HALODIFLUOROMETHYLPHOSPHONIUM SALTS-HALOMETHYLTRANSFER AGENTS
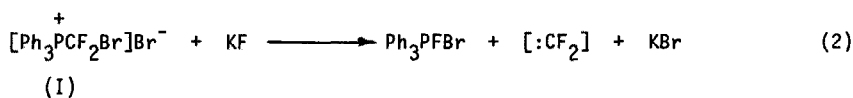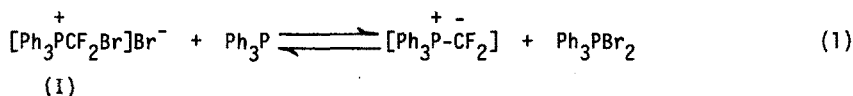
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In recent reports we have shown that fluorinated phosphonium salts serve as useful precursors to both nucleophilc[1,2] and electrophilic intermediates.[3] Dehalogenation with tertiary phosphines generates the nucleophilic phosphonium ylides,[1,2] (eq. 1), whereas reaction with fluoride ion produces the electrophilic carbene[3] (eq. 2).

$$[Ph_3PCF_2Br]^+ Br^- + Ph_3P \rightleftharpoons [Ph_3P-CF_2]^{+-} + Ph_3PBr_2 \qquad (1)$$
$$(I)$$

$$[Ph_3PCF_2Br]^+ Br^- + KF \longrightarrow Ph_3PFBr + [:CF_2] + KBr \qquad (2)$$
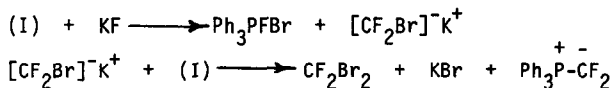$$(I)$$

This report outlines another unique capability of these versatile salts- namely, their ability to serve as halomethyl transfer agents - particularly of the bromodifluoro-methyl or chlorodifluoromethyl groups, which in other reported anionic reactions rapidly collapse directly to difluorocarbene without the intermediacy of the halodifluoromethyl anion.[4]

Our attention was directed to this interesting behavior by our observations on the hydrolysis or alcoholysis of (I). The almost quantitative formation of CF_2HBr[5] suggested either the capture of $[CF_2Br]^-$ or an electrophilic cleavage of an alkoxyphos-phorane intermediate by HBr (Scheme I).[6] Via either mechanism the $[CF_2Br]$ was transferred intact and our interest was focused on the capture of this halodifluoromethyl group by other electrophilic agents.

Scheme I

$$[Ph_3\overset{+}{P}CF_2Br]Br^- + ROH \longrightarrow [Ph_3\overset{+}{P}OR]Br^- + [CF_2Br]^- + HBr$$

or

$$[Ph_3\overset{+}{P}CF_2Br]Br^- + ROH \longrightarrow [Ph_3\overset{OR}{\underset{|}{P}}CF_2Br] + HBr \longrightarrow CF_2HBr$$

$$\downarrow ROH$$

Cleavage of (I) with KF/I_2 gave a 41% isolated yield of CF_2BrI[9] (II) and 9% iso-lated yield of CF_2I_2[10] (III), (eq. 3). The formation of (II) again can be envisioned

$$[Ph_3\overset{+}{P}CF_2Br]Br^- + KF + I_2 \longrightarrow CF_2BrI + CF_2I_2 \qquad (3)$$
$$\quad\ (I) \qquad\qquad\qquad\qquad\qquad (II) \qquad (III)$$

as either capture of $[CF_2Br]^-$ by I_2 or electrophilic cleavage of (I) by IF.[12] (III) is most likely formed by capture of difluorocarbene with I_2 similar to the work of Mitsch[11] and Mahler.[13] Similarly chlorodifluoromethyl-_tris_-(dimethylamino)phosphonium chloride with KF/I_2 gave a 68% yield of CF_2ClI,[14] demonstrating that the halodifluoromethyl transfer reaction is also applicable to the $[CF_2Cl]$ group.

Transfer of the $[CF_2Br]$ group from (I) to an electrophilic fluoroolefin, such as 2-phenylpentafluoropropene, gave a 35% isolated yield of the (Z)- and (E)- 1-bromo-3-phenyl-hexafluoro-2-butene isomers[15] (eq. 4).

$$(I) + KF + CF_2=C(CF_3)Ph \longrightarrow Ph(CF_3)C=CFCF_2Br \quad Z/E = 4/1 \qquad (4)$$

The transfer reaction to an acid halide acceptor does not stop at the ketone stage. Subsequent reaction of the initially formed ketone gives the allylic bromide[17] (eq. 5). Olefin formation is believed to arise by further reaction of the ketone with the

$$(I) + KF + Ph\overset{O}{\overset{\|}{C}}F \longrightarrow Ph\overset{O}{\overset{\|}{C}}CF_2Br \xrightarrow{[Ph_3\overset{+}{P}-\overset{-}{CF_2}]} F_2C=C(Ph)CF_2Br \quad 57\% \qquad (5)$$
$$\qquad\qquad\qquad\qquad\qquad\quad 9\%$$

difluoromethylene ylide, since in a control reaction, cleavage of (I) by KF in the presence of trifluoroacetophenone gave 33% of 2-phenylpentafluoropropene. Several mechanisms can be developed to account for ylide formation; abstraction of bromine from (I) by initially formed $[CF_2Br]^-$ is the simplest operational view of this process[18] (Scheme 2).

Scheme 2

$$(I) + KF \longrightarrow Ph_3PFBr + [CF_2Br]^-K^+$$

$$[CF_2Br]^-K^+ + (I) \longrightarrow CF_2Br_2 + KBr + Ph_3\overset{+}{P}-\overset{-}{C}F_2$$

In the presence of an aromatic compound, such as pentafluoropyridine, which is susceptible to nucleophilic attack, transfer of the $[CF_2Br]$ group can also be achieved to afford 4-bromodifluoromethyl pentafluoropyridine (14% isolated yield).[19]

Thus with a variety of classic nucleophilic trapping agents, capture of the halodifluoro-methyl group can be achieved. Additional work with other halogenated phosphonium salts and trapping agents is in progress to determine the scope of this transfer process and gain insight into the mechanistic aspects of this reaction.

NOTES AND REFERENCES

1. D. G. Naae and D. J. Burton, J. Fluorine Chem., 1, 123 (1971/1972).

2. D. G. Naae and D. J. Burton, Synthetic Comm., 3, 197 (1973).

3. D. J. Burton and D. G. Naae, J. Amer. Chem. Soc., 95, 8467 (1973).

4. Cf. Fluorine In Organic Chemistry by R. D. Chambers, Wiley, Interscience 1973, Chpt. 6 for a review of the older classic work on halodifluoromethyl anions.

5. Hydrolysis with water gave 86% (via gas buret measurement) CF_2HBr; ethanolysis gave 74% CF_2HBr and 26% $EtOCF_2H$ (via ^{19}F NMR integration).

6. Non-fluorinated phosphonium salts undergo hydrolysis to eject a carbanion which can be trapped by protonation.[7] Formation of $(CF_2Br)^-$ from (I) is consistent with this type of behavior. In view of Hine's work,[8] trapping of difluorocarbene by HBr in a hydroxylic medium is unlikely to compete with hydrolysis of difluorocarbene, but we cannot definitively rule it out here.

7. L. Horner, H. Hoffmann, H. Wippel and G. Hassel, Chem. Ber., 91, 52 (1958).

8. J. Hine and P. B. Langford, J. Amer. Chem. Soc., 79, 5497 (1957).

9. (II), bp 64-65°/740 mm was characterized by a sharp singlet in the ^{19}F NMR at ∅* -13.8 ppm and a parent ion in the mass spectrum at m/e 258 (33%) and 256 (35%).

10. (III) was identical to the ^{19}F NMR and ir reported by Mitsch.[8]

11. R. A. Mitsch, J. Heterocyclic Chem., 1, 233 (1964).

12. Control reactions show that (I) does <u>not</u> undergo cleavage reactions with HBr, IBr, ICl, I_2, Br_2, or Cl_2. No evidence has been found for the formation of IF, and the pentavalent intermediate required for cleavage of (I) by IF has not been detected. However, cleavage of (I) by IF cannot be definitively ruled out.

13. W. Mahler, <u>Inorganic Chem.</u>, <u>2</u>, 230 (1963).

14. CF_2ClI was characterized by a singlet in the ^{19}F NMR at $\emptyset*$ -7.4 ppm and parent ions in the mass spectrum at m/e 214 (5.7%) and 212 (17.8%). The base peak in the mass spectrum corresponded to the loss of I^+ and was observed at m/e 87 (34.9%) and 85 (100%) CF_2Cl^+.

15. The (Z)- isomer in the ^{19}F NMR showed a doublet (CF_2Br) at $\emptyset*$53.4 ppm, J_{F,CF_2Br} 14 Hz; a doublet (CF_3) at $\emptyset*$ 61.3 ppm J_{F,CF_3} 24.7 Hz; and a quartet of triplets (vinyl F) at $\emptyset*$ 111.4 ppm; ir (neat) 1693 cm^{-1} ($\diagup C=C\diagdown$); mass spectrum gave parent ions at 320 and 318, ratio of P/P+2 = 1. The (E)- isomer in the ^{19}F NMR gave a doublet of doublets (CF_2Br) at $\emptyset*$ 56.6 ppm, J_{F,CF_2Br} 14 Hz and J_{CF_3,CF_2Br} 16.2 Hz; a triplet of doublets (CF_3) at $\emptyset*$ 56.0 ppm; J_{F,CF_3} 11 Hz; and a quartet of triplets (vinyl F) at $\emptyset*$ 108.0 ppm; ir ($CHCl_3$) 1697 cm^{-1} ($\diagup C=C\diagdown$); mass spectrum gave parent ions at m/e 320 and 318, P/P+2 ratio = 1. Assignments of (Z)- and (E)- were based on the magnitude of the vinyl F, CF_3 coupling constant.[16]

16. D. J. Burton and H. C. Krutzsch, <u>J. Org. Chem.</u>, <u>35</u>, 2125 (1970) and <u>J. Org. Chem.</u>, <u>36</u>, 2351 (1971) for the use of such stereochemical assignments.

17. The allylic halide formed from benzoyl fluoride was identical to a sample of this olefin independently synthesized <u>via</u> the Wittig reaction of bromodifluoroacetophenone and the difluoromethylene ylide.

18. Other mechanisms can be formulated for the generation of the ylide in this reaction and this scheme is <u>merely</u> meant to be an operational view. It should be noted that when (I) is reacted with KF in the absence of a trapping agent, 21% CF_2Br_2 was found.

19. ^{19}F NMR, ir, and the mass spectrum are consistent with the assignment of the pyridine product.