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Amidation through carbamates

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ABSTRACT

N-Alkyl carbamates of primary amines are easily converted into amides under treatment with Grignard reagents. Consequently, primary amines can be converted into amides in a one-pot reaction through carbamate protection and Grignard addition.

1. Introduction

Carbamates and amides are widely used protecting groups for amines.[1] While some recent reports have described the conversion of carbamates into amides,[2] more general and convenient methods to accomplish this transformation are desirable.

During the course to the attempted preparation of diphenyl-L-prolinol, we reacted *N*-CBZ-L-proline methyl ester[3] with phenyl magnesium bromide. Unexpectedly, we obtained *N*-benzoyl-L-prolinol **1** as the main product (Scheme 1).

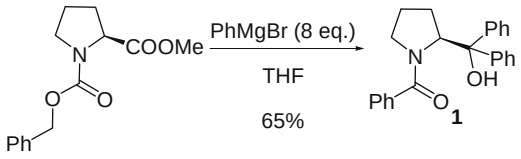
This result prompted us to examine the reactivity of carbamates with Grignard reagents. When carbamates of secondary amines are treated with Grignard reagents or organolithium compounds, the corresponding amine and ketone are obtained (Scheme 2).[4] Interestingly the reaction between carbamates of primary amines and Grignard reagents has been reported before as an undesired process.[5] We are pleased to report herein that carbamates of primary amines when treated with Grignard reagents gave rise to amides in high yield and that primary amines can be converted into amides in a one-pot reaction through carbamate protection and Grignard addition (Scheme 2).

2. Results

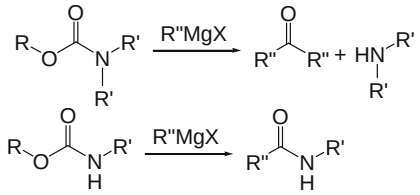
N-Alkyl carbamates (benzyl, methyl, and *terc*-butyl) of primary amines (benzylamine, allylamine, and 3-phenylpropylamine) were prepared according to standard procedures.[1] The resulting carbamates were reacted with Grignard reagents in THF at room temperature for 24 h (Table 1).

In all cases, starting carbamates were transformed into the corresponding amides[6] in good to high yield. The broad availability of Grignard reagents permitted the preparation of a wide variety of amides, which is an advantage over similar procedures in the literature.[2]

We are also glad to report a new one-pot procedure for the conversion of amines into amides. When a primary amine was treated with an alkoxy carbonyl chloride in the presence of triethyl amine, followed by addition of a Grignard reagent, the corresponding amide was obtained in good to high yield (Table 2).



Scheme 1. Treatment of *N*-CBZ-L-proline methyl ester with phenyl magnesium bromide.



Scheme 2. Treatment of carbamates of secondary and primary amines.

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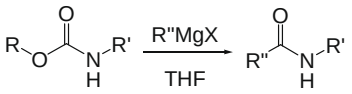
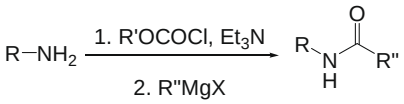
Table 1
Treatment of carbamates with Grignard reagents



Entry	R	R′	Grignard (R″MgX)	Yield (%)
1	Bn	Bn	MeMgBr	66
2	Bn	Bn	EtMgBr	70
3	Bn	Bn	PhMgBr	73
4	Bn	Bn	*t*-BuMgCl	74
5	Bn	$PhCH_2CH_2CH_2$	MeMgBr	77
6	Bn	$PhCH_2CH_2CH_2$	EtMgBr	72
7	Bn	$PhCH_2CH_2CH_2$	*t*-BuMgCl	89
8	Bn	$PhCH_2CH_2CH_2$	*i*-PrMgCl	62
9	Bn	CH_2=$CHCH_2$	MeMgBr	43
10	Bn	CH_2=$CHCH_2$	EtMgBr	43
11	Bn	CH_2=$CHCH_2$	*t*-BuMgCl	69
12	Bn	CH_2=$CHCH_2$	*i*-PrMgCl	99
13	Me	$PhCH_2CH_2CH_2$	MeMgBr	95
14	Me	$PhCH_2CH_2CH_2$	EtMgBr	71
15	Me	$PhCH_2CH_2CH_2$	*t*-BuMgCl	79
16	Me	$PhCH_2CH_2CH_2$	*i*-PrMgCl	83
17	*t*-Bu	$PhCH_2CH_2CH_2$	EtMgBr	85

Table 2
One-pot conversion of amines into amides



Entry	R	R′	R″	Yield (%)
1	$PhCH_2CH_2CH_2$	Me	Et	87
2	$PhCH_2CH_2CH_2$	Bn	Et	92
3	$PhCH_2CH_2CH_2$	Bn	Me	66
4	CH_2=$CHCH_2$	Bn	Me	70
5	CH_2=$CHCH_2$	Bn	*t*-Bu	47
6	CH_2=$CHCH_2$	Bn	*i*-Pr	58
7	CH_2=$CHCH_2$	Bn	Et	36
8	CH_2=$CHCH_2$	Me	Et	41
9	CH_2=$CHCH_2$	Me	Me	83
10	$PhCH_2CH_2CH_2$	*t*-Bu	Et	90

This one-pot process represents a new approach to synthesizing amides from amines.

3. Discussion

When carbamates of secondary amines are treated with Grignard reagents, the corresponding amines and ketones are obtained.[3] However, carbamates of primary amines give amides. Carbamates of primary amines probably react with Grignard reagents through an *N*,*O*-magnesium chelate **2** (Fig. 1) whilst carbamates of secondary amines cannot form this intermediate. The unexpected formation of the amide of diphenyl-L-prolinol from *N*-CBZ-L-proline methyl ester could be explained by formation of chelate **3** (Fig. 1).

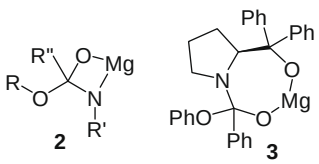


Figure 1. Chelation intermediates.

4. Conclusions

In summary, we have shown that carbamates of primary amines give rise to amides when treated with Grignard reagents. Primary amines can then be transformed into amides through protection as a carbamate followed by Grignard treatment in a one-pot procedure.

5. Experimental

5.1. General experimental methods

All solvents used in reactions were freshly distilled from appropriate drying agents before use. ^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz Mercury Varian or on a 500 MHz Innova Varian NMR spectrometer at the Serveis Centrals d'Instrumentació Científica de la Universitat Jaume I. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with E. Merck precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all reactions were carried out under argon atmosphere with magnetic stirring.

5.2. General experimental procedure for the protection of amines

To an ice-bath cooled solution of the amine (1 mmol) in an aqueous solution of 2 M sodium hydroxide (1 mL, 2 mmol) was added the corresponding alkyl chloroformate (see Table 1) (1 mmol). The resulting mixture, cooled with the ice-bath, was stirred for 1 h and then was stirred at room temperature for 45 min. The reaction mixture was carefully neutralized using 1 M HCL solution and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was submitted to the next step without any further purification.

5.3. General experimental procedure for addition of Grignard reagents to carbamates

To an ice-bath cooled solution of the carbamate (1 mmol) in THF (6 mL) was added the corresponding Grignard reagent (6 mmol) (see Table 1). The resulting mixture was stirred while being cooled with an ice-bath for 10 min and then stirred at room temperature for 24 h. The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified by silica gel chromatography, eluted with hexanes/EtOAc (7:3), (6:4) and EtOAc to afford the corresponding amide (see Table 1).

5.4. General experimental procedure for one-pot transformation of amines into amides

To an ice-bath cooled solution of the amine (1 mmol) in THF (6 mL) was added triethylamine (3 mmol) and then the corresponding alkyl chloroformate (1 mmol). The resulting mixture was stirred while being cooled by an ice-bath for 1 h and then stirred at room temperature for 45 min. The reaction mixture was cooled with an ice-bath and the corresponding Grignard reagent (6 mmol) was added (see Table 2). The resulting mixture was stirred while being cooled with the ice-bath for 10 min and then stirred at room temperature for 24 h. The reaction was cautiously

quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified by silica gel chromatography, eluted with hexanes/EtOAc (7:3), (6:4) and EtOAc to afford the corresponding amide (see Table 2).

Acknowledgment

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