TRANSFORMATION OF CHLOROFLUOROETHYLDIETHYLAMINES TO N,N-DIETHYLDIFLUOROACETAMIDE*

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Hydrolysis of 2-chloro-1,1,2-trifluoroethyldiethylamine (*I*) and 2,2-dichloro-1,1-difluoroethyl-diethylamine (*II*) in the presence of triethylamine afforded N,N-diethylchlorofluoroacetamide (*VII*) and N,N-diethyldichloroacetamide (*VIII*), respectively. Triethylamine hydrofluoride, arising in the reaction, was used for fluorination and transformation of the amides *VII* and *VIII* to N,N-diethyldifluoroacetamide (*VI*). The C—Cl bond of the CHClF group in *VII* proved to be more reactive in nucleophilic substitution with fluoride ion than the corresponding bond in the $CHCl_2$ group of *VIII*.

In our previous communications[1,2] we found a different course of reaction of 1-(fluoroalkyl)alkanols with 2-chloro-1,1,2-trifluoroethyldiethylamine (*I*) and with 2,2-dichloro-1,1-difluoroethyldiethylamine (*II*). We explained this fact by different reactivity of the CH_2—O and C—Cl bonds in the intermediate iminium ethers *III* and *IV* towards fluoride ions present in the reaction mixture. Thermal decomposition of the iminium ether *III* involves predominantly an attack of the C—Cl bond in the CHClF group by fluoride anion: this leads to the isomeric ether *V* which decomposes further into alkyl chloride and N,N-diethyldifluoroacetamide (*VI*). On the other hand, in the decomposition of the iminium ether *IV* the CH_2—O bond undergoes substitution with fluoride ion more readily than the C—Cl bond in the $CHCl_2$ grouping; consequently, the main products are alkyl fluoride and N,N-diethyldichloroacetamide (*VIII*). The different reactivity of C—Cl bonds in the CHClF and $CHCl_2$ groupings in a nucleophilic substitution was already discussed[3]. On the basis of our previous studies[1,2] and the mentioned discussion[3] we decided to prove once more the different reactivity of C—Cl bonds towards fluoride ions in the amides *VII* and *VIII*, and to utilize this fact preparatively. Hydrolysis ($R = H$) or ethanolysis ($R = C_2H_5$) of fluoroalkylamines *I* and *II* in dimethyl sulfoxide in the presence of triethylamine afforded reaction mixtures in which we followed the reaction of *VII* and *VIII* with fluoride ion and their conversion to difluoroacetamide (*VI*).

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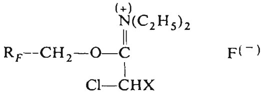
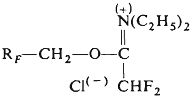


$$R_F{-}CH_2{-}O{-}\overset{\overset{(+)}{N}(C_2H_5)_2}{\overset{\|}{C}}{-}CHX{-}Cl \quad F^{(-)}$$

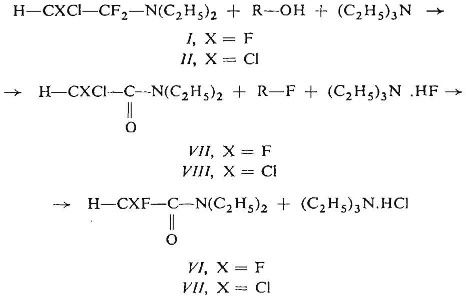
III, X = F
IV, X = Cl
R_F = $HCFClCF_2$-, HCF_2CF_2



$$R_F{-}CH_2{-}O{-}\overset{\overset{(+)}{N}(C_2H_5)_2}{\overset{\|}{C}}{-}CHF_2 \quad Cl^{(-)}$$

V

Hydrolysis of the amine I liberates two equivalents of hydrogen fluoride and therefore in the reaction mixture after hydrolysis of I the amide VII is converted to VI faster than in the analogous mixture, obtained by ethanolysis of I, in which only one equivalent of hydrogen fluoride is available for reaction with the chlorine atom of the CHClF group. Transformation of the amide VIII is substantially slower, the principal product being difluoroacetamide (VI); the expected chlorofluoroacetamide (VII) was formed in yields not higher than 1% (rel.). This fact indicates that the intermediate chlorofluoroacetamide (VII) undergoes immediately a faster subsequent reaction to give the amide VI. The reaction conditions are given in Table I (experiments 11 – 13) and the time dependence is depicted in Fig. 1.



$$H{-}CXCl{-}CF_2{-}N(C_2H_5)_2 + R{-}OH + (C_2H_5)_3N \rightarrow$$

I, X = F
II, X = Cl

$$\rightarrow H{-}CXCl{-}\underset{\underset{O}{\|}}{C}{-}N(C_2H_5)_2 + R{-}F + (C_2H_5)_3N\,.HF \rightarrow$$

VII, X = F
VIII, X = Cl

$$\rightarrow H{-}CXF{-}\underset{\underset{O}{\|}}{C}{-}N(C_2H_5)_2 + (C_2H_5)_3N.HCl$$

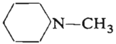
VI, X = F
VII, X = Cl

The hitherto used methods of preparing difluoroacetic acid derivatives are based on hydrolysis of adducts of alcohols[4], ammonia[5] or amines[6] to tetrafluoroethylene. Recently, Tolman[7] used the amine I for the preparation of VII which was then transformed into VI by reaction with potassium fluoride in diethylene glycol. We perform the fluorination using the fluoride anions generated directly in the reaction mixture by solvolysis of I. The transformation of VII to VI was studied in protic (water, methanol, ethanol, ethylene glycol) as well as aprotic (tetrahydrofuran, dimethylformamide, dimethyl sulfoxide) solvents. Hydrogen fluoride, liberated in the hydrolysis, was neutralized with triethylamine, 1-methylpiperidine, diethylamine or ethyl-

TABLE I

Transformation of Amines *I* and *II* to the Amide *VI*

Experiment No Procedure	Amine, g (mol) (solvent, ml)[a]	Reagent, g (mol) (solvent, ml)[a]	Base g (mol)	Solvent[a] ml	Reaction time, h (yield, %)[b]	Weight of amides, g percentage (rel.)		
						VI	*VII*	*VIII*
1	*I*, 19·0 (0·10)	C_2H_5OH, 4·6 (0·10)	$(C_2H_5)_3N$	CH_3OH	29·5		11·0	
B	(ether, 15)	(ether, 15)	10·1 (0·10)	20		63	37	—
2	*I*, 19·0 (0·10)	C_2H_5OH, 4·6 (0·10)	$(C_2H_5)_3N$	DMF	15·5		9·3	
B	(ether, 15)	(ether, 15)	10·1 (0·10)	20		93	7	—
3	*I*, 19·0 (0·10)	H_2O, 2·0 (0·11)	$(C_2H_5)_3N$	H_2O[c]	13·0		10·2	
B	(ether, 15)	(ether, 15)	20·2 (0·20)	20		87	13	—
4	*I*, 19·0 (0·10)	H_2O, 2·0 (0·11)	$(C_2H_5)_2NH$	DMF	42·0		12·5	
B	(ether, 15)	(ether, 15)	14·6 (0·20)	20	(82·3)	100	—	—
5	*I*, 19·0 (0·10)	H_2O, 2,0 (0·11)	$(C_2H_5)_3N$	THF	42·0		10·9	
B	(ether, 15)	(ether, 15)	20·2 (0·20)	20		50	50	—
6	*I*, 19·0 (0·10)	H_2O, 2·0 (0·11)	$(C_2H_5)_3N$	$(HOCH_2)_2$	46·5		12·3	
B	(ether, 15)	(ether, 15)	20·2 (0·20)	20	(81·0)	100	—	—
7	*I*, 19·0 (0·10)	H_2O, 2·0 (0·11)	$C_2H_5N(CH_3)_2$	C_2H_5OH	46·5		15·1	
B	(ether, 15)	(ether, 15)	14·6 (0·20)	20		37	63	—

8	*I*, 19·0 (0·10)	H_2O, 2·0 (0·11)	 N—CH_3	H_2O[c]	56·0		9·3	
B	(ether, 15)	(ether, 15)	19·8 (0·20)	20	(58·9)	100	—	—
9	*I*, 37·5 (0·20)	H_2O, 4·0 (0·22)	$(C_2H_5)_3N$	DMF	15·0		32·0	
A	(DMF, 20)	(DMF, 20)	20·4 (0·20)	40		60	40	—
10	*II*, 51·5 (0·25)	H_2O, 4·5 (0·25)	$(C_2H_5)_3N$	DMF	40·5		19·3	
A	(DMF, 20)	(DMF, 20)	50·6 (0·50)	40		26·6	0·3	73·1
11	*I*, 56·9 (0·30)	H_2O, 5·4 (0·30)	$(C_2H_5)_3N$	DMS	13·5		38·6	
A	(DMS, 20)	(DMS, 20)	60·7 (0·60)	40	(84·8)	100	—	—
12	*I*, 56·9 (0·30)	C_2H_5OH, 13·8 (0·30)	$(C_2H_5)_3N$	DMS	9 0		18·4	
A	—	(DMS, 40)	30·4 (0·30)	40		90	10	—
13	*II*, 43·4 (0·21)	H_2O, 3·8 (0·21)	$(C_2H_5)_3N$	DMS	28·0		10·1	
A	(DMS, 20)	(DMS, 20)	42·5 (0·42)	40		22·3	0·3	77·4
14	*I*, 390·0 (2·06)	H_2O, 38·0 (2·11)	$(C_2H_5)_3N$	$(HOCH_2)_2$[d]	16·0		181·0	
A	(DMF, 70)	(DMF, 80)	417·0 (4·13)	260	(58·0)	100	—	—
15	*I*, 640·0 (3·38)	H_2O, 61·0 (3·39)	$(C_2H_5)_3N$	$(HOCH_2)_2$[d]	10·0		309 0	
	(DMF, 120)	(DMF, 220)	681·0 (6·73)	340	(60·0)	100	—	—

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[a] DMF dimethylformamide, DMS dimethyl sulfoxide, THF tetrahydrofuran; [b] yield of *VI* based on *I*; [c] reaction carried out in the presence of 0·5 g of benzyltriethylammonium chloride; [d] reaction performed in dimethylformamide and ethylene glycol.

dimethylamine. In aqueous solution, an acceptable conversion of *VII* to *VI* was achieved only in the presence of benzyltriethylammonium chloride as phase transfer catalyst. Thus, our results, listed in Table I, represent an experimentally simple modification of synthesis[4,8] of diethyldifluoroacetamide (*VI*) and difluoroacetic acid or its derivatives, starting from chlorotrifluoroethylene.

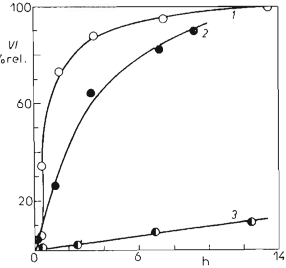

FIG. 1

Transformation of Amides *VII* and *VIII* to the Amide *VI*

1 VII, Obtained by hydrolysis (Table I, experiment 11); *2 VII*, obtained by ethanolysis of *I* (Table I, experiment 12); *3 VIII*, obtained by hydrolysis of *II* (Table I, experiment 13).

EXPERIMENTAL

Transformation of the Chlorofluoroethylamines *I* and *II* to N,N-Diethyldifluoroacetamide (*VI*)

A) Amine *I* or *II* (or its solution in an appropriate solvent) was added dropwise to a stirred mixture of water, triethylamine and a solvent (dimethyl sulfoxide or dimethylformamide) at a temperature not exceeding 50°C. The thus-obtained solution of *VII* or *VIII* was then stirred at 110°C. In the experiments 11—13 (Table I), samples (1 ml) were withdrawn from the mixture; these were shaken with water and analyzed by gas-liquid chromatography to determine the conversion of *VII* to *VI* or *VIII* to *VI* and *VII*. Time dependences of the transformations are depicted in Fig. 1.

B) An ethereal solution of the amine *I* was added dropwise to a stirred emulsion of an organic base, ether and water, or to a solution of a tertiary amine, ethanol and ether. After two hours' stirring, the ether and/or ethyl fluoride was distilled off, the residue was mixed with solvent (methanol, ethanol, ethylene glycol, dimethylformamide, water) and the mixture refluxed.

The reaction mixtures were poured into water and the products were taken up in ether or steam-distilled and the distillate extracted with ether. After drying over magnesium sulfate and evaporation of ether, the conversion of *VII* to *VI* was determined by gas-liquid chromatography. The amounts of the reaction components, reaction conditions and results are given in Table I. The amides *VI*—*VIII* were identified by gas-liquid chromatographic comparison with standards[1,2].

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