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UNEXPECTED FORMATION OF O-ACYLHYDROXAMATE FROM THE OXIDATION OF A DIHYDROISOQUINOLINE IMINE

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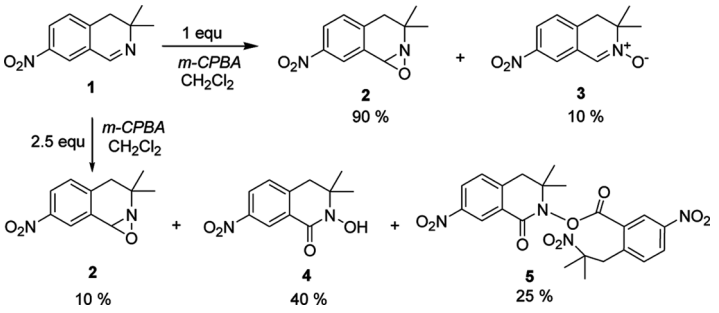
GRAPHICAL ABSTRACT



Abstract *The reaction of 3,3-dimethyl-7-nitro-3,4-dihydroisoquinoline* ***1*** *with m-chloroperbenzoic acid (m-CPBA) mainly yielded oxaziridine and nitrone, with their selectivities being dependent on the solvents. The reaction with 2.5 equivalents of m-CPBA gave small amounts of oxaziridines and hydroxamic acids as well as isolated O-acylhydroxamate compounds.*

Keywords Hydroxamic acid; oxaziridine; oxidation; X-ray diffraction

INTRODUCTION

The development of efficient synthetic methods for the preparation of oxaziridines, which have important applications in organic syntheses, is an important but challenging goal.[1–5] Oxaziridines have long been employed both as nitrogen-transfer[6,7] and oxygen-transfer[8,9] reagents in synthetic organic chemistry. They

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have also been extensively used in asymmetric syntheses.[4,5] Oxaziridines are attainable through several synthetic methods.

In fact, the electrophilic amination of carbonyl compounds,[6] the double 1,4-conjugate addition of hydroxamic acids to propiolates, and the photoisomerization of nitrone[10] represent some of the nonoxidative methods commonly used for the preparation of a variety of oxaziridines. Other oxidative methods that have been developed for the oxidation of imines include the use of several oxidizing agents, such as buffered oxone,[4] tetrabutylammonium oxone,[11] cobalt-mediated oxidation using molecular oxygen,[12] hydrogen peroxide,[13] urea–hydrogen peroxide,[14] and a nitrile–hydrogen peroxide system.[15,16] Ultimately, the first method of oxaziridine preparation, which still continues be to be favored these days, was the oxidation of an imine with a peracid, usually m-chloroperbenzoic acid (m-CPBA). [4,17] In general, the action of peracid with an imine leads to oxaziridine. In some cases, however, the formation of nitrone can also be observed. The selectivity change with the reaction conditions and imine structures.[18]

In the present article, we describe the results of oxidation of the representative imine **1** with m-CPBA. We also describe the effects of the solvent as well as the amount of m-CPBA on the selectivity of the reaction.

RESULTS AND DISCUSSION

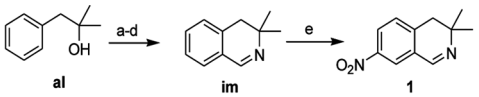
The representative imine **1** was synthesized[19] from the commercially available tertiary alcohol (**al**) as indicated in Scheme 1. In fact, this imine (**im**) was previously used in an earlier work[19] to prepare the corresponding iminium salt, which is a convenient catalyst with regard to the oxaziridinium-mediated epoxidation system.

The reaction of imine **1** with m-CPBA gave both oxaziridine and nitrone, with the selectivity being dependent on the solvent (Scheme 2).

While the oxidation of imine **1** with m-CPBA in a solution of dichloromethane or acetonitrile gave oxaziridine **2**, with a small apparent formation of nitrone **3**, the reaction in the methanol solvent led quantitatively to oxaziridine **2**.[20] This reaction (Scheme 2) shows that the product selectivity depends on the solvents. Oxaziridine formation is, therefore, predominant and nitrone formation is enhanced in the aprotic solvent.

The regioselectivity of oxygen transfer on an imine in these reactions depends on the steric and electronic factors. It was, for instance, observed that the use of a protic solvent disfavors the formation of nitrone.

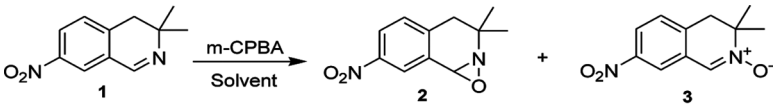
Imine **1** was also oxidized at room temperature in CH_2Cl_2 with 2.5 equivalents of m-CPBA. The m-CPBA disappeared after 24 h, and the reaction led to a mixture of oxaziridine **2** and compound **5**, as two minor products, and hydroxamic acid **4** as the major product. Those products were isolated with the yields of 10%, 25%, and



al im 1

(a) KCN; H_2SO_4-AcOH; rt; (b) oxalyl chloride; CH_2Cl_2; (c) $FeCl_3$; (d) MeOH; H_2SO_4 (e) KNO_3-H_2SO_4, rt 2h, 60°C 4h.

Scheme 1. Synthesis of the imine **1**.



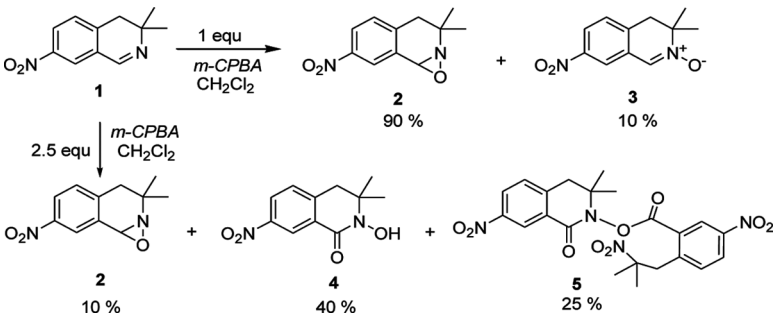
Scheme 2. Reaction of imine **1** with 1 equivalent of m-CPBA.

40%, respectively (Scheme 3). The structure of this hydroxamic acid **4**[21] was previously established by x-ray diffraction. The latter product has always been reported to be highly required particularly because it has excellent biological activities in a wide range of organic syntheses and processes[22]

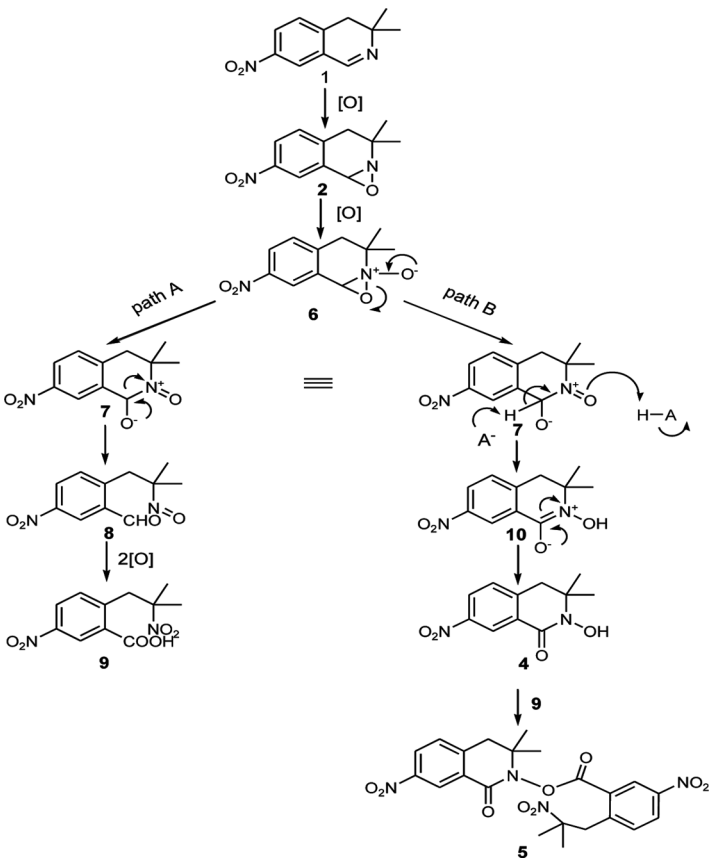
Oxaziridine **2** and nitrone **3**[20] were especially sensitive to overoxidation, and the two major products formed were hydroxamic acid **4** and a new derivative **5**, which were both isolated by column chromatography. Among the methods commonly used for the preparation of hydroxamic acid **4**, the direct oxidation of imine **1** with 2.5 equivalents of peracid has often been preferred. This is particularly because it is faster and easier than the oxidation of oxaziridine **2** or nitrone **3** with 1 equivalent of peracid.

Imine **1** was first oxidized to obtain oxaziridine **2**. The latter was also oxidized in situ to the product **6**, which was isomerized into the intermediate **7**. Two paths were considered (Scheme 4). In the first path, the resulting **7** led directly to the ring-opened nitroso compound **8** by rearrangement[23] In contrast to common nitroso compounds, this exhibited no tendency to dimerize, presumably because of steric hindrance,[24] but instead by oxidation. Under the conditions described for similar substrates,[25] it directly led to the nitro intermediate **9**.

In the second pathway, the resulting **7** led through rearrangement to the hydroxamic acid **4** after two steps. The O-acylhydroxamate compound was eventually prepared through the nucleophilic attack at the intermediate **9** by the hydroxamic acid compound **4**.



Scheme 3. Result of the oxidation of imine **1** with m-CPBA.



Scheme 4. Mechanistic hypothesis of compound **5** formation.

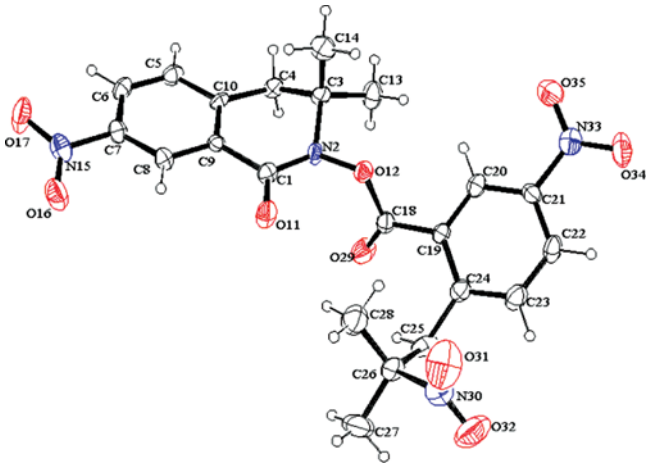


Figure 1. Molecular structure of compound **5**. (Figure is provided in color online.)

The oxidation mechanism (Scheme 4) presumes the formation and subsequent fragmentation of intermediate **7**, leading to the formation of hydroxamic acid **4** and O-acylhydroxamate **5**.

The structure of the new compound **5** was confirmed by single-crystal x-ray structure determination. The experimental details of data collection and structure refinement are summarized in the experimental section. An ORTEP diagram of the molecular structure of **5** in the crystal form is shown in Fig. 1.

In all subsequent work, the O-acylhydroxamate-derived compounds were formed from hydroxamic acid by nucleophilic attacks at the acylnitroso carbonyl,[26] which generally represent transient intermediates in the oxidative cleavage of hydroxamic acids with several oxidizing agents[27] or direct acylation.[28]

CONCLUSION

The present study investigated the peracid oxidation of imine **1**. This reaction showed that the product selectivity depended on the operating conditions. The process involved the isolation of four interesting products, namely oxaziridine **2**, nitrone **3**, hydroxamic acid **4**, and O-acylhydroxamate **5**. The structure of this yet unknown compound **5** was established by x-ray diffraction. The unexpected formation of product **5** could open a new pathway for the synthesis of derivatives of imine.

EXPERIMENTAL

Preparation of Compound 5

A solution of the imine **1** (3 mmol) in CH_2Cl_2 (100 ml) was stirred at rt while a solution of m-chloroperbenzoic acid 86% (7.5 mmol) in CH_2Cl_2 (50 ml) was added slowly. After 24 h, the mixture was washed with saturated aqueous sodium bicarbonate (3×150 ml), dried, and evaporated. An aliquot of the crude product was analyzed by ^{1}H NMR in $CDCl_3$. A mixture of **2**, **4**, and **5** in the molar ratio 1:2:4 was detected. These products were separated by chromatography on silica gel (hexane/ether 4/1) with the yields of 10%, 40%, and 25%, respectively.

Selected Physical Data for Compound 5

Colorless crystals; mp: 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (br s 3H), 1.49 (br s 3H), 1.68 (br s 3H), 1.82 (br s 3H), 3.13–4.14 (m, 4H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 8.37 (dd, $J = 2.5$, 8.0 Hz, 1H), 8.41 (dd, $J = 2.5$, 8.0 Hz, 1H), 8.54 (d, $J = 2.5$ Hz, 1H); 8.96 (d, $J = 2.5$ Hz 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 27.6, 28.7, 41.7, 43.0, 62.6, 89.1, 124.1, 125.6, 127.3, 127.6, 129.4, 132.9, 128.7, 129.6, 142.9, 144.5, 146.9, 147.6, 159.3, 160.1, 163.4. Anal. calc. for $C_{22}H_{22}N_4O_9$: C, 54.32; H, 4.56; N, 11.52. Found: C, 54.43; H, 4.61; N, 11.58.

Crystal Data for Compound 5

Data were collected at room temperature using a Bruker-APEX II Kappa CCD diffractometer, M = 486.14, monoclinic, C2/c, a = 26.950 (3) Å, b = 7.8778

(7) Å, c = 24.092 (3) Å, β = 112.695 (3)°, V = 4718.8 (8) Å^3, Z = 8, Dc = 1.369 g/cm^{-3}, X-ray source Mo-Kα (radiation), λ = 0.71073 Å, F (000) = 2068, T = 293 K, colorless prism 0.44 × 0.31 × 0.19 mm. The structure solution was obtained by direct methods and refined with anisotropic thermal parameters using full-matrix least squares procedures on F2 to give R = 0.113, wR = 0.177 for 5387 independent observed reflections and 316 parameters.

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