Novel, New Aromatic SF_5 Derivatives !

Prepared in High Yield via Highly Versatile & Cost Competitive Methods

Aromatic SF_5 compounds are expected to be useful as BUILDING BLOCKS for pharmaceutical, agricultural and other bio-active agents, pesticides, liquid crystals, novel structural and conductive polymers, dyes, organic semiconductors, high energy compounds, propellants and explosives, and many other higher performance organic materials.

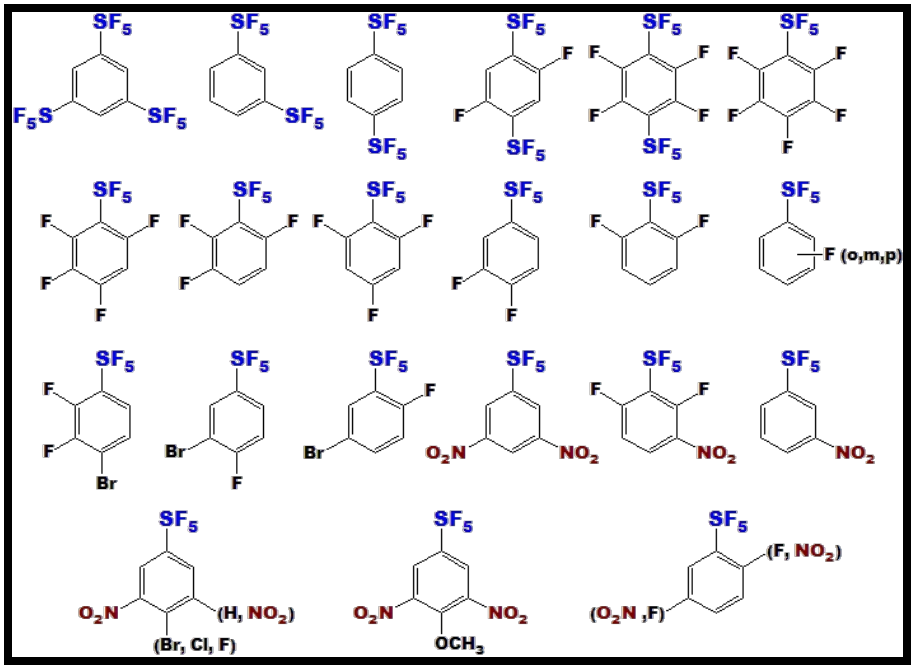
Many SF_5 containing intermediates have recently become available, but only in small quantities priced at hundreds to thousands of dollars per gram, currently made by inefficient and expensive processes. The new recently developed procedures (described below) when commercialized, promise to make these compounds more readily available, much more affordable, and in greater variety for research and production of many useful products.

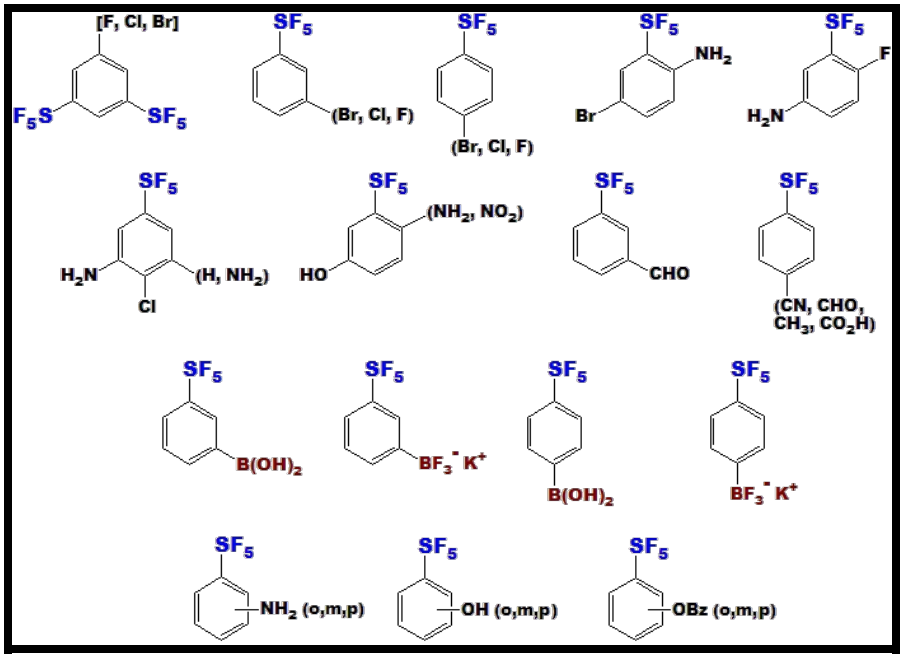
A new era in chemistry has begun, with the introduction of the first new functional group in over a century!

I {Lloyd Garrick} prepared the compounds below [*as well as many others not listed*] in 10-100 g. quantities as part of my Research and Process Development work at UBE America Inc., in Denver. The facility has been closed down as of August 2013. Research, Development and Production of these type compounds is no longer in progress in this country to any significant extent, as far as I know at this time.

The compounds were made either directly by the new process(es) from the appropriate thiol or disulfide starting material, or, in many cases, by standard derivatizations of ring-fluorine containing compounds. Other common manipulations (nitration, metalation, methyl oxidation), were also used; *SF_5 is inert to all but the most drastic reaction conditions*.

In addition, I have a number of new research ideas which, if successful, would be improvements even on these "new" procedures, and would also skirt the patents. They haven't been tested yet; I need a lab!

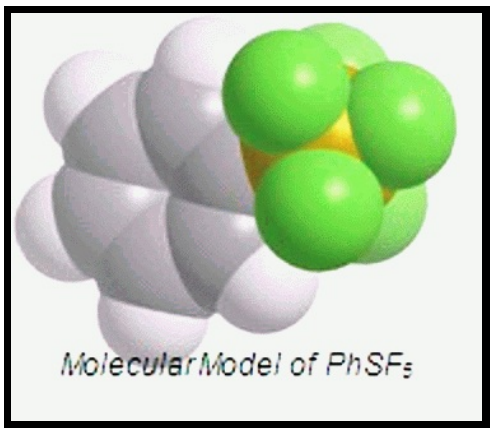




Introduction:

Concurrent with significant developments in the synthetic methodology for the preparation of SF_5 containing compounds, many potential applications, derived from the interesting and unique properties of the SF_5 function, have been proposed, particularly in certain advanced specialty chemical fields such as pharmaceuticals, agrochemicals and electronics.

The SF_5 function, ***one of the most electron-withdrawing groups known, imparts outstanding lipophilic properties*** to compounds which incorporate it, as well as added chemical and thermal stability. It is expected that the higher lipophilicity and other properties of SF_5 compounds will show ***interesting and unique influences*** on biological activities other than those observed with fluorine or trifluoromethyl-groups.



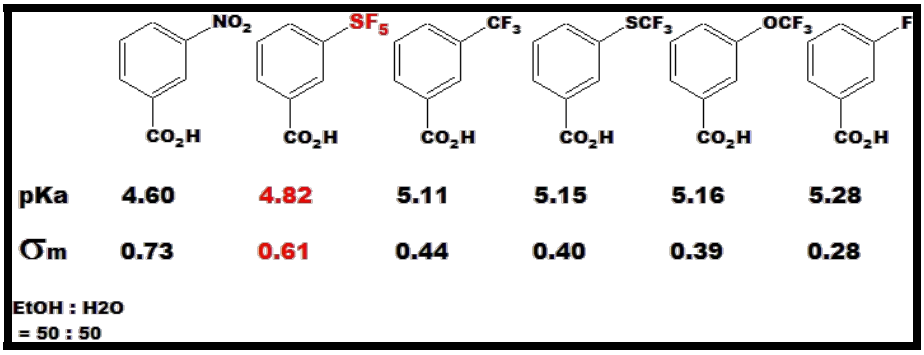
Regarding electronics chemicals, it is reported that there has been a ***rapid increase in the number of patents which list the SF_5 group in liquid crystals due to the strong dipole moment*** which can be achieved by the SF_5 group.

Properties of Aromatic SF_5 compounds:

SF_5 group is called "**Super-trifluoromethyl group**", and the expected properties of SF_5-containing compounds are similar to the ones which are seen in general fluorine compounds, although most of them are significantly enhanced by the increment of the number of fluorine atoms in SF_5 group.

Electron-withdrawing Effect

SF_5 group is recognized as a strong electron-withdrawing group. Figure below shows the comparative values of pKa in the substituted benzoic acid derivatives which have SF_5, CF_3, SCF_3, OCF_3 and F, respectively. The SF_5 derivative is ranked as the second strongest group after the nitro-substituted one.



Lipophilicity

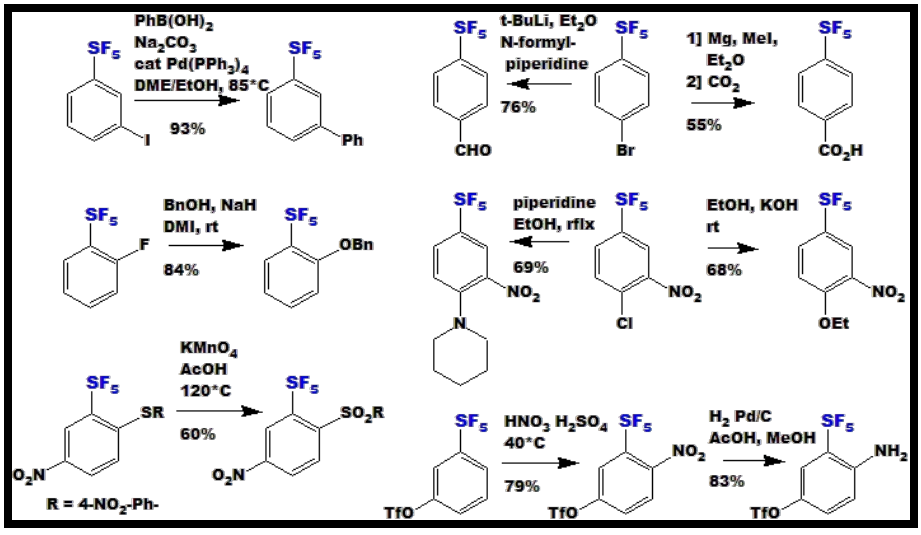
It is well known that compounds which incorporate fluorine(s) show greater lipophilicity. SF_5 substituted compounds are expected to show excellent lipophilicity compared with other fluorine-containing compounds. The lipophilicity indices of several functional groups are shown below. These values are calculated by formula from the Xow-values (octanol/water partition coefficient).

In particular in agrochemistry [agricultural chemistry, compounds such as herbicides, fungicides, insecticides, plant growth regulators, etc.] this quality of lipophilicity is often exploited, as it is very important. Many examples of agents bearing CF_3, OCF_3 and SCF_3 groups are in use or still being developed. Illustrative examples are displayed elsewhere on this page.

Substituent X	t-Butyl	SCF_3	SF_5	OCF_3	CF_3	Cl	CH_3	SO_2CF_3	F	H	NO_2
π_p	1.68	1.44	1.23	1.04	0.88	0.71	0.56	0.55	0.14	0.00	-0.28

Thermal and Chemical Stability

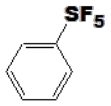
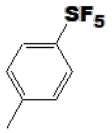
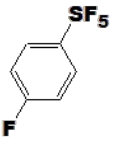
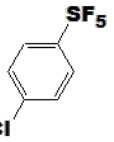
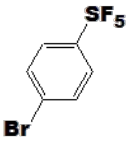
Aromatic SF_5 compounds possess excellent thermal and chemical stability. For example, it was demonstrated that the thermal decomposition rate of $PhSF_5$ (PSF) was less than 20% after it was heated in a sealed tube at 400*C for 7 hours. It was also demonstrated that ***aromatic SF_5 compounds are more tolerant than aromatic CF_3 compounds under strong conditions of Bronsted acids and bases***, and can be widely applied for common synthetic transformations in high yield. Examples of reactions for Aromatic SF_5 compounds are shown below.



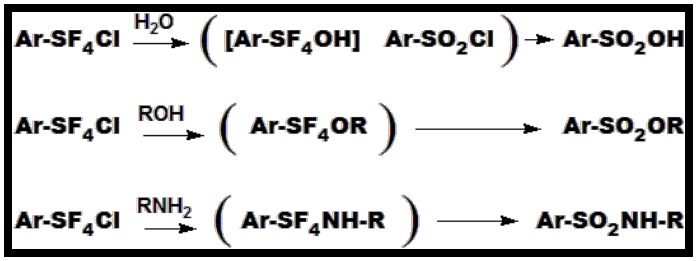
Toxicity

Regarding the assessment of toxicity of Aromatic SF_5 compounds, the aromatic SF_5 compounds shown below were assayed for both Ames and Acute Oral Toxicity. Table below shows both results including the empirical data obtained from the Acute Oral Toxicity test. 4MPSF showed weak toxicity, with range 50-300mg/Kg and ranked as Category 3 in UN GHS. This, and other data so far, have shown that SF_5 has little (if any) intrinsic toxicity, and it isn't metabolized. ***Thus it should be a significant improvement in bioactive compounds, where it can replace toxic groups like NO_2, Br and CN***.

Safety Testing of Aromatic SF_5 Compounds; AMES Tests

NAME	PSF	4MPSF	4FPSF	4CPSF	4BPSF
STRUCTURE					
AMES TEST	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE
Acute Oral Toxicity (Rat): LD_{50}	>2000 mg/Kg	50-300 mg/Kg	>2000 mg/Kg	300-2000 mg/Kg	300-2000 mg/Kg

ALL of the Chloropentafluorosulfanate compounds **[Ar-SF_4Cl]**, even the crystalline solids, are ***extremely noxious !*** They have strong, penetrating, persistant, irritating ***mustard*** like odors. If/When you succeed in making any, ***you will know it !*** *Skin contact will produce irritation and blistering*. They are not "alkylating agents" in the classical sense, but rather "sulfonating agents" as depicted in the equations just below.
Electron ***withdrawing*** groups on the ring tend to make the compounds ***more*** **stable** and ***less*** **reactive**; electron ***donating*** groups have the opposite
effect of course.



In contrast, the Pentafluorosulfanate **[SF_5]** compounds are **quite pleasant**. The inert SF_5 substituent gives it's molecules crystallinity, volatility, stability, and *a host of other pleasant attributes*, including odor. $PhSF_5$ is a dense (1.55) liquid with an odor between toluene and lemon juice. Many of the solids and polyfunctional SF_5 compounds resemble camphor, mint, clove, etc.

Hydrolytic Stability and Physical Characteristics

- $ArSF_5$ can be held for 4 hours at 100*C in 1N NaOH without measurable hydrolysis, whereas $ArCF_3$ is well known to be succeptible to alkaline hydrolysis, especially if ortho or para to a ring hydroxyl.
- In a 2.0 N NaOH solution at room temperature, 4-CF_3-aniline readily hydrolyzed whereas 4-SF_5-aniline was recovered in high yield (91%).
- $ArCF_3$ in conc. H_2SO_4 at 90*C is completely hydrolyzed within minutes. Under similar conditions [such as my nitration reactions on $PhSF_5$], no significant hydrolysis occured; mono-nitration product(s) always recovered in ~quantitative yield.
- Although SF_5 appears to be stable to even strong alkaline condiditons, very vigorous acid conditions will hydrolyze it; for example, $ArSF_5$ in 90% HNO_3 / 30% Oleum at 80*C for 4-7 days [my reaction for di-nitration of $PhSF_5$] gave about 60% hydrolysis to the sulfonate, and product(s) recovered were about 40%.

- **The volume of SF_5 is larger than CF_3 and slightly smaller than tert-butyl:**
  Lentz&Seppelt, In Chemistry of Hypervalent Compounds, K. Akiba(Ed.), Wiley-VCH, New York, 1998, 295
- **The SF_5 group is more electronegative than CF_3:**
  Sæthre, Berrah, Bozek, Børve, Carroll, Kukk, Gard, Winter&Thomas, J.Am. Chem. Soc. 2001,123, 10729;
  Wipf, Henninger&Geib, J. Org. Chem. 1998, 63, 6088
- ***Unlike CF_3*, the SF_5 group is *very stable* under strong acid and basic conditions:**
  Bowden, Comina, Greenhall, Kariuki, Loveday&Philp, Tetrahedron 2000, 56, 3399
- ***The utility of SF_5 derivatives in drug discovery*** was recently showcased by Wipf and coworkers in the design of improved Mefloquine:
  Wipf, Mo, Geib, Caridha, Dow, Gerena, Roncal&Milner, Org. Biomol. Chem. 2009, 7, 4163

Biological Activities

Organopentafluorosulfanyl Chemistry

The pentafluorosulfanyl (SF_5) group is one of only a very few truly new functional groups to be introduced to the armentarium of the synthetic organic chemist in the last 100 years. The pseudooctahedral symmetry of the SF_5 group, presenting a square pyramid of electron density, as defined by the fluorine ligands, is not otherwise known to the medicinal or pharmaceutical chemist. However only with the recent availability of the necessary reagents and building blocks has this functional group found applications as an aromatic substituent in agrochemicals, pharmaceuticals and liquid crystals. In aliphatic chemistry, pentafluorosulfanylated materials are even more rarely encountered with applications largely limited to polymer or oligomer preparations. The SF_5 group is profoundly electron withdrawing but with the highly polarizable carbon-sulfur bond may directly influence reactivity in a manner different from that associated with the trifluoromethyl group.

Treflan Analogs

The synthesis of 2,6-dinitro-4-pentafluorosulfanyl-*N,N*-dipropylaniline, **2**, was achieved in a straightforward manner from commercially available 1-nitro-4-pentafluorosulfanylbenzene. In post-emergence screening **2** was found to be approximately twice as potent as trifluralin with the same general spectrum of activity. In contrast, in pre-emergence tests, **2** was nearly 5 fold more potent against quackgrass and crabgrass.

References

- **Synthesis and Herbicidal Activity of a Pentafluorosulfanyl Analog of Trifluralin**
  D.S. Lim, J.-S. Choi, C. S. Pak and J. T. Welch, *J. Pesticide Science*, **2007**, in press
- **pentafluorosulfanyl analog of trifluralin ref 1**
- **pentafluorosulfanyl analog of trifluralin ref 2**

Serotonin Analogs

The trifluoromethyl group of fluoxetine and fenfluramine and norfenfluramine was substituted by the pentafluorosulfanyl group. On examination of the efficacy of the pentafluorosulfanyl containing compounds as inhibitors of 5-hydroxytryptamine receptors, it was found that substitution could lead to enhanced selectivity and in the case of the pentafluorosulfanyl analog of fenfluramine, led to significantly enhanced potency against the 5-HT_{2b}, 5-HT_{2c} and 5-HT_6 receptors.

References

- **The synthesis and biological activity of pentafluorosulfanyl analogs of fluoxetine, fenfluramine and norfenfluramine**.
  J. T. Welch, D. S. Lim, Bioorg. Med. Chem. 2007, 15, 6659.

Antineoplastic Agents:

Much potential for **SF_5** exists in the field of chemotherapy, and it is largely unresearched (ie., *wide open*) right now. It is well known that the internal environments of neoplasms (tumor cells etc.) are particularly lipophilic; thus the **SF_5** function, as it confers strong lipophilic character to molecules incorporating it, should offer considerable improvement in these therapeutics, particularly those that target neoplasms in lipophilic tissues and environments, such as brain and CNS.

References

- **Bis(pentafluorosulfanyl)phenyl azide as an expeditious tool for click chemistry toward antitumor pharmaceuticals #1**
- **Bis(pentafluorosulfanyl)phenyl azide as an expeditious tool for click chemistry toward antitumor pharmaceuticals #2**

Cannabinoid Receptor Ligands:

An array of cannabinoid ligands, bearing meta- and para-substituted pentafluorosulfanyl (SF_5) aniline groups in position 3 of the pyrazole ring, was efficiently synthesised and ***compared with the exact trifluoromethyl and tert-butyl analogues***.

In general, the SF_5 substituted ligands showed **higher lipophilicity** (i.e. log P values) than the CF_3 counterparts and *lower* lipophilicity than the tert-butyl ones. In terms of pharmacological activity, SF_5 pyrazoles generally showed ***slightly higher or equivalent*** CB1 receptor affinity (Ki), always in the nanomolar range, and selectivity towards the CB2 ***relative*** to both CF_3 and tert-butyl analogues. Functional ß-arrestin recruitment assays were used to determine equilibrium dissociation constants (Kb) and showed that all of the tested SF_5 and CF_3 compounds are CB1 neutral antagonists.

These results **confirm** the possibility of ***successfully using an aromatic SF_5 group as a stable, synthetically accessible and effective bioisosteric analogue of the electron-withdrawing CF_3 group***, and possibly also of bulky aliphatic groups, for **drug discovery and development applications**.

References

- **The pentafluorosulfanyl group in cannabinoid receptor ligands:
  synthesis and comparison with trifluoromethyl and tert-butyl analogues**.

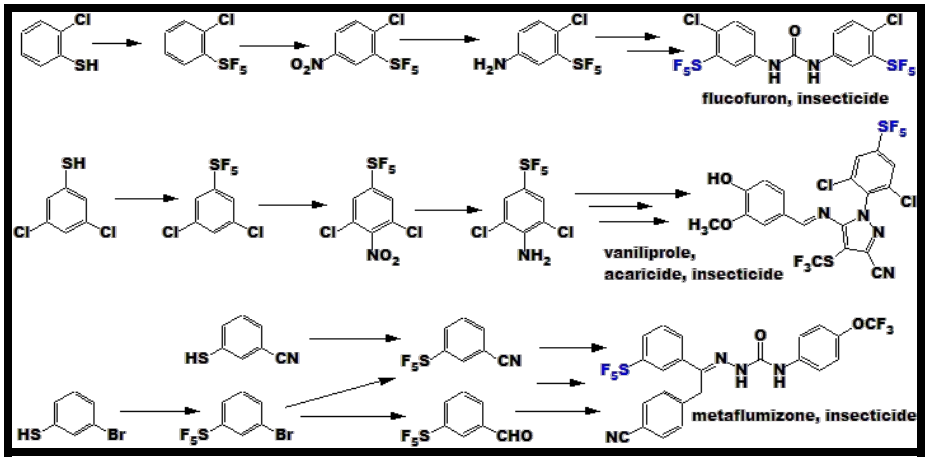
Agricultural Compounds

The SF_5 moiety should find considerable utility in the agricultural (herbicide, pesticide, insecticide, fungicide etc.) sector, perhaps more so *and sooner* than in pharmaceuticals, as SF_5 will confer many desired properties to these bio-active molecules, and they do not require the lengthy (and expensive) trials mandated with compounds for human use.

References [I'll be adding more as I find them]

- **Herbicide**

There are ***many*** examples of agricultural compounds now in use or being developed, which employ the CF_3 function, or Cl, Br, etc., where a large electronegative lipophilic group is needed. It is a ***virtually certain bet*** that replacement of these group(s) with **SF_5** would yield a ***much better and more potent compound***. Agricultural compounds are also usually simpler than human pharmaceuticals; the chemistry is thus more direct and simple. Some contemporary examples are shown just below, also the Fipronil example a little further down:

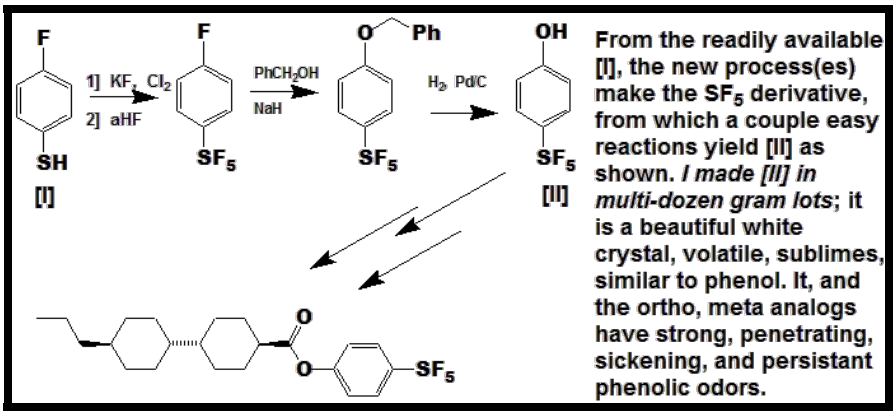


Liquid Crystals

Another wide open area of research with much growth potential; the SF_5 group imparts a strong crystalline nature to compounds, they also tend to be lower melting and more volatile than one would expect from the molecular weight; in addition, the SF_5 substituent can impart a very strong dipole moment to a molecule, critical for liquid crystals:

References

- **Liquid crystalline medium and liquid crystal display**
- **Liquid Crystals Based on Hypervalent Sulfur Fluorides: Pentafluorosulfuranyl as Polar Terminal Group**



High Tech and Specialty Polymers; other Chemistry uses

Some research has been done, much more is needed, as this area offers much promise for thermally and chemically stable polymers; the SF_5 group, due to it's tendency to impart strength and crystallinity to it's compounds, may also have value in high strength polymers.

References

- **SF_5 incorporated into polymers**
- **3,5-Bis(pentafluorosulfanyl)phenylboronic acid:**
  A new organocatalyst for Conia-ene carbocyclization of 1,3-dicarbonyl compounds having terminal alkynes
- **SF_5 and conducting polymers**

Environmental Considerations

Since SF_5 does not occur in nature, it is rationally expected that there are no enzyme systems to handle it, nor any general bio-metabolic mechanisms to deal with it. This, along with it's extreme chemical inertness, might suggest that SF_5 would build up in the environment and accumulate.

However, some research has already been done, and more will be in the future. What has become known at this time is that SF_5 does indeed break down in the open environment, particularly under the influence of sunlight.

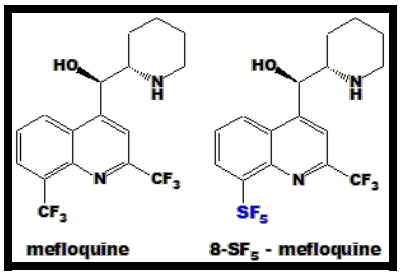
The products formed are the corresponding sulfonate ($ArSO_3H$) compounds (generally innocuous), and HF (instantly buffered to fluoride, which is ubiquitous in nature anyway).

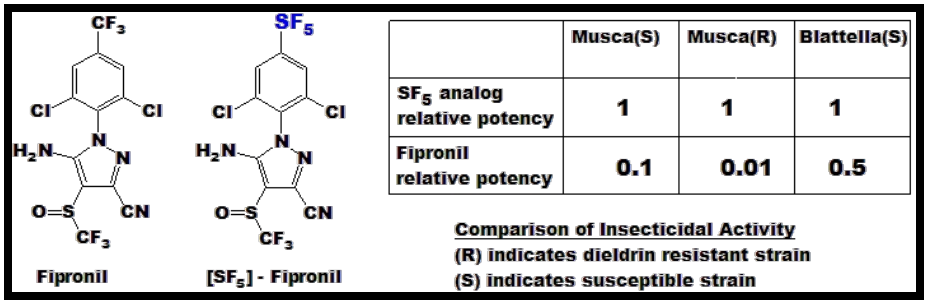
References

- Environmental properties of pentafluorosulfanyl compounds: physical properties and photodegradation
- Environmental Toxicology and Chemistry - Wiley Online Library

Currently, the introduction of fluorine into organic molecules has become very common methodology in biomedical fields, and numerous fluorine containing molecules have been developed and many have shown significant promise and advantages in this field.
In particular, ***the pentafluorosulfanyl (SF_5) group, which is a highly fluorinated functional group, has shown remarkable activity in biochemical molecules***. The introduction of the SF_5 group brings not only the novel properties which originate from Fluorine element (Strong electronegativity, high lipophilicity and high chemical stability) to the molecule, but also a larger steric effect than the CF_3 group, which is also recognized as a highly fluorinated functional group. The relative steric demand of the SF_5 group is slightly less than that of a tert-butyl group and considerably larger than that of a CF_3 group. Examples of biological activities comparing the CF_3 substituted agent vs. the SF_5 analog are shown below;

Mefloquine is used for both treatment and prophylaxis of malaria. 8-SF_5-Mefloquine showed a ***longer half-life***(68h) than Mefloquine(23h) after administration to mice. **Fipronil** is a broad spectrum insecticide. The SF_5 analogue of Fipronil was not only ***more active*** than Fipronil but showed ***no loss of potency*** towards the resistant strain of housefly, *in contrast* to the Fipronil.

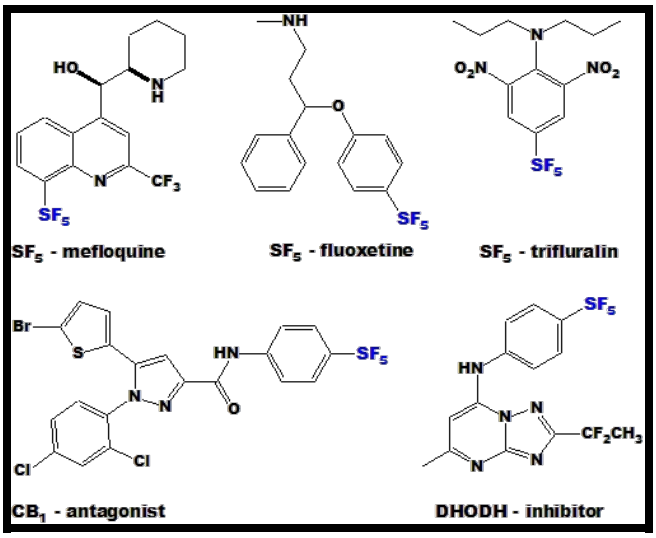




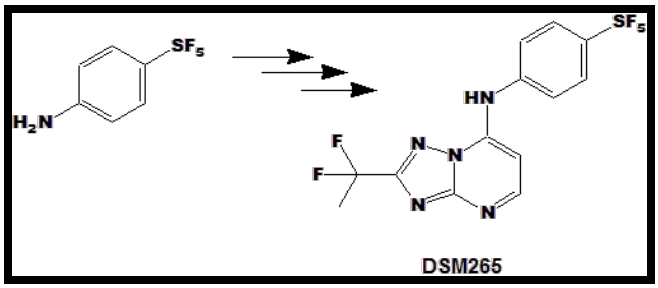
	Musca(S)	Musca(R)	Blattella(S)
SF_5 analog relative potency	1	1	1
Fipronil relative potency	0.1	0.01	0.5

Comparison of Insecticidal Activity
(R) indicates dieldrin resistant strain
(S) indicates susceptible strain

These 5 are examples of SF_5 analogs of current bio-active compounds, ***all of which are better than the originals***:



A new anti-malarial drug (DSM265), very promising so far and currently in clinical trials, contains a p-SF_5-anilino substituent as shown:



The synthesis [see DSM265 links just below] involves replacement of chlorine on the triazolopyrimidine ring with

para-amino phenyl pentafluorosulfanate, a compound **I made in 50 gr. lots** (new process),
but which is *now only available in gram quantities and prohibitive price* (old/current procedures).

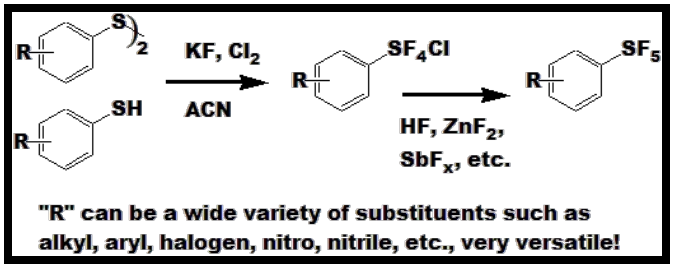
This is a perfect example of how a new and very promising drug will (would) be **prohibitively expensive** if it employs the SF_5 function ***now***, but with the new SF_5 processes will be ***much cheaper and more available*!** Also, SF_5 *building blocks will be cheaper and more readily available* thus **enabling more research into novel pharmaceutical (and agricultural) candidates!**

More links concerning bio-active compounds; CF_3 vs. SF_5 :

- Dopamine Receptor Research patent
- Direct Comparison, CF_3 and SF_5
- Pentafluorosulfanyl compounds; manufacture and use as pharmaceutical agents
- Structures of new Anti-Malarial Candidates
- DSM265 Structure-guided lead optimization
- DSM265 chemistry

The New Preparation Methods

In order to contribute to and improve SF_5 chemistry above, UBE has started to deliver a series of aromatic pentafluorosulfanyl compounds prepared by new innovative processes including our KF/Cl2 method, which was developed by IM&T Research Inc.



Our patented KF/Cl_2 method is widely applicable to various aromatic disulfide compounds, which are direct starting materials for the corresponding aromatic SF_5 compounds. This has enabled us to introduce the SF_5 group into various aromatic rings via a ***two step*** process from the corresponding aryl-disulfide, as compared to the direct fluorination process utilizing elemental fluorine, which is limited by the use of only nitro-aryl compounds as starting materials.

With the KF/Cl2 process, aryl-disulfide is converted to the corresponding aryl tetrafluorosulfanyl- chloride. This process is equally applicable to aromatic thiophenol compounds. The obtained Aryl-SF_4Cl from the KF/Cl_2 process can then be converted to the corresponding aryl-pentafluoro-sulfanyl compound with zinc difluoride or anhydrous HF. Aryl-SF_4Cl preparation proceeds with high yield around 80-90% at room temperature, and the starting materials provided for this reaction, aryl-disulfide, KF and Cl2, are commodity materials, which can be obtained conveniently and at relatively low prices for industrial scale production.

The conversion to Aryl-SF5 from the corresponding Aryl-SF_4Cl, proceeds with high yield (around 70-80%) with zinc difluoride at 100*C, and it also has been demonstrated that this reaction proceeds with aHF in high yield (70-75%) below 20*C. ***Certain other metal fluorides, and mixtures thereof, have been found to work as well***.

The following links will take you to the detailed descriptions of the new procedure(s)
:

The original paper detailing the processes can be accessed *here*.

This UBE patent details the procedure(s) for the *poly-functional SF_5 compounds*. I must point out here that *I did all of the hands-on lab work and development*, not most of it, *all of it*, 100%. Due to UBE policies and legal technicalities, my name is not listed; only the author of the original concept is credited. And the same deal with this one. [Yes, that sucks, but it is the real world]

In addition, I have some new research ideas which would not only ***improve even the existing new process significantly***, *but would* ***also skirt the existing patents*** - all I need is a lab to develop the **"new process"!**
[And as I no longer work for UBE, I can thus work for *you* !]

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Incorporation of SF_5 into Explosives and High Energy Compounds and Molecules

As a part of continuing research for energetic materials that combine high performance with low vulnerability toward accidental detonation, the effect of introduction of the pentafluorosulfanyl (SF_5) group on the properties of explosive nitro compounds has been reported. This is based on the fact that more energy is released due to the formation of HF in the detonation of SF_5 explosives.

It is also well - established that substitution of H by F in hydrocarbons leads to a significant increase in density. It implies that SF_5 group would provide nitro explosives with higher density or, in other words, improved performance, as explosive "power" is proportional to the *square* of the compound density. To illustrate, $PhSF_5$ has fully *twice the density* of the analogous $PhCH_3$ (toluene).

Based on these assumptions, some polynitro SF_5 explosives have been designed and their performance predicted which is in agreement with their actual performance. The initial experiments of Sitzmann et al. support the hypothesis that ***the SF_5 group may provide explosives with improved properties: increased density, increased insensitivity and increased energy coupled with better thermal stability*** – a unique combination of properties. Some examples of dense, thermally stable, impact insensitive polynitro*aliphatic* explosives with SF_5 groups are:

$SF_5CH_2CO_2CH_2C(NO_2)_2F$ density 1.86 gcm-3
$SF_5CF_2CF_2CF_2SF_5$ density 2.04 gcm-3
$(SF_5)_2NCF_2CH_2SF_5$ density 2.13 gcm-3

Corresponding work with aromatic compounds, although limited at this time, has given similar results; this is a wide-open area for research now, and the new production processes for aromatic SF_5 compounds will be applicable.

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Recently, there has been increased interest regarding the incorporation of the SF_5 group into energetic materials. It is known that **the inclusion of SF_5 generally increases the thermal and chemical stability of organic molecules**, and in addition to this, it has been demonstrated that **the presence of SF_5 also will increase the density, and thus the performance of the energetic material**, as such performance is a function of the square of the density.

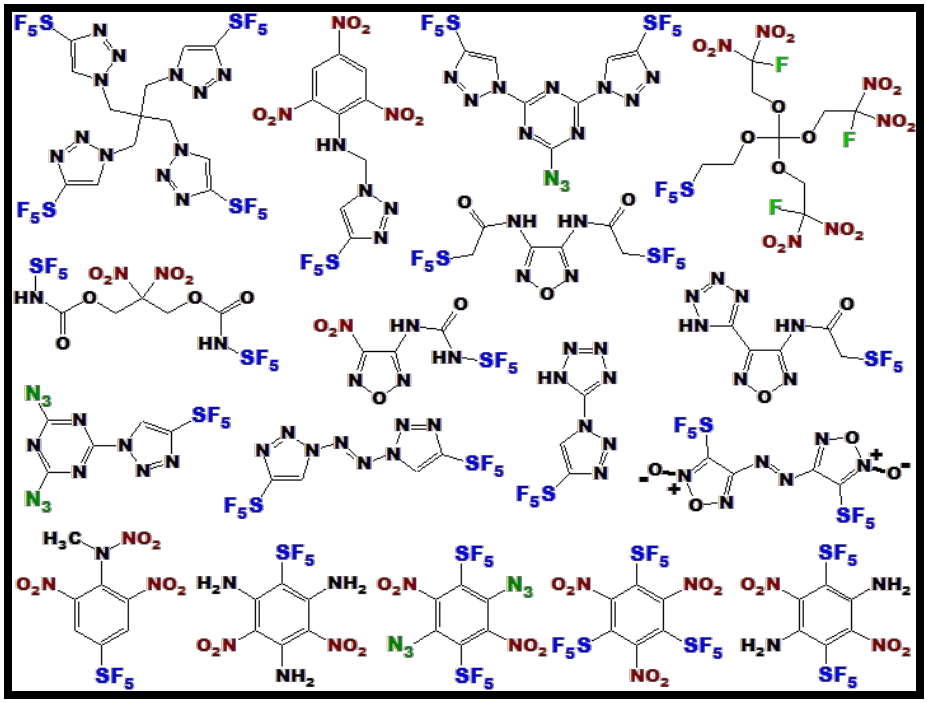
***The possibility of a higher density, larger energy release, and better thermal and chemical stability without increasing the sensitivity make the SF_5 group attractive in the synthesis of high energy materials*. (explosives).**

The high fluorine content along with the presence of hydrogen leads to the formation of hydrogen fluoride (HF) upon detonation, generating a large amount of energy. The S-F Bond Dissociation Energy (BDE) is 79 kcal/mol, while the BDE of H-F is 136 kcal/mol. Much energy is also released in the formation of C-F bonds, as well as Al-F, if aluminum (or other metal) is included in the formulation.

The formation of C-F, H-F or Al-F bonds, which have a higher bond dissociation energy (BDE) than the S-F bond in the pentafluorosulfanyl group, allows the release of large amounts of energy upon detonation. ***This combined with the possibility of higher density, higher thermal and chemical stability and low sensitivity makes the pentafluorosulfanyl group very attractive for the synthesis of high performance energetic materials*. (explosives).**

A large number of SF_5-containing energetic materials have been synthesized where the predicted performance is close to those for HMX, RDX and TNT, but with the benefit of lesser or no impact sensitivity.

Most of these are built up from triazoles, furazans, and other high-nitrogen/oxygen heterocycles, which, **if the corresponding thiol is available, would be *easily accessible by these new methods*, thus accelerating research efforts.**



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Chemistry; SF_5 in explosive compounds:

- Pentafluorosulfanyl polynitroaliphatic urea, monocarbamate, and dicarbamate explosive compounds
- Polynitroaliphatic explosives containing the pentafluorosulfanyl (SF_5) group: The selection and study of a model compound
- Recent Trends in New Energetic Materials
- 1,3,4-Oxadiazoles containing the pentafluorothio (SF_5) Group
- Pentafluorosulfanylnitramide Salts
- Pentafluorosulfanyl Polynitroaliphatic Urea Explosive Compounds
- Pentafluorosulfanyl Monocarbamate and Dicarbamate Explosive Compounds
- Pentafluorosulfanyl Carbamate Explosives
- High Energy Pentafluorosulfanyl Polynitroaliphatic Urea Monocarbamate and Dicarbamate Compounds
- Pentafluorosulfanyl-substituted-poly-123-triazole-compounds

EMAIL

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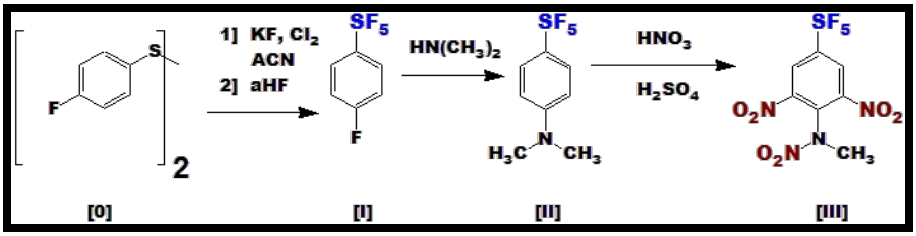
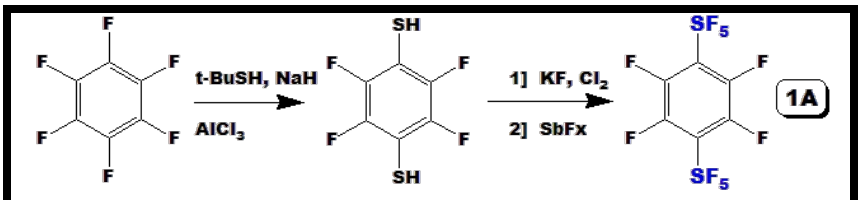
Following are some ideas for high energy compounds:



[III] is the SF_5 analog of TETRYL, which has a NO_2 instead. TETRYL is a very powerful secondary explosive, once in widespread use, but no longer as it is too unstable and sensitive.

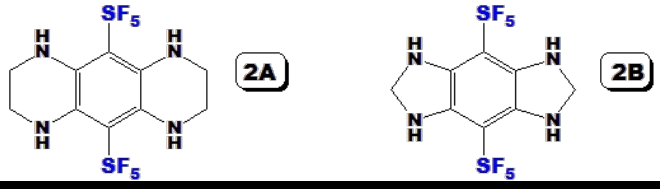
Since SF_5 is known to stabilize these types of compounds, [III] is reasonably expected to be a very powerful tertiary explosive, stable enough for use; *it's main advantage here is the ease of synthesis* !!!

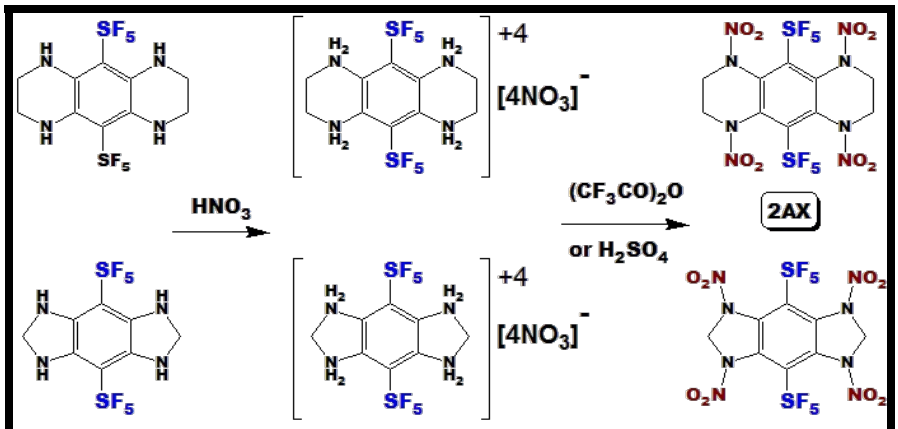
[I] is made from the readily available [0] by the new process(es), then reacted with dimethylamine to produce [II]. Substitution of fluorines on these SF_5 compounds by nucleophiles generally procedes well - I have done countless such reactions. Then, the activating and directing effects of the amine and SF_5 *enable nitration to procede under relatively mild conditions* (similar to the TETRYL reaction from dimethylaniline) to yield the product [III].



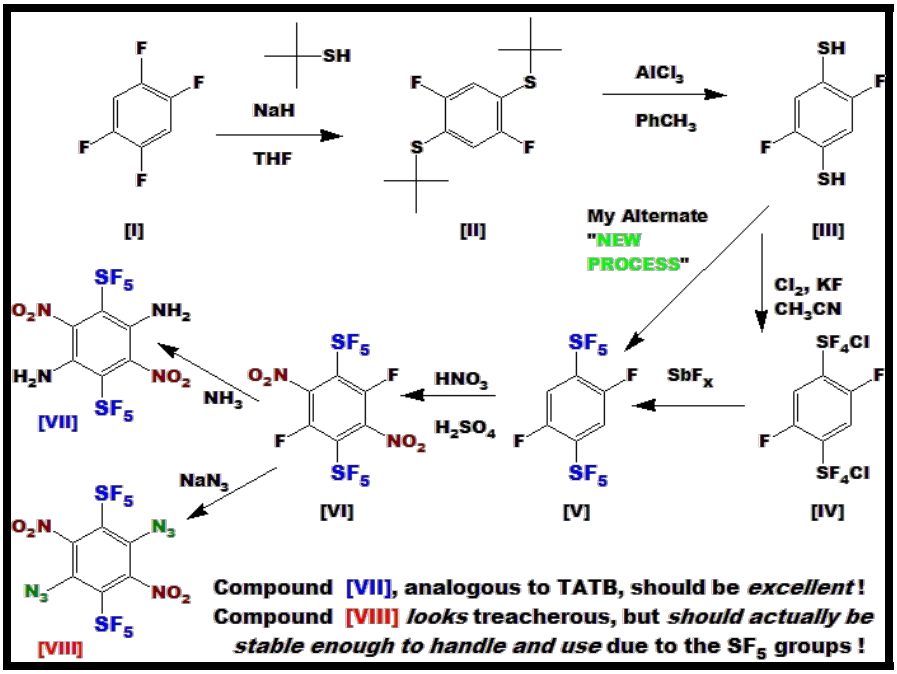
I believe I am the only one in the world (universe?) to ever have ever made compound [1A]. It is absolutely gorgeous! A volatile (sublimes like phenol) highly crystalline solid, readily sublimes. Odor like mint or camphor, colorless, looks like crushed diamonds! Seems to have a high R_f , as there are rainbows around the crystals, but I didn't have the equipment to measure that.

Now it shouldn't be too difficult to make the hexahydro-benzo-diimidazole or octahydro -pyrazino-quinoxalines as shown, since the fluorines are quite labile to nucleophilic substitution. I imagine the tetra-amine could be condensed with formaldehyde to form [2B], and a protected ethylene-diamine type reaction could form [2A]. I need a lab!





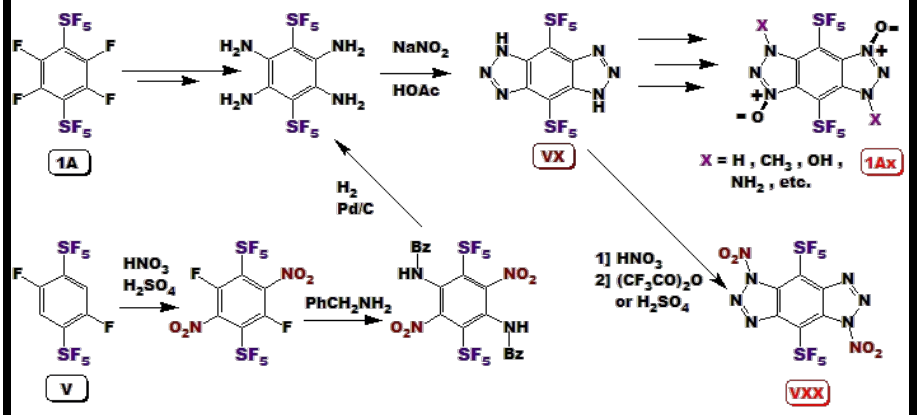
A good way to make nitroamines is to simply form the nitrate salt of the amine, followed by acid dehydration as shown. Both [2AX] and [2BX] should be very dense solids, very powerful explosive, and *more stable* than nitroamines (like RDX, HMX) usually are!



I have proceeded to the bifunctional compound [V] in good yield, it is a clear oil, pleasant odor.
The dinitration should be straightforward, I just haven't done it yet - I need a lab!

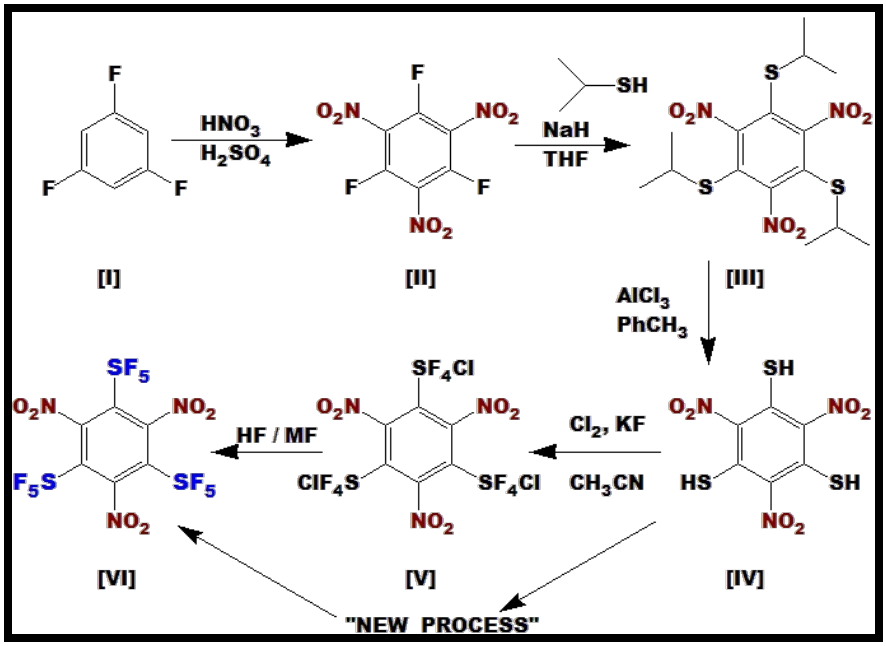
Compound [VII], analogous to the known and currently used TATB,
would be even *more* stable, and very likely *more* powerful !
***And lookie how EASY it is to make* !**

Here's another possibility for *pretty pretty* crystals of [1A] :



Although the path from [V] might actually work better. From the tetra-amine, make the triazole by the standard diazo type reaction.

[VX] should have a *pretty good kick* as it is; forming [1Ax] by making the amine oxide and perhaps functionalizing the NH bond would make it even better! Generating nitroamine [VXX] by acid dehydration of the nitrate salt would be even *better better*!!

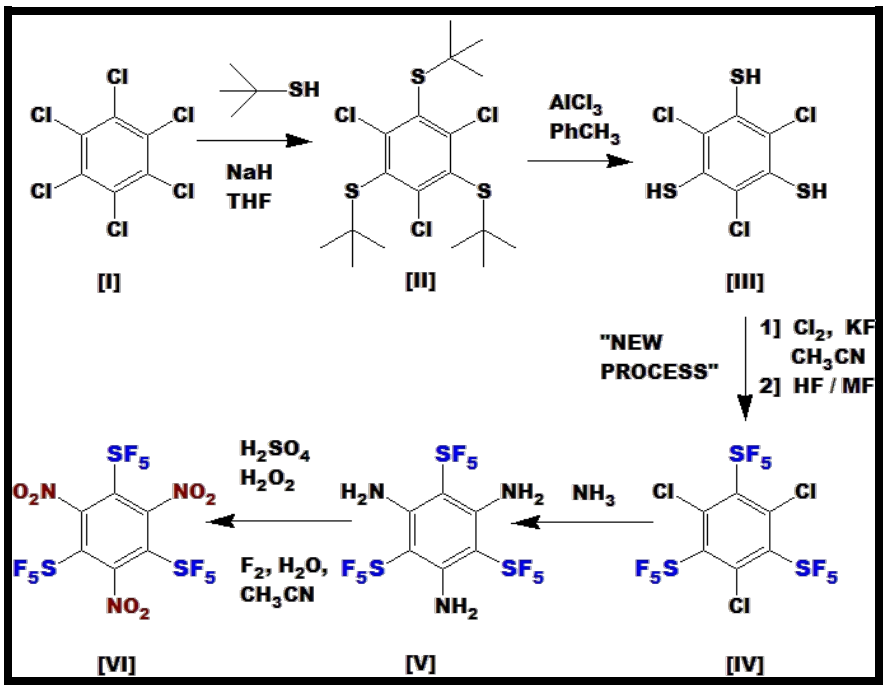


Compound [I] is commercially available; nitration to [II] should be easy, facilitated by the fluorines. Formation of [III] will be easy; I have done many such reactions. Deprotection reaction to [IV] would normally use catalytic (5 mol %) $AlCl_3$, however the nitro groups may coordinate also, thus stoichiometric quantity may be needed; alternatively, this deprotection can also be done with TFA or HF. The *new processes* can then form the SF_5 compound from the thiol.

Although nitration can easily be done *ortho* to SF_5, (I have done it), the converse is sometimes difficult. Steric effects can interfere with the formation of the intermediate SF_4Cl. *Don't know here* - I need a lab to find out!

Compound [VI] *should be very dense* due to the SF_5 groups and the symmetry; since explosive power is proportional to the square of the density, *this compound should be an extremely powerful explosive* - perhaps the best yet (non nuclear). It also has an excess of oxidant, thus it could be formulated with aluminum, titanium, magnesium, etc., further increasing the power.

I have several alternate approaches to this molecule. If I only had a lab .....

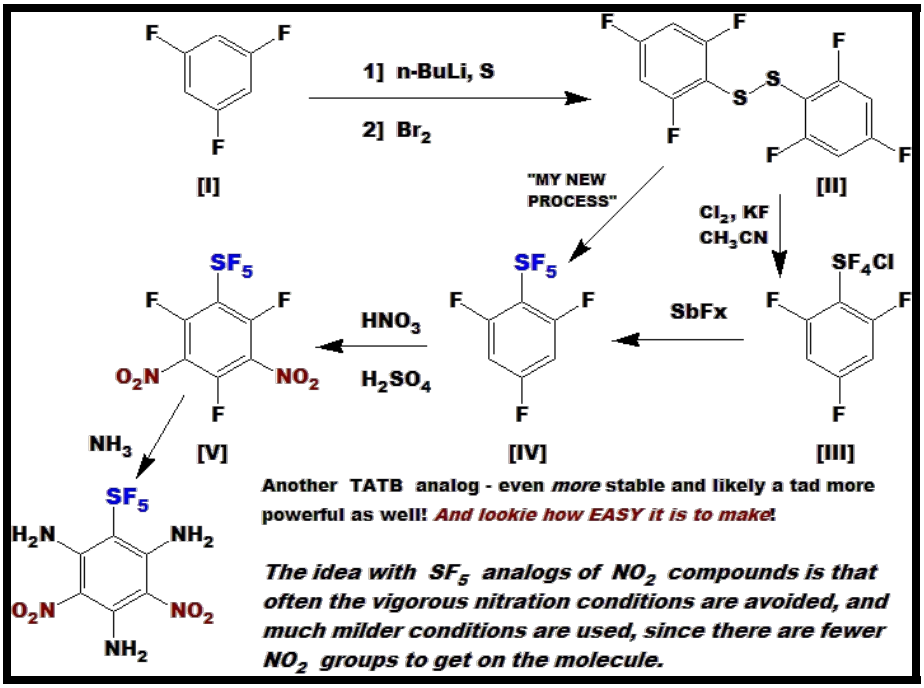


***Another way to do it*:**

Hexachlorobenzene is commercially available and cheap; hexafluorobenzene would actually work better, but it is more expensive. Hexabromobenzene would prevent the 3rd step (formation of SF_5) due to steric hindrance.

Proceeding to compound [III] would be uneventful – this reaction works quite well and I have done it countless times. The new UBE/Umemoto process (*or my new process*) would then make the trichloro tri(pentafluorosulfanyl) compound [IV].

Reaction with NH_3, possibly aided by NaH, should form [V]. This reaction works well with the analogous nitro compound; as SF_5 is similar to NO_2 in electronegativity, I expect it also to work here. Oxidation of amines to nitro is effected by the "persulfuric acid" mix; this drastic reaction condition *should not affect the rock-stable SF_5*. Alternatively, the much milder fluorine/acetonitrile/water oxidizer is known to effect this conversion well, I just haven't tried it yet – *I need a lab*!

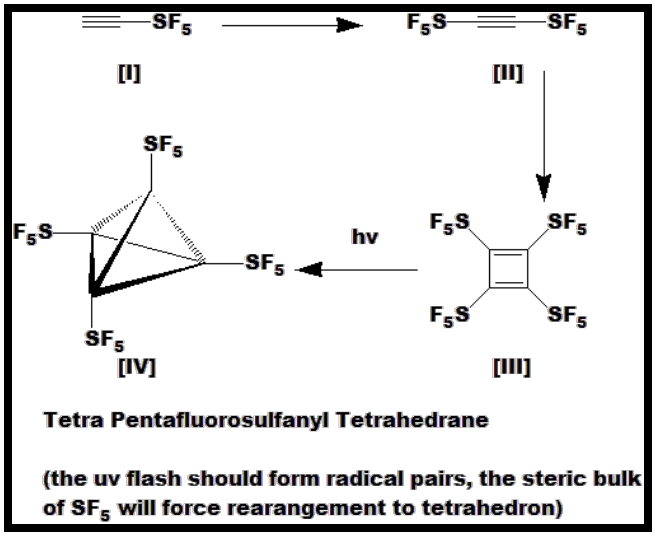


Compound [I] is commercially available also; I have made multi-dozen gram lots of [IV]. Like most of these compounds, it is a clear fragrant oil. The fluorines are activating and direct *ortho*, and there are three for additive effect. SF_5 is deactivating and directs *meta*; all effects point to the open positions, thus this dinitration should also be straightforward; again - I just need a lab!

I expect [V] to be a dense explosive solid, very stable also, perhaps difficult to detonate even.

The fluorines are very labile, and could easily be substituted with appropriate nucleophiles giving even better compounds. Some possibles are phenyl or triazine with ring nitros or azides, using an amine, hydrazine or diazo bridge. Heck - simple amine or hydrazine should work nice! Even azide! Compound [VI] might start looking real treacherous with these substituents, but remember - the SF_5 is stabilizing it!

.

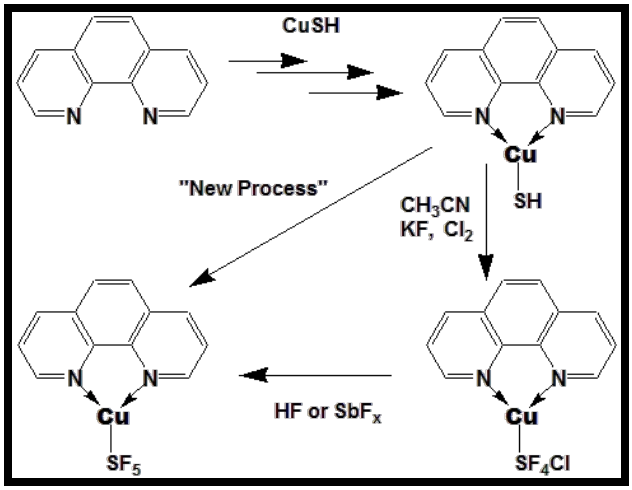


Tetra Pentafluorosulfanyl Tetrahedrane

[I] and [II] are known compounds; I haven't worked with them yet. They are made from $ClSF_5$. Et_3B, LiOH; addition/elimination reactions on unsaturated compounds. Many variations, and much room for improvement yet.

I don't know how to get from [II] to [III]; perhaps the right *cobalt* or palladium complex should do it; it looks like a simple [2 + 2]. [III] is of course *anti*-aromatic, thus unstable and prone to polymerization and decomposition, however, the electron pull of the SF_5 groups might stabilize it somewhat; if I can get it into the photolysis apparatus quick enough, a blast of 254 should create [IV].

I expect [IV] to be a dense, highly explosive solid; perhaps too unstable for practical uses; it may not be possible to exist at all. Currently, only the tetra-t-butyl-tetrahedrane has been made. Despite considerable effort, the tetra-nitro and parent compounds have eluded synthesis. The electron pull of the SF_5 groups would further weaken the already highly strained cage and might make this compound impossible. Don't know - *I need a lab*!



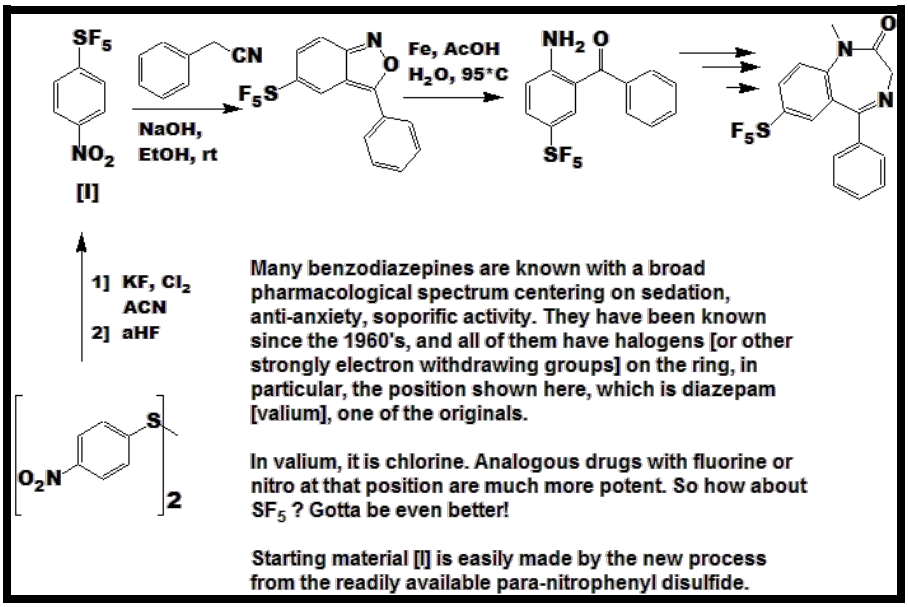
It's a longshot but I'd like to try it anyway!
The crazier it looks the more fun it is to play with.
We have trifluoromethyl transfer agents; how about a *pentafluorosulfanyl* transfer reagent!?

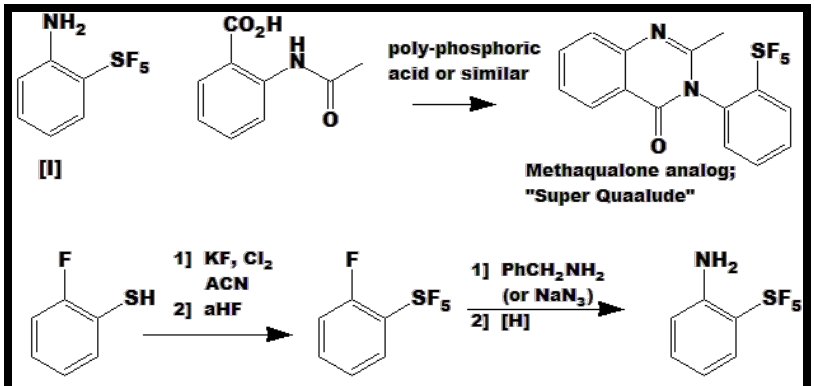
The two functions share many of the same characteristics, and copper likes bonding to sulfur - *it just might work*! [although I have never used the *new processes* on metal-sulfur bonded compounds - no idea what to expect], but isn't that what research is all about!?

Quite a number of currently marketed drugs [and more will be coming!) contain the CF_3 function; some examples are depicted below, with the CF_3 replaced by SF_5 to demonstrate hypothetical concepts.

Now here is an idea for bold, daring entrepreneurial spirited individuals and/or companies :

1. **Take any currently marketed drug [or agricultural compound] containing CF_3, make the SF_5 analog, and submit it as a new compound.**
2. ***It is a better than even bet* that it will be a *significantly better* compound, enough so that the FDA will accept it as such, and not just another "copycat".**
3. **Since *all* of the research, time, expense, and manpower *has already been done* on the "rest" of the molecule, *you will be spared that* !**
4. **And it is *unlikely* that the original patent(s) would cover the carbon-sulfur bond at that position, (but you will need to verify that to avoid legal issues).**
5. ***You get a fast-track short-cut one-up on the competition in the cut-throat competitive arena of drug development* !**
6. **I could do this myself, but as I said above - *I need a lab* !!!**



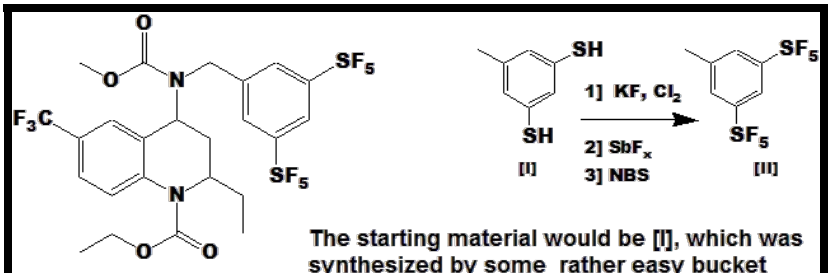


[I]

Methaqualone analog;
"Super Quaalude"

Methaqualone was developed as a soporific [sleep inducer]; it actually worked quite well as such, but was pulled from the market due to abuse issues. It has a methyl group in the 2 position on the ring. An analog with chlorine instead has the same profile, only more potent. A number of derivatives have been investigated with diverse substituents at that position. I believe the SF_5 analog might be interesting, certainly easy to make and try! It should be much more potent than the rather weak quaalude, maybe a better profile as well. We do need a good sleeping pill available.

Starting material [I] is a waxy orange solid, easily made by substituting a fluorine at that position as shown. The 2-fluoro thiophenol is commercially available.



Torcetrapib

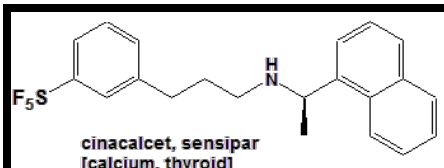
experimental;
hypercholesterolemia

[I]

[II]

The starting material would be [I], which was synthesized by some rather easy bucket chemistry from 3,5-dibromotoluene.

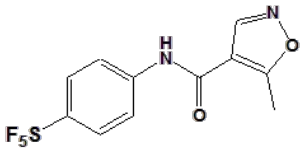
My (untested, I need a lab!) new procedure(s) are particularly adaptable to the poly-SF5 compounds.



cinacalcet, sensipar
[calcium, thyroid]

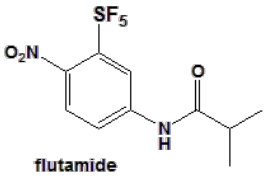
The starting material for this one would be the appropriate meta-alkyl phenylthiol, if possible substituted at the terminal position with halogen or amine synthon intermediate.

The KF/Cl_2/HF procedure is adaptable to a wide variety of substrates, the only real limitation is availability.



leflunomide, arava
[rheumatoid arthritis]

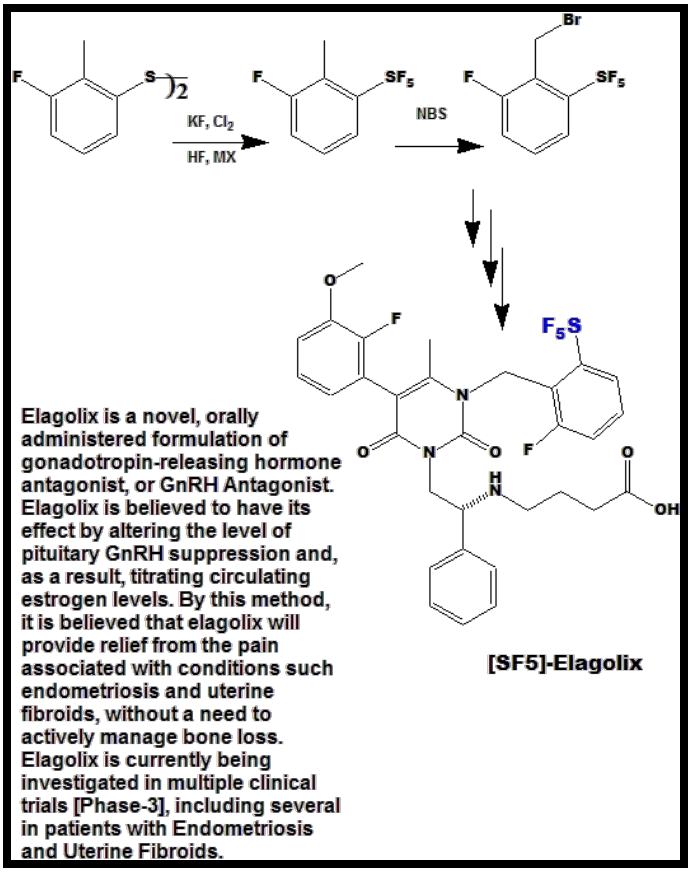
The starting material would be the para-amino phenyl-SF_5 compound. This orange amorphous solid is easily made by reduction of the corresponding nitro (see above); alternatively, the para-fluoro compound can be substituted with azide or benzylamine, also shown above.



flutamide
[prostate cancer]

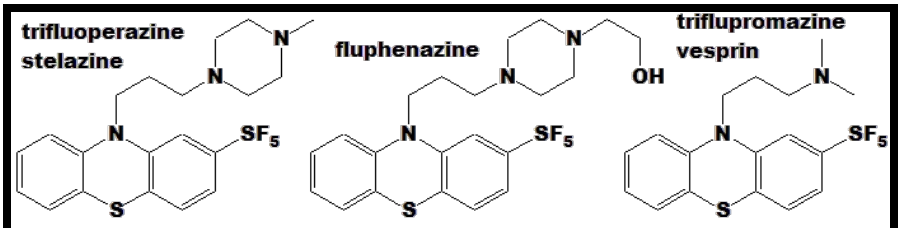
This might take a little research (ie., fun). The meta-fluoro phenyl-SF_5 intermediate should nitrate para to the fluorine; if so, the fluorine can be converted to amine as shown above. [most likely, an ortho/para mix would form; then need to be separated]. Best idea: direct nitration of compound with a suitably protected amine synthon function already present.

Generally, SF_5 can not be formed ortho to large groups like nitro or bromo, however, nitration is readily done ortho to an SF_5 if a suitable directing group is also present on the ring; this would be the angle to work for this synthesis.



Elagolix is a novel, orally administered formulation of gonadotropin-releasing hormone antagonist, or GnRH Antagonist. Elagolix is believed to have its effect by altering the level of pituitary GnRH suppression and, as a result, titrating circulating estrogen levels. By this method, it is believed that elagolix will provide relief from the pain associated with conditions such endometriosis and uterine fibroids, without a need to actively manage bone loss. Elagolix is currently being investigated in multiple clinical trials [Phase-3], including several in patients with Endometriosis and Uterine Fibroids.

[SF5]-Elagolix

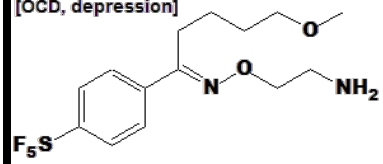


Phenothiazine drugs, of which 3 common examples are shown, again (as above) with their CF_3 functions replaced by SF_5, have been known for decades and are still widely used as neuroleptics, antidepressants, anti-schizophrenics, etc.

The original, chlorpromazine, has a chlorine in that 2 position. The des-chloro analog is very weak, essentially inactive. It has been shown that the electron withdrawing group pulls the side chain towards it; this alteration in the molecular geometry is essential for activity. So wouldn't SF_5 be super?! Needs to be investigated!

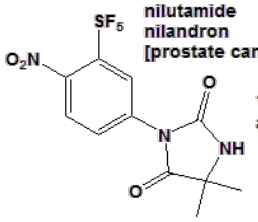
The starting material would be meta-anilino-phenyl-SF_5, easily prepared from meta-fluoro-phenyl-SF_5 and aniline by nucleophilic substitution. Then tie the rings together with sulfur and $AlCl_3$ or somesuch conditions. After that, alkylation and derivatization of the amine as desired.

fluvoxamine
[OCD, depression]



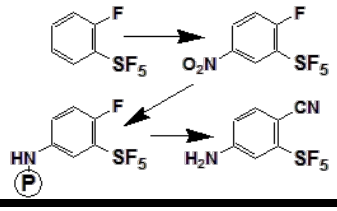
Current synthesis methods would require 4-(SF_5) aniline, 4-(SF_5) benzonitrile, or 4-(SF_5) benzoic acid. The aniline is described above; the benzoic acid can be obtained by oxidation of the analogous methyl compound, or as I did, by substitution of the para-fluoro compound with cyanide, followed by hydrolysis. The benzonitrile - that would be the intermediate in the benzoic acid reaction. Easy!

nilutamide
nilandron
[prostate cancer]

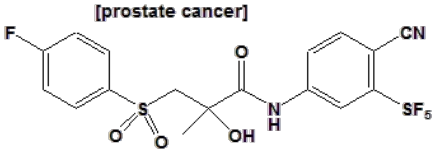


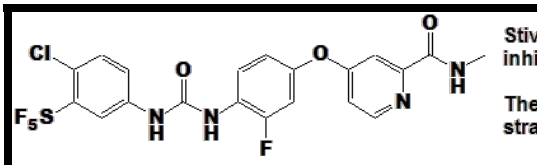
This looks like it would need the same starting material as for flutamide, see above.

For this starting material I would imagine a sequence something like this:



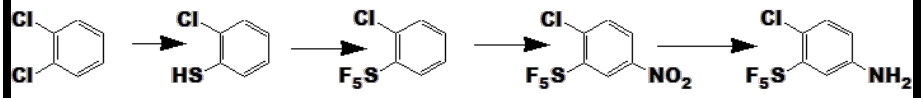
bicalutamide
casodex
[prostate cancer]

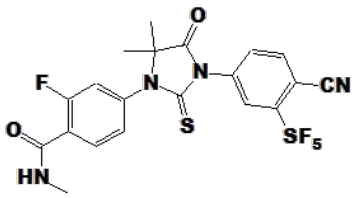




Stivarga - anti-angiogenic,multi-kinase inhibitor, antineoplastic.

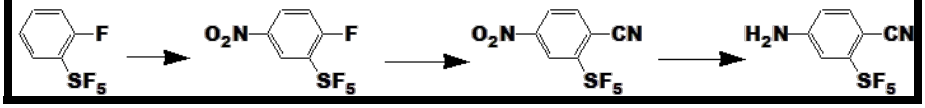
The starting material synthesized by straitforward chemistry as shown:

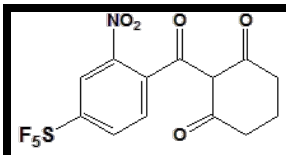




Xtandi - androgen receptor antagonist, prostate cancer.

Another easy, straitforward synthesis for this starting material:



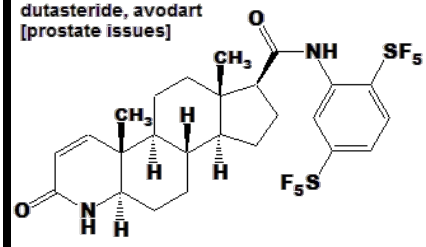


nitisinone, orfadin
[hereditary tyrosinemia type 1]

Here you would start with para-methyl-phenyl-SF_5, a dense liquid with a scent between toluene and lemon juice, which we made at UBE in kilo quantities.

Nitration ortho to the methyl (easy), followed by oxidation and derivitization of the methyl.

dutasteride, avodart
[prostate issues]

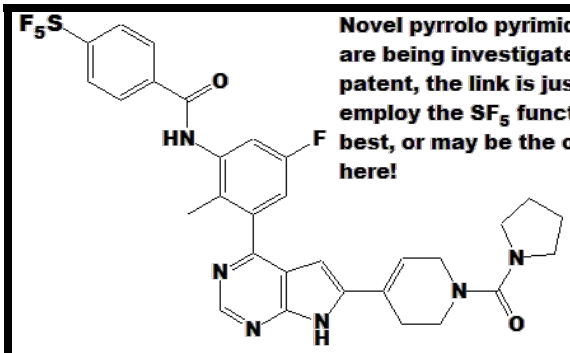


The marketed drug of course has two CF_3 functions, here replaced by SF_5 to illustrate.

ALL of the BI and TRI functional SF_5 compounds require strong reaction conditions - a peculiar concoction of HF and Antimony Fluorides.

However, my new (untested) procedures do away with HF and SbF_X ; I need a lab to check!

From phenyl 1,4-dithiol, available commercially (expensive!) or by synthesis (Easy! That's what I did), the KF/Cl_2/HF/MF process yielded Phenyl 1,4-Di(SF_5) in 70+% yield as a high melting white crystalline solid. I haven't actually tried it yet, but previous experience lets me think that mononitration should be no problem - just might have to kick it a little. Then reduction to the amine with H_2/Pd-C (works beautifully) gives the starting material.



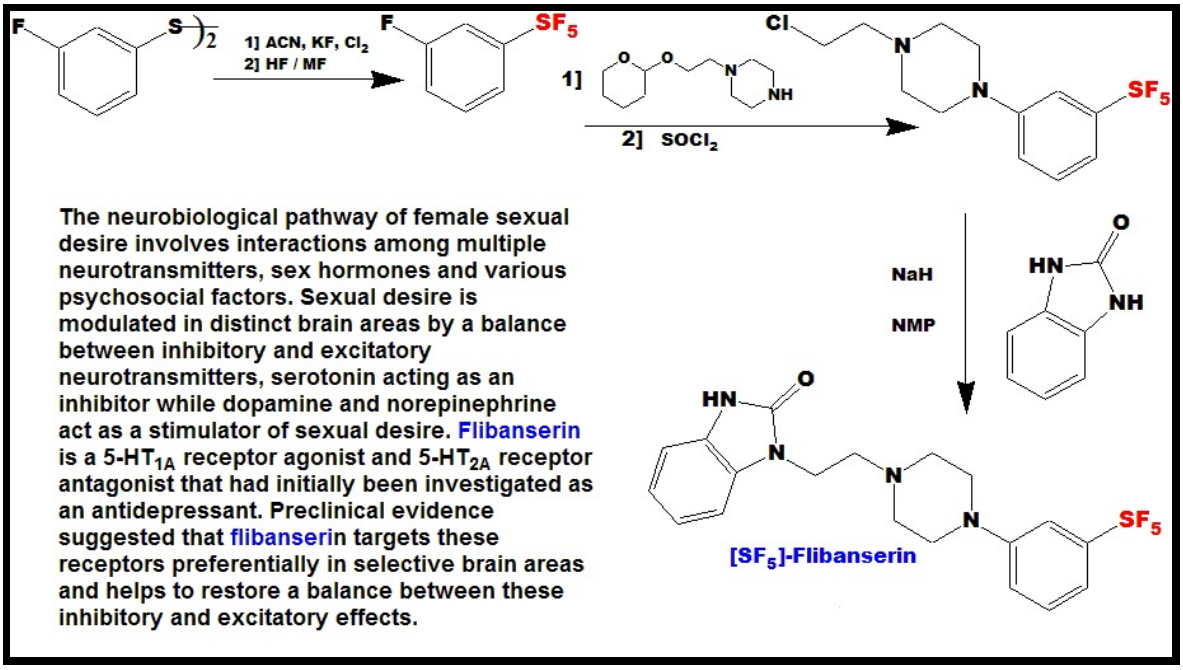
Novel pyrrolo pyrimidine derivatives such as this are being investigated ***now***; this is from a 2013 patent, the link is just below. They ***already*** employ the SF_5 function; presumeably it works best, or may be the only thing that works at all here!

These compounds appear to interact with Bruton's tyrosine kinase (Btk) and may be effective in the treatment of autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), transplant rejection, cancers e.g. of hematopoietic origin or solid tumors.

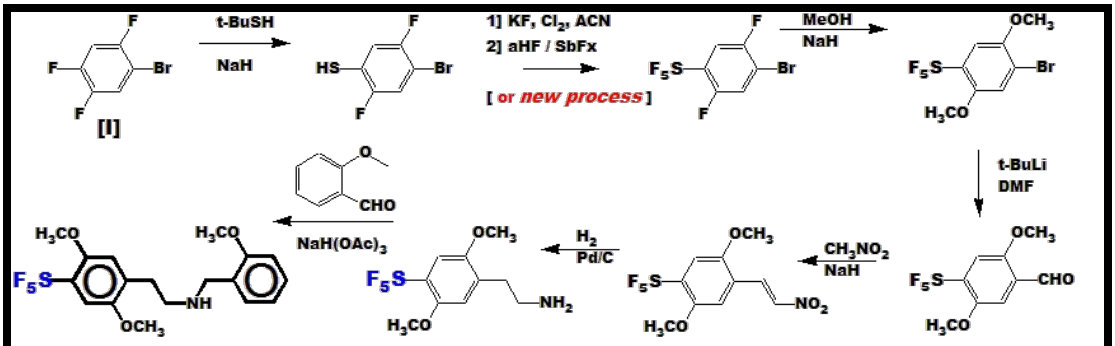
Thus you can see a very big pharmaceutical potential here! The starting material here is obviously the carboxylic acid (SF_5-Ph-CO_2H) which is easily made as described above for fluvoxamine.

See the full WO 2013008095 A1 patent *HERE*.

[SF_5] - Flibanserin

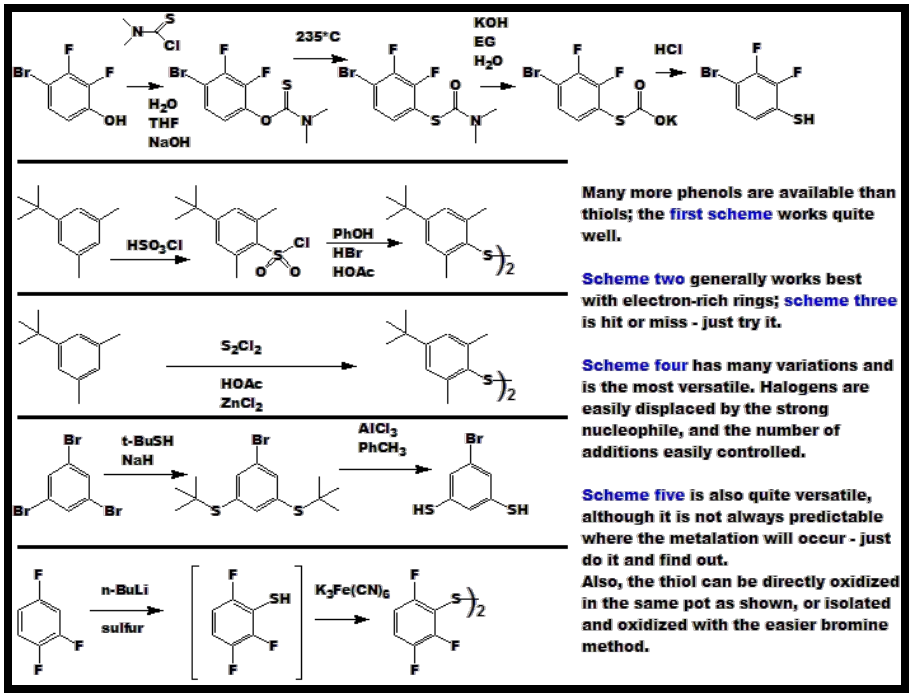


The neurobiological pathway of female sexual desire involves interactions among multiple neurotransmitters, sex hormones and various psychosocial factors. Sexual desire is modulated in distinct brain areas by a balance between inhibitory and excitatory neurotransmitters, serotonin acting as an inhibitor while dopamine and norepinephrine act as a stimulator of sexual desire. Flibanserin is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist that had initially been investigated as an antidepressant. Preclinical evidence suggested that flibanserin targets these receptors preferentially in selective brain areas and helps to restore a balance between these inhibitory and excitatory effects.



A large variety of phenethylamines and phenylisopropylamines, with diverse substituents on the ring, are known. Most of these are CNS stimulants in a broad sense, also psychedelics, euphoriants, and intoxicants with a rather broad pharmacological profile. Aside from the "street drugs", many such compounds are useful in research as molecular probes, as they interact strongly with various norepinephrine, dopamine and seratonin receptors in the CNS. A number of them have found clinical use, and many more are (and will be) investigated as antidepressants and other psychopharmacological therapeutics.

A *very large pool* of possible compounds can be made, essentially limited only by the availability of the appropriate halogenated starting material [I]. *It is known that the ring "4" position is critical, often having a large, electronegative lipophilic substituent* such as Br, I, CF_3, etc. What then of SF_5 ? Can only be *very interesting* to find out !



Many more phenols are available than thiols; the first scheme works quite well.

Scheme two generally works best with electron-rich rings; scheme three is hit or miss - just try it.

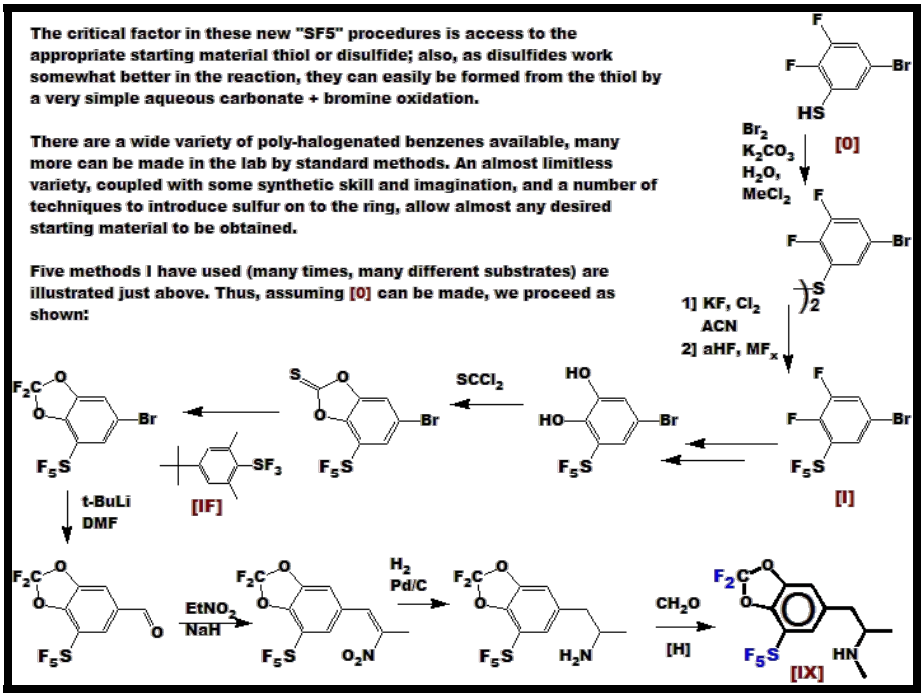
Scheme four has many variations and is the most versatile. Halogens are easily displaced by the strong nucleophile, and the number of additions easily controlled.

Scheme five is also quite versatile, although it is not always predictable where the metalation will occur - just do it and find out.
Also, the thiol can be directly oxidized in the same pot as shown, or isolated and oxidized with the easier bromine method.

The critical factor in these new "SF5" procedures is access to the appropriate starting material thiol or disulfide; also, as disulfides work somewhat better in the reaction, they can easily be formed from the thiol by a very simple aqueous carbonate + bromine oxidation.

There are a wide variety of poly-halogenated benzenes available, many more can be made in the lab by standard methods. An almost limitless variety, coupled with some synthetic skill and imagination, and a number of techniques to introduce sulfur on to the ring, allow almost any desired starting material to be obtained.

Five methods I have used (many times, many different substrates) are illustrated just above. Thus, assuming [0] can be made, we proceed as shown:



Compound [IX] has *got* to have a very interesting pharmacological (CNS) profile! The interesting, but scarcely known and used difluoro-methylene-dioxy function is conveniently made using the new FLUOLEAD deoxofluorinating reagent [IF], which we developed at UBE concurrently with the new SF_5 process.

WebSite by Lloyd Garrick.

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