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SYNTHESIS OF BROMODIFLUOROMETHYL PHENYL SULFIDE, SULFOXIDE AND SULFONE [1]

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SUMMARY

Sodium thiophenoxide reacts with dibromodifluoromethane to give bromodifluoromethyl phenyl sulfide. Peracid oxidation of the sulfide gives the corresponding sulfoxide and sulfone. The formation of the sulfide is suggested to proceed via attack of thiophenoxide on halogen to produce difluorocarbene. Capture of carbene by thiophenoxide followed by a second positive halogen abstraction reaction yields the sulfide, $PhSCF_2Br$. The use of excess sodium thiophenoxide yields difluorobis(thiophenyl)methane, $(PhS)_2CF_2$, via a similar mechanistic scheme.

INTRODUCTION

In the past few years research in our laboratory has focused on the preparation and synthetic utility of halofluoromethanes, especially CF_2Br_2, $CFBr_3$, and $CFCl_3$ [2]. In the reaction of these methane derivatives with tertiary phosphines or trialkylphosphites [2], we have demonstrated that the mechanistic sequence involves a succession of events in which attack by phosphorus is on halogen rather than on carbon. In the case of dibromodifluoromethane, the intermediacy of difluorocarbene has also been demonstrated [1], cf. Scheme 1.

Our success in the use of phosphorus derivatives with these methanes encouraged us to explore the utility of other nucleophiles as attacking agents to abstract positive halogen from these halofluoromethanes.

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$$R_3P: + CF_2Br_2 \longrightarrow [R_3\overset{+}{P}Br]Br^- + [:CF_2]$$

$$R_3P: + [:CF_2] \rightleftharpoons [R_3\overset{+}{P}\text{-}\overset{-}{C}F_2]$$

$$[R_3\overset{+}{P}\text{-}\overset{-}{C}F_2] + [R_3\overset{+}{P}Br]Br^- \longrightarrow [R_3\overset{+}{P}CF_2Br]Br^- + R_3P:$$

Scheme 1

Overall Reaction:

$$R_3P: + CF_2Br_2 \longrightarrow [R_3\overset{+}{P}CF_2Br]Br^-$$

Our interest was two fold: (a) to elucidate the scope of nucleophilic reagents that would attack halogen rather than carbon of the methane derivative; and (b) to explore the utility of the resultant product of the reaction as a synthetic intermediate in other functional group elaboration reactions.

Thiophenoxide has been reported by Hine [3] to be an excellent trapping agent for difluorocarbene - generated from chlorodifluoromethane. Thus, our initial efforts [1] focused on the reaction of thiophenoxide ion (with dibromodifluoromethane) as both the positive halogen abstraction agent and sink for the difluorocarbene produced - similar to the dual role played by the tertiary phosphine in Scheme 1. After the inception of these studies, Rico and Wakselman [4] reported some related work, which prompts us to disclose our results and the elaboration of the initial products of the PhS^-/CF_2Br_2 reaction. In addition, some mechanistic experiments are also reported as confirmatory evidence of the dualistic role played by the thiophenoxide ion.

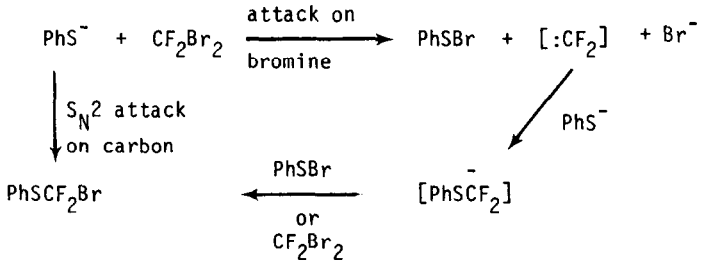
RESULTS AND DISCUSSION

When sodium thiophenoxide is reacted with excess (20%) of dibromodifluoromethane in ether at room temperature, bromodifluoromethyl phenyl sulfide, $PhSCF_2Br$ (1), is isolated in 25% yield, after fractional distillation. No attempts have been made to optimize the yield of (1) [5]. Mass spectral and NMR data are in full agreement with the assigned structure (cf. experimental).

$$PhS^-Na^+ + CF_2Br_2 \xrightarrow[RT]{Et_2O} PhSCF_2Br$$

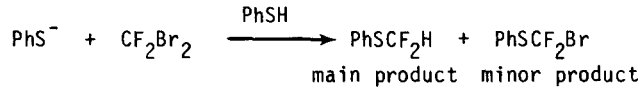
(1), 25%

(1)can be formed either via nucleophilic displacement on carbon (S_N2) or via attack on halogen followed by carbene capture (Scheme 2).



Scheme 2

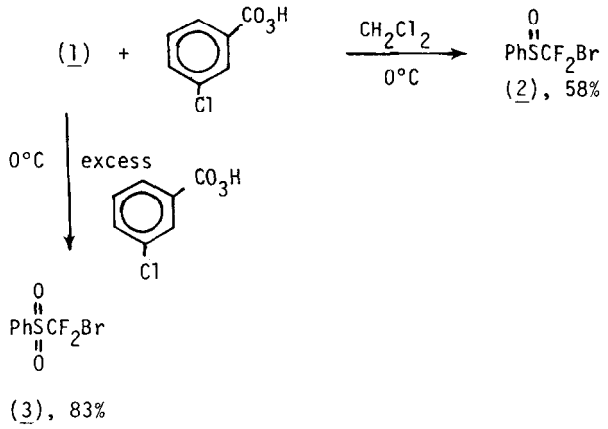
When the PhS^-/CF_2Br_2 reaction is carried out in the presence of thiophenol, the yield of (1) is decreased and the main product of the reaction is $PhSCF_2H$. This result is consistent with initial attack of thiophenoxide



on halogen (Scheme 2) with subsequent capture of the $[PhS\bar{C}F_2]$ anion by thiophenol.

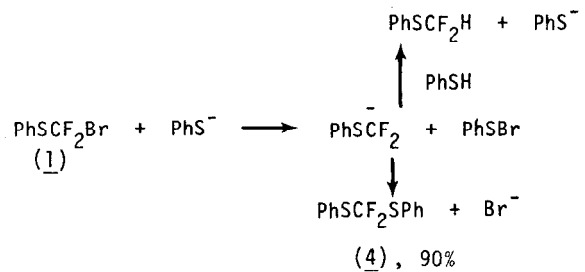
The PhS^-/CF_2Br_2 reaction was also carried out in the presence of tetramethylethylene (TME) in an attempt to capture the carbene intermediate. However, no 1,1-difluorotetramethylcyclopropane was detected; the main product of the reaction was again (1). This result could be interpreted either as: (a) carbene is not involved in the reaction sequence, or (b) thiophenoxide is a much superior carbene interceptor than TME [6]. In order to compare the efficiency of PhS^- and TME as carbene interceptors, we generated difluorocarbene from bromodifluoromethyl triphenylphosphonium bromide [7] in the presence of PhS^- and TME. No cyclopropane adduct was detected. Only products arising from $[PhS\bar{C}F_2]$ and (1) were observed. Thus, olefins do not compete with thiophenoxide for difluorocarbene and cannot be used to elucidate carbene intermediates in mercaptide reactions.

Oxidation of (1) with m-chloroperoxybenzoic acid gives cleanly either the sulfoxide (2) or sulfone (3) [8]. Spectroscopic data for (2) and (3)



were in full agreement with the assigned structure. In (2) the two fluorines are nonequivalent and appear as an AB pattern in the ^{19}F NMR spectrum [10].

When (1) is reacted further with sodium thiophenoxide, difluorobis-(thiophenyl)methane (4) is formed in excellent yield [11]. If the reaction of (1) with PhS^-Na^+ is carried out in the presence of thiophenol, the yield of (4) is decreased and the major product becomes $PhSCF_2H$. This result is again consistent with attack on halogen followed by protonation of the resultant carbanion (Scheme 3) rather than nucleophilic displacement on carbon.



Scheme 3

CONCLUSIONS

Thiophenoxide ion readily attacks dibromodifluoromethane to give the bromodifluoromethyl sulfide derivative. Further reaction of the initial sulfide product with thiophenoxide gives the bis-derivative. These reactions

are best interpreted as initial attack on bromine by thiophenoxide. The resultant intermediates from halogen abstraction undergo further capture by thiophenoxide to produce the observed products. Thus, the dualistic role played by thiophenoxide in these reactions is similar to that observed previously in phosphine and phosphite reactions of dibromodifluoromethane [2].

EXPERIMENTAL

^{1}H NMR and ^{19}F NMR spectra were recorded on a Jeol FX-90Q spectrometer. ^{1}H NMR chemical shifts are reported in δ values downfield from internal tetramethylsilane (TMS). ^{19}F NMR chemical shifts are reported in Φ^{*} values upfield from internal fluorotrichloromethane. All ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.635 MHz. The ^{13}C NMR chemical shifts are reported in δ values downfield from internal TMS. Mass spectra were determined on a Hewlett Packard Model 5985 GC/MS instrument.

All boiling points are uncorrected and were obtained during fractional distillation.

Diethyl ether was dried over sodium wire prior to use. Methylene chloride and sulfolane were distilled from calcium hydride. Triglyme was distilled from a sodium benzophenone ketyl.

Preparation of bromodifluoromethyl phenyl sulfide (1)

A three liter three-necked flask was equipped with a Trubore® stirrer, a reflux condenser topped with a nitrogen tee, and a septum port. The flask was charged with 132.1 g (1 mole) of sodium thiophenoxide [12] and two liters of dry ether. The heterogeneous reaction mixture was cooled with an ice water bath, followed by the dropwise addition (*via* syringe) of 110 ml (1.2 moles) of dibromodifluoromethane. After the addition of the dibromodifluoromethane was completed, the reaction mixture was stirred at room temperature for 24 hours.

Work-up of the reaction mixture was accomplished by pouring into 700 ml of water; extraction of the aqueous layer with ether (3 x 300 ml); followed by washing with water (3 x 150 ml) of the combined ether extracts, and subsequent drying of the combined ether and organic layer with anhydrous magnesium sulfate.

After removal of the ether *via* rotoevaporation, fractional distillation through a Vigreaux column yielded 59.7 g (25%) of (1), bp 62-64°C (2 mm). Reported [4] for (1), bp 97°C (34 mm). ^{1}H NMR ($CDCl_3$) δ 7.4-7.6 (m); ^{19}F NMR ($CDCl_3$) Φ^* 22.5 ppm (s); ^{13}C NMR ($CDCl_3$) δ 119.3 (t), $J_{C,F}$ = 338.3 Hz. Mass Spectrum: parent ion at m/e 238 and 240 (1:1 ratio), 159 (100%, parent -Br), 109 (30%, parent -CF_2Br), 77 (52%, parent -SCF_2Br).

Preparation of bromodifluoromethyl phenyl sulfoxide (2) nc

A 250 ml three-necked flask equipped with a reflux condenser topped by a nitrogen tee and a magnetic stir bar, was charged with 23.5 g (0.10 mole) of (1) and 100 ml of dry methylene chloride. The solution was cooled with an ice water bath, and then 22.2 g (0.13 mole) of m-chloroperoxybenzoic acid was added. The reaction mixture was stirred for one hour at 0°C followed by stirring at room temperature overnight.

Work-up of the reaction mixture was accomplished by pouring into 300 ml of a saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride (3 x 100 ml). The combined methylene chloride extracts were washed with water (3 x 100 ml) and then the combined methylene chloride extracts and organic layer were dried over anhydrous magnesium sulfate. After removal of the methylene chloride *via* rotoevaporation, fractional distillation through a Vigreaux column gave 14.7 g (58%) of (2), bp 63-65°C (1 mm). ^{1}H NMR ($CDCl_3$) δ 7.3-7.5 (m), ^{19}F NMR ($CDCl_3$) Φ^* 53.7 ppm (d) and Φ^* 55.4 ppm (d), $J_{F,F}$ = 146.5 Hz. Mass Spectrum: parent ion at m/e 254 and 256 (1:1 ratio), 125 (100%, parent -CF_2Br), 109 (14%, parent -OCF_2Br), 77 (37%, parent -$SOCF_2Br$).

Preparation of bromodifluoromethyl phenyl sulfone (3) nc

The apparatus utilized was identical to that described in the previous experiment. The flask was charged with 12.0 g (0.05 mole) of (1) and 150 ml of dry methylene chloride. After cooling to 0°C, 25.6 g (0.15 mole) of m-chloroperoxybenzoic acid was added. The reaction mixture was stirred at room temperature for 24 hours, filtered, and the precipitate washed with 25 ml of methylene chloride. The filtrate was washed with 10% Na_2SO_3 (2 x 100 ml), 5% $NaHCO_3$ (4 x 50 ml), and saturated NaCl solution (2 x 100 ml) and the combined organic material dried over anhydrous magnesium sulfate. After removal of the methylene chloride *via* rotoevaporation, a crude crystalline product was obtained. Sublimation of this material yielded

11.2 g (83%) of (3) mp 33-34°C. ^{1}H NMR($CDCl_3$) δ 7.4-7.6 (m) ^{19}F NMR ($CDCl_3$) Φ^* 58.7 ppm (s), ^{13}C NMR ($CDCl_3$) δ 114.7 (t), $J_{C,F}$ = 285.3 Hz. Mass Spectrum: parent ion at m/e 270 and 272 (1:1 ratio), 141 (85%, parent $-CF_2Br$), 125 (37%, parent $-OCF_2Br$),77 (100%, parent $-SO_2CF_2Br$).

Preparation of difluorobis(thiophenyl)methane (4) nc

To a 100 ml three-necked flask, equipped with a reflux condenser topped with a nitrogen tee and a magnetic stir bar, was charged 4.0 g (0.03 mole) of sodium thiophenoxide and 30 ml of dry sulfolane. Then, 3.5 g (0.015 mole) of (1) was slowly added to the solution. After stirring at room temperature for two hours, the reaction mixture was poured into 200 ml of water. The aqueous layer was extracted with methylene chloride (3 x 100 ml). The combined organic material was dried over anhydrous magnesium sulfate and the methylene chloride removed by rotoevaporation. Fractional distillation of the residue gave 3.6 g (90%) of (4), bp 101-103°C (1 mm). ^{1}H NMR ($CDCl_3$) δ 7.5-7.7 (m); ^{19}F NMR ($CDCl_3$) Φ^* 48.7 ppm (s); ^{13}C NMR ($CDCl_3$) δ 119.2 (t), $J_{C,F}$ = 338.3 Hz. Mass Spectrum: parent ion at m/e 268, 159 (100%, parent -SPh), 109 (13%, parent $-CF_2SPh$).

(1) + PhS^-Na^+ + PhSH

To a 25 ml flask, equipped as in the previous experiment, was charged 0.92 g (0.007 mole) of sodium thiophenoxide, 0.51 ml (0.005 mole) of thiophenol, and 15 ml of dry sulfolane. (1), 1.2 g (0.005 mole) was then slowly added to the reaction mixture. After the addition of (1) was completed, the reaction mixture was stirred at room temperature for four hours. Then, 0.52 g (0.0036 mole) of benzotrifluoride was added to the reaction mixture, and the solution subjected to ^{19}F NMR analysis. Found: 2.7% (1), 28.9% (4), and 65.1% $PhSCF_2H$ [13].

(1) + PhS^-Na^+ + TME

A 25 ml flask, equipped with a reflux condenser, magnetic stir bar, and a nitrogen blanket, was charged with 0.92 g (0.007 mole) of sodium thiophenoxide, 0.59 ml (0.005 mole) of tetramethylethylene (TME) and 15 ml of dry sulfolane. (1), 1.2 g (0.005 mole) was slowly added to the reaction mixture. After completion of the addition of (1), the reaction mixture was stirred at room temperature for four hours. Then, 0.53 g (0.0037 mole)

of benzotrifluoride was added to the reaction mixture and the solution subjected to ^{19}F NMR analysis.
Found: 3.3% (1); 25.7% (4), and 57.9% $PhSCF_2H$. No 1,1-difluorotetramethylcyclopropane was detected.

$[Ph_3\overset{+}{P}CF_2Br]Br^-$ + PhS^-Na^+ + TME

A 50 ml two-necked flask, equipped with a reflux condenser topped with a nitrogen tee and a magnetic stir bar, was charged with 2.4 g (0.005 mole) of $[Ph_3\overset{+}{P}CF_2Br]Br^-$ [14] and 15 ml of dry triglyme. A solution of 1.3 g (0.010 mole) of sodium thiophenoxide, 1.2 ml (0.010 mole) TME, and 10 ml of dry triglyme was then added to the phosphonium salt solution. After the reaction mixture was stirred at room temperature for three hours, 0.50 g (0.0034 mole) of benzotrifluoride was added to the reaction mixture and the solution subjected to ^{19}F NMR analysis.
Found: 5.7% (1), 29.8% (4), 10.4% $[Ph_3\overset{+}{P}CF_2Br]Br^-$, and 30.5% $PhSCF_2H$.

PhS^-Na^+ + CF_2Br_2 + TME

A 25 ml flask was fitted with a Teflon magnetic stir bar and a reflux condenser topped with a nitrogen tee. The flask was charged with 0.92 g (0.007 mole) of sodium thiophenoxide, 0.59 ml (0.005 mole) TME, and 10 ml of dry ether. The reaction mixture was cooled with an ice bath, and 0.45 ml (0.005 mole) of dibromodifluoromethane was slowly added. After the addition of the methane was completed, the reaction mixture was stirred at room temperature for four hours. Then, 0.49 g (0.0034 mole) of benzotrifluoride was added to the reaction mixture, and the solution subjected to ^{19}F NMR anlaysis.
Found: 21% CF_2Br_2, 35.5% (1), 1.8% $PhSCF_2H$. No 1,1-difluorotetramethylcyclopropane was detected.

PhS^-Na^+ + CF_2Br_2 + PhSH

To a 25 ml flask, equipped as in the previous experiment, was charged 0.92 g (0.007 mole) of sodium thiophenoxide, 0.51 ml (0.005 mole) thiophenol and 10 ml of dry ether. The reaction solution was cooled with an ice bath and 0.45 ml (0.005 mole) of dibromodifluoromethane added. After addition of the methane was completed, the reaction mixture was stirred at room temperature for four hours. Then, 0.51 g (0.0035 mole) of

benzotrifluoride was added to the reaction mixture, and the solution subjected to ^{19}F NMR analysis.
Found: 18% CF_2Br_2, 15.2% (1) and 36.7% $PhSCF_2H$.

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13 $PhSCF_2H$, Φ^* 92.2 ppm (d), $J_{F,H}$ = 56.1 Hz.

14 Prepared from Ph_3P and CF_2Br_2.