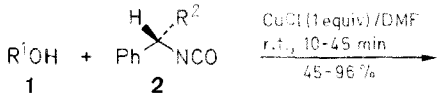
Copper(I) Chloride Catalyzed Addition of Alcohols to Alkyl Isocyanates. A Mild and Expedient Method for Alkyl Carbamate Formation

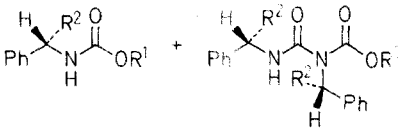
M.E. Duggan,* J.S. Imagire

Merck Sharp & Dohme Research Laboratories, West Point, PA 19486, USA

Treatment of alkyl isocyanates with copper(I) chloride in the presence of primary, secondary or tertiary alcohols provides a mild and efficient method for alkyl carbamate formation.

It is well known that aryl isocyanates are much more reactive toward alcohols than are their alkyl counterparts.[1] Aryl isocyanates react with alcohols at room temperature while alkyl isocyanates react only at elevated temperatures. This feature presents a problem when either a reactant or product is thermally unstable. Although the effects of metal complexes on polyurethane formation have been studied extensively, no general synthetic method has been developed.[2] We envisioned that copper(I) chloride might serve as an efficient catalyst for urethane formation since it catalyzes the reaction of alcohols with diimides.[3] In this communication we report a mild method for the formation of alkyl carbamates **3** via copper(I) chloride activation of alkyl isocyanates **2** in the presence of primary, secondary, or tertiary alcohols.





3 4

Educts		Product
1	R^2 of **2**	**3**
benzyl alcohol	H	**a**
endo-bicyclo[2.2.1]heptan-2-ol	H	**b**
(*S*)-(−)-ethyl lactate	CH_3	**c**
1,2,3,4-tetrahydro-1-naphthol	H	**d**
(*d,l*)-1-hydroxy-1-phenyl-3-butane	H	**e**
1-adamantanol	H	**f**
1-adamantanol	CH_3	**g**
tert-butyl alcohol	H	**h**
mevalonolactone	H	**i**

Table. Alkyl Carbamates **3** Prepared

Product	Yield (%)	mp (°C) (ethyl acetate/hexanes)	Molecular Formula[a]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$, TMS) δ, J (Hz)	MS (70 eV) m/z (%)
3a	96	68–69	$C_{15}H_{15}NO_2$ (241.3)	3440, 1715	7.30 (m, 10H); 5.16 (s, 2H); 5.06 (br s, 1H); 4.39 (d, J = 5, 2H)	241 (M^+, 4)
3b	84	83–84	$C_{15}H_{19}NO_2$ (245.3)	3440, 1710	7.30 (m, 5H); 4.5 (m, 1H); 4.36 (d, J = 6, 1H); 2.50–1.20 (m, 10H)	245 (M^+, 7)
3c	81	35–37	$C_{14}H_{19}NO_4$ (265.3)	3430, 1730, 1710	7.30 (m, 5H); 5.50 (m, 1H); 5.08 (q, J = 7, 1H); 4.82 (m, 1H); 4.18 (m, 2H); 4.17 (q, J = 7, 2H); 1.48 (d, J = 7, 3H); 1.41 (d, J = 7, 3H); 1.27 (t, J = 7, 3H)	265 (M^+, 5)
3d	77	94–95	$C_{18}H_{19}NO_2$ (281.3)	3440, 1705	7.40–7.10 (m, 10H); 5.94 (t, J = 4, 1H); 4.98 (br s, 1H); 4.40 (d, J = 6, 2H); 2.80 (m, 2H); 2.00 (m, 4H)	281 (M^+, 6)
3e	55	oil	$C_{18}H_{19}NO_2$ (297.3)	3440, 1705	7.27 (m, 10H); 6.16 (br t, J = 6, 1H); 4.99 (br s, 1H); 4.34 (br s, 2H); 3.10 (dd, J = 17, 8, 1H); 2.82 (dd, J = 17, 4, 1H); 2.16 (s, 3H)	297 (M^+, 6)
3f	58	110–111	$C_{18}H_{23}NO_2$ (285.4)	3430, 1710	7.30 (m, 5H); 4.91 (m, 1H); 4.30 (d, J = 5, 2H); 2.15 (m); 1.65 (m)	285 (M^+, 7)
3g	78	123–125	$C_{19}H_{25}NO_2$ (299.4)	3440, 1710	7.30 (m, 5H); 5.00 (m, 1H); 4.78 (br s, 1H); 2.15 (m); 1.61 (m); 1.42 (d, J = 7, 3H)	299 (M^+, 3)
3h	45 (91)[b]	48–50	$C_{12}H_{17}NO_2$ (207.3)	3440, 1710	7.27 (m, 5H); 4.8 (br s, 1H); 4.32 (d, J = 6, 2H); 1.47 (s, 9H)	150 (M^+ − t-Bu, 11)
3i	80	167–168	$C_{14}H_{17}NO_4$ (263.3)	3440, 1710	7.30 (m, 5H); 5.18 (m, 1H); 4.36 (m, 4H); 3.08 (dd, J = 18, 2, 1H); 2.67 (m, 1H); 2.51 (dd, J = 18, 1, 1H); 2.00 (m, 1H); 1.61 (s, 3H)	263 (M^+, 16)

[a] Satisfactory microanalyses obtained: C, H, N ±0.30.

[b] Alcohol (5.0 equiv).

A typical procedure involves the addition of the alkyl isocyanate (1.0 mmol) to a stirred green mixture of the alcohol **1** (1.0 mmol), reagent grade CuCl (1.0 mmol), and dry DMF at ambient temperature. When all isocyanate was consumed (monitored by TLC), the reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel. A number of examples utilizing this method are depicted in the table. In all cases the only products detected were the carbamate **3** and the *N*-carbamoylated urethane **4**.[4] The carbamate **3a** was quantitatively converted to the *N*-carbamoylated **4a** when treated with excess **2** in the presence of CuCl, thus implicating **3** as the precursor to **4**. Diminished yields of **3** with less reactive alcohols, such as *tert*-butyl alcohol **1h**, are due to an increase in the amount of **4**. This problem was circumvented by using excess alcohol to afford a high yield of the *tert*-butoxycarbonyl(Boc)-protected amine **3h**. The scope of this method is further demonstrated by the preparation of the unstable carbamate **3c** and lactone **3i**.[5] Under thermal conditions, in the absence of CuCl, none of the desired products **3c** and **3i** were isolated. Although one equivalent of CuCl was used in these examples, equivalent product yields were obtained by the use of 0.1 equivalents of CuCl albeit at longer reaction times. In addition, while CuI also serves as catalyst, CuCN, $CuCl_2$, and $CuBr \cdot SMe_2$ do not.

This new method constitutes a mild and efficient route to alkyl carbamates from the corresponding alkyl isocyanates and alcohols. It is especially useful for hindered alcohols and thermally sensitive compounds.

The alcohols **1a–i** were purchased from Aldrich Chemical Company except for **1e** which was prepared by a previously reported procedure.[6] Anhydrous DMF was obtained from Aldrich Chemical Company and CuCl was obtained from J. T. Baker Chemical Company. Melting points were taken using a Thomas-Hoover apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian XL-300 (300 MHz) instrument. IR spectra were recorded on a Perkin-Elmer 1420 instrument. Mass spectra were obtained using a VG model 7035 spectrometer with either EI or FAB ionization.

Alkyl Carbamates 3; General Procedure:
Alkyl isocyanate **2** (1.0 mmol) is added to a green heterogeneous mixture of alcohol **1** (1.0 mmol), reagent grade CuCl (1.0 mmol), and dry DMF (5 mL) at r.t. After 10 to 45 min the reaction mixture is diluted with Et_2O (20 mL), washed with H_2O (10 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The crude product **3** is chromatographed on a silica gel column (20 cm, 2 cm, 230–400 mesh, eluent 10 to 20% EtOAc/hexanes) to furnish pure **3**.

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