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Novel ruthenium-catalyzed cleavage of allyl protecting group in lactams

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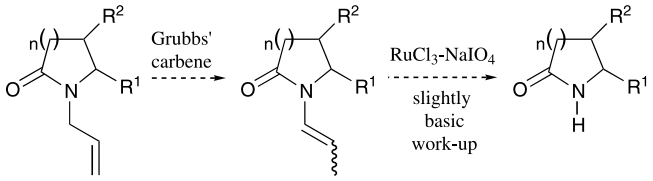
Abstract—A convenient and general method of synthesis of *NH*-lactams via Grubbs' carbene promoted isomerization of the respective *N*-allyl lactams followed by $RuCl_3$-catalyzed enamide cleavage has been developed.

NH-Lactams are nitrogen-containing heterocycles which have long attracted synthetic interest due to their relatively simple structural features and wide range of pharmacologic activity coupled with serving as crucial intermediates for numerous natural products. In particular, *N*-unsubstituted β-lactams play a central role as key intermediates in the synthesis of several biologically active antibiotics,[1] and the anti-cancer agents paclitaxel and docetaxel.[2] There are relatively few methods available for the deprotection of an amide group.[3] Oxidative cleavage by ceric ammonium nitrate of an activated aromatic moiety attached to the nitrogen of the lactam ring offers the most direct synthesis of *NH*-lactams.[4] However, conditions used are quite harsh and in many cases the yields are poor, making such procedure hardly suitable for the synthesis of highly functionalized molecules. There are many other methods known in the literature, but less frequently used.[5,6] Despite that the allyl protecting group cleavage in ethers and amines is a well documented methodology, specially using palladium chemistry,[7] its extension to the deprotection of allylic lactams has been scarcely documented. As far a we know the *N*-allyl deprotections of a 4-unsubstituted-β-lactam as well as a 2-hydroxy-γ-lactam, both induced by rhodium(III) followed by $KMnO_4$ or acidic treatments, respectively, are the only available examples.[8] To overcome these problems, we reported some time ago a stoichiometric cobalt induced cleavage of *N*-propargyl β-lactams.[9] In continuation of these efforts to prepare *N*-unsubstituted lactams, herein we report an efficient strategy for the catalytic deprotection of *N*-allyl lactams via ruthenium complexes in mild conditions.

A growing number of newly discovered catalytic processes mediated by Grubbs' carbene complex broaden its synthetic utility beyond olefin metathesis.[10] In particular, we recently described the first examples accounting for the catalytic cleavage of allylic amines by using reagents different from palladium catalysts.[11] The higher stability of enamides comparing with enamines favours the double bond isomerization, preventing from (CO)*N*-allyl cleavage. On the basis of these principles, it was to be expected that successful catalytic C–N deprotection in *N*-allyl lactams would require and additional step (Scheme 1). We thought in ruthenium(III) chloride which has been probed as an excellent catalyst for the oxidative cleavage of olefins to aldehydes,[12] because it has been reported that *N*-formyl lactams smoothly loss CO under slightly basic conditions to give the corresponding NH-amides.[13]



Scheme 1.

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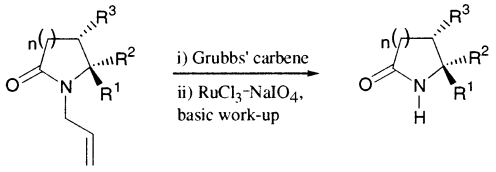
Starting substrates, *N*-allyl lactams **1a–h**, were prepared using standard methodology. *N*-Allyl lactams **1a–c** were obtained via reaction of the corresponding *NH*-lactams with allyl bromide in the presence of sodium hydride,[14] while 2-azetidinones **1d–h** were obtained from the corresponding allyl imine, through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N.[15]

Firstly, we tested as a model reaction the deprotection of *N*-allyl δ-valerolactam **1a**. Treatment of allylic amide **1a** with Grubbs' carbene $Cl_2(Cy_3P)_2Ru{=}CHPh$ under optimised reaction conditions (5 mol% catalyst, 0.03 M, toluene, 110°C)[16] resulted in clean formation of the corresponding enamide as an isomeric mixture (1:1) *E*/*Z* in good isolated yield (71%) after chromatographic purification. The catalytic scission of the internal C=C was attained by using the system of $RuCl_3$–$NaIO_4$ in 1,2-dichloroethane–H_2O (1:1), followed by an aqueous work-up in slightly basic conditions (sat. aq. $NaHCO_3$ containing a catalytic amount of Na_2CO_3). Thus, the *N*-unsubstituted 2-piperidone **2a** was obtained in a 70% yield. Exposure of *N*-allyl γ-butyrolactam **1b** and *N*-allyl L-pyroglutamic acid ethyl ester (+)-**1c** to the above sequential catalytic conditions smoothly afforded the *NH*-lactams **2b** and (+)-**2c**. Next, we decide to test the *N*-allyl cleavage protocol in the strained four-membered lactam series. Racemic as well as enantiopure allylic β-lactams **2d–h** were conveniently deprotected to the corresponding *NH*-β-lactams by using both ruthenium catalysts (Table 1). Under the reaction conditions, the intermediate *N*-formyl lactams accumulate in the reaction mixture immediately after the $RuCl_3$–$NaIO_4$ system is added over the enamide, and can be isolated under a neutral work-up. Importantly, the stereochemical integrity of the stereogenic centres at the lactam rings, when applicable, remained unaltered during the transformation of *N*-allyl compounds **1** into *NH*-products **2**.

This transformation tolerates different substituents at the lactam ring, such as aryl, heteroaryl, alkoxy, silyloxy, dioxolanyl, and carboxyalkyl moieties. Of special interest are the furan and electron-rich arene moieties, both of them sensitive to oxidative deprotection conditions, as well as the acid labile silyl ether and acetonide groups.

In conclusion, we have presented a new convenient methodology for the catalytic deprotection of *N*-allylic lactams. This protocol is tolerant towards different functionalities as well as the stereocentres present in the ring.

Table 1. *N*-Allyl cleavage of different-sized lactams



1 2

Substrate	R^1	R^2	R^3	n	Product	Yield (%)[a]
1a	H	H	H	2	**2a**	50
1b	H	H	H	1	**2b**	78
(+)-**1c**	COOEt	H	H	1	(+)-**2c**	55
(±)-**1d**	H		PhO	0	(±)-**2d**	42
(+)-**1e**	H		PhO	0	(+)-**2e**	62
(±)-**1f**	H		MeO	0	(±)-**2f**	40
(+)-**1g**	H		MeO	0	(+)-**2g**	65
(+)-**1h**	H		TBSO	0	(+)-**2h**	76

[a] Overall yields are for pure isolated products with correct analytical and spectroscopic data.

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References

1. For pertinent reviews, see: (a) Kant, J.; Walker, D. G. In *the Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Wiley-VCH: New York, 1993; p. 121; (b) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.
2. Suffness, M. *Taxol Science and Applications*; CRC Press: Boca Raton, FL, USA, 1995.
3. (a) Greene, T. W.; Wuts, G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, New York, 1994.
4. Kronenthal, D. K.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
5. A new solid-phase approach to *NH*-β-lactams has been recently described: Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett.* **2002**, *43*, 9445.
6. It has been described very recently the radical-promoted deprotection of *N*-Cbz derivatives of amides: Bennasar, M.-L.; Roca, T.; Padullés, A. *Org. Lett.* **2003**, *5*, 569.
7. Guibé, F. *Tetrahedron* **1998**, *54*, 2967.
8. (a) Cainelli, G.; DaCol, M.; Galletti, P.; Giacomini, D. *Synlett.* **1997**, 923; (b) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173.

9. Alcaide, B.; Pérez-Castells, J. P.; Sánchez-Vigo, B.; Sierra, M. A. *J. Chem. Soc., Chem. Commun.* **1994**, 587.
10. For a review on this subject, see: Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1258.
11. Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781.
12. Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814.
13. (a) Aizpurua, J. M.; Cossío, F. P.; Palomo, C. *Tetrahedron Lett.* **1986**, *27*, 4359; (b) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432.
14. For the *N*-alkyl protection of butyl L-pyroglutamate under these conditions, see: Itoh, T.; Miyazaki, M.; Ikeda, S.; Nagata, K.; Yokoya, M.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Tetrahedron* **2003**, *59*, 3527.
15. For recent reviews on the ketene-imine approach to β-lactams, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223; (b) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp. 518–527; (c) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH: Weinheim: New York, 1993; Chapter 3, p. 295.
16. Attempts to effect the reaction at temperatures lower than 50°C slowed the reaction considerably. Incomplete conversion was observed on decreasing the amount of catalyst.