

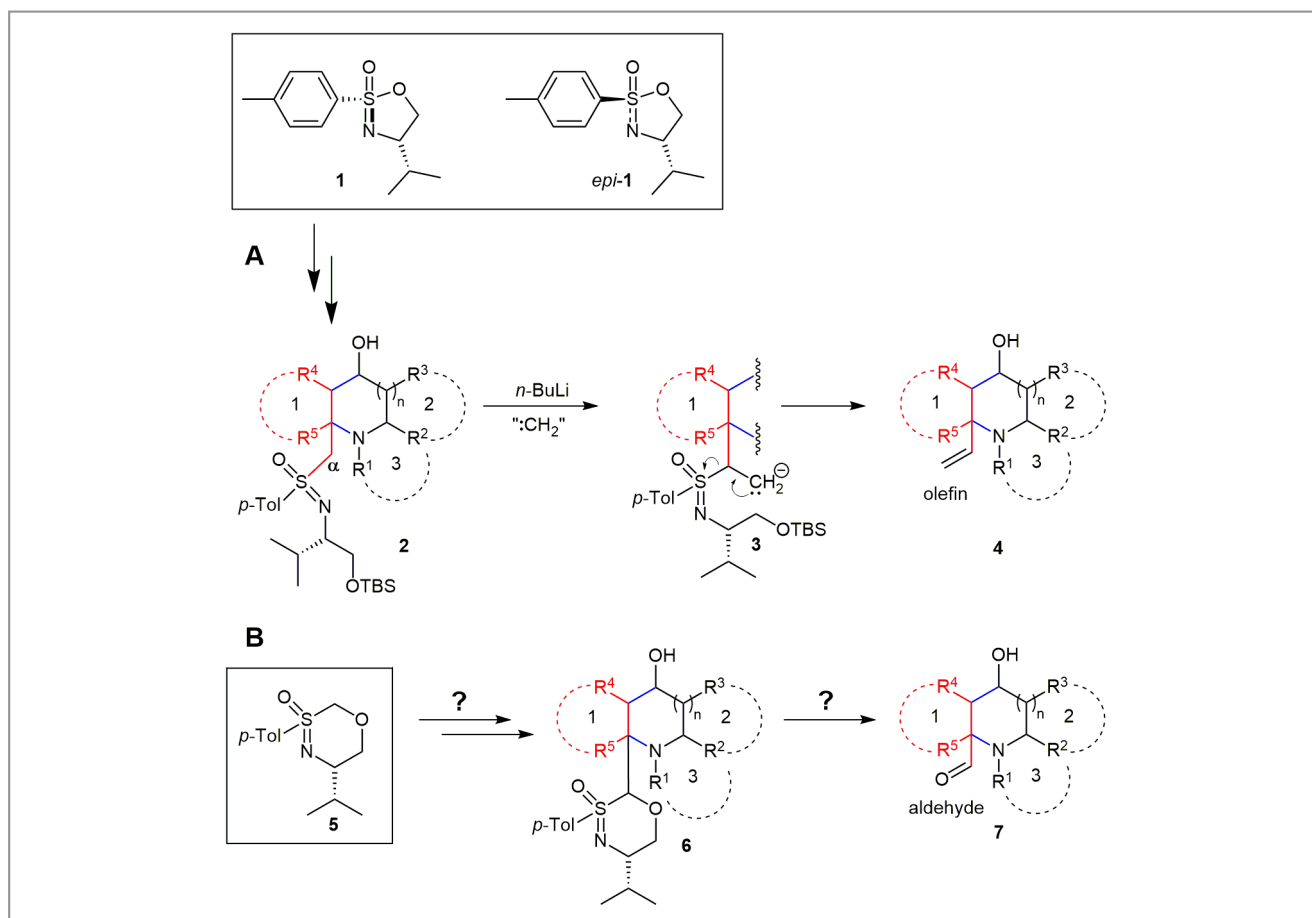
3-Oxo-[1,3λ⁶,4]-oxathiazines: A Novel Class of Heterocyclic S,O-Acetals

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About 30 years ago, during his Ph.D. work, in an attempt to prepare enantiomerically pure sulfonimidoylfluorides, Professor Michael Reggelin of the Technische Universität Darmstadt (Germany) serendipitously synthesized the first cyclic sulfonimidates **1** and *epi-1* (Scheme 1).¹

Since that initial discovery, both *S*-epimeric compounds and derivatives thereof have proven to be valuable starting materials for the synthesis of enantiomerically pure sulfoximines in general and 2-alkenyl sulfoximines in particular.² “These latter compounds are of special importance, because

their preparation via imination of allylic sulfoxides is severely hampered by the racemizing [2,3]-sigmatropic rearrangement (Mislow rearrangement) they tend to undergo,” explained Professor Reggelin. He continued: “Moreover, we found that titanated 2-alkenylsulfoximines can be γ -hydroxyalkylated with exceptional diastereoselectivity and the resulting products were found to be valuable intermediates for the synthesis of highly substituted polyheterocyclic ring systems like **2** (Scheme 1).^{2d,3} Up to this point everything worked out very well but the removal of the sulfonimidoyl auxiliary turned out



Scheme 1 (A) The first enantiomerically pure cyclic sulfonimidates and their successful elaboration into highly substituted polyheterocyclic ring systems; (B) Proposed conversion of a hypothetical oxathiazine **5** into aldehydes **7** via S,O-acetal **6**

to be a nightmare! The α -carbon in **2** is in a neopentyl position rendering nucleophilic substitutions impossible (even after electrophilic activation of the sulfoximine). The carbon can be deprotonated, but with the exception of a deuteron no electrophile reacts there. Only reductions with strong reducing agents like aluminum amalgam, Raney nickel or samarium(II) iodide successfully removed the sulfur yielding angular methylylated compounds.^{2d,4} Obviously this chemistry was rather limited and the group therefore made efforts to find desulfurations with concomitant production of a useful functional group. One successful solution delivering an angular vinyl group is indicated in Scheme 1. Reaction of the deprotonated α -position with a methylene source prepared the system to undergo a β -elimination to the desired olefin **4**.⁵

"At the same time we thought about possibilities to involve the auxiliary itself in its own removal!," remarked Professor Reggelin, continuing: "We reasoned that if we could manage to prepare the α -oxygenated sulfoximines **6** instead of the known derivatives **2** with the acyclic N-bound side chain, a simple hydrolysis reaction should release the auxiliary accompanied by the production of a valuable formyl group. For this chemistry to work we identified the 3-oxo-oxathiazines **5** as potential starting materials. To our surprise these heterocycles were unknown in 2006 (and still were in 2016). Therefore, we developed a procedure to use the sulfonimidates **1** for their synthesis."

Based on Matteson's work⁶ on chloromethylolithium in the mid-1980s, the group tried to use the sulfonimidates as electrophiles in Barbier-type reactions with chloriodomethane and *n*-BuLi (Scheme 2).

It was indeed possible to convert the sulfonimidates **1** and *epi-1* into the target oxathiazines **5** and *epi-5* by refluxing the chloromethyl sulfoximine intermediates **8** and *epi-8* in the

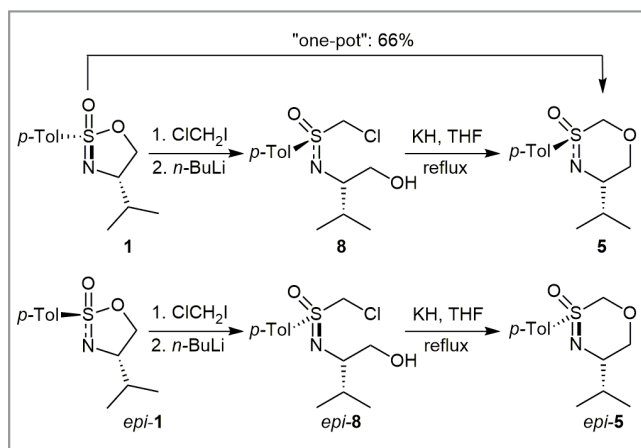
presence of potassium hydride in THF. Professor Reggelin said: "The relative and absolute configurations of the chlorides as well as the final products were verified by crystal structure analyses. Finally, we found that a *one-pot* procedure, avoiding yield losses due to work-up problems with the intermediates **8**, was the superior variant capable of maximizing yield and minimizing the number of steps (Scheme 2)."

"At the time we did these experiments, methodological progress of sulfoximine chemistry was at the center of our interests and efforts. Indeed, after the successful synthesis of the target heterocycles we did some work along the lines depicted in Scheme 1, but we stopped this after Jochen K hl left the group," said Professor Reggelin. Instead, the group changed their interests from stoichiometric to catalytic applications of sulfoximines.⁷ "However, this also changed because of the newly aroused interest of the chemical industry in this neglected functional group," explained Professor Reggelin.⁸ "The sulfoximines themselves became objects of interest and not the compounds prepared with their assistance." Professor Reggelin concluded: "Due to the recent industrial interest in this area, we think that sulfoximine chemistry will experience a renaissance, as will be the case for the even more 'exotic' chiral sulfur(VI) derivatives like sulfonimidamides or sulfur diimides. A strong hint that this is likely to happen is the enormous activity in the field (at the moment the 2013 article of L cking has been cited 72 times!)"⁸ even from groups other than the 'usual suspects' (C. Bolm and M. Harmata to name only two of the latter)."

Matteson funnel

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Scheme 2 The carbenoid route to the oxathiazin-S-oxides **5**

About the authors



Prof. M. Reggelin

Michael Reggelin was born in Elbingerde/Harz (Germany) in 1960. He received his undergraduate education at the universities of Giessen and Göttingen (Germany) and graduated from the University of Kiel (Germany), receiving his Ph.D. with Professor D. Hoppe in 1989. After postdoctoral work at the Technical University of Munich (Germany) with Professor H. Kessler, he completed his Habilitation in 1997 at the University of Frankfurt (Germany) in Professor Griesinger's group. In 1998, he was appointed C3 Professor at the University of Mainz (Germany) and since 2001 he holds his current position as C4 Professor of Chemistry at the TU Darmstadt (Germany). Professor Reggelin's research interests are: (a) development of new stereosymmetric reactions, asymmetric allyl transfer reactions, asymmetric catalysis with helically chiral ligands, and development of sulfoximine-based chiral ligands; (b) NMR spectroscopy in anisotropic media, development of new polymeric chiral alignment media; and (c) development of new materials for organic electronics applications.



Dr. J. Kühl

Jochen Kühl was born in Münster (Germany) in 1972. He studied chemistry at the Westfälische Wilhelms Universität in Münster (Germany), then joined the group of Professor E.-U. Würthwein working on his diploma thesis. He received his diploma degree in 2001 after which he moved to TU Darmstadt (Germany) where he received his Ph.D. under the supervision of Professor M. Reggelin in 2008. Currently, he is working as a project manager, responsible for the supervision of the reconstruction of the chemical department buildings at the TU Darmstadt (Germany).