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

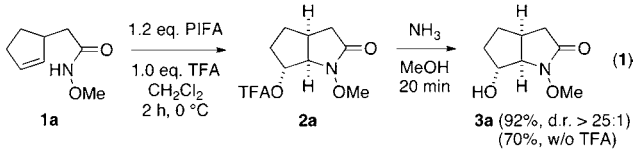
Duncan J. Wardrop,* Edward G. Bowen, Raymond E. Forslund, Adam D. Sussman, and Samanthi L. Weerasekera

University of Illinois at Chicago, Department of Chemistry, 845 West Taylor Street, Room 4500, Chicago, Illinois 60607-7061

Received August 21, 2009; E-mail: wardropd@uic.edu

The reaction of singlet nitrenium ions[1] with alkenes has long been known to proceed in stereospecific fashion to generate aziridinium ions.[2] However, in comparison with the reaction of carbenes, their isoelectronic congeners, until recently this process has 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 also offer a means to accomplish cyclofunctionalization. Herein, we report the successful development of this reaction as a highly versatile method for the preparation of five- to eight-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 the anti addition product **2a** in high yield (eq 1):

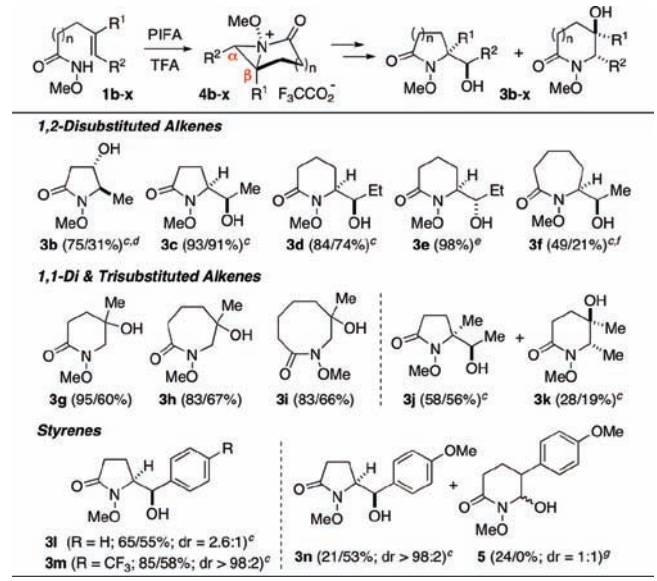


(1)

In light of the lability of this ester, a methanol/ammonia quench was employed to remove the trifluoroacetate group, providing 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]

Under 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. Nonsynchronous 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** served to disfavor carbocation formation, which is thought to be the origin of this loss of diastereoselectivity.

Table 1. Scope of Oxidative *O*-Alkyl Hydroxamate Cyclization[a,b]



[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 without 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 the Supporting Information for the possible origins of rearrangement product **5**.

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 nonbiased nature of the bridged aziridinium ion in this case, the regioselectivity of ring opening can be controlled

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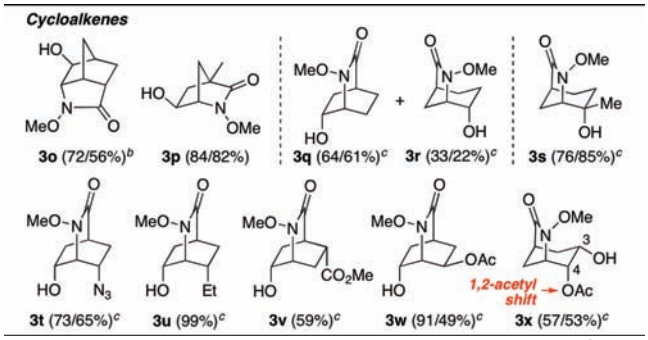
effectively through the introduction of substituents, as in the case of **3s**, or via steric effects, both proximal and distal, as observed with **3t** and **3u**. The exclusive formation of **3w** implies that electron-withdrawing groups have an inhibitory effect on proximal ring opening,[13a] while **3x** is believed to arise through interception of the aziridinium ion by the neighboring *exo* acetoxy group at C3:[13b] selective hydrolysis of the resulting 1,3-dioxenium ion accounts for the 1,2-acetyl migration observed in this case.

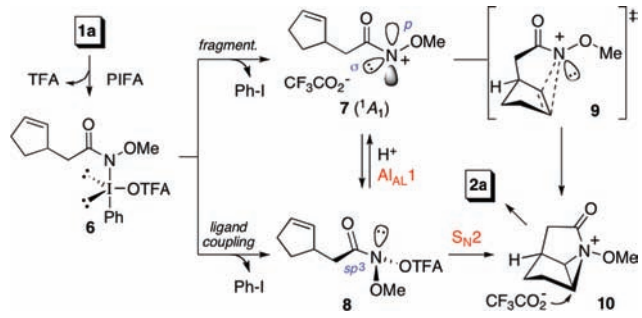
Table 2. Oxamidation of Cyclic *O*-Alkyl Hydroxamates[a]



[a] For conditions and yields, see Table 1, footnotes a and b. [b] Ester hydrolysis carried out with $NaHCO_3$(aq). [c] Oxamidation conducted at 40 °C.

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 give *N*,*N*-bis(heteroatom)-substituted (anomeric) amide **8**,[16a] or fragmentation to yield singlet nitrenium ion **7**. Intramolecular cycloaddition of electrophile **7**, via transition state **9**, would generate **10** and subsequently **2a**. Alternatively, **10** may arise from **8** through an S_N2-like reaction, which while prohibited in conventional amides is feasible at the pyramidalized *N*-center of anomeric amides, as seminal studies by Glover[16b] have revealed. 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 in which rapid and reversible protonation of **8** precedes ionization to give **7**.[17]

Scheme 1



While the precise location of the *N*-electrophile on the continuum between **7** and **8** awaits determination and may prove to be substrate-dependent, 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-λ^3-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 for accessing this important class of targets.[19] Mechanistic studies and the application of this chemistry to natural product synthesis are currently underway.

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

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