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Amidinate Salt of Hexafluoroacetone Hydrate for the Preparation of Fluorinated Compounds by the Release of Trifluoroacetate

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ABSTRACT

A powerful, new reagent, an amidinate salt of hexafluoroacetone hydrate, is an air-stable salt that can be used for the preparation of fluorinated organic molecules. Nucleophilic trifluoromethylation reactions are demonstrated following the base-promoted release of trifluoroacetate. This reagent is soluble in many polar organic solvents and produces fluoroform, following the release of trifluoroacetate. Reactions with this reagent and common electrophiles provide excellent yields of trifluoromethylated products.

The incorporation of fluorine into organic compounds is a powerful strategy to attenuate the biological properties of candidate molecules in the pharmaceutical industry.[1,2] Accordingly, there has been a substantial effort to develop novel reagents and strategies that can install a trifluoromethyl group using nucleophilic,[3−5] electrophilic,[6−8] radical,[9] and metal-mediated approaches.[10−12] Among these methods, nucleophilic trifluoromethylation has been extensively studied, but the incorporation of a CF_3 group remains limited by the high instability of the CF_3 anion by α-elimination to the difluorocarbene.[4] The most common trifluoromethylating reagent, the Ruppert-Prakash reagent ($TMSCF_3$) stabilizes the CF_3 anion through a Si−CF_3 bond (Figure 1).[3,5] Although Prakash et al. additionally developed phenyl trifluoromethyl sulfone to accomplish nucleophilic trifluoromethylations,[13,14] fluoroform also is a major option for installing trifluoromethyl groups by nucleophilic addition or metal-mediated coupling.[11] The primary drawback that hinders its widespread use in many synthetic laboratories is that fluoroform is a gas. Therefore, a reagent that could

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release fluoroform into a reaction would be highly advantageous. Herein, we describe a novel amidinate salt of hexafluoroacetone hydrate that releases fluoroform following the release of trifluoroacetate and demonstrate its application in executing nucleophilic trifluoromethylations for the synthesis of fluorinated organic molecules.

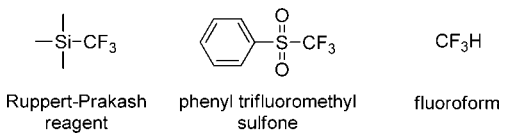
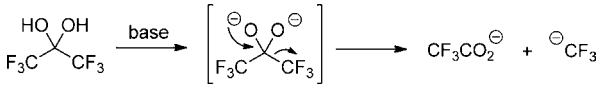


Figure 1. Common nucleophilic trifluoromethylation reagents.

Recently, our laboratory has described the synthetic utility of releasing trifluoroacetate to generate reactive intermediates.[15−17] These studies were based on a report in 1968 from Prager and Ogden that hexafluoroacetone trihydrate fragments in the presence of basic hydroxide into trifluoroacetate and fluoroform (Scheme 1).[18] We hypothesized that this process could be exploited for trifluoromethylations if the CF_3 anion was produced in an anhydrous environment to prevent immediate conversion to fluoroform by the presence of water. Accordingly, the first two goals were to determine an alternative to the hydroxide bases and to generate an anhydrous form of hexafluoroacetone hydrate. Our initial experiments determined that hexafluoroacetone trihydrate fragments in polar organic solvents, such as DMF, DMSO, and CH_3CN, and that metal hydroxides can be replaced by organic bases, such as Et_3N and DBU. Unfortunately, the CF_3 anion cannot be trapped by an appropriate electrophile, such as an aldehyde, due to the immediate conversion to fluoroform in the ^{19}F NMR (data not shown) by the presence of water. Therefore, the need for an anhydrous form of hexafluoroacetone hydrate was paramount.

Scheme 1. Fragmentation of Hexafluoroacetone Hydrate



The anhydrous reagent was developed using an acid−base process, because the protons of the gem-diols of hexafluoroacetone hydrate are highly acidic (pK_{a1} = 6.76 and pK_{a2} = 13.53)[19] compared to fluoroform (pK_a = 30.5).[20] It was found that an ethereal solution of hexafluoroacetone trihydrate would precipitate the amidinate salt **1** upon addition of DBU (Figure 2). Other common organic bases participate in the process, but the DBU-derived salt provided the optimum physical properties (see below).[21] The hexafluoroacetone hydrate amidinate salt **1** is a stable, anhydrous solid that can be freely weighed in air. NMR studies, combustion analysis, and X-ray crystallography verified that the salt **1** does not contain water, unlike the parent hexafluoroacetone trihydrate.[22] Additionally, this salt **1** is not hygroscopic, even after multiple exposures to air for 3 months. It displays high solubility in DMF, DMSO, EtOAc, and CH_3CN and partial solubility in toluene and THF. The salt **1** readily participates in base-promoted trifluoroacetate release to generate fluoroform (Figure 3). Specifically, the fragmentation of **1** in the presence of heat and DBU (1 equiv) were recorded by ^{19}F NMR, and complete conversion of salt **1** into trifluoroacetate and fluoroform was observed.

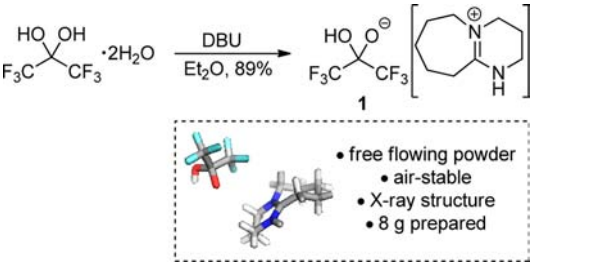


Figure 2. Invention of a new trifluoromethylation reagent, hexafluoroacetone hydrate amidinate salt **1**.

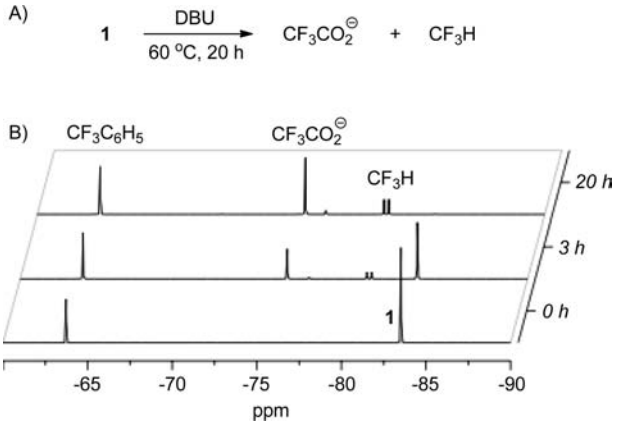


Figure 3. ^{19}F NMR studies of fragmentation of salt **1**.

Fluoroform is the most intrinsic source of a trifluoromethyl group and is available as a side product of the industrial synthesis of Teflon.[23] Shono,[24] Normant,[23,25] Roques,[20] and Langlois[26,27] have reported synthetic methods for the incorporation of the CF_3 anion from

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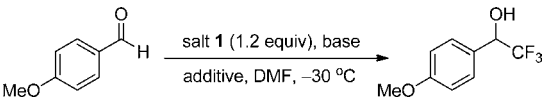
(22) See Supporting Information for details.

fluoroform into organic molecules. Typically, potassium bases, such as KHMDS, KH, *t*-BuOK, and dimsyl-K, are optimal for the deprotonation of fluoroform.[25] However, the decomposition of the CF_3 anion, generated from fluoroform, can occur with metals other than potassium.[23] Also, DMF is the solvent of choice, because the CF_3 anion can be stabilized by solvent trapping to form the DMF-derived hemiaminal.[23,25] Moreover, the hemiaminal trap has been designed into reagents for trifluoromethylation.[4,28] The role of the fluoroform for the synthesis of fluorinated organic molecules has been recently expanded by Grushin in the direct cupration of fluoroform through the use of a potassium base.[11] Therefore, we subjected salt **1** to these potassium bases in DMF at −30 °C to accomplish the trifluoromethylation of *para*-anisaldehyde (Table 1). When the hexafluoroacetone hydrate salt **1** was reacted with KHMDS, no product was observed (entry 1); however, when 18-crown-6 was added to the reaction mixture, the desired product was obtained, albeit in a very low yield of 2%, as determined by ^{19}F NMR (entry 2). Exchanging the base for KH increased the yield of product to 17%, and comparably, the use of dimsyl-K, as described by Normant,[25] provided a similar conversion. The use of *t*-BuOK substantially increased the yield (i.e., 52%) when 18-crown-6 was included (entry 7). Further optimizations were hindered by competing byproducts from Cannizzaro reactions. The final optimization that produced superior yields of the trifluoromethylated product came from exchanging 18-crown-6 with tetrabutylammonium chloride (entry 9). This approach was based on reports from Shono and co-workers that tetraalkylamines are superior counterions when Cannizzaro reactions are observed from potassium counterions during reactions with fluoroform.[24] Thusly, promoting the reaction with a combination of tetrabutylammonium chloride and *t*-BuOK gave an excellent 82% yield of the trifluoromethylated product. The counterions are likely exchanged, and potassium chloride is generated from the mixture. Indeed, a precipitate is observed upon addition of *n*-Bu_4NCl to *t*-BuOK in the reaction mixture. The presumed base is *t*-$BuONBu_4$, which has been reported to have distinct properties compared to *t*-BuOK.[29,30] The ratio of base to the salt **1** (see entry 9) correlated well with the prior work with fluoroform[25] and phenyl trifluoromethyl sulfone,[14] because 2 equiv of base were required for each of the exchangeable protons in **1**. Yields decreased dramatically when fewer equivalents of base were used (entry 8). We presume that the combination of **1** under the optimized basic conditions promotes the generation of the CF_3 anion that adds across the C=O bond.

Table 1. Trifluoromethylations of *p*-Anisaldehyde with Salt **1**



entry	base (equiv)	additive (equiv)	yield[a] (%)
1	KHMDS (4.0)	none	0
2	KHMDS (4.0)	18-crown-6 (1.0)	2
3	KH (2.0)	none	7
4	KH (4.4)	18-crown-6 (1.0)	17
5	dimsyl-K	none	15
6	*t*-BuOK (4.0)	none	10
7	*t*-BuOK (4.0)	18-crown-6 (2.0)	52
8	*t*-BuOK (3.0)	*n*-Bu_4NCl (3.0)	7
9	**t-BuOK (4.4)**	***n*-Bu_4NCl (4.4)**	**82**

[a] Yields based on ^{19}F NMR ($CF_3C_6H_5$ is the internal standard).

With the optimized procedure, a series of aldehydes and ketones were converted to their trifluoromethyl alcohols in good to excellent (78−96%) isolated yields (Table 2). Aryl aldehydes substituted with electron-donating groups or halogens are fully compatible to trifluoromethylation with salt **1**. Similarly, diaryl ketones can also be trifluoromethylated using this method to provide excellent yields of trifluoromethyl alcohols (Table 2, entries 7−10). The workup procedure for this synthetic method is notable, because the byproducts of the reaction (i.e., *t*-BuOH, tetrabutylammonium salts, and trifluoroacetate) are easily removed by an aqueous wash. High-yielding trifluoromethylations with salt **1** can be executed on the milligram scale and up to the gram scale. For example, an 87% isolated yield was obtained with *para*-dimethylaminobenzaldehyde (15 mg, 0.1 mmol) and **1** (Table 2, entry 5), and upon scale-up to 1 g (6.7 mmol), a 75% yield of the trifluoromethylated alcohol was procured. Additionally, phenyl disulfide, a precursor to the phenyl trifluoromethyl sulfone reagent, is trifluoromethylated with salt **1** (eq 1). Overall, the scope of the substrates that participate in this synthetic method with salt **1** is nearly identical to that for the novel phenyl trifluoromethyl sulfone developed by Prakash et al.[13] This reagent provides a substantial improvement in yields when compared to the deprotonation of fluoroform, and only 1.2 equiv of **1** is required. Also, releasing trifluoroacetate into the reaction media is not a concern, because it is already widely present as a counterion in many synthetic reactions and is also nontoxic.[31] Lastly, salt **1** can be prepared in one synthetic step up to a multigram scale without any purification.

$$\mathrm{Ph-S-S-Ph} \xrightarrow[\text{DMF, } -30\ ^\circ\mathrm{C,\ 73\%}]{\text{salt 1, } t\text{-BuOK, } n\text{-Bu}_4\mathrm{NCl}} \mathrm{Ph-S-CF_3} \quad (1)$$

The role of fluoroform in the synthesis of fluorinated organic compounds has expanded substantially following

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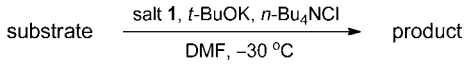
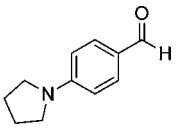
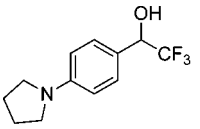
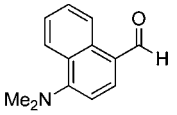
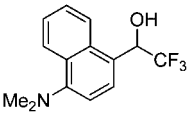
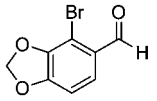
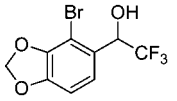
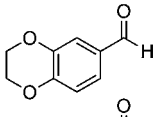
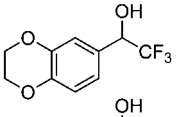
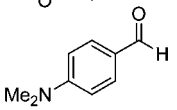
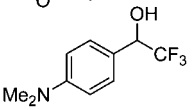
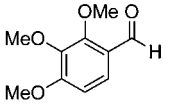
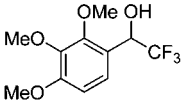
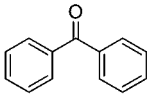
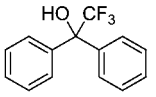
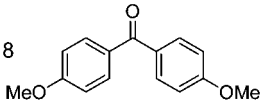
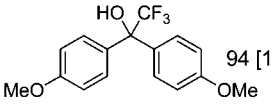
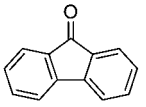
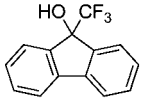
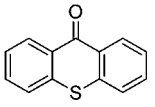
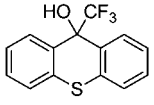
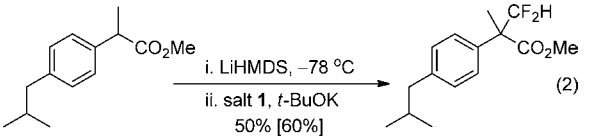
Table 2. Scope of Trifluoromethylations with Salt **1**



entry	substrate	product	yield[a] (%)
1			96 [100]
2			92 [93]
3			80 [82]
4			84 [88]
5			87 [92]
6			95 [100]
7			94 [100]
8			94 [100]
9			88 [99]
10			78 [81]

[a] Isolated yields [^{19}F NMR yields ($CF_3C_6H_5$ is the internal standard)].

the direct cupration methods reported by Grushin in 2011[11] and 2012.[32] Additionally in 2012, Mikami et al. have demonstrated a striking protocol for the C–F activation of fluoroform with lithium enolates for difluoromethylation.[33] Accordingly, we aimed to determine if salt **1** participates in a similar difluoromethylation process by adapting the protocol of Mikami. Using the lithium derived enolate of the methyl ester of ibuprofen, difluoromethylation succeeded by bubbling fluoroform generated from **1** through the reaction media (eq 2). The product was observed in a 60% yield as determined by ^{19}F NMR and obtained in 50% yield after isolation. These modest yields are quite comparable to the previously reported yields (i.e., 33%–82%),[33] yet represent another powerful use of this novel amidinate salt of hexafluoroacetone hydrate (**1**) and the release of trifluoroacetate.



In conclusion, we have discovered an amidinate salt of hexafluoroacetone hydrate and DBU that generates fluoroform following the base-promoted release of trifluoroacetate. This stable reagent is not hygroscopic, can be routinely weighed in air, and will participate as a nucleophilic trifluoromethylation reagent. It can be prepared in one step without any purification (up to a multigram scale) and is not a fluoro-halocarbon-based chemical, which is potentially ozone-depleting. The addition of a trifluoromethyl group occurs from 1 equiv of reagent and in good to excellent yields on carbonyl and disulfide electrophiles. A reaction with this reagent can be executed on a milligram scale and up to a gram scale. This reagent is a dynamic source of fluoroform, as it can either directly release fluoroform into an organic solvent or generate it for bubbling through a reaction mixture. Moreover, this reagent will drive the discovery of new approaches for the incorporation of a trifluoromethyl group that use fluoroform. Such methods have garnered increasing utility from the recent elegant work with fluoroform by Grushin[11] and Mikami.[33] We have additionally demonstrated that this reagent can also prepare a difluoromethylated molecule using a modified version of the latter method. The byproducts from this reagent are innocuous (i.e., trifluoroacetate and DBU). Future studies will describe new avenues of inducing trifluoroacetate release and extending the use of this salt in trifluoromethylation reactions as well as other preparations of fluorinated organic structures.[34]

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Supporting Information Available. Full experimental details, spectroscopic data, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) The reagent **1** has recently been commercialized by Sigma-Aldrich (product #L511315).