

Synthesis and biological screening of trifluoromethylthioarsenicals

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(Received May 15, 1992; accepted December 9, 1992)

Abstract

The title compounds have been prepared from the reaction of trifluoromethylthiocopper and alkyl mono- and di-haloarsines. This communication describes their synthesis, biological screening and mass spectral fragmentation behavior.

Introduction

Thioarsenites derive their pharmacological properties from their ability to react with the sulfhydryl function of biological catalysts, namely enzymes, necessary for carrying out metabolic processes [1]. Although arsenic compounds have attracted considerable interest for a long time, it was their use as sternutators during World War I that attracted world attention to this group of compounds. As a consequence of their inhalation, the kidneys and livers of the affected victims showed considerable evidence of hemorrhagic changes and epithelial degeneration. Exposure of skin and eyes to arsenicals elicits effects reminiscent of those observed with sulfur mustard [2]. The inhalation of arsenicals usually results in sneezing, nausea, vomiting, conjunctivitis, chest and abdominal pain, intestinal cramps, extensive perspiration and feelings of depression. Depending on the severity of exposure, the systemic effects may persist for several hours [3]. However, the irritation effects have recently been described as transitory and that test animals were observed to recover within a few minutes after the cessation of exposure [4]. The chemistry of thioarsenites has been the subject of an exhaustive study [5a] and part of a monograph devoted to the organic chemistry of arsenic [5b].

Trivalent and pentavalent arsenicals react with mercaptans or their salts to furnish thioarsenites, namely compounds of the type $RA(SR')_2$ [6a]. Emeleus and co-workers were the first to prepare thioarsenites containing the trifluoromethyl moiety by treating

bis(trifluoromethylthio)mercury (1) with arsenic(III) chloride and bis(trifluoromethyl) iodoarsine [6b, c]. When arsenic chloride was used, a mixture of three compounds containing mono-, di- and tri-substituted arsenicals was obtained. However, excellent yields of the expected product were obtained when tetraalkyl diarsine (2) was treated with bis(trifluoromethyl) disulfide (3) [7a]. These reactions indicated that the S–S bond of 3 undergoes facile fission in the presence of diarsine. Two additional modifications of the above process involve the reaction of trifluoromethanesulfonyl chloride with 2 [7b]. The same compound was also synthesized in low yield by the reaction of bis(trifluoromethyl)arsenious sulfide with trifluoroiodomethane at 125 °C [7c]. The compounds described in this paper include bis(trifluoromethylthio)mercury (1), tetraalkyl diarsine (2), bis(trifluoromethyl)disulfide (3), trifluoromethylthiocopper (4), dimethylbromoarsine (5), methyldichloroarsine (6), ethyldichloroarsine (7), dimethyl(trifluoromethylthio)arsine (8), bis(trifluoromethyl)trisulfide (9), bis(trifluoromethyl)tetrasulfide (10), dimethylfluoroarsine (11), thiocarbonyl fluoride (12), tris(trifluoromethylthio)methane (13), bis(trifluoromethylthio)methylarsine (14), bis(trifluoromethyl)trithiocarbonate (15), methyldifluoroarsine (16) and bis(trifluoromethylthio)ethylarsine (17) (see Fig. 1).

Recently, we have developed a new procedure for the preparation of trifluoromethylthiocopper (4) in a colorless crystalline form [8]. Since copper reagents usually react more readily than mercury compounds, and since 1 is air-sensitive and require manipulations in a dry inert atmosphere, it was considered of interest

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$(\text{CF}_3\text{S})_2\text{Hg}$ (1)	$(\text{R})_2\text{As}-\text{As}(\text{R})_2$ (2)	CF_3SSCF_3 (3)	CF_3SCu (4)
$(\text{CH}_3)_2\text{AsBr}$ (5)	CH_3AsCl_2 (6)	$\text{C}_2\text{H}_5\text{AsCl}_2$ (7)	$(\text{CH}_3)_2\text{As}(\text{SCF}_3)$ (8)
$\text{CF}_3\text{SSSCF}_3$ (9)	$\text{CF}_3\text{SSSSCF}_3$ (10)	$(\text{CH}_3)_2\text{AsF}$ (11)	$\text{C}(\text{S})\text{F}_2$ (12)
$\text{CH}(\text{SCF}_3)_3$ (13)	$(\text{CF}_3\text{S})_2\text{AsCH}_3$ (14)	$\text{CF}_3\text{SC}(\text{S})\text{SCF}_3$ (15)	CH_3AsF_2 (16)
$\text{C}_2\text{H}_5\text{As}(\text{SCF}_3)_2$ (17)	$\text{CF}_3\text{S}\cdot$ (18)	$(\text{CF}_3\text{S})_2\text{CH}\cdot$ (19)	CS_2 (20)
$(\text{CF}_3\text{S})\text{C}(\text{S})\text{F}$ (21)			

Fig. 1. Structures of compounds cited in the text.

to investigate the reaction of arsenic halides with 4. This communication describes the reaction of 1 and 4 with dimethylbromo-, methylchloro- and ethylchloro-arsines (5, 6 and 7) carried out separately, the nature and distribution of the previously unreported compounds formed during this reaction and their mass spectral behavior.

Results and discussion

The reaction of 5 with 1 and with 4 are complex. In addition to the expected dimethyl-(trifluoromethylthio)arsine (8), six additional compounds, namely 3, 8, 12, 13, 14, 15, and carbon disulfide (20) (Table 1) were characterized from their GC-MS data (Table 2). In the reaction of 4, compound 3 and bis(trifluoromethyl)tri and tetra-sulfides (9, 10) are generally formed along with the expected product(s) of the reaction, namely 3, 8, 11, 12, 13 and 14. The origin of 3, 9 and 10 (Scheme 1) is, no doubt, the trifluoromethylthiyl radical (18) and the participation of free-radical reactions [9]. The formation of dimethylfluoroarsine (11) (Scheme 2, steps 2-4) in this reaction can be considered a case of halogen-exchange. There are precedents for such halogen-exchange reactions [6b, 10]. Trifluoromethanesulfonyl bromide was identified as one of the products of the reaction between 3 and alkylmagnesium bromide [10b]. The origin of thiocarbonyl fluoride, $\text{C}(\text{S})\text{F}_2$ (12), is the trifluoromethylthiyl radical 18 which loses $\text{F}\cdot$ to form 12 (Scheme 2, step 2). The $\text{F}\cdot$ thus liberated may also react with 5 to give 11 in a displacement reaction. Alternatively, the $\text{F}\cdot$ could have come from 9 and 10 which, according to

Haszeldine and Kidd "liberate fluoride quantitatively" [11]. While one could envision the formation of 12 as occurring by thermal decomposition of 8, however, successive distillations of 8 failed to show the presence of 12, thus discounting such a possibility.

It is interesting to note the presence of tris(trifluoromethylthio)methane (13) in the reaction mixture (Scheme 2, step 11). The identification of this known compound [12a] was confirmed by its synthesis from iodoform and 4. It is conceivable that 13 could have originated from the bis(trifluoromethylthio)methyl radical (19) (Scheme 2, steps 9 and 11). The suggestion that 13 is formed from 19 derives its support from the identification of bis[(trifluoromethylthiomethyl)]-dimethylarsine, $[(\text{CF}_3\text{S})_2\text{CH}]\text{As}(\text{CH}_3)_2$ (Table 2), as a component of the higher boiling fraction. Also, bis(trifluoromethylthio)methylarsine (14) was characterized as one of the products of this reaction. The only way 14 could have been formed is from methyl dibromoarsine, which in turn could have been present either as an impurity in the starting material 5 or could have been thermally generated from 5. The formation and characterization of methyl diiodoarsine among the products obtained by heating bis(trifluoromethyl)-iodoarsine alone, through the process of 'thermal equilibrium', lends support to the latter contention [12b]. At elevated temperature, the trifluoromethyl moiety of tris(trifluoromethyl)arsine was found to have been replaced by the methyl radical [12c].

The formation and distribution of the products formed during the reaction of 1 with 5 depend on the reaction temperature. At elevated temperatures, within a short time the reaction mixture assumed an intense red color, which was later shown to be due to increasing con-

TABLE 1. Products of the reaction of dimethylbromoarsine (5) with trifluoromethylthiocopper (4) and bis(trifluoromethylthio)mercury (1)

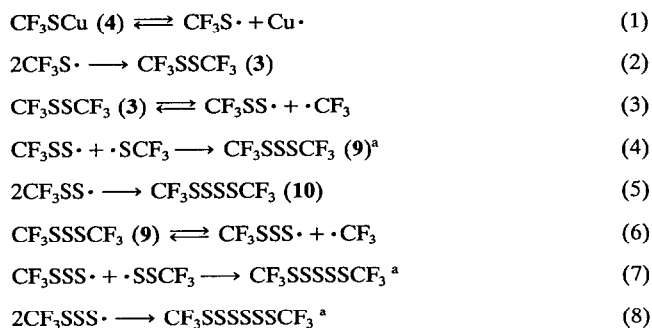
CF_3SCu (4)	$(\text{CF}_3\text{S})_2\text{Hg}$ (1)
CF_3SSCF_3 (3) ^a , $\text{CF}_3\text{SSSCF}_3$ (9) ^a , $\text{CF}_3\text{SSSSCF}_3$ (10) ^a , CSF_2 (12) ^a , $(\text{CH}_3)_2\text{AsF}$ (11) ^a , $(\text{CH}_3)_2\text{AsSCF}_3$ (8) ^b , $\text{CH}(\text{SCF}_3)_3$ (13) ^a , $\text{CH}_3\text{As}(\text{SCF}_3)_2$ (14) ^a	CF_3SSCF_3 (3) ^a , CS_2 ^a , CSF_2 (12) ^a , $\text{CF}_3\text{SC}(\text{S})\text{SCF}_3$ (15) ^a , $(\text{CH}_3)_2\text{AsSCF}_3$ (8), $\text{CH}(\text{SCF}_3)_3$ (13) ^a , $\text{CH}_3\text{As}(\text{SCF}_3)_2$ (14) ^a

^aNot detected previously from analogous reactions, [6b, c, 7].

^bA 98% pure sample (GLC) was obtained after two fractional distillations.

TABLE 2. Mass-spectral fragmentation of thioarsenites

CSF ₂ (12)	M ⁺ = 82; 63 (CSF); 51 (SF); 50 (SF ₂)
CF ₃ SSCF ₃ (3)	M ⁺ = 202; 183 (M-F); 133 (M-CF ₃); 114 (133-F); 101 (SCF ₃); 82 (CSF ₂); 69 (CF ₃); 64 (SS)
(CH ₃) ₂ AsF (11)	M ⁺ = 124; 109 (M-CH ₃); 105 (M-F); 89 (CH ₂ As); 75 (As)
CH ₃ AsF ₂ (16)	M ⁺ = 128; 113 (M-CH ₃); 109 (CH ₃ AsF); 94 (AsF); 89 (AsCH ₂); 75 (As)
(CH ₃) ₂ AsSCF ₃ (8)	M ⁺ = 206; 191 (M-CH ₃); 187 (M-F); 176 (AsSCF ₃); 145 (AsSF ₂); 137 (M-CF ₃); 122 (CH ₃ AsS); 109 (CH ₃ AsF); 105 (M-SCF ₃); 89 (AsCH ₂); 82 (CSF ₂); 75 (As); 69 (CF ₃); 63 (SCF); 45 (CSH)
CH(SCF ₃) ₃ (13)	M ⁺ = 316; 247 (M-CF ₃); 215 (M-SCF ₃); 146 (247-SCF ₃); 82 (CSF ₂); 76 (CS ₂); 69 (CF ₃); 63 (CSF); 45 (CSH)
CF ₃ SSSCF ₃ (9)	M ⁺ = 234; 215 (M-F); 165 (M-CF ₃); 133 (M-SCF ₃); 96 (SSS); 82 (CSF ₂); 69 (CF ₃); 64 (SS); 50 (CF ₂)
CF ₃ SSSSCF ₃ (10)	M ⁺ = 298; 197 (M-SCF ₃); 165 (CF ₃ SSS); 146 (165-F); 133 (CF ₃ SS); 96 (SSS); 83 (SSF); 69 (CF ₃); 64 (SS); 50 (CF ₂)
CH ₃ As(SCF ₃) ₂ (14)	M ⁺ = 292; 273 (M-F); 191 (M-SCF ₃); 176 (AsSCF ₃); 141 (CH ₃ AsSF); 121 (CH ₂ AsS); 107 (AsS); 89 (CH ₂ As); 69 (CF ₃); 63 (CSF)
C ₂ H ₅ As(SCF ₃) ₂ (17)	M ⁺ = 306; 287 (M-F); 249 (287-2F); 205 (M-SCF ₃); 176 (205-C ₂ H ₅); 123 (C ₂ H ₅ AsF); 107 (123-CH ₄); 101 (SCF ₃); 75 (As); 69 (CF ₃); 63 (CSF)
CF ₃ SC(S)SCF ₃ (15)	M ⁺ = 246; 177 (M-CF ₃); 145 (M-SCF ₃); 133 (CF ₃ SS); 101 (SCF ₃); 82 (CSF ₂); 76 (CS ₂); 69 (CF ₃); 64 (SS)
CF ₃ SC(S)F (21)	M ⁺ = 164; 145 (M-F); 133 (CF ₃ SS); 95 (CS ₂ F); 82 (CSF ₂); 69 (CF ₃); 63 (CSF); 50 (CF ₂)



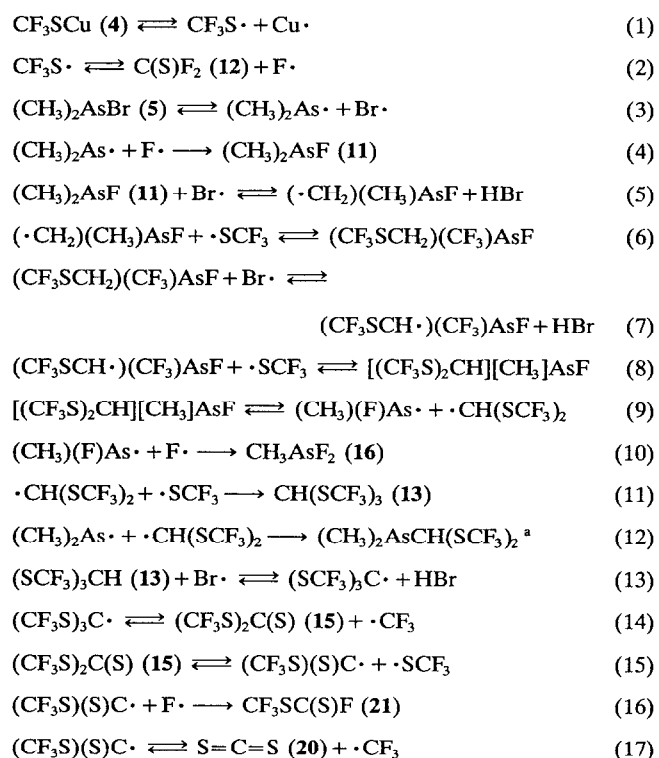
Scheme 1. The formation of bis(trifluoromethyl) di- and polysulfides (cf. ref. 9). Note that compounds marked as 'a' have been characterized as products of the reaction of bis(trifluoromethyl)trisulfide with organolithium and Grignard reagents [15].

centration of bis(trifluoromethyl)trithiocarbonate (15) (Scheme 2, step 14). Haszeldine and Kidd have prepared 15 by treating trifluoromethylthiol with ammonia [13a]. Since then, 15 has been prepared via the pyrolysis of tetrakis(trifluoromethylthio)methane [12a] and through the reaction of 11 with cesium fluoride in a stainless-steel bomb at -78 °C [13c]. The characterization of 15 again points to the presence of 18 in the reaction mixture, for 15 can be formed from 18 (Scheme 2).

The origin of carbon disulfide (20) can be traced to 15 (Scheme 2, step 17). The termination step for this free-radical process is the dimerization of the $\cdot\text{CF}_3$ radical to form hexafluoroethane.

The reaction of methyl- and ethyl-dichloroarsines [(6) and (7)] with 1 is also complex (Table 3). The formation of methyldifluoroarsine (16) can again be rationalized on the basis of halogen-exchange or 'thermal equilibrium' [10, 12c], in that 16 could have arisen from 11 or through the replacement of a methyl radical by F $\cdot$. In the reaction of 1 with 7, 10 compounds were formed (Table 3) and again the color of the reaction mixture turned an intense red. Thus 3, 9, 10, 12, 13, 15, 16, 17, 20, trifluoromethyldithiocarbonyl fluoride (21) and ethyldifluoroarsine were identified as components of the reaction mixture.

The mass spectra of 3 and 9 have already been reported [14, 15]. The mass-spectral fragmentation of 10 follows a similar pattern. In the same way, the mass spectra of 11 and 16 exhibit similar behavior. In addition to the molecular ions, the loss of the methyl group ($m/e = 15$) is observed. The ion $m/e = 75$ corresponding to As is usually seen. Trifluoromethylthioarsenites exhibit common characteristics. In addition to the molecular ions, the loss of F, alkyl and trifluoromethylthiyl moieties and CF₃ is usually observed.



Scheme 2. The reaction of dimethylbromoarsine with trifluoromethylthiocopper. [Bis(trifluoromethylthio)mercury reacts analogously.] The presence of the compound marked as 'a' in the high boiling fraction of the reaction of 5 with 4 was indicated and confirmed by its GC-MS data. Numbered products were identified by their mass-spectral fragmentation patterns.

TABLE 3. Products of the reaction of bis(trifluoromethylthio)mercury (1) with ethyl- and methyl-dichloroarsines

CH_3AsCl_2 (6)	$\text{C}_2\text{H}_5\text{AsCl}_2$ (7)
CF_3SSCF_3 (3), CH_3AsF_2 (16), $\text{CF}_3\text{SC(S)SCF}_3$ (15), $\text{CH}_3\text{As(SCF}_3)_2$ (14) ^a	CSF_2 (12), CS_2 , $\text{C}_2\text{H}_5\text{AsF}_2$, CF_3SSCF_3 (3), $\text{CF}_3\text{SSSCF}_3$ (9), $\text{CF}_3\text{SSSSCF}_3$ (10), $\text{CH(SCF}_3)_3$ (13), $\text{CF}_3\text{SC(S)SCF}_3$ (15), $\text{CF}_3\text{SC(S)F}$ (21), $\text{C}_2\text{H}_5\text{As(SCF}_3)_2$ (17) ^b

^aYield, c. 48%.

^bYield, c. 25%.

Experimental

General procedure

Warning!! Because of the high toxicity associated with arsenicals via inhalation, extreme care should be exercised in working with them and all reactions should be carried out in efficient hoods. NMR spectra (^{13}C and ^{19}F) were recorded in CDCl_3 on a Varian VXR-400S spectrometer at 100 MHz and 376 HMz, respectively. The external reference for the ^{19}F spectra

was CCl_3F . Mass spectra were obtained on a Finnigan model 5100 GC-MS instrument equipped with a silica $25\text{ m} \times 0.31\text{ mm}$ (i.d.) SE-54 capillary column (J and W Scientific, Rancho Cordova, CA). Routine GC analyses were accomplished with a Hewlett Packard 5890A gas chromatograph equipped with a $30\text{ m} \times 0.53\text{ mm}$ (i.d.) DB-5 column (J and W Scientific, Folsom, CA).

The reactions were carried out in a flame-dried, argon-purged 10 ml or 25 ml round-bottom flask equipped with a magnetic stirrer, a gas inlet, a pressure equalizing funnel and a reflux condenser carrying a Dry Ice/acetone trap. The temperature of the coolant passing through the condenser was maintained at -20°C . All reactions were carried out by adding stoichiometric amounts of the reagents (usually 0.01 mol) of the alkylmonohalo- and dihalo-arsines to trifluoromethylthiocopper or bis(trifluoromethylthio)mercury (weighed in an inert atmosphere to avoid decomposition). After the addition was over, the reaction mixtures were stirred, heated and processed as described in each case.

Dimethyltrifluoromethylthioarsine (8)

Method a

Dimethylbromoarsine (5)* (0.01 mol) was added dropwise to a stoichiometric amount of trifluoromethylthiocopper (4). After addition, the reaction mixture was heated at $80\text{--}90^\circ\text{C}$ for 6 h. The reaction mixture was cooled to ambient temperature, flash-distilled and analyzed by GC-MS methods (Table 1). The flash-distillate was further purified by fractional distillation (twice) under reduced pressure to furnish a 98% pure sample of 8 (cf. ref. 7a) in 70% yield.

Method b

In a similar manner, 5 was treated with compound 1. Since 1 is highly sensitive to moisture, transfer operations were carried out in an argon-filled glove bag. The GC-MS analysis of the flash-distillate indicated the presence of 8 and four of the other products obtained above (Method a). In addition, two compounds, viz. bis(trifluoromethyl)trithiocarbonate (15) and carbon disulfide (20), were identified (Table 1).

Tris(trifluoromethylthio)methane (13)

An authentic sample of this compound was needed for comparative purposes. The compound was prepared by heating a mixture of iodoform (4.0 g, 0.01 mol) and 4 (2.1 g, 0.01 mol) in 10 ml of freshly distilled acetonitrile for 24 h at $85\text{--}90^\circ\text{C}$. The product was obtained by flash-distillation of the cooled reaction mixture under vacuum. Fractional distillation of the flash-distillate

*This is a light-sensitive compound and consequently, the reaction was carried out in the absence of light.

gave compound **13**. ^1H NMR δ : 5.93 (s) ppm. ^{13}C NMR (SCF₃) δ : 128 ($J=312$ Hz, CH); 46.7 ($J=3.1$ Hz) ppm.

Methyl bis(trifluoromethylthio)arsine (**14**)

A mixture of **6** (3.12 g, 0.02 mol) and **1** (8.06 g, 0.02 mol) was heated for 4 h at 95–100 °C. The reaction mixture was processed as above and analyzed by GC–MS methods (Table 3). The mass-spectral fragmentation of compound **14** is given in Table 2.

Ethyl bis(trifluoromethylthio)arsine (**17**)

A mixture of **7** (0.01 mol) and **4** (0.01 mol) was heated for 6 h at 85–95 °C. The reaction mixture, processed as above, gave a complex mixture containing 10 components (Table 3) which were characterized and identified by their mass-spectral fragmentation patterns (Table 2).

Biological screening of compound **8**

Test animals were exposed to the vapors of compound **8** in an enclosed chamber. The concentrations of the test compound were monitored both at the entrance and exit of the chamber. Based on the dose response inhalation study [16a] and the suggested classification schemes [16b], it was concluded that concentrations as low as 0.15 ppm may cause significant sensory irritation to the eyes, nose and throat, and that intolerable conditions may develop in humans at concentrations above 1.5 ppm. The lack of mortality and rapid recovery of the test animals within a few minutes after the cessation of their exposure, clearly suggests the transitory nature of the effects elicited by this compound.

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