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Pentafluorosulfanyldifluoroacetic Acid: Rebirth of a Promising Building Block

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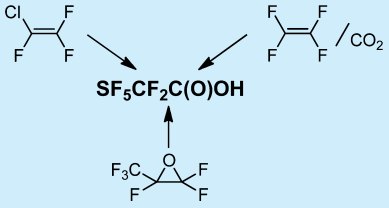
Supporting Information

ABSTRACT: Three novel, easily scalable routes for the synthesis of pentafluorosulfanyldifluoroacetic acid, $SF_5CF_2C(O)OH$, are described. Reactions of its acid chloride with amines and alcohols led to a small library of 15 amides and five esters, respectively. The reaction of the acid chloride with phenylmagnesium bromide gave the corresponding acetophenone. Pentafluorosulfanyldifluoroacetonitrile was obtained from pentafluorosulfanyldifluoroacetamide by dehydration with diphosphorus pentoxide.

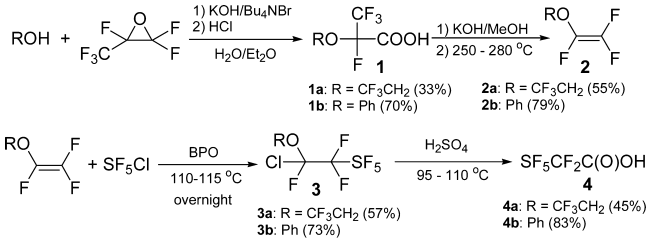


It is well-known that fluorinated molecules play an important role in human everyday life. Currently, about 30% of whole agrochemicals and nearly 25% of drugs have one or more fluorine atoms.[1] Among the fluorine-containing molecules, those with a pentafluorosulfanyl (SF_5) substituent occupy a special place. The pentafluorosulfanyl group brings unique properties to organic compounds and often improves their biological activities because of the group's high chemical and metabolic stability, significant lipophilicity, substantial steric effect, and low surface energy.[2] Compounds with an SF_5 group have been attracting great interest over the last six decades since the first organic SF_5-containing molecules were synthesized.

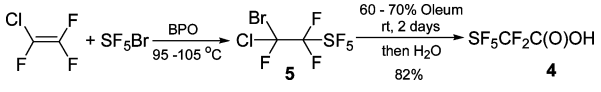
However, for a long time, the development of SF_5 chemistry has been quite slow, primarily due to the lack of pentafluorosulfanyl-containing building blocks and/or useful synthetic methods for their preparation. Pentafluorosulfanyldifluoroacetic acid, $SF_5CF_2C(O)OH$, might be another interesting reagent serving as a key starting material for the synthesis of compounds bearing the SF_5CF_2 moiety that might be of interest for medicinal and agrochemistry, materials science, etc., but all known methods for its preparation are either unsafe or produce the acid in extremely low yield.

Pentafluorosulfanyldifluoroacetic acid was synthesized for the first time in 1956 by Haszeldine and Nyman via electrochemical fluorination of thioglycolic acid with low yield.[3] Several years later, Young et al. tried to improve Haszeldine's method, but unfortunately, the target compound was not even isolated.[4] In 1970, Knunyants and co-workers synthesized esters of $SF_5CF_2C(O)OH$ from alkyl trifluorovinyl ether and pentafluorosulfanyl chloride in several steps.[5] Subsequent hydrolysis of the ester gave the desired acid in 70% yield. Unfortunately, Knunyants' method also could not be widely used, basically because of limited availability of the starting vinyl ether and the substrate needed for its synthesis. Alkyltrifluorovinyl ethers are known as highly reactive compounds that have a tendency to self-polymerize even when stored at low temperature.[6] At the same time, the preparation of such ethers requires the use of

Scheme 1. Preparation of Pentafluorosulfanyldifluoroacetic Acid Based on Hexafluoropropylene Oxide



Scheme 2. Preparation of Pentafluorosulfanyldifluoroacetic Acid from Pentafluorosulfanyl Bromide and Chlorotrifluoroethylene



Scheme 3. Synthesis of Pentafluorosulfanyldifluoroacetic Acid from 1:1 TFE/CO_2 Mixture

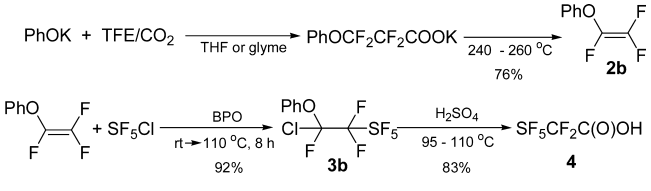


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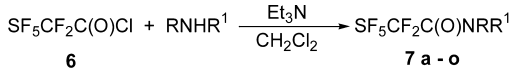
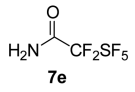
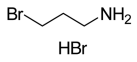
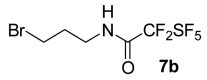
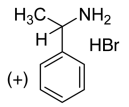
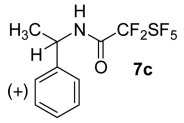
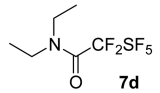
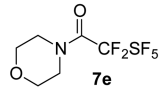
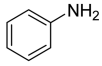
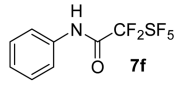
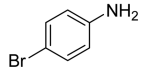
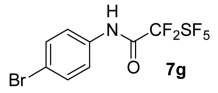
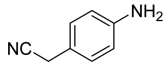
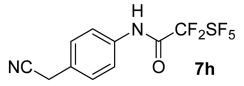
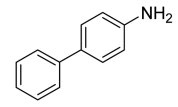
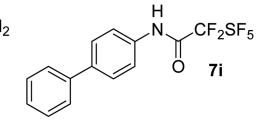
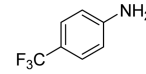
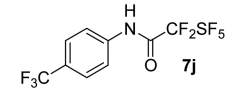
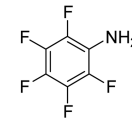
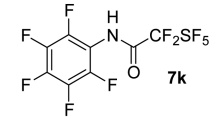
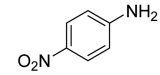
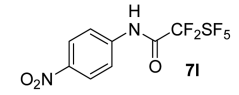
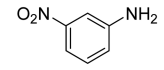
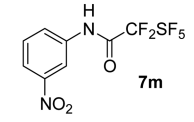
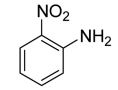
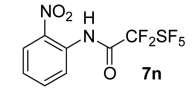
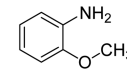
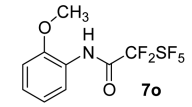
Table 1. Synthesis of SF_5CF_2-Containing Amides



entry	amine	7	yield (%)[a]
1	NH_3	 **7e**	93
2	 HBr	 **7b**	81
3	 HBr (+)	 **7c** (+)	75
4		 **7d**	89[b]
5		 **7e**	63
6		 **7f**	77
7		 **7g**	78
8		 **7h**	71
9		 **7i**	81
10		 **7j**	93
11		 **7k**	93
12		 **7l**	85
13		 **7m**	85
14		 **7n**	56
15		 **7o**	88

[a]Isolated yield. [b]NMR yield.

neat tetrafluoroethylene (TFE), a known deflagrant.[7] In 2007, DesMarteau et al. described the preparation of pentafluorosulfanyldifluoroacetyl fluoride via an elegant rearrangement of pentafluorosulfanyltrifluorovinyl ether.[8] Pentafluorosulfanyloxofluoride (SF_5OF) was used as the starting material in this route. Since the preparation of the SF_5OF requires the use of elemental fluorine, which has its own associated hazards, the aforementioned method does not look attractive or easily scalable.

Now we developed three convenient routes for the synthesis of $SF_5CF_2C(O)OH$, starting from either hexafluoropropylene oxide (HFPO), chlorotrifluoroethylene (CTE), or a mixture of tetrafluoroethylene and carbon dioxide.[7]

Route A: $SF_5CF_2C(O)OH$ from HFPO

First a substrate more stable than alkyltrifluorovinyl ethers was to be found. In 2010, Zeyfman et al. described the synthesis of aryl- and polyfluoroalkyltrifluorovinyl ethers from HFPO and the corresponding alcohol.[9] As shown in Scheme 1, we followed this method to obtain via acids **1** the 1,1,1-trifluoroethyl- and phenyltrifluorovinyl ethers **2**, which were used in further reactions with SF_5Cl in the presence of a radical initiator, such as benzoyl peroxide, for example, to give the corresponding adducts **3a** and **3b**. This addition reaction is exothermic, and thus the reaction temperature should be increased slowly. Hydrolysis of the formed adducts with concentrated sulfuric acid in the presence of glass beads gave $SF_5CF_2C(O)OH$ in 45 or 83% yields, respectively.

Route B: $SF_5CF_2C(O)OH$ from CTE

In this approach, we used SF_5Br instead of SF_5Cl, which reacted with chlorotrifluoroethylene in the presence of a radical initiator. The obtained 1-pentafluorosulfanyl-1,1-difluoro-2,2,2-fluorochlorobromoethane (**5**) was then oxidized into pentafluorosulfanyldifluoroacetyl fluoride with 60% oleum. Subsequent hydrolysis resulted in the desired $SF_5CF_2C(O)OH$ (**4**) in 82% yield (Scheme 2).

Although both of these routes delivered pentafluorosulfanyldifluoroacetic acid **4** without the use of TFE, the results were not completely satisfying. The disadvantage of the first route is the high price of HFPO compared to that of TFE. At the same time, SF_5Br used in the second route is less available than SF_5Cl, and the same is true for the chlorotrifluoroethylene compared to TFE. Therefore, we returned to the original work of Knunyants, and finally came up with a process that not only

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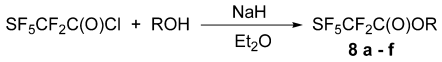
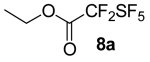
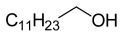
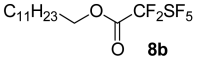
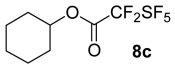
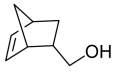
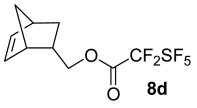
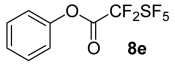
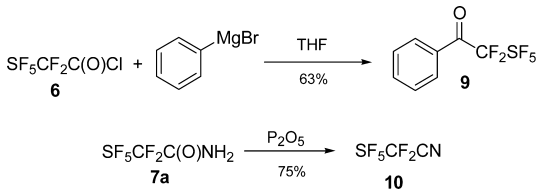
Table 2. Synthesis of SF_5CF_2-Containing Esters



entry	alcohol	8	yield (%)[a]
1		 8a	73[b]
2		 8b	70
3		 8c	71
4		 8d	57
5		 8e	96[b]

[a]Isolated yield. [b]NMR yield.

Scheme 4. Synthesis of SF_5CF_2-Containing Ketone 9 and Nitrile 10



allows for the safe use of tetrafluoroethylene but also can be carried out with SF_5Cl.

Route C: $SF_5CF_2C(O)OH$ from TFE/CO_2

In 1998, Rozen et al. described the preparation of phenyltrifluorovinyl ether from the potassium salt of 2-phenoxy-1,1,2,2-tetrafluoropropionic acid, which was prepared from the corresponding ethyl ester and potassium trimethylsilanolate.[10] The preparation of the starting ester was described in 1984 by Krespan et al.[11] These authors used a mixture of commercially available "neat" TFE, carbon dioxide, and sodium phenoxide. The product of the reaction was then alkylated to give the ethyl ester of 2-phenoxytetrafluoropropionic acid.

We found that in 1951 Hals et al. described the preparation of tetrafluoroethylene as a 50:50 mol % mixture with carbon dioxide via pyrolysis of the potassium salt of pentafluoropropionic acid.[12] Following this procedure, we obtained a mixture of TFE/CO_2, which was reacted with potassium phenoxide to give in one step the potassium salt of 2-phenoxytetrafluoropropionic acid. The latter was then pyrolyzed, giving phenyltrifluorovinyl ether **2b** in 76−85% yield depending upon the scale of the reaction. Along with the target ether, pyrolysis of the potassium 2-phenoxytetrafluoropropionate generates potassium fluoride and carbon dioxide as side products.

Pentafluorosulfanyldifluoroacetic acid was obtained from ether **2b** in the same way as described earlier in route A with slight modification (Scheme 3).

Pentafluorosulfanyldifluoroacetic acid **4** is an extremely hygroscopic solid that liquefies even with traces of moisture. The anhydrous acid can be recovered from its hydrate by distillation from concentrated sulfuric acid. To explore the chemical properties of $SF_5CF_2C(O)OH$, initially some very basic reactions, such as preparation of the corresponding amides and esters, were investigated. Amides can be further used for the synthesis of imidoyl chlorides, amidines, heterocycles, and amines, while esters are also versatile functionalities for subsequent conversions. All of these compounds may be of interest for agro- and medicinal chemistry.

In the initial attempt to prepare an amide, $SF_5CF_2C(O)OH$ and 4-trifluoromethylaniline were mixed in CH_2Cl_2 in the presence of DCC and DMAP. The expected amide **7j** was obtained in only 67% yield. Therefore, we decided to transform the $SF_5CF_2C(O)OH$ into the pentafluorosulfanyldifluoroacetyl chloride (**6**) by heating with excess PCl_5. The acyl chloride **6** obtained in 94% yield had been prepared earlier in situ in 42% yield from the acid and benzoyl chloride.[13] Subsequently, **6** was reacted with 4-trifluoromethylaniline in dichloromethane in the presence of Et_3N, and the corresponding amide **7j** was obtained in 93% yield. Therefore, the acid chloride **6** was applied for further preparation of amides and esters.

In all cases (except entry 1 when ammonia gas was used and entry 4 when an excess of diethylamine was used), the amidation was performed in dichloromethane in the presence of triethylamine, and the yields of the formed products were up to 93%. The yield of the product was lowest for *o*-nitroaniline (entry 14, Table 1), presumably due to steric effects.

Furthermore, isolation of the lower molecular weight amides (e.g., **7d** and **7e**) was difficult due to their high volatility. The same issue was faced in the preparation of esters. Compound **8a** could not be isolated, and its yield was determined only by NMR spectroscopy. Higher molecular weight aliphatic esters (i.e., **8b−d**) were isolated. In contrast, all attempts to purify aromatic ester **8e** failed due to its instability on a silica gel column (Table 2).

Pentafluorosulfanyldifluoroacetyl-containing ketones might be another group of important compounds that should be directly available from pentafluorosulfanyldifluoroacetyl chloride by reaction with corresponding Grignard reagents. The stability of the SF_5 group bonded to aromatic or heteroaromatic rings toward strong nucleophiles is well-documented.[14]

However, it was unclear whether the SF_5 group incorporated into an aliphatic moiety will demonstrate the same stability. In order to ascertain this, $SF_5CF_2C(O)Cl$ was reacted with PhMgBr at −95 °C. The expected fluorinated acetophenone $PhC(O)CF_2SF_5$ **9** was obtained in 63% (NMR yield) (Scheme 4) as a yellowish oil, which was difficult to isolate because of its volatility. Compound **9** had been previously prepared in 36% yield by Gard et al.[15]

Finally, dehydration of amide **7a** by heating with P_2O_5 at 140−170 °C gave pentafluorosulfanyldifluoroacetonitrile **10** in 75% yield.

In conclusion, three different, easily scalable routes for the synthesis of pentafluorosulfanyldifluoroacetic acid (**4**) were developed. This acid, or its acyl chloride **6**, can be used to introduce the SF_5CF_2 moiety into a variety of organic substrates. The preparation of SF_5CF_2-containing compounds that may be of practical interest will be reported in a later publication.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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