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PREPARATION AND SYNTHETIC UTILITY OF FLUORINATED PHOSPHONIUM SALTS, BIS-PHOSPHONIUM SALTS AND PHOSPHORANIUM SALTS [1]

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SUMMARY

The reaction of tertiary phosphines with fluorohalomethanes provides a rapid and high yield synthesis of various types of fluorinated phosphonium salts, bis-phosphonium salts and phosphoranium salts. These salts are useful precursors to fluorine-containing ylides, carbenes and methide ions. Examples of the preparation, mechanism of formation, and synthetic utility of these novel reagents is described.

INTRODUCTION

The Wittig Reaction is one of the most widely used routes for the preparation of olefins and substituted olefin derivatives. It readily permits one to select the substituents attached to the olefinic center via the proper choice of ylide and aldehyde or ketone, and more importantly it allows one to unequivocally predict the position of the alkene center in the final product.

$$R_3\overset{+}{P}\text{-}\overset{-}{C}R^1R^2 \;+\; R^3C(O)R^4 \longrightarrow R_3PO \;+\; R^1R^2C{=}CR^3R^4$$

For the normal Wittig route to be successful two key steps must be accomplished; (1) successful alkylation of the appropriate substrate by the tertiary phosphine to produce the required phosphonium salt; (2) selective removal of an α-hydrogen from the phosphonium salt to produce the ylide - thus, at least one α-hydrogen must be present in the phosphonium salt precursor.

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$$R_3P: + R^1R^2CHX \longrightarrow [R_3\overset{+}{P}CHR^1R^2]X^-$$

$$[R_3\overset{+}{P}CHR^1R^2]X^- + Base \longrightarrow [R_3\overset{+}{P}\text{-}\overset{-}{C}R^1R^2] + [Base\ H]^+X^-$$

Several years ago we decided to investigate the Wittig Reaction as a potentially general and useful route to fluoromethylene olefins. Our initial work focused on the preparation of difluoromethylene olefins and the preparation of the required precursors of the difluoromethylene ylide. If one follows the normal strategy outlined above for a "normal" Wittig reagent, the most likely approach is:

$$R_3P: + CHF_2X \longrightarrow [R_3\overset{+}{P}CF_2H]X^- \xrightarrow{base} [R_3\overset{+}{P}\text{-}\overset{-}{C}F_2] + [Base\ H]^+X^-$$

However, this approach met with little success for the following reasons: (a) the difluoromethane derivatives were not easily or cleanly alkylated by tertiary phosphines; (b) the hydrogen in the $[R_3\overset{+}{P}CF_2H]X^-$ was not very acidic and its abstraction by base was difficult or messy; (c) the ylide $[R_3\overset{+}{P}\text{-}\overset{-}{C}F_2]$, was found to be very unstable and all attempts at pregeneration failed.

Thus, it became obvious that an approach was needed that avoided an SN2 type of displacement reaction in the preparation of the phosphonium salt; an approach that avoided proton abstraction reactions to produce the ylide; and a route that either permitted *in situ* capture of the ylide or provided an *in situ* mechanism of ylide stabilization; or produced an alternative reactive intermediate that either mimicked the ylide in its chemistry or generated the ylide *via* a dissociative process.

This report outlines our approach to solve these problems. It will focus attention on the synthetic utility of several of these reagents and will detail some of our mechanistic interpretations. Indeed, it's only when one understands (or hopefully understands) some of the mechanistic steps in these reactions that a designed intelligent approach to these ylides can be made. Further extrapolations of the initial mechanistic ideas suggested the extensions to *bis*-phosphonium salts and phosphoranium salts, and some of our preliminary work in these areas will be briefly reviewed.

Although we have prepared a wide variety of fluorohalomethyl phosphonium salts [2], for illustrative purposes $[R_3\overset{+}{P}CF_2Br]Br^-$, $[Ph_3\overset{+}{P}CFBr_2]Br^-$, and $[(R_2N)_3\overset{+}{P}CFCl_2]Cl^-$ have been selected for discussion in this paper as they are representative of the mechanistic and synthetic types encountered in fluorohalomethyl phosphonium salt chemistry [3].

RESULTS AND DISCUSSION

Bromodifluoromethylphosphonium salts

In contrast to earlier literature reports on the failure of triphenylphosphine to react with CF_3I and $CFCl_3$, we found that triphenylphosphine reacted readily with CF_2Br_2 in diglyme (usually within 30 seconds) to give essentially a quantitative yield of the phosphonium salt (I) [4]. In glyme solvents salt (I) precipitates and can be easily isolated by

$$Ph_3P: + CF_2Br_2 \xrightarrow[RT]{DG} [Ph_3\overset{+}{P}CF_2Br]Br^- \downarrow$$
$$\sim 100\%, \text{ (I)}$$

filtration. It is easily hydrolyzed by water or protic solvents but with proper attention to the use of anhydrous solvents and Schlenk transfer procedures, it is easily and readily manipulated.

A similar reaction with tris-dimethylaminophosphine and CF_2Br_2 gives the analogous phosphonium salt (II) [5]. In contrast to (I), salt (II) is

$$(Me_2N)_3P: + CF_2Br_2 \xrightarrow{DG} \underset{\text{(II)}}{[(Me_2N)_3\overset{+}{P}CF_2Br]Br^-} \downarrow$$

not hydrolyzed by water or protic solvents, but is hydrolyzed by aqueous OH^-. In fact, this type of solvolytic behavior [6] is characteristic of all types of fluorohalomethyl phosphonium salts that we have worked with: (a) triphenylphosphonium derivatives are readily hydrolyzed by water and alcohol; (b) trialkylphosphonium derivatives are hydrolyzed by water but not by alcohol; (c) tris-dialkylamino phosphonium derivatives are hydrolyzed by neither water nor alcohol.

$$[(R_2N)_3\overset{+}{P}CF_2X]X^- < [R_3\overset{+}{P}CF_2X]X^- < [Ph_3\overset{+}{P}CF_2X]X^- \quad [7]$$
$$\longleftarrow \text{ decreasing ease of hydrolysis}$$

Mechanism of salt formation

At first glance the formation of (I) and (II) would appear to be another example of a typical SN2 displacement type reaction. However, the mechanism of formation of (I) and (II) is much more complicated, and we have proposed the following sequence to explain the formation of these salts [8].

$$R_3P: + CF_2Br_2 \longrightarrow [R_3\overset{+}{P}Br] + [CF_2Br]^- \quad \text{(positive halogen abstraction)}$$
$$R = Ph, Me_2N$$

$$[CF_2Br]^- \rightleftharpoons [:CF_2] + Br^- \quad \text{(carbene formation)}$$

$$R_3P: + [:CF_2] \rightleftharpoons [R_3\overset{+}{P}-\overset{-}{C}F_2] \quad \text{(carbene capture)}$$

$$[R_3\overset{+}{P}-\overset{-}{C}F_2] + [R_3\overset{+}{P}Br] \longrightarrow [R_3\overset{+}{P}CF_2Br]Br^- + R_3P: \quad \text{(positive halogen abstraction)} \qquad [9]$$

The key initial step is abstraction of Br^+ (attack on halogen) - not attack on carbon (SN2)-and formation of difluorocarbene. In this case (CF_2Br_2) carbene may be formed via a concerted process rather than via stepwise formation of $[CF_2X]^-$ followed by dissociation to carbene - we cannot distinguish between a concerted or stepwise pathway - the stepwise pathway is used in the preceding scheme merely for operative simplicity. The electrophilic difluorocarbene is subsequently captured by the nucleophilic tertiary phosphine to give the phosphonium ylide - which captures positive halogen from $[R_3\overset{+}{P}Br]$ or CF_2Br_2 to complete the salt formation and initiate or continue the chain process.

Evidence consistent with this mechanistic proposal is [10]:

(a) Reaction with CF_2BrI

$$Ph_3P: + CF_2BrI \xrightarrow[TG]{0°C} \underset{\text{(III)}}{[Ph_3\overset{+}{P}CF_2I]Br^-} + \underset{\text{(IV)}}{[Ph_3\overset{+}{P}CF_2Br]I^-}$$
$$2 \quad : \quad 1$$

If the mechanism of formation of (I) involved SN2 attack on carbon, one would anticipate that (IV) should be the predominant or exclusive product - based on the better leaving group ability of iodide compared to bromide. However, as noted above, the predominant product is (III) - not (IV). The formation of (III) as the major product is consistent with the carbene mechanism - since in the initial or final step one would anticipate preferential abstraction of the more polarizable iodine compared to bromine [11].

(b) Reaction in the presence of proton donors

$$Ph_3P: + CF_2Br_2 \xrightarrow[THF]{H_2O} \underset{55\%}{[Ph_3\overset{+}{P}CF_2H]Br^-} + \underset{20\%}{CF_2HBr}$$

Since hydrolysis of (I) gives only CF_2HBr, the formation of $[Ph_3\overset{+}{P}CF_2H]Br^-$ can only be explained *via* carbene formation, ylide formation and protonation of the intermediate ylide [12]. If the mechanism of (I) involved SN2 attack on CF_2Br_2, only the methane would be anticipated as the hydrolysis product.

Ylide reaction of (I) and (II)

The availability of (I) and (II) from commercially available or readily prepared reagents makes these salts suitable and attractive precursors to the corresponding difluoromethylene ylides. Abstraction of positive halogen from (I) or (II) by a second equivalent of the tertiary phosphine permits *in situ* formation of the appropriate ylide and *in situ* capture of the ylide by the appropriate aldehyde or ketone

$$\overset{+}{[R_3PCF_2Br]}Br^- + R_3P: \rightleftharpoons \overset{+\ -}{[R_3P\text{-}CF_2]} + \overset{+}{[R_3PBr]}Br^- \qquad [13]$$

R= Ph, Me_2N

$$\overset{+\ -}{[R_3P\text{-}CF_2]} + >C=O \longrightarrow F_2C=C< + R_3PO$$

Illustrative examples of the synthetic applicability of (I) and (II) are given in Table I and II.

Several comments on the mechanism of this reaction and its synthetic applicability are needed to permit one to get the best results with this approach to difluoromethylene olefins.

(a) The reaction of (I) or (II) with a second equivalent of R_3P is an equilibrium reaction [13] - with the equilibrium *far* to the left. Thus, there is always an *excess* of R_3P present in solution. It is important to consider this equilibrium when designing this type of Wittig reaction - since some polyfluorinated ketones [14] and olefins readily react with tertiary phosphines [15]. Thus, in Table I the low yield with C_6F_5CHO is due to rapid and destructive reactions of this aldehyde with Ph_3P. Similarly, the low yield with $PhCOCF_3$ in Table II is due to rapid reaction of this ketone with$(Me_2N)_3P$ [16]. This problem can be often circumvented *via* dehalogenation of the pre-generated phosphonium salt with a metal [15]

TABLE I

$$2\ Ph_3P + CF_2Br_2 + >C{=}O \xrightarrow[70°C]{TG} >C{=}CF_2 + Ph_3PO + Ph_3PBr_2$$

>C=O	>C=CF_2	% yield
C_6H_5CHO	$C_6H_5CH{=}CF_2$	65
C_6F_5CHO	$C_6F_5CH{=}CF_2$	20
$C_6H_5COCF_3$	$C_6H_5C(CF_3){=}CF_2$	85
$C_6H_{11}COCF_3$	$C_6H_{11}C(CF_3){=}CF_2$	90
$C_6H_5COC_2F_5$	$C_6H_5C(C_2F_5){=}CF_2$	82
$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_5CH{=}CF_2$	72
m-$BrC_6H_4COCF_3$	m-$BrC_6H_4C(CF_3){=}CF_2$	83
$C_6H_5COCH_3$	$C_6H_5C(CH_3){=}CF_2$	2

TABLE II

$$2(Me_2N)_3P + CF_2Br_2 + >C{=}O \xrightarrow[RT]{TG} >C{=}CF_2 + (Me_2N)_3PO + (Me_2N)_3PBr_2$$

>C=O	>C=CF_2	% yield
$C_6H_5COCH_3$	$C_6H_5C(CH_3){=}CF_2$	81
$C_6H_5COC_2H_5$	$C_6H_5C(C_2H_5){=}CF_2$	82
$(C_2H_5)_2CO$	$(C_2H_5)_2C{=}CF_2$	75
		71
$(CH_3)_2CO$	$(CH_3)_2C{=}CF_2$	60
$C_6H_5COCF_3$	$C_6H_5C(CF_3){=}CF_2$	25

(b) The choice of which ylide system to utilize is dictated by the electrophilicity of the carbonyl component. Thus, in Table I, a typical aliphatic aldehyde $[CH_3(CH_2)_5CHO]$, a typical aromatic aldehyde (PhCHO), and typical activated (trifluoromethyl) ketones successfully react with $[Ph_3\overset{+}{P}\text{-}\overset{-}{C}F_2]$. However, a typical non-activated ketone ($PhCOCH_3$) gives only traces of olefinic product. However, with the more nucleophilic $[(Me_2N)_3\overset{+}{P}\text{-}\overset{-}{C}F_2]$ ylide [17], all types of non-activated ketones are successfully converted to the difluoromethylene olefin. Thus, by the proper choice of the ylide system most aldehydes and ketones can be easily converted to $CF_2{=}C<$ type olefins. Obviously, because of the equilibrium problem noted above and the enhanced reactivity of $(Me_2N)_3P$: compared to Ph_3P:, the more reactive ylide system is generally employed only with obstinate substrates.

(c) With highly enolizable substrates, these basic ylides undergo an acid-base reaction (which quenches the ylide) and gives poor yields of olefin.

$$[(Me_2N)_3\overset{+-}{P}CF_2] \;+\; \text{cyclopentanone} \rightarrow [(Me_2N)_3\overset{+}{P}CF_2H] \;+\; \text{enolate}$$

However, successful formation of difluoromethylene olefins of this type can be readily accomplished by an ylide-carbene reaction [18, 19].

(d) This route to the difluoromethylene ylides is a mild, clean route and is not characterized by the formation of any significant amounts of fluoride ion. Thus, many of the problems of HF addition and fluoride ion catalyzed isomerization of the initially formed olefins are easily avoided with this approach. For example, $\underline{m}\text{-}BrC_6H_4COCF_3$ (Table I) gives an excellent yield of olefin *via* the phosphonium salt route, whereas this ketone gives mainly (98% of the isolated product) the HF addition product *via* the sodium chlorodifluoroacetate route to the ylide [4]. Similar results were found with chloro substituted derivatives [20] and trifluoromethyl substituted derivatives [21] in the acetate salt route. Similarly, $PhCOCF_2CF_3$ gives only the terminal olefin (Table I) in contrast to the problems of fluoride-ion isomerization encountered with the acetate salt method [20]. Other examples of the preparation of fluoroolefins sensitive to fluoride ion *via* this method have been reported [21].

(e) The reaction can be applied to polyfunctionalized derivatives:

$$EtC(O)(CF_2)_2C(O)Et \xrightarrow[CF_2Br_2]{Ph_3P} F_2C{=}C(Et)(CF_2)_2C(Et){=}CF_2 \quad (50\%) \quad + \text{ enone } (6\%) \qquad [22]$$

$$PhC(O)(CF_2)_3C(O)Ph \xrightarrow[CF_2Br_2]{Ph_3P} F_2C{=}C(Ph)(CF_2)_3C(Ph){=}CF_2 \quad (57\%) \quad + \text{ enone } (16\%)$$

Dihalofluoromethylphosphonium salts

Typical examples of salts of this type are illustrated below:

$$Ph_3P: + CFBr_3 \longrightarrow [Ph_3\overset{+}{P}CFBr_2]Br^- \quad (V)$$

$$(Me_2N)_3P: + CFCl_3 \longrightarrow [(Me_2N)_3\overset{+}{P}CFCl_2]Cl^- \quad (VI)$$

With the more polarizable methane ($CFBr_3$), the less halophilic phosphine (Ph_3P) affords the phosphonium salt (V). However, $CFCl_3$ does not react with Ph_3P to give a phosphonium salt under the normal conditions utilized in the preparation of these materials [23]; hence the more halophilic phosphine must be employed to accomplish salt formation [24].

The initial step in the mechanism of formation of salts of this type is similar to the initial step in the formation of bromodifluoromethylphosphonium salts - namely, abstraction of positive halogen to produce an ion pair. However, at this juncture the mechanistic pathways diverge.

$$R_3P: + CFX_3 \longrightarrow [R_3\overset{+}{P}X]CFX_2^- \longrightarrow [R_3\overset{+}{P}CFX_2]X^-$$

R = Ph, Me_2N X = Br, Cl

Since the methide ion produced from CFX_3 is longer lived than the ion fror CF_2X_2, it recombines with the halophosphonium cation (via nucleophilic attack on the phosphonium center) to give the phosphonium salt.

Evidence consistent with this mechanistic interpretation is:

$$(Me_2N)_3P: + CFCl_3 \xrightarrow[\text{or } H_2O]{EtOH} CHFCl_2 \quad 95\%$$

When the reaction between $(Me_2N)_3P$ and $CFCl_3$ is carried out in the presence of traces of EtOH or H_2O, only $CHFCl_2$ is observed. No (VI) is observed. Since (VI) is stable to both EtOH and H_2O, the $CHFCl_2$ cannot be formed via hydrolysis of (VI). Thus, if (VI) had been formed via SN2 attack on $CFCl_3$, it would not undergo further cleavage to $CHFCl_2$. Similar experiments with $CFBr_3$ and $(Me_2N)_3P$ lead to the same conclusion - that initial attack is on the halogen of the methane and not on carbon (SN2). Similarly if the reaction between tertiary phosphine and the trihalofluoromethane is carried out in the presence of a fluoroolefin as a competitive electrophilic trapping agent, the formation of the chain-extended olefin (via capture of the methide ion) is again consistent with the proposed mechanistic scheme.

$$Ph_3P: + CFBr_3 + CF_2{=}CFCF_3 \longrightarrow CFBr_2\text{–}C(F)=C(F)\text{–}CF_3 \qquad [25]$$

Synthetic utility of dihalofluoromethylphosphonium salts

Salts (V) and (VI) can be further dehalogenated with a second mole of tertiary phosphine to give the respective bromofluoromethylene [26] and chlorofluoromethylene ylides [27].

$$[Ph_3\overset{+}{P}CFBr_2]Br^- + Ph_3P: \longrightarrow [Ph_3\overset{+-}{P}CFBr] + Ph_3PBr_2$$

$$[(Me_2N)_3\overset{+}{P}CFCl_2]Br^- + (Me_2N)_3P: \longrightarrow [(Me_2N)_3\overset{+-}{P}CFCl] + (Me_2N)_3PCl_2$$

Table III summarizes some illustrative examples of the preparation of bromo fluoromethylene olefins via this route. Again, the reaction may be carried out stepwise or via a one-pot procedure. In the case of the bromofluoromethylene olefins both (E) and (Z) isomers are possible. The fluorohalomethylene ylides are not stereospecific reagents and where possible, the geometrical isomers are usually obtained in ~ 1:1 ratio [28]. Since these bromofluoromethylene olefins are readily converted into vinylic lithium [29], Grignard [30], zinc [30], or copper [30] reagents, they provide a useful entry for the preparation of polyfunctionalized fluorine derivatives.

TABLE III

$[Ph_3\overset{+}{P}CFBr_2]Br^-$ + Ph_3P + >C=O $\xrightarrow{\text{solvent}^*}$ >C=CFBr + Ph_3PO + Ph_3PBr_2

>C=O	>C=CFBr	% yield
C_6H_5CHO	C_6H_5CH=CFBr	70
$C_6H_5COCF_3$	$C_6H_5C(CF_3)$=CFBr	97
$C_6H_5CH_2COCF_3$	$C_6H_5CH_2C(CF_3)$=CFBr	59
$C_6H_5COC_2F_5$	$C_6H_5C(C_2F_5)$=CFBr	65
CF_3COCF_3	$(CF_3)_2C$=CFBr	80
$C_6H_5COCH_3$	$C_6H_5C(CH_3)$=CFBr	45
$C_3F_7COC_3F_7$	$(C_3F_7)_2C$=CFBr	79

*Solvents such as THF, CH_3CN, $CHCl_3$ were utilized depending on the solubility of the carbonyl substrate.

The phosphine dehalogenation of (VI) has been reported [27] and is completely analogous to the other previously reported phosphonium salts. An alternative mode of dehalogenation of these salts, however, is via use of an active metal (as noted earlier). With salt (VI) facile dehalogeneration occurs with zinc metal to give a stable solution of a metal-stabilized ylide [31]. The stability of this reagent is remarkable

$$[(Me_2N)_3\overset{+}{P}CFCl_2]Cl^- + Zn \longrightarrow [(Me_2N)_3\overset{+}{P}CFClZnCl]Cl^- \quad \text{(VII)}$$

$$\Updownarrow$$

$$[(Me_2N)_3\overset{+-}{P}CFCl] + ZnCl_2$$

compared to the "free" ylide $[(Me_2N)_3\overset{+\ -}{P}\text{-}CFCl]$. The free ylide has a half-life less than 1/2 hr. [32], whereas this metal-stabilized reagent slowly loses activity (~ 1% per day) over one month. However, (VII) exhibits excellent reactivity with typical carbonyl substrates (cf. Table IV for illustrative examples). Only highly enolizable substrates give poor

TABLE IV

$[(Me_2N)_3\overset{+}{P}CFCl_2]Cl^- + Zn(Cu) + >C=O \xrightarrow{THF} >C=CFCl$

>C=O	>C=CFCl	% yield
C_6H_5CHO	$C_6H_5CH=CFCl$	100
$C_6H_5COCF_3$	$C_6H_5C(CF_3)=CFCl$	100
$C_6H_5COCH_3$	$C_6H_5C(CH_3)=CFCl$	70
$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_5CH=CFCl$	100
		18
$CF_3CO_2CH_3$	$CF_3C(OCH_3)=CFCl$	90

results - due to protonation of the ylide. Since the stereochemical results are identical with either (VII) or the 'free' ylide, we assume that (VII) dissociates to the 'free' ylide, which is the actual olefinating species. Since (VII) is easily prepared in high yields, is storable, and its preparation can be readily scaled up, it is the method of choice for the preparation of chlorofluoromethylene olefins.

The metal dehalogenation route of phosphonium salts and the formation of metal-stabilized ylides is currently under active investigation in our laboratories. Preliminary results indicate that it is a generally useful method and will be the subject of several reports in the near future. One important aspect of this mode of approach is that no excess tertiary phosphine is present in the reaction mixture. Thus, carbonyl or olefinic substrates that are attacked by the tertiary phosphine and fail in the normal ylide approach can be readily converted to olefins via this alternative method. Some of our preliminary results with salt (I) have been reported and some typical examples of the utility of this approach are illustrated in Table (V).

TABLE V

$$RCOR' + Metal\ (M) + [Ph_3\overset{+}{P}CF_2Br]Br^- \xrightarrow[RT]{TG} RR'C{=}CF_2 + MBr_2 + Ph_3PO$$

RCOR'	$RR'C{=}CF_2$	Cd	Hg	Ph_3P[a]
$C_6H_5C(O)CF_2Cl$	$C_6H_5C(CF_2Cl){=}CF_2$	76	21	25
$C_6F_5C(O)CF_3$	$C_6F_5C(CF_3){=}CF_2$	83	71	0
C_6F_5CHO	$C_6F_5CH{=}CF_2$	62	41	20
$C_6F_5C(O)CF_2Cl$	$C_6F_5C(CF_2Cl){=}CF_2$	72	64	0

(a) Yield of olefin when Ph_3P was used as the dehalogenation reagent.

Bis-phosphonium salts

Although our work with phosphonium salts such as (I), (II), (V), and (VI) continues, we have recently begun to examine these salts as precursors to other interesting and novel phosphorus-fluorine synthetic intermediates. This work is of recent vintage and obviously not as complete as the work with the fluorohalomethyl phosphonium salts. However, we would like to present some of our mechanistic and synthetic ideas on this subject and to outline some of the interesting features of these reactions that are being investigated in our laboratory.

As noted earlier the mechanistic scheme for the preparation of the difluoromethylene ylide involved abstraction of Br^+ from (I) or (II) *via* a second equivalent of the tertiary phosphine to establish the following equilibrium [13].

$$[R_3\overset{+}{P}CF_2Br]Br^- + R_3P: \rightleftharpoons [R_3\overset{+}{P}Br]\overset{-}{Br} + [R_3\overset{+-}{P}CF_2]$$

We believe the importance of this equilibrium is the ability of the $[R_3\overset{+}{P}Br]$ cation to donate Br^+ back to the ylide - thus preventing rapid dissociation [33] and decomposition of the ylide. Indeed, in other routes to the ylide which do not involve R_3PBr_2, no stabilization of the ylide has been noted.

In addition to recapture of Br^+ by the ylide, the above equilibrium also suggests an alternative mode of reaction - namely, nucleophilic attack by the ylide on the phosphorus atom of $[R_3\overset{+}{P}Br]$ to give a bis-phosphonium salt.

$$R_3\overset{+-}{P}CF_2 + [R_3\overset{+}{P}Br]Br^- \longrightarrow [R_3\overset{+}{P}CF_2\overset{+}{P}R_3]Br^-$$

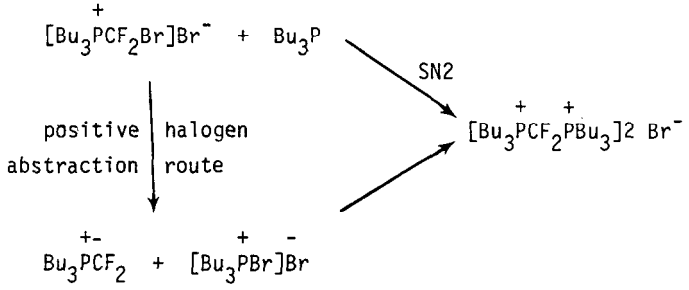
bis-phosphonium salt

(VIII)

When R = Ph or Me_2N, little bis-phosphonium salt formation is observed [10]. However, when R = alkyl, bis-phosphonium salt formation is readily observed, and the bis-phosphonium salt can be easily and rapidly formed in high yield.

$$2\ Bu_3P: + CF_2Br_2 \longrightarrow [Bu_3\overset{+}{P}CF_2\overset{+}{P}Bu_3]2\ Br^-$$

Again, the key mechanistic question is the second step in this sequence [34]. Does the step involve SN2 attack on carbon or abstraction of halogen by a second equivalent of the tertiary phosphine?



When the reaction of $[Bu_3\overset{+}{P}CF_2Br]Br^-$ with Bu_3P is carried out in the presence of $PhCH_2COCF_3$ [35], the difluoromethylene olefin and the reduced phosphonium salt were observed. These products are only consistent with the positive halogen abstraction mechanism - the olefin is formed via capture of the ylide and the reduced salt is formed via proton capture from the enol of the benzyltrifluoromethyl ketone. Thus, again we note the absence of any SN2 type reactions in these processes.

$$[Bu_3\overset{+}{P}CF_2Br]Br^- + PhCH_2COCF_3 \xrightarrow{Bu_3P} CF_2{=}\underset{\underset{CF_3}{|}}{C}CH_2Ph + [Bu_3\overset{+}{P}CF_2H]Br^-$$

50% 50%

The bis-phosphonium salt preparation opens up many new routes to interesting mixed salts as well as mixed valence species, as shown below in the two illustrative examples.

$$[Et_3\overset{+}{P}CF_2Br]Br^- + Bu_3P: \longrightarrow [Et_3\overset{+}{P}CF_2\overset{+}{P}Bu_3]\ 2\ Br^- \quad [10]$$

70%

$$[Bu_3\overset{+}{P}CF_2Br]Br^- + (EtO)_3P: \longrightarrow [Bu_3\overset{+}{P}CF_2P(O)(OEt)_2]Br^- + EtBr \quad [10]$$

A detailed investigation of the scope of these and other bis species is now in progress. Our preliminary work suggests that we can undoubtedly anticipate exciting and novel results.

Phosphoranium salts

Our preliminary work with bis-phosphonium salts outlined in the previous section led us to explore related work with salts such as (V) and related derivatives. Again (based on the earlier work), one might anticipate that nucleophilic attack of the bromofluoromethylene ylide on the bromophosphonium cation would lead to a bis-phosphonium salt.

$$[Ph_3\overset{+}{P}CFBr_2]Br^- + Ph_3P: \rightleftharpoons [Ph_3\overset{+}{P}\overset{-}{C}FBr] + [Ph_3\overset{+}{P}Br]Br^-$$

$$\downarrow$$

$$[Ph_3\overset{+}{P}CF(Br)\overset{+}{P}Ph_3]2\ Br^-$$

(IX)

There is, however, one important difference between (VIII) and (IX). In salt (IX) there is still a polarizable halogen present on the methylene carbon atom - whereas in (VIII) one would not anticipate easy abstraction of F^+ from the difluoromethylene carbon atom. Thus, if another equivalent of tertiary phosphine is added, perhaps this reactive bromine can be abstracted to give the fluorine-containing phosphoranium salt, (X) [36].

$$\underset{(IX)}{[Ph_3\overset{+}{P}CF(Br)\overset{+}{P}Ph_3]\ 2Br^-} + Ph_3P: \longrightarrow \underset{(X)}{[Ph_3\overset{+}{P}\overset{-}{C}F\overset{+}{P}Ph_3]Br^-} + Ph_3PBr_2$$

In fact, one finds that the bromine in (IX) is much more reactive than the bromine in (V) and even with a deficiency of tertiary phosphine, (X) is rapidly formed from (V) in an appropriate solvent [37].

With this information in hand, the obvious questions are: can fluorine-containing phosphoranium salts be directly formed via a one-pot procedure from fluorohalomethanes? Can the cheaper $CFCl_3$ be utilized in these preparations? Fortunately for the synthetic chemist, the answer to these questions is affirmative as outlined below [37,38]. Either $CFBr_3$ or $CFCl_3$ can be used with trialkyl phosphines, such as Bu_3P; $CFCl_3$ does not

$$3\ Ph_3P: + CFBr_3 \longrightarrow [Ph_3\overset{+-}{P}CF\overset{+}{P}Ph_3]Br^- + Ph_3PBr_2\downarrow \quad 90\%$$

$$3\ Bu_3P: + CFBr_3 \longrightarrow [Bu_3\overset{+-}{P}CF\overset{+}{P}Bu_3]Br^- + Bu_3PBr_2\downarrow \quad 80\text{-}90\%$$

$$3\ Bu_3P: + CFCl_3 \longrightarrow [Bu_3\overset{+-}{P}CF\overset{+}{P}Bu_3]Cl^- + Bu_3PCl_2 \quad 95\%$$

react with Ph_3P as noted earlier. These reactions to form the phosphoranium salts are rapid, clean, and give excellent yields from readily available commercial chemicals. They will, in our estimation, find extensive use in the preparation of fluorinated compounds.

A unique application of these reagents has already been discovered in our laboratory - namely, reaction of phosphoranium salts with F-acyl fluorides. In contrast to the normal acylation reaction observed when phosphonium ylides are treated with acyl halides, we have discovered

$$R_3\overset{+-}{P}CR^1R^2 + R^3C(O)X \longrightarrow [R_3\overset{+}{P}CR^1R^2C(O)R^3]X^-$$

that the fluorine-containing phosphoranium salts rapidly undergo a Wittig reaction with F-acyl fluorides to give stereospecifically the (Z)-phosphonium salt. Base hydrolysis give stereospecifically the (E)-1-hydro-F-olefin.

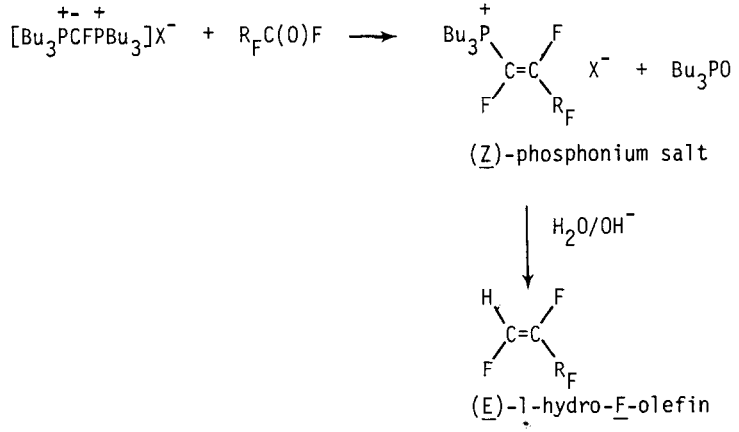
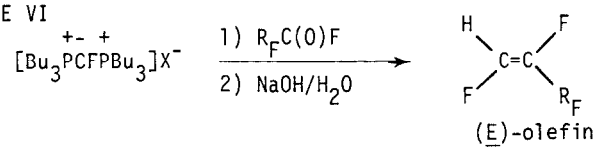


Table (VI) gives illustrative examples of this novel method of preparation of fluoroolefins directly from acyl fluorides. The method is attractive for several reasons: (a) all precursors are readily available; (b) the reaction is a one-pot procedure - the (Z)-phosphonium salt need not be isolated; (c) the olefin is obtained stereospecifically as only the (E)-isomer - the thermodynamically less-stable isomer in at least some of the cases (R_F = CF_3, C_2F_5); (d) the product olefins can be readily metallated [29] and elaborated further via conventional chemistry. A detailed study of these systems as well as related systems is currently in progress and full details will be reported in the future.

TABLE VI



R_F	(E)-olefin	% yield
CF_3	$CF_3CF{=}CFH$	45
CF_3CF_2	$CF_3CF_2CF{=}CFH$	62
$CF_3CF_2CF_2$	$CF_3CF_2CF_2CF{=}CFH$	52
CF_2Cl	$CF_2ClCF{=}CFH$	50
$CH_3O_2CCF_2$	$CH_3O_2CCF_2CF{=}CFH$	20
$CF_3(CF_2)_2OCFCF_3$	$CF_3(CF_2)_2OCF(CF_3)CF{=}CFH$	49

In summary, these easily prepared materials are useful reaction intermediates for the preparation of various types of fluoromethylene olefins *via* the nucleophilic phosphonium ylides; they are also useful for the generation of the electrophilic difluorocarbene [39]; they serve as useful fluorohalomethyl transfer agents [40] as well as chain-extension reagents [25,41]. Mechanistically, the key reactions are halogen abstraction processes rather than attack on carbon, and the key fluorine-containing reaction intermediates are either fluorohalo methide ions or difluorocarbene. The use of these interesting and novel fluorine-containing phosphorus derivatives has already provided some new synthetic approaches to the preparation of fluorine compounds, and the further development of these reagents has a promising and bright future.

ACKNOWLEDGEMENT

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NOTES AND REFERENCES

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4 Unpublished work of D.G. Naae; *cf.* also D.G. Naae and D.J. Burton, Journal of Fluorine Chemistry 1 (1971) 123.
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8 Lectures, 'Chemistry of Halogenated Phosphonium Salts' presented at the ACS Bicentenial Symposium, New York, April 1976, 'Positive Halogen Abstraction Reactions - The Key to Phosphorus-Fluorine Containing Synthetic Intermediates' presented at the 5th Winter Fluorine Conference, Daytona Beach, Florida, February, 1981.

9 The ylide may capture positive halogen either from $[R_3\overset{+}{P}Br]$ or CF_2Br_2 - whichever moiety donates Br^+ does not change the overall mechanistic interpretation.

10 Unpublished work of H.S. Kesling, University of Iowa.

11 Control experiments have established that (III) and/or (IV) do not undergo halogen exchange at the halodifluoromethyl carbon under the reaction conditions used [10].

12 Control experiments have established that Ph_3P does not react with CF_2HBr to give $[Ph_3\overset{+}{P}CF_2H]Br^-$ under the reaction conditions [10].

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