An Efficient Protocol for the Oxidative Hydrolysis of Ketone SAMP Hydrazones Employing SeO_2 and H_2O_2 under Buffered (pH 7) Conditions

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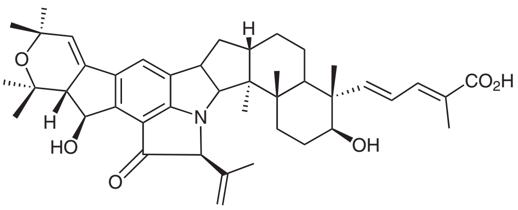
Abstract: An effective oxidative protocol for the liberation of ketones from SAMP hydrazones employing peroxyselenous acid under aqueous buffered conditions (pH 7) has been developed. The procedure proceeds without epimerization of adjacent stereocenters or dehydration, in representative SAMP alkylation and aldol reaction adducts, respectively.

Key words: SAMP, oxidative cleavage, aldol reactions, ketones, SeO_2

The (*S*)- and (*R*)-amino-2-methoxypyrrolidines (SAMP and RAMP), effective chiral auxiliaries introduced by the Enders group,[1] have found wide use in asymmetric alkylation and aldol reactions.[2] Consequently, a large number of methods have been developed to liberate the resultant aldehydes and ketones from the SAMP/RAMP hydrazone products.[3] In conjunction with an ongoing synthetic program directed towards the total synthesis of (+)-nodulisporic acid A (**1**, Figure 1), a wide variety of known oxidative, hydrolytic, or reductive methods were explored to liberate ketone **3** from advanced SAMP intermediate **2**, albeit with limited success (Table 1 entries 1–12). We eventually discovered that peroxyselenous acid, generated in situ from SeO_2 and 30% H_2O_2 (1:4 equiv) was a superior oxidant for the removal of the chiral auxiliary in **2** accompanied by a small amount of epimerization at the α-position of ketone **3** (entry 13).

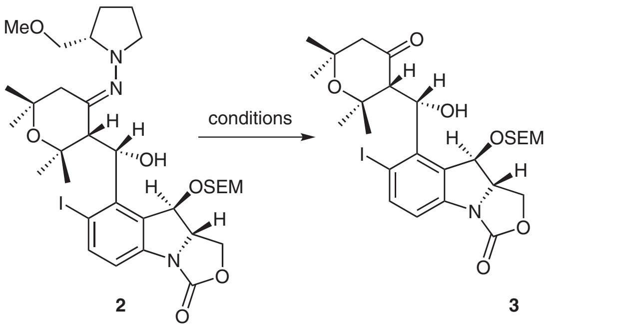


nodulisporic acid A (**1**)

Figure 1 Structure of nodulisporic acid A

Pleasingly, the epimerization problem could be alleviated simply by the introduction of a pH buffer 7 (entry 14). Importantly, no epimerization or retro-aldol fragmentation, which was observed with several of the alternative protocols, occurred under these optimized conditions. To the best of our knowledge, this report presents the first examples exploiting SeO_2 and H_2O_2 under buffered conditions for the oxidative deprotection of ketone-derived hydrazones.

Table 1 Attempted Conditions to Cleave SAMP Hydrazone **2**



Entry	Conditions	Observations
1	Oxalic acid, Et_2O, 23 °C, 15 h	epimerization
2	$CuCl_2$, THF–H_2O, 23 °C, 15 h	epimerization
3	$SnCl_2$, $Pd(OAc)_2$ DMF–H_2O, 23 °C, 15 h	no reaction
4	$SnCl_2$, $Pd(OAc)_2$ DMF–H_2O, 50 °C, 15 h	epimerization
5	$SnCl_2$, DME–H_2O, 23 °C, 15 h	no reaction
6	$SnCl_2$, DME–H_2O, 50 °C, 15 h	epimerization
7	O_3, CH_2Cl_2, –78 °C, 1 min	21%
8	$NaBO_3$, AcOH, 23 °C, 2 h	decomposition
9	$NaBO_3$, pH 7 buffer–*t*-BuOH, 23 °C 5 h	decomposition
10	MMPP, pH 7 buffer–MeOH, 23 °C, 24 h	no reaction
11	30% H_2O_2, pH 7 buffer–MeOH, 23 °C to 70 °C, 19 h	decomposition
12	$NaIO_4$, THF–H_2O–pH 7 buffer, 23 °C, 15 h	decomposition
13	30% H_2O_2/SeO_2, MeOH, 23 °C, 48 h	76%
14	30% H_2O_2/SeO_2, MeOH–pH 7 buffer, 23 °C, 24 h	91%

Previous reports have, however, recorded the oxidative cleavage of aldehyde SAMP hydrazones to furnish the corresponding nitriles, via an oxy-Cope-like elimination

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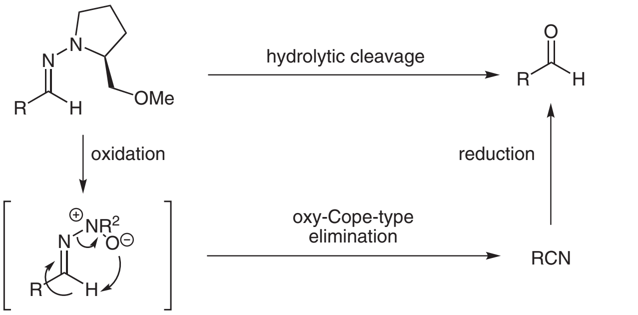
(Scheme 1),[4] with oxidants such as *m*CPBA,[5] MMPP (magnesium monoperoxyphthalate), SeO_2, or 2-nitrobenzeneselenic acid with H_2O_2,[6] and H_2O_2.[7] A similar oxidative fragmentation is of course not an option with SAMP ketone hydrazones.



Scheme 1 Nitrile formation from aldehyde-derived hydrazones

To explore the scope and viability of the pH 7 buffered peroxyselenous acid conditions, a series of ketone SAMP hydrazones were readily prepared from simple ketones **7**–**16** (Figure 2)[8] using SAMP hydrazine and a catalytic amount of TsOH in cyclohexane at reflux; yields ranged from 70–98%. Application of the pH 7 buffered SeO_2/H_2O_2 protocol, optimized during the (+)-nodulisporic acid A synthetic program, regenerated the corresponding ketones **7**–**15** in 68–96% yields.[9] Liberation of cyclohexenone **16** from SAMP hydrazone **17**, however, was not successful. Instead, an epimeric mixture of 2-hydroxy-3-methoxycyclohexanone **18** was isolated in 85% yield (Scheme 2).

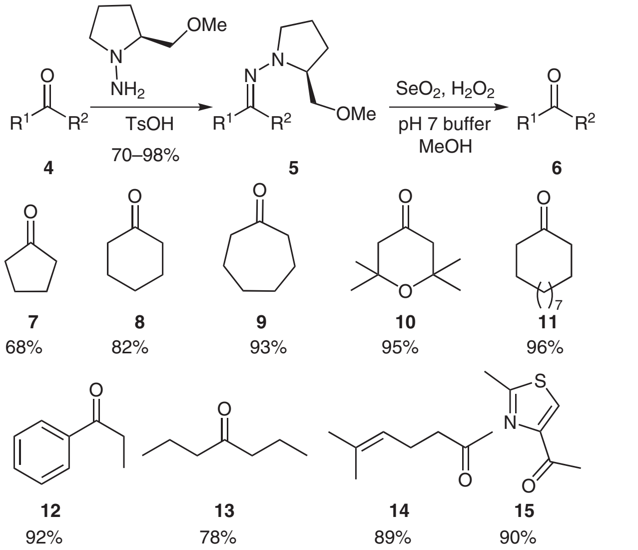
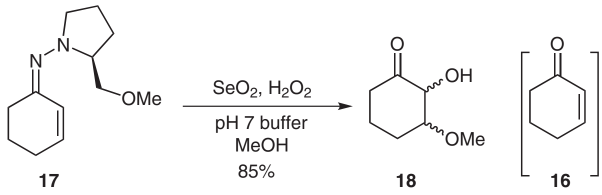


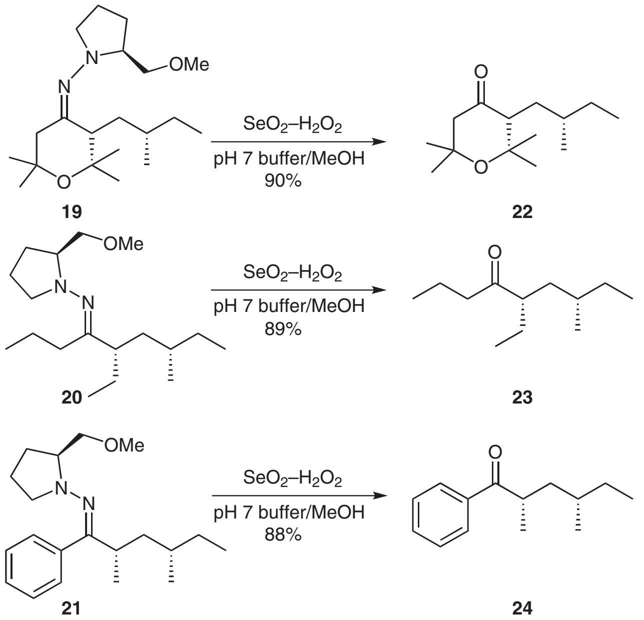
Figure 2 Oxidative cleavage of SAMP hydrazones to simple ketones

We next turned our attention toward to SAMP hydrazones possessing an α-stereogenic center. The requisite substrates were readily prepared by alkylation of a series of ketone SAMP hydrazones with (*S*)-(+)-1-iodo-2-methylbutane (Scheme 3);[10] yields for the alkylated SAMP hydrazones (**19**–**21**) were again excellent (90–96%).



Scheme 2 Oxidative hydrolysis of the SAMP hydrazone generated from cyclohexenone

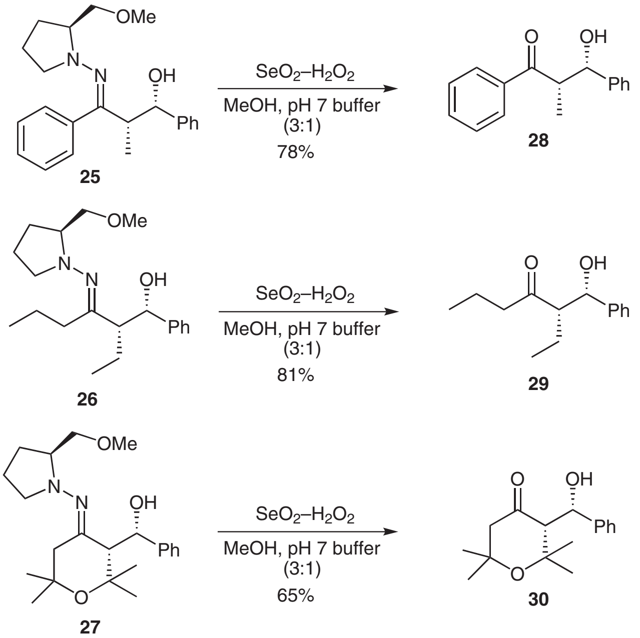
Stereochemical assignments at the α-center were based on the Enders precedent.[11] Treatment of the hydrazones with SeO_2 and H_2O_2, again employing an aqueous buffer (pH 7), led to clean removal of the SAMP moiety to furnish ketones (**22**–**24**) in 88–90% yield. Importantly, no epimerization (>20:1, 500 MHz NMR) at the α-center was observed.



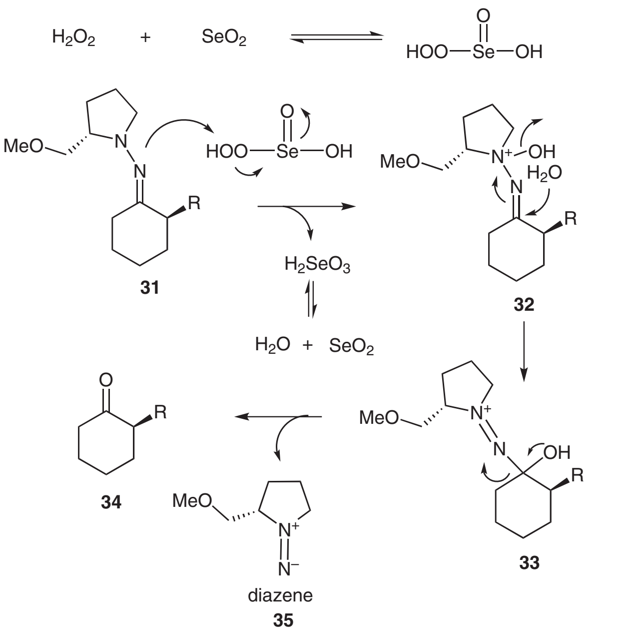
Scheme 3 Cleavage of SAMP hydrazones to regenerate chiral ketones

In addition to the SAMP alkylation products, a third series of hydrazones was examined involving the products derived from an aldol reaction with benzaldehyde (cf. **25**–**27**).[12] As these aldol products are generally sensitive to acid, we were not surprised initially to observe significant elimination (i.e., dehydration) and/or retro-aldol fragmentation. Pleasingly, such side reactions could be suppressed by increasing the amount of pH 7 buffer (i.e., from 1:18 to 1:3 v/v; buffer: MeOH) to afford β-hydroxy ketones **28**–**30** in 65–81% yield (Scheme 4).[13]

A mechanistic picture of the pH 7 buffered oxidative hydrolysis using SeO_2 and H_2O_2 is proposed in Scheme 5. After initial formation of peroxyselenous acid, oxidation of the pyrrolidine nitrogen in **31** is envisioned to generate intermediate **32**, thereby activating the hydrazone toward hydrolysis. Addition of water followed by fragmentation would then deliver the ketone **34** and diazene **35** as a byproduct.



Scheme 4 Oxidative hydrolysis of SAMP aldol products to regenerate β-hydroxy ketones



Scheme 5 Proposed mechanism for the oxidative hydrolysis of SAMP hydrazones using peroxyselenous acid

In summary, an efficient method to regenerate ketones from SAMP ketone hydrazones employing SeO_2 and H_2O_2 under buffered conditions has been developed. Aldol hydrazone adducts derived from the SAMP hydrazone require additional buffer to suppress side reactions. Given the scope of this protocol, this method holds promise as an effective and mild alternative to the more conventional methods to regenerate ketones from SAMP hydrazones.

Acknowledgment

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References and Notes

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(8) **General Procedure for the Synthesis of Hydrazones**
A mixture of SAMP (0.04 mmol), ketone (0.04 mmol), and PTSA (0.004 mmol) was heated at reflux in cyclohexane (1 mL) overnight. The mixture was then cooled to r.t., neutralized with sat. $NaHCO_3$ (3 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to provide the desired hydrazone (70–98%).
(9) **General Procedure for the Synthesis of Ketones 7–15 and 22–24**
To a r.t. solution of hydrazone (0.18 mmol) and SeO_2 (0.14 mmol) in MeOH (2.3 mL) was added pH 7 phosphate buffer (0.066 mL) followed by 30% H_2O_2 (0.066 mL). After completion of the hydrolysis reaction, sat. $NaHCO_3$ (3 mL) was added, and the aqueous layers were extracted with pentane (3 × 3 mL). The combined organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified via flash chromatography to provide the corresponding ketone in 68–96% yield.
(10) **General Procedure for the Synthesis of Alkylated SAMP Hydrazones 19–21**
To a solution of the corresponding hydrazone (0.26 mmol) in THF (2 mL) at –78 °C was added *t*-BuLi (1.6 M in pentane, 0.39 mmol). The mixture was kept at this temperature for 2 h before cooling to –100 °C. (*S*)-(+)-1-Iodo-2-methylbutane (0.52 mmol) was then added via syringe, the solution stirred at –100 °C for 0.5 h, and then at –78 °C for 2 h. The reaction was quenched with sat. NH_4Cl (3 mL). The aqueous layers were extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, concentrated, and the residue was purified by flash chromatography to furnish the alkylated hydrazone in 90–96% yield.
(11) Enders, D.; Bockstiegel, B. *Synthesis* **1989**, 493.
(12) **General Procedure for the Synthesis of SAMP Aldol Products 25–27**
To a solution of hydrazone (0.18 mmol) in THF (1.2 mL) at –78 °C was added *t*-BuLi (1.6 M in pentane, 0.18 mmol). The mixture was maintained at this temperature for 2 h before cooling to –100 °C. Benzaldehyde (0.36 mmol) was then added via syringe, the solution stirred at –100 °C for 0.5 h, and then at –78 °C for 2 h. The reaction was quenched with sat. NH_4Cl (3 mL), the aqueous layer extracted with Et_2O (3 × 5 mL), and the combined organic layers were

dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to furnish aldol products in 68–96% yield

(13) **General Procedure for the Synthesis of β-Hydroxy Ketones 28–30**
To a r.t. solution of the corresponding hydrazone (0.03 mmol) and SeO_2 (0.045 mmol) in MeOH (0.45 mL) was added pH 7 phosphate buffer (0.15 mL) followed by 30% H_2O_2 (0.015 mL). After completion, sat. $NaHCO_3$ (2 mL) was added to the mixture, and the aqueous layers were extracted with EtOAc (2 × 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 deactivated with 18% H_2O) to provide β-hydroxy ketones (65–81%).