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Ruthenium-Catalyzed Oxidation of Tertiary Amines with Hydrogen Peroxide in the Presence of Methanol

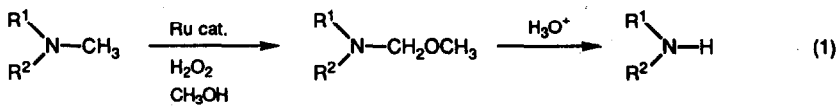
Shun-Ichi Murahashi,* Takeshi Naota, Noriko Miyaguchi and Takeshi Nakato

Department of Chemistry, Faculty of Engineering Science, Osaka University
Machikaneyama, Toyonaka, Osaka 560, Japan

Abstract: α-Methoxylation of tertiary amines can be performed by the ruthenium-catalyzed oxidation of tertiary amines with hydrogen peroxide in the presence of methanol. The reaction provides an efficient method for selective *N*-demethylation of tertiary methylamines and construction of quinoline skeletons.

α-Oxygenation of tertiary amines is of importance from enzymatic[1] and synthetic[2] points of view. We have explored the simulation of enzymatic function of amine monooxygenase with metal complex catalysts, and found the ruthenium-catalyzed P-450 type oxidations of amines[3] and amides[4] with *t*-butyl hydroperoxide giving the corresponding α-*t*-butyldioxygenated compounds with high efficiency. These reactions can be rationalized by assuming the P-450 type mechanism which involves the formation of oxoruthenium species, α-hydrogen abstraction followed by electron transfer affording iminium ion intermediate, and nucleophilic attack of *t*-butyl hydroperoxide.

In order to find a novel P-450 type oxidation of tertiary amines, we have been searching for a catalytic system which includes the generation of oxoruthenium species by using other oxidizing reagents and the trap of the iminium ion with nucleophiles. As a consequence of these studies we have found a novel method for α-methoxylation of tertiary amines. The ruthenium-catalyzed oxidation of tertiary methylamines with hydrogen peroxide in the presence of methanol gives the corresponding α-methoxymethylamines with high efficiency as depicted in eq 1. The reaction provides an efficient method for selective *N*-demethylation of tertiary methylamines and construction of quinoline skeletons from tertiary methylamines.

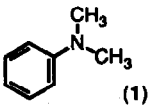
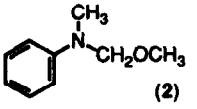
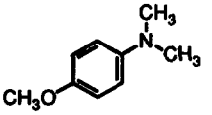
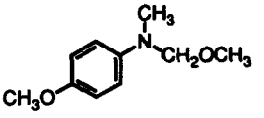
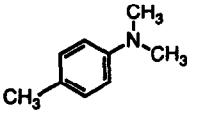
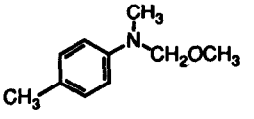
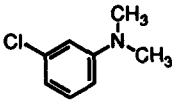
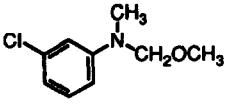
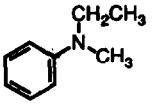
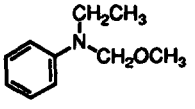
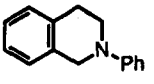
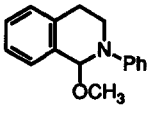


(1)

α-Methoxylation of tertiary amines has been performed by the anodic oxidation in methanol.[5] The present reaction provides an alternative method for the preparation of α-methoxyamines with regard to its simple operation, mild reaction conditions, and high efficiency. The catalytic activity of various metal complexes was examined for the oxidation of *N,N*-dimethylaniline (**1**) with hydrogen peroxide in methanol. $RuCl_3 \cdot nH_2O$ has proven to be the most effective catalyst for the formation of *N*-methyl-*N*-(methoxymethyl)aniline (**2**). $RuCl_2(PPh_3)_3$ also shows catalytic activity.

A typical example for the α-methoxylation of tertiary amines is as follows. To a solution of **1** (0.242 g, 2.0 mmol) and $RuCl_3 \cdot nH_2O$ (0.026 g, 0.1 mmol) in MeOH (15 mL) was added a 30% H_2O_2 aqueous solution (0.45 mL, 4.0 mmol) dropwise at room temperature over a period of 2 h. After the mixture was stirred for 5 min, the reaction was quenched by

Table I. Ruthenium-Catalyzed Oxidation of Tertiary Amines with H_2O_2 in the Presence of MeOH[a]

entry	tertiary amine	H_2O_2 (equiv.)	product[b]	yield[c](%)
1	 (1)	2.0	 (2)	67
2		1.5		87
3		1.5		80
4		3.0		60
5		3.0		55
6		4.0		60

[a]To a stirred solution of tertiary amine (2.0 mmol) and $RuCl_3 \cdot nH_2O$ (0.1 mmol) in MeOH (15 mL) was added a 30% H_2O_2 aqueous solution dropwise at room temperature over a period of 2 h. [b]Satisfactory IR and NMR spectral data were obtained. [c]Isolated yield.

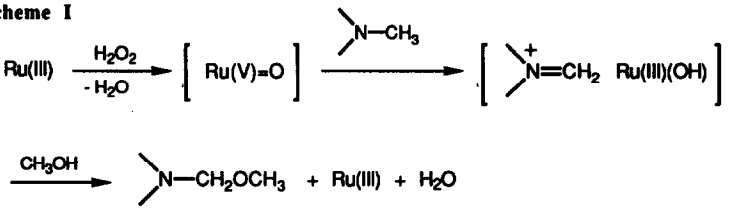
adding a solution of KOH in MeOH. After evaporation of the solvent, the residue was dissolved in ether (20 mL) and the resulting precipitate was filtered through a pad of Celite. Removal of the solvent gave methoxymethylamine 2 (0.209 g, 67%).

Table I shows the representative results of the oxidation of tertiary amines with H_2O_2 in MeOH. Various tertiary methylamines can be converted into the corresponding methoxymethylamines with high efficiency. *N*-Methyl groups are oxidized chemoselectively in the presence of other alkyl groups. Methoxy group can be introduced at C-1 position of 1,2,3,4-tetrahydroquinolines.

In order to gain insight into the mechanism the relative reaction rates of the oxidation of four substituted *N*,*N*-dimethylanilines (X-$C_6H_4N(CH_3)_2$, X = *p*-CH_3O, *p*-CH_3, H, and *m*-Cl) with H_2O_2 in MeOH were determined by the ^1H NMR analysis of the corresponding methoxylated products. The rate data correlate well ($\gamma = 0.993$) with the Hammett

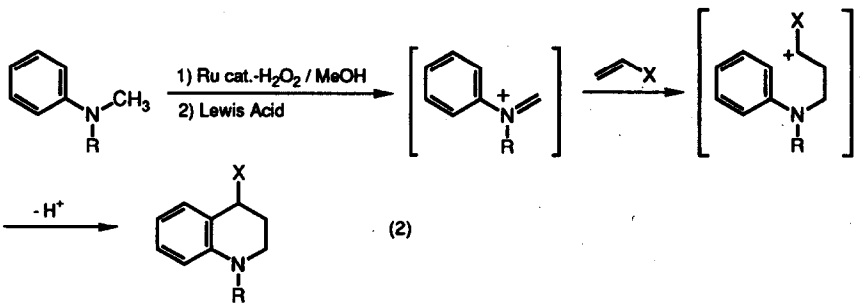
linear free energy relationship with use of σ values. The ρ value is -3.26, which indicates cationic intermediacy at the rate-determining step. The observed ρ value is larger than that obtained from the ruthenium-catalyzed oxidation with *t*-BuOOH (-0.84),[3] which shows that the active ruthenium species of the present reaction is less reactive in comparison with that derived from $RuCl_2(PPh_3)_3$ and *t*-BuOOH. The intramolecular deuterium isotope effect of the the ruthenium-catalyzed oxidation of *N*-methyl-*N*-(trideuteriomethyl)aniline was determined to be 3.47 by means of the NMR analyses of the products. The intermolecular isotope effect of the oxidation of an equimolar mixture of *N,N*-dimethylaniline and *N,N*-bis(trideuteriomethyl)aniline was determined to be 3.72 by the NMR analyses of the products. The observed intra- and intermolecular isotope effects (3.47 and 3.72) are larger than the values observed for P-450 *N*-demethylations (1.6-3.1[6] and 1.0-1.1[7a,8]), suggesting that the C-H bond breaking in the present reaction proceeds with more radical character. Considering from these data the present reaction can be rationalized by the P-450 type mechanism[2-4] as shown in Scheme I. A ruthenium(II) complex reacts with H_2O_2 to give oxoruthenium(V) complex which undergoes α-hydrogen abstraction from tertiary amines followed by electron transfer to afford iminium ion-hydroxyruthenium complex. Nucleophilic attack of MeOH gives the methoxylated amines, water, and Ru(III) to complete the catalytic cycle.

Scheme I

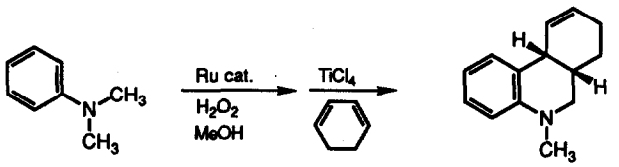


Oxidative *N*-dealkylation of amines is one of the important P-450 specific reactions,[1,7] and several model reactions using metal porphyrins have been reported.[9] We have reported practical method for selective *N*-demethylation of tertiary methylamines by the ruthenium-catalyzed oxidation with hydroperoxides and the subsequent hydrolysis.[3] The present oxidation reaction provides an alternative and efficient method for the selective *N*-demethylation of tertiary methylamines upon treatment of the product methoxyamines with hydrochloric acid (eq 1). For example, the methoxylation of *p*-methoxy-*N,N*-dimethylaniline followed by the treatment with 2 N HCl aqueous solution in ether gave *p*-methoxy-*N*-methylaniline in 71 % yield. Similar treatment with *p*-methyl-*N,N*-dimethylaniline gave *p*-methyl-*N*-methylaniline in 75% yield. Methyl groups are removed chemoselectively in the presence of other alkyl groups. Thus, *N*-ethyl-*N*-methylaniline was demethylated selectively upon similar treatment in 47% yield.

The present oxidation reaction provides an efficient method for construction of quinoline skeletons from tertiary aromatic amines via iminium ion cyclization (eq 2). Similarly, Shono et al. have reported that the anodic oxidation of



amines and subsequent $TiCl_4$-induced reaction with electron-rich olefins give quinoline structures.[10] The ruthenium-catalyzed oxidation of *N*-methyl-*N*-alkylanilines and the subsequent Lewis acid-induced reaction with various olefins give the corresponding tetrahydroquinoline derivatives with high efficiency. For example, the ruthenium-catalyzed methoxylation of **1** gave **2** (67%), which undergoes $TiCl_4$-promoted reaction with allyltrimethylsilane at -78°C in CH_2Cl_2



1 **3**

to give 1-methyl-4-[(trimethylsilyl)methyl]-1,2,3,4-tetrahydroquinoline in 88% yield. The reaction with cyclic conjugated dienes gives *cis*-fused tricyclic amines exclusively. Thus, *cis*-5-methyl-5,6,6a,7,8,10a-hexahydrophenanthridine (**3**) has been obtained from **1** selectively upon similar treatment of the corresponding methoxyamine **2** with 1,3-cyclohexadiene (oxidation 67%; cyclization 91%).

Work is in progress to provide definitive mechanistic information and to apply our method to other system.

Acknowledgment: We thank the Naito Foundation for financial support.

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