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Oxidative cleavage of lactams in water using dioxiranes: an expedient and environmentally-safe route to ω-nitro acids

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We are pleased to dedicate this work to Professor Ruggero Curci (Brown University, Providence, RI) on the occasion of his 75th birthday.

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ABSTRACT

By taking advantage of the appreciable stability of dioxiranes in water, a safe yet efficient route to ω-nitro acids by oxidation of lactams of various ring sizes under mild conditions has been reported. In essentially all the cases examined, reactions proceed selectively to afford products in remarkably high yields (up to 99%) and with high purity (94–99%). Also, an interesting example of higher reaction selectivity in water than in organic solvent (acetonitrile) is discussed.

In recent years, the search for a clean and a more sustainable chemistry has urged chemists to develop synthetic procedures that avoid the use of toxic solvents and hazardous chemicals. In this direction, a number of classical synthetic procedures have simply been turned into their clean version by adopting, for instance, solvent-free conditions or even water as the reaction solvent.[1]

Over the past two decades, we and others have been actively engaged in showing that the three-membered ring peroxides **1** (Fig. 1), that is, the dimethyldioxirane (DDO, **1a**)[2] and its trifluoro analog **1b** (TFDO),[3] are powerful and versatile oxidants, rivaling other popular oxidation methods in efficiency, selectivity, and simplicity of experimental procedures. Dioxirane-mediated oxidations range from epoxidation of olefins,[4,5] oxidation of compounds containing heteroatoms (e.g., sulfides → sulfoxides → sulfones; amines → nitro compounds)[6] to hydroxylation of the C–H bond.[7] Noticeably, all these reactions occur under very mild conditions, i.e. ambient or sub-ambient temperature and pH close to neutrality.

The remarkable versatility of dioxiranes suggests that a restricted array of solvents (usually CH_2Cl_2, $CHCl_3$, CCl_4, acetone, CH_3CN) can be used when performing the oxidation reactions; the others commonly employed in organic synthesis (e.g. ethers, alcohols, alkanes) being easily oxidizable under the typical reaction conditions. Nevertheless, dioxiranes appear sufficiently stable in water to be amenable to convenient oxidations in aqueous media. In spite of the beneficial aspects of this synthetic approach, the chemistry of dioxiranes has not hitherto been thoroughly investigated in water, even though these peroxides are notoriously generated in aqueous media.[2,3]

With this in mind, we describe herein an efficient and environmentally-benign synthesis of valuable ω-nitro acids by oxidation of representative lactams with dioxirane **1b** in water. These compounds, carrying two α,ω-functionalities, are of special interest in the synthesis of valuable targets.[8,9] In general, organic nitro compounds have recently received growing attention as building blocks for the generation of carbon–carbon bond, since it was shown that such reactions can be carried out as efficiently in water solvent as in common organic solvents.[9,10] This represents an undeniable advantage from an industrial stand-point, since the

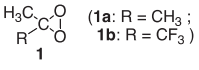

Figure 1. Structure of commonly employed dioxiranes (**1**).

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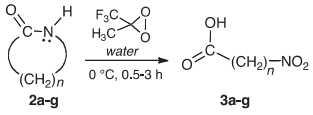
replacement of toxic solvents still remains a crucial challenge, in terms of economical and environmental benefits.

To our knowledge, the only practical approach to ω-nitro acids was described by Ballini et al.[8] Such method appears quite general, consisting in the ring cleavage of α-nitrocycloalkanones in aqueous solution of 0.05 M sodium hydroxide, at 80 °C, in the presence of catalytic amounts of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant. Accordingly, a variety of α-nitrocycloalkanones (from 6-membered to 15-membered rings) can be converted to the corresponding ω-nitro acids in good to excellent yields; the only exception being represented by the fission of the α-nitrocyclooctanone, which leads to a mixture of unidentified products.[8]

It should be recalled that lactams are highly available starting materials, many of which being useful building blocks for the large-scale manufacture of commodities. Thus, concurrent with Ballini's approach mentioned above, we feel that the dioxirane-mediated oxidation of lactams may represent a valuable route to ω-nitro acids. Table 1 collects the results of the dioxirane oxidation of representative small- to large-ring lactams. Earlier attempts to oxidize the 7-membered lactam **2d** with DDO (**1a**) proved unsuccessful. Therefore, oxidations were conveniently performed with the more powerful dioxirane **1b**.

Reactions were routinely carried out by addition (usually 3–5 mL) of a cold solution (0.5–0.7 M) of the oxidant **1b** in 1,1,1-trifluroacetone (TFP) to a solution of the lactam substrate (30–60 mg) in water (4–6 mL) kept at ca. 0 °C under vigorous stirring. The reaction progress was monitored by periodical HPLC analyses of the reaction mixture or by following the oxidant decay iodometrically. Upon reaction completion, TFP (the product of **1b** reduction) was recovered by distillation (80–85%) and reused for regeneration of the oxidant **1b**, thus closing what appears to be a catalytic cycle with an ex-situ regeneration of the active species. Products were obtained by extraction from the aqueous medium or upon removal of the latter by distillation under reduced pressure or by freeze-drying. In most of the cases, crude ω-nitro acids displayed high purity (94–99%, HPLC) so that further purification was not pursued. Characterization by means of ^{1}H, ^{13}C NMR, IR, and GC–MS techniques provided spectra in full agreement with the literature.[8,11]

Table 1
Oxidation of lactams to ω-nitro acids by TFDO (**1b**)[a]



Entry	*n*	Substrate	Ox/Sub[b]	Time (min)	Products	Yield (%)
1	2	**2a**	3.5	30	**3a**	>99
2	3	**2b**	5.0	90	**3b**	>99
3	4	**2c**	5.5	120	**3c**	42[c]
4	5	**2d**	6.5	120	**3d**	>99
5	6	**2e**	6.5	120	**3e**	>99
6	7	**2f**	6.5	120	**3f**	>99
7	10	**2g**[d]	8.0	90	**3g**	95[e]
8	10	**2g**[f]	4.5	90	—[g]	—
9	10	**2g**[h]	4.5	90	—[g]	—

[a] Unless differently specified, all reactions were carried out in distilled water at 0 °C; solutions of 0.5–0.7 M TFDO (**1b**) in TFP were obtained by adopting procedures, equipment, and precautions already reported in detail (Ref. 3).
[b] Oxidant to substrate molar ratio.
[c] Accompanied by 45% of glutaric and 5% of glutarimide.
[d] Run in the presence of cetyltrimethylammonium hydrogensulfate (0.13 M).
[e] Based on the amount of recovered substrate (54%) upon chromatographic separation of the reaction mixture.
[f] Run with substrate finely dispersed in water solvent.
[g] Mixture of unidentified products.
[h] Run in acetonitrile at 0 °C.

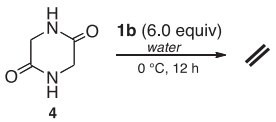
Inspection of data in Table 1 suggests that the oxidation of lactams **2a–f** with TFDO (**1b**) to the corresponding ω-nitro acids **3a–f** is a remarkably efficient process. Indeed, in practically all the cases examined, the use of a moderate oxidant to substrate molar ratio allows to drive the reaction to completion within a few hours. Nonetheless, an outstandingly high selectivity is observed, so that ω-nitro acids could be obtained with excellent yields and high purity (94–99%, HPLC) even as crude products.

The only noticeable gap along the nicely smooth reaction trend of Table 1 is represented by the oxidation of δ-valerolactam (**2c**) (entry 3), in which case the relatively small amount of nitro acid **2c** obtained (42% isolated yield) is accompanied by 45% of glutaric acid and 5% of glutarimide (Table 1, footnote c).

Due to the relatively high cost of 10-, and 11-membered lactams as starting materials, we found it poorly convenient to pursue the synthesis of the corresponding ω-nitro acids by the method described herein. On the other hand, we attempted the synthesis of the valuable fatty ω-nitro acid **3g**[12] by TFDO oxidation of the much accessible laurolactam **2g**. Owing to the limited solubility of **2g** in water (ca. 0.012 mol/L at 25 °C), the oxidation of the latter was performed in the presence of cetyltrimethylammonium hydrogensulfate (CTAHS) as a surfactant. Under the conditions specified in Table 1 (entry 7), the reaction occurs selectively to give 12-nitrododecanoic acid (**3g**) as the unique product in 95% isolated yield (based on the amount of starting material reacted).[13] In spite of the eightfold larger molar amount of oxidant **1b** employed, the reaction conversion was somewhat low (46%), most likely due to the competitive oxidation of the surfactant alkyl chains.

In an attempt to overcome this limitation, a suspension of finely-dispersed **2g** in water was treated with **1b** (4.5 equiv). Under these conditions (entry 8, Table 1), a mixture of unidentified products was obtained, as revealed by the ^{1}H- and ^{13}C NMR analyses of the crude reaction mixture. Yet, the NMR spectral profiles appear even more complex when the oxidation of **2g** with TFDO is run in an acetonitrile solvent under similar conditions (entry 9, Table 1). Thus, it seems likely that the presence of CTAHS would be crucial in order to achieve selectivity. However, its role remains obscure and needs further careful investigations. In any case, this represents a remarkable example of increased reaction selectivity in the aqueous medium with respect to organic solvent.

To our knowledge, the oxidative cleavage of the amide bond with **1b** is unprecedented in dioxirane chemistry. Even in our recent works on the oxyfunctionalization of peptides by dioxiranes,[14] we never reported on sizeable amounts of products deriving from the oxidative cleavage of the peptide bond. In this respect, one might argue that, given the different chemical environment surrounding the amidic bond, peptides and lactams should display a diverse reactivity toward dioxirane oxidation. Consistent with this view, reaction of 1,4-diketopiperazine (**4**) (formally both a cyclic dipeptide and a lactam) with **1b** (Scheme 1) provides no sizeable oxidation products, suggesting that the cyclic arrangement of lactams has little influence over the amide bond reactivity in the transformations at hand. Rather, based on electronic effect arguments, amidic bonds in peptides should experience an electron-withdrawing effect exerted by the proximal amino acid residue along the peptide chain; consequently, their oxidative cleavage by the electrophilic dioxirane attack should be efficaciously prevented.



Scheme 1. Reaction of 1,4-diketopiperazine (**4**) with **1b**, resulting in no products.

We mentioned previously that the oxidative cleavage of the amidic bond by dioxiranes is unprecedented. However, it occurs to us that primary amines provide nitro compounds through an exhaustive, stepwise oxidation of the nitrogen functionality, involving three molecules of dioxirane.[6a,b] Accordingly, one may envisage that a similar reaction pathway is followed in the transformations described herein, while an extra step (most likely involving water) should account for the ring cleavage and the formation of the carboxylic moiety.

In summary, with use of methyl(trifluoromethyl)dioxirane (**1b**), representative small- to large-ring lactams can be cleanly converted to the corresponding ω-nitro acids in water under mild conditions. Besides the benefits of using water as the reaction solvent, the method presents several advantages, the key ones being summarized as follows:

- Many lactams are largely accessible starting materials.
- The high efficiency and selectivity of the oxidations described provide highly pure products, which could be used directly in subsequent reaction steps, avoiding costly and time-consuming product purification procedures.
- The oxidant precursor, that is TFP, can be recovered and reused for dioxirane regeneration, thus increasing the atom economy of the process.
- In the case of the relatively hydrophobic laurolactam **2g**, an increased reaction selectivity in water/surfactant system than in organic solvent (acetonitrile) is achieved. This seems promising on the road of selective oxidations of organic compounds in aqueous media using dioxiranes.

Acknowledgments

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13. In a typical experiment, a 25-mL round-bottom flask was charged with 6 mL of distilled water and 300 mg (0.79 mmol) of CTAHS. To this solution, 60 mg (0.327 mmol) of **2g** were added and the mixture was cooled to 0 °C. Under vigorous stirring, 4.4 mL of a 0.60 M solution of **1b** (2.616 mmol) in TFP were rapidly added and the resulting mixture allowed to react until the oxidant was consumed (1.5 h, iodometry). Then, the reaction flask was surmounted with a distillation column equipped with an efficient condenser kept at ca. 0 °C and the TFP was gently distilled off. The resulting residue was cooled to room temperature, saturated with NaCl, then extracted with ethyl acetate (3×20 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic separation (silica gel, ethyl acetate/hexane 2:3) of the residue afforded 32.4 mg of unreacted **2g** (0.178 mmol, conv. 46%) and 35.2 mg (0.143 mmol, 95% yield based on the amount of substrate reacted; purity >98%, HPLC).
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