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Oxidation of bicyclic oxazolines: applications to glycomimetics and novel saccharide derivatives

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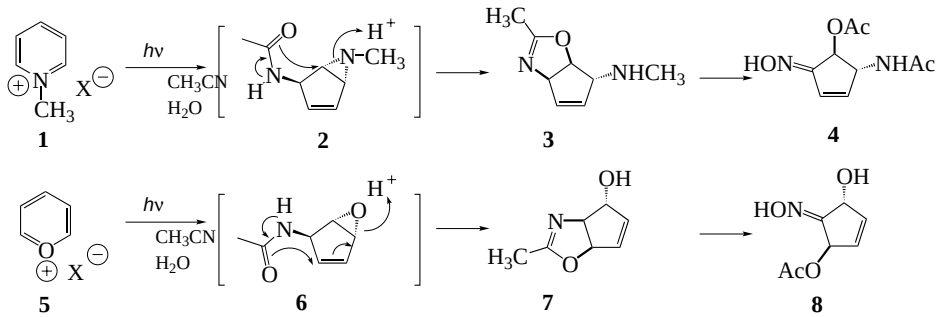
Abstract—A general procedure is reported for the oxidation of substituted oxazolines to α-acyloxyketoximes and the derived α-acyloxyketones. In the case of oxazolines derived from 2-acetamido-2-deoxyhexoses, the resulting 2-oximinoesters can be converted to 2-nitroglycals.

Substituted oxazolines are important synthetic intermediates,[1] and have also been found in natural products and enzyme inhibitors.[2] As part of our continuing interest in new glycomimetic frameworks, we recently investigated the photolysis of pyridinium and pyrylium salts **1** and **5**, respectively, at 254 nm in acetonitrile–water. In that process, solvent capture of the valence bond isomer led, by a stereocontrolled Ritter reaction and subsequent ring opening of the derived aziridine or epoxide, to highly functionalized oxazolines **3** and **7** (Scheme 1).[3] Attempted peracid epoxidation of *N*-acetylated **3** and **7** unexpectedly formed α-acetoxy oximes **4** and **8**, respectively.

Here we present several examples illustrating the scope and generality of this oxazoline oxidation, and further show that the first-formed oxime products can be converted to the corresponding ketones without epimerization or hydrolysis of other sensitive functionality. The synthetic utility of this methodology is demonstrated by the preparation of highly substituted cyclopentenones and novel monosaccharide derivatives.

Prior studies on the oxidation of oxazolines have achieved varying results. While investigating the peracid oxidation of iminoethers, Aue and Thomas found that 2-methyloxazoline reacted with *m*-chloroperoxybenzoic acid (MCPBA, 1 equiv.) to form mixtures of starting material and the corresponding oxaziridine.[4] Attempts to achieve complete conversion using more MCPBA resulted in overoxidation to 2-acetoxyacetaldoxime, which was only detected after distillation (Eq. (1)). The intermediacy of an oxaziridine-*N*-oxide was suggested, although no detailed mechanism was presented. Keana and Lee later reported that the oxidation of 4,4-dimethyl-2-pentyloxazoline with MCPBA afforded an isolable oxaziridine that, upon silica gel chromatography, isomerized to the corresponding nitrone (Eq. (2)).[5]



Scheme 1.

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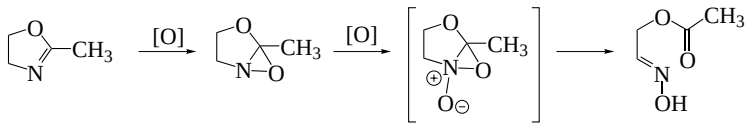
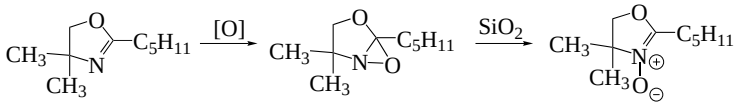


(1)

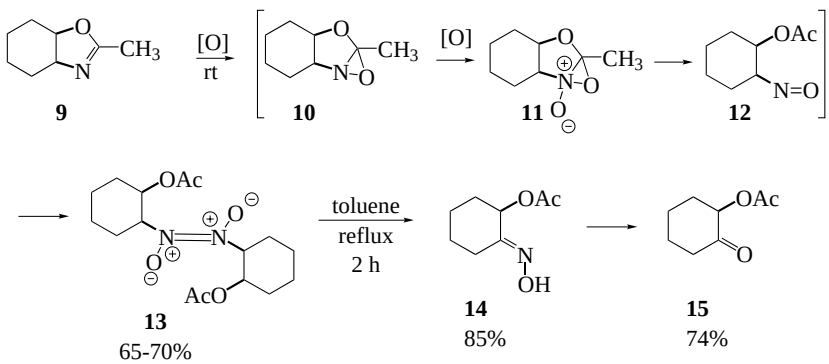


(2)

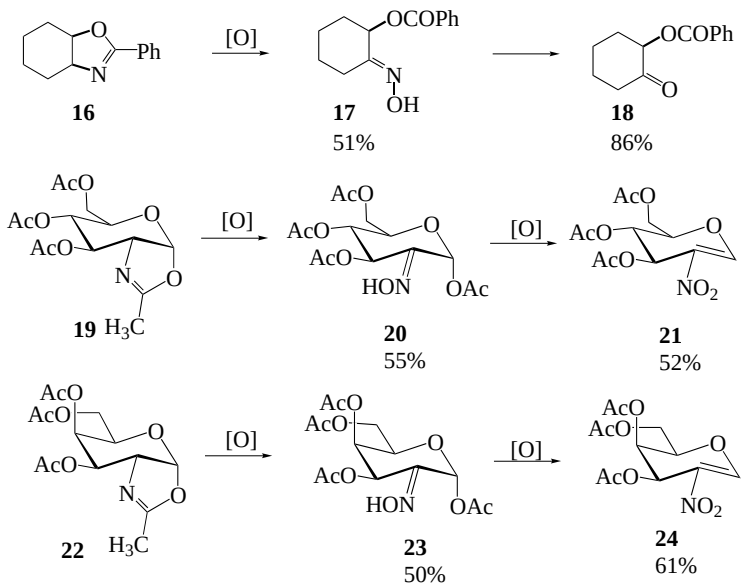
To better understand the mechanism of oxidation, exploratory studies were conducted using the known bicyclic oxazoline **9**, which is readily prepared from cyclohexene by a published method.[6] When oxidations were conducted at rt in either CH_2Cl_2 or CH_3CN using MCPBA (2.5 equiv., Aldrich, 85%), azoxy dimer **13**, was isolated in 65–70% yield (Scheme 2). A plausible mechanism for the formation of **13** involves stepwise oxidation of **9** to the oxaziridine **10**, and then to oxaziridine *N*-oxide **11**. Rearrangement of **11** would afford the nitroso intermediate **12**, which can undergo well-precedented dimerization to the corresponding azoxy compound **13**. Consistent with the product distillation step carried out by Aue and Thomas in Eq. (1), heating the isolated dimer **13** in toluene at reflux furnished the acetoxyoxime **14** in high yield.

Based on these observations, an optimized method was developed for transforming **9** directly to **14** by stirring with MCPBA (2.1 equiv.) at rt, then at reflux. The two stage, one-pot procedure bypassed the need for a radical inhibitor to prevent thermal decomposition of the peracid.[7]

To extend the utility of this oxazoline oxidation, it was of interest to determine whether the oxime group in **14**



Scheme 2.



Scheme 3.

might be transformed to the corresponding ketone without disturbing the adjacent acyloxy group. After screening a variety of deoximation procedures, the process of acid-catalyzed transoximation using excess acetaldehyde,[8] which avoids both hydrolytic and nucleophilic conditions, smoothly transformed **14** to acetoxyketone **15** in 74% yield.

Three additional oxazolines (Scheme 3) were synthesized to test the scope and generality of this new methodology. Like **9**, the previously prepared[6] phenyl-substituted bicyclic oxazoline **16** was smoothly oxidized (50°C, 24 h) and rearranged (reflux, 1.5 h) in one operation to **17**, which could be deprotected using acetaldehyde to the known[9] 2-benzoyloxycyclohexanone **18**.

Saccharide-derived oxazolines **19** and **22** were prepared from 2-acetamido-2-deoxy-d-glucose and 2-acetamido-2-deoxy-d-galactose, respectively, by a known method.[10] Oxazolines **19** and **22** were oxidized (CH_3CN, rt, 9–48 h) and the intermediate azoxy dimers were rearranged in situ (50°C, 12–15 h) to the corresponding acetoxyoximes **20**[11] and **23**, respectively. However, both **20** and **23** were prone to decomposition under the acidic transoximation conditions. Interestingly, a recently reported oxidative deoximation procedure using the Dess–Martin periodinane[12] transformed **20** and **23** to the 2-nitroglucal and galactal derivatives **21** and **24**, respectively.[13] A related oxidative elimination of α-haloketoximes to α-nitroolefins has been reported.[14]

In summary, a general procedure has been devised for the oxidation of substituted oxazolines to α-acyloxyketoximes and the derived α-acyloxyketones. In the case of oxazolines derived from 2-acetamido-2-deoxyhexoses, the resulting oximes can be converted to nitroglycals, which are novel monosaccharide derivatives of potential use in the assembly of di- and oligosaccharides.[15]

Representative procedure: To a solution of **19** (0.71 g, 2.2 mmol) in CH_3CN (70 mL) was added MCPBA (1.03 g, 80–85% pure). The solution was stirred at rt for 9 h, then heated at 50°C for 12 h. After cooling and concentration in vacuo, the residue was dissolved in EtOAc (80 mL), washed with sat $NaHSO_3$, satd $NaHCO_3$, and satd NaCl. The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (2:3 EtOAc:hexanes) afforded 0.43 g (55%) of pure **20**.

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13. For **21**: ^{1}H NMR δ (300 MHz, $CDCl_3$) 8.32 (s, 1H), 5.99 (m, 1H), 5.23 (t, 1H, $J=2$ Hz), 4.70–4.75 (m, 1H), 4.46 (dd, 1H, $J=12$, 8 Hz), 4.16 (dd, 1H, $J=12$, 4 Hz), 2.11 (s, 6H), 2.1 (s, 3H); ^{13}C NMR 170.4, 109.2 (2), 155.6, 128.3, 76.3, 65.7, 61.5, 60.5, 21.0, 20.9, 20.8.
For **24**: ^{1}H NMR δ 8.22 (s, 1H), 6.30 (m, 1H), 5.47 (t, 1H, $J=4.3$ Hz), 4.57–4.62 (m, 1H), 4.46 (dd, 1H, $J=12.4$, 9.1 Hz), 4.32 (dd, 1H, $J=12.4$, 3.2 Hz), 2.12 (s, 6H), 2.09 (s, 3H); ^{13}C NMR 170.7, 169.7, 169.4, 155.6, 129.2, 75.4, 64.2, 60.9, 60.6, 21.0, 20.7 (2).
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15. See for example: Sakakibara, T.; Tachimori, Y.; Sudoh, R. *Carbohydr. Res*. **1984**, *131*, 197–208.