ORGANIC LETTERS

2003
Vol. 5, No. 17
3089−3092

Direct Lactonization of Alkenols via Osmium Tetroxide-Mediated Oxidative Cleavage

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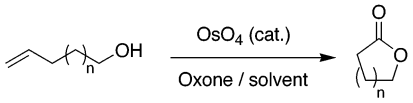
Received June 11, 2003

ABSTRACT



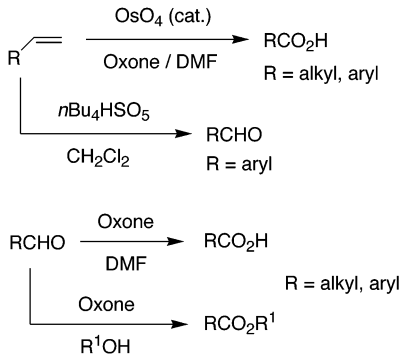
A highly efficient, mild, and simple protocol is presented for the tandem OsO_4-mediated oxidative cleavage/oxidative lactonization of alkenols to lactones. The protocol couples the OsO_4-catalyzed oxidative cleavage of olefins with Oxone as the co-oxidant with the direct oxidation of aldehydes in alcoholic solvents to their corresponding esters.

Oxidative chemistry is essential for the success of organic synthesis as can be attested to by the overwhelming number of manuscripts published in the area.[1−8] Needless to say, the importance of these reactions cannot be overstated, and the discovery of new, more efficient and milder reactions with unique properties would only increase the repertoire of tools available to organic chemists for tackling syntheses of complex molecules on both laboratory and industrial scales.

Recently, the use of the convenient and readily available Oxone as an economical and green oxidant has blossomed for many transformations in organic synthesis. These include, but are not limited to, selective oxidations of boron, nitrogen, phosphorus, and sulfur-containing compounds.[9−14] Oxone is also well-known as a useful reagent for the preparation of dimethyldioxirane (DMDO) in buffered acetone, which is used to epoxidize olefins.[15,16]

We have been engaged in exploring Oxone as a mild oxidant for the OsO_4-mediated oxidative cleavage of olefins to their corresponding aldehydes and carboxylic acids (Scheme 1).[17,18] Aldehydes are the immediate products

Scheme 1



obtained in the oxidation of olefins and can be isolated as the sole product if soluble peroxymonosulfate (nBu_4NHSO_5)

(1) Bentley, T. W. *Org. React. Mech.* **1977**, *12*, 211.
(2) Fischer, R. W.; Herrmann, W. A.; Weskamp, T. *Transition Met. Org. Synth.* **1998**, *2*, 282.
(3) Fleet, G. W. J. *Org. React. Mech.* **1991**, 191.
(4) Haines, A. H. *Methods for the Oxidation of Organic Compounds: Alkanes, Alkenes, Alkynes, and Arenes*; Academic Press: London, 1985.
(5) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.
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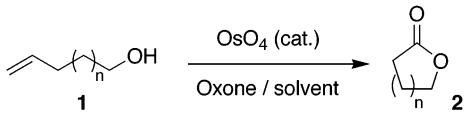
10.1021/ol035057f CCC: $25.00
Published on Web 07/29/2003

is used for the cleavage of aromatic olefins. Along the same lines, we have demonstrated that Oxone can be used as a mild and efficient reagent for conversion of aldehydes to carboxylic acids, and furthermore, in the presence of alcoholic solvents, the oxidation proceeds directly to yield esters (Scheme 1).[19] As a continuation of this work, we were interested in determining whether the oxidative cleavage of olefins could be coupled with intramolecular trapping by an alcohol moiety to form lactones. The reaction envisioned is shown in Scheme 2 (direct conversion of **1** to **2**).

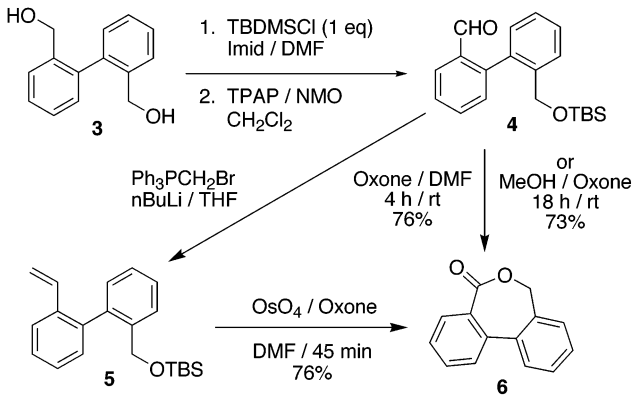
Scheme 2



Other methods that have been reported for the conversion of hydroxy olefins to lactones via oxidative cyclization require stoichiometric chromium or permanganate reagents. Schlecht and Kim[20] have used chromium trioxide in acetic acid/acetic anhydride, and Chandrasekaran and co-workers[21,22] have used a pentavalent $(BiPyH_2)CrOCl_5$ reagent to effect the transformation of various γ- and δ-hydroxy olefins to the corresponding lactones. However, these particular sets of reaction conditions are only useful for hydroxy olefins containing a tertiary alcohol group; otherwise, oxidation of the alcohol to the corresponding carboxylic acid or ketone is a major problem. Chandrasekaran and co-workers soon devised a solution to this problem in the form of cetyltrimethylammonium permanganate, which can be used in the oxidative cyclization of primary, secondary, or tertiary alkenols to the corresponding lactones.[23] Chandrasekaran also reported the use of $KMnO_4$ in the presence of copper sulfate and a small amount of water as being effective in the oxidative cyclization of ω-hydroxy alkenes to ω-lactones under mild conditions.[24] We wish to report on our success in developing a new and mild system for effecting this transformation involving catalytic OsO_4 in the presence of Oxone as the oxidant.

Our initial efforts centered on the proof of concept depicted in Scheme 3. Bis-(hydroxymethyl) biphenyl **3** was mono-

Scheme 3



protected, and the free hydroxyl was oxidized to yield aldehyde **4**. Upon treatment of **4** with either Oxone in DMF or in MeOH, in situ deprotection of the silyl group occurred concomitantly with oxidation of the hydroxy aldehyde intermediate to the lactone **6**. Presumably, the oxidation proceeds via the formation of a hemiacetal intermediate, since we have demonstrated previously that hydroxy carboxylic acids do not esterify/lactonize under the given reaction conditions.[19]

Olefination of **4** to deliver **5** provided the prerequisite silyl-protected alkenol poised for a tandem oxidative cleavage/oxidative lactonization to deliver **6**. Treatment of **5** with catalytic OsO_4 (1 mol %) and Oxone in DMF led to the isolation of **6** in good yields, thus demonstrating the intramolecular trapping of the unmasked hydroxyl upon oxidative cleavage of the olefin.

Subsequent experiments focused on the conversion of alkenols to their corresponding lactones, specifically the conversion of 4-penten-1-ol and 5-hexen-1-ol to butyrolactone and valerolactone, respectively (Table 1, entries 1 and 2). These lactones were obtained in good yields, thus demonstrating that alkyl-substituted olefins can also undergo the lactonization in preference to oxidation to carboxylic acids. Due to the water solubility of the smaller lactones, these reactions were monitored by using 1,2,3,4-tetramethylbenzene or dodecane as an internal standard and sampling by gas chromatography. Although previous experience with Oxone/OsO_4 systems had shown that DMF was a very effective solvent for oxidative cleavage of olefins, a preliminary solvent screen was performed. Acetonitrile, acetone/water, DMF, methanol, and HMPA were all shown to yield lactone product. Hexane, glyme, dioxane, and xylene did not yield appreciable amounts of product. It was later shown that the yield of oxidative lactonization in solvents such as acetonitrile and methylene chloride could be increased, provided that 10−50 equiv of DMF was added. This is important in facilitating easier workup of water-soluble or volatile lactones.

DMF was chosen as the initial solvent for study due to fast reaction times and higher yields of product as compared to other solvents. It was found that the use of a 0.1 M solution of the alkenol in DMF with 4.0 equiv of Oxone and

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(20) Schlecht, M. F.; Kim, H. *Tetrahedron Lett.* **1985**, *26*, 127.
(21) Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* **1987**, 1175.
(22) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1980**, *21*, 1583.
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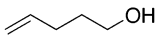
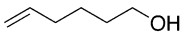
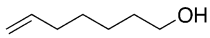
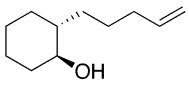
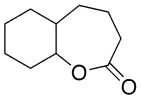
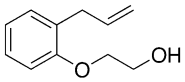
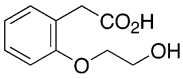
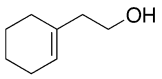
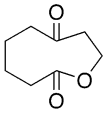
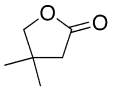
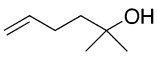
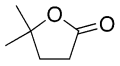
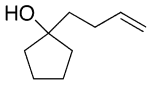
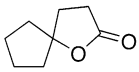
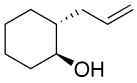
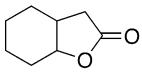
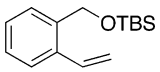
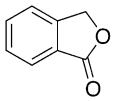
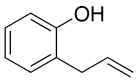
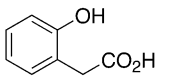
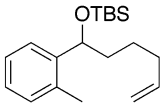
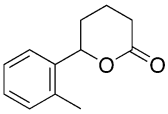
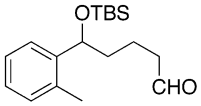
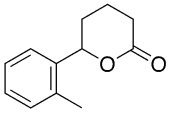
Table 1. Oxidative Lactonization of Alkenols

entry	substrate		product		yield (%)[a]
1		**7**		**7a**	73[b]
2		**8**		**8a**	68[b]
3		**9**		**9a**	42[b]
4		**10**		**10a**	59
5		**11**		**11a**	69
6		**12**		**12a**	45
7		**13**		**13a**	84[c]
8		**14**		**14a**	85[c]
9		**15**		**15a**	73
10		**16**		**16a**	82
11		**17**		**17a**	76
12		**18**		**18a**	52
13		**19**		**19a**	65
14		**20**		**19a**	76[d]

[a] Isolated yields, unless specified otherwise. [b] GC yields. [c] NMR yields. [d] Reaction conditions are the same except that OsO_4 was omitted.

1.0 mol % OsO_4 was effective at converting primary, secondary, and tertiary alcohols to the corresponding lactones in good yields (Table 1).

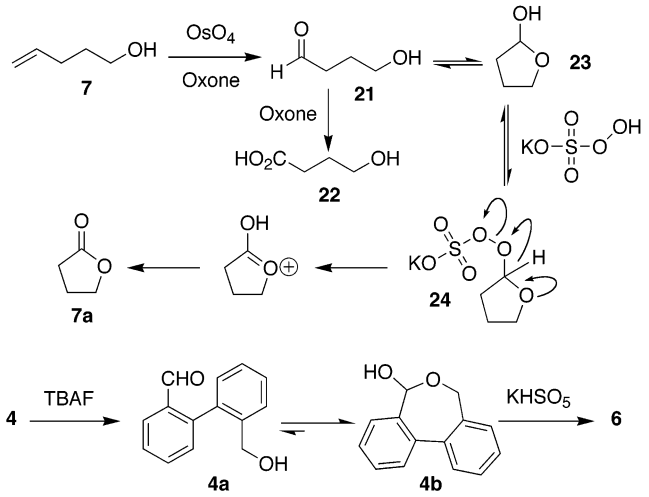
While the formation of five- and six-member lactones was facile as expected, the yield dropped precipitously on formation of caprolactone (Table 1, entry 3). Longer chain alken-1-ols gave no discernible amounts of lactone, and the carboxylic acids were isolated as the sole products. This is likely due to the small equilibrium presence of the cyclized hemiacetals for larger rings. Therefore, following oxidative cleavage, the oxidation of the intermediate aldehyde to carboxylic acids predominates. The yield of seven-member lactones could be improved, provided that conformational freedom was restricted (Scheme 3 and entry 4 in Table 1). Attempts to form an eight-member lactone (entry 5) were unsuccessful and led only to the carboxylic acid product **11a**, albeit in good yield. We were disappointed with these results, since we had hoped that this protocol could be extended to the formation of macrocyclic ring systems, thus providing the opportunity for masking a carboxylic acid as an alkene during the course of a synthesis. While this might still prove to be a viable strategy for more highly substituted systems with preferred conformations that could increase the cyclic hemiacetal intermediate necessary for lactonization, another route to larger macrocycles can be pursued by tethering an alcohol functionality to an endocyclic double bond (Table 1, entry 6).[25]

Entries 7 and 8 in Table 1 illustrate the effect of substitution on the yield of lactonization. The anticipated Thorpe−Ingold effect[26] for alkenol **13** did result in higher yields of **13a**. However surprisingly, the tertiary alcohols **14** and **15** with steric crowding of the hydroxyl groups reacted efficiently to yield **14a** and the spirolactone **15a**, respectively. Fused 5/6 and 6/7 ring systems **16a** and **10a**, respectively, could be obtained in good isolated yields (Table 1, entries 10 and 4). Protected benzylic alcohol **17** with an olefinic appendage was also lactonized under the same reaction conditions. However, phenolic systems such as **18** did not undergo oxidative lactonization, presumably because of the tempered nucleophilicity of the hydroxyl group (Table 1, entry 12). Oxidative lactonization of the silyl-protected alkenol **19** yielded **19a**, once again demonstrating the in situ deprotection/lactonization sequence under the reaction conditions. Aldehyde **20**, presumably the intermediate in the oxidative lactonization of **19**, also yields **19a** in good yields upon treatment only with Oxone.

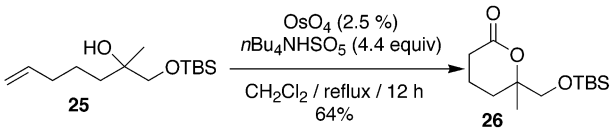
We believe that the lactonization occurs via an initial cleavage of the alkene **7** to aldehyde **21** (Scheme 4), which can be either further oxidized to the carboxylic acid **22** (nonproductive process) or trapped intramolecularly by the alcohol moiety to form the hemiacetal **23**. Oxone, which contains peroxymonosulfate as its active oxidant, is slightly acidic, and thus equilibration of the hemiacetal **23** to the hemiperoxymonosulfate acetal **24** can be effected under the reaction conditions shown in Scheme 4. Baeyer−Villeger-like rearrangement of **24** can lead to the isolation of lactone **7a**.[5,27−30] We have some experimental evidence to suggest the latter to be true. Deprotection of **4** with TBAF leads to the hydroxy-aldehyde **4a**, which exists mainly in the hemiacetal form **4b** as evident by NMR (see Supporting Informa-

(25) Das, J.; Chandrasekaran, S. *Tetrahedron* **1994**, *50*, 11709.
(26) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205.
(27) Lethinen, C.; Nevalainen, V.; Brunow, G. *Tetrahedron* **2001**, *57*, 4741.
(28) Syper, L. *Synthesis* **1989**, 167.
(29) McNesby, J.; Heller, C. *Chem. Rev.* **1954**, *54*, 325.
(30) Godfrey, I.; Sargent, M.; Elix, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

Scheme 4



Scheme 5



tion for spectra). Exposure of **4a**/**4b** to $KHSO_5$ leads to lactone **6**, which can be qualitatively followed by NMR (see Supporting Information). Detailed mechanistic studies are ongoing to fully elucidate the mechanism of lactonization, and thus other mechanistic pathways such as radical-mediated oxidations cannot be excluded at this time. However, what is clear is that the path to lactones is not through oxidation of the olefin to carboxylic acids, followed by an intramolecular lactonization event. Carboxylic acids containing internal hydroxyl groups are immune to lactonization if placed in identical reaction conditions.[19]

The use of a soluble form of Oxone (nBu$_4$NHSO$_5$)[17] was briefly studied. Difficulty in separating excess oxidant and oxidation byproducts from highly polar products was not trivial, and thus nBu$_4$NHSO$_5$ is not recommended for use with water-soluble lactones. However, nBu$_4$NHSO$_5$ is a convenient reagent for more nonpolar substrates and, unlike the Oxone/DMF system, allows for silyl groups to be retained during the lactonization (Scheme 5). The reason for the observed difference in reactivity between nBu$_4$NHSO$_5$ and Oxone is not apparent; however, it could be a result of Oxone's much higher water content and its inherent acidity that could lead to the hydrolysis of silyl ethers. A previous report by Sabitha and co-workers has demonstrated the ability of Oxone to deprotect TBDMS groups in aqueous MeOH.[31] As such, the tandem oxidative cleavage/oxidative lactonization of the tertiary alcohol **25** with nBu$_4$NHSO$_5$ in dichloromethane provided lactone **26** in good yields without the deprotection of the TBS group.

In conclusion, we have shown that a new and mild osmium-catalyzed tandem oxidative cleavage/oxidative lactonization reaction can be used to prepare lactones from a wide variety of hydroxy olefins.

Acknowledgment. Generous support was provided in part by Michigan State University Startup funds to B.B. and the Michigan Economic Development Corporation (GR-183). J.M.S. is supported by the Michigan State University Distinguished Fellowship. B.R.T. is supported by a fellowship from the American Chemical Society, Division of Organic Chemistry.

Supporting Information Available: Detailed experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035057F

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