A Convenient and General Synthesis of Alkylcarbamates from Tertiary Isocyanates and Alcohols

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Reaction of primary, secondary and tertiary alkyl isocyanates with benzyl alcohol, *tert*-butyl alcohol or 1-adamantanol in the presence of 5% hydrogen chloride provides a mild and convenient method for alkyl alkylcarbamate synthesis.

Alkyl isocyanates react slowly at room temperature with secondary and tertiary alcohols and, under thermal conditions, often give low yields of expected carbamates and variable amounts of elimination products. 1,2 Therefore, catalysis of alcohol/isocyanate reactions is a topic which has received a great deal of interest³ resulting in the use of several effective catalysts including organolead4 and organotin⁵ compounds, lithium alkoxide,² carboxylic acids, 6 tertiary amines 7 and light. 8 Recently, Duggan et al.9 recommended the activation of alkyl isocyanates with copper(I) chloride in the presence of one equivalent of primary, secondary or tertiary alcohols in dimethylformamide at room temperature. Moderate to good results were obtained with 1-adamantanol whereas with tert-butyl alcohol, it was necessary to use five equivalents of alcohol to ensure good yields.

We report here a very simple high yield method for the formation of alkyl alkylcarbamates 3 via hydrogen chloride activation of alkyl isocyanates 1 in the presence of alcohols according to the Scheme.

In a typical procedure, the alcohol (1.5 equiv) was added to a mixture of the isocyanate (1 equiv) and HCl (0.05 equiv) in dichloromethane at room temperature. After 5 hours, the reaction was complete leading to carbamates 3 which were isolated in excellent yields (Table).

In the absence of catalyst, the reaction was observed to be sluggish as it is demonstrated by the following observations. The reaction of benzyl alcohol and propyl isocyanate proceeded only to about 20% completion at room temperature in two days, but was complete after 23 hours in refluxing benzene. With *tert*-butyl alcohol and 1-adamantanol, no reaction was observed after 48 hours at ambient temperature. In refluxing benzene, the isocyanate was completely consumed after 70 and 88 hours, respectively.

The hydrogen chloride catalyzed addition¹⁰ of alcohols to isocyanates proceeds quite efficiently at room tempera-

Table. Alkylcarbamates 3 Prepared

Prod- uct	Yield ^a (%)	mp (°C) ^b [bp (°C)/mbar]	Molecular Formula c	IR (Nujol or film) v_{NH} , $v_{C=0}$, (cm ⁻¹)	1 H-NMR (CDCl ₃ /TMS) δ , J (Hz)
3a	92	34 [74/0.001]	C ₁₁ H ₁₅ NO ₂	3330, 1705	0.87 (t, 3H, $J = 7.2$), 1.47 (sext, 2H, $J = 7.2$), 3.12 (q, 2H,
3b	94	[40/0.001]	$C_8H_{17}NO_2$	3340, 1690	J= 6.6), 5.0 (br s, 1 H), 5.10 (s, 2 H), 7.0-7.30 (m, 5 H) 0.87 (t, 3 H, J = 7.2), 1.40 (s, 9 H), 1.47 (sext, 2 H, J = 7.2), 3.03
3c	86 d	68	$\mathrm{C_{14}H_{23}NO_2}$	3340, 1680	(q, 2H, J = 6.6), 4.6 (br s, 1 H) 0.93 (t, 3 H, J = 7.2), 1.50 (sext, 2 H, J = 7.2), 1.6–1.8 (m, 6 H),
3d	98	57 [60/0.001]	$\mathrm{C_{11}H_{15}NO_2}$	3330, 1690	2.0–2.3 (m, 9H), 3.08 (q, 2H, J = 6.6), 4.55 (br s, 1H) 1.10 (d, 6H, J = 6.5), 3.80 (oct, 1H, J = 6.5), 4.85 (br s, 1H), 5.05
3e	96	74 [42/0.001]	$C_8H_{17}NO_2$	3340, 1700	(s, 2H), $7.1-7.4$ (m, 5H) 1.15 (d, 6H, $J = 6.5$), 1.47 (s, 9H), 3.75 (oct, 1H, $J = 6.5$), 4.5
3f	89 ^d	100	$\mathrm{C_{14}H_{23}NO_2}$	3320, 1670	(br s, 1 H) 1.15 (d, 6 H, J = 6.5), 1.5–1.8 (m, 6 H), 2.0–2.3 (m, 9 H), 3.75 (oct, 1 H, J = 6.5), 4.37 (br s, 1 H)
3g 3h 3i 3j	90 85 96 ^d 96	[64/0.001] 50 [34/0.001] 120 88 [58/0.001]	$\begin{array}{c} C_{12}H_{17}NO_2 \\ C_9H_{19}NO_2 \\ C_{15}H_{25}NO_2 \\ C_{13}H_{19}NO_2 \end{array}$	3340, 1710 3300, 1700 3350, 1675 3380, 1675	1.33 (s, 9 H), 4.7 (br s, 1 H), 5.05 (s, 2 H), 7.1–7.4 (m, 5 H) 1.30 (s, 9 H), 1.45 (s, 9 H), 1.45 (s, 9 H), 4.5 (br s, 1 H) 1.33 (s, 9 H), 1.5–1.8 (m, 6 H), 2.0–2.2 (m, 9 H), 4.5 (br s, 1 H) 1.42 (s, 9 H), 1.45 (d, 3 H, $J = 6.9$), 5.1–4.5 (m, 2 H), 7.1–7.4 (m, 5 H)

^a Yield of isolated pure product based on 1.

Uncorrected

Satisfactory microanalyses obtained: $C \pm 0.40$, $H \pm 0.26$, $N \pm 0.32$.

Purified by column chromatography (eluent hexane/Et₂O, 80: 20: 3c R_f 0.44; 3i R_f 0.46).

ture with benzyl, tert-butyl and 1-adamantyl alcohols and isocyanates substituted with primary, secondary and tertiary alkyl groups as can be seen from the Table. Concerning the mechanism of this reaction, the key to this successful catalysis appeared to be the formation of the carbamoyl chlorides 4 which may be considered as an activated form of an isocyanate through the contribution of 4'. This addition product has already been described in the literature¹¹ and its structure has been confirmed by following the addition of hydrogen chloride to isopropyl isocyanate using 75.5 MHz ¹³C-NMR. The ¹³C signal of the sp carbon of the isocyanate at $\delta = 120$ was replaced by the signal at $\delta = 146$ of the sp^2 carbon of the carbamoyl chloride. Almost the same chemical shift ($\delta = 148$) was observed in the case of the commercially available diethylcarbamoyl chloride.

This approach constitutes therefore a mild an efficient route to carbamates derived from sterically hindered alcohols. For example, N-Boc derivatives are easily prepared from isocyanates which are accessible from a wide variety of substrates.¹²

The alcohols and isocyanates were purchased from Janssen Chemical Company and distilled under N_2 prior to use. Anhydrous CH_2Cl_2 was prepared by distillation over P_2O_5 under N_2 . The column chromatography was performed on silica gel (70–230 mesh) purchased from Merck, a 80:20 mixture of hexanes and Et_2O being used as the eluent. 1H -NMR spectra were recorded on

a Bruker WP 80 C (80 MHz) spectrometer. IR Spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Melting points were taken on a Kofler apparatus and are uncorrected. Microanalyses were performed by the Central Laboratory for analysis, C.N.R.S., Lyon (France).

Alkyl Alkylcarbamates 3; General Procedure:

Alcohol 2 (15 mmol) is added to a solution of alkyl isocyanate 1 (10 mmol) and HCl (0.5 mmol, 1.7 mL of a 0.3 M HCl solution in CH₂Cl₂) in CH₂Cl₂ (20 mL). After 5 h, the solvent is removed under vacuum and the crude product is purified by distillation or by column chromatography on silica gel.

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- (10) It is also noteworthy that the use of 5% commercial Me₃SiCl instead of HCl gives essentially the same result. It could be the consequence, either of the presence of HCl in the unpurified Me₃SiCl or of the formation of HCl from the reaction of Me₃SiCl with ROH.
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