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REACTION OF AMIDE CHLORIDES WITH CYCLIC ETHERS

Y. Ito, S. Katsuragawa, M. Okano and R. Oda
Department of Synthetic Chemistry, Kyoto University
Kyoto, Japan

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LIKE the Vilsmeier reagent, the amide chlorides are strong electrophiles. They readily react with various active hydrogen compounds such as alcohols, amines, carboxylic acids and dimethylaniline (1). However, the reactions with other nucleophiles which possess no active hydrogens have not yet been studied, and this investigation was undertaken to explore such possibility.

When dimethylamide chlorides of formic or propionic acids were treated with ethylene oxide, propylene oxide, trimethylene oxide and tetrahydrofuran, the corresponding chloroalkyl formates or propionates were obtained by successive treatment with water, though the yields were not so high. Owing to the incomplete separation of the desired esters and the corresponding amides, all yields were determined by g.l.c. analyses. Some data are shown in Table I.

When propylene oxide was used as the ether component, g.l.c. analyses using a D.O.P. column showed the formation of two

TABLE I

Formation of Esters from Amide Chlorides and Cyclic Ethers

Amide Chloride (mole)	Ether (mole)	Reaction Conditions	Ester (Yield)
$\mathrm{H\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{\underset{\diagdown O \diagup}{CH_2\text{-}CH_2}}$ (0.3)	in $\mathrm{CHCl_3}$ 25°, 25hr.	$\mathrm{HCOO(CH_2)_2Cl}$ (30%)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{\underset{\diagdown O \diagup}{CH_2\text{-}CH_2}}$ (0.3)	in $\mathrm{CH_3CN}$ 25°, 25hr.	$\mathrm{C_2H_5COO(CH_2)_2Cl}$ (23%)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{\begin{array}{l} CH_2\text{-}CH_2 \\ \vert \quad\ \ \vert \\ CH_2\text{-}O \end{array}}$ (0.14)	in $\mathrm{CH_3CN}$ 25°, 25hr.	$\mathrm{C_2H_5COO(CH_2)_3Cl}$ (32%)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{\begin{array}{l} CH_2\text{-}CH_2 \diagdown \\ \vert \qquad\qquad O \\ CH_2\text{-}CH_2 \diagup \end{array}}$ (0.3)	in $\mathrm{CH_3CN}$ 25°, 25hr.	$\mathrm{C_2H_5COO(CH_2)_4Cl}$ (0.5%)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{(n\text{-}C_4H_9)_2O}$ (0.3)	in $\mathrm{CH_3CN}$ 25°, 25hr.	Unreacted
$\mathrm{H\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{CH_3\underset{\diagdown O \diagup}{CH\text{-}CH_2}}$ (0.3)	in $\mathrm{CHCl_3}$[a] 25°, 25hr.	$\mathrm{HCOOC_3H_6Cl}$[d] (24%)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{CH_3\underset{\diagdown O \diagup}{CH\text{-}CH_2}}$ (0.3)	in $\mathrm{CH_2Cl_2}$ 25°, 25hr.	Two isomers of $\mathrm{C_2H_5COOC_3H_6Cl}$ (18%) (I:II=1:1)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{CH_3\underset{\diagdown O \diagup}{CH\text{-}CH_2}}$ (0.3)	in $\mathrm{CH_2Cl_2}$[b] 25°, 25hr.	Two isomers of $\mathrm{C_2H_5COOC_3H_6Cl}$ (26%) (I:II=1:1)
$\mathrm{C_2H_5\text{-}\overset{+}{\underset{Cl}{C}}\text{-}NMe_2\ Cl^-}$ (0.1)	$\mathrm{CH_3\underset{\diagdown O \diagup}{CH\text{-}CH_2}}$ (0.3)	in $\mathrm{CH_2Cl_2}$[c] 25°, 25hr.	Two isomers of $\mathrm{C_2H_5COOC_3H_6Cl}$ (53%) (I:II=2:3)

a. $\mathrm{TiCl_4}$ catalyst (0.1 mole) was added.

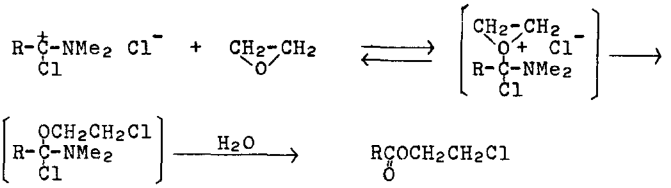
b. $\mathrm{TiCl_4}$ catalyst (0.06 mole) was added.

c. $\mathrm{ZnCl_2}$ catalyst (0.07 mole) was added.

d. Unexpectedly, the retention times of two isomers were equal and the composition of this product could not be determined by g.l.c. analysis.

isomeric esters, $\mathrm{RCOOCH_2CHClCH_3}$ (I) and $\mathrm{RCOOCH(CH_3)CH_2Cl}$ (II), as expected. The use of Lewis acid catalysts in this reaction resulted in an increase in yields ; however, it was accompanied by some formation of a high boiling fraction (probably an oligomer of the epoxide).

A reasonable path for the reaction would involve initial coordination of the oxygen lone pairs with amide chloride cation, followed by slow ring-opening of the resulting oxonium ion.



The ease of the reaction appears to depend largely on both the basicity and internal strain of the ether used. A better yield of the ester from trimethylene oxide may be attributed to its greater basicity. The difficulty of cleavage of the five-membered ring ether is almost comparable to that of an aliphatic ether. Similar observations were also reported by Searles in the acid-catalyzed reaction of thiosulfate with cyclic ethers (2).

The identity of all esters was established by comparison of i.r. spectra and retention times with those of authentic specimens.

Attempts to obtain new adducts from other nucleophiles such as thioethers and isocyanides are also in progress in this laboratory.

REFERENCES

(1) H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960) ; H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta.*, **42**, 1659 (1959).

(2) S. Searles, *J. Am. Chem. Soc.*, **73**, 4515 (1951).