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A Mechanism-Based Cleavage of Lactam-Carbamates

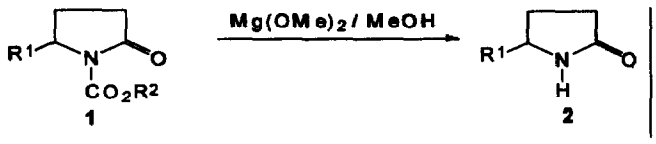
Zhong-Yong Wei and Edward E. Knaus*

Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

Abstract. Magnesium methoxide is a simple, effective and highly selective reagent for the deprotection of N-alkoxycarbonyl lactams. The cleavage occurs via six-membered ring transition states involving coordination of magnesium ion with the oxygens of the carbamate and lactam carbonyl groups.

Lactams are important structural units present in many biological compounds and are valuable intermediates for organic syntheses.[1-4] Syntheses employing lactams usually require protection of the NH moiety, often as a carbamate, which is used extensively in organic syntheses.[5] Nevertheless, their utility for protecting the NH group of lactams may be curtailed by a problematic deprotection step, and the absence of appropriate methods which proceed under mild conditions.

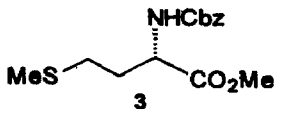
We now describe a highly selective procedure for the deprotection of a variety of lactam-carbamates, using $Mg(OMe)_2$ in MeOH at 25°C, which affords the corresponding lactams in excellent yields (see Scheme 1) using the following representative procedure. A mixture of N-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolidinone (**1a**, 261 mg, 1.0 mmol) and $Mg(OMe)_2$ (5.0 mmol) in MeOH (5 mL) was stirred at 25° for 12 hr. After neutralization with aqueous acetic acid, the mixture was extracted with $CHCl_3$ (2 x 20 mL). The combined organic fractions were successively washed with 10% aqueous NH_4Cl, saturated brine (15 mL) and dried ($MgSO_4$). Filtration, removal of the solvent *in vacuo*, and purification of the product by silica gel flash column chromatography using $CHCl_3$ as eluent gave 5-phenyl-2-pyrrolidinone (**2a**, 145 mg, 90%).

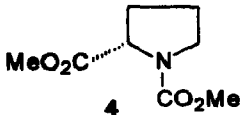


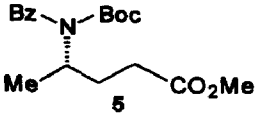
	R1	R2	2 (% Yield)
1a	Ph	*t*-Bu	90
1b	*i*-Bu	*t*-Bu	87
1c	CH_2=CH-	*t*-Bu	83
1d	H	*t*-Bu	82
1e	H	Me	86
1f	H	$PhCH_2$-	78

Scheme 1

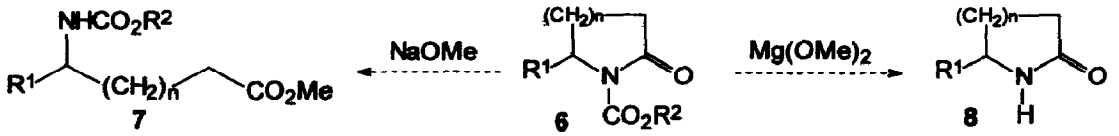
The N-alkoxycarbonyl bond of lactam-carbamates having N-Cbz, N-Boc and N-CO_2Me protecting groups were cleaved by $Mg(OMe)_2$. This is an important reaction, since N-Boc and N-Cbz groups are usually very stable under basic conditions.[5] In contrast, non-lactam carbamates such as **3**, **4** and **5** were not cleaved by $Mg(OMe)_2$. Thus, this $Mg(OMe)_2$ procedure can be used to selectively cleave lactam-carbamates in the presence of other carbamate groups.





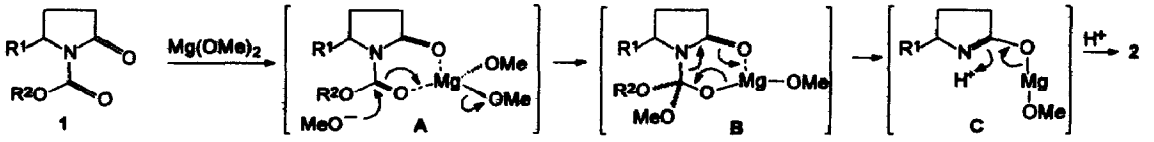


On the other hand, it was reported[6,7] that lactam-carbamates undergo regioselective methanolysis by NaOMe to afford acyclic γ- or ω-amino acid methyl esters. Therefore, $Mg(OMe)_2$ is the reagent of choice for the removal of N-alkoxycarbonyl groups of lactam-carbamates, whereas NaOMe is the reagent of choice for the cleavage of the lactam bond of lactam-carbamates (see Scheme 2).



Scheme 2

The difference in reactivity between $Mg(OMe)_2$ and NaOMe dictates product formation. NaOMe acts as a nucleophile to attack the more reactive "amide" carbonyl group leading to ring-opened products. However, in the case of $Mg(OMe)_2$, the magnesium ion likely coordinates with the oxygens of the two carbonyl groups to form a six-membered ring transition state **A**. Nucleophilic attack at the carbamate carbonyl by methoxide gives rise to transition state **B**, which undergoes cleavage of the carbamate group (see Scheme 3). This mechanism suggests that the $Mg(OMe)_2$ procedure may also be an effective method to selectively cleave carbamate derivatives of secondary amides since treatment of 3-pyridyl-N-CO_2Bu-*t*(COBu-*t*) with 1 equiv. $Mg(OMe)_2$ (-78°C → 0°C) gave 3-pyridyl-NHCOBu-*t* and 3-pyridyl-NH-CO_2Bu-*t* in a ratio of 4:1.



Scheme 3

In conclusion, $Mg(OMe)_2$ is a mechanism-based reagent for the removal of N-alkoxycarbonyl groups. The methodology described provides a mild and highly selective procedure for deprotection of lactam-carbamates to prepare the corresponding lactams.

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