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Oxidative cleavage of the C=N bond during singlet oxygenations of amidoximates†

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Abstract—Amidoximes are inert toward singlet oxygen ($^1O_2$), however, the photooxygenation of amidoximate anions proceeds smoothly and in high yield to give mixtures of amides and nitriles. The mechanism of these reactions appears to involve carbonyl oxide intermediates. The oxidative cleavage of amidoximates closely resembles the results obtained from nitric oxide synthase (NOS) oxidations of *N*-hydroxyarginine.

The oxidation of *N*-hydroxyarginine by the nitric oxide synthase (NOS) to citrulline and nitric oxide (NO) is an important biological process since nitric oxide has been shown to play a significant role as a biological mediator in the cardiovascular system and in the brain, as well as in the immune system.[1] Superoxide in the form of NOS-Fe(II)-O_2 (or NOS-Fe(III)-O_2·$^-$) has been implicated as the active species in these oxidations.[2–4] Liver cytochrome enzymes P450 have also been shown to catalyze the oxidative cleavage of the C=NOH bonds in ketoximes, amidoximes and *N*-hydroxyguanidines.[5] Also potassium superoxide has been shown to efficiently cleave C=N bonds in amidoximes and *N*-hydroxyguanidines to give mixtures of amides and nitriles.[6] Previously we reported a survey of the reactions of singlet oxygen with C=N containing compounds, including nitrones, nitronate and oximate anions, silyl nitronates and hydrazones.[7,8] In the present study we have investigated the role of singlet oxygen ($^1O_2$) in the oxidative cleavages of amidoximate anions. Our results from the these reactions closely resemble those obtained from model studies on iron(III) porphyrin catalyzed oxidation of the *N*-hydroxyguanidine group under aerobic conditions.[9,10]

Oximes which, except for benzophenone oxime, are inert toward $^1O_2$, react readily with the latter in the form of their oximate anions since the C=N bond is rendered more electron-rich upon deprotonation. Upon combination with $^1O_2$ the 1-peroxy-1-nitroso intermediates typically undergo oxidative C=N cleavage to give mixtures of esters, carboxylic acids and aldehydes (from aldoximate anions) or ketones (from ketoximate anions), respectively. Our studies showed that amidoximes likewise do not participate in photooxygenations unless they are converted to the corresponding amidoximate anions with base prior to singlet oxygenation and herein we report on our results from these reactions.

When amidoximes,[11] after treatment with sodium methoxide, were photooxygenated[12] in methanol in the presence of rose bengal at room temperature, the corresponding amidoximates cleanly underwent oxidative cleavage to give mixtures of amides and nitriles, with the former as dominant products (Table 1). The products were separated by chromatography on silica gel, eluting with diethyl ether. Structural identifications rest on ^{1}H NMR spectra of the purified products, matching those taken of authentic samples.

A plausible mechanism for the observed oxidations involves electrophilic attack of the oximate anion by $^1O_2$, followed by extrusion of NO^- giving rise to a carbonyl oxide (**3**) (Scheme 1). The latter is an excellent oxygen atom donor and is converted to the amide by oxygen atom loss.[13] Alternatively, tautomerization of **3** to the peroxycarboximidic acid **5**[14] and base-induced extrusion of H_2O_2 would then lead to the nitrile **6**.[15]

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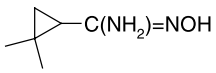
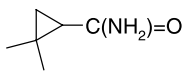
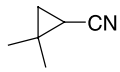
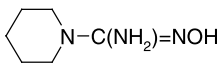
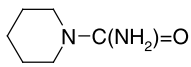
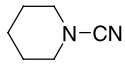
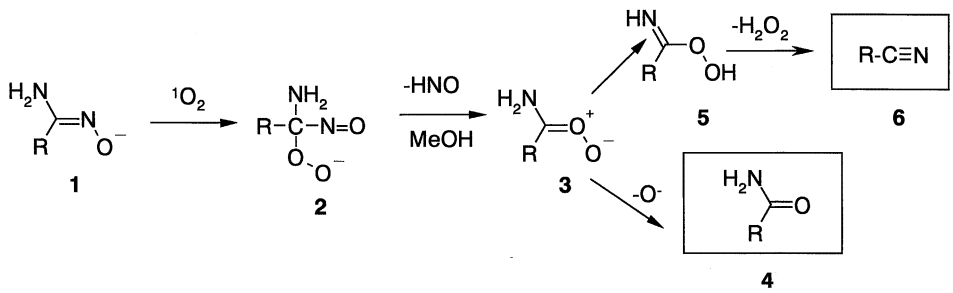
Table 1. Products and yields from the singlet oxygenation of amidoximates

Entry	Amidoxime	Amide	Nitrile
a	$PhC(NH_2)=NOH$	$PhC(NH_2)=O$ 74%	PhCN 12%
b	$PhCH_2C(NH_2)=NOH$	$PhCH_2C(NH_2)=O$ 77%	$PhCH_2CN$ 18%
c	$C_5H_{11}C(NH_2)=NOH$	$C_5H_{11}C(NH_2)=O$ 83%	$C_5H_{11}CN$ 9%
d	$PhCH=CHC(NH_2)=NOH$	$PhCH=CHC(NH_2)=O$ 69%	PhCH=CHCN 24%
e	$PhCH_2CH_2C(NH_2)=NOH$	$PhCH_2CH_2C(NH_2)=O$ 70%	$PhCH_2CH_2CN$ 11%
f		 82%	 10%
g		 58%	 22%



Scheme 1.

Table 1 depicts the results from photooxygenations of a variety of amidoximate anions. In a few cases small amounts of the corresponding methyl esters were also isolated, presumably from the amide in the presence of methoxide ions.

The conversion of amidoximes to nitriles is remarkable in that it represents a net loss of NH_2OH, a transformation without precedent in singlet oxygen chemistry. Our results should provide insight into the mechanistic details of the nitric oxide synthase reaction since some of the intermediates postulated in the aforementioned reaction resemble those proposed in this report.

The present study provides a nonenzymatic alternative to the oxidative cleavage of the amidoxime moiety in L-arginine, a process of considerable importance in terms of nitric oxide production, and nicely complements other model studies using Fe(III) porphyrin catalysis, directed at elucidating the oxidative processes involved in the NOS mediated amidoximate cleavages. Moreover, cleavage reactions of C=N containing compounds with $^1O_2$ constitute clean, high-yield and environmentally friendly oxidative methods in organic chemistry. Our studies on the photooxygenations of other C=N containing compounds, including α-oximinoketones, are forthcoming.

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12. In a typical experiment, 2–3 mmol of amidoxime was treated with 1.2 equiv. of NaOMe in 20 mL of methanol, and irradiated at room temperature under a positive pressure of oxygen, using a 250 W high-pressure sodium vapor lamp and rose bengal as sensitizer.
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