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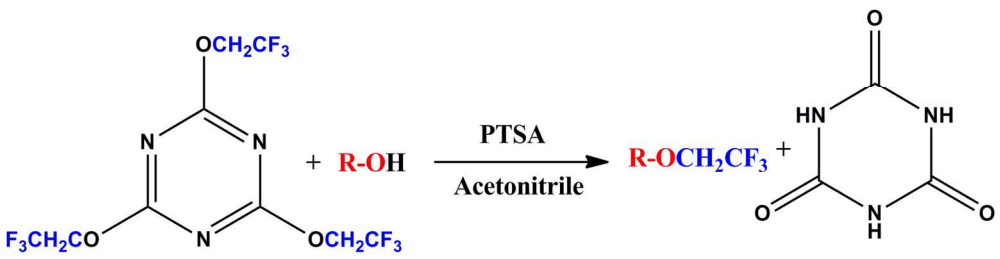

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Expedient and Efficient One Pot Synthesis of Trifluoroethyl Ethers From Metal Free 2,4,6-tris-(2,2,2-Trifluoro-Ethoxy)-[1,3,5] Triazene

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An efficient synthesis of fluorinated alkyl and aryl ethers was achieved by the use of *s*-triazene derived fluorinated reagent 2,4,6-tris-(2,2,2-trifluoro-ethoxy)-[1,3,5] triazene (TriTFET). The procedure offers a very attractive alternative for the synthesis of fluorinated motifs that are found in various bioactive molecules. Moreover, TriTFET is a synthetic non-toxic, non-ozone depleting and stable reagent. All compounds were characterized by ^{1}H, ^{13}C and ^{19}F NMR.

Fluorinated ethers (FEs) are one of the most important classes of organic compounds.[1] It is well known that trifluoroethoxy (CF_3CH_2O-) group increase metabolic stability and lipophilicity.[2] High molecular weight fluorinated ethers are extensively used in industry as lubricants, dielectric fluids, diffusion pump oils.[3] Due to high O_2 solubility of fluorinated ethers these are also used as blood substitute.[4] Low molecular weight fluorinated ethers such as Desflurane, Enflurane and Sevofluoraane are used as anaesthetics. Further, some blockbuster drugs viz., Lansoprazole (used as antibacterial), Silodosin (treatment of benign prostatic hyperplasia) and Flecainide (introduced into the treatment of arrhythmias in the pediatric population) bearing a trifluoroethyl aryl ether pharmacophore are commercially available (figure 1).[5] Fluorinated ethers (FEs) have a lower ozone depletion potential (ODP) and low global warming potential (GWP).[6] Chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), hydrofluorocarbon (HFCs) and perfluorocarbons (PFCs) are replaced by fluorinated ethers due to their vast industrial applications such as use in cleaning solvents, heat transfer agents, refrigeration and carrier fluids.[7]

The popular fluorous analogues t-butyl, benzyl, and fluorenylmethyloxycarbonyl groups are used for fluorous protection of amino groups.[8] Trifluoroethanol (TFE) can be used as an efficient substitute for fluorous protecting groups. It is also used in the total synthesis of Vinigrol proposed by Njardarson *et al*.[9]

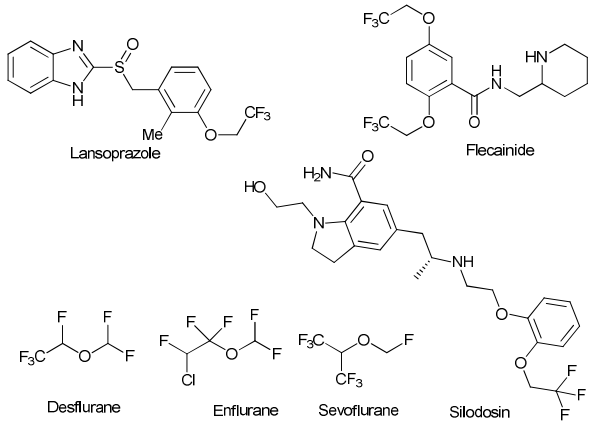


Figure 1. Example of drugs which have fluorous motifs

Generally, fluorinated ethers are prepared by nucleophilic addition of alcohols and fluorinated substrates using strong base.[10] Other choice for synthesizing fluorinated ethers are direct fluorination of chlorinated ethers with fluorine gas,[11a] 2,2,2-trifluorodiazoethane,[11b] Cobalt trifluoride,[12] alkenes under the catalysis of boron tetrafluordiethyl ether complex catalyst[13a] or by electrochemical methods.[13b] Williamson etherification is the most simple and convenient method for preparing fluoroethers using alcohols and alkyl halides.[14] However, these fluorinated alkyl halides are responsible for ozone layer depletion. Another simple method is etherification i.e, alkoxylation of tosylate esters (perfluoroalkanesulfonate) with alkoxide (phenoxide) anions.[15] Fluorinating reagent, fluorous silanes, THP, ethoxylethyl ether

acetals, fluorous methoxymethyl ether (^{F}MOM) fluorous benzyl groups and acyclic polyfluoro siloxanes are also used for fluorous protection of alchohols.[16] In these reports, reactions proceed at elevated temperature in high boiling point solvents. Few research articles have also reported the synthesis of trifluoroethyl aryl/alkyl ethers, in which harsh conditions were used in the presence of aryl/alkyl halides at high temperatures.[10] However, there is still need for mild and efficient reaction conditions. In this context, we now report a general process for the synthesis of an acid catalyzed fluorinated alkylating reagent and its use in the synthesis of alkyl/aryl TFE ethers.

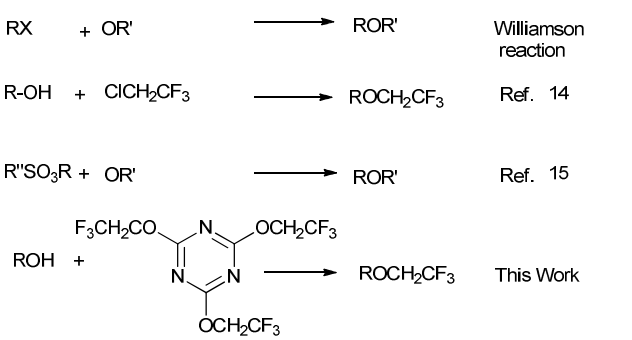
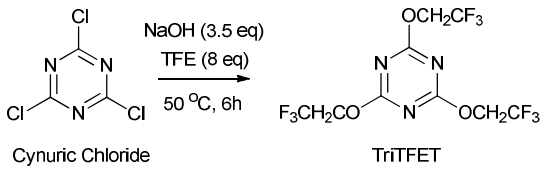


Figure 2. Procedure for the synthesis of fluorinated ethers.

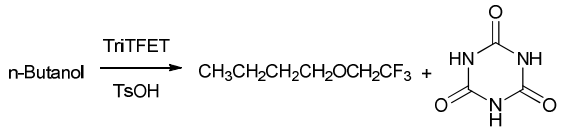
Synthesis of fluorinated alkylating reagent TriTFET (2,4,6-Tris-(2,2,2-trifluoro ethoxy)-[1,3,5] triazene) is shown in scheme 1. Chang *et al*[17] in 1961 introduced the reactions of cyanuric chloride with several electronegative substituted primary alcohols in which the electronegative substituents were fluoro, bromo, nitro, or nitroxy groups. Here we report the synthesis of TriTFET with slight modification in previously reported methods using the trifluoroethanol and NaOH as base. The side product cyanuric acid can be easily removed by filtration because of its low solubility in organic solvents. Further, during the synthesis and using TriTFET, we did not observe any irritating properties in our laboratory while its precursor cyanuric chloride is harmful, corrosive to skin and irritating to the respiratory tract. These features classify this reagent as an eco- and user friendly. TriTFET was characterized by ^{1}H NMR, ^{13}C NMR and ^{19}F NMR. In ^{1}H NMR spectra only one multiplet is observed at 4.8 due to $-OCH_2-$ protons. ^{13}CNMR spectra shows one singlet at δ 172 due to triazene carbons, quartet at δ 126-118 is due to $-CF_3$ carbon and multiplet at δ 64 is due to $-CH_2$ carbons. ^{19}FNMR show a singlet at δ -73 is due to fluorine atom of $-CF_3$ groups.



Scheme 1. Synthesis of TriTFET

To optimize the reaction conditions for fluorinated etherification, we choose different equivalents (0.4 and 0.6) of TriTFET in different solvents using n-butanol as substrate (scheme 2**)**. We found that 0.6 equivalent of TriTFET gave the optimum yield. Further, while performing this reaction in different solvents *viz.* ACN, AcOEt, DMF, 1,4-dioxane and toluene, the best result was obtained in CH_3CN. Thus, the reaction of n-butanol in the presence of 0.6 equivalent TriTFET in acetonitrile was found to be the optimum condition for the synthesis of fluorinated ethers (Table 1) and all reaction were carried out in this conditions.

Table 1. Optimization of reaction conditions for the synthesis of fluorinated ethers using TriTFET.



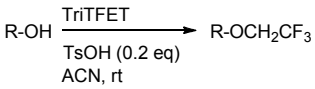
Entry	Solvent	TriTFET (Equiv)	Yield[a]
1	CH_2Cl_2	0.6	20
2	CH_2Cl_2	0.4	10
3	**CH_3CN**	**0.6**	**94**
4	CH_3CN	0.4	68
5	DMF	0.6	78
6	DMF	0.4	60
7	AcOEt	0.6	52
8	AcOEt	0.4	40
9	1,4-Dioxane	0.6	84
10	1,4-Dioxane	0.4	72
11	Toluene	0.6	45
12	Toluene	0.4	32

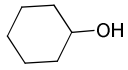
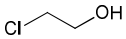
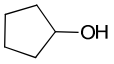
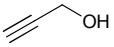
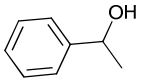
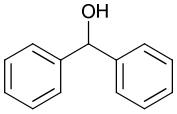
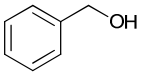
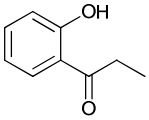
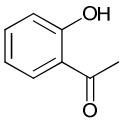
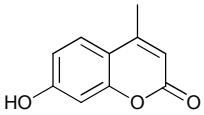
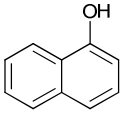
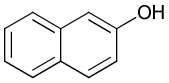
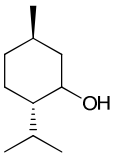
[a]Experimental yield determined by ^{1}H NMR. All reactions carried at room temperature, TsOH; *p*-toluenesulphonic acid

^{19}F NMR of TriTFET and all synthesized fluorinated ethers showed identical peaks at ca. -73 ppm, which can be attributed to the presence of $-OCH_2CF_3$ group (see supporting information). The scope of the use of TriTFET for fluorinated alkylation was investigated with various substrates. (Table 2). Simple alcohols such as primary and secondary alcohols (Table 2, entries 1-7) gave desired TFE protected ethers **1a-7a** in excellent yields. Propargyl alcohol also yielded corresponding TFE ether in good yield (82%, Table 2, entry 8). Benzyl and benzil alcohols also provided TFE protected ethers in moderate yields (Table 2, entries 9-11). Interestingly, reaction of α-hydroxyacetophenones, phenols, biologically active hydroxy coumarin and natural product menthol also afforded corresponding TFE protected ethers in moderate to good yields (62-94%, table 2, entries 12-17). Further, α and β-naphthols also undergo TFE etherification with TriTFET, although the yields are lower than hydroxy acetophenones (Table 2, entries 15 and 16). It is noteworthy that our method is more superior and economic for fluorinated ether synthesis in comparison with the other results reported earlier in literature because in our method no metal and aryl/alkyl halides are used.

TriTFET is protonated with the help of *p*-toluenesulphonic acid (PTSA) to form the trifluoroethyl cation, which reacts with alcohols via S_N1 mechanism to form trifluoroethane ethers. Further, the final concomitant leaving group isocyanuric acid is obtained and easily removed by filtration. However, reaction did not proceed in the absence of PTSA. Mechanistic results were rationalized on the basis of previous reports,[18] which is shown in following plausible mechanism (Figure 2).

Table 2. Scope of various alcohol and phenols for the synthesis of fluorinated ethers using TriTFET



S. NO.	Substrate (R-OH)	Prod-uct	TriTFET	Time	Yield[a]
1	$CH_3CH_2CH_2CH_2OH$	1a	0.6	4h	94
2		2a	0.6	4h	96
3		3a	0.6	4h	90
4	$CH_3CH_2CH_2CH_2CH_2OH$	4a	0.6	4h	94
5		5a	0.6	4h	80
6		6a	0.6	4h	89
7	$CH_3CH_2CH_2OH$	7a	0.6	4h	88
8		8a	0.6	4h	82
9		9a	0.6	4h	78
10		10	0.6	5h	80
11		11a	0.6	4h	86
12		12a	0.6	4h	92
13		13a	0.6	4h	94
14		14a	0.6	6h	79
15		15a	0.6	3h	83
16		16a	0.6	3h	85
17		17a	0.6	5h	78

[a]Experimental yield determined by ^{1}H NMR; Solvent acetonitrile; TsOH= *p*-toluenesulphonic acid

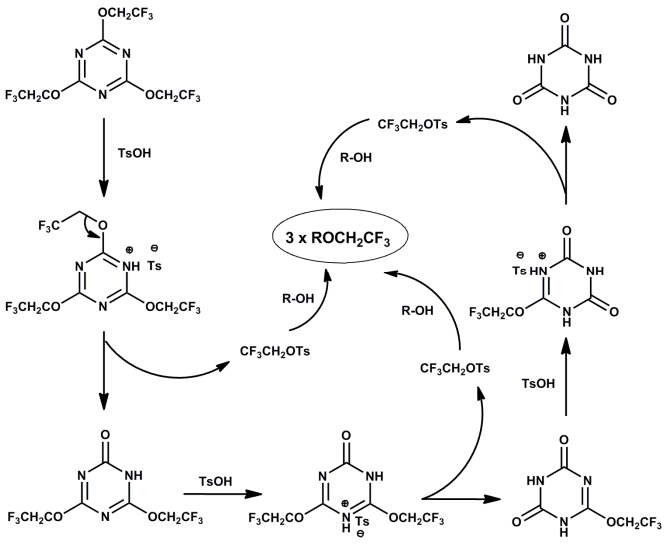


Figure. 2 Reaction Mechanism of TFE alkylation using TriTFET

Conclusions

In conclusion, the present study introduces the 1,3,5-triazine based TriTFET as a new reagent for the synthesis of various fluorinated ethers in higher yield. The inexpensive and easily available cyanuric chloride and 2,2,2-trifluoroethanol in one step gives TriTFET. Its use in the protection of alcohol and phenols by TFE group allows the synthesis of fluorinated ethers without using a large amount of halogenated alkyl halides as previously reported. Thus it is an expedient and eco-friendly approach. Further, TriTFET is also suitable for the conversion of sterically hindered secondary hydroxyl groups and converts menthol into the corresponding fluorinated ether.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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