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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2599–2602

Metalloporphyrin and heteropoly acid catalyzed oxidation of C=NOH bonds in an ionic liquid: biomimetic models of nitric oxide synthase

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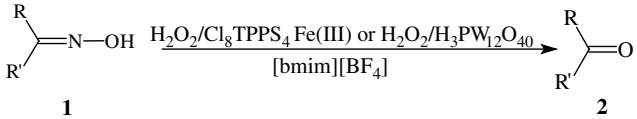
Received 21 December 2004; revised 5 February 2005; accepted 15 February 2005

Abstract—Water soluble iron(III) porphyrins and phosphotungstic acid in an ionic liquid are effective catalysts for the H_2O_2 mediated oxidation of the C=NOH bond in *N*-hydroxyarginine and other oximes. The carbonyl compounds generated as the oxidation products can be easily isolated from the reaction media. These systems serve as biomimetic models of nitric oxide synthase (NOS) and the catalyst immobilized in an ionic liquid can be easily recycled and reused.

Nitric oxide synthase (NOS) catalyzes the five-electron oxidation of L-arginine to L-citrulline and nitric oxide (NO) by O_2 in two steps.[1] In the first step, two NADPH derived reducing equivalents and O_2 lead to the formation of *N*-hydroxy-L-arginine (NHA) **3**.[2] The redox stoichiometry for this step is that of a typical cytochrome P450 hydroxylation. The second step of the NOS reaction involves a three electron oxidation of *N*-hydroxy-L-arginine to NO and citrulline **4** by O_2.[3] Several mechanisms have been proposed to account for the unusual redox chemistry of the NOS catalyzed oxidation of NHA.[4] These include generation of either a high valent iron-oxo intermediate[5] or a nucleophilic peroxo Fe(III)P species during the reaction.[6]

Metalloporphyrins as chemical models of cytochrome P450 and related monooxygenases have been used to carry out oxygenation and oxidation reactions of various drugs and biologically active compounds.[7–10] Air- and moisture-stable room temperature ionic liquids (ILs) based on imidazolium cations are environmentally benign solvents for carrying out various chemical and biochemical transformations[11–13] and for immobilization of transition metal catalysts in biphasic and monophasic processes.[14,15] We have reported the enhanced stability of anionic water soluble iron(III) porphyrins and cobalt(II) phthalocyanines in imidazolium ionic liquids.[16,17] In continuation of our ongoing research into the application of ionic liquids as green solvents in organic synthesis,[18] herein we report the oxidative cleavage of the C=NOH bond in *N*-hydroxyarginine, the typical biological precursor of nitric oxide in the NOS reaction, as well as other oximes with hydrogen peroxide catalyzed by water soluble iron(III) porphyrins as chemical models of NO synthase and molecular oxygen (Schemes 1 and 2).[19,20] We have also examined the same reaction using another catalyst, phosphotungstic acid immobilized in an ionic liquid. Phosphotungstic acid belongs to the class of heteropoly acids, sometimes referred to as inorganic metalloporphyrins,[21] which are useful and versatile catalysts in a number of homogeneous, biphasic and heterogeneous liquid phase reactions.[22,23] Aqueous hydrogen peroxide coupled with a tungstate complex and a quaternary ammonium hydrogen sulfate is a clean, safe and ideal oxidant for oxidative dehydrogenation and epoxidation of alkenes and



1 **2**

Scheme 1. Oxidation of the C=NOH bond by hydrogen peroxide catalyzed by Cl_8TPPFe(III) **5** or phosphotungstic acid in an ionic liquid.

Keywords: Nitric oxide synthase (NOS); Heteropoly acid; Porphyrins; Ionic liquid.
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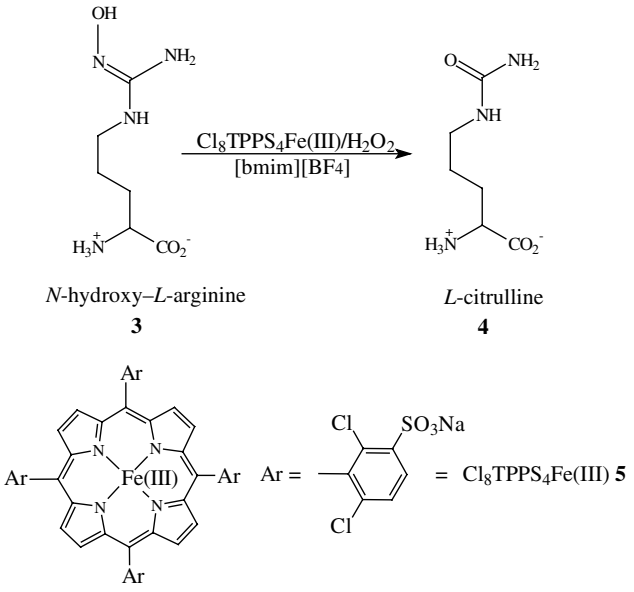
doi:10.1016/j.tetlet.2005.02.088



Scheme 2. Oxidation of *N*-hydroxyarginine with hydrogen peroxide catalyzed by **5** in an ionic liquid.

for oxidation of alcohols, glycols, phenols and sulfides.[24–26] To the best of our knowledge, this is the first report for the use of water soluble iron(III) porphyrins and heteropoly acids in an ionic liquid as model catalysts of NO synthase (Table 1).

The reaction of **3** with hydrogen peroxide catalyzed by **5** in [bmim][BF_4] gave **4** in 37% yield after 4 h. The product analysis and yield determination were based on HPLC analysis. The oxidation was more facile with ketoximes which gave higher yields of the carbonyl compounds as compared to aldoximes. A range of aldoximes were examined for this reaction and it was found that aldoximes **1b**,**c** possessing electron donating substituents gave higher yields of the products than aldoximes **1f–h** having electron withdrawing substituents. The mechanism of deoximation may involve formation of a hydroperoxide intermediate which adds in a nucleophilic sense to the C=N bond to give a peroxy anion adduct **6** which on subsequent decomposition yields **4** (Scheme 3). Nucleophilic attack of a ferric peroxy anion (Fe^{III}–O–O^-) to C=O and C=N groups in substrates has been reported in the literature.[27] The same mechanism may be operative in the oxidation of oximes into carbonyl compounds by hydrogen peroxide in the presence of iron(III) porphyrins in ionic liquids, although a detailed mechanistic study would be required to prove this.

The oxidation of oximes with H_2O_2 catalyzed by the second catalyst, phosphotungstic acid in ionic liquid gave higher yields of the carbonyl compounds in comparison to **5**. It is believed that the interaction of phosphotungstic acid with hydrogen peroxide in an ionic liquid leads to initial formation of an active peroxo polyoxometalate species **7**, which reacts with respective aldoxime or ketoxime in a nucleophilic manner followed by subsequent transformations leading to the formation of the corresponding aldehyde or ketone (Scheme 4). This peroxo species **7** has been identified as a tungsten dioxygen intermediate by its characteristic peak at 866 cm^{-1} in its IR spectrum indicating a tungsten dioxygen ring.[28]

Table 1. Oxidation of oximes (**1a–p**) with hydrogen peroxide catalyzed by phosphotungstic acid or **5** in [bmim][BF_4][a]

Entry	Substrate **1**	Product **2**[b]	Time (h)	Yield[c](%)	
				$H_3PW_{12}O_{40}$	**5**
a	Benzaldehyde oxime	Benzaldehyde	3	80	57
b	4-Methylbenzaldehyde oxime	4-Methylbenzaldehyde	4	86	68
c	4-Methoxybenzaldehyde oxime	4-Methoxybenzaldehyde	4	90[d]	71
d	Piperonal oxime	Piperonal	4	88	64
e	4-Methylamino-3-nitrobenzaldehyde oxime	4-Methylamino-3-nitrobenzaldehyde	6	83	62[e]
f	4-Chlorobenzaldehyde oxime	4-Chlorobenzaldehyde	5	78	59
g	4-Fluorobenzaldehyde oxime	4-Fluorobenzaldehyde	5	74	45
h	4-Nitrobenzaldehyde oxime	4-Nitrobenzaldehyde	5	70	49
i	Cinnamaldehyde oxime	Cinnamaldehyde	3	80	63
j	2-Furancarboxaldehyde oxime	2-Furancarboxaldehyde	4	84	57
k	3-Pyridine carboxaldehyde oxime	3-Pyridine carboxaldehyde	5	76	45
l	2-Butanone oxime	2-Butanone	4	74	70
m	Acetophenone oxime	Acetophenone	3	92	81
n	Benzophenone oxime	Benzophenone	3	86	73
o	Cyclohexanone oxime	Cyclohexanone	3	97[f]	85
p	9-Fluorenone oxime	9-Fluorenone	6	71	65

[a] Reaction conditions: All reactions were performed under nitrogen. Oxime (1.0 mmol), H_2O_2 (1.0 mmol), $H_3PW_{12}O_{40}$ or $Cl_8TPPS_4Fe(III)Cl$ (0.01 mmol), [bmim][BF_4] (3.0 mL).

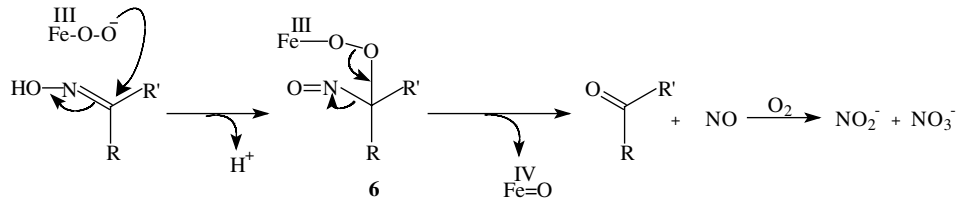
[b] All products were characterized by ^1H NMR, IR and EI-MS spectroscopic methods.

[c] Yields refer to isolated products.

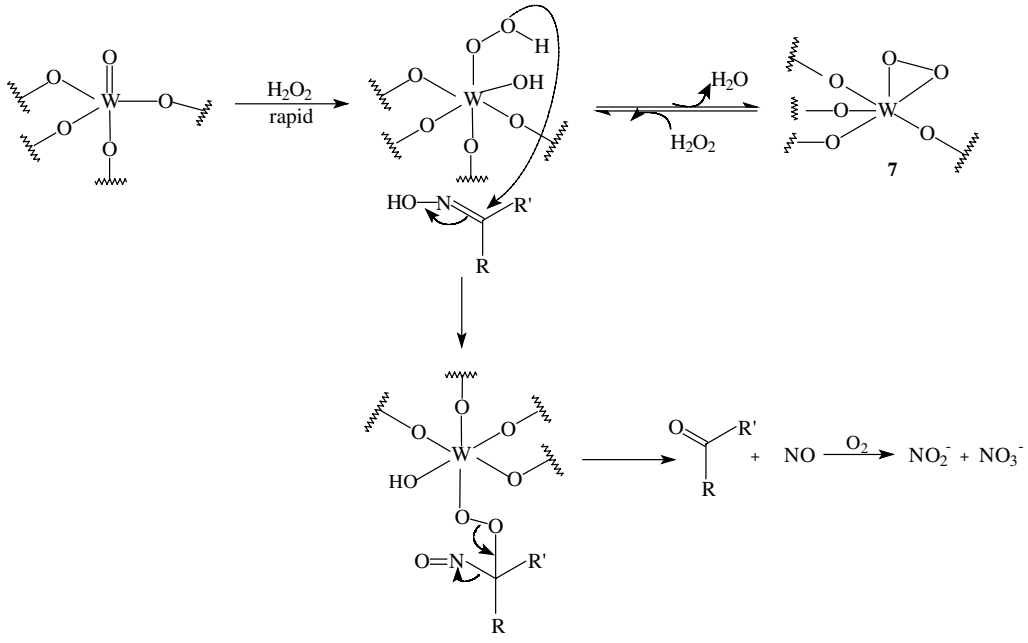
[d] Yield of 4-methoxybenzaldehyde was only 10% when deoximation was carried out under phase transfer conditions in dichloromethane/water using tetrabutylammonium bromide as the phase transfer reagent and the starting oxime was recovered in 80% yield. 10% of 4-methoxybenzoic acid was obtained as an over-oxidation product.

[e] *N*-Demethylated aldehyde was also obtained in 7% yield after 6 h.

[f] Cyclohexanone was not regenerated and starting material was recovered unchanged on reaction of cyclohexanone oxime (1.0 mmol) with H_2O_2 (1.0 mmol), $H_3PW_{12}O_{40}$ (0.01 mmol) in dichloromethane and methanol. Instead, the over-oxidized product adipic acid was obtained in 20% yield after 1 h.



Scheme 3.



Scheme 4.

Further, on addition of hydrogen peroxide to phosphotungstic acid immobilized in an ionic liquid, the colour of the solution changed to yellow, which is also characteristic of a three-membered tungsten dioxygen ring system. The ionic liquids are believed to stabilize this reactive intermediate as they have been reported earlier to stabilize manganese-oxo intermediate in manganese(III) porphyrins catalyzed oxygenation reactions.[29] Furthermore, on addition of H_2O_2 to the solution of phosphotungstic acid in the ionic liquid, a new peak at 275 nm was observed in the UV–visible spectra which in the presence of oximes decreased and finally disappeared depending on the amount of oxime (see Supplementary data). However, the peak reappeared on addition of fresh H_2O_2 and subsequently decreased in the presence of substrate. A similar peak at 280 nm was reported in the oxygen atom transfer reactions catalyzed by peroxotungstate complexes.[30]

In conclusion, a simple chemical model for biomimetic oxidation of C=NOH bonds has been developed with H_2O_2 catalyzed by water soluble iron(III) porphyrins as well as phosphotungstic acid. Phosphotungstic acid was found to be more efficient in bringing about this transformation as compared to water soluble iron(III) porphyrins. This study provides eco-friendly and reusable biomimetic model systems to study oxidation reactions of nitric oxide synthase in ionic liquids.

Acknowledgements

The author (N.J.) thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for providing a senior research fellowship (SRF).

Supplementary data

A detailed experimental section and spectroscopic data of the oximes and carbonyl compounds prepared is available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.088.

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