Oxidative Decarboxylation of α-Amino Acids with *in situ* Generated Dimethyl Dioxirane

Vidyadhar M. Paradkar*#, Tamara B. Latham and Donald M. Demko

Ohmeda Pharmaceutical Products Division, 100 Mountain Avenue, Murray Hill, NJ 07974, USA

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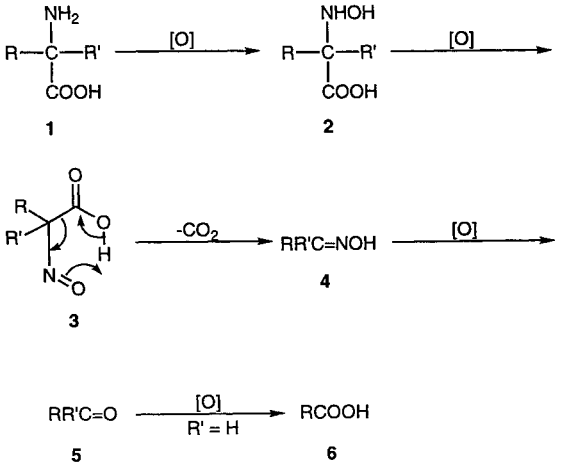
Abstract: Oxidative decarboxylation of α-amino acids with acetone-potassium peroxymonosulfate (oxone®) is described. The reaction represents the first example of oxidative decarboxylation of an α-amino acid $RCH(NH_2)COOH$ in which a product other than an aldehyde RCHO or a carboxylic acid RCOOH has been isolated as the major component.

Oxidative decarboxylation of an α-amino acid is a widely documented biochemical reaction which entails formation of an aldehyde RCHO or a carboxylic acid RCOOH from an α-amino acid $RCH(NH_2)COOH$.[1-3] Chemically, this conversion can be effected by *N*-bromoacetamide,[2] iodosobenzene,[4] hypohalite,[5] *N*-chlorosuccinimide,[6] silver(II) picolinate[7] or potassium peroxydisulfate in the presence of silver(I).[8] Silverman has proposed the intermediacy of an α-amino radical in the case of silver(I) catalyzed oxidations, and an electrocyclic mechanism for silver(II) based oxidations.[9] In most cases the imine RCH=NH is the putative intermediate. In the literature, dimethyl dioxirane, prepared either as a solution in acetone or generated *in situ* from acetone and oxone®, has been cited as the reagent of choice for various oxidative transformations including oxidation of aliphatic and aromatic amines to the corresponding nitro compounds.[10-12] We wish to report a novel application of this reagent for oxidative decarboxylation of various α-amino acids and its utility to prepare the congeners of desaminoarginine. Depending on the structure of the α-amino acid, varying proportions of the carboxylic acid, ketone, and oxime with one carbon atom fewer than the starting amino acid are formed. The reaction was utilized to prepare γ-guanidinobutyric acid, γ-nitroguanidinobutyric acid and desaminoarginine from L-arginine, L-nitroarginine and L-homoarginine, respectively. When L-arginine was treated with dimethyl dioxirane generated by the method of Zabrowski,[12] γ-guanidinobutyric acid was obtained in 57% yield. Similarly, L-nitroarginine was converted into nitroguanidinobutyric acid which was isolated as its methyl ester in 34% overall yield. On the other hand, 2-phenylglycine gave a 3:1 mixture of benzaldoxime and benzoic acid. In addition, 1-aminocyclohexane-1-carboxylic acid, which lacks the alpha hydrogen, gave a 3:1 mixture of cyclohexanone oxime and cyclohexanone. The overall conversion in these two cases was over 70%.

The proposed mechanism is depicted in the scheme. The hydroxylamine and the nitroso compounds have been isolated as intermediates in the oxidation of amines with dimethyl dioxirane.[12,13] The *N*-hydroxyamino acid (**2**) formed in the first step is oxidized to the α-nitrosocarboxylic acid (**3**), with the excess reagent. The decarboxylation of **3** via a cyclic transition state leads to the formation of oxime (**4**). In the case of arginine analogs, the oxime probably undergoes facile oxidative hydrolysis to the carboxylic acid (**6**) via aldehyde (**5**). On the other hand, with 2-phenylglycine and 1-aminocyclohexane-1-carboxylic acid the oxime (**4**) is stable to the reaction conditions employed, and therefore can be isolated. When the oxidative decarboxylation was carried out without acetone, the yields were much lower and a number of side products were obtained. Olah has recently reported the oxidative hydrolysis of ketoximes to the corresponding carbonyl compounds with dimethyl dioxirane in acetone.[14] The ease of hydrolysis varied with the structure of the ketoxime, whereas aldoximes were recovered unchanged. To our knowledge, the reaction of α-amino acid with *in situ* generated dimethyl dioxirane is the first example of oxidative decarboxylation in which the amine nitrogen undergoes a direct oxygenation with the oxidizing species. The commonly proposed imine, RCH=NH, is not a likely intermediate in the present case.



Scheme

Table: Oxidative decarboxylation of α-amino acids with oxone®-acetone.

Starting Material	Product(s), [% Yield]
L-Arginine	γ-Guanidinobutyric acid, [57]
L-Nitroarginine	γ-Nitroguanidinobutyric acid, [34]*
2-Phenylglycine	Benzaldoxime:Benzoic Acid (3:1), [74]
1-Aminocyclohexane-1-carboxylic acid	Cyclohexanone oxime:Cyclohexanone (3:1), [88]
L-Homoarginine	Desaminoarginine, [56]

* Isolated as a methyl ester

Typical Procedures:

Oxidative decarboxylation of L-nitroarginine. A mixture of L-nitroarginine (1.0 g, 4.56 mmol) and acetone (10 mL) in 65 mL of pH 8 aq. phosphate buffer was cooled to 5 °C and a solution of oxone® (8.4 g, 13.65 mmol) in 50 mL of water was added dropwise. Throughout the addition, pH was maintained between 7.5 and 8.5 by addition of 2N KOH solution. After addition was complete, the reaction mixture was stirred at room temperature until the disappearance of the starting material was evident (*ca.* 7 h). The excess oxone® was destroyed by addition of sodium sulfite and the pH was adjusted to 2 with 6N HCl. The water was removed on a rotavapor and the dried residue was triturated with 50 mL of methanol. After filtration, the solvent was removed and the crude γ-nitroguanidinobutyric acid was esterified using methanol and HCl gas. The resulting methyl γ-nitroguanidinobutyrate was purified by chromatography on silica gel using ethyl acetate:hexane (9:1) as the solvent, yield 0.3 g (34%). The analytical sample was crystallized from hexane-ethyl acetate, mp 84 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.89 (br s, 1 H, N*H*), 3.56 (s, 3 H, OCH_3), 3.10-3.20 (m, 2 H, NCH_2), 2.33 (t, 2 H, J = 7.4 Hz, CH_2CO), 1.65-1.80 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C-NMR (75.4 MHz, DMSO-d_6): δ 172.8, 159.3, 51.3, 39.8, 30.4, 23.8.

Anal. Calcd. for $C_6H_{12}N_4O_4$: C, 35.29; H, 5.92; N, 27.44. Found: C, 35.28; H, 5.79; N, 26.87.

Oxidative decarboxylation of 2-phenylglycine. A mixture of phenylglycine (1.0 g, 6.6 mmol) and acetone (10 mL) in 65 mL of pH 8 aq. phosphate buffer was cooled to 5 °C and a solution of oxone® (12.2 g, 19.8 mmol) in 50 mL of water was added dropwise. Throughout the addition, pH was maintained between 7.5 and 8.5 by addition of 2N KOH solution. After addition was complete, the reaction mixture was stirred at room temperature until the disappearance of the starting material was evident (*ca.* 7 h). The excess oxone® was destroyed by

addition of sodium sulfite and the aqueous layer was extracted with ether. Evaporation of the ether layer provided 0.45 g of benzaldoxime. The aqueous layer was acidified to pH 2 and extracted repeatedly with ether. Evaporation of the ether layer gave 0.15 g of benzoic acid.

All previously known compounds were characterized by comparison of their ^{1}H and ^{13}C NMR spectra with that of the authentic samples. γ-Guanidinobutyric acid and desaminoarginine were prepared similarly from L-arginine and L-homoarginine, and were purified by ion-exchange chromatography.

References and Notes

Address correspondence to this author at: Pharmacopeia Inc., 2000 Cornwall road, Monmouth Junction, NJ 08852, USA.

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