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The photochemistry of amides and amide derivatives 3: The photolysis of methyl-2-phenoxybenzohydroxamate [1]

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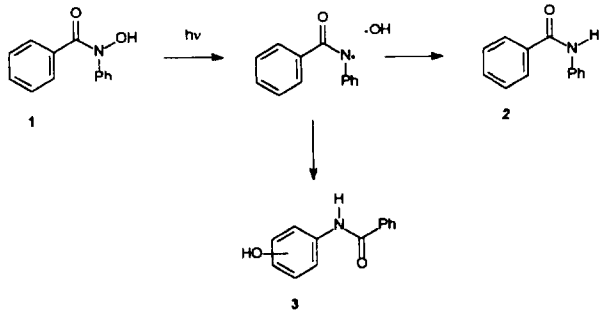
Abstract

The photochemistry of methyl-2-phenoxybenzohydroxamate was studied. This compound was found to undergo the type I reaction followed by intramolecular cyclization to generate xanthone, the type II reaction to generate 2-phenoxybenzamide, and a formal 1,5 shift of the phenyl group from the benzohydroxamate ring to the nitrogen. It was also found that the relative amounts of the type II product and the phenyl migration product were solvent dependent. Photolysis in methanol favored the phenyl migration process whereas photolysis in cyclohexane favored the type II process. These results are attributed to an increased amount of single electron transfer from the phenoxy group to the carbonyl group relative to the type II process in methanol. The photolysis of *N,N*-dimethyl-2-phenoxybenzamide, which cannot undergo phenyl migration, gives xanthone as the only product.

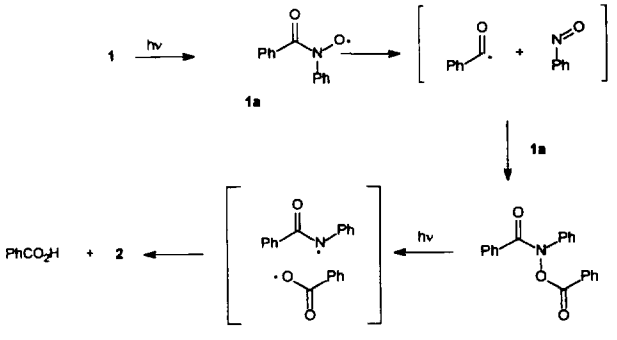
Keywords: Amides; Electron transfer; Hydroxamate; Phenyl migration

1. Introduction

The photochemistry of benzohydroxamic acids and their derivatives has received considerable attention in recent years and a review has been published [1]. In a report on the photolysis of *N*-phenylbenzohydroxamic acid [2] it was proposed that cleavage of the N–O bond occurs as the primary photochemical step to give an amidyl radical. The amidyl radical either abstracts a hydrogen atom to give benzanilide (**2**) or undergoes the Fries rearrangement to give the ortho and para isomers of *N*-benzoylhydroxyaniline (**3**).



A reinvestigation of this same reaction led to the conclusion that the primary photochemical step was cleavage of the O–H bond rather than the N–O bond [3].



In a study by Hosangadi et al. of alkyl benzohydroxamates such as methyl benzohydroxamate (**4**), it was reported that these compounds were quantitatively recovered after photolysis which led to the conclusion that they were photostable [4]. It was later found that these compounds undergo a relatively efficient ($\Phi \approx 0.2$) triplet state Norrish type II reaction to produce benzamide (**5**) along with the corresponding carbonyl compound [5].

[1] J.E. Johnson, M. Arfan, R. Hodzi, L.R. Caswell and S. Rasmussen, Part 1, *Photochem. Photobiol., 51* (1990) 139.J.E. Johnson and R.C. White, Part 2, *J. Photochem. Photobiol. A: Chem., 83* (1994) 217.

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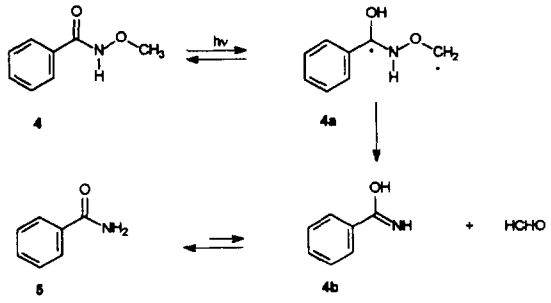
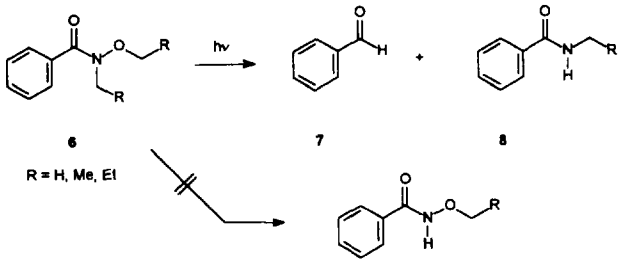
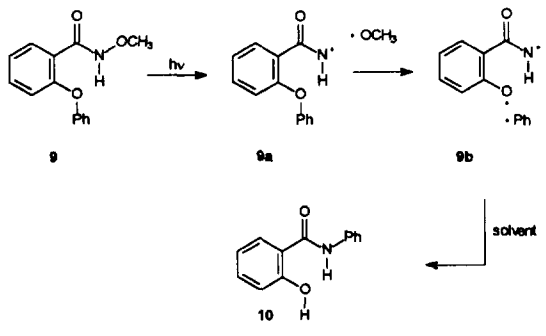


The conversion of methyl benzohydroxamate to benzamide could be rationalized by a process in which the initial photochemical step is N–O bond cleavage followed by hydrogen abstraction. The photolysis of alkyl *N*-alkylbenzohydroxamates (**6**) produces benzaldehyde in a type I photoreaction via the singlet state and the corresponding *N*-alkylbenzamides (**8**) as the type II photoproduct from both the singlet and triplet states [6]. Only one of two possible type II products, **8**, was formed in the photolysis.



However, the observation of photoracemization of a chiral hydroxamate containing an asymmetric carbon alpha to the hydroxylamine oxygen, demonstrates that the mechanism for this reaction is a type II process involving reversible 1,4-diradical formation [5].

It has been reported by Hosangadi et al. [7] that methyl 2-phenoxybenzohydroxamate (**9**) undergoes photolysis to give salicylanilide (**10**) as the only product. Since the photochemistry of acyclic alkyl benzohydroxamates can be described in terms of a Norrish type II process, we were intrigued by Hosangadi's proposed mechanism for this reaction which was described as an initial cleavage of the N–O bond followed by extrusion of a phenyl radical and radical recombination as shown below.



This seemed to be an unlikely mechanism. Unless this is a two-photon process, the initial photochemical cleavage of the N–O bond would result in the formation of **9a** as a ground state radical which would not easily extrude a phenyl radical to produce **9b**. Even if one proposed that **9a** did not extrude a phenyl radical, but rather underwent a 1,5 phenyl migration to give **10**, the process would still require either a two-photon process to induce the aryl migration or a very rapid thermal 1,5 shift at room temperature, both of which are unlikely. Based on our previous results for benzohydroxamate photochemistry [5,6] we felt that a more likely mechanism would involve a Norrish type II reaction to produce 2-phenoxybenzamide (**11**) which could then undergo a secondary photoreaction involving aryl migration to produce anilide **10**. We therefore undertook a mechanism study on the conversion of benzohydroxamate **9** to the anilide **10**.

2. Experimental details

High performance liquid chromatography (HPLC) analyses were carried out with an LDC Analytical HPLC with the detector set at 254 nm and a C-18 reversed phase analytical column connected to a Hewlett Packard 3396A integrator. Analyses were carried out using methanol–water (55:45) at a flow rate of 0.75 ml min^{-1} with biphenyl as an internal standard. Reaction products were verified by comparison of their GC retention times and mass spectra with those of authentic samples as well as coinjection of the photolysate with authentic samples via HPLC. Low resolution mass spectra were recorded using a Varian Saturn 3 ion trap gas chromatograph/mass spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian EM-360-L spectrometer. Acetonitrile, methanol (Sigma Aldrich) and cyclohexane (EM) were used as received. Benzohydroxamate **9** was prepared by a literature procedure [7]. Benzamide **11** was prepared by the action of 2-phenoxybenzoyl chloride with aqueous ammonia [8]. Authentic samples of salicylanilide and xanthone were purchased from Sigma Aldrich.

Photochemical reactions were carried out in a Rayonet photochemical reactor (Southern New England Ultraviolet Co.) equipped with either eight RPR 2537 lamps or four RPR 3000 lamps and a merry-go-round apparatus. Solutions of the reactant (5 ml, 0.02 M) were placed in quartz tubes (13 mm × 100 mm), sealed with a rubber septum and sparged with deoxygenated nitrogen for 20 min prior to photolyses. The photolysis of a mixture of **9** and **12** was carried out in a solution that was 0.02 M in **9** and 0.001 M in **12** so that **9** absorbed more than 95% of the incident light.

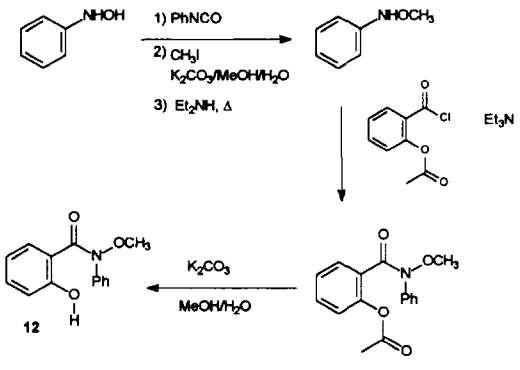
2.1. Methyl N-phenyl-2-hydroxybenzohydroxamate (12)

A solution of *N*-phenyl-*O*-methylhydroxylamine [9] (0.79 g, 7.2 mmol) in ether (20 ml) was added dropwise to a stirred solution of acetylsalicyloyl chloride (1.44 g, 7.2 mmol) and triethylamine (1 g) in ether (20 ml). The reaction

mixture was allowed to stir overnight and then filtered. The ether layer was washed with water (3×25 ml), dried (magnesium sulfate), and the ether removed to give a dark oil which was chromatographed over silica gel (20% ethyl acetate/hexanes) to generate 1.2 g of an oil (NMR: δ 6.6–7.8, m; 9H, δ 3.43, s, 3H; δ 2.16, s 3H) which was subjected to hydrolysis (potassium carbonate, aqueous methanol) to yield 0.93 g of an oil which darkened on standing (NMR: δ 6.3–7.8, m, 9H; δ 3.4, s, 3H).

3. Results and discussion

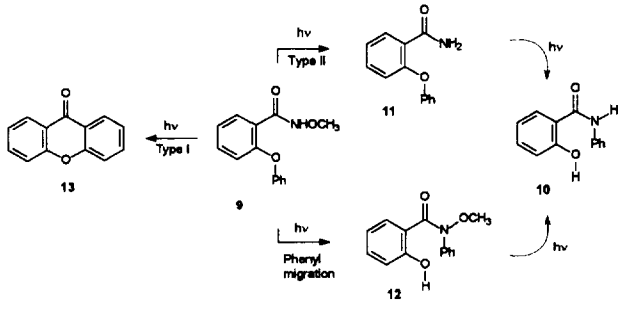
In a reinvestigation into the photolysis of **9** (300 nm, methanol, 1 h), it was found that in addition to **10**, the reaction mixture includes 2-phenoxybenzamide (**11**), methyl *N*-phenyl-2-hydroxybenzohydroxamate (**12**) and xanthone (**13**). There was no formation of biphenyl in the reaction which would be a possible photoproduct if phenyl radicals were formed. It has also been found that an independent photolysis of amide **11** produces anilide **10** which negated the need for N–O bond cleavage and supported our initial mechanistic proposal which involved a type II photoreaction. However, rate studies showed that anilide **10** is produced faster from **9** than from amide **11**. This suggests that **10** might be produced primarily via a secondary photoreaction of benzohydroxamate **12**. An authentic sample of **12** was obtained by the reaction of *N*-phenyl-*O*-methylhydroxlamine [9] with acetylsalicyloyl chloride followed by hydrolytic removal of the acetyl group.



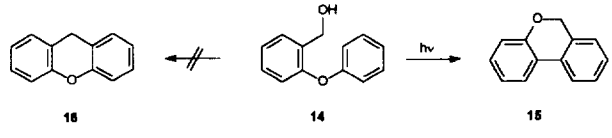
HPLC analyses of the reaction mixture from the photolysis of **9** revealed that **12** is maintained at a low concentration throughout the reaction. It was also found that **12** is converted smoothly to **10** under both direct and sensitized conditions. This suggests that benzohydroxamate **9** forms **12** under direct conditions and then sensitizes its conversion to anilide **10**. In support of this, it was found that photolysis of a mixture of **9** and **12** such that **9** absorbed greater than 99% of the incident light results in increased yields of **10**. Thus, it appears that the aryl migration competes very effectively with the type II reaction and that most of **10** arises from **12**.

Table 1
The formation of **10** and **11** from **9**

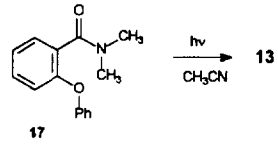
Experiment	Conditions	**10** (%)	**11** (%)
1	Methanol, 300 nm	48	35
2	Acetonitrile, 300 nm	25	31
3	Cyclohexane, 300 nm	34	62
4	Methanol, 254 nm	47	28
5	Acetonitrile, 254 nm	29	25
6	Cyclohexane, 254 nm	31	52



The formation of xanthone (**13**) in the reaction mixture (less than 5%) is likely to be a result of a type I cleavage followed by intramolecular cyclization. The formation of **13** is interesting in that this radical cyclization is successful while the photolysis of 2-phenoxybenzyl alcohol (**14**) in aqueous acetonitrile failed to produce the corresponding xanthene (**16**) via cyclization of a benzylic cation [10], but rather gave **15**.

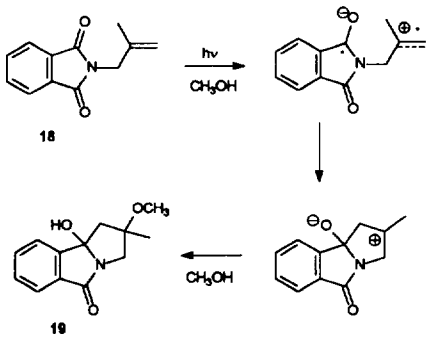


In this regard, we have found that irradiation of *N*,*N*-dimethyl-2-phenoxybenzamide (**17**), which cannot undergo a type II reaction or a phenyl migration, produces **13** in over 80% yield in acetonitrile solution.

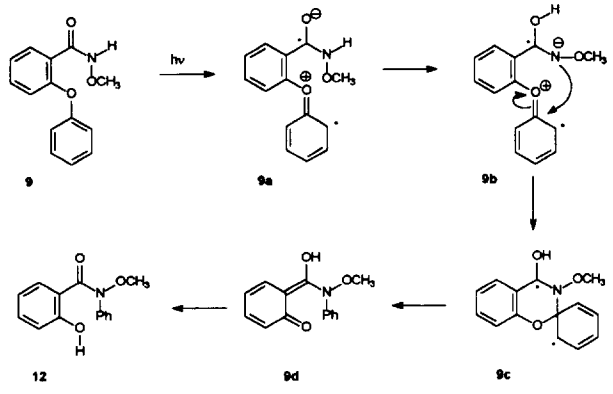


We have found that the formation of **10** and **11** from the photolysis of **9** is solvent dependent. The results, shown in Table 1, reveal that in cyclohexane there is a higher amount of **11** (the type II product) while in methanol there is a higher amount of **10**, the aryl migration product. This seems to be inconsistent with Wagner's results [11] in which the type II reaction of aryl alkanones is facilitated by polar protic sol-

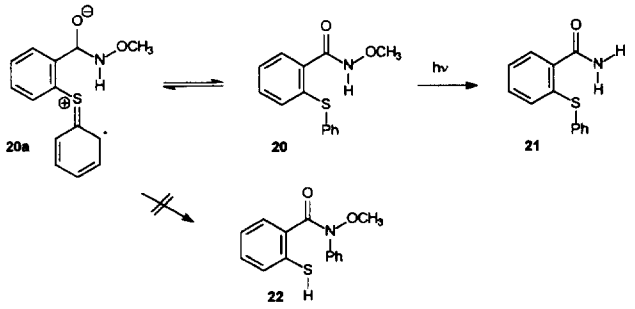
vents. However, Mazzochi and Fritz [12] have shown that the photolysis of substituted phthalimides proceeds by an intramolecular single-electron transfer process to generate the radical cation/radical anion pair. This radical cation/radical anion pair undergoes cyclization as shown below.



We therefore propose a mechanism for the photolysis of benzohydroxamate **9** in which methanol facilitates the one-electron transfer relative to the type II process to give the radical cation/radical cation pair **9a**. After proton transfer, the amide nitrogen reacts at the ipso position on the phenyl group to generate the diradical **9c**. This diradical can decay to the ortho-quinoidal intermediate **9d** which then forms **12** via tautomerism.



It is interesting in this regard that the hydroxamate **9** forms salicylanilide **10** in high yield, but the sulfur analog **20** apparently gives only amide **21** with no thiosalicylanilide (**22**) detected [13]. This may be due to an increased stability of the radical cation/radical anion pair. In this pair, the carbon–sulfur bond should be less polar which reduces the reactivity such that the type II process dominates.



The following is a summary of the photochemical behavior of the benzohydroxamic acid derivatives that we have investigated so far: (a) alkyl benzohydroxamates undergo the type II reaction, (b) alkyl *N*-alkylbenzohydroxamates undergo both the type I and the type II reaction and (c) alkyl *o*-phenoxy benzohydroxamates undergo the type I reaction and the type II reaction as well as a phenyl migration from the ring oxygen to nitrogen (a formal 1,5 shift) possibly via a single-electron transfer mechanism.

Acknowledgements

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