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First Carbamates Conversion to Amides by Simple Alkyl Group Transfer from Trialkylalanes

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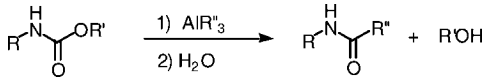
ABSTRACT



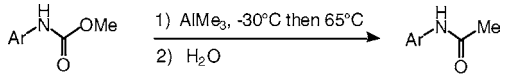
***N*-Monosubstituted carbamates are cleanly converted to amides under treatment with trialkylaluminum. This reaction involves an aluminum-assisted internal delivery of alkyl groups. It can be applied to new and mild protecting group strategies for alcohols.**

Adding a nucleophile to an ester or an amide without touching a ketone either present or formed in the medium has been a challenging problem for chemists in the past decades.[1] Most solutions proposed have dealt with the stabilization of the ketones through tetrahedric adducts stable in the reaction medium. The overall transformation represents a formal reactivity inversion between ketones and esters. Similar conversion of carbamates into amides is less well documented; it has been mostly performed with lithium anions or dianions whose nucleophilicity does not allow the presence of sensitive groups.[2] Furthermore, these lithium anions are all characterized by the presence of a proximal chelating function (ketone,[2a] oxazol,[2b] sulfone,[2c] phosphonate[2d]) associated with the stabilization of the adducts. There is still a need for a simple and mild conversion of carbamates.

Following our recent study on the interaction of trialkylaluminums with hydrazones and aldehydes,[3] we became interested in the reactions of trialkylaluminum compounds with carbamates. We expected that easy formation of *N*-aluminated complexes from monosubstituted carbamates may promote vicinal alkyl group delivery under mild conditions.

When $AlMe_3$ (3 equiv) was added to a solution of **1a** in 1,2-dichloroethane at −30 °C, fast gas evolution was observed; the solution was then heated to 65 °C forming after 2 days acetamide **2a** in good yield (Scheme 1).

Scheme 1



1a **2a**

Several *N*-monoalkyl and -monoaryl carbamates gave similar results with various alkylaluminum derivatives as shown in Table 1. Trimethylaluminum was the most reactive alane giving faster and higher yielding reactions for all carbamates tested (Table 1). In the case of carbamate **1e**, benzyl alcohol could be recovered in good isolated yield (80%) along with expected amide **2h**.

This reaction represents one of the first straightforward transformations of carbamates into simple alkylamides (ac-

(1) For typical examples see: (a) Nahm, S.; Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Hlasta, D.; Court, J. *Tetrahedron Lett.* **1989**, *30*, 1773−1776. (c) Chung, E.; Cho, C. W.; Ahn, K. *J. Org. Chem.* **1998**, *63*, 7590−7591.

(2) (a) Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566−2570. (b) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231−234. (c) White, J. D.; Blakemore, P. R.; Milicevic, S.; Choudhry, S. C.; Cupano, J.; Serico, L. *Org. Lett.* **2002**, *4*, 1803−1806. (d) Tay, M. K.; About-Jaudet, E.; Savignac, P. *Tetrahedron* **1989**, *45*, 4415−4430.

(3) El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* **2003**, *68*, 8733−8735.

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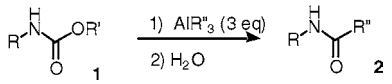
Table 1. Trialkylaluminum-Induced Reaction of Carbamate **1** To Form Amide **2**



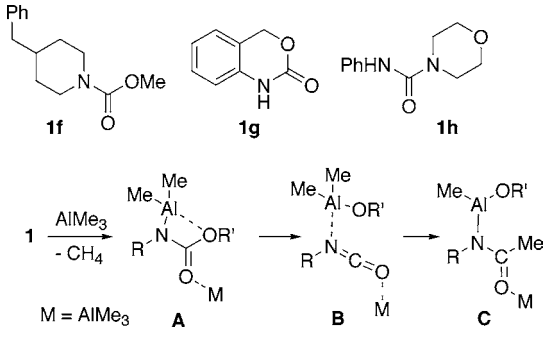
entry	**1**	**2** (yield %)	R[a]	R′	R″	time[b] (h)
1	**1a**	**2b** (67)	4-ClPh	Me	Et	72
2	**1a**	**2c** (63)	4-ClPh	Me	*i*-Bu	168
3	**1b**	**2d** (66)	CH_2Ph	Me	Et	72
4	**1b**	**2e** (67)	CH_2Ph	Me	Me	48
6	**1c**	**2f** (73)	$Ar(CH_2)_2$	Me	Et	96
7	**1d**	**2g** (71)	$Ar(CH_2)_2$	Ph	Et	72
8	**1e**	**2h** (73)	$Ar(CH_2)_2$	CH_2Ph	Et	84

[a] Ar = 3,4-dimethoxyphenyl. [b] To a solution of **1** (2 mmol) in dry 1,2-dichloroethane (10 mL) at −30 °C is added AlR″$_3$ (6 mmol as a 2 M solution in toluene). After removal of the cold bath, the mixture is stirred at 65 °C for the time given in the table. Addition of a saturated aqueous solution of dipotassium L-(+)-tartrate followed by usual workup and column chromatography afford amides **2**.

etamides, propionamides, ...); besides several one-pot conversions limited to specific carbamates,[4] the synthesis of amides from carbamates usually requires a two-step procedure with intermediate conversion to amine under strong basic medium.[5]

The mechanism of the reaction probably involves an activation of the carbamate through *N*,*O*-aluminated chelate **A**[6] followed by alkoxy migration to give isocyanate **B** and amide **C** (Scheme 2); the latter remains unreactive under the

Scheme 2



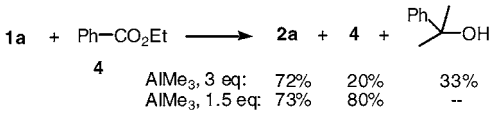
reaction conditions, forming the final amide **2** after hydrolysis. The absence of reaction observed with carbamate **1f**, **1g** and urethane **1h** is consistent with an activation of the reaction through intermediates related to **A**.

(4) (a) Li, W. R.; Yo, Y. C.; Lin, Y. S. *Tetrahedron* **2000**, *56*, 8867−8875. (b) Nazih, A.; Heissler, D. *Synthesis* **2002**, 203−206. (c) Ihara, M.; Hirabayashi, A.; Taniguchi, N.; Fukumoto, K. *Heterocycles* **1992**, *33*, 851−858.

(5) For typical examples of carbamates conversion to acetamides, see: (a) Masatshi, K.; Kunitomo, A.; Toshiyuki, K.; Masanori, H.; Tokushi, H.; Yoshiyuki, A.; Tadashi, M.; Masafuni, A.; Noriyoshi, N.; Makio, O.; Yukio, H. *J. Med. Chem.* **2000**, *43*, 2946−2961. (b) Tanida, H.; Tsuji, T.; Irie, T. *J. Org. Chem.* **1966**, *31*, 3941−3947.

The importance of *N*-aluminated complex type **A** in the vicinal delivery of the alkyl group from the alane can be further substantiated by the following competitive experiment using an equimolar mixture of carbamate **1a** and ethylbenzoate **4**. With 3 equiv of trimethylaluminum and after complete conversion of carbamate **1a** into amide **2a**, the starting ester was recovered in low yield along with alcohol **5** resulting from double addition of the alane to the ester. Though slower, the reaction is still effective with 1.5 equiv of alane, leaving now the ester unaffected after complete conversion of the starting carbamate (Scheme 3).

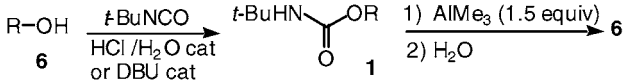
Scheme 3

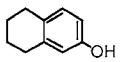
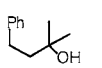
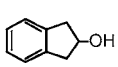


This reaction opens the way for new protection/deprotection strategies using carbamates. Besides the usual benzyl or BOC-type carbamates amenable to easy degradation through hydrogenolysis or acidic treatments, carbamate deprotection usually suffers from the need for harsh basic conditions.

Taking into account the very easy carbamate formation by HCl-catalyzed addition of alcohol to isocyanate,[7] this new alkylaluminum cleavage of carbamates brings a very efficient way to recover unprotected alcohols. This strategy was applied successfully using *tert*-butyl isocyanate and various alcohols, as shown in Table 2. Most noteworthy is the ability

Table 2. Trialkylaluminum-Induced Reaction of Carbamate **1** To Form Amide **2** and Alcohol **6**[a]



Entry	**1** (Yield from 6)*	**6** (Yield from **1**)**		Time
1	**1i** (91% -DBU)	**6a** (95%)		13 h
2	**1j** (81% -HCl)	**6b** (89%)		18 h
3	**1k** (95% -HCl)	**6c** (87%)		17 h

[a] Notes as follows: (*) To a solution of **6** in CH_2Cl_2 (1 M) was added *t*-BuNCO (1 equiv) and a 37% solution of HCl in water (0.05 equiv, **1j**,**1k**) or DBU (0.05 equiv, **1i**). (**) To a solution of carbamate **1** (2 mmol) in dry 1,2-dichloroethane (10 mL) at −30 °C is added $AlMe_3$ (3 mmol) as a solution in toluene. After removal of the cold bath, the mixture was let for 15 min at room temperature and then stirred at 65 °C for the time given in the table. Usual treatment affords alcohol **6**.

to protect tertiary alcohol **6b** without formation of elimination compounds during carbamate synthesis and cleavage.

In summary, we have disclosed a mild cleavage reaction of carbamates that can find uses in new protection, depro-

tection strategies for alcohols. This reaction represents to our knowledge the first formation of amides by simple alkyl group additions to carbamates. This was made possible by an activation of the carbamate through the formation of an *N*-aluminated complex. Further activations of NH acidic compounds using alkylaluminum chemistry are under study in our research group.

(6) Though adducts between alanes and carbamates have been described as solids and shown to exhibit a reversible Al shift from N to O (carbonyl), the lack of reactivity of **1g** makes us believe that adducts type A could be the reactive intermediate in this reaction: Hirabayashi, T.; Sakakibara, T.; Ishii, Y. *J. Organomet. Chem.* **1971**, *32*, C5−C6.

(7) These additions are described using an ether solution of HCl as catalyst. A few drops of concentrated HCl in water gives also satisfying results: Benalil, A.; Roby, P.; Carboni, B.; Vaultier, M. *Synthesis* **1991**, 787−788.

Supporting Information Available: Synthetic procedures for carbamate formation and cleavage to amides along with analytical data for unknown carbamatesand amides. This material is available free of charge via the Internet at http://pubs.acs.org.

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