

Highly Selective Generation of Urethanes from Amines, Carbon Dioxide and Alkyl Chlorides

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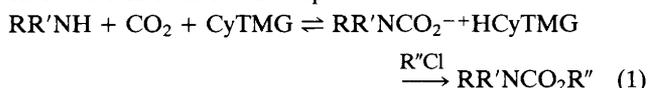
Generation of carbamate anions from either a primary or secondary amine, carbon dioxide and a stoichiometric amount of a pentaalkylguanidine followed by the addition of alkyl chlorides gives high yields of urethanes.

The most important pathway towards the synthesis of polyurethanes rests on phosgene/isocyanate technology.¹ Because of the toxicity of these materials a significant effort has been undertaken to find new methods for making polyurethane materials.² Our approach centres on the use of carbon dioxide as a phosgene replacement.

We have successfully synthesized urethanes in excellent yields with virtually 100% selectivity under mild conditions from amines, carbon dioxide and alkyl chlorides using conditions which enhance the nucleophilic nature of the oxygen centre of the carbamate anion.³ The key to this chemistry lies in the use of sterically hindered, powerful organic bases (*i.e.* pentaalkylguanidines)⁴ to drive the formation of carbamate and also to increase the nucleophilicity of the oxygen centre of the carbamate anion.

For example, addition of carbon dioxide, 80 psig, to an acetonitrile solution of diethyl amine and a stoichiometric amount of *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine (CyTMG) causes an exothermic reaction generating the carbamate anion of diethylamine. Rapid addition of a solution of benzyl chloride in acetonitrile to the reaction mixture under 80 psig of carbon dioxide, followed by heating the reaction mixture to 40 °C for 1 h gives a 95% yield of *N,N*-diethyl

benzylcarbamate by GC and a 64% isolated yield of the carbamate ester after work-up.



This procedure was repeated with *n*-butylamine giving a 95% GC yield (64% isolated) of *N*-butyl benzylcarbamate, eqn. (1) (see Table 1 for additional examples—isolated yields are unoptimized).

An initial study of the reaction conditions of the formation of benzyl carbamates was completed using *n*-butylamine as a model system and the results of this study which show the sensitivity of this reaction to the nature of added base is given in Table 2. Key to the successful generation of urethanes *via* oxygen centred attack *vs.* nitrogen attack of a carbamate anion on alkyl chlorides rests in the choice of base. The appropriate base must not only be capable of driving the equilibrium of carbamate formation (*i.e.* high basicity) but also capable of generating a counterion that is highly polarizable. The use of highly polarizable cationic counterion (*i.e.* the pentaalkylguanidinium cations) creates a 'naked' anion which is more available for nucleophilic attack on an electrophilic substrate (initial results from conductance measurements supports this).

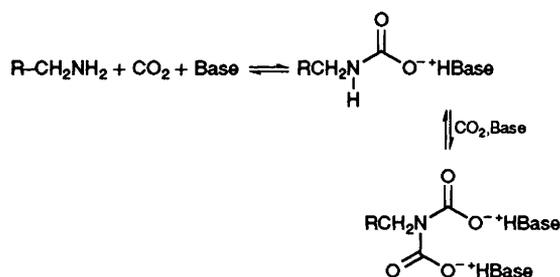


Table 1 Reaction of carbamate (generated from RR'NH and CO₂) with alkyl chloride^a

RR'NH	R'Cl	T/°C	Urethane (GC) (%)	Urethane (isolated) (%)
Et ₂ NH	PhCH ₂ Cl	40	95	47
Bu ₂ NH	PhCH ₂ Cl	40	95	64
BuNH ₂	PhCH ₂ Cl	55	95	64
Bu ^s NH ₂	PhCH ₂ Cl	55	89	44
Bu ⁿ NH ₂	PhCH ₂ Cl	55	90	41
CyNH ₂	PhCH ₂ Cl	55	97	50
PhNH ₂	PhCH ₂ Cl	55	90	64
1,4-(NH ₂ Cy) ₂ CH ₂ ^b	PhCH ₂ Cl	55	—	78
1,4-H ₂ NC ₆ H ₄ NH ₂	PhCH ₂ Cl	55	—	70
Et ₂ NH	BuCl	70	97	61
BuNH ₂ ^b	Cl(CH ₂) ₄ Cl	85	91.5	77
Et ₂ NH	ClCH ₂ CH ₂ Cl	70	85	45
1,4-NH ₂ C ₆ H ₄ NH ₂	EtCl	85	—	73
1,2-(NH ₂) ₂ Cy	EtCl	80	—	60
1,4-(NH ₂) ₂ Cy	EtCl	80	—	60.5

^a All reactions run under 80–160 psig (1 psig = 689 Pa) CO₂ in acetonitrile using CyTMG as base and isolated yields are unoptimized. All reactions were run to completion and GC yields were calculated *vs.* biphenyl used as internal standard. ^b Reaction run in 1-methyl-2-pyrrolidinone.

Table 2 Effect of base on conversion of butyl amine, carbon dioxide, and benzyl chloride to *N*-butylbenzyl carbamate^a

Base ^b	Urethane GC yield (%)	Nitrogen derived products ^c (%)
Butyl amine	2	77
PMP	7	92.5
Bu ^t DEF	48	34
TMG	62	22
DBU	69	18
MTDB	86	14
CyTEG	92	14
CyTEG	94	9

^a All reactions run at 55 °C under 80 psig carbon dioxide pressure and run to completion based on butyl amine. GC yields determined using biphenyl as internal standard. ^b PMP = 1,2,2,6,6-pentamethylpiperidine; Bu^tDEF = *N*-*tert*-butyl-*N'*,*N'*-diethylformamidine; TMG = *N,N,N',N'*-tetramethylguanidine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; MTDB = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; CyTEG = *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetraethylguanidine. ^c Nitrogen derived products include, *N*-butyl-*N*-benzyl amine, *N*-butyl-*N,N*-dibenzyl amine and *N*-butyl-*N*-benzyl benzylcarbamate (secondary product derived from the *N*-butyl-*N*-benzyl amine generated). A small amount of dibenzylcarbonate resulting from trace amounts of water in reagents was also detected by GC.

Table 3 Activation parameters for reaction of amine, CO₂, CyTMG^a with benzyl chloride in MeCN

Nucleophile	E _a /kcal mol ^{-1b}	ΔH [‡] /kcal mol ^{-1b}	ΔS [‡] /e.u. ^c
Et ₂ NCO ₂ ⁻	12.4	11.8	-33
Bu ^s NHCO ₂ ⁻	13.4	12.8	-33
Bu ⁿ NHCO ₂ ⁻	24	23.4	-3
PhNHCO ₂ ⁻	14.9	14.3	-28

^a All parameters calculated at 40 °C. ^b kcal mol⁻¹ = 4.184 kJ mol⁻¹. ^c e.u. = 4.184 J K⁻¹.

This effect is similar to that reported for the use of crown ethers or cryptands with potassium salts of carboxylic acids in nucleophilic substitution reactions.⁵

We have also compiled a relative rate of reactivity profile based on the nature of the carbamate anion. The relative rate of reactivity follows the order: $\text{Et}_2\text{NCO}_2^-$ (32) = $\text{Bu}_2\text{NCO}_2^-$ (29) > CyNHCO_2^- (14.5) = $\text{Bu}^s\text{NHCO}_2^-$ (11.9) > PhNHCO_2^- (8.2) \gg n -octyl NHCO_2^- (1.1) = $\text{Bu}^n\text{NHCO}_2^-$ (1). Insight into the large difference in reactivity between various carbamates was obtained from experimentally derived activation parameters in the $\text{S}_{\text{N}}2$ reaction of various carbamates with benzyl chloride giving *O*-benzylic urethanes (Table 3).

Further insight into the difference in reactivity was gained by an investigation of the dependence of rate on carbon dioxide pressure. With *n*-butyl carbamate the rate of reaction significantly decreased with an increase of carbon dioxide pressure (20 psig, $k = 4.8 \times 10^{-4} \text{ dm}^{-3} \text{ mol}^{-1} \text{ s}^{-1}$; 120 psig, $k = 1.8 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$). This effect was not observed with either the diethyl or *s*-butyl carbamates. We postulate that this is owing to the reaction of a second equivalent of carbon dioxide with the *n*-butyl carbamate thereby lowering the reactivity of the oxygen of the carbamate anion; thus, reversible insertion of a second equivalent of carbon dioxide into the remaining N-H occurs giving a dianion as shown below.

In order to determine the viability of possible double carbon dioxide insertion, the addition of $^{13}\text{CO}_2$ to $\text{Et}^{15}\text{NH}_2$ and $\text{Et}_2^{15}\text{NH}$ was studied by ^{15}N NMR spectroscopy. The appearance of a doublet at δ 87.6 for the addition of $^{13}\text{CO}_2$ (atmospheric pressure of carbon dioxide) to $\text{Et}_2^{15}\text{NH}$ with CyTMG as base indicates the generation of $\text{Et}_2^{15}\text{N}-^{13}\text{CO}_2-\text{H}^+\text{CyTMG}$ with $J_{\text{N-C}} = 19.3 \text{ Hz}$. The appearance of a triplet centred at δ 129.1 in the ^{15}N NMR spectrum of the product from the addition of $^{13}\text{CO}_2$ (atmospheric pressure of carbon dioxide) to $\text{Et}^{15}\text{NH}_2$ with two equivalents of CyTMG indicates the formation of $\text{Et}^{15}\text{N}(^{13}\text{CO}_2^-)_2$ ($^+\text{HCyTMG}$)₂ with $J_{\text{N-C}} = 15.2 \text{ Hz}$. This result clearly indicates that with ethylamine (and with other amines with the general structure:

RCH_2NH_2) two equivalents of carbon dioxide interact and that this pathway must be considered in reactions involving these substrates.

The discovery that the use of pentaalkylguanidines as a base in the generation of carbamate anions increases the nucleophilicity of the oxygen centre of the carbamate anion has allowed us to generate urethane materials in high yields and with high selectivities. It has also given us the opportunity to investigate the nucleophilic behaviour of the carbamate anion in greater detail.

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