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Citric acid mediated catalytic osmylation/oxidative cleavage of electron deficient olefins: a vinyl sulfone study

Thomas P. Bobinski, Philip L. Fuchs *

Department of Chemistry, Purdue University, 560 Oval Dr., West Lafayette, IN 47907, United States

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ABSTRACT

The first broad catalytic dihydroxylation of enantiopure cyclic vinyl sulfones followed by oxidative cleavage of the resulting acyloin provides linear termini-differentiated polyketide fragments. This mild vinyl sulfone cleavage provides an effective alternative to the current ozonolysis protocol.

Introduction

Efforts toward optimization of vinyl sulfone polyketide methods for the synthesis of natural products illustrate the effectiveness of five-, six-, and seven-membered cyclic vinyl sulfones to assemble contiguous chiral centers.[1] The vinyl sulfone polypropionate methodology has been utilized to provide cyclic vinyl sulfones for use as termini differentiated polyketide precursors primarily via ozonolysis.[2]

Ozonolysis of electron-rich olefins is widely used and fully documented, as electron-rich olefins are an estimated 10,000 times more reactive to ozone than electron-deficient olefins.[3] Oxidative cleavage of electronically deactivated and/or sterically hindered olefins has proven historically quite difficult. Griesbaum[4] and Fuchs[5] reported the first ozonolysis of vinyl triflates, vinyl nitriles, and vinyl sulfones,[1,2] respectively, in the 1990s. Ozonolysis of seven-membered vinyl sulfones was more extensively studied for the synthesis of polypropionate fragments of apoptolidin and aplyronine A.[6–8]

While ozonolysis of vinyl sulfones has been established as an effective method, it has limitations in the construction of polyketide fragments. Many frequently used protecting groups are incompatible with ozolytic cleavage conditions. Methoxymethyl (MOM) ether used in the total synthesis of lepranthin by Miyashita,[9] methylthiomethyl (MTM) ether employed in the assembly of aplyronine A by Yamada,[10] 2-methoxyethoxymethyl (MEM) ether utilized in anti-fungal soraphen $A_{1\alpha}$ analogs[11] and 1-ethoxyethyl ether included in an examination of the C16–C22 part of irumamycin[12] all react in the presence of ozone.[13] Ozonolysis has also been responsible for unwanted oxidation of secondary alcohols on select cyclic vinyl sulfones to ketones.[14]

The aforementioned considerations demand alternative experimental methods for oxidative cleavage. Mild, more versatile methods would be highly desirable.

Results and discussion

Osmium tetroxide addition to electron-deficient alkenes is typically slow because of diminished reactivity.

Phenyl vinyl sulfones bear a tetrahedral sulfone moiety which is highly sterically shielded (A value >2.5)[15] in addition to being electronically deficient. These features are clearly apparent in the regio- and enantiospecific Jacobsen epoxidation of the terminal olefin of 6- and 7-membered 1,3-dienyl phenyl sulfones (>99% de and ee), leading to the genesis of our polypropionate method.[16–18] Earlier strategies for dealing with the oxidative inertness of vinyl sulfones originally involved reductive cleavage of the sulfone moiety via treatment with BuMgCl/Pd(II)OTf,[19] or Na amalgam.[20] The resulting electron-neutral olefin can then be readily cleaved, but the transformation sacrifices the inherent olefin dissymmetry.

Previous reports on osmium catalyzed dihydroxylation of vinyl sulfones are scarce and highly substrate dependant. Backvall[21] and Fuchs[22] reported osmium catalyzed dihydroxylation of

* Corresponding author. Tel.: +1 765 494 5242.
E-mail address: pfuchs@purdue.edu (P.L. Fuchs).

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torsionally-activated vinyl sulfones α to bridged tetrahydrofurans in yields of 57% for a system with no substituents and 90% with two substituents in the syn position to the oxo bridgehead. In addition Fuchs reported a 90% yield on a cyclic vinyl sulfone with all three substituents occupying the same face of the molecule.

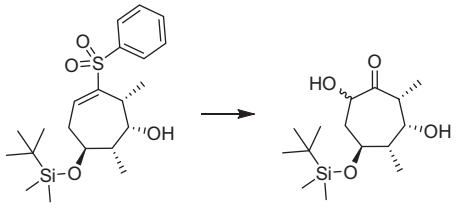
Citric acid has been shown to improve the rates and the yields of *cis*-dihydroxylations of various electron-deficient alkenes (Scheme 1).[23] In addition to acting as a pH buffer by retarding formation of insoluble Os(VIII) dioxoosmate **iii**, citric acid strongly binds to OsO_4 to form **i**. Studies on the effects of citric acid buffered osmium catalyzed dihydroxylation on cyclic vinyl sulfones are herein examined.

Addition of citric acid to improve the catalytic osmylation system led to a greater understanding of the dihydroxylation mechanism as it applies to vinyl sulfone substrates (Scheme 1). As previously mentioned, addition of citric acid to osmium tetroxide gives rise to monoglycolate (**i**). Red-Ox addition of monoglycolate to the vinyl sulfone substrate provides mixed (bis)glycolate (**ii**) Os(VI) species. Rate-limiting hydrolysis of the mixed (bis)glycolate **ii** affords the desired acyloin and Os(VI) monoglycolate **iv**. When the osmylation is performed under homogeneous conditions the co-oxidant *N*-methylmorpholine *N*-oxide (NMO) and base *N*-methylmorpholine (NMM) have access to all intermediates in the catalytic cycle. Alternatively (bis)glycolate **ii·H$_2$O** can be deprotonated by NMM equilibrating to dioxoosmate **iii** thereby causing cessation of the catalytic cycle.

Addition of citric acid assists catalyst turnover by preventing formation of the catalytically unreactive dioxoosmate dianion species **iii**, which is formed upon deprotonation of hydrated (bis)glycolate **ii·H$_2$O** at higher pH. The strong electron withdrawing ability of the sulfone contributes to the acidity of symmetric hydrated (bis)glycolate species, which forms in the absence of citric acid, increasing the concentration of symmetric dioxoosmate and arresting the cycle at high pH. Proximal acidic moieties act as a buffer in hydrated (bis)glycolate **ii·H$_2$O** preventing buildup of dioxoosmate **iii**. The equilibrium favors increased concentration of hybrid (bis)glycolate **ii** allowing continuation of the cycle (Scheme 1).

In an effort to find an optimum procedure, cyclic vinyl sulfone **1**, a pivotal aplyronine A intermediate,[6] was subjected to a variety of osmium catalyzed dihydroxylation conditions (Table 1). Entry 1 represents the results of the Upjohn[24] protocol as a point of departure. Consistent with scheme 1, no reaction ensued. It was postulated that substrate insolubility could be an issue in 10:1 H_2O/acetone. Entry 2 employed a THF/water (4:1) system employed by Cho,[25] in the total synthesis of (+)-trans-dihydronarciclasine. The homogenous reaction solution showed no product

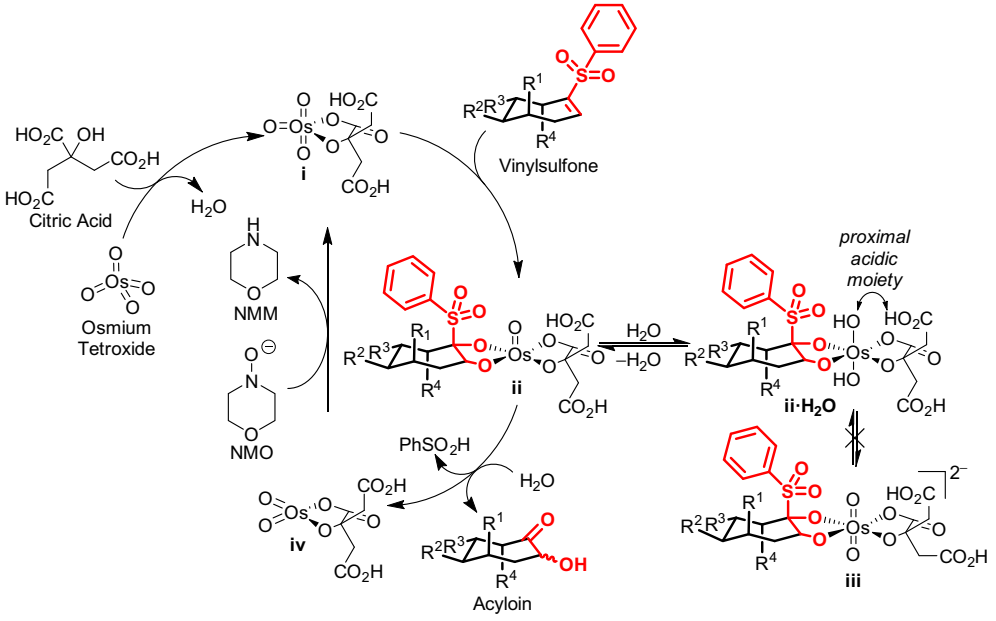
Table 1
Survey of osmium catalyzed dihydroxylation of vinyl sulfones



1 **2**

Entry	Reaction conditions	% Yield[a] (%)	Recovered SM (%)
1	NMO (1.05 equiv), OsO_4 (0.7 mol %), 10:1 H_2O/acetone (0.35 M), rt, 6 h	0	100
2	NMO (2.0 equiv), OsO_4 (1 mol %), 4:1 THF/H_2O (0.05 M), rt, 24 h	0	100
3	NMO (1.10 equiv), $MeSO_2NH_2$ (1.10 equiv), OsO_4 (2 mol %), 10:1 acetone/H_2O (0.1 M), rt, 24 h	35	65
4	NMO (1.10 equiv), OsO_4 (1 mol %), citric acid (0.20 equiv), 4:1 THF/H_2O (0.07 M), rt → 80 °C, 24 h	40	60
5	Citric acid (1.05 equiv), NMO (1.10 equiv), K_2OsO_4 (1 mol %), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	56	35[b]
6	Citric acid (2.05 equiv), NMO (1.10 equiv), K_2OsO_4 (0.10 equiv), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	65	⩽15[b]
7	Citric acid (3.05 equiv), NMO (1.10 equiv), K_2OsO_4 (0.10 equiv), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	73	0[c]

[a] % Yield after column chromatography.
[b] % by NMR analysis.
[c] Conversion of starting material monitored by disappearance of UV activity on TLC.



Scheme 1. Citric acid assisted osmylation of cyclic vinyl sulfones. R^1, R^2, R^3, R^4 = H = Me = OH = OTBS = *i*-Pr.