BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (5), 1094—1096 (1977)

A Three-Component Reaction of Isocyanides with Halogens and Cyclic Ethers

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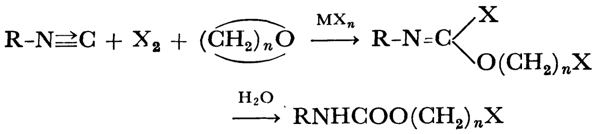
(Received October 8, 1976)

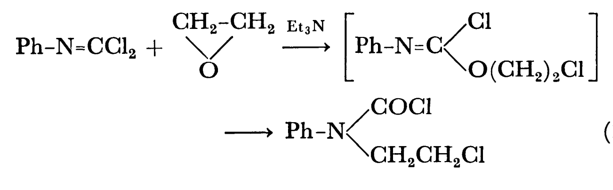
In the presence of a Lewis-acid catalyst, such as $HgCl_2$ or $ZnCl_2$, cyclohexyl isocyanide reacted with chlorine and tetrahydrofuran to give, after hydrolysis, 4-chlorobutyl cyclohexylcarbamate in a fair yield. When one of the reactants was replaced by another isocyanide, bromine, or another cyclic ether, the reactions proceeded similarly, but the corresponding carbamate yields were rather poor.

Isocyanides are known to undergo multi-component reactions[1] in which more than two reactants selectively combine to form a single product, as represented by the Passerini reaction. In an attempt to find a new example of triple addition reactions, reactions of isocyanides with halogens and 3- to 5-membered cyclic ethers were examined in the presence of Lewis-acid catalysts. The ω-haloalkyl carbamates, $RNHCOO(CH_2)_nX$ (n=2—4), which correspond to the hydrolysis products of the 1 : 1 : 1 adducts, were successfully obtained in various yields, by treatment of the reaction mixtures with water. The present paper deals with the new reaction:



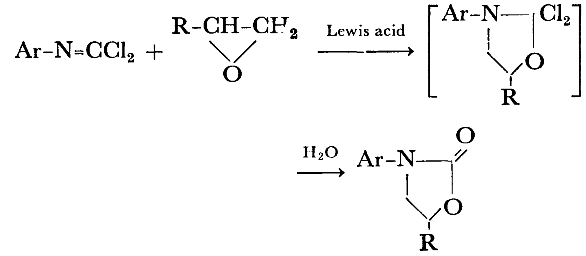
$$\mathrm{R{-}N{\geqq}C + X_2 + (CH_2)_nO \xrightarrow{MX_n} R{-}N{=}C{<}^{X}_{O(CH_2)_nX} \xrightarrow{H_2O} RNHCOO(CH_2)_nX} \qquad (1)$$

In connection with this, phenylcabonimidoyl dichloride has been known to undergo an insertion reaction of ethylene oxide into the C–Cl bond of the dichloride in the presence of triethylamine, the isolated product being not 2-chloroethyl *N*-phenylchloroformimidate, but the isomeric carbamoyl chloride resulting from a Chappmann rearrangement of the expected product (Eq. 2).[2]



(2)

On the other hand, it has also been reported that the $ZnCl_2$- or $SnCl_4$-catalyzed cycloaddition of arylcarbonimidoyl dichlorides to aliphatic epoxides, followed by hydrolysis, gives 3-aryl-5-alkyl-2-oxazolidinones, although the yields are very low (Eq. 3).[3]



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Results and Discussion

When cyclohexyl isocyanide was treated with chlorine in tetrahydrofuran (hereinafter abbreviated as THF) at room temperature in the presence of $HgCl_2$ or $ZnCl_2$ and the reaction mixture was hydrolyzed before isolation, 4-chlorobutyl cyclohexylcarbamate was obtained in a good yield, along with small amounts of various by-products which will be described below. Some results are shown in Table 1.

TABLE 1. REACTION OF CYCLOHEXYL ISOCYANIDE WITH HALOGENS AND THF

Isocyanide 24 mmol: Halogens 72 mmol; THF 360 mmol.
Reaction conditions: 5—10 °C, 1.5 h and 20—25 °C, 50 h.

X_2	Catalyst (mmol)	Yield (%) of cyclo-$C_6H_{11}NHCOO(CH_2)_4X$[c]
Cl_2	None	0[d]
Cl_2	$HgCl_2$, 3	2[e]
Cl_2	$HgCl_2$, 8[a]	0[f]
Cl_2	$HgCl_2$, 8	70
Cl_2	$HgCl_2$, 8[b]	80
Cl_2	$HgCl_2$, 24	67
Br_2	$HgBr_2$, 8	32
Cl_2	$ZnCl_2$, 8	59
Cl_2	$ZnCl_2$, 24	68

a) Reaction conditions: −15 °C, 1 h and −10—0 °C, 5 h. b) Reaction conditions: 55—60 °C, 6.5 h. c) Based on isocyanide (determined by GLC). d) cyclo-$C_6H_{11}N{=}CCl_2$, 90%. e) cyclo-$C_6H_{11}N{=}CCl_2$, 69%. f) cyclo-$C_6H_{11}N{=}CCl_2$, 87%.

When $AlCl_3$ or $FeCl_3$ was used as the catalyst, the reaction was considerably exothermic and afforded mainly a polymeric substance which consists mostly of oligomers of THF rather than the desired carbamate. Moreover, the rcaction without the catalyst yielded only cyclohexylcarbonimidoyl dichloride and no amount of the carbamate could be found in the reaction mixture. In the case of a $HgCl_2$ catalyst, *ca.* 4 mol% (based on chlorine) was found to be insufficient to yield the carbamate predominantly, and the optimum amount was estimated to be *ca.* 10 mol%, although no accurate determination was made.

An increase in the yield of the carbamate was observed for a rise in the reaction temperature. However, the reaction below 0 °C, even in the presence of 11.5 mol% of $HgCl_2$, afforded only the carbonimidoyl dichloride as the reaction product.

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When bromine and $HgBr_2$ were used in place of chlorine and $HgCl_2$, respectively, the reaction with cyclohexyl isocyanide proceeded similarly affording 4-bromobutyl cyclohexylcarbamate, but the yield was rather poor compared with the preparation of the corresponding chlorine compound. An analogous reaction with iodine and HgI_2, however, did not give the desired compound and yielded only a tarry product.

Data on the reaction of some aliphatic and aromatic isocyanides with chlorine in THF are shown in Table 2a. In the case of *t*-butyl isocyanide, the yield of carbamate was rather low. This is probably due to the decreased stability of the intermediate *t*-butylchloroimidoyl cation, which tends to decompose to *t*-butyl cation and ClCN rather easily.[4] Phenyl isocyanide afforded carbamate in a low yield, although the recorded yield was only the isolated yield in this case.

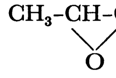
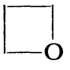
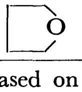
Table 2. Reaction of isocyanides with chlorine and cyclic ethers

(a) Variation of the isocyanide component.
Isocyanides 24 mmol; Cl_2 72 mmol; THF 360 mmol; $HgCl_2$ 8 mmol. Reaction conditions: 55—60 °C, 6.5 h.

Isocyanide	Yield (%) of $RNHCOO(CH_2)_4Cl$[a]	
n-BuNC	R = *n*-Bu,	67
cyclo-$C_6H_{11}NC$	R = cyclo-C_6H_{11},	80
t-BuNC	R = *t*-Bu,	49
PhNC	R = Ph,	44[b]

a) Based on isocyanide (determined by GLC).
b) Isolated yield.

(b) Variation of the cyclic ether component.
Cyclohexyl isocyanide 24 mmol; Cl_2 72 mmol; Cyclic ethers 360 mmol; $HgCl_2$ 8 mmol. Reaction conditions: 5—10 °C, 1.5 h and 20—25 °C, 50 h.

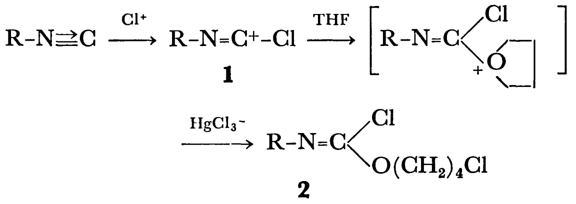
Cyclic ether	Yield (%) of cyclo-$C_6H_{11}NHCOOR$[a]	
	R = $CH_2CH(CH_3)Cl$,	12
	R = $(CH_2)_3Cl$,	37
	R = $(CH_2)_4Cl$,	68

a) Based on isocyanide (determined by GLC).

The $HgCl_2$-catalyzed reaction of cyclohexyl isocyanide with chlorine was also carried out in trimethylene oxide and propylene oxide, for comparison with that in THF. The results are shown in Table 2b. The yields of the corresponding carbamates decreased as the ring size changed from 5 to 3 *via* 4. This order is the same as that obtained for the case of Lewis acid-catalyzed ring-opening polymerization of cyclic ethers.[5]

In this reaction, the chloroimidoyl cation (**1**), formed by the electrophilic addition of Cl^+ to isocyanide, appears to act as a key intermediate. This reacts with THF, and with a complex halide anion successively to afford a chloroformimidate (**2**), which then forms 4-chlorobutyl carbamate (**3**) when hydrolyzed.

$$Cl_2 + HgCl_2 \rightleftharpoons Cl^+ + HgCl_3^- \quad (4)$$



(5)

$$2 \xrightarrow{H_2O} RNHCOO(CH_2)_4Cl \quad (6)$$

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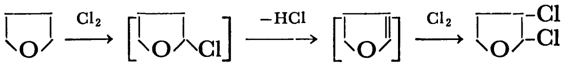
Here, the intermediate **1** may be formed by another route *via* carbonimidoyl dichloride. However, when cyclohexylcarbonimidoyl dichloride was treated with THF in the presence of $HgCl_2$ under the same reaction conditions (20—25 °C, 50 h), the expected carbamate was obtained in only a 6% yield and most of the unreacted dichloride was recovered. Therefore, such a possibility can be ruled out as the main course of the reaction.

Finally, a short comment on the by-products of the reaction must be added. From the reaction mixture of cyclohexyl isocyanide, chlorine, and THF, small amounts of 1,4-dichlorobutane, 4-chloro-1-butanol, bis(4-chlorobutyl) ether, and 2-(4-chlorobutoxy)-3-chlorotetrahydrofuran (**4**) were isolated, along with the carbamate and occasionally with the carbonimidoyl dichloride. It is obvious that all the minor products come from the reaction between THF and chlorine. It has been reported that the chlorination of THF at room temperature results only in 2,3-dichlorotetrahydrofuran (**5**) (Reaction 7).[6] In the presence of a $ZnCl_2$ catalyst, cleavage of THF by **5** is known to afford **4** (Reaction 8).[7] 4-Chloro-1-butanol is probably formed by the action of HCl on THF during the chlorination of THF. This compound would be a precursor of 1,4-dichlorobutane and bis(4-chlorobutyl) ether.



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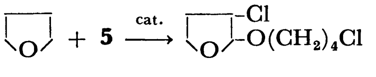

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Experimental

GLC analysis was carried out on a Shimadzu 5APTF apparatus using an EGSS-X(30%)-Chromosorb-W (1 m) column (with N_2 as the carrier gas). The IR spectrum was recorded with a Hitachi EPI-S2 apparatus.

Isocyanides (RNC) were prepared using the method of Ugi *et al.*:[8] R = C_6H_{11}, bp 67—69 °C/20 Torr (lit,[8] bp 67—72 °C/13 Torr); R = *n*-Bu, bp 48 °C/20 Torr (lit,[8] bp 40—42 °C/11 Torr); R = *t*-Bu, bp 48 °C/60 Torr (lit,[8] bp 92—93 °C/750 Torr); R = Ph, bp 61—62 °C/18 Torr (lit,[8] bp 50—51 °C/11 Torr). Trimethylene oxide was prepared from 3-chloropropyl acetate[9] (bp 47—49 °C, lit,[9] bp 47—48 °C). Commercial THF and propylene oxide were used after distillation, while the inorganic substances were used without further purification.

$HgCl_2$-Catalyzed Reaction of Isocyanides with Chlorine and THF. A typical example is given below. Into a stirred solution of $HgCl_2$ (2.2 g, 8 mmol) in THF (29 ml, 360 mmol) containing cyclohexyl isocyanide (2.6 g, 24 mmol), chlorine gas (5.1 g, 72 mmol) was bubbled over a period of 1.5 h, the temperature being maintained at 5—10 °C by cooling with ice water. After stirring for an additional 50 h at 20—25 °C, the reaction mixture was added to a suspension of $CaCO_3$ (5 g) in water (20 ml). The resulting heterogeneous mixture was stirred at 20—25 °C for 3 h. Then ether was added and inorganic precipitates were filtered off. The ether extract was separated from the aqueous layer. This was combined with a dichloromethane extract in the aqueous phase. The combined organic layer was washed with aqueous K_2CO_3 and aqueous NaCl, successively, dried over anhydrous $MgSO_4$, and most of the solvents were evaporated. GLC analysis of the residue using isopropylbenzene, *p*-methoxyacetophenone, and triphenylmethane as internal standards showed the presence of 1,4-dichlorobutane (**6**) (1.4 g, 10.9 mmol), 4-chloro-1-butanol (**7**) (3.5 g, 32.3 mmol), bis(4-chlorobutyl) ether (**8**) (0.6 g, 2.8 mmol), 2-(4-chlorobutoxy)-3-chlorotetrahydrofuran (**4**) (2.9 g, 13.6 mmol), and 4-chloro butyl cyclohexylcarbamate (**3**, R=cyclo-C_6H_{11}) (4.0 g, 17.3 mmol, 72% yield). Distillation afforded the following fractions: fraction A, bp 55—90 °C/25 Torr (3.4 g), fraction B, bp 90—100 °C/3 Torr (3.1 g), fraction C, bp 131—133 °C/3 Torr (4.5 g), and a black semi-solid residue D (1.7 g). The fractions A and B were shown by GLC to be a mixture of **6** and **7**, and of **7**, **8**, and **4**, respectively. The fraction C was revealed to contain **3** (89%) and **8** (11%), and redistillation gave the pure carbamate, bp 132 °C/3 Torr, mp 55—56 °C (from hexane) (lit,[10] mp 57—58 °C). The IR spectrum of residue D showed the characteristic absorptions due to carbamate [1710 cm^{-1} (CO), 1530, 3380 cm^{-1} (NH) and 1055 cm^{-1} (C–O–C)] and ether [1120 cm^{-1} (C–O–C)] groups, indicating the existence of oligomers of **3**, cyclo-$C_6H_{11}NHCO[O(CH_2)_4]_nCl(n>1)$, and of THF.

Reaction of Cyclohexyl Isocyanide with Chlorine in THF without the Catalyst. Chlorine gas (5.1 g, 72 mmol) was slowly bubbled into a stirred solution of cyclohexyl isocyanide (2.6 g, 24 mmol) in THF (29 ml, 360 mmol) at 5—10 °C, as described above. After being maintained for an additional 50 h at 20—25 °C with stirring, the mixture was poured into water. The resulting mixture was extracted with ether, and the extract was dried over anhydrous $MgSO_4$. Distillation gave cyclohexylcarbonimidoyl dichloride (3.9 g, 90% yield), bp 91—92 °C/20 Torr (lit,[11] 79—82 °C/13 Torr).

Authentic Samples for GLC Analysis. All ω-haloalkyl carbamates were prepared by the reaction of ω-halo-1-alkanols with isocyanates.[10,12] cyclo-$C_6H_{11}NHCOOR$: R=$(CH_2)_4Cl$, bp 132 °C/3 Torr; R=$(CH_2)_3Cl$, bp 126 °C/3 Torr (Found: C, 54.42; H, 8.52; N, 6.27%. Calcd for $C_{10}H_{18}NO_2Cl$: C, 54.67; H, 8.26; N, 6.38%); R=$CH_2CH(CH_3)Cl$, bp 107 °C/5 Torr (Found: C, 54.54; H, 8.22; N, 6.28%. Calcd for $C_{10}H_{18}NO_2Cl$: C, 54.67; H, 8.26; N, 6.38%); R=$(CH_2)_4Br$, bp 148 °C/2.8 Torr (Found: C, 47.73; H, 7.21; N, 5.17%. Calcd for $C_{11}H_{20}NO_2Br$: C, 47.49; H, 7.25; N, 5.04%). $RNHCOO(CH_2)_4Cl$: R=*n*-Bu, bp 115—118 °C/4 Torr (Found: C, 51.89; H, 9.03; N, 6.95%. Calcd for $C_9H_{18}NO_2Cl$: C, 52.05, H, 8.74; N, 6.74%); R=*t*-Bu, bp 92 °C/3 Torr (Found: C, 51.97; H, 9.03; N, 6.54 %. Calcd for $C_9H_{18}NO_2Cl$: C, 52.05, H, 8.74; N, 6.74%); R=Ph, mp 54—55 °C (from hexane) (lit,[12] mp 54 °C).

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