Ring-Closing Metathesis (RCM) for the Synthesis of Cyclic Sulfoximines

Carsten Bolm, a Hélène Villar
Institut für Organische Chemie, RWTH Aachen, Landoltweg 1, 52056 Aachen, Germany
Fax +49(241)8092391; E-mail: carsten.bolm@oc.rwth-aachen.de
Received 9 February 2005
This paper is dedicated to Professor Dr. Bernd Giese on the occasion of his 65th anniversary

Abstract: Chiral heterocycles can be prepared starting from doubly unsaturated sulfoximine derivatives by ring-closing metathesis reaction in good yields.

Key words: catalysis, heterocycles, macrocycles, ring-closing metathesis, sulfoximines

Sulfoximines are useful sulfur reagents in asymmetric synthesis and biological chemistry. Since their discovery in 1946, cyclic sulfoximine derivatives have attracted particular attention, and several methods have been devised for their synthesis. For example, Harmata and co-workers used annulation reactions of alkynes with sulfonimidoyl chlorides, and domino sequences involving palladium catalyses followed by ring closures for the preparation of benzothiazines. Palladium-catalyzed intramolecular α-arylations of sulfoximines affording heterocyclic products and were recently introduced by us.

We wondered, if the recently developed ring-closing metathesis (RCM) could also be used for the preparation of sulfoximine-containing heterocycles. With appropriately designed starting materials macrocyclic sulfoximine derivatives should result, which are difficult to prepare by other means. To the best of our knowledge, RCM has only once been employed in sulfoximine chemistry, and there, its efficiency was used as indication for conformational issues of the cyclizing pseudopeptide.

Various routes were developed for the synthesis of the doubly unsaturated starting materials, which were required for the RCM. Initially, readily accessible racemic S-methyl-S-phenyl sulfoximine served as the precursor. Its deprotonation with KH in the presence of Bu4NBBr and subsequent treatment with allyl bromide or 5-bromopentene afforded N-substituted products (80%) and (71%), respectively, in good yields. A second deprotonation/alkylation sequence using n-BuLi as base and 5-bromopentene or 4-bromobutene gave in yields up to 90% (Scheme 1).

Oxidation of allyl phenyl sulfide followed by standard imination of the resulting sulfoxide afforded the corresponding sulfoximine. Attempts to allylate selectively at the sulfoximine nitrogen to give led to a mixture of and (Figure 2).

As depicted in Scheme 2, N-acylated sulfoximines were prepared through the intermediacy of NH-sulfoximines and N-allylated derivatives. For the synthesis of the latter compound a standard MCPBA oxidation of sulfide followed by rhodium-catalyzed imination of the resulting sulfoxides (not shown) was applied. Treatment of with acryloyl chloride in the presence of a base afforded acylated products.
N-Allylated 22 was obtained by allylation of 18 with allyl bromide (5a).

The investigation of the RCM reaction began with a catalyst screening using sulfoximine 22 as test substrate. To our surprise we found that only one (25, ‘2nd generation Grubbs’) out of the five tested ruthenium carben complexes 24–28 was catalytically active affording 7-membered cyclic sulfoximine 23 in reasonable yield. Thus, with 20 mol% of 25, product 23 was obtained in 65% yield. Gratifyingly, the catalyst loading could be reduced to 10 and even 5 mol% affording sulfoximine 23 in 97 and 85% yield, respectively (Scheme 3). Toluene was the solvent of choice, and under reflux full conversion was achieved within 15 minutes. Use of dichloromethane proved to be unsuitable for this catalysis.

Next, the substrate scope was evaluated. To our delight a variety of cyclic sulfoximines could be prepared by the RCM reaction (Table 1). The best results were achieved with 20 mol% of 25, which generally led to sulfoximine-

### Table 1  RCM of Unsaturated Sulfoximines Catalyzed by 25

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>23</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>23</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>29</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>33</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>34</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>35</td>
<td>75</td>
</tr>
</tbody>
</table>

* The yield refers to the amount of heterocycle obtained after column chromatography. At that stage, the product still contained traces of the metal catalyst, which could not be removed in this manner.
based heterocycles in good to excellent yields. For example, 8- and 11-membered cyclic products 30 and 33 were obtained in 90 and 61% yield, respectively (Table 1, entries 3 and 6). Also, acrylated sulfoximines 19–21 reacted well affording the corresponding cyclic products 34–36 in high yields (entries 7–9).

As indicated by the $^{13}$C NMR spectra, the 9- to 11-membered ring products 31–33 were obtained as E/Z mixtures, and we are currently exploring the selective formation of those compounds as well as derivatives thereof.

In summary, we investigated the RCM reactions of doubly unsaturated sulfoximines and prepared novel heterocycles in this manner. Ruthenium-benzylidene complex 25 proved to be the most active catalyst for the ring closure providing cyclic sulfoximines in good to excellent yields.

All reactions were carried out under argon using standard Schlenk techniques. Toluene was distilled over sodium/benzophenone and stored under argon. NH-Sulfoximines were prepared according to the literature. All other starting materials were obtained from commercial suppliers and used without further purification. NMR spectra were recorded in CDCl$_3$, with TMS as internal standard on a Varian Gemini 300 spectrometer (300 and 100 MHz for $^1$H and $^{13}$C NMR spectra, respectively) or an Innova 400 spectrometer (400 and 100 MHz for $^1$H and $^{13}$C NMR spectra, respectively). FTIR spectra were obtained on a Perkin-Elmer PE-1760 FT apparatus and MS spectra on a Variquest 100 MHz for $^1$H and $^{13}$C NMR spectra, respectively), FTIR spectra and MS spectra on a Varian Gemini 300 spectrometer (300 and 75 MHz for $^1$H and $^{13}$C NMR spectra, respectively) or an Innova 400 spectrometer (400 and 100 MHz for $^1$H and $^{13}$C NMR spectra, respectively).

Ring-Closing Metathesis Reactions; 1-Phenyl-1-but-3-enyl-22

Yield: 80%.

IR (CHCl$_3$): 3075, 1642, 1444, 1412, 1266, 1222, 1139, 1086, 997, 893, 747 cm$^{-1}$.

$^{1}$H NMR: $\delta$ = 7.92–7.88 (m, 2 H$_{arom}$), 7.67–7.55 (m, 3 H$_{arom}$), 6.01–5.90 (m, 1 H), 5.77–5.66 (m, 1 H), 5.32–5.25 (m, 1 H, $J$ = 16.8 Hz), 5.10–4.98 (m, 3 H), 3.70–3.62 (md, 1 H, $J$ = 15.4 Hz), 3.54–3.46 (md, 1 H, $J$ = 15.4 Hz), 3.36–3.18 (m, 2 H), 2.62–2.49 (m, 1 H), 2.47–2.35 (m, 1 H).

$^{13}$C NMR: $\delta$ = 137.9, 137.8, 134.0, 132.9, 129.4, 129.3, 116.9, 114.5, 55.8, 46.1, 27.1.

MS: m/z = 234.2 (M$^+$, 3%).

Anal. Calcd for C$_9$H$_{12}$NOS: C, 66.34; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.70; N, 5.61.

Synthesis 2005, No. 9, 1421–1424 © Thieme Stuttgart · New York

References


(2) For the use of sulfoximines as chiral ligands in asymmetric catalysis, see: (a) Okamura, H.; Bolm, C. Chem. Lett. 2004, 33, 482. (b) Harmata, M. Chemtracts - Org. Chem. 2003, 26, 143.


(10) In this study racemic sulfoximine 4 was used. However, since the preparation of 4 in both enantiomeric forms is well established, a ‘chiral switch’ should be easy to achieve. For key references describing the preparation of enantiopure 4, see: (a) Fusco, R.; Tericoni, F. Chem. Ind. (Milan) 1965, 47, 61. (b) Johnson, C. R.; Schroock, C. W. J. Am. Chem. Soc. 1973, 95, 7418. (c) Johnson, C. R.; Schroock, C. W.; Shanklin, J. R. J. Am. Chem. Soc. 1973, 95, 7424. (d) Brandt, J.; Gais, H.-J. Tetrahedron: Asymmetry 1997, 8, 909.

(11) These products are shown with defined stereochemistry at the double bond, although it was not determined if an E or Z olefin was formed.
