N-PERHALOFLUOROALKYLATION OF SECONDARY AMINES BY THE REACTIONS OF THE AMINES AND AMIDES WITH PERHALOFLUOROALKANES. HALOPHILIC ATTACK OF NITROGEN NUCLEOPHILE ON C-Br BOND.
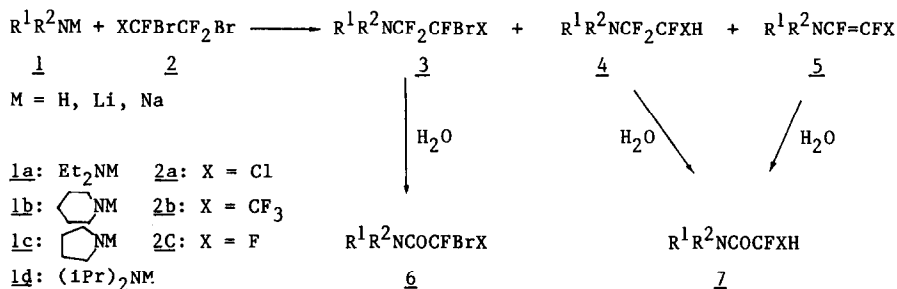
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Abstract   Secondary amines and amides react spontaneously with perhalofluoroalkanes $CF_2BrCFBrX$(X = F, Cl, CF_3) to afford N-perhalofluoroalkylated tertiary amines in fair to good yields. Evidence for an anionic chain process initiated by the bromophilic attack of nitrogen nucleophiles on C-Br bonds is given.

We have recently reported the spontaneous reactions of some perhalofluoroalkanes with thiophenoxides[1a,1b], aryloxides and alkoxides[1c,1d]. Evidence has been given to show that in these reaction systems halophilic attacks of sulfur and oxygen nucleophiles on C-Br or C-Cl bonds are involved. Our continuing interests in all types of halophilic attacks led us to examine the reactions of secondary amines and amides (1) with $CF_2BrCFBrX$ (2, X = F, Cl, CF_3). Only a few cases of halophilic attacks by nitrogen nucleophiles have been reported, and they are limited to C-I bonds[2,3]. Although the n_{CH_3I} scale indicates that amines are fairly good nucleophiles in S_N2 reactions, Baciocchi and Lillocci have found that they are less reactive in making nucleophilic attacks on iodine[2]. Tertiary amines are known to form donor-acceptor complexes with perfluoroalkyl iodides and bromides[4]. Our results indicate, however, that nitrogen nucleophiles are capable of engaging in bromophilic attacks on C-Br bonds. Thus slow but spontaneous reactions between secondary amines and perhalofluoroalkanes 2 take place in some polar aprotic solvents to afford N-perhaloalkylated amines 3 as main products. Slight heating and the presence of tertiary amines facilitate the reactions and considerably increase the product yields. Lithium and sodium amides, as expected from their high reactivity, react readily at room temperature or below with 2 to give the same products as those from the
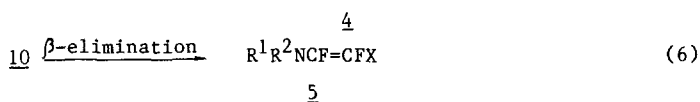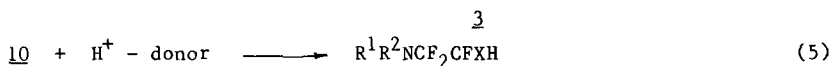
Scheme I

$$R^1R^2NM + XCFBrCF_2Br \longrightarrow R^1R^2NCF_2CFBrX + R^1R^2NCF_2CFXH + R^1R^2NCF=CFX$$

$\underline{1}$ $\underline{2}$ $\underline{3}$ $\underline{4}$ $\underline{5}$

M = H, Li, Na

$\underline{1a}$: Et_2NM $\underline{2a}$: X = Cl

$\underline{1b}$: ⬠NM $\underline{2b}$: X = CF_3

$\underline{1c}$: ⬡NM $\underline{2c}$: X = F $R^1R^2NCOCFBrX$ $R^1R^2NCOCFXH$

$\underline{1d}$: $(iPr)_2NM$ $\underline{6}$ $\underline{7}$
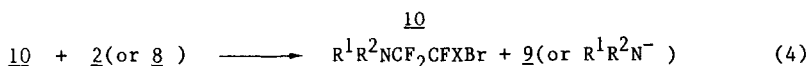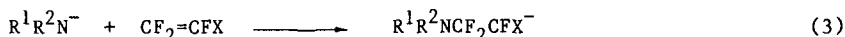
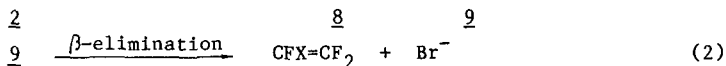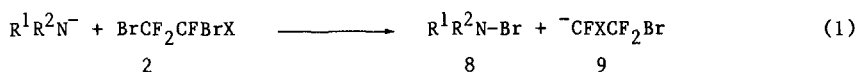with arrows labeled H_2O leading to 6 and 7.

reactions of the corresponding amines, but with improved yields of the main products $\underline{3}$. These reactions can be summarized in scheme I.

Perfluoroalkyl or perfluoroalkenyl amines are easily hydrolyzed[5-7]. In fact, small amounts of the hydrolysis products $\underline{6}$ and $\underline{7}$ were often formed during the course of work-up, and sometimes even before the work-up. However, the perhalofluoroalkyl tertiary amines $\underline{3}$ can be isolated and thus seem to be more stable towards hydrolysis than the β-hydro-perfluoroalkyl tertiary amines which were claimed to be inseparable[5]. The enamines $\underline{5}$ were found only in the reactions of $\underline{2b}$. Table 1 shows a part of our results.

Evidently, the role of amines and amides in these reactions is quite similar to those of the sulfur and oxygen nucleophiles previously studied[1]. To illustrate, the reactions of amides can be analogously described in terms of an anionic chain mechanism with a bromophilic step accomplished by a nitrogen nucleophile(scheme II).

Scheme II

$$R^1R^2N^- + BrCF_2CFBrX \longrightarrow R^1R^2N-Br + {}^-CFXCF_2Br \qquad (1)$$
$$\underline{2} \qquad\qquad\qquad \underline{8} \qquad\quad \underline{9}$$

$$\underline{9} \xrightarrow{\beta\text{-elimination}} CFX=CF_2 + Br^- \qquad (2)$$

$$R^1R^2N^- + CF_2=CFX \longrightarrow R^1R^2NCF_2CFX^- \qquad (3)$$
$$\underline{10}$$

$$\underline{10} + \underline{2}(\text{or } \underline{8}) \longrightarrow R^1R^2NCF_2CFXBr + \underline{9}(\text{or } R^1R^2N^-) \qquad (4)$$
$$\underline{3}$$

$$\underline{10} + H^+ - donor \longrightarrow R^1R^2NCF_2CFXH \qquad (5)$$
$$\underline{4}$$

$$\underline{10} \xrightarrow{\beta\text{-elimination}} R^1R^2NCF=CFX \qquad (6)$$
$$\underline{5}$$

Both the regiospecificity of the nitrogen attachment and the formation of the side-products $\underline{4}$ and $\underline{5}$ are fully consistent with this mechanism. The GC detection of small amounts of the corresponding olefins in the reaction systems and the fact that addition of small amounts of the olefins remarkably accelerates the reactions may serve as further evidence for the intermediacy of the olefins and for the chain process. Interestingly, only $BrCF_2CFBrCF_3(\underline{2b})$ yields considerable amounts of the enamines $R^1R^2N-CF=CFCF_3(\underline{5})$. This observation accords with the previous report on the addition of secondary amines to hexafluoropropene[5]. Possibly, the potential hyperconjugative interaction of the CF_3-group with the lone-pair of the nitrogen through the developing double bond could facilitate the β-elimination step-(6)[8].

Although the spontaneity of the reactions of secondary amines in the absence of other bases indicates that they are also able to make the bromophilic attack, they are much less reactive than the amides. Notably, for R^1R^2NH, steps (1) and (3) in Scheme II will lead to the formation of quaternary ammonium ions $R^1R^2HN^+Br$ and $R^1R^2HN^+CF_2CFX^-$, which are proton-donors and would participate in the chain terminating step-(5) and thus retard the desired reactions. The favorable effect of adding triethylamine to the system might be partly related to its ability to remove HBr effectively from the reaction system. However, rather surprisingly,

Table 1. Selected results of the reactions of 1 and 2 in DMF under various conditions

CF$_2$BrCFBrX	R^{1}R^{2}NH	additive	Yield,%[b] 3	4	5
	Et$_2$NH	none , 40°, 48h	21	4	
		Et$_3$N, 40°, 20h	57	2	
		BuLi,-5°, 2h	32	0	
		BuLi + Et$_3$N,-5°, 2h	53	0	
		NaH, -5°, 6h	(26)		
2a		NaH + Et$_3$N, -5°, 6h	77(65)	5	
	(piperidine)NH	Et$_3$N, 40°, 20h	45(29)	8	
X = Cl		NaH + Et$_3$N, -5°, 6h	87(83)	3	
	(pyrrolidine)NH	Et$_3$N, 40°, 20h	25		
		NaH + Et$_3$N, -5°, 6h	68	1	
	(iPr)$_2$NH	BuLi + Et$_3$N,-5°, 6h	5		
	Et$_2$NH	Et$_3$N, 40°, 20h	11	1^c	1^c
2b		NaH + Et$_3$N, -5°, 6h	42(32)	1	19(21)
		BuLi + Et$_3$N,-5°, 2h	65	1^c	20
X = CF$_3$	(piperidine)NH	NaH + Et$_3$N, -5°, 6h	44(33)	1^c	29(20)
	(pyrrolidine)NH	Et$_3$N, 40°, 20h	13	15	1
		NaH + Et$_3$N, -5°, 6h	42(21)	1^c	15
	Et$_2$NH	Et$_3$N^a, 40°, 72h	29	57	
2c		BuLi + Et$_3$N,-5°, 6h	42	6	
	(piperidine)NH	Et$_3$N^a, 40°, 72h	12	35	
X = F		NaH + Et$_3$N, -5°, 6h	45(35)	1	
	(pyrrolidine)NH	NaH + Et$_3$N, -5°, 6h	31(20)	4	

a. HMPA was used as the solvent.

b. The yields were measured by ^{19}F-nmr. The numbers in parenthesis are isolated yields. Various amounts of 6 and 7 were also found.

c. Considerable amounts of their hydrolyzed products 7 were found before work-up.

even in the cases of amides, the presence of Et₃N increases the product yields considerably, although no HBr formation would be expected. One wonders whether molecular complexes between tertiary amines and the per(bromo, fluoro)alkanes might be involved[4]. Thus the role played by Et₃N remains to be clarified.

In order to gain additional evidence for our mechanistic scheme, we have made use of the notion that steric effects for the bromophilic front-side attack, i.e. reaction-(1), is expected to be smaller than those for the addition step, i. e., reaction-(3). Thus a bulky nucleophile might lead to an accumulation of the unreacted olefin. In fact, in the reaction of iPr₂NLi with 2a, after 80% conversion of the substrate 2a, only 5% of the alkylated product 3 was formed, and the main product turned out to be CF₂=CFCl.

In summary, the results presented above show that both the negatively charged and uncharged nitrogen nucleophiles are capable of making bromophilic attacks on the C-Br bonds of the per(bromo, fluoro)alkanes, whereas previous results for oxygen and sulfur nucleophiles indicate that only their anionic species can do this. Furthermore, the title reaction can provide us with a useful method for the preparation of N-perhalofluoroalkyl amines which are seldom synthesized before.

References

1a. X.-Y. Li, H.-Q. Pan, X.-K. Jiang, Acta Chimica Sinica, 42, 297(1984)

 b. X.-Y. Li, H.-Q. Pan, W.-M. Fu, X.-K. Jiang, J. Fluorine Chem. 31(1986) 213

 c. X.-Y. Li, H.-Q. Pan, X.-K. Jiang, Tet. Lett. 25,4937(1984)

 d. X.-Y. Li, H.-Q. Pan, X.-k. Jiang, Z.-Y.Zhan, Angew. Chem. Int. Ed. Engl. 24(1985)872

2. E. Baciocchi, C. Lillocci, J.Chem.Soc. Perkin II, 38(1973); idem. ibid, 802(1975)

3. Q.-Y. Chen, X.-K. Jiang, B.-Q. Chen, M.-L. Liang, Scientia Sinica, 15, 498(1966)

4. N.F.Cheetham, I.J.McNaught, A.D.E. Pullin, Aus. J. Chem. 27, 987(1974)

5. I.L. Knunyants, L.S. German, B.L. Dyatkin, Izv. Akad. Nauk SSSR, 1353(1956)

6. W. Miller, J. Am. Chem. Soc. 70, 431(1948)

7. A.P. Sergeev, T.I. Novozhilova, A.Y. Yakubovich, Zh. Org. Khim. 6, 747(1970)

8. D.A. Dixon, T. Fukunaga, B.E. Smart, J. Am. Chem. Soc. 108, 4027(1986) and the references cited therein.

9. Satisfactory MS and NMR spectroscopic data for all products and microanalytical data for products 6 were obtained.
    ^{19}Fnmr for 3 (CF₃COOH external,positive upfield): Et₂NCF₂CFBrCl: (neat) -9.7(t, J=11.3Hz 1F) 8.7 10.3(AB,dq J_{AB}=188Hz J=11.3Hz 2F), C₅H₁₀NCF₂CFClBr: (neat) -11.3(t, J=11.3Hz 1F) 13.2 14.8(AB dq, J_{AB}=188Hz J=11.3Hz 2F), C₄H₈NCF₂CFClBr: (CCl₄) -11.3 (t, J=11.3Hz 1F) 15.5(d,J=11.3Hz 2F), (i-Pr)₂NCF₂CFClBr: (CCl₄) -7.5(t,J=11.3Hz 1F) 9.5(d,J=11.3Hz 2F), Et₂NCF₂CFBrCF₃: (CCl₄) -2.5 (m, 3F) 12.7 (m, 2F) 58 (m, 1F), C₅H₁₀NCF₂CFBrCF₃: (neat) -2.2(m, 3F) 12.5 (m, 2F) 56 (m, 1F), C₄H₈NCF₂CFBrCF₃: (neat) -1.7(m, 3F) 10(m, 2F) 57.8(m, 1F), Et₂NCF₂CF₂Br: (neat) -15.7(t,J=5.6Hz 2F) 12.2(t,J=5.6Hz 2F), C₅H₁₀NCF₂CF₂Br: (CCl₄) -18(t,J=5.6Hz 2F) 17.3(t,J=5.6Hz 2F) C₄H₈NCF₂CF₂Br: (CCl₄) -21.0(t,J=5.6Hz 2F) 15.8(t,J=5.6Hz 2F).