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Intramolecular Oxamidation of Unsaturated *O*-Alkyl Hydroxamates: A Remarkably Versatile Entry to Hydroxy Lactams

Duncan J. Wardrop*, **Edward G. Bowen**, **Raymond E. Forslund**, **Adam D. Sussman**, and **Samanthi L. Weerasekera**
University of Illinois at Chicago, Department of Chemistry, 845 West Taylor Street, Room 4500, Chicago, Illinois 60607-7061

Abstract

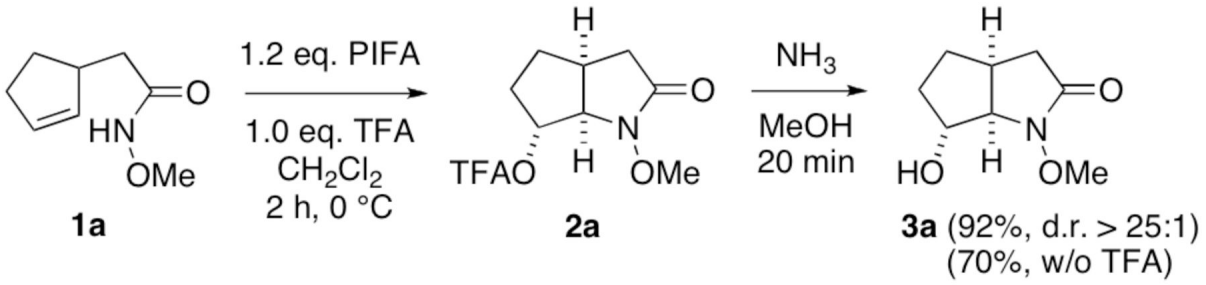
The development of a versatile method for the preparation of 5 to 8-membered hydroxy lactams, involving the iodine(III)-mediated oxamidation of unsaturated *O*-alkyl hydroxamates is described. This transformation, which is believed to proceed through the intermediacy of singlet nitrenium and bicyclic *N*-acyl-*N*-alkoxyaziridinium ions, is in most of the 22 cases examined, both stereospecific and/or highly regioselective.

The reaction of singlet nitrenium ions1 with alkenes has long been known to proceed in stereospecific fashion to generate aziridinium ions.2 However, in comparison to the reaction of carbenes, their isoelectronic congeners, this process has until recently, received scant attention,3[–5] despite the growing importance of both aziridines and aziridinium ions in organic synthesis.6 While this reflects the harsh conditions traditionally required for formation of these reactive electrophiles, the iodine(III)-mediated oxidation of *O*-alkyl hydroxamates **1** offers convenient access to *O*-stabilized nitrenium ions (**7** in Scheme 1).[1b] Having successfully employed the cyclization of these species with arenes as a route to azaspiranes,[7] we became intrigued by the possibility that intramolecular addition of nitrenium ions generated from unsaturated hydroxamates **1** would not only yield bicyclic *N*-acyl-*N*-alkoxyaziridinium ions **4**, but through concerted ring opening of these products, offer a means to accomplish cyclofunctionalization. Herein, we report the successful development of this reaction as a highly versatile method for the preparation of 5 to 8-membered hydroxy lactams **3**.[8,9]

Our preliminary studies focused on substrate **1a** which, upon treatment with phenyliodine(III) bis(trifluoroacetate) (PIFA) in CH_2Cl_2, smoothly underwent cyclization to form *anti*-addition product **2a** in high yield (eq 1). In light of the lability of this ester, a methanol-ammonia quench was employed to remove the trifluoroacetate group and provided α-hydroxyalkyl lactam **3a** as a single diastereomer in excellent yield. Importantly, we have found that *addition of trifluoroacetic acid to the oxamidation reaction significantly accelerates this process and, in most cases, improves its efficiency* (Table 1). That acid catalysis plays a significant role in the formation of **2a** is also apparent from the inhibitory effect of acid scavengers and the failure of both $PhI(OAc)^2$ and Pb(OAc)4 to mediate cyclofunctionalization.10,11

wardropd@uic.edu.

Supporting Information Available: Characterization, procedures and stereochemical assignments. This material is free of charge via the Internet at http://pubs.acs.org.



(1)

Employing these optimal conditions, a range of unsaturated hydroxamates was screened. As is apparent from Table 1, this reaction is characterized by broad substrate scope and, in most cases, is both stereospecific and highly regioselective. In the case of 1,2-disubstituted alkenes, concerted ion pair collapse of bicyclic aziridinium ions **4c–e** occurs solely at the less encumbered α position to yield α-hydroxyalkyl lactams, while bicyclo[2.1.0] ion **4b** (n = 0) undergoes ring expansion to form **3b**. The isomer outcome of this process is predictable, and is highlighted by the formation of diastereomers **3d** and **3e** from the corresponding *E*- and Z-alkenes. Aziridinium ions generated from 1,1-disustituted substrates **1g–i**, in contrast, undergo opening at the β position (**4**, $R_1 \neq H$), suggesting that substitution occurs with significant charge separation.[12] Although the cyclization of trisubstituted alkene **1j** proceeded with modest regioselectivity, the stereospecificity associated with formation of **3j** and **3k** is remarkable given the highly-substituted nature of the bicyclo[3.1.0] ion (R_1/R_2 = Me, *n* = 1) from which these products arise. Non-synchronous ring opening was observed with styrene **1l**, which afforded a mixture of oxamidation products. Significantly, the presence of a *p*-CF_3 group in **1m** serves to disfavor carbocation formation, which is thought to be the origin of this loss of diastereoselectivity.

Extension of our methodology to cyclic substrates was also successful and provides stereocontrolled entry to a number of functionalized tricyclic systems, including 6-azabicyclo [2.2.2] and [3.2.1]octanes (Table 2). Notwithstanding the modest selectivity observed during the formation of **3q** and **3r**, which reflects the sterically non-biased nature of the bridged aziridinium ion in this case, the regioselectivity of ring opening can be controlled effectively through introduction of substituents, as in the case of **3s**, or via steric effects, both proximal and distal, as observed with **3t–u**. The exclusive formation of **3w** implies that electron-withdrawing groups have an inhibitory effect on proximal ring opening,[13a] while **3x** is believed to arise through interception of the aziridinium ion by the neighboring *exo*-C3 acetoxy group:[13b] selective hydrolysis of the resulting 1,3-dioxenium ion accounts for the 1,2-acetyl migration observed in this case.

In order to account for our observations, we have developed the mechanistic rationale outlined in Scheme 1. In this case, cyclization begins with ligand substitution of PIFA by **1a** to form amido-λ^3-iodane **6**,[14] which undergoes ligand coupling,[15] to *N*,*N*-bisheteroatom-substituted (anomeric) amide **8**,[16a] or fragmentation to yield singlet nitrenium ion **7**. Intramolecular cycloaddition of this electrophile, via transition state **9**, would generate **10**, and subsequently **2a**. Alternatively, **10** may arise from **8**, through an S_N2-like reaction, which although prohibited in conventional amides, is feasible at the pyramidalized *N*-center of anomeric amides, as seminal studies by Glover have revealed.[16b] However, in light of Glover's observation that these atypical amides also undergo $A_{Al}1$ acid-catalyzed solvolysis to form nitrenium ions,[16c] and in consonance with the effect of TFA upon oxamidation, we believe that conversion of **8**

to **10** is more likely to proceed via an S_N1 process, where rapid and reversible protonation of **8** precedes ionization to **7**.[17]

While the precise location of the *N*-electrophile on the continuum between **7** and **8** awaits determination, and may prove to be substrate dependant, the absence of *syn*-oxamidation and lactone products in these reactions implies that cyclization does not occur via addition of PIFA to the double bond and subsequent nucleophilic displacement of an aryl-λ3-iodanyl group.[18]

Lactam rings are embodied within a wealth of physiologically active natural products and pharmaceutical agents and, as a result, methods that facilitate the preparation of these saturated *N*-heterocycles are of great importance. In this context, the intramolecular alkene oxamidation method described herein represents a remarkably versatile method to access this important class of targets.[19] Mechanistic studies and the application of this chemistry to natural product synthesis are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. Oae S, Uchida Y. Acc. Chem. Res 1991;24:202.
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17. That the approach of the alkene to the *N*-center, in this case, may be intimately involved with, and assist in, the departure of the protonated trifluoroacetate group is not discounted.
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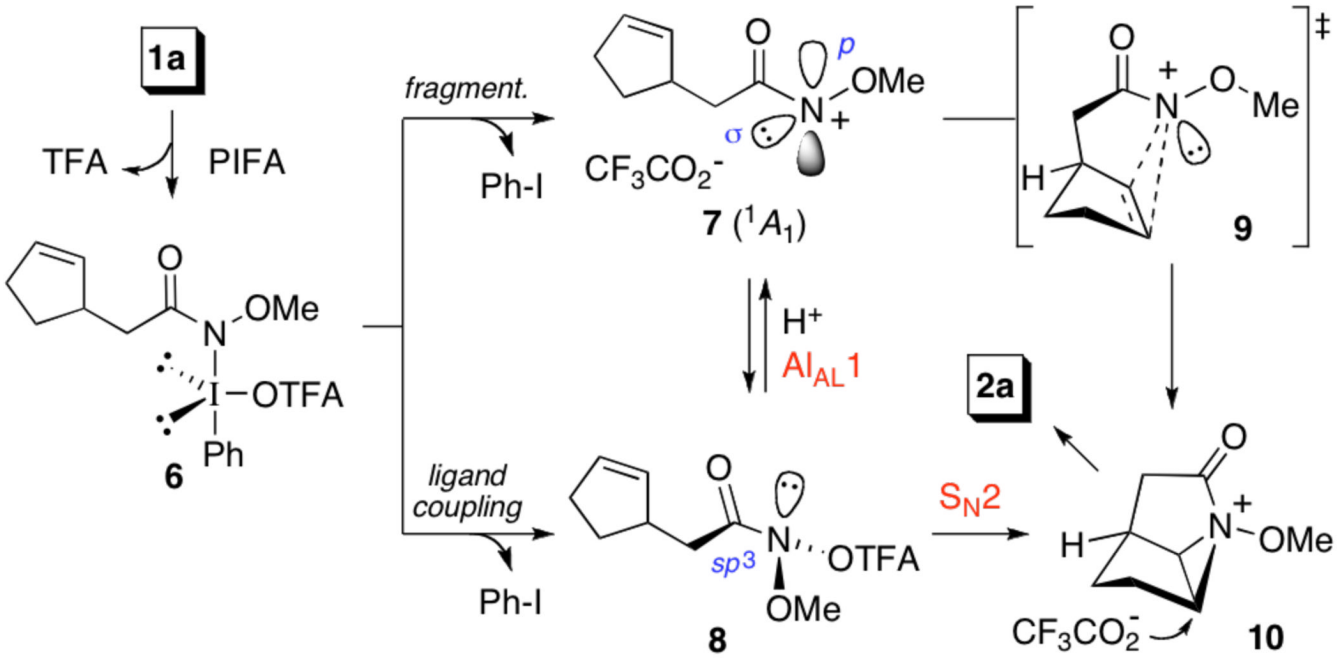
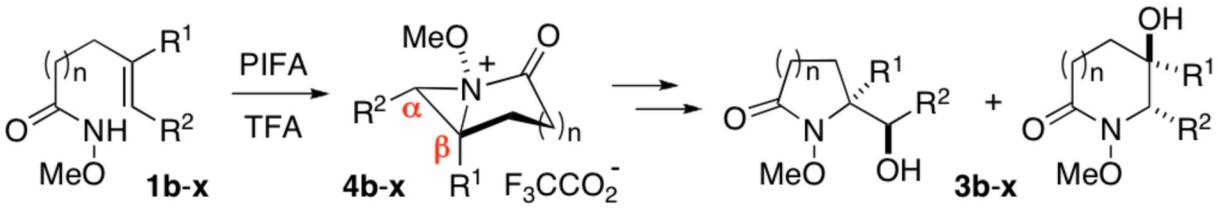
19. Reductive cleavage of *N*-methoxy lactams to the corresponding *N-H* lactams can be accomplished with range of reducing agents, including $Mo(CO)_6$ (ref. 7). For experimental details, see Supporting Information.



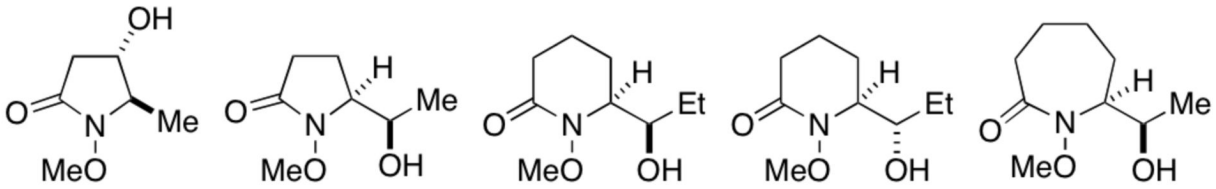
Scheme 1.

Table 1

Scope of Oxidative *O*-Alkyl Hydroxamate Cyclization[a,b]

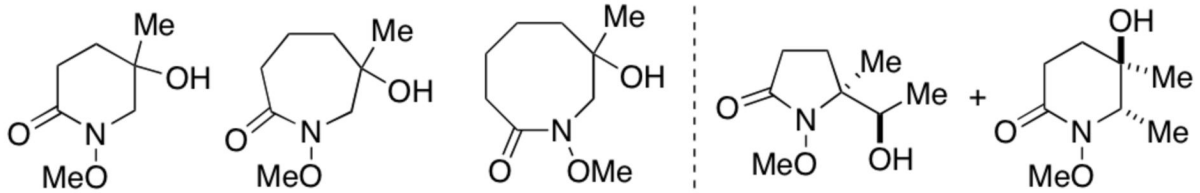


1,2-Disubstituted Alkenes



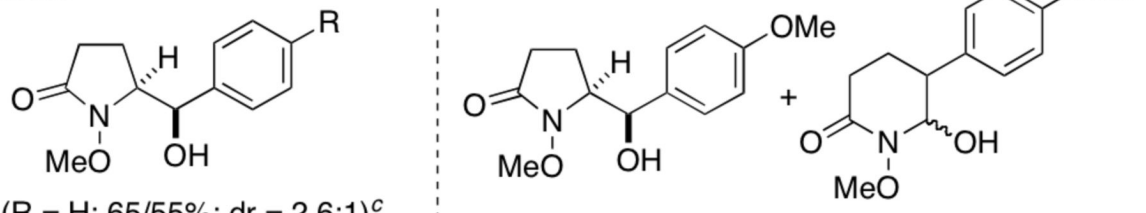
3b (75/31%)[c,d] **3c** (93/91%)[c] **3d** (84/74%)[c] **3e** (98%)[e] **3f** (49/21%)[c,f]

1,1-Di & Trisubstituted Alkenes



3g (95/60%) **3h** (83/67%) **3i** (83/66%) **3j** (58/56%)[c] **3k** (28/19%)[c]

Styrenes



3l (R = H; 65/55%; dr = 2.6:1)[c]
3m (R = CF_3; 85/58%; dr > 98:2)[c]
3n (21/53%; dr > 98:2)[c] **5** (24/0%; dr = 1:1)[g]

[a] *Conditions:* **1**, PIFA (1.2 equiv), TFA (1.0/0.0 equiv), CH_2Cl_2 (0.15 M), 0 °C; then NH_3-MeOH, 20 min.

[b] Isolated yields of oxamidations conducted with and w/o TFA, after purification by flash chromatography.

[c] Generated from *E*-**1**.

[d] Workup via hydrazinolysis.

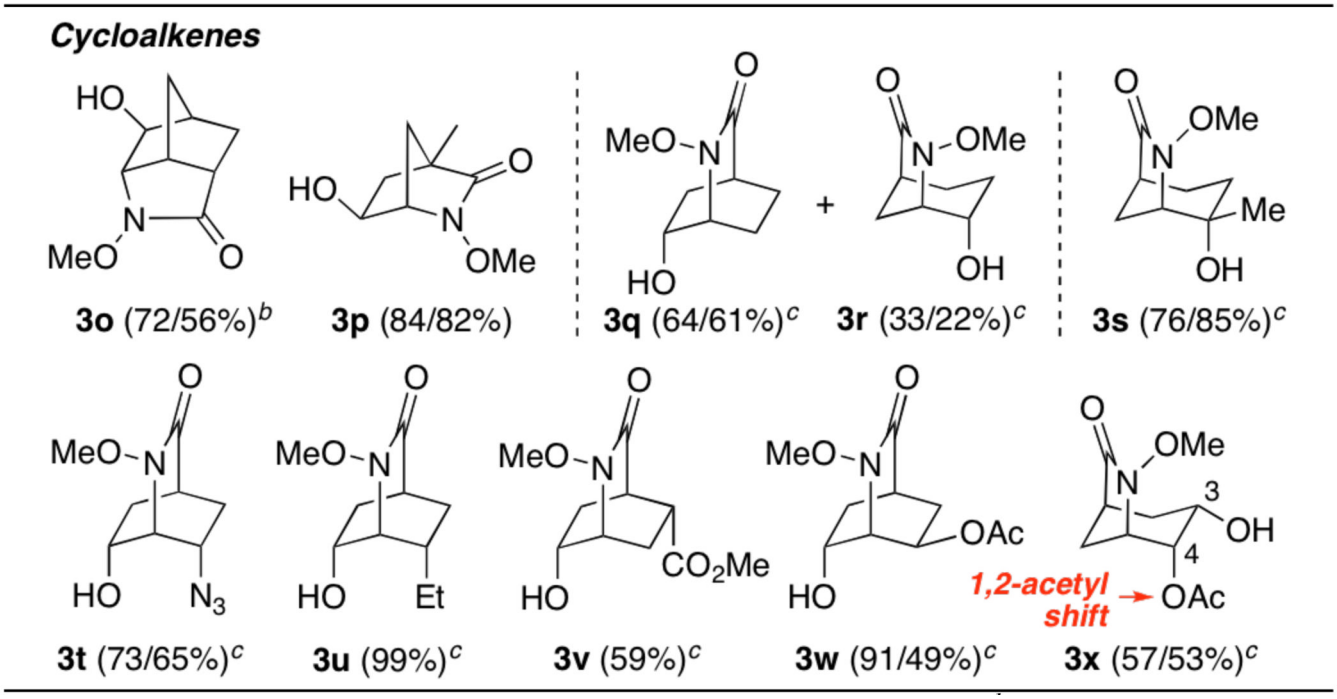
[e] Generated from *Z*-**1**.

[f] An azocan-2-one, resulting from β-opening, was also isolated as a single diastereomer in 18/10% yield.

[g] See supporting information for the possible origins of rearrangement product **5**.

Table 2

Oxamidation of Cyclic *O*-Alkyl Hydroxamates[a]



[a] *Conditions and yields*: see Table 1, footnotes a/b.

[b] Ester hydrolysis carried out with aq. $NaHCO_3$.

[c] Oxamidation conducted at 40 °C.