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A General Synthesis of Trifluoromethyl Selenides Utilizing Selenocyanates and Fluoroform

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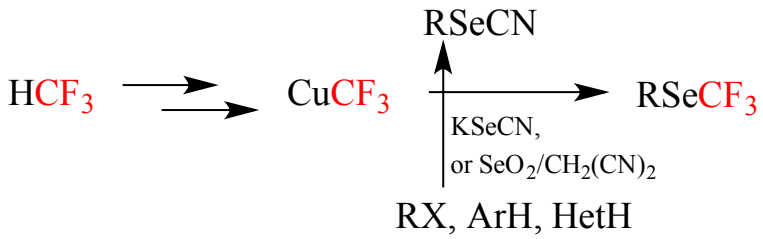
Graphical Abstract



Abstract

Trifluoromethylated selenoethers are quite rare despite their potential and interest they arise. A series of trifluoromethylseleno derivatives, being either primary and secondary aliphatic or aromatic and heterocyclic is described herein by the reaction of easily prepared organic selenocyanates and $CuCF_3$. Another beneficial feature of this reaction is the use of fluoroform as a source for the CF_3 group, a compound whose chemistry is currently under intensive research focus, as it is a potent greenhouse gas, which should not be released to the atmosphere.

Introduction

The trifluoromethyl group is of great interest since among other features it brings about remarkable biological properties, probably due to the increased lipophilicity it grants to molecules attached to it.[1]

Thus, trifluoromethylation has been a subject of a remarkable research efforts especially in the last two decades. Among the various trifluoromethyl compounds, trifluoromethylated ethers and thioethers, $ROCF_3$ and $RSCF_3$ respectively, have attracted special interest since these families have some of the highest lipophilicity parameter values.[2] One general way for their preparation is through the formation of carbon - fluorine bonds at specific sites[3] while the other concentrates on transferring the whole CF_3 group from an appropriate reagent.[4,5]

While the procedures for the preparation of the aforementioned trifluoromethylated families are quite general and well established, considerably less efforts were devoted to the development of synthetic methods toward trifluoromethylated selenoethers. Attaining this goal becomes increasingly desirable because of the medicinal potential,[6] the expected high lipophilicity,[7] and the fast expending of the organo selenium chemistry.[6,8]

Yagupolskii developed a trifluoromethylselenation applicable for some aryl iodides.[9] This synthetic method uses $CuSeCF_3$, made from copper and $CF_3SeSeCF_3$, which in its turn is difficult to prepare.[10] Several groups reported the synthesis of $PhSeCF_3$ (**2e**) by the reactions of different trifluoromethylating agents with PhSeSePh (**3e**).[11] These reactions, aside from being limited to the formation of **2e**, suffer from the fact that generally half of the organic diselenide is lost in a form of a leaving group.

Recently, a general procedure was reported for the synthesis of trifluoromethyl selenoethers, by substituting the appropriate iodides or bromides [12] using the $[(bpy)Cu(SeCF_3)]_2$ complex, which is prepared in a two pot reaction from $TMSCF_3$, CuI, KF, Se and bipyridine in 41% yield.

Fluoroform, CHF_3, is of course, one of the most attractive trifluoromethylation agent. It is a side product of manufacturing Teflon, PVDF, refrigerants and fire extinguishing agents, and is generated in large volumes of over 20000 tons yearly.[5a,13] Unfortunately although nontoxic and ozone-friendly, it is still a very potent greenhouse gas. As a result, the Kyoto protocol of 1997 obligated industrialized countries to reduce its emissions. Since it could be destroyed in what is a costly incineration process, it is much more preferably to be used as a feedstock for manufacturing, but this is a nontrivial challenge. Therefore large quantities of it are stored without a great demand, turning CHF_3 into an inexpensive reagent indeed.[13]

In an effort to put this gas to good use, considerable research energy has been invested to turn it into a synthetic reagent.[14] Still, its current scope in organic chemistry is somewhat limited and confined mostly to formations of C-CF_3 bonds.[15] Recently work in this field led to trifluoromethylation of B, Si and S centers in addition to carbon ones.[13] An important reagent is the fluoroform derived $CuCF_3$, which was used as a general reagent for formations of different C-CF_3 bonds and enables convenient usage of fluoroform in large scales.[5,16]

For developing a general synthesis of $RSeCF_3$ using the nucleophilic trifluoromethyl moiety of $CuCF_3$, a good electrophilic selenium source is needed. Organic selenocyanates, RSeCN can fulfill this requirement.[17] Such compounds are easy to

prepare by nucleophilic substitution of alkyl halides[18] with the relatively inexpensive KSeCN or by electrophilic substitutions with $SeO_2/CH_2(CN)_2$ mixture.[19]

Results and Discussion

$CuCF_3$ solution was prepared following Grushin's procedure,[5] by bubbling fluoroform gas through a DMF solution of CuCl and *t*-BuOK with a slight variation calling for conducting the reaction under atmospheric pressure and without any $Et_3N/3HF$. The resultant $CuCF_3$ solution (1.5 mole/equivalents) was reacted with 1-selenocyanatotetradecane (**1a**),[18] and the previously unknown *n*-tetradecyl(trifluoromethyl)selane (**2a**), was formed in quantitative yield after 1.5 h at room temperature. The progress of these type of reactions was monitored by ^{19}F NMR (vs. calibrated amount of $PhCF_3$).

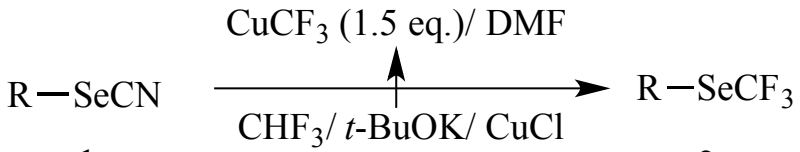
The $CuCF_3$ solution was reacted with (3-selenocyanatopropyl)benzene (**1b**)[18] as well, forming quantitatively (3-phenylpropyl)trifluoromethylselane (**2b)**. In order to demonstrate the efficiency of this reaction, the doubly selenated, 1,10-diselenocyanatodecane (**1c**)[18] was reacted with 3 mole-equivalents of the fluoroform derived $CuCF_3$ (50% excess) for 2.5 h at room temperature yielding the previously unknown 1,10-bis(trifluoromethylseleno)decane (**2c**) in 95% yield.

Cyclohexyltrifluoromethylselanes are of special interest since secondary trifluoromethylselanes in general and cyclohexyl ones in particular are not known. The reaction of cyclohexene with KSeCN and $CuCl_2$ in ethanol yielded mainly *trans*-1-ethoxy-2-selenocyanatocyclohexane (**1d**) with less than 10% of the *cis* isomer. The reaction of $CuCF_3$ with **1d** showed that the stereochemistry around the C-Se bond is

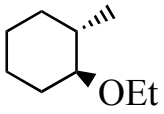
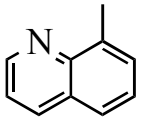
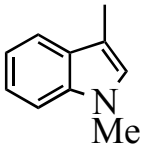
retained and the secondary trifluoromethylseleno ether, *trans*-(2-ethoxycyclohexyl)trifluoromethylselane (**2d**) was formed in 80% in 4 h at R.T.

Aromatic selenocyanates are also reactive towards the nucleophilic trifluoromethylating reagent $CuCF_3$. When the commercial PhSeCN (**1e**) was added to this fluoroform derived agent, the reaction was completed in 3 hours and phenyltrifluoromethylselane (**2e**) was formed in 85% yield. The trifluoromethylation is also suitable for electron-rich aromatic selenocyanates, which are readily prepared by electrophilic aromatic substitution. For example, treatment of *N,N*-dimethylaniline with selenium (IV) oxide and malononitrile gives *para*-substituted *N,N*-dimethyl-4-selenocyanatoaniline (**1f**).[19] When this compound was reacted with the $CuCF_3$ suspension for 4 h at R.T., the *N,N*-dimethyl-4-(trifluoromethylselanyl)aniline (**2f**) was formed in 80% yield. The trifluoromethylation of selenocyanates with $CuCF_3$ is also effective with electron-poor aromatics, as evident from the reaction of 8-selenocyanatoquinoline (**1g**)[20] with 1.5 equivalents of the fluoroform derived $CuCF_3$ which led to quantitative formation of the previously unreported 8-(trifluoromethylselanyl)quinoline (**2g**). In this case the reaction rate was faster and was completed within 1.5 h, probably due to copper-nitrogen interactions, which could hold the trifluoromethylating agent closer to the reaction center. Nitrogen heterocyclic substrates such as the electron rich 1-methyl-3-selenocyanato-1*H*-indole (**1h**), prepared by direct electrophilic aromatic substitution, also reacted with $CuCF_3$ to form the new 1-methyl-3-(trifluoromethylselanyl)-1*H*-indole (**2h**) in 80% after 4 h at room temperature (Scheme 1).

Scheme 1: From selenocyanates to trifluoromethyl selenoethers



1 **2**

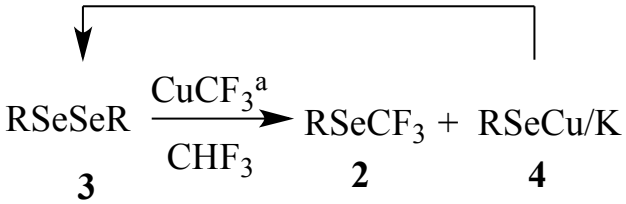
a	R = n-$C_{14}H_{29}$	1.5h, R.T	> 95%
b	R = $Ph(CH_2)_3$	1.5h, R.T	> 95%
c	R = —$(CH_2)_{10}$—	2.5h, R.T	95%[a]
d	R = 	4h, R.T	80%
e	R = Ph	3h, R.T	85%
f	R = 4-Me_2N-C_6H_4	4h, R.T	80%
g	R = 	1.5h, R.T	>95%
h	R = 	4h, R.T	80%

(a) using 3 mol/eq of $CuCF_3$

While selenocyanates are probably the best starting point for the synthesis of trifluoromethylselenides, occasionally diselenides (RSe-SeR) could be more readily available, or prepared by air oxidation of the corresponding selenols (RSeH) and hence from the corresponding Cu or K salts. These diselenides[21] could also serve as substrates

for trifluoromethyl selenides by using almost the same procedure as with selenocyanates, and the reactions are even somewhat faster as shown for **2e** and **2i**.[17] Although mole per mole the yields were about 90%, when based on the Se atoms they are around 45% only with the balance being the corresponding selenide salts – RSeCu/K ejected as the leaving group. These salts, of course, are easy to protonate by acidic workup to the corresponding selenols, RSeH, which in their turn could be oxidized by air to the parent diselenides, **3**. As the recovery is a simple, high – yield process, the recovered diselenides can be reused to form trifluoromethyl selenides, and thus increasing the yield and minimizing the waste (Scheme 2).

Scheme 2: From diselenides to trifluoromethyl selenoethers



e	R = Ph	90%[b]	45%
i	R = n-C_8H_{17}	90%[b]	45%

a) 1.5 mol/eq; 1h; R.T.; b) when calculated mole per mole. 45% when based on the Se atom.

Conclusion

In conclusion, a diverse series of trifluoromethylseleno derivatives was prepared from the corresponding alkyl, aryl or heterocyclic selenocyanates. As these

trifluoromethylseleno compounds are expected to be highly lipophilic, their popularity is on the rise and it was important to find a general and simple procedure that combines an easily accessible selenium source coupled with an attractive trifluoromethylating agent. These requirements are satisfied in the reaction of selenocyanates and fluoroform derived $CuCF_3$. It was also shown that similar conditions are compatible for the reaction with diselenides serving as starting materials, resulting again in the corresponding trifluoromethylseleno compounds.

Experimental

General Procedures:

The fluoroform cylinder was purchased from commercial sources. ^{1}H, ^{19}F, and ^{13}C NMR spectra were obtained with $CDCl_3$ as a solvent at 400, 376, and 100 MHz, respectively, with Me_4Si as an internal standard for the ^{1}H and ^{13}C NMR and $CFCl_3$ for the ^{19}F NMR spectra. HRMS samples of **2f** and **2g** were measured under ASAP conditions. In all other cases this method could not detect any molecular ion, so we have used successfully the unique Amirav's supersonic GC-MS technique which without practically any exceptions could reveal such ions. In these cases, the isotope abundance analysis provided very satisfactory results, as shown for the specific compounds. This type of analysis confirmed the proposed elemental formulas as it ranked them in first place and hence as the best choice, with very good matching factors of better than 940 (out of 999).[22]

Selenocyanates formation:

We have referenced the known selenocyanates. In particular, we have prepared the primary selenocyanates **1a** and **1b** via the substitution of 1-bromotetradecane and 1-bromo-3-phenylpropane with 1.2 equivalent potassium selenocyanate in a refluxing ethanolic solution for 1 h (>95% yields). Bis–selenocyanate **1c** was similarly prepared using 2.5 equivalent potassium selenocyanate and 1,10-dibromodecane in 90% yield. The cyclic selenocyanate **1d** was prepared by the reaction of cyclohexene with 2 equiv. copper(II) chloride and potassium selenocyanate each in refluxing ethanol in 60% yield.[23] Selenocyanate **1g** was prepared by the diazotation of 8-aminoquinoline, followed by substitution with potassium selenocyanate at 0 ^{o}C (60% yield). The preparations of the electron-rich selenocyanates **1f** and **1h** were achieved by electrophilic aromatic substitutions using selenium(IV) oxide and malononitrile in DMSO as described in reference 19 in 85% and 90% yield respectively.

General Trifluoromethylation Procedure:

To a two necked flask equipped with a glass pipette inlet for argon, 40 ml of dry DMF were inserted and the solvent was degassed for 5 minutes followed by addition of 4.7 g of finely ground potassium *tert*-butoxide. The suspension was stirred for about 5 minutes until most of the solid was dissolved. Two g of copper (I) chloride were added, the suspension turned black within a minute and was vigorously stirred while argon was passed through for 1 h at room temperature. The argon inlet was replaced with a fluoroform inlet and this gas was bubbled through the black solution for 5 minutes at a rate of about 600 ml per minute (about 6 mole-equivalents, based of Cu). This procedure produced about 16 mmol $CuCF_3$ (calibrated using ^{19}F NMR with $PhCF_3$ as a standard). A measured volume was added to the DMF solution of the selenocyanate ensuring about

50% excess of $CuCF_3$ over the starting selenocyanate, and the suspension was stirred under argon atmosphere for 3 – 5 hours till completion (monitored by TLC or UV for **2e** – **2h**). The suspension was added to cold water and extracted with ether. The ethereal solution was passed through a short pad of celite to remove inorganic salts and evaporated. The product was purified by flash column chromatography using pentane (compounds **2a**, **b**, **c**, **e**) or pentane/ether mixtures (compounds **2d**, **f**, **g**, **h**). Specific amounts of selenocyanates, $CuCF_3$ suspension, reaction times and temperatures are specified herein. As these reactions were conducted in small scale, excess fluoroform was not destroyed, for large scale applications a continuous flow process for preparation and reactions of $CuCF_3$ was reported.[16]

Tetradecyl(trifluoromethyl)selane (**2a**). Prepared from selenocyanate **1a** (0.80 g, 2.9 mmol) and about 4.0 mmol $CuCF_3$ as described in the general procedure. Quantitative yield; 0.91 g, clear oil, ^{1}H NMR 2.98 (2 H, t, J = 7.6 Hz), 1.78 (2 H, quin, J = 7.6 Hz), 1.40 (2 H, m), 1.26 (20 H, m), 0.88 (3 H, t, J = 6.4 Hz) ppm. ^{13}C NMR 122.8 (q, J = 328 Hz), 32.0, 30.3, 29.7-29.4 (8 C), 29.0, 25.9, 22.8, 14.2 ppm. ^{19}F NMR -39.5 ppm (3 F, s). The common MS methods failed to show any molecular peak. Amirav's supersonic GC-MS revealed a strong molecular ion peak of m/z 340.1 $(M)^+$ with an isotope abundance analysis matching factor of 998 out of 999. Anal. calc. for $C_{15}H_{29}F_3Se$: C, 52.17; H, 8.46; F, 16.5. Found: C, 51.95; H, 8.45; F, 16.11.

(3-Phenylpropyl)(trifluoromethyl)selane (**2b**).[12] Prepared from selenocyanate **1b** (0.55 g, 2.4 mmol) and fluoroform derived $CuCF_3$ (about 3.7 mmol) as described in the general procedure, in quantitative yield: 0.65 g, clear oil, ^{1}H NMR 7.30 - 7.32 (2 H, m), 7.18 - 7.24 (3 H, m), 2.99 (2 H, t, J = 7.2 Hz), 2.75 (2 H, t, J = 7.6 Hz), 2.14 (2 H,

quin, J = 7.2 Hz), ppm. ^{13}C NMR 141.6, 128.6, 128.5, 126.3, 122.7 (q, J = 328 Hz), 35.5, 31.8, 25.2 ppm. ^{19}F NMR -32.7 ppm (3 F, s).

1,10-Bis(trifluoromethylseleno)decane (**2c**). Prepared from selenocyanate **1c**[18] (0.80 g, 2.3 mmol) and the fluoroform derived $CuCF_3$ (about 5.7 mmol) as described in the general procedure, in 95% yield: 0.95 g, clear oil, ^{1}H NMR 2.98 (4 H, t, J = 7.2 Hz), 1.78 (2 H, quin, J = 7.6 Hz), 1.37 - 1.401 (4 H, m), 1.25 - 1.37 (8 H, m) ppm. ^{13}C NMR 122.8 (q, J = 330 Hz), 30.3, 29.6, 29.3, 28.9, 25.9 ppm. ^{19}F NMR -32.8 ppm (3 F, s). The common MS methods failed to show any molecular peak. Amirav's supersonic GC-MS revealed a strong molecular ion peak of m/z 426.0 $(M)^+$ with an isotope abundance analysis matching factor of 940 out of 999.

***Trans*-(2-ethoxycyclohexyl)(trifluoromethyl)selane** (**2d**). Prepared from selenocyanate **1d**[23] (1.0 g, 4.1 mmol) and the fluoroform derived $CuCF_3$ (about 6.5 mmol) as described in the general procedure, in 80% yield: 0.95 g, clear oil, ^{1}H NMR 3.28 - 3.68 (2 H, m), 2.04 - 2.35 (1 H, m), 1.60 - 1.79 (2 H, m), 1.18 - 1.43 (7 H, m), 0.83 - 0.91 (3 H, m) ppm. ^{13}C NMR 123.2 (q, J = 329 Hz), 96.2, 80.1, 64.5, 47.6, 31.2, 25.8, 23.2, 15.4 ppm. ^{19}F NMR -30.2 ppm (3 F, s). The common MS methods failed to show any molecular peak. Amirav's supersonic GC-MS revealed a strong molecular ion peak of m/z 270.0 $(M)^+$ with an isotope abundance analysis matching factor of 980 out of 999.

Phenyl(trifluoromethyl)selane (**2e**).[11] Prepared from commercial selenocyanate **1e** (3.00 g, 16.4 mmol) the fluoroform derived $CuCF_3$ (about 24.7 mmol) as described in the general procedure, in 85% yield: 3.15 g, clear oil, ^{1}H NMR 7.74 - 7.77 (2 H, m), 7.46 - 7.50 (1 H, m), 7.38 - 7.42 (2 H, m) ppm. ^{13}C NMR 137.1, 130.4, 129.6, 122.6, 122.6 (q, J = 330 Hz) ppm. ^{19}F NMR -34.8 ppm (3 F, s).

***N,N*-Dimethyl-4-(trifluoromethylselanyl)aniline** (**2f**). Prepared from selenocyanate **1f**[19] (1.00 g, 4.4 mmol) and the fluoroform derived $CuCF_3$ (about 6.7 mmol) as described in the general procedure, in 80% yield: 0.95 g, pinkish solid, m.p. 58 – 59 ^oC. ^1H NMR 7.56 (2 H, d, J = 9.2 Hz), 6.66 (2 H, d, J = 8.8 Hz), 3.00 (6 H, s) ppm. $^{13}CNMR$ 152.3, 139.4, 123.3 (q, J = 332 Hz), 113.3, 107.7, 40.8 ppm. $^{19}FNMR$ -36.7 ppm (3 F, s). HRMS (ASAP): calcd. for $C_9H_{11}NF_3Se$ $(M+H)^+$ 266.0036; found 266.0047. Anal. calc. for $C_9H_{10}NF_3Se$: C, 40.31; H, 3.76; F, 21.26; N, 5.22. Found: C, 40.11; H, 3.63; F, 20.83; N, 4.71.

8-(Trifluoromethylselanyl)quinoline (**2g**). Prepared from selenocyanate **1g**[20] (0.61 g, 2.6 mmol) and the fluoroform derived $CuCF_3$ (about 3.9 mmol) as described in the general procedure, in quantitative yield: 0.72 g, clear oil, ^1H NMR 8.88 (1 H, dd, J_1 = 4.3 Hz, J_2 = 1.7 Hz), 8.15 (1 H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.99 (1 H, t, J = 7.4 Hz), 7.76 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.51 (1 H, t, J = 8.0 Hz), 7.45 (1 H, dd, J_1 = 8.3 Hz, J_2 = 4.3 Hz) ppm. ^{13}C NMR 150.5, 146.5, 137.2, 131.3, 130.2, 129.1, 128.1, 124.2 (q, J = 330 Hz), 122.9 ppm ^{19}F NMR -35.2 ppm (3 F, s). HRMS (ASAP): calcd. for $C_{10}H_7F_3NSe$ $(M + H)^+$ 273.9723; found 273.9727.

1-methyl-3-(trifluoromethylselanyl)-1*H*-indole (**2h**). Prepared from selenocyanate **1h**[19] (0.52 g, 2.2 mmol) and the fluoroform derived $CuCF_3$ (about 3.3 mmol) as described in the general procedure, in 80% yield: 0.49 g, beige solid, m.p = 59 ^oC. ^1H NMR 7.75 (1 H, d, J = 7.6 Hz), 7.26-7.39 (4 H, m), 3.85 (3 H, s) ppm. ^{13}C NMR 137.3, 137.1, 130.9, 122.9, 122.3 (q, J = 333 Hz), 121.2, 120.2, 109.8, 33.3 ppm. ^{19}F NMR -36.7 ppm (3 F, s). The common MS methods failed to show any molecular peak. Amirav's supersonic GC-MS revealed a strong molecular ion peak of m/z 273.0 $(M)^+$

with an isotope abundance analysis matching factor of 999 out of 999. Anal. calc. for $C_{10}H_8NF_3Se$: C, 43.18; H, 2.90; F, 20.49; N, 5.04. Found: C, 43.17; H, 2.79; F, 20.94; N, 4.76.

Octyl(trifluoromethyl)selane (**2i**)[17]. Prepared from diselenide **3i** (2.69 gr, 7.0 mmol) and about 10.5 mmol $CuCF_3$, whose preparation was described in the general procedure. The suspension was stirred under argon atmosphere for one hour (monitoring by TLC) then added to cold 2% aqueous HCl, stirred for 5 minutes and extracted with pentane. The organic solution was passed through a short pad of celite to remove inorganic salts and evaporated. The product was purified by flash column chromatography using pentane. The product was isolated in 90% yield (45% based on Se atoms): 1.65 g, 6.3 mmol, clear oil. ^{1}H NMR 2.98 (2 H, t, J = 7.2 Hz), 1.78 (2 H, quin, J = 7.6 Hz), 1.43 - 1.22 (10 H, m), 0.88 (3 H, t, J = 6.4 Hz) ppm. ^{13}C NMR 123.4 (q, J = 332 Hz), 32.5, 30.9, 30.3, 29.8, 29.6, 26.6, 23.3, 14.7 ppm. ^{19}F NMR -32.9 ppm (3 F, s).

ASSOCIATED CONTENT

Supporting Information. 1H NMR and 13C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes and References

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7. As SCF_3 compounds were measured to be more lipophilic than the corresponding OCF_3 and CF_3 derivatives, the less electronegative $SeCF_3$ compounds are expected to even more lipophilic. See also reference 2.

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