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Hydrozirconation of four-, five-, six- and seven-membered *N*-alkoxycarbonyl lactams to lactamols

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ABSTRACT

A general, practical, and efficient reduction of four-, five-, six- and, seven-membered *N*-alkoxycarbonyl lactams to the aldehyde oxidation state is reported. The reduction methodology involves the hydrozirconation reaction by $Cp_2Zr(H)Cl$ under mild conditions and proceeds with very short reaction times and in excellent to good yields. The hydrozirconation of *N*-alkoxycarbonyl lactams with the Schwartz reagent demonstrated to be the mildest and most general method for the formation of lactamols with a high functional group tolerance.

The amide group is an important moiety in the areas of polymers, natural products, and pharmaceuticals and is fairly inert to many reductive conditions.[1] The simple reduction of amides to the corresponding alcohol or amine, by metal hydride reagents, has been realized under different experimental conditions, several of which proceed in high yields.[2] The reduction of an amide to the aldehyde oxidation state has proven to be more difficult and has been performed with several reducing agents.[3] To address these issues, direct reduction methods have been described to yield the corresponding aldehyde or imine. Among these, the use of Weinreb amides[4] or morpholine-derived amides[5] in combination with DIBAL is known to control the outcome of the reduction to aldehydes. Also, Buchwald reported a more general and chemoselective reduction of α-enolizable amides to aldehydes in the presence of $Ti(Oi\text{-}Pr)_4$ and Ph_2SiH_2.[6] Alternatively, the use of stoichiometric or excess amounts of Schwartz's reagent (Cp_2ZrHCl) can lead to the formation of a variety of aldehydes[7] or imines[8] with a great functional group tolerance. However, till now the utility of Cp_2ZrHCl has not been shown in the reduction of lactams. In the investigated cases, β-lactams and caprolactams, a complete loss of starting material without the formation of aldehydic products was observed[7a]; only the reduction of 2-azacyclotridecanone to 1-azacyclotridecene was effectively achieved in 25% yield.[8b] In the latter case the procedure for the reduction of secondary carboxamides to imines with potassium hydride and Cp_2ZrHCl (2.4 equiv) at −20 °C was applied, following a nonaqueous workup. Generally, the controlled reduction of lactam type **1** leads to lactamols **2** which may evolve into the enamine derivatives **3** by dehydration or afford the tautomeric aldehydes **4** by ring opening (Fig. 1). Literature data report that *N*-acyl γ-, δ-, and ε-lactams can be converted into the corresponding hemiaminals (also termed lactamols or α-hydroxycarbamates) employing DIBAL-H,[9] $LiEt_3BH$,[10] or $NaBH_4$,[11] while no procedure is known for the controlled reduction of β-lactams to β-lactamols.

Hemiaminals are important intermediates in the preparation of azanucleosides with antiviral, antiprotozoan, and anticancer properties.[12] Furthermore, the dehydration reaction of α-hydroxycarbamates leads to enecarbamates which are useful building blocks for the synthesis of nitrogen-containing heterocycles with biological significance.[13] In this Letter we exploited the use of $Cp_2Zr(H)Cl$ in the reduction of four-, five, six-, and seven-membered *N*-alkoxycarbonyl lactams to lactamols in the presence of different protecting groups on the nitrogen atom.

In order to determine the feasibility of the reduction of lactams to the corresponding lactamols, we have investigated the reaction of the chosen model γ-lactams **5a–f**, bearing different substituents on the nitrogen atom, with $Cp_2Zr(H)Cl$ (Fig. 2). The reaction was carried out in THF, under nitrogen, at room temperature by varying the equivalents of Cp_2ZrHCl and the reaction times (Table 1). The nonaqueous workup was performed by loading the reaction mixture into a short plug of silica gel (~1 g) and eluting with ethyl acetate. In the first experiment (Table 1, entry 1) the protocol developed for the reduction of secondary amides and lactams to imines was

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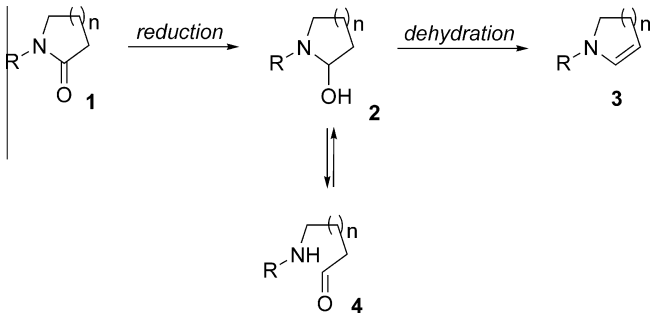

Figure 1. General reduction pathways of γ-lactams.

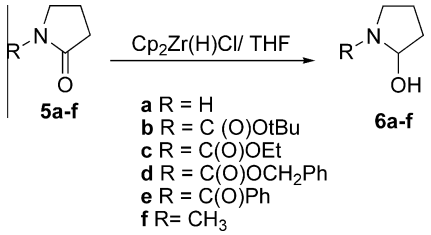

Figure 2. Reduction of γ-lactams with $Cp_2Zr(H)Cl$.

applied. However, the addition of 2 or more equiv of $Cp_2Zr(H)Cl$ to the unsubstituted lactam **5a** was not able to elicit product formation after 12 h of reaction. The MPLC purification of the crude reaction mixture afforded the unreacted lactam **5a** in 73% yield and no discernable amount of reduced products was observed. Lactam carbamates **5b–d** were efficiently reduced to the corresponding lactamols **6b–d** in high yields (90–95%, Table 1, entries 4–6) by using 2 equiv of $Cp_2Zr(H)Cl$ for 1 h. The amount of Schwartz reagent appeared essential for the reduction; increasing the equivalents from 1.5 to 2 or 2.5, an improvement of the conversion, from 75 to 95%, respectively, was detected; prolonged reaction times did not affect the conversion rate (Table 1, entries 2–3).

In order to investigate the dependence of the substituent on the nitrogen atom on the efficiency of the lactam reduction, 1-benzoylpyrrolidin-2-one **5e** and 1-methylpyrrolidin-2-one **5f** were treated with bis(cyclopentadienyl)zirconium chloride hydride under the experimental reaction conditions applied for **5b–d** (Table 1, entries 7–8). The attempted hydrozirconation of **5f** did not result in the product formation and the substrate was recovered in 95% yield. The reduction of the bis-amide **5e** led to removal of the N-protecting group affording **5a** in 80% yield. This is likely due to the exclusive reduction of the *exo* carbonyl group in **5e**, as confirmed by tlc and ^1H NMR benzaldehyde detection.

Table 1
Reaction of γ-lactams **5a–f** and **7** with $Cp_2Zr(H)Cl$

Entry	Lactam	Conditions	Product	Yield%
1	**5a**	$Cp_2Zr(H)Cl$ (2.5 equiv), 12 h	—	—[a]
2	**5b**	$Cp_2Zr(H)Cl$ (2.5 equiv), 12 h	**6b**	95
3	**5b**	$Cp_2Zr(H)Cl$ (1.5 equiv), 12 h	**6b**	75[b]
4	**5b**	$Cp_2Zr(H)Cl$ (2 equiv), 1 h	**6b**	95
5	**5c**	$Cp_2Zr(H)Cl$ (2 equiv), 1 h	**6c**	90
6	**5d**	$Cp_2Zr(H)Cl$ (2 equiv), 1 h	**6d**	92
7	**5e**	$Cp_2Zr(H)Cl$ (2 equiv), 1 h	**5a**[d]	80
8	**5f**	$Cp_2Zr(H)Cl$ (2 equiv), 1 h	—	—[c]
9	**7**	$Cp_2Zr(H)Cl$ (1.5 equiv), 1 h	**8a,b** (1:1 ratio)	95

[a] The unreacted lactam **5a** (73%) was recovered after MPLC.
[b] The unreacted lactam **5b** (15%) was recovered after MPLC.
[c] The unreacted lactam **5f** (95%) was recovered after MPLC.
[d] tlc and ^1H NMR revealed the benzaldehyde formation.

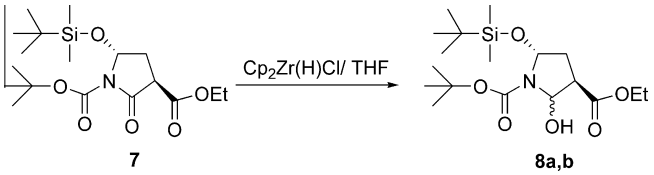

Figure 3. Reduction of γ-lactam **7** with $Cp_2Zr(H)Cl$.

The reduction of methyl (4*R*)-*trans*-*N*-Boc-4-*tert*-butyldimethylsilyloxy pyroglutamate **7** to hemiaminals **8a,b** (a 4:1 mixture of anomers, 80% yield) with $LiBEt_3H$ in dry THF at −78 °C, is the key step in the preparation of anti-HCV 3′-deoxy-4′-azaribonucleosides.[13a] Having optimized the reduction condition of γ-lactams, we have investigated the ability of $Cp_2Zr(H)Cl$ to reduce **7** (Table 1, Fig. 3, entry 9). Notably, an almost complete conversion was observed in 1 h, using 1.5 equiv of reducing agent and a 1:1 mixture of hemiaminals **8a,b** was recovered in 95% yield.

The conversion of amides into aldehydes via $Cp_2Zr(H)Cl$ was experimentally studied in depth, but the reaction mechanism has not yet been completely elucidated.[7a,14] The reaction of secondary amides with 2 equiv of Cp_2ZrHCl involves the formation of enolate zirconium(IV) salt and its subsequent reduction to imine derivative (Eq. 1, Fig. 4). The reduction of tertiary amides into the corresponding aldehydes requires 1 equiv of the reducing agent and the residual amine component, probably bounded to the zirconium byproduct, was unrecoverable. Additionally, the reaction shows a minimal substrate dependence and the tertiary amide is selectively reduced in the presence of an ester group. On the basis of the experimental evidence[7a] which considers that the hydrogen atom of the aldehyde group comes from $Cp_2Zr(H)Cl$ and that the carbonyl oxygen comes from water, the more plausible reaction pathway is reported in Figure 4, Eq. 2.

Comparing the literature data on the reduction of tertiary amides into the corresponding aldehydes with our results on the reduction of the γ-lactam systems, some experimental differences came out: (1) the lactams reduction depends on the nature of the nitrogen substituent: lactam carbamates were reduced to hemiaminals while *N*-methyl lactam did not react and *N*-benzoyl lactam reacted on the *exo* carbonyl group; (2) the residual amine components were always recovered from the reaction mixture and (3) the reduction required 1.5–2 equiv of reagent. According to the literature data none of the over- reduction product was detected even in the presence of an excess of $Cp_2Zr(H)Cl$. Thus, the experimental results suggest the presence of a seemingly stable zirconacycle intermediate in the reaction pathway; while there is no evidence of iminium ions formation involved in the reaction mechanism of lactam carbamate.

The experimental protocol (2 equiv of $Cp_2Zr(H)Cl$, THF, 1 h, rt) was applied successfully to four-, six-, and seven-membered *N*-alkoxycarbonyl lactams (Fig. 5).

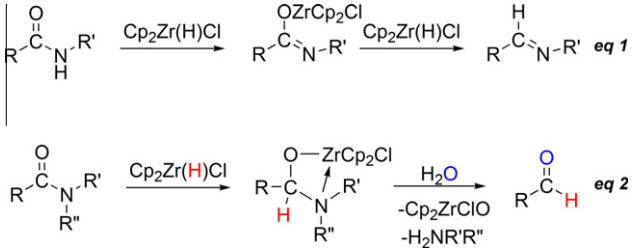

Figure 4. Mechanism of converting amides to aldehydes using $Cp_2Zr(H)Cl$.

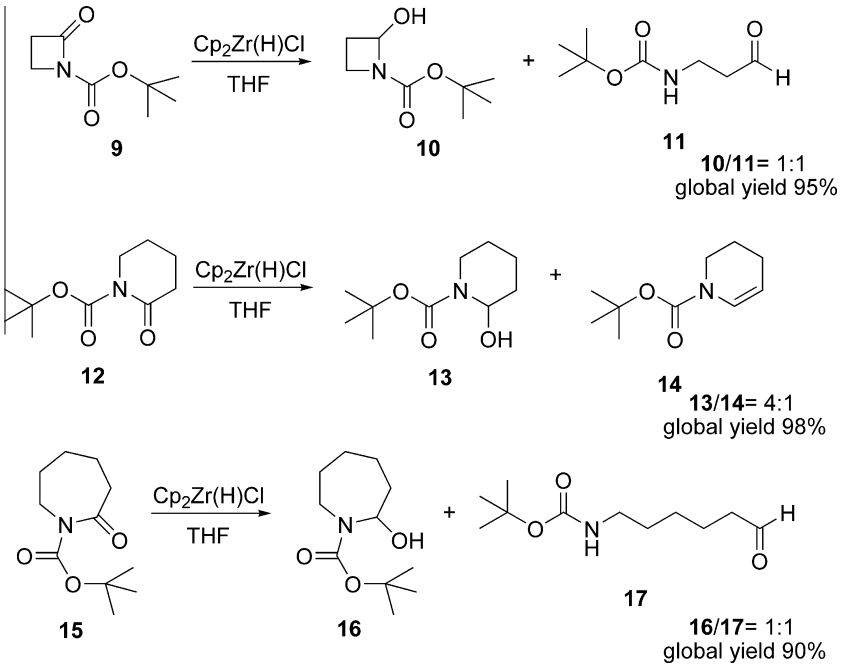

Figure 5. Reduction of β-, δ-, and ε-lactams with $Cp_2Zr(H)Cl$.

In the reduction of γ-lactams **5b–d** only the corresponding lactamols **6b–d** have been detected in the reaction with $Cp_2Zr(H)Cl$, while the reduction of δ-lactam **12** afforded a 4:1 mixture of the hemiaminal **13** and enecarbamate **14** in 98% global yield. The constrained β-lactam carbamate **9** was efficiently reduced to the aldehyde oxidation state and a 1:1 inseparable mixture of the corresponding hemiaminal/aldehyde **10**/**11** was recovered after workup; to our knowledge, this reaction represents the first example of reduction of a constrained β-lactam carbamate to hemiaminal. Compound **10** was detected in the ^1H NMR spectrum but it is not isolable from **11** to which in a short time, it is converted; thus, the column silica gel purification affords only compound **11**, as a colorless oil in 95% yield. The *tert*-butyl-oxoazepane-1-carboxylate **15** reacted in the same way affording a 1:1 mixture of hemiaminal/aldehyde **16**/**17** in 90% global yield.

In summary, we reported here a mild procedure for the reduction of *N*-alkoxycarbonyl lactams to the aldehyde oxidation state in high yields, by using bis(cyclopentadienyl)zirconium chloride hydride. This reaction proceeds with very short reaction times, and constitutes an alternative to existing methods which use metal hydrides at −78 °C and works on a four-, five-, six-, and seven-membered *N*-alkoxycarbonyl lactams.

Supplementary data

Supplementary data (experimental procedures and characterization data for each reaction) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.006.

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