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Cycloaddition of Δ^2-Thiazolines and Acyl Ketenes under Acidic Conditions Results in Bicyclic 1,3-Oxazinones and Not 6-Acylpenams as Earlier Reported

Nils Pemberton,[†] Hans Emtenäs,[†] Dan Boström,[‡] Peter J. Domaille,[§] William A. Greenberg,[§] Michael D. Levin,[§] Zuolin Zhu,[§] and Fredrik Almqvist*,[†]

Organic Chemistry and Inorganic Chemistry, Umeå University, S-901 87 Umeå, Sweden, and Diversa Corporation, 4955 Directors Place, San Diego, California 92121

fredrik.almqvist@chem.umu.se

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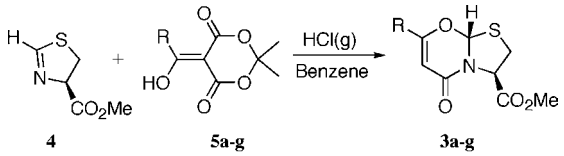
ABSTRACT



Optically active Δ^2-thiazolines 4 were previously reported to react with acyl Meldrum's acid derivatives 5 under acidic conditions (HCl (g) in benzene) to stereoselectively give 6-acylpenams 1. Recently we have discovered that the structure elucidation of these compounds was incorrect. Thus, we report new data showing that instead of acyl β-lactams, the optically active isomers 3*R*,9*R*-1,3-oxazinones 3a–g are obtained stereoselectively in 38–93% yields.

Recently, compounds able to interfere with bacterial chaperones necessary for pilus biogenesis have been designed and synthesized in our laboratories. The main focus has been to advance bicyclic 2-pyridones in this direction, and new synthetic methods suitable for library synthesis have been developed.[1] Earlier in this process, computer-aided design suggested acyl-substituted bicyclic β-lactams, 6-acylpenams **1**, as suitable scaffolds for the development of bacterial chaperone inhibitors. Yamamoto et al. had shown that monocyclic acyl-substituted β-lactams **2** (Figure 1) could be prepared by an acylketene/imine cycloaddition under acidic conditions (HCl (g) in benzene).[2] Since we were aiming for 6-acylpenams **1**, we used the same synthetic protocol, only changing the acyclic imine to an optically active Δ^2-thiazoline (Scheme 1). We were happy to find a highly selective conversion to an optically active compound that had the correct molecular mass together with ^{1}H and ^{13}C NMR spectroscopic data that appeared to support the desired product. This stereoselective synthesis was described in *Organic Letters* in 2000, showing that the synthesis worked well with yields >80% in several cases.[3] Further work to

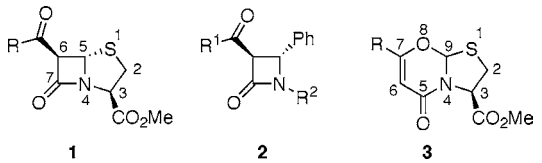


Figure 1.

[†] Organic Chemistry.
[‡] Inorganic Chemistry.
[§] Diversa Corporation.

(1) (a) Emtenas, H.; Alderin, L.; Almqvist, F. *J. Org. Chem.* **2001**, *66*, 6756−6761. (b) Emtenas, H.; Ahlin, K.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *J. Comb. Chem.* **2002**, *4*, 630−639. (c) Emtenas, H.; Taflin, C.; Almqvist, F. *Mol. Diversity* **2003**, *7*, 165−169.

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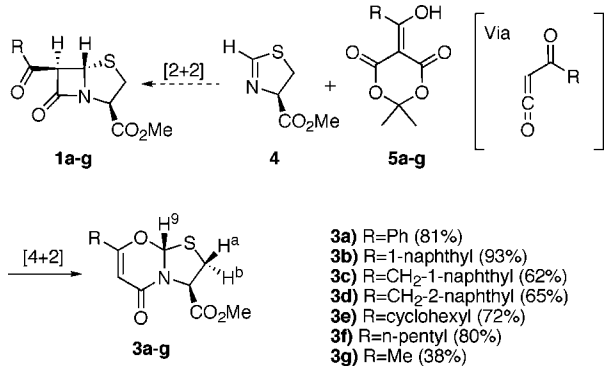
Scheme 1



hydrolyze the methyl ester showed that the compounds were very sensitive, as one might expect from an acyl-substituted penam, and a mild and quick saponification procedure was developed to obtain the desired carboxylic acids.[4]

Lately we have studied different substituted cyclic imines and their reactions with acyl ketenes generated from acyl Meldrum's acids. Here we discovered that together with 2-pyridones, a small amount of 1,3-oxazinone was formed under similar conditions as had been published earlier.These results shows that the outcome of the reaction is dependent on the nature of the imine, as Yamamoto clearly showed that acyclic imines yield monocyclic acyl β-lactams **2**.[2] In addition, subsequent attempts to modify the 6-benzoylpenam **1a** were unsuccessful. Various attempts to reduce the acyl functionality were unproductive, as were attempts to prepare the corresponding enol phosphate by using conditions (LDA or NaH, $(EtO)_2POCl$, THF, 0 °C) that successfully formed the enol phosphate of *tert*-butyl acetoacetate.

These results led us to question the assignment of a 6-acylpenam structure to the product of the reaction between acyl Meldrum's acids **5** and Δ^2-thiazolines[3] **4** and to reexamine the NMR spectral data on which this assignment had been based. 6-Acetylpenicillinate has been previously prepared, and the chemical shifts of the 5,6 protons were reported[5] to be δ 5.42/4.60 ($J = 4$ Hz) and δ 5.63/4.38 ($J = 2$ Hz) for the *cis* and *trans* isomers, respectively. This was significantly different from the δ 6.7/6.0 ($J = 0$ Hz, broad singlet) observed in our case. All together, these findings made us realize that the structure elucidation for the published 6-acylpenams **1** was incorrect. We now present new data that show that the cycloaddition of Δ^2-thiazolines **4** and acylketenes results in a stereoselective synthesis of optically active bicyclic 1,3-oxazinones **3** instead of the earlier published 6-acylpenams **1**.

1,3-Oxazinones are isomers to the acyl-substituted β-lactams with the same molecular mass, and they are suggested to be formed via a concerted [4 + 2] cycloaddition instead of the [2 + 2] cycloaddition that results in β-lactam formation (Scheme 1). Alternatively, the process can be stepwise where the β-lactams are formed via an enol attacking the imine carbon forming a carbon−carbon bond, while the oxazinones corresponds to the oxygen alkylation product.

Recently, a thorough investigation of the mechanisms involved in the reactions between different nucleophiles and acyl ketenes, generated from acyl Meldrum's acids, was published.[6] Also here a 6-acylpenam was reported to be formed when a Δ^2-thiazoline was reacted with an acyl Meldrum's acid derivative under identical conditions as we had reported earlier.[3,7]

To further prove that oxazinones **3a**−**g** were formed instead of the earlier reported 6-acylpenams **1**, additional NMR experiments were required. Thus, the putative 6-benzoylpenam product **1a** was subjected to a series of NMR experiments. Though ^{1}H, ^{13}C-APT, ^{13}C-^{1}H HSQC and ^{13}C-^{1}H HMBC spectra allowed the assignment of all atoms, the two halves of the structure could not be connected to one another on the basis of these experiments alone and the structural ambiguity was not resolved. However, inclusion of a 2D ^{13}C−^{13}C INADEQUATE spectrum clearly identified the one bond connectivity of both C5−C6 and C6−C7 in the oxazinone with the total absence of any C9 connectivity. The corresponding C5−C6 connectivity in the β-lactam structure was not observed, thus ruling it out (Figure 1).

Still, these experiments could not give information regarding the absolute stereochemistry of the product. To determine the absolute configuration at the newly formed stereocenter in the oxazinone, NOE and ROE experiments were conducted. Unfortunately, the intensity difference between the (H9, Ha) and (H9, Hb) (Scheme 1) was too small to permit unambiguous stereochemical assignment. We were therefore delighted when compound **3c** crystallized from diethyl ether to give crystals with properties suitable for X-ray crystallography. Thus, a *syn* relationship between H9 (Scheme 1) and the methyl ester could be established from the X-ray data (Figure 2) resulting in the 3*R*,9*R* stereoisomer.

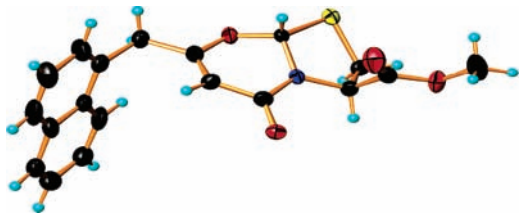


Figure 2. X-ray structure of 1,3-oxazinone **3c**.

In conclusion, the reaction between Δ^2-thiazolines **4** and acyl Meldrum's acid derivatives **5** under acidic conditions

(2) Yamamoto, Y.; Watanabe, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1871−1879.
(3) Emtenas, H.; Soto, G.; Hultgren, S. J.; Marshall, G. R.; Almqvist, F. *Org. Lett.* **2000**, *2*, 2065−2067.
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results in optically active bicyclic 1,3-oxazinones **3a**−**g** in 38−93% yield with complete stereoselectivity.[8]

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Supporting Information Available: Experimental procedures, $^{13}C-^{13}C$ INADEQUATE characterization data, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) This specific compound has not been synthesized and characterized in our laboratory.

(8) Compounds **3b,d,e,g** were also confirmed as oxazinones by comparison of ^{1}H NMR, ^{13}C NMR, and HMBC data, which were in agreement with the data recorded for **3a** and **3c**.