Oxidation of diazenyl-protected N-heterocycles - a new entry to functionalized lactams

Petrovic, Martina

2017


http://hdl.handle.net/10138/178986
https://doi.org/10.1039/c6ra26546d

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.
Oxidation of diazenyl-protected N-heterocycles – a new entry to functionalized lactams†

Martina Petrović,ab Dina Scarpi, b Martin Nieger, c Nicole Jung, a,b,d Ernesto G. Occhiatob and Stefan Bräse*a,d

Functionalized lactams are an important class of heterocycles since they are useful intermediates in organic synthesis and show biological activity in diverse therapeutic applications. In the herein presented study, a strategy for the synthesis of N-aryldiazenyllactams, offering the direct access to protected lactam derivatives is described. After the formation of triazenes from diazonium salts and commercially available N-heterocycles, oxidation (directed CH activation) with periodate under ruthenium catalysis furnished N-diazenyllactams in one step. To demonstrate the suitability of the resulting lactams for further functionalizations, the alkylation of a N-diazenyllactam is presented for one example.

Introduction

Functionalized lactams are a highly important class of heterocycles in materials science and medicinal chemistry as their core structure is not only part of amide-based materials but also of different well established therapeutics. It has been shown in the past that lactams can be synthesized from the corresponding ketones via the well-known Beckmann rearrangement or from the corresponding heterocyclic amines by oxidation. Although the oxidizing methods are known with any N-substitution, most strategies rely on N-protected amines. In most of the cases, the amines are protected as amides, carbamates (Boc, Cbz) or sulfonamides but groups based on nitrogen as e.g. diazenyls are known as well (Fig. 1 for examples with diazenyls).

Being modified by one of these protecting groups, oxidation of the amines with ring sizes from four to eight-membered rings have been reported. In most of the oxidation procedures, ruthenium catalysis has been used, but other methods including the use of manganese as an oxidant or electro-chemical oxidation have also been described. Although the oxidation of N-derived cyclic amines to the corresponding lactams are known, several challenges still have not been mastered yet. For the oxidation of four-membered N-heterocycles for example, only very few reactions based on N-carbon and N-oxygen derived heterocycles have been shown so far. In addition, the oxidation of N-diazenyl-protected cyclic heterocycles (piperidines), has been shown for only a couple of compounds producing the corresponding lactams in very low yields (up to 25%). The lack of tools for the latter conversion inspired us to search for novel oxidation protocols.

In this report we show that diazenyl-protected N-heterocycles can be oxidized by Ruthenium catalysts in good yields to produce the corresponding functionalized lactams.
Results and discussion

Diazenyl protection of N-heterocycles is a common tool in organic synthesis and has been used not only in solution but also on solid phases. We were interested in the diazenyl protecting group as a valuable derivatization that could allow the modification of cyclic amines and the synthesis of interesting chemical entities. Therefore, we synthesized a set of N-diazenyl heterocycles that have been investigated towards their potential to form functionalized lactams with a diazenyl unit (Fig. 2). The required N-diazenyl heterocycles 3a–d (Fig. 2), among which the quite rare azetinyl diazenes (3a, Fig. 2),25–29 were prepared by standard procedures30 from the corresponding amines and diazonium salts in good yields. We have chosen different ring sizes from 4 to 7, substituted piperidines and various arenes to investigate scope and limitations. All of the N-diazenyl heterocycles are stable and in a few cases even crystalline materials. From the NMR analyses of these compounds resulted that only pyrrolidine derivative 3b exhibits restricted rotation noticeable in the broad NMR signal for the nitrogen-adjacent CH$_2$ groups (for selected X-ray structures of triazenes 3b and 3c see ESI†).

Aiming for the identification of an efficient oxidation strategy for the generated N-diazenyl amines 3a–d, compound 3c(1) was chosen as a model system to screen for the best reaction conditions. Preliminary experiments based on formerly published oxidation strategies31–44 revealed ruthenium based catalytic systems being the most promising choice (additional data referring to experiments with other catalytic systems are given in Table S1 in the ESI†). In Table 1, a summary of the different ruthenium-based experiments with RuCl$_3$ and RuO$_2$ as a pre-catalyst is given. It has been shown that the choice of the solvent has high influence on the outcome of the reaction and in accordance with previously published results for similar conversions,45 a CCl$_4$/acetoniitrile/H$_2$O mixture gave the highest yields in the oxidation. The yield of 44% for the synthesis of compound 6c(1) has been further improved by the use of phosphate buffer instead of water giving a yield of 52% for the model system. Reducing the amount of catalyst and oxidant to 15% and 2.5 eq. respectively caused a slight decrease of the obtained yields (entry 3) while the use of another ruthenium-based pre-catalyst (RuO$_2$ etc.) had no detectable effect on the outcome of the oxidation procedure (entries 2 and 6, Table 1).

Triazenes 3 were thus oxidized to the lactams 6 in yields ranging from 10 to 65%, i.e. much higher than those reported with KMnO$_4$.46 While all of the results given in Table 2 have been gained in reactions using 1 mmol of the starting material, the reaction to give 3c(1) (entry 3, Table 2) has been repeated on a 2 mmol scale to prove the results with a higher amount of material. The obtained yield (61%) even surpasses the results that have been gained in smaller scale (52%) which was assigned to a better handling during the purification on silica gel. Under the herein described conditions, the obtained arenes are not degraded,47 and also the triazene is not oxidized. The stability of the target compounds under the conditions of the oxidation procedure has been proven for at least 24 h. Only with the four-membered ring compound 3a the oxidation yield was very low (10%). As far as we know, diazenyl β-lactams 6a have not been reported before and synthetic procedures for their preparation haven’t been accomplished so far.

Table 1  Oxidation of triazenes 3c to give lactams 6c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pre-catalyst</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl$_3$H$_2$O 30% NaIO$_4$ 5 eq.</td>
<td>CCl$_4$/ACN/buffer</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RuCl$_3$H$_2$O 30% NaIO$_4$ 5 eq.</td>
<td>CCl$_4$/ACN/H$_2$O</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RuCl$_3$H$_2$O 15% NaIO$_4$ 2.5 eq.</td>
<td>CCl$_4$/ACN/H$_2$O</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RuCl$_2$H$_2$O 45% NaIO$_4$ 5 eq.</td>
<td>EtOAc/ACN/H$_2$O</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>RuCl$_3$H$_2$O 30% NaIO$_4$ 5 eq.</td>
<td>DCM/H$_2$O</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RuO$_2$H$_2$O 30% NaIO$_4$ 5 eq.</td>
<td>CCl$_4$/ACN/H$_2$O</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Oxidation of triazenes 3a–d to give lactams 6a–d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Triazene</th>
<th>n</th>
<th>R$^1$</th>
<th>X</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>1</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>6a</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>2</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>6b</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>3c(1)</td>
<td>3</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>6c(1)</td>
<td>52 (61$^a$)</td>
</tr>
<tr>
<td>4</td>
<td>3c(2)</td>
<td>3</td>
<td>H</td>
<td>OMe</td>
<td>6c(2)</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>3c(3)</td>
<td>3</td>
<td>H</td>
<td>NO$_2$</td>
<td>6c(3)</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>3c(4)</td>
<td>3</td>
<td>H</td>
<td>Br</td>
<td>6c(4)</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>3c(5)</td>
<td>3</td>
<td>-(CH)$_3$-</td>
<td>CO$_2$Et</td>
<td>6c(5)</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>3c(6)</td>
<td>3</td>
<td>-OCH$_2$CH$_2$O-</td>
<td>CO$_2$Et</td>
<td>6c(6)</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>4</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>6d</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$ Upscaling of the reaction to 2 mmol scale.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

The herein described procedure presents as far as we know the first strategy for the synthesis of functionalized lactams with diazenyl unit. The conversion of triazenes (and azo compounds) allows e.g. the synthesis of 4- and 7-membered diazenyl heterocycles that are reported for the first time. The scope of the reaction has been demonstrated by an α-alkylation of an exemplarily chosen amide allowing the application of the herein presented oxidation for diverse modifications of diazenyl protected heterocycles.

Conclusions

The herein described procedure presents as far as we know the first strategy for the synthesis of functionalized lactams with diazenyl unit. The conversion of triazenes (and azo compounds) by Ru-catalyzed oxidation to give N-diazenyl protected lactams allows e.g. the synthesis of 4- and 7-membered diazenyl heterocycles that are reported for the first time. The scope of the reaction has been demonstrated by an α-alkylation of an exemplarily chosen amide allowing the application of the herein presented oxidation for diverse modifications of diazenyl protected heterocycles.

Acknowledgements

This work was supported by the Helmholtz program Bio-interfaces in Technology and Medicine (BIFTM). M. P. thanks the European Commission for a Marie Curie fellowship (FP7-PEOPLE-2012-ITN, Project: ECHONET "Expanding Capability in Heterocyclic Organic Synthesis", no. 316379).

Notes and references


