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γ-SUBSTITUENT EFFECTS ON THE OXIDATIVE CYCLIZATION OF O-ACYL β,γ-UNSATURATED HYDROXAMATES

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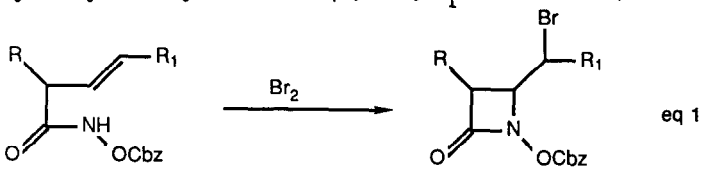
Summary: Bromine induced cyclization of O-acyl β,γ-unsaturated hydroxamates to β-lactams is compatible with a variety of γ-substitutents.

We previously described a simple and efficient procedure for the oxidative cyclization of β,γ-unsaturated hydroxamates to simple 4-bromomethyl β-lactams (eq 1, R=R_1=H).[1] More recently, we demonstrated that variation of the α-substituents (R) can have a significant effect on the stereochemistry of the β-lactam products formed.[2] Most notably, when R was a protected amino group, cis-β-lactams formed preferentially, but when R was an alkyl group the trans products were favored. These interesting results prompted further study. Oxidative cyclization reactions leading to five and six membered ring systems have been extensively studied.[3] However, no systematic studies of oxidative cyclization reactions of β,γ-disubstituted acyclic alkenes leading to four membered ring systems have been reported.[4] Herein we describe the effect of the γ-substituent on the oxidative cyclization of γ-substituted O-acyl-vinylacetohydroxamates (**1**, R=H, R_1=substitutent).



eq 1

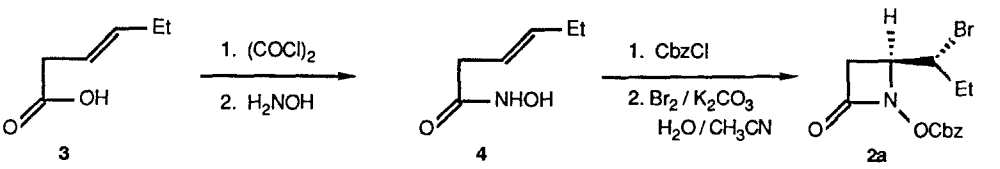
1a R=H, R_1=Et
1b R=H, R_1=CH_2CO_2Me
1c R=H, R_1=CH=CH_2
1d R=H, R_1=Ph

2a
2b

The choice of the substituents (R_1) on the unsaturated hydroxamates was made to reflect the scope and limitations of the synthesis of β-lactams by this oxidative cyclization approach. A simple alkyl group (R_1=ethyl) was chosen for the first case. Accordingly, commercially available (Aldrich) trans-3-hexenoic acid (**3**) was treated with oxalyl chloride followed by hydroxylamine to provide the hydroxamic acid **4**[5] in 93% overall

yield. Subsequent reaction of **4** with carbobenzyloxychloride (CbzCl) provided the desired substrate **1a**[5] cleanly (Scheme 1). Isolation of the intermediate free hydroxamic acid **4** was not necessary and the overall yield of **1a** from **3** was 79%. Treatment of **1a** with bromine (102 mole %) under the usual oxidative cyclization conditions (0.05 mmol of **1**/mL with 105 mole % of K_2CO_3 in CH_3CN containing 5-10 volume % of H_2O at 0^oC to room temperature for less than 5 min)[1,2] provided the β-lactam **2a**[5] in 53% isolated yield.

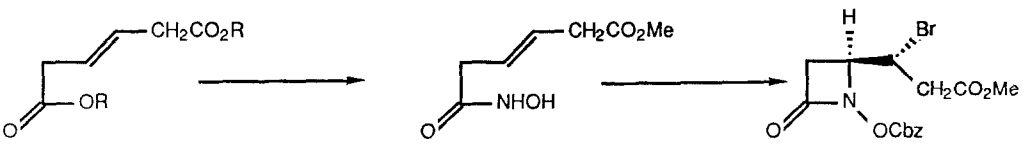
Scheme 1



3 **4** **2a**

The second substrate considered (**1b**) was chosen to test the compatibility of the cyclization process with functionality that might be useful for the eventual construction of bicyclic β-lactams. Thus, trans-3-hexenedioic acid (**5a**, trans-β-hydromuconic acid, Fluka) was first converted to its dimethylester **5b** (89%) by reaction with $SOCl_2$ in methanol. Careful treatment of **5b** with only 33 mole % of NH_2OH/KOH (CH_3OH, RT, 14h) allowed selective formation of the desired monohydroxamate **6**[5] in 71% yield, based on recovered **5b**.[6] Treatment of **6** with Cbz-Cl/pyridine provided the desired substrate **1b**[5] in 98% yield. Bromine induced cyclization of **1b** produced the β-lactam **2b** quantitatively, clearly demonstrating the utility of this process for the synthesis of functionalized β-lactams.

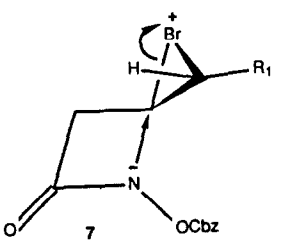
Scheme 2



5a R=H
5b R=Me

6 **2b**

The remarkable stereoelectronic control demonstrated by the specific formation of β-lactams rather than the corresponding γ-lactams in these reactions is reminiscent of epoxy nitrile cyclizations to cyclobutanes.[7] Thus, collinear approach may also be indicated for the formation of 4-membered lactam rings (structure **7**).



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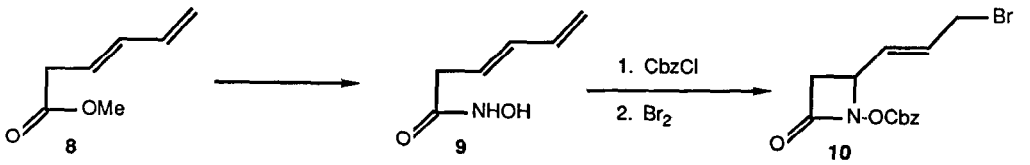
The presence of the γ-vinyl substituent on substrate **1c** was anticipated to provide a very interesting test of the cyclization procedure. Several products might be expected from the initial addition of bromine to either of the alkenes in this system and subsequent attack of the hydroxamate at a number of positions. The required

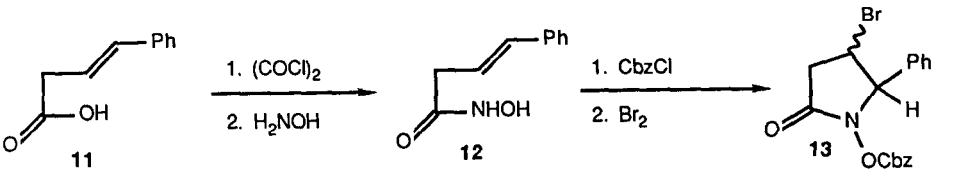
3,5-hexadienohydroxamate **1c** was prepared in a straightforward manner from deconjugated methyl sorbate 8.[8] (Scheme 3). Careful treatment of 8 with NH_2OH provided the desired hydroxamic acid 9[5] in 81% yield without reconjugation. Subsequent acylation with CbzCl provided **1c**[5] in 81% yield. The bromine induced cyclization provided β-lactam **10**[5] in nearly quantitative yield! This apparent 1,4-addition process was surprisingly clean considering all of the other reaction pathways possible.

Scheme 3



Noting the facile formation of β-lactams from all of the previous substrates (**1a-c**), we decided to further test the limits of the cyclization process by studying styrylacetohydroxamate **1d** (Scheme 4), since the γ-position would now also be benzylic. Styrylacetic acid (**11**) was converted to the hydroxamic acid 12 (78% overall yield) by first treatment with oxalyl chloride followed by hydroxylamine. Acylation with CbzCl provided **1d** in 93% yield. Reaction of **1d** with bromine under the usual conditions furnished a 2:1 diastereomeric mixture of γ-lactams **13**.[5] No β-lactam products were detected even in the crude reaction mixture.

Scheme 4



In summary, the oxidative cyclization of γ-substituted-β,γ-unsaturated hydroxamates is an efficient method for the synthesis of substituted β-lactams. The stereoelectronic control of the reaction, clearly demonstrated by the cyclization of **1a-c** to 4-membered rings instead of the corresponding five membered rings,[7] was disrupted only with the biased substrate **1d**. The utility of this methodology for the synthesis of a variety of heterocycles is being explored.

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References and Notes.

‡Recipient of an NIH Research Career Development Award (1983 - 1988).

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4. Ganem's earlier description of the oxidative cyclization of β,γ-unsaturated tosyl amides included one example, a dihydrobenzoyl derivative: Biloski, A. J.; Wood, R. D.; Ganem, B. **J. Am. Chem. Soc. 1982**, 104, 3233.

5. Since nonchiral starting materials were used, all of the cyclization products obtained were racemic. However, a single (racemic) diastereomer of yet undefined stereochemistry, was obtained for **2b**. Another product was isolated from the cyclization of **1a**. The structure of this product has not yet been elucidated. Selected characterization data includes: **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93-1.03 (t, 3H), 1.96-2.13 (m, 2H), 2.88-2.98 (m, 2H), 5.32-6.25 (m, 2H); IR 3600-2400 br, 1635 cm^{-1}; mass spectrum. Exact mass, Calcd. 129.0789; found 129.078. **2a**: oil; ^{1}H NMR 200 MHz, $CDCl_3$) δ 0.96-1.07 (t, 3H, J = 6), 1.58-1.98 (m, 2H), 2.55-3.08 (ddd, 2H, J = 2, 6 and 14), 3.92-4.07 (m, 1H), 4.15-4.27 (m, 1H), 5.22 (s, 2H), 7.35 (s, 5H); ^{13}C NMR δ 11.26, 28.15, 37.97, 56.44, 61.56, 71.60, 128.28, 128.44, 128.79, 152.97, 162.92; IR (thin film) 1810, 1780 cm^{-1}. **6**: oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.87-3.23 (br m, 4H), 3.67 (s, 3H), 5.60-5.83 (m, 2H), 8-9 (br, 1H); IR (thin film) 3600-2400, 1735, 1650 cm^{-1}; ^{13}C NMR δ 36.55, 37.50, 51.90, 126.48, 126.67, 169.92, 172.60; mass spectrum (DCl/isobutane) 174 (M+1) 100%, 158 (M+1-16). **2b**: oil; NMR (90 MHz, $CDCl_3$/TMS) δ 2.16-3.27 (m, 4H), 3.7 (s, 3H), 4-4.2 (m, 2H), 5.27 (s, 2H), 7.43 (s, 10H); IR (thin film) 1805, 1780, 1735 cm^{-1}. **9** ^{1}H NMR (200 MHz, Acetone-d_6) δ 2.85-3.05 (d, 2H), 4.95-5.25 (m, 2H), 5.68-5.92 (m, 1H), 6.05-6.45 (m, 2H), the exchangable protons were not observed; IR ($CDCl_3$)3500-2500 ν br, 1630 cm^{-1}br; mass spectrum m/e 128 (M+1), 127 (M^+), 116 (M+1-16) 100%. **10**: oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.57-3.20 (ddd, 2H), 3.82-4.00 (m 2H), 4.47-4.60 (m, 1H), 5.24 (s, 2H), 5.70-6.15 (m, 2H), 7.37 (s, 5H); IR (thin film) 1798, 1775, 960 cm^{-1}; mass spectrum (DCl/isobutane) m/e, 340 (M+1), 300. **13**: oil; (2:1 mixture of diastereomers); major isomer; ^{1}H NMR (crude product mixture, since attempted chromatography resulted in decomposition, 300 MHz, $CDCl_3$) δ 3.13-3.53 (ddd, 2H), 4.35-4.45 (m, 1H), 5.20-5.24 (d, 1H), 5.30-5.35 (d, 1H), 5.70-5.80 (d, 1H), 7.22-7.55 (m, 10H); minor isomer: ^{1}H NMR (crude product mixture, 300 MHz, $CDCl_3$) δ 2.92-3.32 (ddd, 2H), 4.12-4.22 (m, 1H), 5.09-5.12 (d, 1H), 5.29 (s, 2H), 7.22-7.55 (m, 10H); IR (thin film) 1778, 1725 cm^{-1}.

6. Use of larger amounts of NH_2OH resulted in lower yields, presumably because of bishydroxamate formation. The desired monohydroxamate was isolated by concentrating the reaction mixture, dissolving the residue in methyl acetate and performing an acid / base extraction.

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