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A New and Efficient Method for the Synthesis of Trifluoromethylthio- and Selenoethers

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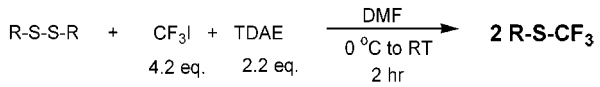
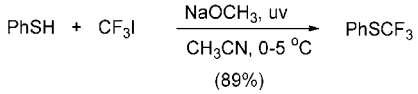
ABSTRACT



A new atom-economic procedure for preparation of trifluoromethyl thio- and selenoethers is reported, wherein both halves of aryl and alkyl disulfides and diselenides are able to be utilized with high efficiency.

Aryl trifluoromethyl thioethers continue to attract much interest within pharmaceutical and agrochemical companies, as witnessed by the significant number of process patent applications recently submitted that are devoted to their preparation.[1] This interest derives from the recognized potential of the SCF_3 group to have a positive influence on biological activity. Diverse methods have been reported for the synthesis of aryl trifluoromethyl thioethers,[2] but two seem to have emerged as preferred methods. The first is the classic $S_{RN}1$ reaction of aryl thiolates with trifluoromethyl iodide or bromide. This method, first reported by Yagupolskii using CF_3I and UV irradiation in 1977,[3] by Wakselman and Tordeux using CF_3Br (at 2 atm) in 1984,[4,5] along with later variations,[6,7] has proved to be generally useful when using *aryl* thiolates but less efficient when using alkanethiolates.[8]

Scheme 1. Thiolate Method



The other popular method involves the reaction of trifluoromethyl anion (generated in situ by various methods) with aryl and alkyl disulfides.[9−15] Although good yields can be obtained, as exemplified below, the method suffers from the fact that half of the disulfide is wasted in the process.[16−18]

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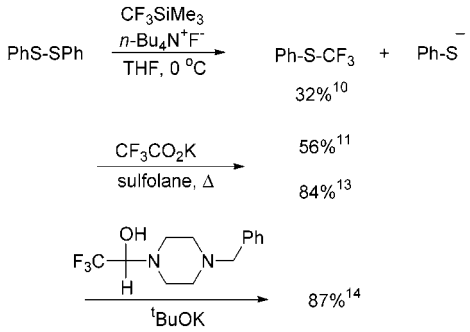
(1) For example: Okano, K.; He, L. (Mitsubishi Chemical Corp.). PCT Int. Appl. 2002 066423. Forat, G.; Mas, J.-M.; Saint-Jalmes, L. (Rhone-Poulenc Chimi). U.S. Patent Appl. Publ. 2002 042542.
(2) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.
(3) Boiko, V. N.; Shchupak, G. M.; Yagupolskii, L. M. *J. Org. Chem., USSR* **1977**, *13*, 972−975.
(4) Wakselman, C.; Tordeux, M. *Chem. Commun.* **1984**, 793−794.
(5) Wakselman, C.; Tordeux, M. *J. Org. Chem.* **1985**, *50*, 4047−4051.
(6) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579−3582.
(7) Koshechko, V. G.; Kiprianova, L. A.; Fileleeva, L. I. *Tetrahedron Lett.* **1992**, *33*, 6677−6678.
(8) Popov, V. I.; Boiko, V. N.; Yagupolskii, L. M. *J. Fluorine Chem.* **1982**, *21*, 365−369.
(9) Wakselman, C.; Tordeux, M.; Clavel, J. L.; Langlois, B. R. *Chem. Commun.* **1991**, 993−994.
(10) Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **1996**, *37*, 6865−6868.
(11) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057−9058.
(12) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771−13782.
(13) Roques, N. *J. Fluorine Chem.* **2001**, *107*, 311−314.
(14) Blond, G.; Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **2001**, *42*, 2473−2475.
(15) Inschauspe, D.; Sortais, J.-P.; Billard, T.; Langlois, B. R. *SynLett* **2003**, 233−235.
(16) This disadvantageous atom-inefficiency has been somewhat overcome by using aryl and alkyl thiocyanates or sulfenyl chlorides as the substrates with CF_3TMS, instead of the disulfides.[17,18]
(17) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65−68.
(18) Movchen, V. N.; Kolomeitsev, A. A.; Yagupolskii, L. M. *J. Fluorine Chem.* **1995**, *70*, 255−257.

Scheme 2. Nucleophilic Trifluoromethylation Methods



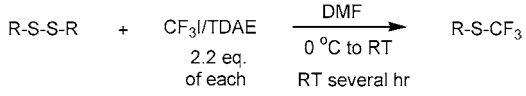
Recently, we have developed a trifluoromethyl anion reagent that is derived directly from trifluoromethyl iodide. When reduced by the organic reducing agent tetrakis-(dimethylamino)ethylene (TDAE), the CF_3I forms a reagent anion that has been found to be effective for additions of CF_3^- to aldehydes, ketones, acyl chlorides, and cyclic sulfates.[19−22] As can seen by the data in Table 1, this reagent

Table 1. Trifluoromethylation of Disulfides

entry	R	stirring time at rt (h)	NMR yield (%)
1	phenyl	12	80
2	butyl	12	>98
3	ethyl	12	>98
4	butyl	4	>98
5	butyl	2	>98

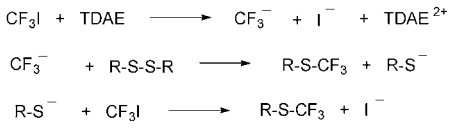
also proves to be an excellent choice for the conversion of aryl and alkyl disulfides into their trifluoromethyl thioethers. The reaction is very fast, and only 2 h of stirring at room temperature was sufficient to give a quantitative yield, as shown in the entries 4 and 5.

Scheme 3. CF_3I/TDAE Method



However, it occurred to us that this same CF_3I that we are using to generate the trifluoromethyl anion could also be a substrate for reaction, via the $S_{RN}1$ mechanism, *with the thiolate coproduct*, thus potentially enabling both halves of the disulfide to be used in a one-pot reaction, where the CF_3I would be used productively in two different reactions, both of which lead to the same desired product.

Scheme 4. Tandem CF_3I Process



Indeed, when a total of 5 equiv of CF_3I are used, while maintaining the quantity of TDAE at 2.2 equiv, yields of trifluoromethylthioether reached as high as 200%, based on the numberr of equivalents of disulfide![23]

Entries 1−3 show that with 5 equiv of CF_3I, yields of almost 200% could be obtained with both diaryl and dialkyl disulfide. Entries 4−7 indicate attempts to optimize the procedure. Although 3.2 equiv of CF_3I (entry 3) were not sufficient, more than 4.2 equiv gave nearly quantitative yields. Moreover, 2 h of stirring at room temperature appears to be sufficient. The lack of reactivity of *t*-butyl disulfide had been noted previously, when CF_3TMS was used as the trifluoromethyl anion source.[10]

It might be argued that these results could derive simply from reduction (by TDAE) of the disulfide to 2 equiv of thiolate anion, which then could react with the CF_3I, with the reaction proceeding entirely via reaction of thiolate anions with CF_3I. However, if that were the case, the 2.2 equiv of TDAE (along with 2.2 equiv of CF_3I) should have been sufficient to obtain the high yields observed in Table 2.

Table 2. Trifluoromethylation of Disulfides Using Excess CF_3I

entry	R	equiv of CF_3I	stirring time at rt (h)	NMR yield (%)	ref
1	phenyl	5	12	186	5, 24
2	butyl	5	12	170	25
3	4-pyridyl	5	12	∼200	26
4	butyl	5	4	170	25
5	butyl	4.2	4	175	25
6	butyl	3.2	4	130	25
7	butyl	4.2	2	170	25
8	ethyl	4.2	2	180	27
9	2-pyridyl	4.2	2	180	28
10	*t*-butyl	4.2	12	0	

However, in those cases where 2.2 equiv of TDAE were used (Table 1), yields never exceeded 100%. This probably means that the CF_3I is reduced faster than the disulfides.

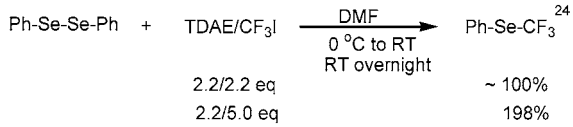
Nevertheless, a control reaction was carried out to provide more definitive evidence for the proposed dual-mechanism synthetic process. CF_3I (5 equiv) and TDAE (2.2 equiv) were added together in DMF at −20 °C, at which temperature a deep red solution was formed as the TDAE was fully oxidized by reaction with CF_3I. The solution was then

(19) Aït-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2001**, *3*, 4271−4273.
(20) Takechi, N.; Ait-Mohand, S.; Medebielle, M.; Dolbier, W. R., Jr. *Tetrahedron Lett.* **2002**, *43*, 4317−4319.
(21) Takechi, N.; Ait-Mohand, S.; Medebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2002**, *4*, 4671−4672.
(22) Petrov, V. A. *Tetrahedron Lett.* **2001**, *42*, 3267−3289.

allowed to warm to −5 °C, at which time *n*-butyl disulfide was introduced. At this point there should be little, if any TDAE remaining to react with the disulfide. Despite this, the observed yield from this reaction was 160%, which compares well with the 170% observed when using the normal procedure (Table 2, entry 5). One can therefore conclude that the reaction likely proceeds via the two-stage process described above.

Since diselenides have reactivities that are similar to disulfides, this nucleophilic trifluorination procedure was applied to diphenyl diselenide. Again, when only 2.2 equiv each of TDAE and CF_3I were used, the reaction proceeded well to give ∼100% yield. However, when 5 equiv of CF_3I were used, the reaction efficiently converted the diselenide to 2 equiv of the selenoether[24] (198% yield).

Scheme 5. Synthesis of Phenyl Trifluoromethyl Selenide



In conclusion, a new, atom-economic procedure for preparation of trifluoromethyl thio- and selenoethers is reported, wherein both halves of aryl and alkyl disulfides and diselenides are able to be used with high efficiency. Future work will demonstrate the extension of this methology to the use of other perfluoroalkyl iodides.

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(23) **Typical Procedure.** In a 25 mL flask equipped with a reflux condenser and a N_2 inlet was added 10 mL of anhydrous DMF and 0.8 g (3.7 mmol) of diphenyl disulfide. After cooling to −5 °C, 2 mL (8.1 mmol) of TDAE and then 3.6 g of CF_3I (18.4 mmol) were added. As the CF_3I was added, the solution gradually became dark orange and a white solid started forming after a few minutes. The reaction mixture was maintained at around 0 °C for 30 min, and then the solution was allowed to warm to room temperature, after which it was stirred at rt for an additional 2 h. The orange solution was filtered and the solid washed with Et_2O, which was combined with the DMF filtrate. Water (25 mL) was added to the DMF filtrate and the mixture extracted three times with Et_2O. The combined ether layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the crude product purified by silica gel chromatography (CH_2Cl_2/hexanes, 1:9) to give 1.6 g of phenyl trifluoromethyl sulfide (178% yield, based upon the number moles of disulfide).

(24) Billard, T.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **1999**, *64*, 3813−3820.

(25) Ignatev, N. V.; Boiko, V. N.; Yagupolskii, L. M. *J. Org. Chem., USSR* **1985**, *21*, 592−592.

(26) ^{1}H NMR, AB system: δ 7.37 (dd, J = 4.7, 1.75 Hz, 2H), 8.51 (dd, J = 4.8, 2.0 Hz, 2H). ^{19}F NMR: δ −41.0.

(27) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, L. M. *J. Fluorine Chem.* **2003**, *119*, 101−107.

(28) Yagupolskii, L. M.; Kondratenko, N. V.; Sambur, V. P. *Synthesis* **1975**, 721−723.