c)** via C−N bond cleavage. Compound **1b** was supposed to be further oxidized at the alpha position of the amide to afford **1c** by ring closure. Compounds **2a** and **3a** were also oxidized to ring-opened products. Compound **3c** may be a precursor of **3b**, as discussed later. The oxidation of **4a** and Boc-protected **5a** proceeded efficiently to give **4b** and **5b** via selective C−N bond cleavage at the less-substituted carbon. This selectivity probably arises because attack of an active species would be restricted to axial hydrogen at the 6-position under the influence of both Coulombic repulsion between oxo-Ru species and carbonyl oxygen, and steric hindrance of the *N*-acyl group (see Supporting Information). The turnover number reached 5000 in the oxidation of **4a**.

Table 1. Oxidation of *N*-Acyl Cyclic Amines by Ru Porphyrin/2,6-Dichloropyridine *N*-Oxide System[a]

entry	substrate	product, isolated yield
1[b]	 **1a**	 **1b**, 66 % **1c**, 11 % **1d**, 4.6 %
2[b]	 **2a**	 **2b**, 51 %
3[b]	 **3a**	 **3b**, 41 % **3c**, 30 %
4	 **4a**	 **4b**, 89 %
5	 **5a**	 **5b**, 84 %

[a] Reaction conditions: substrate (0.16 M), Ru(TMP)Cl_2 (0.6 mol %), and 2,6-dichloropyridine *N*-oxide (0.40 M) were stirred in benzene at 40 °C under Ar overnight, unless otherwise noted. Yields are based on the substrate used. [b] 0.32 M 2,6-dichloropyridine *N*-oxide was used.

Table 2. Oxidation of L-Proline Derivatives

entry	substrate	product, isolated yield
1	 **6a**	 **6b**, 91 %
2	 **7a**	 **7b**, 87 %
3	 **8a**	 **8b**, 63 %

[a] Reaction conditions were the same as described in Table 1.

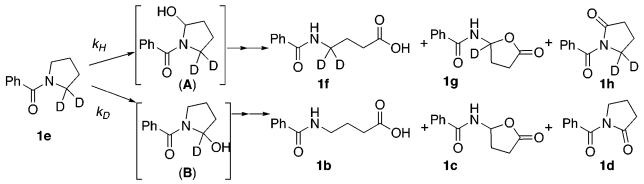
We next applied this catalytic system to the oxidation of *N*-acylproline. If the selectivity between secondary and tertiary carbons is a general phenomenon in this system, prolines could be converted directly to glutamates. *N*-Benzoyl-L-proline (*N*-Bz-L-Pro) **6a** was indeed efficiently oxidized to *N*-Bz-L-Glu **6b** (Table 2, entry 1). The configuration of the product **6b** was confirmed to be retained by checking the optical rotation of **6b** methyl ester ($[\alpha]_D = -25°$). Next, we extended this reaction to L-Pro-containing peptides (entries 2 and 3). *N*-Bz-L-Pro-L-Ala-OEt **7a** and *N*-Bz-L-Pro-L-Val-OEt **8a**

10.1021/ja045603f CCC: $30.25

were converted to *N*-Bz-L-Glu-L-Ala-OEt **7b** and *N*-Bz-L-Glu-L-Val-OEt **8b**, respectively. The proline residue in the peptides was selectively converted to glutamate; this type of reaction could be a useful method in peptide chemistry. Many researchers have reported on the conversion of L-Pro to L-Glu, but all reported methods require two steps.[9] As a representative example, *N*-acyl-L-Pro esters were oxidized by RuO_4 to afford the 2-pyrrolidones, followed by hydrolysis with aqueous HCl. In contrast, our system can directly convert *N*-acyl cyclic amines to *N*-acyl amino acids under mild conditions.

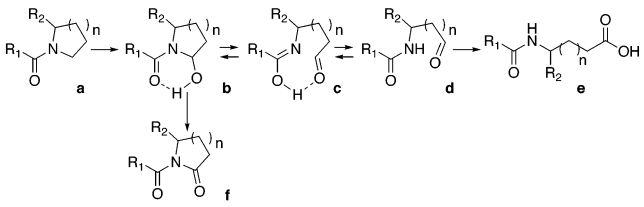
Oxidative *N*-dealkylations catalyzed by heme enzyme or metalloporphyrin model compounds are known to involve the generation of a carbinolamine. Although the mechanism of this reaction is still controversial, the electron-transfer pathway has received more support than the hydrogen atom-transfer route.[10]

To obtain insight into the mechanism of our reaction, the kinetic isotope effect was measured using *N*-benzoyl[2,2-d_2]pyrrolidine **1e**. The effect of the acyl functionality on H and D was confirmed to be the same; the rotation of the N−C(O) bond was observed by ^{1}H NMR spectroscopy at room temperature (see Supporting Information). The intramolecular kinetic isotope effect in the oxidation of **1e** with this system was evaluated from the product ratio of **1f**−**h** vs **1b**−**d** as **A**/**B**. The k_H/k_D value was found to be 9.8 ± 0.2 (see Supporting Information), strongly suggesting that the rate-determining step is hydrogen abstraction and not one-electron oxidation.



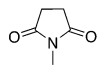
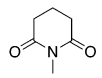
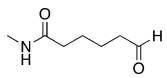
When hydrogen abstraction occurs, aldehydes are supposed to be formed as precursors of the carboxylate. We confirmed that various aldehydes were oxidized and converted to carboxylic acids in good yields with this catalytic system (see Supporting Information).

On the basis of the above observations, we propose the following reaction mechanism. The cleavage of the C−N bond occurs via the equilibrium of the hydroxylated amide **b** and the ring-opened aldehyde **d**, which is critical for the unique reactivity of this catalytic system. Some hydroxylated amide is oxidized to give the imide form **f**, but this is not the main pathway. The detection of **b** and **d** at the initial stage of the reaction by ^{1}H NMR supports the validity of this mechanism (see Supporting Information).



The oxidation reactions of lactams are also consistent with the above scheme. In the case of **9a**, the cyclic form is more stable than the ring-opened form of hydroxylated amide, and **9a** was efficiently converted to the imide **9b**, whereas in the case of **11a**, the ring-opened form is more stable, and **11a** was mainly converted to the ring-opened product **11b** (Table 3).

Table 3. Oxidation of Lactams[a]

entry	substrate	product, isolated yield
1	 **9a**	 **9b**, 91 %[b]
2[c]	 **10a**	 **10b**, 21 %[b]
3	 **11a**	 **11b**, 65 %[d]

[a] Reaction conditions were the same as described in Table 1, except that the reaction time was 2 d. [b] Isolated yield. [c] Ring-opened products were also formed. [d] This yield was estimated from the NMR spectra.

In summary, we present the first direct conversion of *N*-acyl cyclic amines to *N*-acyl amino acids via oxidative C−N bond cleavage with pyridine *N*-oxides catalyzed by ruthenium porphyrin. Our system should be useful to prepare biologically active compounds such as γ- and δ-amino acids. The occurrence of this novel reaction with metalloporphyrin suggests that P450 or peroxidases might also catalyze a similar type of oxidation. Further investigation is in progress.

Acknowledgment. This research was supported in part by a Grant-in-Aid for University and Society Collaboration (No. 12793009) from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Experimental details and further information concerning the catalytic system and the oxidation of aldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA045603F