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Conversion of Amines to Carbamoyl Chlorides Using Carbon Dioxide as a Phosgene Replacement

William D. McGhee*, Yi Pan and John J. Talley

Monsanto Company, 800 N. Lindbergh Blvd., St Louis MO 63167

Abstract: Dialkyl carbamates, generated from amines and carbon dioxide, are converted to their corresponding carbamoyl chlorides using thionyl chloride in the presence of added tertiary amine base.

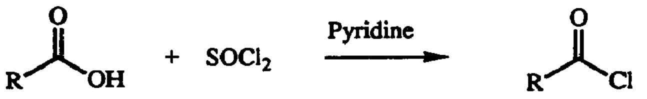
In a previous report we had described the generation of isocyanates from primary amines, carbon dioxide, two equivalents of a strong organic base and various electrophilic dehydrating agents.[1] Of the dehydrating agents investigated we showed that the traditional carbonyl activating agent phosphorous oxychloride gave exceptionally high yields of isocyanates, eq. 1.

$$RNH_2 \quad + \quad CO_2 \quad + \quad 2\,\text{Base} \quad \xrightarrow{POCl_3} \quad RNCO \qquad (1)$$

In this report we will show that under extremely mild conditions secondary amines are converted to their corresponding carbamoyl chloride derivatives with good isolated yields using agents such as $POCl_3$ and $SOCl_2$.

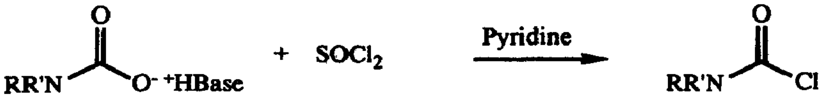
Carbamoyl chlorides are useful intermediates in the synthesis of unsymmetrical ureas and N,N-dialkyl carbamate esters. The most practical method for the generation of carbamoyl chlorides involves the controlled addition of phosgene to a secondary amine.[2] This method is plagued by the use of highly toxic phosgene and the overreaction of the carbamoyl chloride to urea.

It is well known that electrophilic agents such as thionyl chloride readily convert oxygenated organic compounds to chloro derivatives (eq. 2).[3]



(2)

In analogy to the transformation of a carboxylic acid to the acyl chloride we have examined the conversion of a carbamate anion to its corresponding carbamoyl chloride (eq. 3).



(3)

Results: Rapid addition of a pre-formed carbamate anion solution (generated from dialkyl amine, 1 eq. N-cyclohexyl-N',N',N",N"-tetramethylguanidine,[4] and 1 eq. pyridine under atm. carbon dioxide pressure) at -10°C to a solution of thionyl chloride (1 eq.) gave an exothermic reaction. Rapid aqueous extraction (to remove salts and "SO_2") of the crude reaction mixture and distillation of the residue gave good isolated yields of carbamoyl chloride (40-80%). The results of varying the identity of various reagents in this reaction are shown in Table 1.

N,N-Dibutyl Carbamoyl Chloride: In a 100 mL round-bottom flask was added 6.45 g (0.05 mol) dibutyl amine, 4 g (0.05 mol) pyridine, 12.7 g (0.05 mol) N-cyclohexyl-N',N',N",N"-tetraethylguanidine[4] and 40 mL toluene. This solution was cooled to -10°C using an ice salt bath and carbon dioxide was added subsurface to this cooled solution for 30 min. After this period of time the preformed carbamate solution was added all at once by cannula to a cooled (-10°C) toluene (40 mL) solution of thionyl chloride (6 g, 0.05 mol). The reaction mixture was allowed to stir at -10°C for 45 min.

The crude reaction mixture was poured into 100 mL 0.1 M aqueous HCl giving rise to two layers. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. The residue was distilled under vacuum (1 mmHg) at 95-98°C giving 7.62 g (79%) of N,N-dibutyl carbamoyl chloride. I.R. (film) 1734.

Piperidine Carbamoyl Chloride: In a 100 mL round-bottom flask was added 4.25 g (0.05 mol) piperidine, 4 g (0.05 mol) pyridine, 12.7 g (0.05 mol) N-cyclohexyl-N',N',N",N"-tetraethylguanidine and 40 mL toluene. This solution was cooled to -10°C using an ice salt bath and carbon dioxide was added subsurface to this cooled solution for 30 min. After this period of time the preformed carbamate solution was added all at once by cannula to a cooled (-10°C) toluene (40 mL) solution of thionyl chloride (6 g, 0.05 mol). The reaction mixture was allowed to stir at -10°C for 30 min.

The crude reaction mixture was poured into 100 mL 0.1 M aqueous HCl giving rise to two layers. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. The residue was distilled under vacuum (1 mmHg) at 82-84°C giving 4.22 g (52%) of piperidine carbamoyl chloride. I.R. (film) 1732.

Table 1: Conversion of Piperidine to Piperidine Carbamoyl Chloride.[1]

Base[2]	Electrophile	Solvent	%Carbamoyl Chloride[3]
CyTEG	$POCl_3$	CH_2Cl_2	67
CyTEG	$POCl_3$	Toluene	67
CyTEG	$SOCl_2$	CH_2Cl_2	44
CyTEG	"	Toluene	72
CyTEG/pyr	"	Toluene	85
CyTEG/2 pyr	"	Toluene	87
CyTEG/pyr	"	CH_2Cl_2	80
CyTMG/pyr	"	Toluene	79
DBU/pyr	"	Toluene	89
MTBU/pyr	"	Toluene	93
$(i\text{-}Pr)_2NEt$/pyr	"	Toluene	82
Et_3N/pyr	"	Toluene	45
Piperidine/pyr	"	Toluene	77
Piperidine/pyr	"	CH_2Cl_2	75

[1] All reactions run at -10°C under an atmospheric pressure of carbon dioxide and reactions judged to be complete within 15 min. [2] CyTEG = N-cyclohexyl-N',N',N",N"-tetraethylguanidine, CyTMG = N-cyclohexyl-N',N',N",N"-tetramethylguanidine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MTBU = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, pyr = pyridine. [3] All yields are G.C. yields based on biphenyl as internal standard.

Summary: In analogy to the conversion of carboxylic acids to acyl chlorides we have found that carbamic acid derivatives can be converted to carbamoyl chlorides. This reaction was shown to be successful using various bases, including amidines and guanidines. As was shown in the conversion of primary amines to isocyanates, the nature of the base is somewhat important; but is not limited to the guanidines and amidines. Good yields are obtained using di-isopropylethylamine (82% by G.C., see Table 1). It is not clear as to the reasons why added pyridine improves the yield of carbamoyl chloride (from 72 to 85%). It is possible that the pyridine acts as a trap for the sulfur dioxide which is likely formed during the course of the reaction.

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