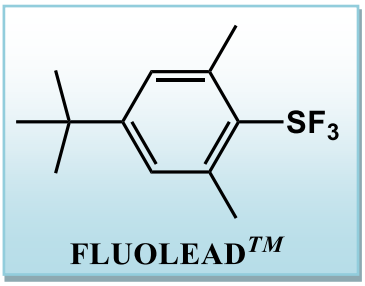
UBE Corporation

FLUOLEAD™

4-tert-Butyl-2,6-dimethylphenylsulfur trifluoride

A widely applicable fluorinating agent with high stability and ease of handling



CAS # 947725-04-4

Our novel fluorinating reagent, FLUOLEAD™, is designed as the best alternative to current fluorinating agents for use in the synthesis of a wide variety of specialty chemicals and intermediates, such as pharmaceuticals, agrochemicals and electronic chemicals. FLUOLEAD™ is a nucleophilic fluorinating agent useful for deoxyfluorination reaction.

Excellent thermal stability and ease of handling:

FLUOLEAD™ is a crystalline solid with excellent physical and chemical properties. It does not fume and reacts with water very slowly. Thus, it is allowed to be handled in open air. FLUOLEAD™ has good thermal stability, it can tolerate temperatures up to 100°C, and can carry out difficult reactions that other deoxyfluorinating agents (DAST, Deoxo-fluor™, etc.) have never yet achieved.

Physical Properties of FLUOLEAD™

Chemical formula: $C_{12}H_{17}F_3S$
Molecular weight: 250.32 g/mol
Appearance: Off-white to light pink crystalline powder
Melting point: 66-67°C (Purity ~95%)
Boiling point: 92-93°C/0.5 mmHg
Solubility: very soluble in usual organic solvents


FLUOLEAD™ Crystal

Contacts:

Multi-gram quantities of FLUOLEAD™ are currently available from

ABCR GmbH & Co. KG
Apollo Scientific Ltd.
Tokyo Chemical Industry Co., Ltd.
Sigma-Aldrich

For quotes of 1kg or more quantities of FLUOLEAD™ as well as technical questions in use of FLUOLEAD™, please kindly feel free to contact us directly:

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Packaging information:

FLUOLEAD™ is packed:

- **For 50g and less:** in a PP bottle (volume 100ml and specification: PP treated with fluorine gas). It enhances the durability by the fluorination treatment toward the HF could come from the unexpected hydrolysis occurrence of FLUOLEAD during the storage.
- **For more than 50g:** in a 2kg plastic bottle (volume 3L, specification: HDPE treated with fluorine gas)
- **The bottle is further packed in Aluminum laminated bag with drying agent (Silica gel) to avoid the contact from the outside moisture.**

If the aluminum bag is unopened, it could be stored at room temperature (under dry condition, such as desiccator, is preferable.)

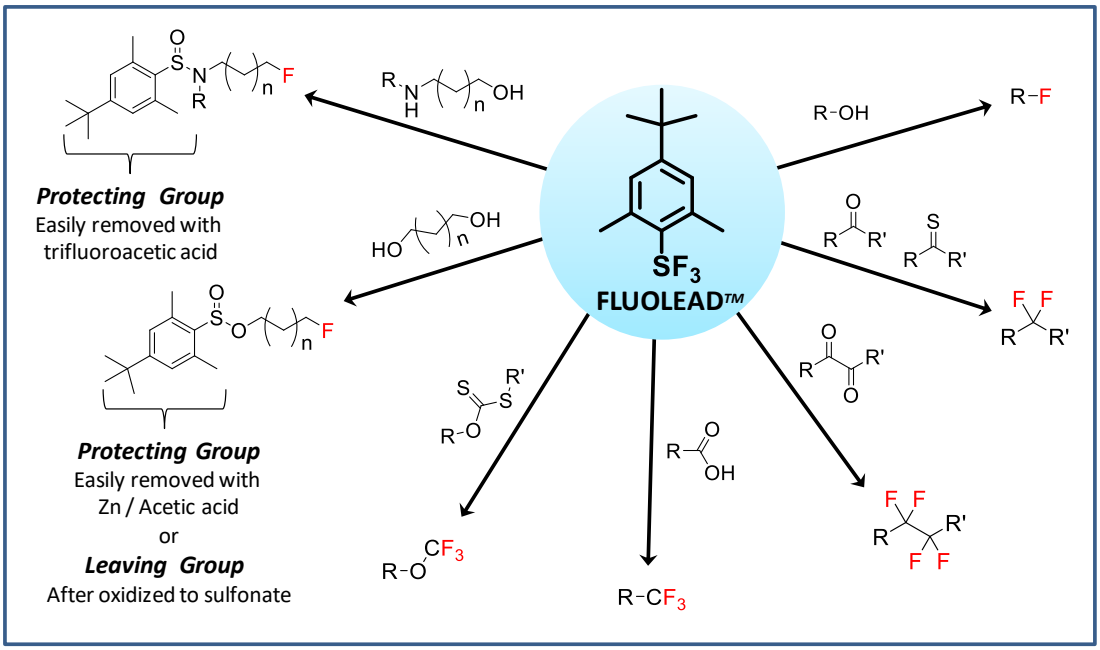
After the bag opened, the bottle should be stored under the dry conditions (inside the desiccator).

1. FLUOLEAD™ [1), 2)]: a product with a wide range of applications for

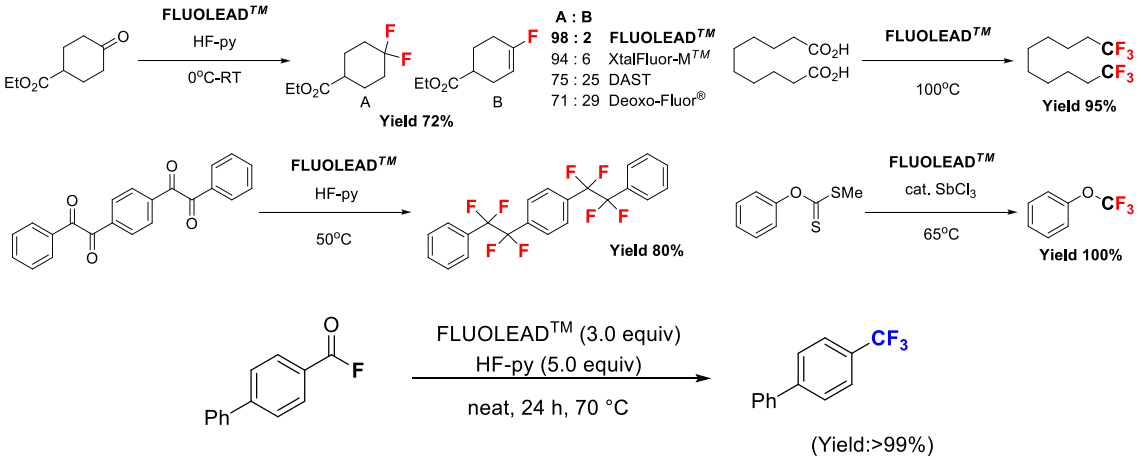
Equivalent to the existing deoxyfluorination agents, FLUOLEAD™ converts the hydroxy group (-OH) and carbonyl group (>C=O) to (–F) and (>CF_2), respectively. In contrast to the currently available agents, it can directly convert carboxyl functions (-COOH) to trifluoromethyl group (-CF_3) thanks to its good thermal stability. Furthermore, FLUOLEAD™ can fluorinate sulfide compounds.

The fluorination reaction with FLUOLEAD™ proceeds well under acidic conditions. In this respect, the addition of Olah's reagent*was especially effective in our examples. The amount is usually added up to 3eq. vs. FLUOLEAD, although it varies widely for different substrates.

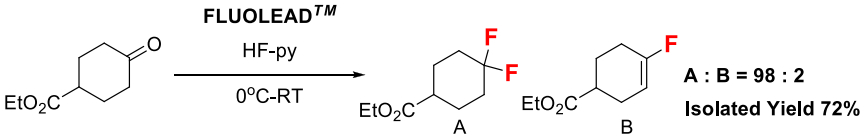
*Olah's reagent (HF-py): a mixture of 70% Hydrogen fluoride and 30% pyridine



Significant examples:



A typical procedure:

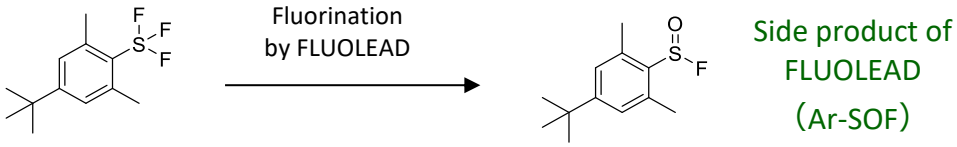


A dry fluoro-polymer vessel was provided to this reaction. 80ml of *n*-Hexane was initially charged into the vessel under nitrogen atmosphere, followed by 22.5 grams of FLUOLEAD™ (90mmol). The mixture was stirred and dissolved until uniformly in ice bath. 5.72ml of $Py(HF)_{9.2}$ was slowly added , then 10.2 g of Ethyl 4-cyclohexanonecarboxylate(60 mmol) was added dropwise. The ice bath was removed and the reaction mixture was stirred for 5hrs at room temperature. The obtained reaction mixture was cooled in ice bath again, and 15.8ml of ethanol was added to it. The mixture was stirred for an hour at room temperature. The obtained reaction mixture was slowly poured into 235 grams of 24% potassium carbonate solution (K_2CO_3). After the separation of the organic layer, the water layer was extracted with *n*-Hexane, and the combined organic layers were washed with water, followed by 1M HCl solution. The solvent was evaporated, and the residue was distilled under reduced pressure. 8.34 grams of the product, Ethyl 4, 4-difluorocyclohexanecarboxylat, was distilled out (yield=72%).

2. Tips for Workup

The main side product after treated with FLUOLEAD™ is Aryl-Sulfinic fluoride (Ar-SOF, Ar=4-*tert*-butyl-2,6 -dimethylphenyl), which is the hydrolysis form of FLUOLEAD™ (Scheme 1).

Scheme 1:

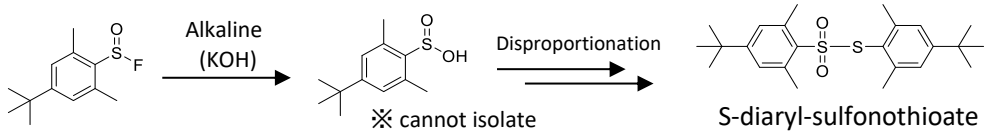


Regarding the removal of Ar-SOF from the desired fluorinated product, there could be various methods depending on the physical and chemical properties of the reaction system. We hereby would like to introduce the following 2 methods as part of examples.

Hydrolysis method by strong alkaline solution

Aryl-Sulfinic fluoride (Ar-SOF) is to some extent more stable than the corresponding halide, chloride and bromide. It reacts with strong alkaline solution, such as potassium hydroxide, however takes time, mostly overnight, to complete the hydrolysis. In addition, the hydrolysis reaction eventually gives S-diaryl-sulfonothioate (Ar-S(O2)-S-Ar), which is totally different from the expected hydrolysis product, Aryl-sulfinic acid (Ar-SO2H) because the Ar-SO2H undergoes multiple disproportionation reactions during the hydrolysis (Scheme 2), and by this means, is transferred to the sulfonothioate. It is also difficult to remove this sulfonothioate from the desired fluorinated product by recrystallization, due to its low polarity. In this case, column chromatography is recommended.

Scheme 2: Hydrolysis reaction of Ar-SOF with alkaline solution and their products



Amino-alcohol method

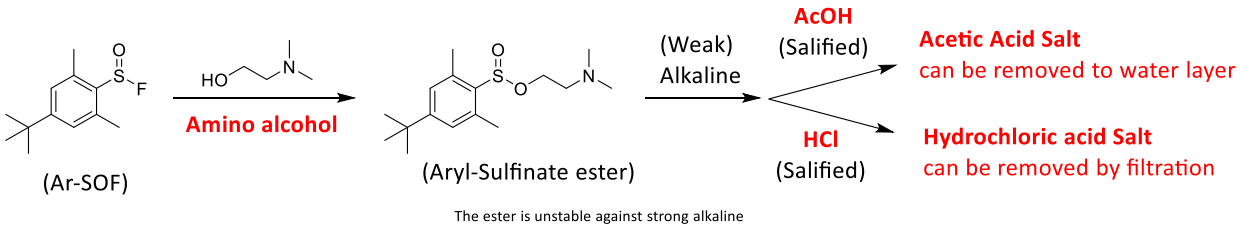
In order to overcome the difficulty of the side product removal, the recently developed ***amino-alcohol method*** shows clear advantages compared to others in terms of quality (isolating purer product) and ease of operation.

In this method, we normally use the tertiary amino alcohol, such as 2-(dimethylamino) ethanol, to avoid reaction between Ar-SOF and amino group of amino alcohol. The charging amount of amino alcohol to the reaction mixture is estimated to be 1.5 molar equivalent vs. its FLUOLEAD amount. The reaction of amino alcohol with Ar-SOF proceeds quantitatively, even at ice bath temperatures, and affords the corresponding Aryl-Sulfinate ester shown in Scheme 3. This reaction is highly exothermic, because the amino alcohol is neutralized with the free HF in the mixture as well as reacts with Ar-SOF.

After the formation of the Sulfinate ester, the mixture is neutralized with a weak base, such as potassium carbonate, to remove the excess HF. Acetic acid is added, which converts the Aryl-Sulfinate to a water-soluble acetic acid salt. This salt can be removed from the organic layer to the water layer by washing the organic layer.

Alternatively, hydrochloric acid can be used instead of acetic acid. In this case, water-insoluble salt is produced which can be removed by filtration. The choice of acid depends on the properties of the products and solvents used in the reaction (Scheme 3).

Scheme 3. The outline of amino-alcohol method

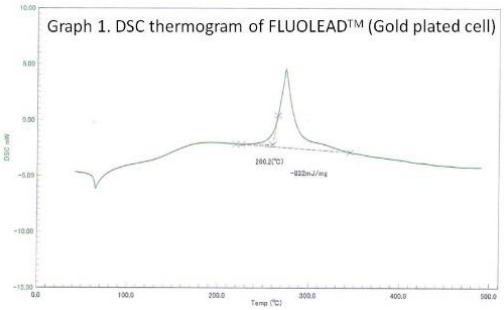


3. Thermal Stability of FLUOLEAD™

FLUOLEAD™ provides a greater thermal stability than other deoxyfluorinating agents such as DAST and Deoxo-fluor™. It was evaluated by two methods; the Differential Scanning Calorimetry (DSC) and the Accelerated Rate Calorimetry (ARC).

Thermal Stability test result by DSC method.

According to the DSC thermogram (Graph 1), the thermal decomposition temperature of FLUOLEAD was 260°C with a released energy of 832 J/g whereas with DAST, the respective values are 140°C and 1700 J/g [3)].



Thermal Stability test result by ARC method.

Thermal hazards of FLUOLEAD™ in Process, Storage and Transportation were assessed by ARC.

From this ARC test, TNR* temperature in Process and SADT** temperature in Storage and Transportation were estimated in two volumes, 25L and 210L, respectively (Tabale1). The respective temperatures shown in Table 1 (by materials and by volumes) indicate the maximum safe temperature when handling FLUOLEAD™ in Process from TNR, Storage and Transportation from SADT.

Table 1. Estimated TNR and SADT values of FLUOLEAD™ obtained by ARC

	25L Drum		210L Drum	
TNR	158.5°C	(Hastelloy C)	157.3°C	(Hastelloy C)
	152.6°C	(SS316)	151.5°C	(SS316)
SADT	157°C	(Hastelloy C)	155°C	(Hastelloy C)
	151°C	(SS316)	150°C	(SS316)

*TNR (Temperature No Return)

**SADT (Self Accelerating Decomposition Temperature)

According to Table 1, FLUOLEAD™ can tolerate temperatures over 150°C even when contained in a 210L drum. Thus, this novel deoxyfluorinating agent is suitable for higher temperature reactions and has a good thermal tolerance for commercial scale production.

FLUOLEAD™ is now available at commercial scale (Capacity: 12 MT).

For quotes of 1kg or more quantities of FLUOLEAD™ as well as technical questions in use of FLUOLEAD™, please kindly feel free to contact us directly.

FLUOLEAD™ should be handled in a ventilated area and stored at room temperature or less in a dry atmosphere. Solid FLUOLEAD™ gradually reacts with water and moisture to form HF. Reaction vessels made of fluoro polymer or metal are recommended; glass is not recommended.

Hazards Information of FLUOLEAD™: *FLUOLEAD has been known to incorporate the following hazardous*

risks in GHS classification from our safety tests;

- Acute toxicity (oral), Category 3,
- Skin corrosion/irritation, Category 1A
- Serious eye damage/eye irritation, Category 1

More information about Toxicity and Safety are also available from a Material Safety Data Sheet (MSDS). Please be sure to check the MSDS before use. MUST wear appropriate protective equipment under well-ventilated condition to avoid contact with skin, eyes when use this substance.

First aid measures: *Flush eyes and skins with copious amounts of water for at least 15 min. and contact a physician immediately.*

DISCLAIMER*:*

All information herein is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. UBE Corporation shall not be held liable for any damage resulting from handling, treatment or from contact with FLUOLEAD™.

Reference:

1) T. Umemoto, R. P. Singh, Y. Xu, and N. Saito, *J. Am. Chem. Soc.* 2010 *132* (51), 18199-18205
2) Y. Liang, A.Taya, Z. Zhao, N. Saito, and N. Shibata, *Beilstein J. Org. Chem.* 2020 *16,* 3052–3058
3) G. S. Lal, *et al*. *J. Org. Chem.* 1999*, 64,* 7048-7054.