Tungstate-Catalyzed Decarboxylative Oxidation of *N*-Alkyl-α-amino Acids: An Efficient Method for Regioselective Synthesis of Nitrones

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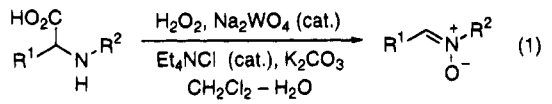
Summary: The tungstate-catalyzed oxidation of *N*-alkyl-α-amino acids with hydrogen peroxide under phase-transfer conditions gives the corresponding nitrones in satisfactory yield.

Nitrones are excellent spin trapping reagents,[1] highly versatile synthetic intermediates,[2] and 1,3-dipoles for construction of biologically active nitrogen heterocycles.[3] The preparation of regio- and stereochemically defined nitrones is still an important task in organic synthesis, since there is an increasing demand for highly functionalized nitrones as a tool in the synthesis of complex nitrogen compounds. Among the methods for the preparation of nitrones, the catalytic oxidation of secondary amines with hydrogen peroxide is the most simple and effective method;[2,4] however, the disadvantage of this method is that the oxidation of unsymmetrical secondary amines often gives a mixture of regioisomeric nitrones.

We wish to report that catalytic oxidative decarboxylation of *N*-alkyl α-amino acids gives the corresponding nitrones as depicted in eq 1. The reaction provides an



(1)

efficient method to introduce a substituent at the α-position of amines selectively, since the nitrones thus obtained react with various nucleophiles and 1,3-dipolarophiles. This method is advantageous over the previous methods, that is, oxidative transformation of *N*-acyl-α-amino acids by either electrochemical oxidation[5] or lead tetraacetate-promoted oxidation[6] to give the corresponding *N*-acyl-*N*,*O*-acetals and their subsequent treatment with nucleophiles, because of excellent reactivity of nitrones toward various reagents.

The oxidation of 2-(*N*-ethylamino)phenylacetic acid (**1**)[7] was examined based on our reported method.[2,4] However, the oxidation of **1** with hydrogen peroxide did not proceed in the presence of selenium dioxide catalyst or sodium tungstate catalyst. After the numerous trials, we found that the use of 1 equiv of base under phase-transfer conditions gives good results. Thus, the treatment of amino acid **1** with aqueous 30% hydrogen peroxide solution (3.0 equiv) in the presence of sodium tungstate (5 mol %), tetraethylammonium chloride (5 mol %), and K_2CO_3 (1.2 equiv) in water-dichloromethane (1:3) gave nitrone **2** as a single regioisomer in 78% isolated yield. The use of the other bases such as NaOH (69%), K_3PO_4 (71%), and $NaHCO_3$ (72%) also gave the nitrone **2** in somewhat lower yields.

The scope of the oxidation of *N*-alkyl-α-amino acids can be seen from the representative results shown in Table 1. Although the tungstate-catalyzed oxidation of *N*-benzylethylamine gave a mixture of nitrones **2** (39%) and **4** (41%), the present oxidation of *N*-benzylalanine (**3**) gave nitrone **4** as a single isomer in 70% isolated yield (entry 2). The acyclic amino acids **5** and **7** were converted into the corresponding nitrones **6** and **8**, respectively (entries 3 and 4). Cyclic nitrones **12** and **14** also have been prepared from **11** and **13** in moderate yields (entries 6 and 7). From the above results it becomes evident that the tungstate-catalyzed oxidation of *N*-alkyl-α-amino acids is an efficient method for the regioselective synthesis of nitrones.

The synthesis of nitrone **2** is described as a typical experimental procedure. To a suspension of amino acid **1** (5.00 mmol) in CH_2Cl_2 (15 mL) were added successively an aqueous solution (5 mL) of $Na_2WO_4{\cdot}2H_2O$ (0.25 mmol) and Et_4NCl (0.25 mmol) and then aqueous 30% H_2O_2 (1.5 mL). After addition of K_2CO_3 (6.0 mmol) portionwise at 0 °C, the solution was stirred at 30 °C for 12 h. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residual oil was purified by silica gel column chromatography to give the nitrone **2** in 78% yield.

The present method is especially useful for preparation of chiral cyclic nitrones.[8] Typically, enantiomerically pure (4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-pyrroline *N*-

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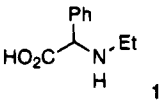
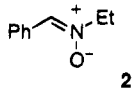
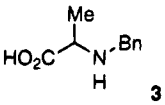
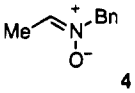
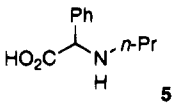
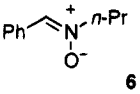
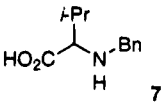
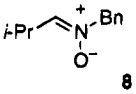
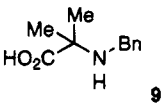
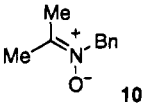
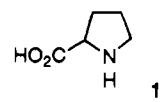
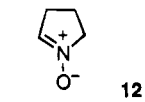
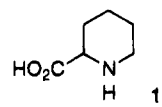
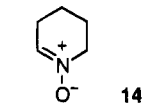
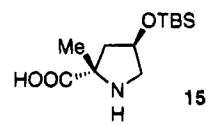
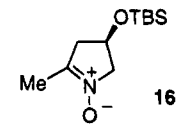
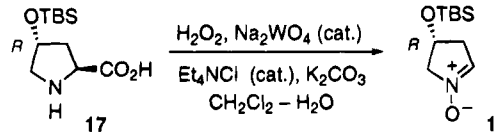
Table 1. Decarboxylative Oxidation of *N*-Alkyl-α-amino Acids[a]

entry	amino acids	nitrones[b]	yield (%)[c]
1	 1	 2	78
2	 3	 4	70
3	 5	 6	69
4	 7	 8	66
5	 9	 10	65
6	 11	 12	55
7	 13	 14	52
8	 15	 16	99

[a] The reaction was carried out as described in the text. [b] Satisfactory IR, NMR, and analyses have been obtained. [c] Isolated yield.

oxide (**18**),[9] which is a useful synthetic intermediate for synthesis of optically active pyrrolidines, can be prepared from *trans*-4-(silyloxy)-L-proline (**17**)[10] simply upon treatment with hydrogen peroxide under the present reaction conditions in 70% isolated yield.



On the other hand, (3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-pyrroline *N*-oxide (**20**), a regioisomer of **18**, can be obtained by the tungstate-catalyzed oxidation of (3*R*)-3-((*tert*-butyldimethylsilyl)oxy)pyrrolidine (**19**), which was prepared by silylation of (3*R*)-*N*-(benzyloxycarbonyl)-3-hydroxypyrrolidine[11] followed by hydrogenation (70% yield), in the ratio of **20**/**18** = 6.8:1 (70% yield). Enantiomerically pure crystalline **20**[9] was obtained easily by column chromatographic separation (SiO_2) in 61% yield.

(9) Optical purities of **18** ($[\alpha]^{28}_D$ −50.9 (*c* 1.14, MeOH); mp 72.1−72.9 °C) and **20** ($[\alpha]^{28}_D$ +55.9 (*c* 1.14, MeOH); mp 73.8−75.5 °C) were determined on the basis of HPLC analysis using CHIRALCEL OD.

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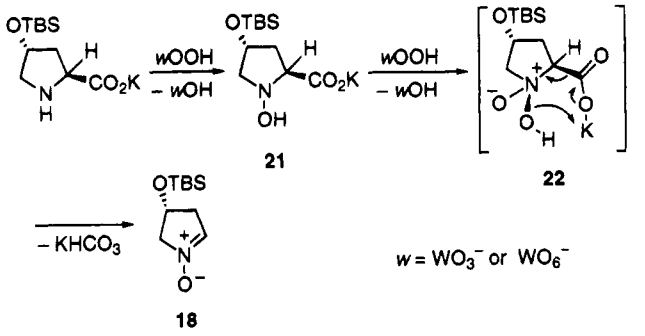
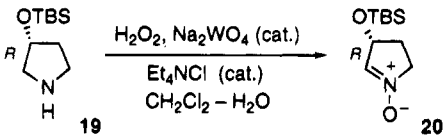
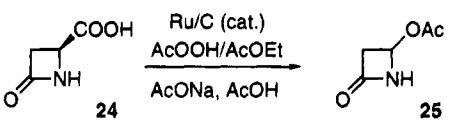
Scheme 1



The decarboxylative oxidation of amino acids can be rationalized by assuming Scheme 1. The oxidation is



accompanied by decarboxylation, and nitrones are formed regioselectively in the direction of the carbon-attached carboxylic acids. Initially, peroxytungstate (*w*OOH) (*w* = WO_3^- or WO_6^-),[12] generated from sodium tungstate and hydrogen peroxide, reacts with the amino group to give *N*-hydroxyamino acid **21**. Sequential oxidation of **21** with peroxytungstate (*w*OOH) gives the *N*-oxide of the hydroxylamine **22**, which undergoes elimination of $KHCO_3$ to give (4*R*)-4-(silyloxy)-1-pyrroline *N*-oxide (**18**). The oxidation of *N*-hydroxyamino acid **21** is proved by the fact that the oxidation of (4*R*)-*N*-hydroxy-4-(silyloxy)-L-proline (**23**), the CO_2H analogue of **21**, under the same reaction conditions gives **18** (70% yield). The possibility of the initial dehydration of **21** and subsequent decarboxylation is removed by the fact that the oxidation of (2*S*,4*R*)-4-(silyloxy)-2-methylproline (**15**) having no hydrogen at the α-position also proceeded smoothly to give (4*R*)-4-(silyloxy)-2-methyl-1-pyrroline *N*-oxide (**16**) in 99% yield (entry 8 in Table 1). It is noteworthy that ruthenium-catalyzed oxidation of 2-oxoazetidine-4-carboxylic acid (**24**) with peracetic acid in acetic acid gives 4-acetoxyazetidine-2-one (**25**) efficiently, where four-membered acyliminium ion intermediate is trapped with acetate ion.[13]



One can imagine various synthetic applications by using nitrones thus obtained.[2] The most simple and important application is the synthesis of [1-^{14}C]-labeled amino acids, which are an important class of compounds with respect to the tracer experiments for the study of metabolism and biosynthesis, by the oxidation and subsequent treatment with labeled K^{14}CN.[14] Further work is currently in progress on the extension of this highly efficient reaction to the other system and application to the synthesis of nitrogen-containing biologically active natural products.

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Supplementary Material Available: Complete experimental details for preparation of **18** and **20** and spectral and characterization data for all new compounds (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.