

Nucleophilic substitutions of perhalofluoroalkanes initiated by halophilic attacks

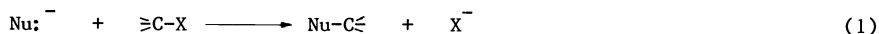
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Abstract - Perhalofluoroalkanes, CXYZCFYZ (X = Cl, Br, I; Y, Z = F, Cl, Br, CF₃), have been found to react spontaneously with many kinds of nucleophiles, e.g., RO⁻, RS⁻, R₃N and R₂N⁻, enamines and enolate, phosphorus ylides, etc. A host of perhalofluoroalkyl compounds, namely, R_fOR, R_fSR, R_fNR₂, etc., can thus be conveniently synthesized by these reactions. Most of the reactions have been shown to proceed via anionic chain processes initiated by different types of halophilic attacks, although different and competitive pathways have been found in some other cases. Lines of evidence for the chlorophilic attacks on C-Cl bonds by sulfur and oxygen nucleophiles and the bromophilic attacks on C-Br bonds by oxygen and nitrogen nucleophiles are presented for the first time. These reactions are often highly solvent dependent and can be facilitated by crown ethers, especially when they are carried out in nonpolar solvents. Phosphorus ylides are also capable of making halophilic attacks on C-X bonds (X = Cl, Br, I) of the perhaloalkanes. In this case, however, the products turn out to be α-halogenated phosphonium salts.

INTRODUCTION

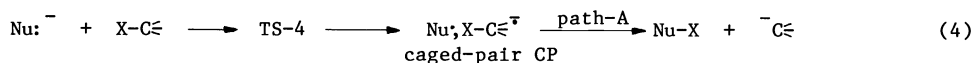
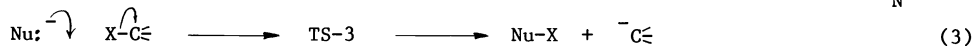
Replacement of the X-group of a saturated substrate ≡C-X by a nucleophile Nu:⁻ (or Nu:) can be a consequence of quite a number of different reaction pathways, but for many years textbooks have only thoroughly covered the most well-known paths, namely, S_N2 and S_N1 and their inbetween paths. Another important class of nucleophilic substitutions is character-



ized by its first step which involves a direct frontside attack on X, as shown by eq.2.



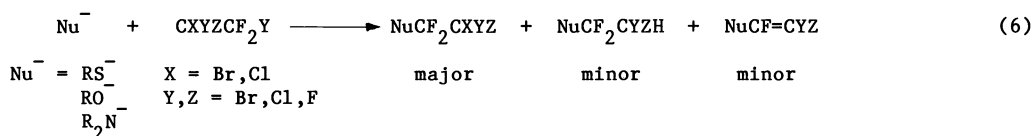
This type of reactions has aroused much interest among chemists and has been recently considered as one of the whole class of "X-philic reactions" (ref. 1). Actually, the situation is more complicated than what eq.2 might suggest, not only because the carbanion can be transformed into different types of products via different types of intermediates, but also because even the first step might possess different transition states (TS), e.g., eq.3 and eq.4. Equation-3 depicts a 2-electron attack on X by Nu⁻ with a TS-3 resembling S_N2 or



deprotonation by a base B⁻; eq.4 describes a single-electron-transfer (SET) process (TS-4) followed by immediate collapse of the caged-pair to products (ref. 2,3). Furthermore, the carbanions first formed, be they extremely ephemeral or longer-lived, may lead to all sorts of products, and the corresponding reactions are traditionally classified (by the nature of the product) as, e.g., reductions, eliminations, etc., but not as "X-philic reactions". Therefore, in order to avoid possible confusions or misunderstandings in communication, we propose to define the "nucleophilic substitution initiated by halophilic attack" as a reaction between an organic substrate X-C≡ (X = halogen) and a nucleophile Nu:⁻ (or Nu:) which is characterized by: (1) an initial nucleophilic attack that leads to the formation of a

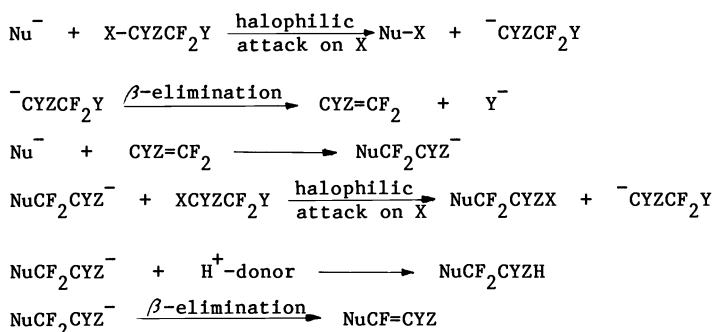
carbanion intermediate $\geq C^-$, irrespective of the nature of the TS and the life-span of the carbanion, and (2), a second step or later steps that transform the carbanion into the product Nu-C \equiv . To conform with tradition, we further propose that other reactions, e.g., reductions which are initiated by a X-philic attack, be described as, e.g., reductions initiated by X-philic attack, but not simply as "X-philic reactions". One feature which might differentiate between the two modes of reactions (eq.3 and eq.4) could be the possibility of a second mode of caged-pair collapse, i.e. path-B in eq.5. Therefore, in mechanism studies of the reactions, attempts should also be made to trap possible radical intermediates in the bulk. Of course, we should also bear in mind that carbanions and radicals are interconvertible by SET processes.

In recent years we have continued our interests in the nucleophilic reactions of perhalofluoroalkanes involving halophilic attacks as the key steps. We have demonstrated examples of bromophilic attacks by phenoxide (ref. 4) as well as chlorophilic attacks by sulfur and oxygen nucleophiles (ref. 5-8), which had not been firmly established before. Perhalofluoroalkanes were chosen as our substrates because: (1) they, especially the perchlorofluorocarbons, had been regarded as relatively unreactive towards nucleophiles; (2) they possess most of the favorable structural features for halophilic attack (*vide infra*), and we believe that their reactions might be very general; (3) they are either commercially available or easily prepared and their reactions might have synthetic applications (ref. 9). The halofluorocarbanions produced by halophilic attacks are very prone to undergo α - or β -eliminations



yielding halofluoro olefins or carbenes which are susceptible to further nucleophilic additions (ref. 10). In fact, it has been found that the reactions of these substrates with various types of nucleophiles often follow an anionic chain mechanism involving intermediary olefins (Scheme I) or carbenes (ref. 4-9,11). Solvent effects may change the course of reaction which lead to different major products (ref. 8).

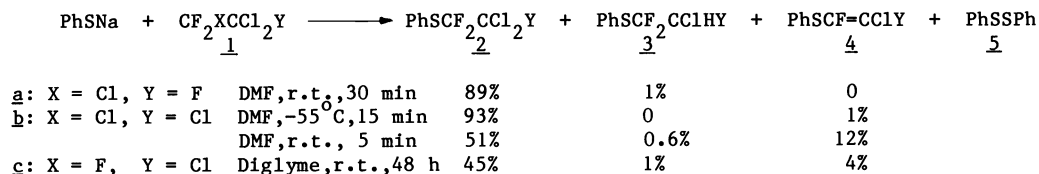
Scheme I



Very recently, we have further extended these reactions by using nitrogen nucleophiles (ref. 12). Thus a host of perhaloalkyl compounds, namely, $R_f\text{-OR}$, $R_f\text{-SR}$, $R_f\text{-NR}_2$, etc, can now be conveniently synthesized by these halophilic attack-initiated nucleophilic substitution reactions. By using phosphorus ylides as the nucleophile, α -halogenated phosphonium salts are formed in good yields (ref. 13). This appears to be a feasible approach to these useful reagents.

SULFUR NUCLEOPHILES

Sulfur nucleophiles (e.g., $C_6H_5S^-$) have been shown to react spontaneously with perfluoroalkyl iodides and per(bromo,fluoro)alkanes to give fluorinated thioethers (ref. 14-16). We have recently found that, at room temperature or even below, such spontaneous reactions will also occur with per(chloro,fluoro)alkanes, the least reactive species in the family of perhalofluoroalkanes (ref. 5,8). The main products are thioethers of the type 2. The relative

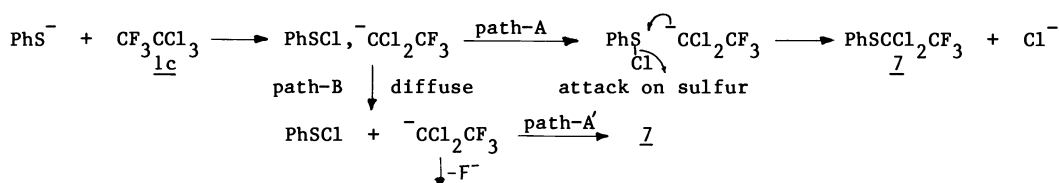


amounts of the products (2,3,4,5, etc.) have been found to be solvent and temperature dependent, and the formation of the main products 2 are favored mostly by polar aprotic solvents and low reaction temperatures.

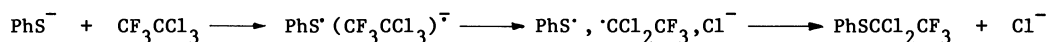
Although the mechanism for many reactions of thiophenoxide with perfluoroalkyl iodide and bromine-containing Freons has been considered to involve SET initiation and radical-chain processes (ref. 14-16), the above mentioned reactions have been shown to be initiated by a chlorophilic attack and follow the anionic chain mechanism described in Scheme I on the basis of the following lines of evidence. (1) GC detection of the intermediate fluoroolefins; (2) protic additives retard the reaction and decrease the yields of 2; (3) The entering PhS group ends up on CF₂, in accordance with the usual regioselective nucleophilic additions to CF₂=CClY (ref. 17); (4) the products 3 and 4 cannot be derived from a S_N2 process, but they are natural products of the intermediate carbanion PhSCF₂CClY⁻; (5) No inhibition was observed when the reactions were carried out in the dark or when nitrobenzene or styrene was added; (6) In the reaction of 1b, one highly reactive intermediate product, i.e., PhSCl, has been successfully trapped by PhSO₂⁻ to give PhSO₂SPh (25% yield). This may serve as good evidence for the chlorophilic attack of PhS⁻ on C-Cl bonds.

It is worthy to mention that the reaction of PhSNa with CF₃CCl₃ (1c) in polar aprotic solvents afforded 7 as the main product, which indicates a competitive pathway. The path-A in Scheme II is analogous to the reactions of triphenylphosphine and haloalkylmethanes yielding haloalkylmethylphosphonium salts (ref. 18). A radical chain mechanism like S_{RN}1 is unlikely

Scheme II



since no notable effects were observed when the reactions were carried out in the dark, by exposure to air, or in the presence of 20 mol% of nitrobenzene or styrene. However, a non-chain mechanism involving SET process could not be ruled out. The reactions of 1a and 1b

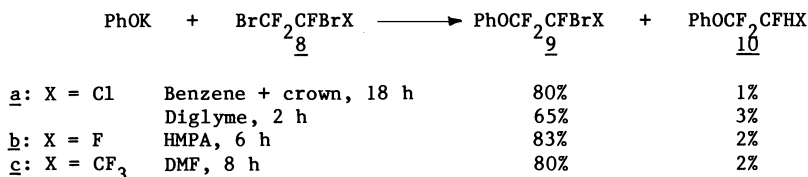


do not follow the path-A in Scheme II, probably because they both have a chlorine, a much better leaving group than fluorine, on the β-carbon and the intermediate carbanions could undergo extremely fast β-elimination.

Although the condensation of PhSNa with CF₂Br₂ has been previously studied, e.g., a 25% yield of the product PhSCF₂Br (8) can be obtained in ether after 24 h (ref. 19), we have re-investigated this reaction in detail and found that the crown ether can exert a dramatic effect on both the rate and product yield of this reaction (ref. 6). For instance, in 5 min, the yield of PhSCF₂Br in benzene is 70% (0% in 24 h without crown ether), and in ether, 80%. Interestingly, in CCl₄, besides 8 (11%), another major product, PhSCF₂Cl (9), was formed together with small amounts of BrCCl₃ and HCCl₃. Formation of these products can be rationalized by either of two possible mechanisms, one involving the key intermediates CF₂⁻, PhSCF₂⁻ and ⁻CCl₃, the other involving ⁻CF₂Br, PhSCF₂⁻ and ⁻CCl₃. However, only the latter path would lead to the formation of some CCl₃CCl₃. Careful GC analysis showed no trace of CCl₃CCl₃, thus again an anionic chain mechanism is indicated.

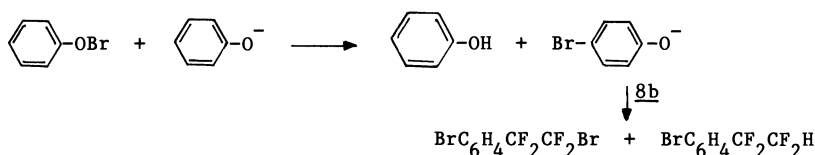
OXYGEN NUCLEOPHILES

Phenoxide and other aryloxides and alkoxides are less nucleophilic than the thiolates, and not long ago bromophilic and chlorophilic attacks by oxygen nucleophiles have never been firmly established. Thus we were pleased to find that the reactions of phenoxides with 8 actually can proceed smoothly at room temperature or below without extra initiation or UV irradiation to afford the perhalofluoroalkyl ethers in fair to good yields (ref. 4). Substituted phenoxides and alkoxides behave similarly in the reactions with 8 (ref. 20).

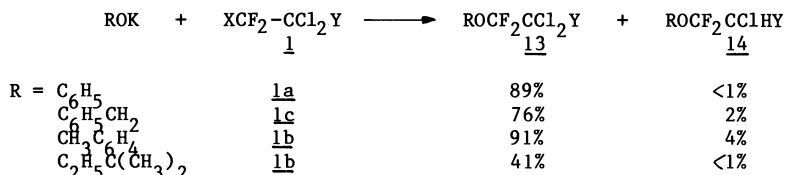


Lines of evidence for an anionic chain similar to those mentioned previously were obtained. Furthermore, additional support for an initiation step involving bromophilic attack by an oxygen nucleophile was obtained by the identification of ring-brominated products Br-C₆H₄OCF₂CF₂Br (11) and Br-C₆H₄OCF₂CF₂H (12) in the reaction system of 8b/PhOH/KOH/diglyme,

since most likely they were formed from the following reactions which involve the intermediate PhOBr.



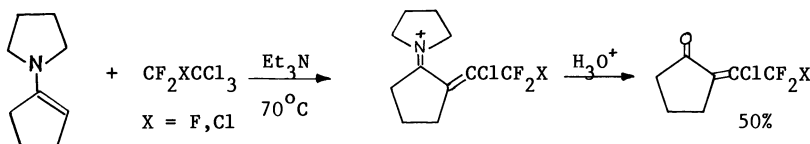
Rather surprisingly, even the poorly reactive per(chloro,fluoro)ethanes will undergo this reaction very smoothly. In the case of *p*-methyl and *p*-methoxy substituted phenol, the anhy-



drous phenoxides can even be replaced by a mixture of the corresponding phenol and potassium hydroxide without much effect on the product yields (ref. 7). Thus a chlorophilic attack by oxygen nucleophiles RO⁻ is indicated. All the evidence supports the proposition that the mechanism is similar to the two above-mentioned reactions which involve chlorophilic attack by PhS⁻ and bromophilic attack by PhO⁻, respectively.

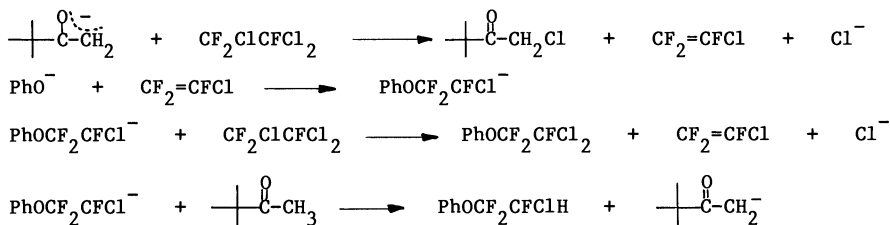
ENAMINE AND ENOLATE AS NUCLEOPHILES

Enamines have been reported to react with perfluoroalkyl iodides and halomethanes yielding haloalkylated ketones (ref. 21). We have extended this reaction to per(chloro,fluoro)-ethanes, and fluoroalkylated α,β -unsaturated ketones in moderate yields were obtained with CF₂XCCl₃ (ref. 22). The behaviour of per(chloro,fluoro)ethanes in this reaction is quite different from their behavior in the reactions with sulfur and oxygen nucleophiles and, it is



probably a SET initiated process (ref. 22).

Enolate ions have been shown to be reactive nucleophiles in halophilic attacks (ref. 23), but their reactions with perhaloalkanes failed to give the alkylation products (ref. 24). However, an enolate initiated condensation of PhONa and the less reactive CF₂ClCFCl₂ in diglyme has been achieved. The reactions in diglyme or in pinacolone gave only trace amounts of the products. But when the reactions were carried out in diglyme containing 0.4% of pinacolone, PhOCF₂CFCl₂ (53%) and PhOCF₂CFClH (13%) were obtained (ref. 24). This observation provides a convincing evidence for the inference that the mechanism of an early reported reaction, i.e., the reaction of PhONa with CF₂ClCCl₃ in butanone giving PhOCF₂CCl₂H in 30% yield (ref. 25), is an enolate initiated process. This procedure also provides a promising

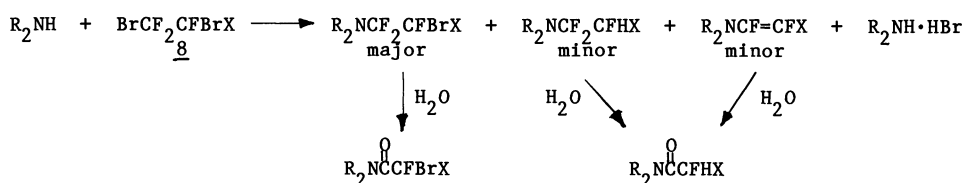


approach for achieving such condensations between otherwise poorly reactive species.


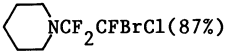
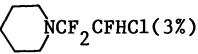

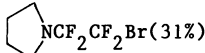
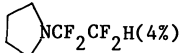
NITROGEN NUCLEOPHILES

Amines are fairly good nucleophiles in the S_N2 type substitution reactions. It has been found, however, that they are less reactive in making nucleophilic attacks on iodine (ref. 26). Nevertheless, slow but spontaneous reactions of secondary amines with per(bromo,

fluoro)alkanes can still proceed in some typical polar aprotic solvents to furnish the N-alkylated products (ref. 27). Slight heating and addition of triethylamine can facilitate



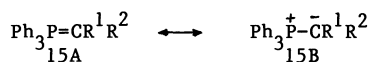
the reaction and increase the product yields. The enamines were found only in the reactions of **8b**. Lithium and sodium amides, as expected, react readily with per(bromo,fluoro)alkanes to give the same products as those of the reactions of the corresponding secondary amines, but with better yields. The role of amines and amides in these reactions is quite similar to those of the sulfur and oxygen nucleophiles and can be analogously described in terms of an anionic chain mechanism with a bromophilic step accomplished by a nitrogen nucleophile (cf. Scheme I).

R^1R^2NH	additive	$CF_2BrCFBrX$	products (yield)	
Et_2NH	none	8a , X = Cl	$Et_2NCF_2CFBrCl$ (21%)	Et_2NCF_2CFHCl (4%)
	NaH + Et_3N	8a	$Et_2NCF_2CFBrCl$ (77%)	Et_2NCF_2CFHCl (1%)
	BuLi + Et_3N	8b , X = CF_3	$Et_2NCF_2CFBrCF_3$ (65%)	$Et_2NCF_2CFHCF_3$ (1%)
	NaH + Et_3N	8a , X = Cl	 (87%)	 (3%)
	NaH + Et_3N	8c , X = F	 (31%)	 (4%)

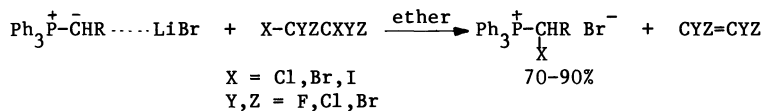
A bulky nucleophile should be equally capable of making halophilic front-side attack but less reactive in nucleophilic addition to fluoroolefins. In fact, iPr_2NLi reacted with **8a** to give only 5% of the halofluoroalkylamine and the main product turned out to be $CF_2=CFCl$.

PHOSPHOROUS YLIDES AS NUCLEOPHILES

The nucleophilic character of ylides has been well recognized. As indicated by the 1,2-dipolar resonance structure (**15b**), these uncharged species can be considered as heteroatom-stabilized carbanions. Therefore, it seems reasonable to consider that ylides might also be able to make halophilic attacks. However, this possibility had not yet been examined until we recently started our project with phosphorus ylides, the most well-known and useful reagents



in this class of compounds. Our results have shown that alkylidenephosphorane react readily with perhalofluoroalkanes, yielding α -halogenated phosphonium salts in good yields (ref. 13). This reaction has been successfully extended to other types of phosphorus ylides,



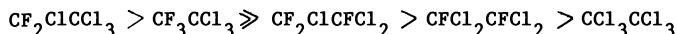
such as moderate ylides and β -oxido ylides (ref. 28).

This observation is not only mechanistically significant but also synthetically useful, since previous methods for the preparation of α -halogenated phosphonium salts and α -halo ylides are neither effective nor convenient, and are limited to some special cases (ref. 29). The present result provides a feasible approach to the preparation of these useful reagents, and from them to haloalkenes via Wittig-type reactions.

STRUCTURE AND REACTIVITY OF PERHALOFLUOROALKANES IN HALOPHILIC REACTIONS

The perhalofluoroalkanes possess some structural features favorable to halophilic attack, e.g.: (1) steric and electronic shielding of the carbon from back-side attack by fluorine and other halogen atoms; (2) The presence of a number of strongly electron-attracting halogen substituents facilitates nucleophilic attacks on X and disfavors ionization of the C-X bond (in the S_N1 sense); (3) Absence of H-atoms susceptible to deprotonation, and multiple bonds susceptible to addition-elimination.

Notably, the fluorine substitution might play some special role. Experimental results showed that perfluoroalkyl chloride and highly fluorinated perchloroalkanes possess little reactivity in halophilic reactions. Unexpectedly, perchloroalkanes like CCl_4 , CCl_3CCl_3 are also less reactive. The overall reactivity of ethane derivatives seems to be in the order:



Interestingly, the reactivity depends not only on the number of fluorine atoms but also on their locations. Several factors might be responsible for the overall reactivity of these Freons. For instance, the relative susceptibility of the chlorine atom to halophilic attack, the relative stability of the incipient carbanion, the leaving aptitude of the leaving group, and the susceptibility of the intermediate olefins to nucleophilic additions, should all be taken into consideration. In general, if the carbon bearing the Cl atom undergoing attack is referred to as the α -carbon, then the above-mentioned reactions seem to be most favored by α -chloro substitution and β -fluoro substitution. β -trifluoro substitution will prolong the life-span of the intermediate carbanion because Cl is better than F as a leaving group. Furthermore, the presence of fluorine will make the intermediate olefins more prone to undergo the next step, nucleophilic addition.

An MNDO calculation of the chlorofluoroethanes afford some information which is in agreement with this assumption (ref. 30). The fluorine substitution lowers the LUMO (σ^*) energy and, therefore, favors the HOMO-LUMO interactions. But the α -fluorination increases the negative charge on Cl-atom and they may disfavor the chlorophilic attack. Furthermore, the molecular orbital coefficients of the LUMO at Cl-atoms in haloethanes are considerably increased in comparison with those in alkyl halides. This is also a favorable factor for halophilic attack.

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