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

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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 piperidine).[1–4]

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[5,6] as an oxidant or electrochemical oxidation[7] 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-[5] and *N*-oxygen-[8–11] 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%).[6] The lack of tools for the latter conversion inspired us to search for novel oxidation protocols.

It has been shown by us[12–16] and others[17–34] that diazenyl-substituted amines – triazenes – can serve as very valuable starting materials and intermediates. They are stable towards many bases, but can be cleaved under mild acidic conditions to release the free amine or amine-derivative in a simple manner.[14] In addition, triazenes can also be used as versatile linkers for the immobilization of amines or anilines in solid phase syntheses. This allows the transfer of triazene chemistry developed in solution to methods that allow combinatorial chemistry on solid phases.

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.
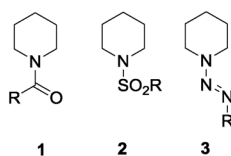

Fig. 1 Suitable protecting groups for CH activation of piperidine: amides/carbamates **1**, sulfonamides **2**,[1] diazenyls **3**.[2–4]

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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 azetinyldiazenes (**3a**, Fig. 2),[35–39] were prepared by standard procedures[40] 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{5}** 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 strategies[41–44] 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/acetonitrile/H_2O 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

Table 1 Oxidation of triazenes **3c{1}** to give lactams **6c{1}**

Entry	Pre-catalyst		Oxidant		Solvent	Yield [%]
1	$RuCl_3 \cdot H_2O$	30%	$NaIO_4$	5 eq.	CCl_4/ACN/buffer	52
2	$RuCl_3 \cdot H_2O$	30%	$NaIO_4$	5 eq.	CCl_4/ACN/H_2O	44
3	$RuCl_3 \cdot H_2O$	15%	$NaIO_4$	2.5 eq.	CCl_4/ACN/H_2O	39
4	$RuCl_3 \cdot H_2O$	45%	$NaIO_4$	5 eq.	EtOAc/ACN/H_2O	16
5	$RuCl_3 \cdot H_2O$	30%	$NaIO_4$	5 eq.	DCM/H_2O	10
6	$RuO_2 \cdot H_2O$	30%	$NaIO_4$	5 eq.	CCl_4/ACN/H_2O	47

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

Entry	Triazene	n	R^1	X	Product	Yield [%]
1	**3a**	1	H	CO_2Et	**6a**	10
2	**3b**	2	H	CO_2Et	**6b**	65
3	**3c{1}**	3	H	CO_2Et	**6c{1}**	52 (61[a])
4	**3c{2}**	3	H	OMe	**6c{2}**	38
5	**3c{3}**	3	H	NO_2	**6c{3}**	49
6	**3c{4}**	3	H	Br	**6c{4}**	25
7	**3c{5}**	3	–$(CH)_4$–	CO_2Et	**6c{5}**	47
8	**3c{6}**	3	–OCH_2CH_2O–	CO_2Et	**6c{6}**	59
9	**3d**	4	H	CO_2Et	**6d**	47

[a] Upscaling of the reaction to 2 mmol scale.

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 $KMnO_4$.[5,6] 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,[46] 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.
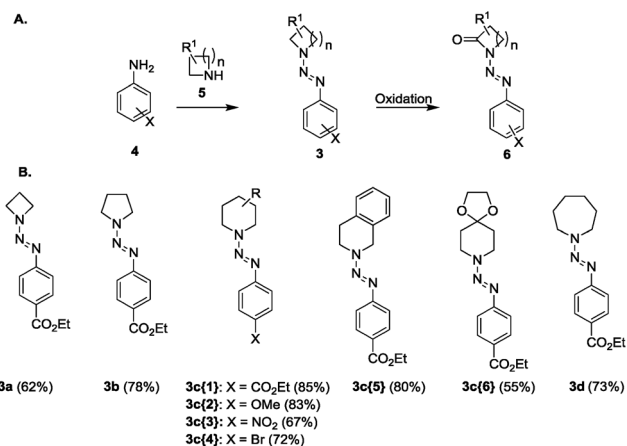

Fig. 2 General synthetic outline (A) and building blocks that have been prepared for the oxidation (B).
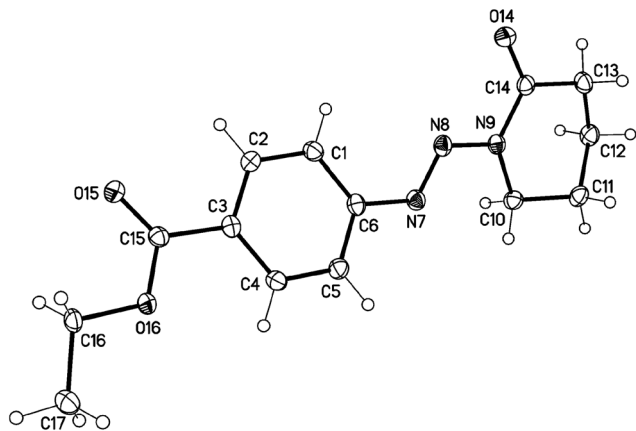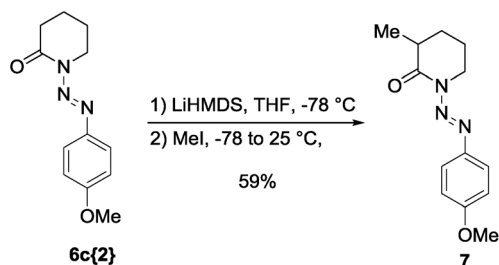
Fig. 3   Molecular structure of the *N*-diazenyllactam **6c{1}** (displacement parameters are drawn at 50% probability level).

Scheme 1   Alkylation of lactam **6c{2}** to give α-alkylated heterocycle **7**.

The structure of the target triazenes has been confirmed by standard techniques as well as X-ray crystallography for one selected example **6c{1}** (Fig. 3, details of the crystallographic studies of **6c{1}** and triazenes **3b** and **3c{5}** are given in the ESI†) by which we found that the lactams crystallize as s-*trans* compounds.

As a preliminary investigation of the potential of this protecting group, we carried out the alkylation of lactam **6c{2}** under strong basic conditions, using LiHMDS as the base and MeI as the electrophile. Gratifyingly, the reaction provided the 3-methyl substituted lactam **7** in good yield (59%) without decomposition or degradation of the protecting group (Scheme 1). The removal of the diazenyl protecting group can be achieved *via* standard conditions for the cleavage of triazenes[14] and has been shown in quantitative conversion for the alkylated heterocycle **7** (see ESI†).

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

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