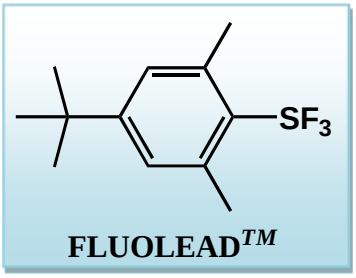
Ube Industries, Ltd.
https://www.ube.com/

FLUOLEAD™

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

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



CAS # 947725-04-4

Our novel new fluorinating reagent, FLUOLEAD™, is designed as a convenient alternative to current fluorinating agents for use in the synthesis of a wide variety of specialty chemicals and intermediates, such as pharmaceuticals, agrochemicals and electronics chemicals. FLUOLEAD™ is a nucleophilic fluorinating agent useful for deoxo-fluorination reactions, and is a crystalline solid with excellent physical and chemical properties. FLUOLEAD™ has high reactivity comparable to SF_4 and has high thermal stability and is easy to handle, and as such it is superior to current reagents (DAST, Deoxo-fluor™, etc.). The reagent may also be handled in open air. The crystalline reagent does not fume, and reacts with water very slowly. Reactions with FLUOLEAD™ generally occur under mild conditions. In terms of general chemical reactivity, FLUOLEAD™ converts the hydroxy group (-OH) and carbonyl group (>C=O) to (–F) and (>CF_2), respectively. Differing from the current reagents, FLUOREAD™ directly converts carboxyl functions (-COOH) to trifluoromethyl (-CF_3); furthermore, FLUOLEAD™ can fluorinate sulfide compounds. Examples of these and other reactions are detailed in the accompanying pages.

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.

Contact:

Multi gram quantities of FLUOLEAD™ are currently available from

ABCR GmbH & Co. KG (DE)
Apollo Scientific LTD (UK)
Sigma-Aldrich Co. (US)
Tokyo Chemical Industry Co., Ltd.(JP)

For quotes on orders of 1 Kg or more, and for other questions regarding FLUOLEAD™, please contact us directly at the address below;

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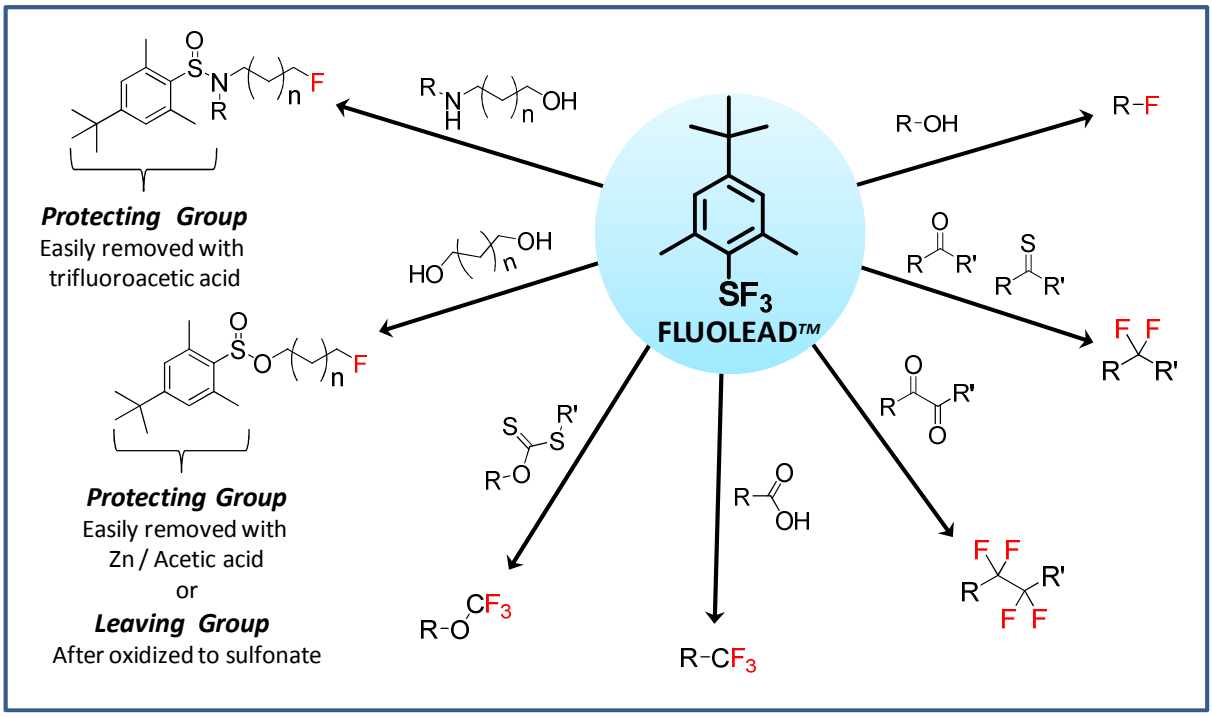
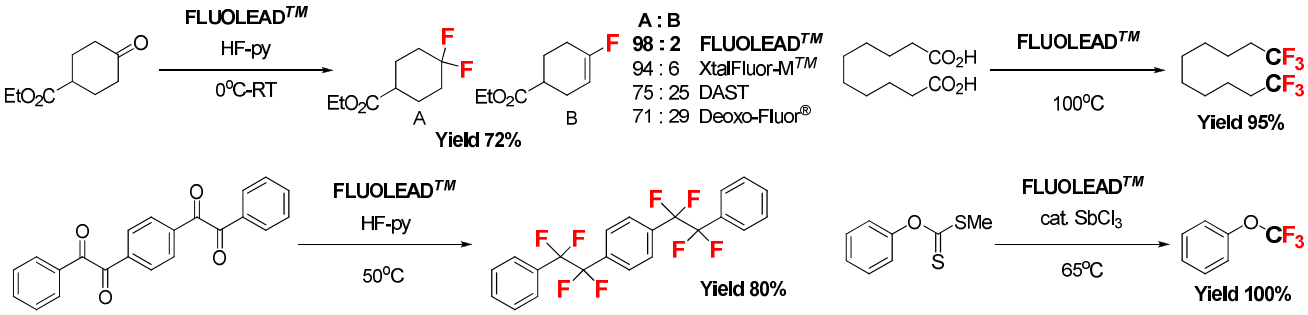
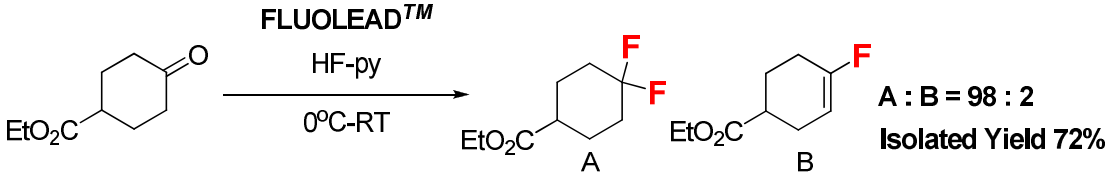
Fluorinations with FLUOLEAD™ [1, 2, 3)]



Significant examples



A typical procedure:



A dry fluoro-polymer vessel was provided for the fluorination reaction above. At first, 80ml of *n*-Hexane was charged into the vessel under nitrogen atmosphere, followed by 22.5 grams of FLUOLEAD™ (90mmol). The mixture was stirred and dissolved uniformly in the ice bath. 5.72ml of $Py(HF)_{9.2}$ was 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 5 hrs 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 neutralized 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%).

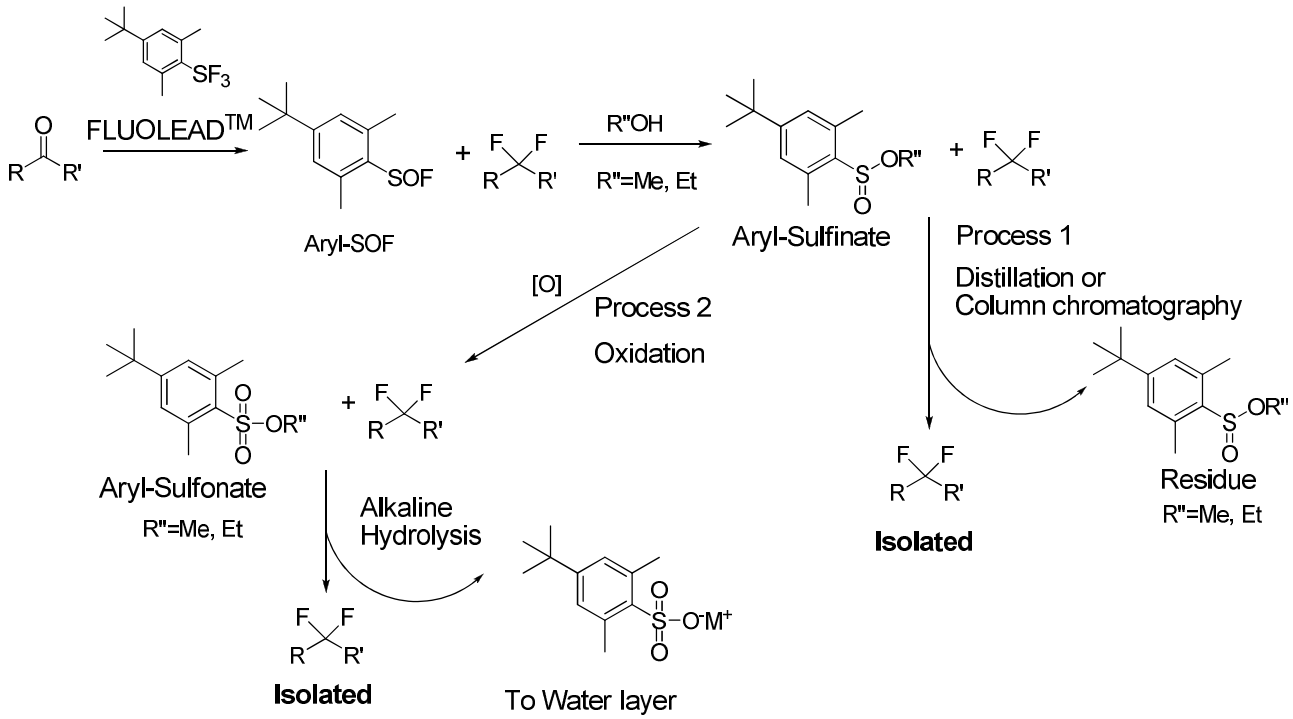
Please refer to the reference 1) and its technical support information, where many fluorination reaction examples regarding FLUOLEAD™ are introduced and discussed.

Workup methods after the fluorination with FLUOLEAD™ – Introduction of New "Alcohol method"

Side products, after the fluorination with FLUOLEAD™, could be formed from FLUOLEAD™; the one is Hydrogen Fluoride, HF, and the other is the corresponding Aryl-sulfinic fluoride, Aryl-SOF, Aryl=4-*tert*-butyl-2,6-dimethylphenyl, which is the hydrolysis product of FLUOLEAD™.

As for the removal of Ar-SOF from the product, there could be various methods, depending on the physical and chemical properties of the reaction system. Our newly developed "alcohol method", which is introduced as the typical procedure above, will be more effective among all in terms of the control of the unexpected disproportionation reaction products, which with sulfur compounds often occurs innately, so that this new method enables us to handle and remove Ar-sulfinate as the "sole side product", which comes from the reaction between Ar-SOF and the alcohol in the scheme 1 below.

There are various methods which includes the silica-gel column chromatography method to remove the Ar-sulfinate from the products. The distillation method (Process 1 in scheme 1 below) as well as the oxidation process (Process 2 in scheme 1 below) will also work for it effectively.

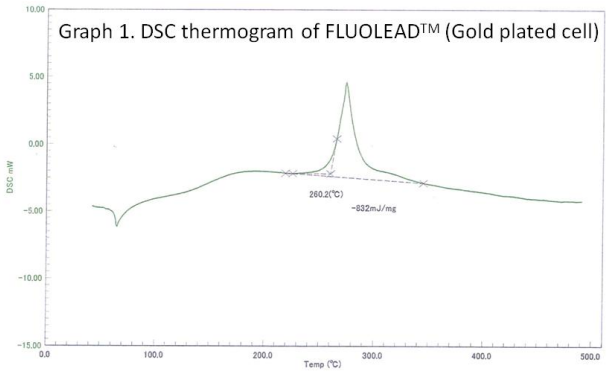


Scheme 1. Workup procedure by the alcohol method after the fluorination with FLUOLEAD

Thermal Stability of FLUOLEAD™

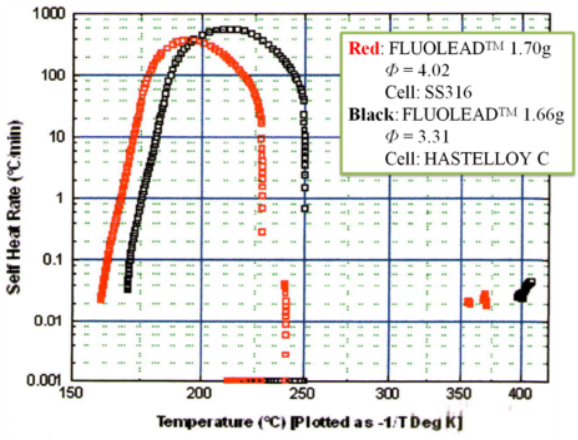
FLUOLEAD™ has greater thermal stability than other deoxofluorinating agents such as DAST and Deoxo-fluor™. In differential scanning calorimetry (DSC) measurement of FLUOLEAD™, the thermal decomposition started at 260°C (Gold plated cell), and the released energy was 832 J/g (Graph 1), whereas it is reported that DAST and Deoxo-fluor™ decomposed at 140°C (both are in Gold Cell), and the released energy was 1700 J/g and 1100 J/g, respectively [4].

Graph 1. DSC thermogram of FLUOLEAD™ (Gold plated cell)



The assessment of the thermal hazards of FLUOLEAD™ in process, storage and transportation was evaluated by Accelerated Rate Calorimetry (ARC). From self heat rate (SHR) measurement (Graph 2) , the onset temperature of self-heated decomposition of FLUOLEAD™ was 170°C (Hastelloy C).

Graph 2. SHR thermograms of FLUOLEAD™ in Hastelloy C and SS 316 cell



From "Time to Maximum Rate (TMR)" measurement (Graph 3), the TMR value of FLUOLEAD™ was approximately 10 minutes if FLUOLEAD™ was kept at 170°C. From a series of test results on ARC, the "Temperature of No Return (TNR)" values to assess the thermal hazard of FLUOLEAD™ in process was estimated for 25L and 210L scale, and these values are illustrated in Table 1, respectively.

Similarly, the "Self Accelerating Decomposition Temperature (SADT)" values to assess the thermal hazard in storage and transportation of FLUOLEAD™ was also estimated for 25L and 210L scale, and these values are also illustrated in Table 1, respectively.

Graph 3. Time to Maximum Rate (TMR)" measurement

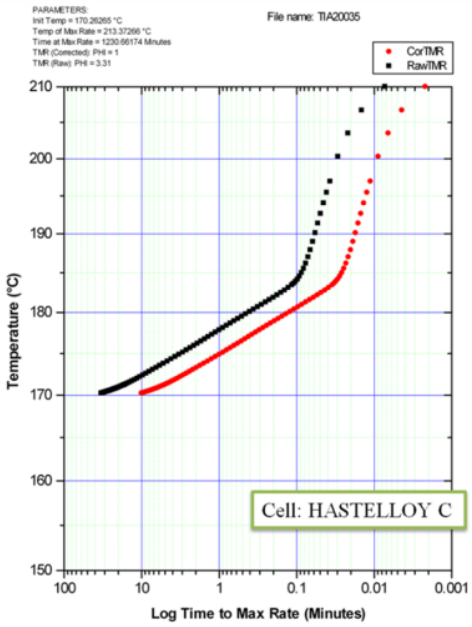


Table 1. Estimated TNR and SADT values of FLUOLEAD™ obtained by AR

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

In general, TNR and SADT from ARC measurement indicate the maximum safe temperature for the handling of FLUOLEAD™ in process, storage and transportation, and it has been shown from these estimated values that FLUOLEAD™ has excellent thermal stability above 150°C that current deoxofluorination reagents do not. This demonstrates that FLUOLEAD™ has application for reactions requiring temperatures in excess of 100°C, such as the conversion of carboxylic acids (-COOH) to trifluoromethyl groups (-CF3).

It also demonstrates the applicability of FLUOLEAD™ for deoxofluorination reactions in large scale industrial production.

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.

Regarding toxicity of FLUOLEAD™: Ames test is negative. Oral toxicity in rats LD_{50} >50, but <300 mg/Kg. *However, the health risks have not been fully determined. Toxicity and safety data that become available will be supplied on a Material Safety Data Sheet (MSDS).*

Avoid contact with skin, eyes, etc. First aid measures: Flush eyes and skins with copious amounts of water for at least 15 min. And contact a physician immediately.

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 AMERICA INC. shall not be held liable for any damage resulting from handling, treatment or from contact with FLUOLEAD™.

References

1) (a) T. Umemoto, R. P. Singh, Y. Xu, and N. Saito; *J. Am. Chem. Soc*. **2010**, *132*, 18199-18205.
(b) R. P. Singh and T. Umemoto, *J. Org. Chem*., **2011**, *76*, 3113–3121.

2) T. Umemoto and Y. Xu; *US patent* 7,265,247 B1.

3) T. Umemoto and R. P. Singh; *US patent* 7,381,846 B2.

4) G. S. Lal, *et al*.; *J. Org. Chem.* **1999***, 64,* 7048-7054.

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