REACTIONS IN ANHYDROUS HYDROGEN FLUORIDE*

COMMUNICATION 5. FLUOROAMINOMETHYLATION AND FLUOROACYLAMINOMETHYLATION OF HALOOLEFINS†

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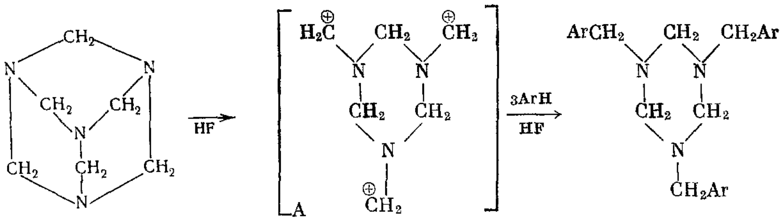
As we have shown [1], in the reaction of aromatic hydrocarbons with hexamethylenetetramine in anhydrous hydrogen fluoride at room temperature mainly symmetrically substituted hexahydrotriazines are formed:

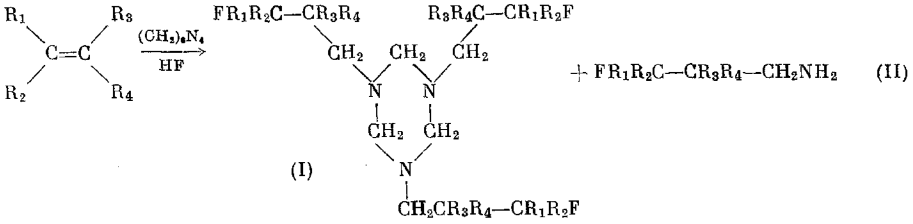


Since the ion A is a powerful electrophilic agent, it may be assumed that it will be possible to bring about its reaction with olefins. Aminomethylation in acid media has been effected previously on olefins with a strongly marked nucleophilic character, and it has been described in detail only in the case of α-methylstyrene. With aqueous solutions of formaldehyde and primary amine or ammonium salts, usually substituted 1,3-oxazines [2, 3] are formed together with piperidinols [4]. With secondary amine salts under the same conditions unsaturated tertiary amines are formed [2, 5-7]. In individual cases products of conjugated aminomethylation have been isolated: amino alcohols [5] or amino acetates [6].

For these transformations the authors propose the following schemes (schemes at top of next page), $X^{\ominus}$ is the anion of the corresponding acid.

It was not found possible to bring about the aminomethylation of less nucleophilic olefins [6].

It was found that in presence of HF hexamethylenetetramine readily condenses with vinylidene chloride, vinylidene fluoride, and trifluoroethylene under extremely mild conditions (5-20°, atmospheric pressure). With tetrafluoroethylene the reaction could be brought about only at 50° under pressure. The main reaction products were the corresponding symmetrical N-(fluoroalkyl)-substituted hexahydrotriazines (Ia)-(Id) and the propylamines (IIa) - (IId):



(I)

$+ FR_1R_2C{-}CR_3R_4{-}CH_2NH_2$ (II)

a) $R_1 = R_2 = Cl$; $R_3 = R_4 = H$ b) $R_1 = R_2 = R_3 = F$; $R_4 = H$

c) $R_1 = R_2 = F$; $R_3 = R_4 = H$ d) $R_1 = R_2 = R_3 = R_4 = F$

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[*] For Communications 3 and 4 see Zh. Vses. khim. obshch. im. D. I. Mendeleeva 11, 354, 356 (1966).

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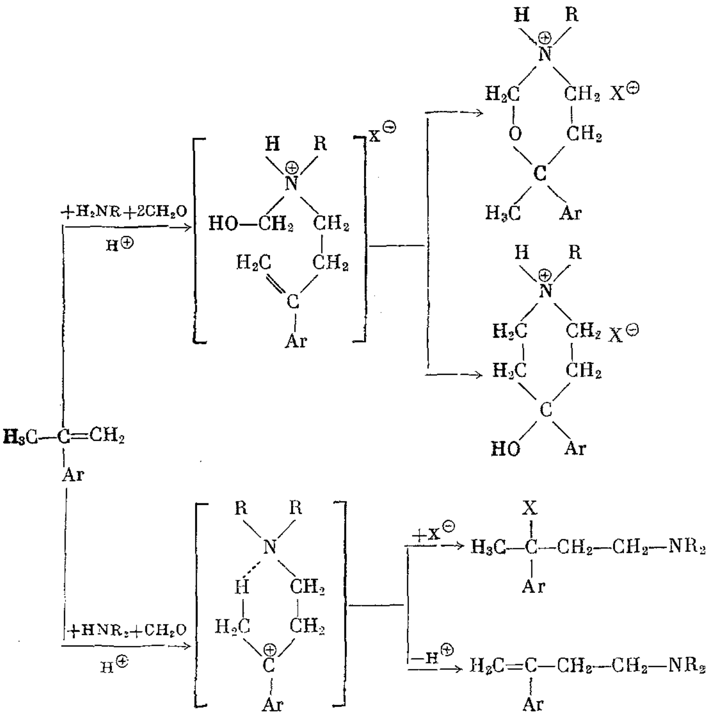
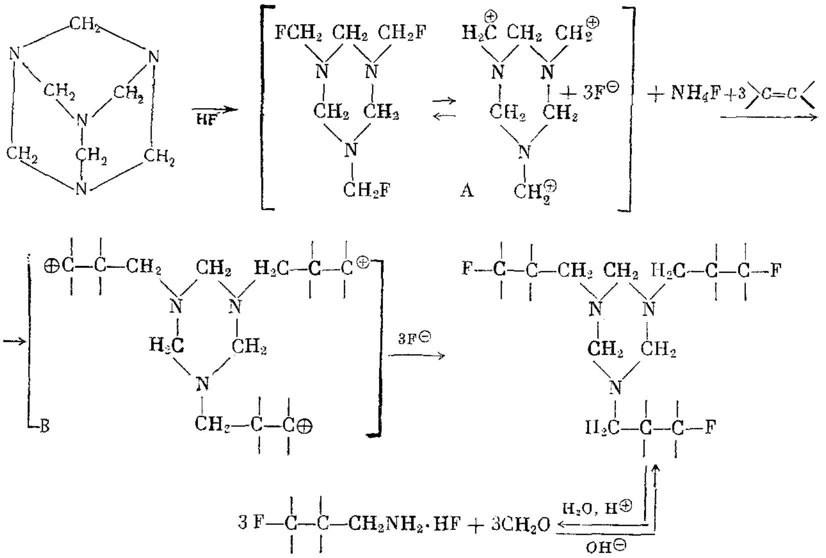


(Ib) was obtained as a mixture of crystals and liquid. The liquid product had an IR spectrum which was completely identical to that of the crystalline product, and it was converted into the crystalline form on long standing and also on distillation; on acid hydrolysis both substances gave the hydrochloride of (IIb). The formation of the above-described products can be explained by the following reaction scheme:



We have already established the mechanism of the cleavage of hexamethylenetetramine in anhydrous hydrogen fluoride [1]. The ion A makes an electrophilic attack on the double bond of the olefin. The intermediate ion B formed becomes stabilized by combining with $3F^{\ominus}$. The hexahydrotriazine formed is partially hydrolyzed by water to the corresponding amine and formaldehyde. It may be supposed that with N-(hydroxymethyl)acetamide in HF conjugated fluoroacetamidomethylation of olefins will occur in a similar way as in the case of hexamethylenetetramine. We have been able to find only one communication in the literature on the reaction of N-(hydroxymethyl)acetamide with olefins: from compounds with an activated multiple bond (α-methylstyrene, terpenes) substituted 1,3-oxazines were obtained [8].

TABLE 1

Cpd. No.	B.p., °C (p, mm Hg)	M. p., °C (solvent)	n_D^{20}	d_4^{20}	Found					
					C, %	H, %	F, %	N, %	*MR*	*M*[a]
Ia	—	41 (benzene)	—	—	29.60 29.72	3.57 3.76	11.01 10.77	8.55 8.68	—	461 491
Ib	—	73 (heptane)	—	—	38:64 38.53	4.85 4.84	44.88 44.86	11.35 11.54	—	376 394
Ic	90 — 92 (2)	—	1.3756	1.470	33.79 33.73	3.72 3.71	52.81 52.29	9.51 9.81	67.0	398 433
Id	76 — 96 (7)	—	1.3498	1.513	30.28 30.45	2.77 2.70	60.18 59.80	—	68.7	441 481
IIa	63—65 (76—77)	—	1.4448	1.344	24.19 24.42	4.10 4.29	12.27 12.56	9.80 9.88	28.99	—
IIa—HCl	—	250	—	—	19.54 19.90	3.66 4.04	8.98 8.54	7.87 7.62	—	—
IIb[d]	67.5—67.8 (742)	—	1.3305	—	31.58 31.74	5.44 5.43	49.79 42.70	12.54 12.25	—	—
IIb-HCl[d]	—	217 (dioxane)	—	—	24.19 24.14	4.41 4.58	37.81 38.08	9.35 9.47	—	—
IIc[e]	72.3—73 (753)	—	1.3215	1.332	—	—	—	—	19.60	—
IIc-HCl	—	Decomp > 240[b]	—	—	21.83 21.54	3.74 3.61	44.70 44.79	8.67 8.78	—	—
IId[f]	48—48.5 (755)	—	1.297	—	—	—	—	—	—	—
IId-HCl	—	248 (ethanol)	—	—	19.46 19.45	2.75 2,82	50.92 51.02	8.07 8.17	—	—
IIIa	106—108 (2)	—	1,4622	—	31.96 31.81	4.61 4.41	10.16	7.19	—	—
IIIb	—	62—63[g]	—	—	—	—	36.67	8.58	—	—
IIIc	—	69—70[g]	—	—	—	—	44.25	7.95	—	—
IIId	—	66—68[g]	—	—	—	—	—	—	—	—

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a) The molecular weight was determined cryoscopically in benzene.

b) From a mixture of ethanol and ether.

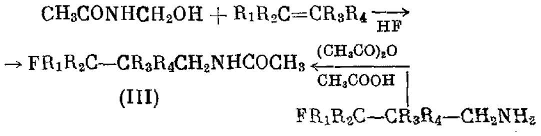
c) Total yield inclusive of hexahydrotriazine, based on olefin that reacts.

d) [13] gives: b.p. 67.8° (742 mm) n_D^{20} 1.3332; hydrochloride, m.p. 222-225°.

e) Benzoyl derivative, m.p. 102-103° (chloroform–heptane).

Our experiments showed that in HF N-(hydroxymethyl)acetamide reacts with the above-mentioned halo olefins at room temperature (heating is necessary only in the case of tetrafluoroethylene).

As a result of the reactions we obtained acetyl derivatives of the corresponding propylamine (IIIa)-(IIId). The same substances were prepared by an independent method.



$$CH_3CONHCH_2OH + R_1R_2C{=}CR_3R_4 \xrightarrow[HF]{} $$

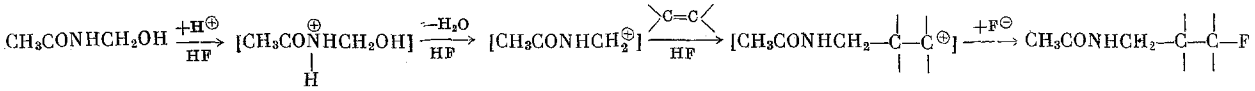
$$\rightarrow FR_1R_2C{-}CR_3R_4CH_2NHCOCH_3 \xleftarrow[CH_3COOH]{(CH_3CO)_2O} FR_1R_2C{-}CR_3R_4{-}CH_2NH_2$$

(III)

a) $R_1{=}R_2{=}Cl$; $R_3{=}R_4{=}H$ b) $R_1{=}R_2{=}R_3{=}F$; $R_4{=}H$

c) $R_1{=}R_2{=}F$; $R_3{=}R_4{=}H$ d) $R_1{=}R_2{=}R_3{=}R_4{=}F$

The reaction probably has the following mechanism:



$$CH_3CONHCH_2OH \xrightarrow[HF]{+H^{\oplus}} [CH_3CO\overset{\oplus}{N}HCH_2OH] \xrightarrow[HF]{-H_2O} [CH_3CONHCH_2^{\oplus}] \xrightarrow[HF]{>C=C<} [CH_3CONHCH_2{-}C{-}C^{\oplus}] \xrightarrow{+F^{\ominus}} CH_3CONHCH_2{-}C{-}C{-}F$$

Table 1 (continued)

Molecular formula	Calculated						Yield, %	NMR spectra, ppm		
	C, %	H, %	F, %	N, %	*MR*	*M*		$\delta(\rangle N-CH_2-N\langle)$	$\delta(-CH_2-N\langle)$	$\delta(-CH_2-)$
$C_{12}H_{18}Cl_6F_3N_3$	30.41	3.83	12.03	8.86	—	474	—	2.8	2.4	2.2
$C_{12}H_{18}F_9N_3$	38.51	4.83	45.56	11.20	—	375	—	3.0	2.5	2.0
$C_{12}H_{15}F_{12}N_3$	33.58	3.52	53.11	9.79	68.2	429	—	3.6	3.0	—[i]
$C_{12}H_{12}F_{15}N_3$	29.83	2.50	58.98	—	69.3	483	—	3.6	3.1	—
								$\delta(-NH_2)$		
$C_3H_6Cl_2FN$	24.64	4.14	13.01	9.59	29.35	—	—	1.8	2.9	2.3
$C_3H_7Cl_3FN$	19.75	3.87	10.04	7.68	—	—	43[c]	—	—	—
$C_3H_6F_3N$	31.86	5.35	50.40	12.39	—	—	—	1.1	2.8	2.2
$C_3H_7ClF_3N$	24.09	4.72	38.11	9.37	—	—	60[c]	—	—	—
$C_3H_5F_4N$	—	—	—	—	19.79	—	—	1.8	3.0	—[j]
$C_3H_6ClF_4N$	21.51	3.61	45.36	8.36	—	—	62[c]	—	—	—
$C_3H_4F_5N$	—	—	—	—	—	—	—	1.3	3.1	—
$C_3H_5ClF_5N$	19.42	2.72	51.20	7.55	—	—	44[c]	—	—	—
								$\delta(-NH-)$		$\delta(-C(O)CH_3)$
$C_5H_8Cl_2FNO$	31.94	4.29	10.10	7.45	—	—	13	8.2	3.4	2.0
$C_5H_8F_3NO$	—	—	36.74	9.03	—	—	33[h]	8.1	3.3[k]	2.0
$C_5H_7F_4NO$	—	—	43.90	8.09	—	—	46[h]	6.5	3.9	2.0
$C_5H_6F_5NO$	—	—	—	—	—	—	—	6.5	—	2.0

f) [14] gives: b.p. 49-49.5°, n_D^{20} 1.297.

g) From a 1 : 2 mixture of chloroform and heptane.

h) Based on olefin that reacted.

i) $\delta(-CFH-) = 4.9$.

j) $\delta(-CFH-) = 4.7$.

k) $\delta(-CH_2-) = 2.1$.

The initially formed carbonium ion* attacks the double bond of the olefin, and the ion formed stabilizes itself by combining with $F^{\ominus}$.

EXPERIMENTAL

1. Reaction of Hexamethylenetetramine with Vinylidene Chloride. 15 g of hexamethylenetetramine was sprinkled with stirring in the course of 10 min into 80 g of HF contained in a 140-ml steel reactor cooled with ice water, and then 41.5 g of vinylidene chloride was added dropwise. Stirring was continued further for 7 h at 15-20°. HF was evaporated from the reaction mixture, which was treated with 100 ml of water and made alkaline with 50% KOH solution. The alkaline solution was extracted with ether, and the extract was dried over magnesium sulfate. Ether was driven off, and the amine formed was distilled off at 18 mm at temperatures of up to 80°. By redistillation we obtained 3 g of 3,3-dichloro-3-fluoropropylamine (IIa). The constants, analyses, and yields of the products are given in Table 1. The residue after the removal of the amine crystallized. We obtained 22 g of 1,3,5-tris(3,3-dichloro-3-fluoropropyl)hexahydro-s-triazine (Ia). 8 g of (Ia) was hydrolyzed in a mixture of 20 g of concentrated hydrochloric acid and 100 g of water with removal of the formaldehyde liberated by steam distillation. Distillation was stopped when the condensate no longer gave a precipitate with 2,4-dinitrophenylhydrazine solution. The mixture remaining in the flask was vacuum-evaporated in a rotary evaporator. We obtained 7.8 g of the crystalline hydrochloride of (IIa).

2. Reaction of Hexamethylenetetramine with Vinylidene Fluoride. A 350-ml steel reactor fitted with stirrer and tube for the passage of gas was charged with 200 g of HF, and 28 g of hexamethylenetetramine was added gradually with stirring. The reactor was then placed in a bath of ice water, and 0.624 mole of

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[*] The mechanism with formation of a carbonium ion was proposed for reactions of this kind by Wagner [9].

vinylidene fluoride was passed in the course of 7 h; 0.444 mole of the gas was absorbed. The mixture was left until the next day. HF was evaporated, and the residue was treated with 150 ml of water and, with strong cooling, made alkaline with 40% KOH solution. The mixture was extracted with ether, the ether extract was dried over $MgSO_4$, ether was driven off, and the residue was heated at 20 mm so that the temperature in the vapor rose to 50°, and the vapor condensed in a trap cooled to – 78°. The contents of the trap were combined with ethereal distillate and saturated with dry HCl. We obtained 5.5 g of 3,3,3-trifluoropropylamine hydrochloride (IIb-HCl). The residue remaining after the amine had been distilled off consisted of crystals impregnated in an oil; total weight 36 g. The crystals (19 g) were hexahydro-1,3-5-tris(3,3,3-trifluoropropyl)-s-triazine (Ib). By the hydrolysis of 12.6 g of the mixture of (Ib) and the oily product with dilute HCl as described above we obtained 15.1 g of the crystalline hydrochloride of (IIb). To this we added 5 ml of water and then, with strong cooling, 12 g of solid KOH. The amine liberated was distilled off from an air bath. The bulk of it boiled at 66-70°. It was dried over KOH and distilled three times through a column, and we obtained 9 g of (IIb).

3. Reaction of Hexamethylenetetramine with Trifluoroethylene. 0.925 mole of trifluoroethylene was passed for 8 h into a mixture of 10 moles of HF and 0.2 mole of hexamethylenetetramine under conditions similar to that of Expt. 2, and 0.268 mole of the gas was absorbed. After the usual treatment we obtained 3.5 g of the hydrochloride of 2,3,3,3-tetrafluoropropylamine (IIc), and in the vacuum distillation of the residue was obtained 22 g of hexahydro-1,3,5-tris(2,3,3,3-tetrafluoropropyl)-s-triazine (Ic). In the hydrolysis of 8.2 g of (Ic) with dilute HCl we obtained 9.2 g of the hydrochloride of (IIc). For identification, benzoyl derivatives of (IIc) were prepared by the standard procedure [10] from the amine obtained directly in the synthesis and the amine obtained by the hydrolysis of (Ic). A mixture of these melted without depression. 12 g of the hydrochloride of (IIc) was treated with saturated KOH solution, and a fraction of b.p. 73-90° was driven off from an air bath. This was dried over KOH, and redistillation gave 8.4 g of 2,3,3,3-tetrafluoropropylamine (IIc).

4. Reaction of Hexamethylenetetramine with Tetrafluoroethylene. 0.6 mole of $CF_2 = CF_2$ was condensed in a 250-ml steel ampule cooled with liquid nitrogen and containing 6 moles of HF and 0.15 mole of hexamethylenetetramine. The reaction mixture was heated with shaking for 5 h at 50°. Unchanged $CF_2 = CF_2$ (0.48 mole) was passed to a gas holder, and the residue was treated as described above. From the ethereal distillate we obtained 3 g of the hydrochloride of 2,2,3,3,3-pentafluoropropylamine (IId), and from the residue from the distillation we isolated 7 g of hexahydro-1,3,5-tris(2,2,3,3,3-pentafluoropropyl)-s-triazine (Id). In acid hydrolysis, from 6.7 g of (Id) we obtained 6.6 g of the hydrochloride of (IId). A mixture with a known sample melted without depression.

5. Reaction of N-(Hydroxymethyl)acetamide with Vinylidene Chloride. A 140-ml steel reactor cooled with ice water was charged with 50 g of HF, 11.7 g of N-(hydroxymethyl)acetamide,* and 12.5 g of $CH_2 = CCl_2$. The mixture was stirred for 5 h at a temperature which gradually rose to that of the room, and it was left overnight. After the evaporation of HF the mixture was poured onto ice, neutralized with ammonium carbonate, made alkaline with aqueous ammona, and extracted with ether. The extract was dried over $MgSO_4$, and after distillation we obtained 3.1 g of N-(3,3-dichloro-3-fluoropropyl)acetamide (IIIa). The product darkened rapidly on standing.

6. Reaction of N-(Hydroxymethyl)acetamide with Vinylidene Fluoride. 0.56 mole of $CF_2 = CH_2$ was passed in the course of 9 h under the conditions of Expt. 2 into a mixture of 140 g of HF and 12 g of N-(hydroxymethyl)acetamide; 0.16 mole of the gas was absorbed. The mixture was treated further as in Expt. 5; the residue remaining after the removal of ether crystallized. We obtained 8.1 g of N-(3,3,3-trifluoropropyl)acetamide (IIIb).

7. Reaction of N-(Hydroxymethyl)acetamide with Trifluoroethylene. 0.72 mole of $CF_2 = CFH$ was passed in the course of 9 h under the conditions of Expt. 6 into a mixture of 8 moles of HF and 0.26 mole of N-(hydroxymethyl)acetamide, and 0.1 mole of the gas was absorbed. After the usual treatment we obtained 8 g of N-(2,3,3,3-tetrafluoropropyl)acetamide (IIIc).

8. Reaction of N-(Hydroxymethyl)acetamide with Tetrafluoroethylene. Under the conditions of Expt. 4 from 120 g of HF, 23 g of N-(hydroxymethyl)acetamide, and 0.6 mole of $CF_2 = CF_2$ we obtained 0.8 g of N-(2,2,3,3,3-pentafluoropropyl)acetamide (IIId). The low yield of (IIId) is due to the polymerization of a con-

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*N-(Hydroxymethyl)acetamide was prepared in the crystalline state by the procedure described in [11] and was used without further purification.

siderable part of the tetrafluoroethylene under the conditions of the reaction. The acetamides (IIIb)-(IIId) give no depression of melting point in admixture with known substances prepared by the acylation of the amines (IIb)-(IId) with acetic anhydride in glacial acetic acid by the procedure described in [12].

The structures of the compounds obtained were confirmed by their NMR spectra, which are given in Table 1. NMR spectra were investigated with a TsLA-5535 spectrometer with a working frequency of 40 MHz and with proton stabilization of the conditions of resonance. As solvent for the acetamides we used dimethyl sulfoxide, and for the hexahydrotriazenes— benzene; benzene was used as internal standard. Chemical shifts are given on the δ scale.

We thank É. I. Fedin and P. V. Petrovskii for determining and interpreting the spectra.

CONCLUSIONS

The new reaction of conjugated fluoroaminomethylation of chloro and fluoro olefins is described; it may be used for the synthesis of various fluorine-containing amines.

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