Isocyanates From Primary Amines and Carbon Dioxide: 'Dehydration' of Carbamate Anions

Thomas E. Waldman and William D. McGhee*

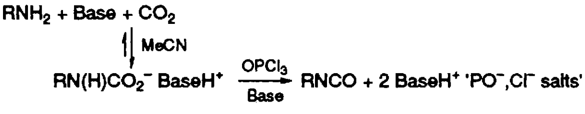
Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63167, USA

Carbamate anions, derived from primary amines CO_2 and an added base (*e.g.* NEt_3), undergo rapid reaction with electrophilic 'dehydrating agents' (*e.g.* $POCl_3$, P_4O_{10}) to give the corresponding isocyanates in excellent yields.

Isocyanates, the primary feedstocks of the polyurethane industry, may be prepared *via* a number of routes, of which only phosgenation is practiced on a significant industrial scale.[1] Owing to the synthetic limitations and toxicity issues associated with phosgenation, much effort has been directed toward alternative routes for the preparation of isocyanates or urethanes.[2,3] In continuing our investigations into the synthetic utility of carbamate anions derived from amines and carbon dioxide, we have examined the reactivity of carbamate anion nucleophiles with electrophilic 'dehydrating agents' (*e.g.* $POCl_3$) as a route to isocyanates.[4]

Herein the facile, high yield conversion of carbamate anions into the corresponding isocyanates is reported. No evidence of carbodiimide or isocyanurate formation is observed under the extremely mild conditions employed (1 atm. CO_2, 0–25 °C, <1 h) and inhibition of symmetric urea formation is readily accomplished *via* appropriate choice of reaction conditions. The mild conditions allow for the preparation of highly functionalised isocyanates as well as polyisocyanates in excellent yield.

Generation of carbamate anions is readily accomplished by the addition of carbon dioxide (1 atm) to a solution of the primary amine and 1–4 equiv. of an organic base [*e.g.* NEt_3, *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetraethylguanidine, *tert*-butyliminotris(dimethylamino)phosphorane (P_1-Bu^t), quinuclidine]. In general, carbamate anions derived from NEt_3 and CO_2 are utilised as slurries regardless of solvent, whereas the pentaalkylguanidine or phosphazene bases give homogeneous solutions. In either case, the addition of one equivalent of $POCl_3$ or PCl_3/NH_2 to the reaction mixture gives rise to an exothermic reaction following which the desired isocyanate could be isolated in excellent yield [Table 1, eqn. (1)]. Studies of the reaction stoichiometry suggest that only two chlorides are sufficiently reactive to give high yields of the isocyanate. For example, the dehydration of cyclohexyl carbamate (prepared from 5 mmol cyclohexylamine and 15 mmol NEt_3) at 0 °C in acetonitrile under one atm. CO_2 with 0.3–1.0 equiv. of PCl_3/amine gave the following yields of cyclohexyl isocyanate CyNCO: 0.3 equiv. PCl_3, 28% CyNCO; 0.6 equiv. PCl_3, 58% CyNCO; 1.0 equiv. PCl_3, 98% CyNCO.



$$\begin{array}{l} RNH_2 + Base + CO_2 \\ \quad\quad \Big\updownarrow \text{MeCN} \\ RN(H)CO_2^- \; BaseH^+ \xrightarrow[\text{Base}]{\text{OPCl}_3} RNCO + 2\,BaseH^+ \text{ 'PO}^-\text{,Cl}^- \text{ salts'} \end{array} \quad (1)$$

Table 1 Dehydration of carbamate anions with $POCl_3$[a]

RNH_2[b]	Base[c]	CO_2	RNCO GC yield (%)	Isolated yield (%)
C_8H_{17}	NEt_3	80 psig	94	86
C_8H_{17}	NEt_3	1 atm	95	—
Cy	NEt_3	80 psig	98	82
HDA	NEt_3	1 atm	>98	90
MeO-Leu-NH_3Cl[c]	CyTEG/NEt_3	1 atm	—	81
trans-1,4-CHDA	NEt_3	1 atm	96	72
PPDA[c]	CyTEG/NEt_3	80 psig	—	69
Jeffamine D-400[c]	CyTEG/NEt_3	1 atm	—	48
H_6-TDA	NEt_3	1 atm	98	81
TAN	NEt_3	1 atm	94	88

[a] All reactions run as follows: 5 mmol of amine, 15 mmol base/NH_2 and 154 mg of biphenyl (internal standard) were dissolved in 25 ml of acetonitrile and CO_2 (1 atm.) was added for up to 1 h. $POCl_3$ (1 equiv./NH_2) was diluted in 25 ml of acetonitrile and both solutions were cooled to 0 °C prior to addition of the carbamate solution to the $POCl_3$. Reaction progress was monitored by GC analysis until appearance of isocyanate ceased. Isolated yields are reported following an aqueous acid extraction to remove the phosphorous salts and purification by distillation. Virtually identical yields were obtained using 1 equiv. PCl_3/NH_2 under identical conditions. [b] HDA = 1,6-hexamethylenediamine. *trans*-1,4-CHDA = *trans*-1,4-cyclohexyldiamine. PPDA = 1,4-diaminobenzene. Jeffamine D-400® (Texaco) = polyoxoalkylenediamine *ca.* M_r = 400. H_6-TDA = 20% 2,6-diaminomethylcyclohexane; 80% 2,4-diaminomethylcyclohexane (various mixtures of *cis* and *trans* isomers). TAN = 4-aminomethyl-1,8-diaminooctane. [c] 1 equiv. of CyTEG and 2 equiv. of NEt_3 per NH_2 moiety in cases where CyTEG (CyTEG = *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetraethylguanidine) was used. [d] CH_2Cl_2 was used as the solvent.

The extremely powerful dehydrating nature of P_4O_{10} is well documented;[5] thus, it should be an ideal candidate for the dehydration of carbamate anions. When slurries of triethylammonium octyl carbamate anions were added to suspensions of P_4O_{10} in acetonitrile the reactions proceeded only slowly with formation of the symmetric urea as the principle product (Table 2). Formation of the urea co-product can be explained by reaction of the isocyanate with free amine generated by equilibrium loss of CO_2 from the carbamate. Prevention of this 'side-reaction' could be accomplished by either increasing the rate of dehydration relative to urea production or by inhibiting the rate of urea formation. Because of the heterogeneous nature of the reactions the dissolution of P_4O_{10} should increase the rate of dehydration without affecting the rate of urea formation. Indeed, dissolution of P_4O_{10} in acetonitrile[6] followed by addition of the resulting dark brown solution to slurries of octyl carbamate anions gives the desired isocyanate in high yield with only traces of the urea by-product. The reaction stoichiometry is based on 1 equiv. P_4O_{10}/NH_2 and attempts to utilise additional anhydride linkages of P_4O_{10} have led to correspondingly lower yields of the isocyanate.

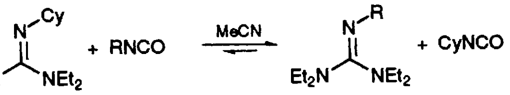
A second approach to inhibiting the formation of urea co-

Table 2 Dehydration of octyl carbamate with P_4O_{10}[a]

Base (equiv. NH_2)	Equiv. P_4O_{10} (equiv. NEt_3)[b]	$C_8H_{17}NCO$ (%)	Dioctyl urea (%)
NEt_3 (2)	1 (0)	2	98
NEt_3 (2)	1 (2)	97	1
NEt_3[c] (4)	1 (0)	62	37
NEt_3[d] (2)	1 (0)	82	17
P_1Bu^t[e] (2)	1 (0)	>99	—
P_1Bu^t (2)	0.5 (0)	27	59
P_1Bu^t (2)	0.5 (2)	19	75
CyTEG[f] (2)	1 (0)	95	5
CyTEG[f] (2)	0.5 (0)	37	58

[a] GC yields are reported relative to biphenyl as internal standard and are based on octyl amine. [b] Triethylamine added to an acetonitrile suspension of P_4O_{10}. [c] P_4O_{10} used as a slurry in acetonitrile. [d] The reaction was performed in a Fisher-Porter apparatus under 1 atm CO_2, 18 h at 25 °C. [e] P_1 Bu^t = *tert*-butyliminotris(dimethylamino)phosphorane. [f] solvent = CH_2Cl_2, CyTEG = *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetraethylguanidine.

products lies in preventing the formation of 'free' amine. The use of strong organic bases *e.g.* pentaalkylguanidines or phosphazenes[7] yields homogeneous carbamates and effectively prevents the equilibrium loss of CO_2 from the carbamate. As expected, the addition of soluble carbamate anions derived from phosphazenes to suspensions of P_4O_{10} in acetonitrile gives rise to exothermic reactions and dissolution of the phosphorous oxide within seconds. Analysis of the reaction mixtures by gas chromatography after five minutes shows virtually quantitative yields of the isocyanates with only trace amounts of the corresponding symmetric ureas. With pentaalkylguanidine bases in polar solvents such as acetonitrile, a subsequent metathesis reaction occurs between the newly generated isocyanate and the guanidine base, [eqn. (2)].[8] Circumvention of this exchange reaction is accomplished by utilizing less polar solvents such as CH_2Cl_2. The utilisation of higher CO_2 pressure also effectively inhibits urea formation; however, for triethylammonium carbamates the reactions proceed slowly.



(2)

The preparation of polyisocyanates, as well as the conversion of functionalized primary amines (*e.g.* isocyanates of amino acid esters and polyether amines) has also been demonstrated. For example, the conversion of 2,4-diaminomethylcyclohexane or hexamethylene diamine at atmospheric CO_2 in acetonitrile with $POCl_3$ gives virtually quantitative yields of the corresponding isocyanates. This is particularly notable in that the corresponding conversion of 2,4-diaminomethylcyclohexane *via* phosgenation gives only low yields of the diisocyanate due to intramolecular formation of cyclic ureas.[9] Similarly, the high yield preparation (>90%) of 4-isocyanatomethyl-1,8-diisocyanatooctane at atmospheric CO_2 pressure and 0 °C in <1 h is unique and demonstrates the synthetic utility of this methodology.

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