Diastereoselective synthesis of a hydroxamate containing bicyclo-[3.2.0] β-lactam aminal via ruthenium alkene isomerization and Pd(II)-catalyzed oxidative amidation

Maria O. Jobbins, Mark W. Majewski, Allen G. Oliver, Marvin J. Miller

PII: S0040-4039(14)02138-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.12.072
Reference: TETL 45596

To appear in: *Tetrahedron Letters*

Received Date: 15 November 2014
Revised Date: 11 December 2014
Accepted Date: 12 December 2014

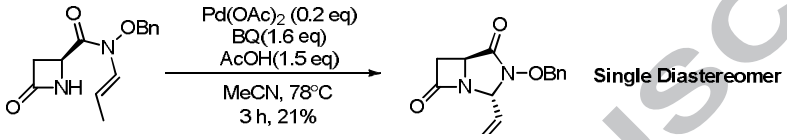
Please cite this article as: Jobbins, M.O., Majewski, M.W., Oliver, A.G., Miller, M.J., Diastereoselective synthesis of a hydroxamate containing bicyclo-[3.2.0] β-lactam aminal via ruthenium alkene isomerization and Pd(II)-catalyzed oxidative amidation, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.12.072

Graphical Abstract

Diastereoselective synthesis of a hydroxamate containing bicyclo-[3.2.0] β-lactam aminal via ruthenium alkene isomerization and Pd(II)-catalyzed oxidative amidation

Leave this area blank for abstract info.

Maria O. Jobbins, Mark W. Majewski, Allen G. Oliver, and Marvin J. Miller*



Tetrahedron Letters
journal homepage: www.elsevier.com

Diastereoselective synthesis of a hydroxamate containing bicyclo-[3.2.0] β-lactam aminal via ruthenium alkene isomerization and Pd(II)-catalyzed oxidative amidation

Maria O. Jobbins, Mark W. Majewski, Allen G. Oliver, and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, 46556, USA
Telephone: 574 631 7571
Fax: 574 631 6652
Email: mmiller1@nd.edu

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
β-Lactam, bicyclic β-Lactam, hydroxamate, ring closure, aminal oxidative amidation

ABSTRACT

With antibiotic resistance on the rise, the need for new medicinal scaffolds is needed. The synthesis of an aminal bicyclic β-lactam core is described. The key synthetic step is Pd(II)-catalyzed oxidative amidation. The product is a single diastereomer, confirmed by x-ray crystallography.

1. Introduction

The β-lactam family continues to be a mainstay in the never ending microbial war. Despite being discovered over 80 years ago, this class of antibiotics has almost single-handedly substantially increased life expectancy. First starting out with the classic penam (penicillin) core, this family has undergone significant evolution in response to bacterial resistance. Bacteria have a multitude of mechanisms which render β-lactams inactive, such as porin depletion and β-lactamases which inactivate β-lactams via hydrolysis.[1] Thus there is dire need to both innovate and improve upon the current β-lactam medicinal arsenal. Herein we report the synthesis of a bicyclic aminal β-lactam core featuring hydroxamate functionality.

We have become interested in the incorporation of hydroxamates and hydroxamic acids into bicyclic β-lactam scaffolds. Recently, we reported on the syntheses of hydroxamate and hydroxamic acid containing bicyclic β-lactams via palladium-catalyzed oxidative amidation of alkenes.[2] With this work in mind, we were interested to see if the methodology could be extended to other bicyclic hydroxamate containing β-lactam cores. Of particular interest was the aminal core, one in which the hydroxamate functionality has been moved around the ring (Figure 1).

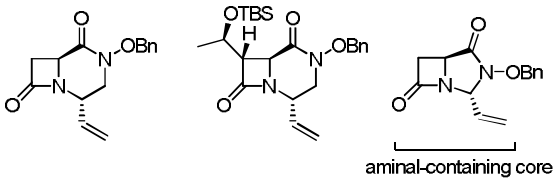
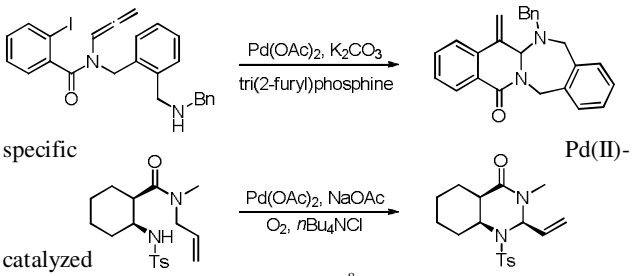


Figure 1. Previously Reported Cores and Proposed Core.

The aminal, or *N,N*-acetal[3] functional group has been previously incorporated into bicyclic β-lactams.[4-5] As a ready example, Branch and Pearson utilized a 1,3-dipolar cycloaddition which underwent thermolysis to access amide-containing bicyclic-[3.2.0] and [4.2.0] β-lactams. Additionally, there have been reports of transition metal catalyzed amidations to give aminal cores of varying sizes. Grigg synthesized aminals through Pd(0)-catalyzed cyclization of allenes with aryl iodides, followed by attack of an amine on the resulting π-allyl complex. (Scheme 1).[6-7] Balazs demonstrated that aminal heterocycles of varying size could be obtained when tosyl protected cis and trans *N*-allyl-2-aminocyclohexanecarboxamides were subjected to



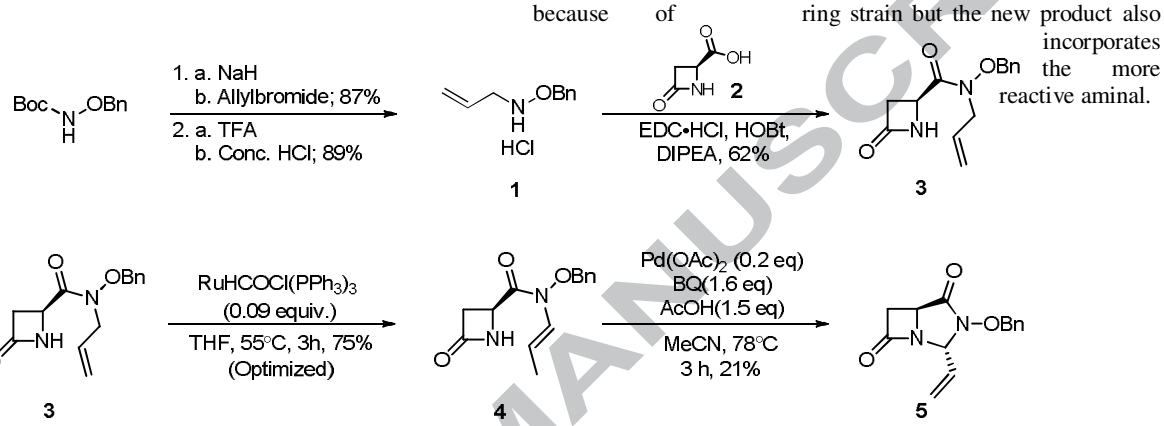
specific Pd(II)-catalyzed intramolecular oxidative conditions.[8]

Scheme 1. Sample Precedented Cyclizations to Afford Aminals.

2. Synthesis and Discussion

While our earlier studies[2] provided methodology for direct incorporation of a hydroxamate into a bicyclic β-lactam and the precedents noted above indicated that cyclic aminals can be

formed using Pd-mediated chemistry, generation of a highly strained bicyclic aminal with one nitrogen as part of a β-lactam and the other a hydroxamate was anticipated to be a significant test of the methodology and inherent stability of the potential product. With these concerns in mind, we decided to first test the ability to form the novel bicyclic β-lactam aminal core. Our successful synthesis of the aminal bicyclic core is shown in Scheme 2. First *N*-Boc-*O*-benzylhydroxylamine was alkylated with allylbromide followed by treatment with TFA and concentrated HCl to give *N*-allyl-*O*-benzylhydroxylamine



Scheme 2. Synthesis of Bicyclo-[3.2.0] β-lactam Aminal.

hydrochloride[9] **1** in good yield. This hydroxylamine was then coupled to 4-carboxy β-lactam **2**[10] with EDC•HCl and HOBt to give β-lactam hydroxamate **3**. Alkene isomerization[11-12] conditions were then screened (Table 1). Among the catalysts screened, $RuHCOCl(PPh_3)_3$[13-14] (0.09 equiv.) in refluxing THF with careful NMR monitoring resulted in an optimized 75% yield of **4**. With **4** in hand, we then tested conditions for cyclization to aminal **5**. Aza-Wacker cyclization conditions ($Pd(OAc)_2$, pyridine, and O_2) resulted in the decomposition of **4**. However Pd(II)-catalyzed oxidative amidation conditions ($Pd(OAc)_2$, 1,4-benzoquinone, and AcOH) in freshly distilled MeCN at 50˚C for 22 h gave **5** with an initial yield of 18%. The yield was slightly enhanced by changing both the Pd loading and reaction time (Scheme 2).

Table 1. Conditions Employed for Alkene Isomerization .

Catalyst, Additive(s)	Solvent	Conditions	Results
$RhCl(PPh_3)_3$ DBU, Sieves	EtOH	40˚C, 23 h	No Rxn
Grubbs 2nd Generation	MeOH	60˚C, 20 h	No Rxn
$RuHCOCl(PPh_3)_3$ (0.03 eq)	THF	60˚C, 4 h	Mixture of **3**&**4**
$RuHCOCl(PPh_3)_3$ (0.03 eq)	THF	60˚C, 28 h	Decomposition
$RuHCOCl(PPh_3)_3$ (0.09 eq)	THF	50-60˚C, 3 h	**4**, 71 %

While we were pleased that the β-lactam-containing aminal core could be made, low yields during the cyclization process reinforced our initial concerns about the inherent stability of this unique system. Indeed, while studying this reaction, we noticed a persistent by-product. Based on our preliminary data, we hypothesized that **5** may engage in a competitive elimination to give benzaldehyde. To further substantiate this notion we performed a benzaldehyde trapping experiment. During the reaction for conversion of **4** to **5**, an aliquot was removed and added to a stirring solution of phenylhydrazine. LC/MS analysis of this reaction mixture confirmed the formation of the phenylhydrazone from reaction with released benzaldehyde. With this data, a plausible mechanism is proposed in Figure 2. Thus, as expected, the bicyclo-[3.2.0] β-lactam aminal is inherently more reactive than our previously reported hydroxamate-containing bicycle-[4.2.0] β-lactam, not only because of ring strain but the new product also incorporates the more reactive aminal.

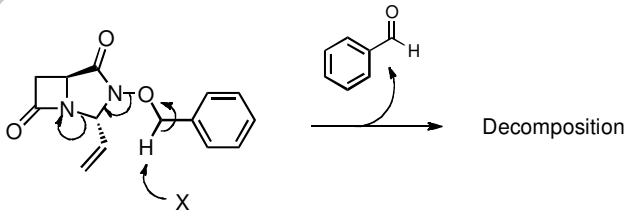


Figure 2. Proposed Mechanism for the Formation of Benzaldehyde.

Lastly, the stereochemistry of **5** was confirmed with X-ray crystallography. We were delighted to see that only the *trans* diastereomer was formed, corresponding to the configuration normally associated with classic β-lactam scaffolds that are active antibiotics.[15]

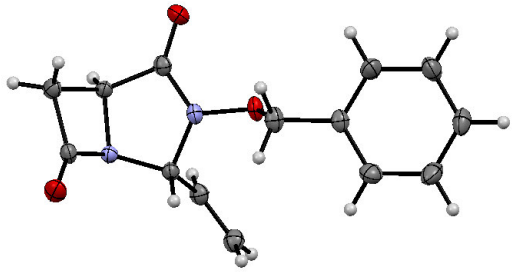


Figure 3. X-ray Structure for Bicyclo-[3.2.0] β-Lactam Aminal **4.**

To close, we have developed diastereoselective methodology for the synthesis of a hydroxamate containing bicyclo-[3.2.0] β-lactam aminal. Future work includes both the extension of our methodology to synthesize other hydroxamate-containing β-lactam cores and the incorporation of peripheral functionalization.

Acknowledgments

M.O.D. thanks Eli Lilly for supporting this research through a graduate fellowship. M.W.M acknowledges an ECK Institute Global Health Fellowship. We also gratefully acknowledge Nonka Sevova and Dr. Bill Boggess (Mass Spectrometry and Proteomics Facility, UND) for mass spectroscopic analyses.
We also are pleased to dedicate this manuscript to the memory of Professor Harry H. Wasserman. Not only was Harry an enthusiastic supporter of organic chemistry, including beta-lactam chemistry, but his service as long-time editor of *Tetrahedron Letters*, had a positive impact on many of us and our profession.

References and notes

1. Llarrull, L. I.; Testero, S.A.; Fisher, J.F.; Mobashery, S. *Curr. Opin. Microbiol.* **2010,** *13,* 551-557.
2. Jobbins, M.O.; Miller, M.J. *J. Org. Chem.* **2014**, *79*, 1620-1625.
3. Hiersemann, M.; Katritzky, A. R.; Taylor, R. J. K. *Functions Bearing Two Nitrogens;* Elsevier: Amsterdam, 2005; Vol. 4, pp. 411-441.
4. Brown, D.; Brown, G.; Andrews, M.; Large, J.; Urban, D.; Butts, C.; Hales, N.; Gallagher, T. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2014-2021.
5. Branch, C.; Pearson, M. *J, Chem.. Soc. Perkin Trans. 1* **1986**, 1077-1095.
6. Grigg, R.; Sridharan, V.; Xu, L. *J. Chem. Soc. Chem. Comm.* **1995**, 1903-1904.
7. Grigg, R.; Koppen, I.; Rasparini, M.; Sridharan, V. *Chem. Comm.* **2001**, 964-965.
8. Balazs, A.; Hetenyi, A.; Szakonyi, Z.; Sillanpaa, R.; Fulop, F. *Chem. Eur. J.* **2009**, *15*, 7376-7381.
9. Sulsky, R.; Demers, J. *Tetrahedron Lett.* **1989**, *30*, 31-34.
10. Baldwin, J.; Adlington, R.; Gollins, D.; Schofield, C. *Tetrahedron* **1990**, *46*, 4733-4748.
11. Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819-1841.
12. Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014-1017.
13. Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperezyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257-5261.
14. Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270-1281.
15. Page, M.I. *Acc. Chem. Res.* **1984**, *17*, 144-151.

Highlights:

- Emerging resistance to antibiotics requires development of new antibiotic scaffolds
- Methodology is described for synthesis of a new bicyclic beta-lactam core structure
- Oxidative amidation of a monocyclic beta-lactam produces a new bicyclic core