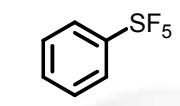
Aug, 2012

UBE Aromatic SF5 Derivatives

Prepared in High Yield via Highly Versatile & Cost Competitive Methods

Contact: fluorine@ube.com

UBE Aromatic SF5 compounds are expected to be useful as BUILDING BLOCKS for pharmaceutical agents, pesticides, liquid crystals, conductive polymer, and higher performance organic materials.



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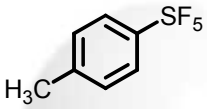

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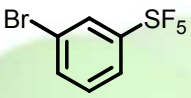

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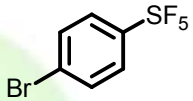

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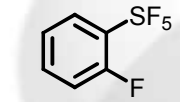

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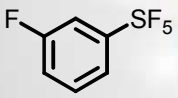

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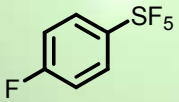

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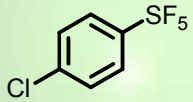

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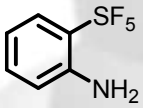

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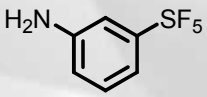

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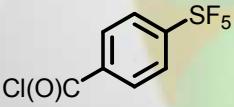

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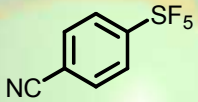

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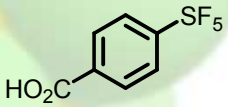

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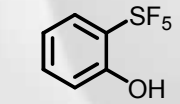

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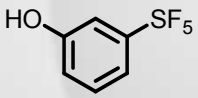

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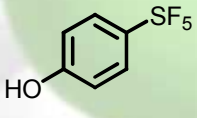

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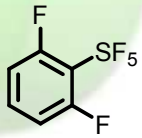

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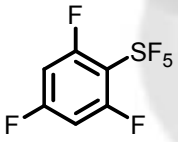

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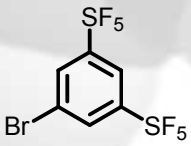

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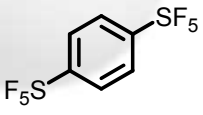

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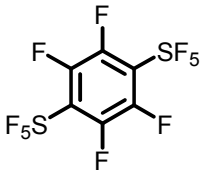

CAS# 1219501-60-6

Contact us to inquire about availability and pricing.

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E-mail: fluorine@ube.com

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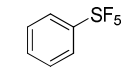
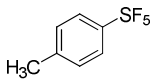
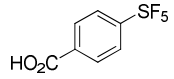
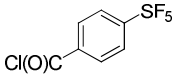
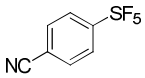
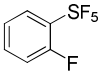
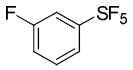
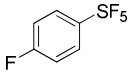
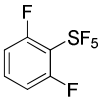
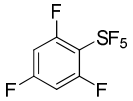
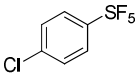
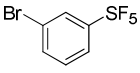
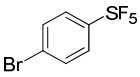
PRODUCT LINE-UP

Aromatic hydrocarbon	
	Phenylsulfur pentafluoride CAS# 2557-81-5
	4-Tolylsulfur pentafluoride CAS# 203126-21-0
Carboxylic acid and derivatives	
	4-(Pentafluorosulfanyl)benzoic acid CAS# 832-32-6
	4-(Pentafluorosulfanyl)benzoyl chloride CAS# 197384-98-8
	4-(Pentafluorosulfanyl)benzonitrile CAS# 401892-85-1
Aryl halide	
	2-Fluorophenylsulfur pentafluoride CAS# 864230-02-4
	3-Fluorophenylsulfur pentafluoride CAS# 1422-41-9
	4-Fluorophenylsulfur pentafluoride CAS# 1422-39-5
	2,6-Difluorophenylsulfur pentafluoride CAS# 864230-03-5
	2,4,6-Trifluorophenylsulfur pentafluoride CAS# 1062610-12-1
	4-Chlorophenylsulfur pentafluoride CAS# 5310-68-9
	3-Bromophenylsulfur pentafluoride CAS# 672-30-0
	4-Bromophenylsulfur pentafluoride CAS# 774-93-6

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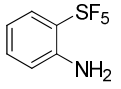
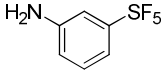
	2-Aminophenylsulfur pentafluoride CAS# 1246998-10-6: ***Limited quantities available for research only***
	3-Aminophenylsulfur pentafluoride CAS# 2993-22-8
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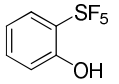
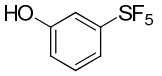
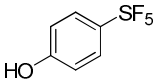
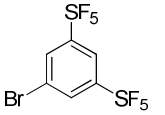
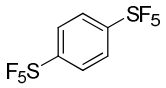
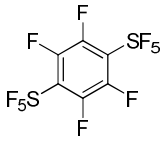
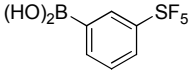
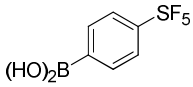
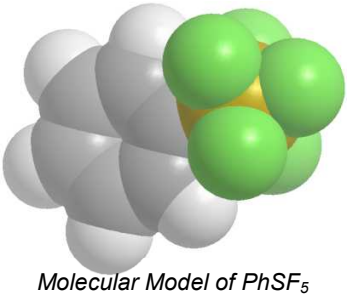
	2-Hydroxyphenylsulfur pentafluoride CAS# 1126968-75-9
	3-Hydroxyphenylsulfur pentafluoride CAS# 672-31-1
	4-Hydroxyphenylsulfur pentafluoride CAS# 774-94-7
Poly-SF5	
	1,3-Bis(pentafluorosulfanyl)- 5-bromobenzene CAS# 432028-10-9
	1,4-Bis(pentafluorosulfanyl)benzene CAS# 1219501-58-2
	1,4-Bis(pentafluorosulfanyl)- 2,3,5,6-tetrafluorobenzene CAS# 1219501-60-6
Aryl boron reagent	
	3-(Pentafluorosulfanyl)phenylboronic acid CAS# 871507-67-4
	4-(Pentafluorosulfanyl)phenylboronic acid CAS# 871507-70-9

Aug, 2012

UBE Aromatic SF5 derivatives, prepared in high yield via highly versatile & cost competitive methods.



Molecular Model of $PhSF_5$

Introduction: *Concurrent with significant developments in the synthetic methodology for the preparation of SF5 containing compounds, many potential applications, derived from the interesting and unique properties of the SF5 function, have been proposed, particularly in certain advanced specialty chemical fields such as pharmaceuticals, agrochemicals and electronics.*

The SF5 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 SF5 compounds will show interesting and unique influences on biological activities other than those observed with fluorine or trifluoromethyl-groups [1].

Regarding electronics chemicals, it is reported that there has been a rapid increase in the number of patents which list the SF5 group and other groups in liquid crystals due to the strong dipole moment which can be achieved by the SF5 group [1), 2)].

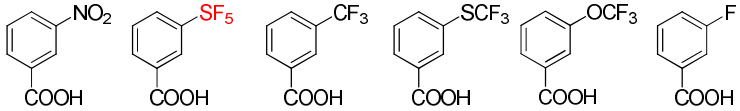
Properties of Aromatic SF5 compounds:

*SF5 group is called **"Super-trifluoromethyl group"**[2], and the expected properties of SF5-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 SF5 group.*

A) Electron-withdrawing Effect [3]

SF5 group is recognized as a strong electron-withdrawing group. Fig.1 below shows the comparative values of pKa in the substituted benzoic acid derivatives which have SF5, CF3, SCF3, OCF3 and F, respectively. In Fig.1, SF5 derivative is ranked as the second strongest group after the nitro-substituted one.

Fig. 1



pKa EtOH:H_2O = 50:50	4.60	4.82	5.11	5.15	5.16	5.28
σ_m	0.73	0.61	0.44	0.40	0.39	0.28

B) Lipophilicity [2]

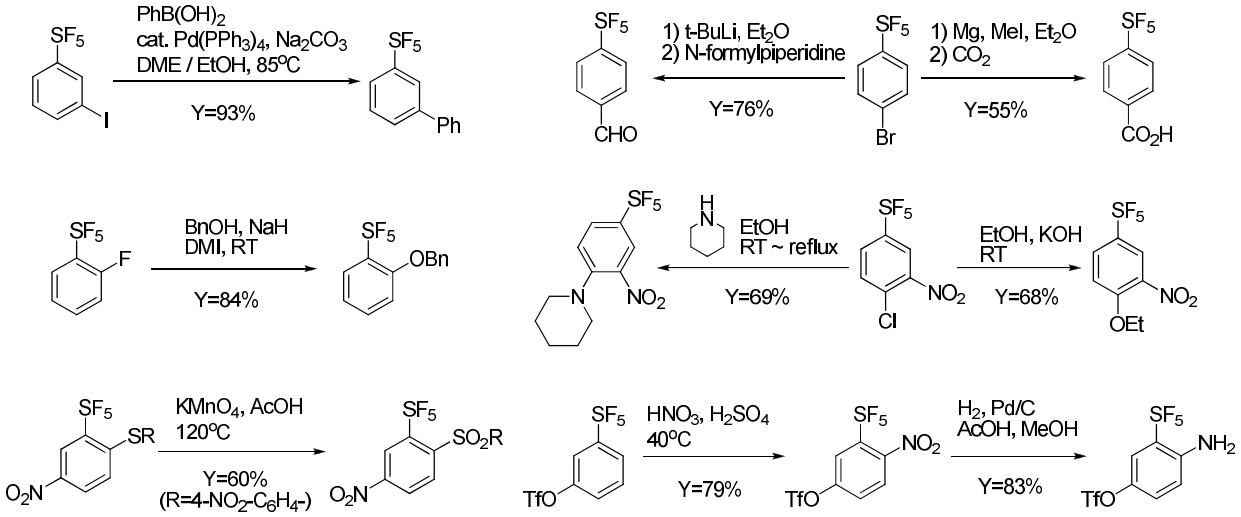
It is well known that compounds which incorporate fluorine(s) show greater lipophilicity. Table 1 shows the comparative values of lipophilicity with varying substituents in the molecule. SF5 substituted compounds are expected to show excellent lipophilicity compared with other fluorine-containing compounds.

Table 1 Lipophilicity(π) of substituent X

Substituent X	SCF_3	**SF_5**	OCF_3	CF_3	F	H	NO_2
π_p	1.44	**1.23**	1.04	0.88	0.14	0	-0.28

C) Thermal and Chemical Stability

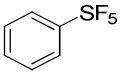
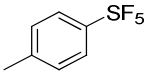
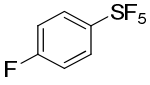
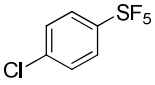
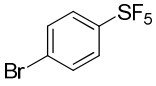
Aromatic SF5 compounds possess excellent thermal and chemical stability. For example, it was demonstrated that the thermal decomposition rate of PhSF5 (PSF) was less than 20% after it was heated in a sealed tube at 400°C for 7 hours [3a]. It was also demonstrated that aromatic SF5 compounds are more tolerant than aromatic CF3 compounds under strong conditions of Brønsted acids and bases [3a, 4a] and can be widely applied for common synthetic transformations in high yield. Examples of reactions for Aromatic SF5 compounds are shown below [4].



D) Toxicity

Regarding the assessment of toxicity of Aromatic SF5 compounds, the aromatic SF5 compounds shown in Table 2 below were assayed for both Ames and Acute Oral Toxicity. Table 2 below shows both results including the empirical data obtained from the Acute Oral Toxicity test. 4MPSF showed the weak toxicity, whose range is 50-300mg/Kg and ranked as Category 3 in UN GHS (Table 2).

Table 2 Safety testing of Aromatic SF_5 compounds

NAME	PSF	4MPSF	4FPSF	4CPSF	4BPSF
Structure					
Ames Test	Negative	Negative	Negative	Negative	Negative
ACUTE ORAL TOXICITY (Rat): LD_{50}	>2000mg/Kg	50-300mg/Kg	>2000mg/Kg	300-2000mg/Kg	300-2000mg/Kg

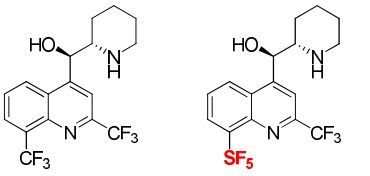
E) Biological Activities

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 (SF5) group, which is a highly fluorinated functional group, has shown remarkable activity in biochemical molecules. The introduction of the SF5 group brings not only the

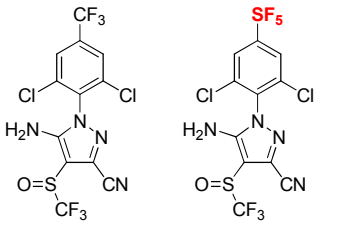
novel properties which originate from Fluorine element (Strong electronegativity, high lipophilicity and high chemical stability) to the molecule, but also a larger steric effect than the CF3 group, which is also recognized as a highly fluorinated functional group. The relative steric demand of the SF5 group is slightly less than that of a tert-butyl group and considerably larger than that of a CF3 group [5]. Examples of biological activities comparing the CF3 substituted agent vs. the SF5 analog are shown below;

*Mefloquine is used for both treatment and prophylaxis of malaria (**Fig. 2**). 8-SF5-Mefloquine showed a longer half-life(68h) than Mefloquine(23h) after administration to mice [4e), 6)]. Fipronil is a broad spectrum insecticide (**Table 3**).SF5 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 [7)].*



Mefloquine 8-SF5-Mefloquine

Fig. 2



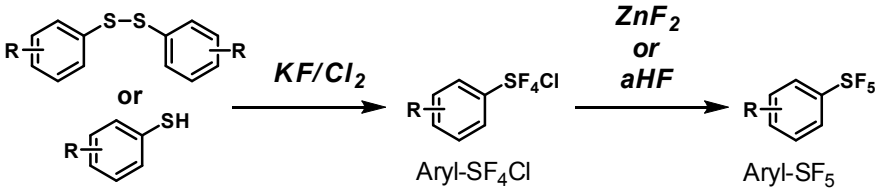
Fipronil SF5 Analogue

Table 3. Comparison of the insecticidal activity

	Musca (S) [a)]	Musca (R) [a)]	Blattella (S) [a)]
SF5 Analogue Relative potency	1	1	1
Fipronil Relative potency	0.1	0.01	0.5

a) (R) indicates a strain resistant to dieldrin and (S) is a susceptible strain.

UBE Preparation Methods: *In order to contribute to and improve SF5 chemistry above, UBE has started to deliver a series of aromatic pentafluorosulfanyl compounds prepared by new innovative processes including our KF/Cl_2 method, which was developed by IM&T Research Inc. (**Scheme 1**) [8)].*



Scheme 1

Our KF/Cl_2 method is widely applicable to various aromatic disulfide compounds, which are direct starting materials for the corresponding aromatic SF5 compounds. This has enabled us to introduce the SF5 group into various aromatic rings via a 2 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 [9)].

With the KF/Cl_2 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 Cl_2, are commodity materials, which can be obtained conveniently and at relatively low prices for industrial scale production.

The conversion to Aryl-SF_5 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.

Products: *Based on these patented synthetic technologies [10], UBE has prepared the following Aryl-SF_5 compounds in page 1, which can be employed as "building blocks" for the preparation of more valuable SF5 compounds by customers. To elaborate on our highly extensive and applicable methodology, we have succeeded in applying it to the preparation of aromatic poly-SF5 compounds. Also, UBE will continue to develop and produce additional novel new Aryl-SF_5 compounds. Some new compounds are illustrated in Fig. 3.*

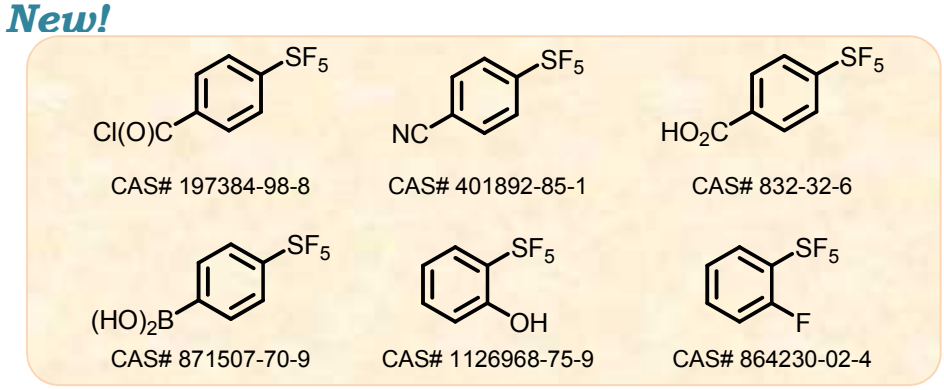


Fig. 3

Contact: *For quotes, requests, and other questions, please contact us directly at the address below;*

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9) *R. D. Bowden et al., WO 97/05106,* ***1997****.*
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