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OXIDATIVE CYCLIZATION OF β,γ-UNSATURATED O-ACYL HYDROXAMATES TO β-LACTAMS

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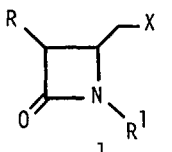
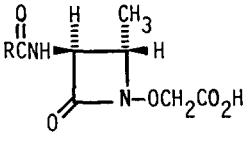
Summary: Reaction of O-Acyl vinylacetohydroxamates with bromine and base in aqueous acetonitrile provides a direct route to substituted 4-(bromomethyl)-N-hydroxy β-lactams.

The structural diversity of the many recently discovered β-lactam antibiotics has prompted the search for versatile and efficient syntheses of variously substituted β-lactams.[1] 4-(Halomethyl)-2-azetidinones **1** are useful intermediates for the synthesis of *nuclear analogues of penicillins and cephalosporins*,[2a] *carbapenems*,[2b] *and functionalized* monocyclic β-lactams.[2c] However, the 4-(halomethyl) group is usually introduced by a multistep sequence after synthesis of the β-lactam ring system.[2] Because of the recent demonstration of the significant biological activity of substituted N-hydroxy β-lactams (oxamazins **3**),[3a-c] we were especially interested in developing an efficient route to 4-(halomethyl)-N-hydroxy-2-azetidinones **2**. Herein, we report the direct oxidative cyclization of substituted β,γ-unsaturated hydroxamates to the corresponding substituted 4-(bromomethyl)-N-hydroxy β-lactams **10** (Scheme 2).



1 R^1=H, alkyl
2 R^1=OH



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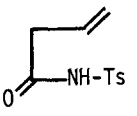

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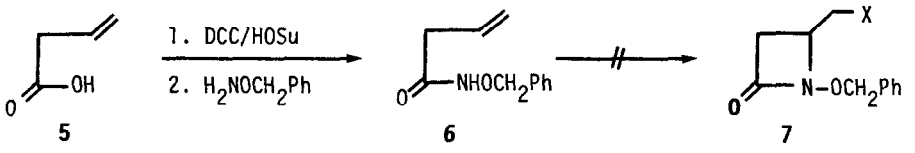
Although halolactonizations and related oxidative cyclizations of olefins are well known,[4a,b] early attempts to form lactams from olefins by similar procedures produced the lactones from the corresponding intermediate cyclic imidates instead.[4c,d] Recently, however, several efficient oxidative cyclizations of olefinic amides to lactams have been reported.[5a-c,6a,b] Especially interesting was Ganem's observation[6a] that the lowered pK of the carboxamide group of β,γ-unsaturated N-tosyl amides **4** promoted bromine induced oxidative cyclizations to β-lactams. Our previous success in utilizing the acidity of O-substituted hydroxamates to facilitate cyclization of β-hydroxy and β-halohydroxamates to β-lactams,[7] encouraged us to study the oxidative cyclization of β,γ-unsaturated hydroxamates as a route to the desired 4-(halomethyl)-N-hydroxy-2-azetidinone derivatives **2**. Since O-benzyl hydroxamates

(pK~9-10) had functioned so well in our previous work,[7] we first attempted oxidative cyclizations of O-benzyl vinyl acetohydroxamate **6**. This substrate was readily prepared by DCC/N-hydroxy succinimide activation of vinyl acetic acid **5**[8] followed by reaction of O-benzylhydroxylamine (Scheme 1). Unfortunately, all attempts to convert **6** to the β-lactam **7** by the use of halolactonization or mercuration conditions resulted in either formation of complex mixtures or recovery of starting materials.

Scheme 1

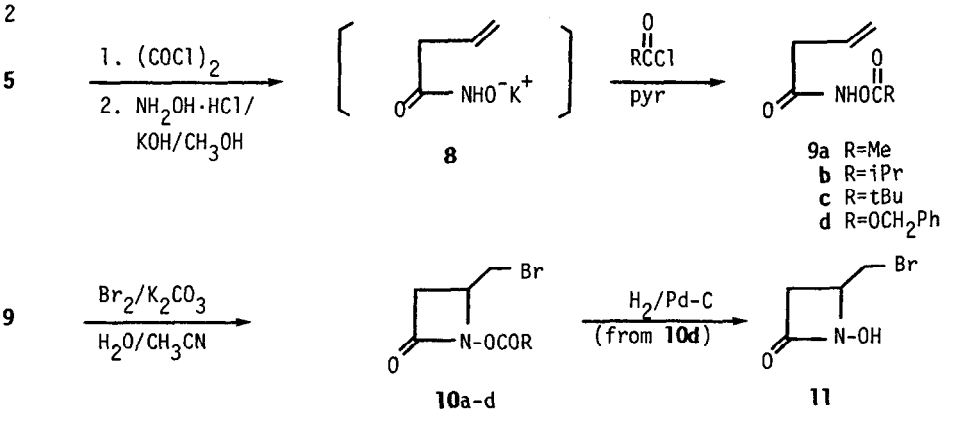


5 **6** **7**

Although they are prone to Lossen rearrangement,[9] the increased acidity of O-acyl hydroxamates (pK 6-7)[7,9] prompted us to attempt the oxidative cyclization of O-acylhydroxamates **9a-d**. Since O-acetyl and other O-acyl hydroxylamines require multistep syntheses and are often unstable,[9] we developed the alternate route to **9a-d** shown in Scheme 2.[10] Indeed, subjection of the O-acetyl derivative **9a** to Ganem's cyclization conditions (K_2CO_3, Br_2, H_2O:CH_2Cl_2 (1:1), 5 min) provided the desired β-lactam **10a** in 73% isolated yield, with no detectable Lossen rearrangement products. Unfortunately the O-acetyl β-lactam **10a** itself was unstable upon storage at room temperature longer than one day.

In order to test the generality of this oxidative cyclization, and to obtain stable β-lactams suitable for eventual further elaboration, several other hydroxamates (**9b-d**) were prepared and studied. Suprisingly, subjection of **9b-d** to the same conditions used for **9a** produced mixtures containing little or no β-lactam products. After studying several different solvent systems (CH_2Cl_2, THF, CH_3OH, CH_3CN, all with or without added H_2O), 5-10% aqueous CH_3CN was found to promote efficient cyclization of all hydroxamates **9a-d**[10] to the corresponding β-lactams **10a-d**[10] (75-90% yields) upon treatment with Br_2/base under carefully controlled conditions.

Scheme 2



Preparative scale procedures were developed for the series **9d** → **10d** → **11** since the hydroxamate **9d** is a stable crystalline solid and the β-lactam **10d** can be readily converted to the desired N-hydroxy β-lactam **11** by catalytic hydrogenation. Thus, 10 ml of vinyl acetic acid (**5**, 117.7 mmole) was added to a dry flask fitted with a stir bar and $CaCl_2$ drying tube. The flask was cooled to 0°C and 11.2 ml (109 mole %) of oxalyl chloride was added slowly (neat). The mixture was stirred at 0°C for 2 h and then at room temperature for 40-48 h. The resulting pale yellow liquid was added over a period of 5 to 8 min to a premixed and cooled (0°C) solution of 8.2 g (100 mole %) of $H_2NOH{\cdot}HCl$ and 19.9g (205 mole %) of KOH (prepared separately in 100 and 75 ml of CH_3OH respectively). The cooling bath was removed and the mixture was allowed to stir for 15-20 min. Filtration and concentration gave the crude hydroxamate **8** as a pale yellow oil. The oil was dissolved in 250 ml of dry THF, cooled to 0°C and 10 ml (105 mole %) of pyridine was added with stirring. After 5 min, 18.6 ml (105 mole % at 95% purity) of neat carbobenzoxy chloride was added over 30 min. The solution was stirred for another 60-90 min at RT and then filtered. The filtrate was concentrated to one fourth of its volume, taken up in ethyl acetate, and washed successively with three portions of H_2O, two portions of 1% HCl and two portions of brine. After drying over $MgSO_4$, filtration, evaporation and recrystallization from ethyl acetate - hexanes, hydroxamate **9d** was obtained in 82-87% overall yield from vinyl acetic acid **5**.

To a solution of the hydroxamate **9d** (10-15 mmol) in CH_3CN (~0.05 mmol of **9d**/ml) was added 105 mole % of solid K_2CO_3 followed by 5-10 volume % of H_2O. The mixture was stirred vigorously for 20-30 sec, then 110 mole % of Br_2 in CH_3CN (1 mmol/ml) was added through a dropping funnel over a period of 2-4 min with continued vigorous stirring. After the addition, the mixture was stirred for 1 min before being transferred to a separatory funnel containing ethyl acetate (10 ml/mmol of starting **9d**). The mixture was then successively washed with H_2O, 10% Na_2SO_3 and brine before drying over $MgSO_4$, filtration, chromatography (silica/ethyl acetate - hexane) and crystallization (ethyl acetate - hexanes) to provide **10d** in 80-90% yield. Standard hydrogenation (H_2,Pd-C/MeOH) provided the N-hydroxy β-lactam **11** (> 90%).

Thus, oxidative cyclization of O-acyl-β,γ-unsaturated hydroxamates **9** under carefully controlled conditions provides an efficient route to substituted 4-(bromomethyl)-N-hydroxy-2-azetidinones **10**. Extensions to the synthesis of a variety of 3- and 4-substituted monocyclic and bicyclic β-lactams will be described subsequently.

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10. Selected characterization data includes (90 MHz NMR, unless otherwise specified): **8**: IR, 3600-2500 v broad, 1640 cm^{-1}; NMR, 2.96 (d, 2H), 4.94-5.28 (m, 2H), 5.66-6.25 (m, 1H), 9-10(b, 1H). **9a**: IR, 3200 broad, 1800, 1680 cm^{-1}; NMR, 2.16 (s, 3H), 2.96-3.16 (d, 2H), 5.1-5.37 (m, 2H), 5.68-6.2 (m, 1H), 10.2-10.8 (b, 1H). **9b** NMR, 1.23 (d, 6H), 2.76 (Sept, 1H), 3.0-3.17 (d, 2H), 5.1-5.33 (m, 2H), 5.7-6.20 (m, 1H). **9c** NMR, 1.25 (s, 9H), 3.00-3.23 (d, 2H). 5.03-5.33 (m, 2H), 5.7-6.20 (m, 1H), 10.3 (b, 1H). **9d** Mp. 71-74°C; IR, 3210 br, 1800, 1690 cm^{-1}; NMR (200 MHz), 3.025-3.14 (d, 2H), 5.2-5.35 (m, 4H), 5.8-6.03 (m, 1H), 7.38 (s, 5H), 8.85 (b, 1H). **10a**: IR, 1820, 1780 cm^{-1}; NMR, 2.22 (s, 3H), 2.62-3.24 (ddd, 2H), 3.43-3.8 (m 2H), 4.22-4.44 (m, 1H). **10b**: NMR, 1.25 (d, 6H), 2.43-2.96 (m, 3H), 3.4-3.87 (m, 2H), 4.23-4.5 (m, 1H). **10c**: NMR, 1.30 (s, 9H), 2.56-3.33 (ddd, 2H), 3.36-3.83 (m, 2H), 4.23-4.5 (m, 1H). **10d**: Mp 73.5-75.5°C; IR, 1815, 1785 cm^{-1}; NMR (200MHz), 2.61-3.16 (ddd, 2H), 3.45-3.71 (ddd, 2H), 4.28-4.41 (m, 1H), 5.21 (s, 2H), 7.39 (s, 5H). **11**: IR, 3700-2400 v broad, 1750 cm^{-1}; NMR, 2.47-3.07 (ddd, 2H), 3.13-3.90 (m, 2H), 4.03-4.3 (m, 1H), 8.3-9.0 (b, 1H).

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