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Quaternary Ammonium Trifluoromethoxide Salts as Stable Sources of Nucleophilic OCF_3

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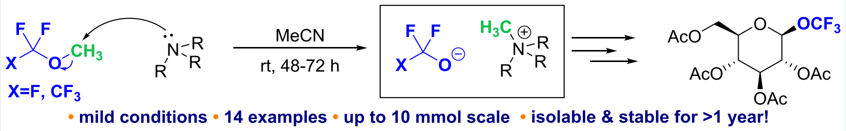

• mild conditions • 14 examples • up to 10 mmol scale • isolable & stable for >1 year!

ABSTRACT: The reaction of nucleophilic tertiary amines with trifluoromethyl and pentafluoroethyl methyl ethers provides quaternary ammonium trifluoromethoxide (NR_4OCF_3) and pentafluoroethoxide ($NR_4OCF_2CF_3$) salts, respectively, in good yields. The new trifluoromethoxide salts disclosed herein are uniquely stable for extended periods of time in both the solid state and in solution, which complements contemporary reagents. Here we describe the preparation of a range of NR_4OCF_3 salts, their long-term stability, and utility in substitution reactions.

The trifluoromethoxide group has become an emerging feature in pharmaceuticals, agrochemicals, and materials.[1−9] In pharmaceuticals, trifluoromethyl ethers often exhibit improved drug properties including increased lipophilicity[10] and metabolic stability,[11] and can adopt unique conformations when compared with aliphatic ethers.[1] The inclusion of a trifluoromethyl ether can also increase the potency of a drug lead.[12] For example, the CGPR receptor antagonist **1**, a lead candidate for the treatment of migraines,[12] and the CB2 agonist **2**[13] both incorporate aliphatic trifluoromethyl ethers as key structural elements. Likewise, several commercial pesticides also incorporate trifluoromethyl ethers (e.g., **3** and **4**).[14]

The introduction of a trifluoromethyl ether into a target molecule can be accomplished via one of several methods that include fluorination,[15] electrophilic trifluoromethylation,[16] or nucleophilic or electrophilic trifluoromethoxylation.[17] Nucleophilic trifluoromethoxylation is generally accomplished with the use of trifluoromethoxide salts generated *in situ* using one of several processes.[18,19] Notably, it was recently reported that a diverse range of aryl and heteroaryl diazoniums could be transformed into aryl and heteroaryl trifluoromethyl ethers using silver(I) trifluoromethoxide.[20] Early efforts relied on the reaction of a fluoride source (e.g., KF, RbF, and CsF) with carbonyl fluoride (COF_2, fluorophosgene **5**), a highly toxic gas.[19] More recently, trifluoromethoxide has been prepared *in situ* from OCF_3-containing reagents such as trifluoromethyl benzoate (**6**),[21] trifluoromethyl triflate (**9**),[6,22,23] trifluoromethylbenzenesulfonates (e.g., trifluoromethyl tosylate, **7**),[24] and trifluoromethyl dinitrophenyl ether (**8**)[25] (Figure 1B, Type I reagents). Each of these reagents generate trifluoromethoxide upon treatment with a fluoride source, forming benzoyl fluoride, sulfonyl fluorides, or aryl fluorides, respectively, as reactive byproducts. As an alternative, tris(dimethylamino)sulfonium trifluoromethoxide (TAS-OCF_3, **10**)[18,26] can be prepared from the reaction of tris(dimethylamino)sulfonium difluorotrimethylsilicate and fluorophosgene. While this reagent is isolable, it was found to decompose entirely after brief heating (0.25 h, 45 °C, MeCN).[27] The preparation of tetramethylammonium trifluoromethoxide has previously been reported using tetramethylammonium fluoride and **9**.[28] Several additional isolable trifluoromethoxide salts have been prepared, including NHC-stabilized gold and copper trifluoromethoxides, although these reagents also suffer from poor thermal stability and generally decompose at room temperature.[29] More recently silver(I) trifluoromethoxide reagents have been reported that are stabilized by imine or pyridine ligands (e.g., **11**, **12**; Figure 1B, Type II reagents).[27,30] These later reagents have demonstrated utility in reactions with benzyl bromides[30] and alkyl 4-nitrobenzenesulfonates.[27] However, the cost, multistep preparation, and low atom economy[27] ($OCF_3 \approx 20\%$ of MW) may limit their general utility. Notably, among these reagents **12** demonstrates the best stability (<10% decomposition after 2 days in various solvents) and can be used at temperatures up to 80 °C.[27] Recently, a method for the preparation of pure solutions of silver(I) trifluoromethoxide from triphosgene was reported.[31] Despite intense efforts, preparation of isolable trifluoromethoxide salts remains a significant synthetic challenge.

Recently, tetramethylammonium trifluoromethylthiolate has been explored as a stable SCF_3 source, and it has been used in a

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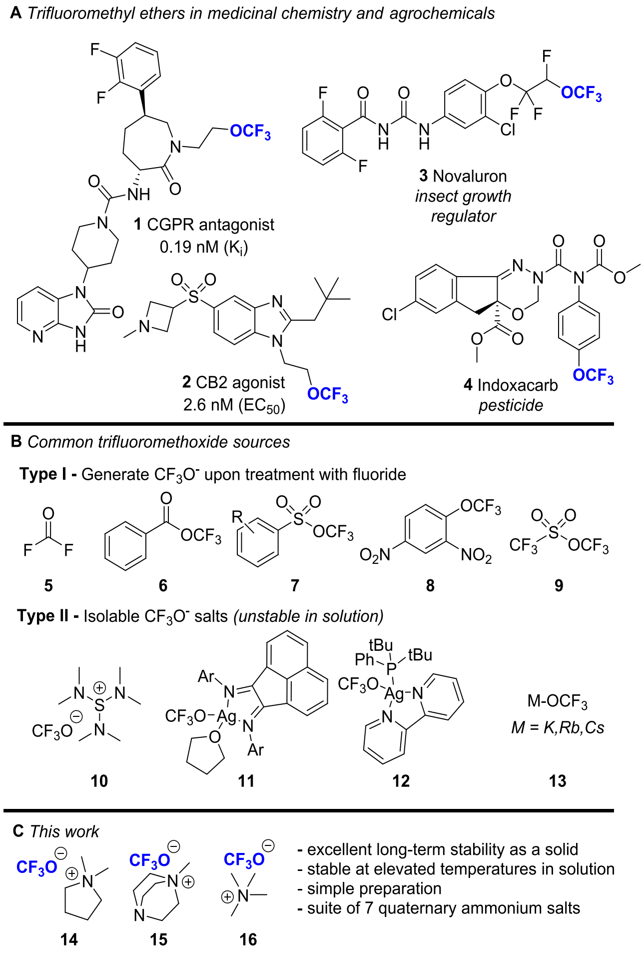
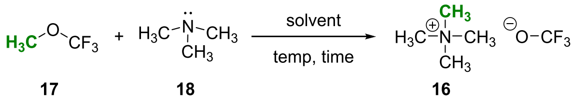


Figure 1. Select examples of trifluoromethyl ethers in agrochemicals and medicinal chemistry. Commonly utilized trifluoromethoxide reagents and a new family of quaternary ammonium trifluoromethoxide salts.

Table 1. Synthesis of Tetramethylammonium Trifluoromethoxide (16)[a]



entry	temp (°C)	time (h)	solvent	yield (%)[b]
1	50	24	dioxane	21
2	50	72	dioxane	40
3	50	72	MeCN	86
4	50	72	dioxane	70[c]
5	rt	72	dioxane	29
6	50	18	MeCN	71
7	rt	18	MeCN	53

[a] Conditions: NMe_3 (free base, 5 mmol), CF_3OCH_3 (6 mmol), solvent (5 mL). [b] Isolated yields. [c] 4 equiv of NMe_3.

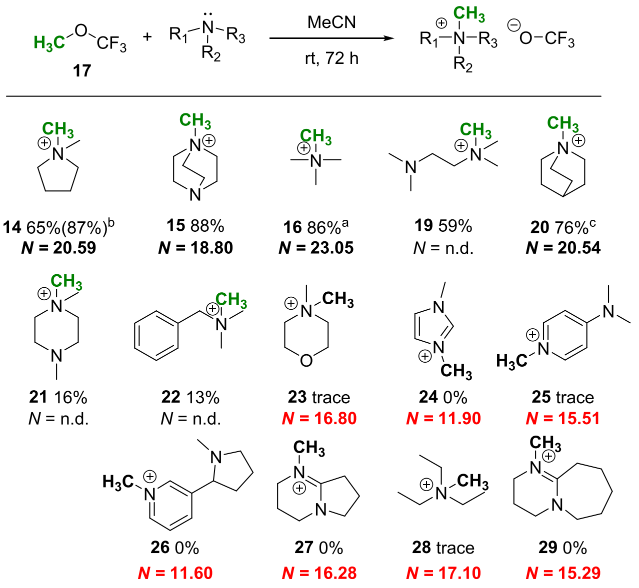


Figure 2. Scope of quaternary ammonium trifluoromethoxides synthesized from trifluoromethyl methyl ether. *N* = nucleophilicity parameter.[50] Reaction conditions: tertiary amines (5 mmol) were dissolved in MeCN (5 mL), treated with CF_3OCH_3 (5−6 mmol), and stirred at rt for 72 h. All yields are reported as isolated yields. [a] Reaction at 50 °C for 72 h. [b] 3.3 equiv of *N*-methylpyrrolidine were used. [c] Reaction at rt for 48 h.

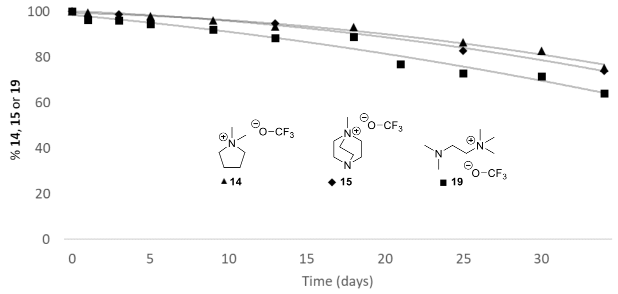
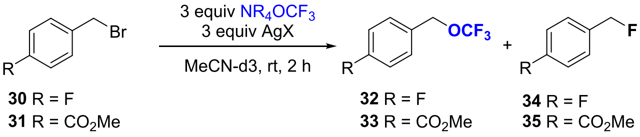


Figure 3. Stability of select quaternary ammonium trifluoromethoxides in MeCN-d_3 at room temperature. Relative concentration determined via ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as an internal standard using a 1D-^{19}F NMR experiment with a 30° pulse to maximize T1 relaxation, allowing the fluorines in each chemical environment to relax completely (see SI for details).

large number of synthetic transformations.[32−40] Other members in the chalcogenide series including tetramethylammonium trifluoromethylselenide[33,34,41−44] and trifluoromethyltelluride[45,46] have also been explored and utilized synthetically.[45,46] We previously reported the synthesis of heptafluoropropoxide, nonafluorobutoxide, and nonafluoroisobutoxide from the reaction of perfluoroalkyl methyl ethers with tertiary amines.[47] In an effort to address existing limitations with trifluoromethoxide reagents noted above, we were intrigued to investigate the corresponding reaction of trifluoromethyl methyl ether (CF_3OCH_3; HFE-143a), a relatively safe and inexpensive gas[48] that is used as a refrigerant or foam-blowing agent and a replacement for chlorofluorocarbons. Notably, this process would advantageously generate metal-free, readily isolable trifluoromethoxide salts that may offer improved stability over existing reagents. Additionally, it was envisioned that the properties of the quaternary ammonium trifluoromethoxides would be tunable through the choice of tertiary amines. Toward this goal, we investigated the reaction of CF_3OCH_3 with trimethylamine. The addition of CF_3OCH_3 was measured via a manometer on a metal line, and condensed into an Ace glass reactor inside a Dewar flask filled with liquid nitrogen. As summarized in Table 1, a solvent optimization identified MeCN as the ideal solvent for this reaction, and we found that the trifluoromethoxide salt was produced in the highest yield when the reaction mixture was stirred for 72 h (entry 3). However, the

Table 2. Reaction of 4-Fluorobenzyl Bromide (30) with Trifluoromethoxide[a,b]



entry	bromide	NR$_4$OCF$_3$	Ag(I)	yield (%)[b]
1	30	15	AgBF$_4$	32 (3); 34 (1)[c]
2	30	14	none	32 (17); 34 (9)
3	30	14	AgOTf	32 (60); 34 (33)[d]
4	30	14	AgBF$_4$	32 (72); 34 (27)
5	31	14	AgBF$_4$	33 (73);[e] 35 (20)

[a] Conditions: 0.3 mmol of trifluoromethoxide, 0.25 mmol of silver salt, 0.5 mL of MeCN-d3, 0.1 mmol of BnBr, rt. [b] Yields (in parentheses) determined by analysis of ^{1}H NMR spectra using an internal standard. [c] Accompanied by 96% of the *N*-methyldabconium adduct. [d] Accompanied by 7% of 4-fluorobenzyltriflate. [e] Isolated yield.

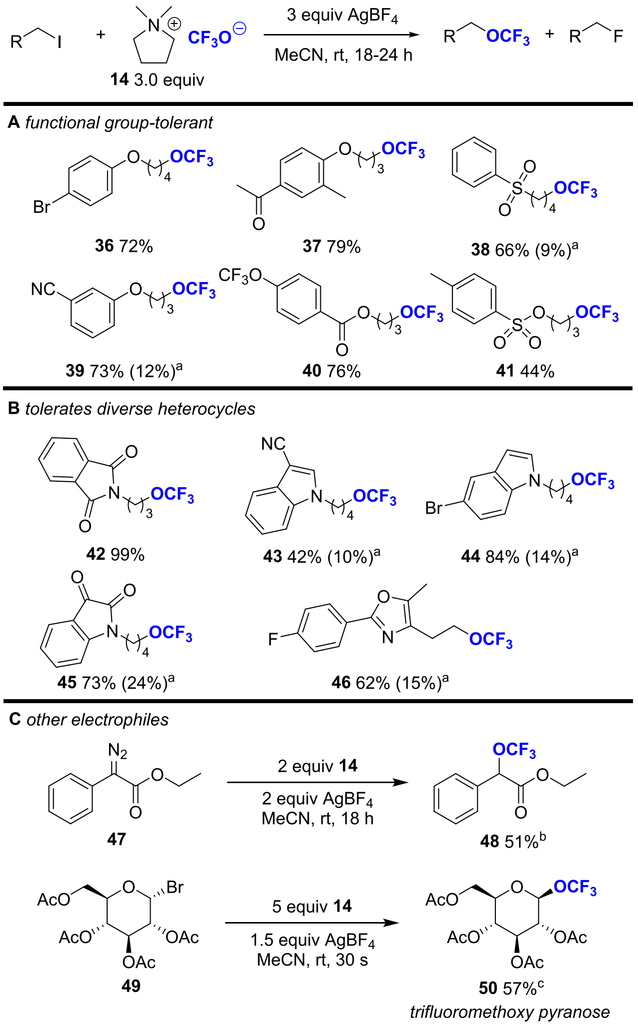


Figure 4. Compatibility of **14** with various functional groups/heterocycles. Reaction conditions: **14** (0.3 mmol) and AgBF$_4$ (0.3 mmol) were dissolved in MeCN (0.5 mL) with alkyl iodide (0.1 mmol). Reaction mixture stirred at rt for 18−24 h. [a] Product inseparable from the alkyl fluoride; yields of alkyl fluorides in parentheses. [b] Diazoester (0.1 mmol) in MeCN (0.5 mL) was mixed with a solution of **14** (0.5 mmol) and AgBF$_4$ (0.15 mmol) in MeCN (0.65 mL) at rt for 18 h. [c] Alkyl bromide (0.1 mmol) was dissolved in MeCN (0.8 mL) with **14** (0.2 mmol) and AgBF$_4$ (0.2 mmol) in MeCN (0.5 mL) at rt for 30 s.

visible appearance of the trifluoromethoxide salt proved best when the reaction was carried out at room temperature for 18 h, a process that afforded the tetramethylammonium salt **16** as a colorless solid, albeit in lower yield (53%, entry 7).

To evaluate the scope of compatible amines, we further explored the reactivity of CF$_3$OCH$_3$ with the range of tertiary amines as summarized in Figure 2. Here, we observed that conversion to the corresponding quaternary ammonium trifluoromethoxide was largely dictated by the nucleophilicity of the tertiary amine (denoted by nucleophilicity parameter, *N*).[49] Specifically, we found that the reactivity parameters collected by Mayr[50,51] proved a good indicator of compatibility with this process and that only the most nucleophilic tertiary amines ($N > 18$) provided trifluoromethoxide salts. For example, *N*-methylpyrrolidine ($N = 20.59$), 1,4-diazabicyclo[2.2.2]octane (DABCO; $N = 18.80$), and quinuclidine ($N = 20.54$) all reacted with CF$_3$OCH$_3$ to produce trifluoromethoxide salts in good yield. Conversely, less nucleophilic tertiary amines including *N*-methyl morpholine ($N = 16.80$) and triethylamine ($N = 17.10$) gave only a trace amount of the corresponding trifluoromethoxide salt. In cases where two amine groups were present, such as tetramethylethylenediamine (TMEDA) and DABCO, no dialkylation was observed. Importantly, all of the trifluoromethoxide salts depicted in Figure 2 are readily isolated by simply concentrating the crude reaction mixture and washing the resulting trifluoromethoxide salt with diethyl ether. This procedure afforded analytically pure quaternary ammonium trifluoromethoxides.

To assess the stability of these new trifluoromethoxide salts, we prepared solutions of the three most readily accessible salts in MeCN-d$_3$ under a nitrogen atmosphere and monitored their composition over one month (Figure 3). Tetramethylammonium salt **16** was excluded from this panel due to its poor solubility in MeCN. Here, we found that roughly 75% of **14** and *N*-methyl dabconium (**15**) salts remained, while 64% of the *N*-methyl TMEDA salt (**19**) persisted. This result highlights the long-term stability of this new class of trifluoromethoxide salts and compares favorably to other reported sources of trifluoromethoxide. In fact, samples of the salts stored in the solid state under a nitrogen atmosphere showed no decomposition after more than one year (see Supporting Information (SI)). We briefly examined the stability of **14** in solution at elevated temperatures and only observed trace decomposition after heating in MeCN-d$_3$ at 90 °C for 12 h (see Supporting Information).

With a suite of stable quaternary ammonium trifluoromethoxides, we assessed their nucleophilicity in the displacement of bromide from the benzyl bromide **30**. Here we found the reaction reached equilibrium at ratios of benzyl bromide/trifluoromethyl ether of ∼4:1 unless a silver source was present to precipitate AgBr (Table 2, entry 4). This proposed role of silver is consistent with Langlois' reported findings.[52] Additionally, we found formation of the trifluoromethyl ether **32** was accompanied by the benzyl fluoride **34**, a common byproduct in substitution reactions involving trifluoromethoxide.[52] It was also observed that when *N*-methyl-DABCO-OCF$_3$ (**15**) was used, the major product was a dabconium adduct (Table 2, entry 1), suggesting that the free amine function persisting in this salt renders it unsuitable for substitution chemistry. In general, the use of AgBF$_4$ as an additive in MeCN and reaction times of 2 h were

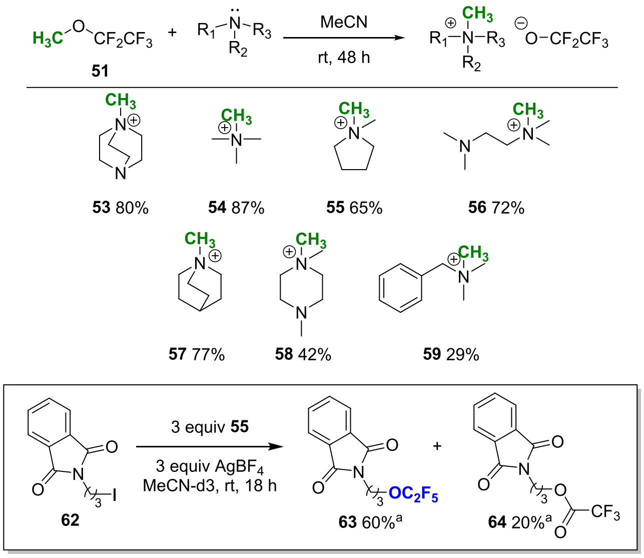


Figure 5. Synthesis of quaternary ammonium pentafluoroethoxides. Reaction conditions: the tertiary amine (10 mmol) was dissolved in MeCN (10 mL) and $CF_3CF_2OCH_3$ (10 mmol) was added. Reaction mixture stirred at rt for 48 h. All reported yields are isolated yields. [a] Produced as a 3:1 mixture with the corresponding alkyl trifluoroacetate.

optimal for production of 4-fluorobenzyl trifluoromethyl ether (**32**).

To further explore the compatibility of **14**, we examined the reaction of this salt with a collection of alkyl iodides containing various functional groups or heterocycles. As summarized in Figure 4, this reagent proved tolerant to aryl ketone, ester, sulfone, sulfonate, and nitrile groups, generating a small library of trifluoromethyl ethers **36**−**41** in 44−85% yield. Additionally, we found that **14** is compatible with several nitrogen-containing heterocycles including indole, oxazole, phthalimide, and isatin, providing the trifluoromethyl ethers **42**−**46** in 42 to 99% yield. We further explored the reaction of **14** with both the diazoester **47** and glycosyl bromide **49** and found in both cases the reagent provided the expected trifluoromethyl ethers **48** and **50**, respectively, in 51% and 57% yield.

To further expand this strategy to generate other perfluoroalkoxide salts not reported previously,[47] we also explored the reactivity of pentafluoroethyl methyl ether with various tertiary amines (Figure 5). Here we found that similar yields of pentafluoroethoxide salts were obtained in only 48 h (*cf.* 72 h, Figure 2), due to the increased reactivity of these reagents as methylating groups. In a single example, we also demonstrated that the reactivity of **55** is analogous to that of **14** in the preparation of the pentafluoroethyl ether **63**. Notably, the commercial anesthetic methoxyflurane (**52**, $CCl_2HCF_2OCH_3$)[53] also contains a difluoroether moiety, and as such we explored its reactivity with tertiary amines and found that it was, in fact, sufficiently reactive to methylate trimethylamine and DABCO (see SI; **60**, **61**), albeit in moderate yield. Here, however, the quaternary ammonium salt was formed with a complex mixture of inseparable side products, and the anticipated alkoxide was not observed (see SI for details).

In conclusion, we have developed a suite of trifluoromethoxide and pentafluoroethoxide salts from trifluoromethyl methyl ether and pentafluoroethyl methyl ether, respectively. These salts exhibit improved stability, both in the solid state and in solution, and will likely complement the existing methods of introducing the valuable trifluoromethoxy group in organic synthesis. While several types of trifluoromethoxide sources have been reported, this new collection of inexpensive quaternary ammonium trifluoromethoxides and pentafluoroethoxides have the advantage that they are readily produced and are applicable for substitution reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00099.

All experimental information and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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