Study of Carbamoyl Fluoride: Synthesis, Properties and Applications

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Abstract: Carbamoyl fluoride is a fluorinated group which, to this date, remains underexplored, probably due to the lack of data concerning their properties. In this paper, a study of carbamoyl fluoride is proposed. Stability studies, in particular under physiological conditions, and lipophilicity measurement have been performed. A new easy, safe, inexpensive and metal-free synthesis method has also been described. Finally, a potential use in radiochemistry through a $^{18}F/^{19}F$ isotopic exchange has been demonstrated.

Introduction

Due to the intrinsic properties of the fluorine atom, fluorinated compounds have become increasingly popular in recent decades for various applications. This is mainly due to the specific properties brought by fluorinated groups to molecules.[1] Thus, fluorinated substrates are present in a wide range of applications such as materials,[2] agrochemicals,[3] medicinal chemistry[4] or medical imaging.[4f, 5]

Due to such an interest, the design of new molecules with innovative fluorinated moieties is still a very active research topic in order to propose new specific properties and applications. For this purpose, the fusion of fluorine with other heteroatoms is a fruitful approach that has been considered in recent years.[6]

In this context, carbamoyl fluorides have appeared to be clearly underexplored. This could be explained by the scarcity of methods to synthesize these compounds. Historically, they were obtained by reaction of amines with difluorophosgene or chlorocarbonyl fluoride, which are gaseous and toxic.[7] Fluorination, with a fluoride source, of carbamoyl chlorides, which are also difficult to synthesize, was also carried out.[8] More recently, a few methods have been described, circumventing the previous drawbacks. Thus, carbamoyl fluorides were obtained by reaction of amines with $AgOCF_3$, with CO_2/DAST system or with $CF_3SO_2OCF_3$. However, these methods required either an excess of silver salt or the use of toxic and explosive or volatile reagents.[9] Other starting substrates than amines have also been considered. Isothiocyanates can react with triphosgene and AgF to give N-CF_3 carbamoyl fluorides.[9a, 10] This approach is limited to N-CF_3 substituted compounds and also required an excess of silver salt. A DAST-mediated Beckmann fluorinative fragmentation of α-oximinoamides, mediated by DAST, has also been described.[11] Not only did this method require the prior synthesis of the starting α-oximinoamides but it also used the toxic and explosive DAST.[12] Finally, the reaction of difluorocarbene, thermally generated from $BrCF_2CO_2Na$, with hydroxylamines provided the corresponding carbamoyl fluorides.[13] Again, this strategy requires the prior synthesis of starting materials and only average yields have been obtained (up to 63%).

Perhaps due to the underdevelopment of efficient and easy to perform synthesis methods, the properties of carbamoyl fluorides have not been well studied. Nevertheless, these data would be of a great interest in determining the potential applications of these fluorinated moieties.

Results and Discussion

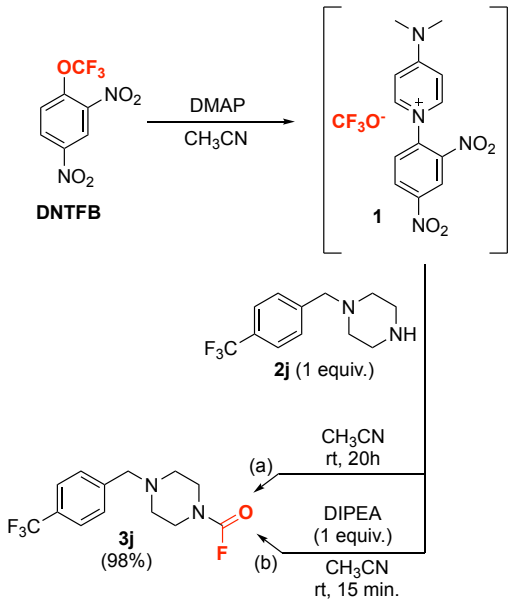
As part of our goal to develop new emerging fluorinated groups, we decided to study in detail the carbamoyl fluoride group, especially in terms of stability, in order to gain better information regarding its potential field of applications.

In view of literature reports, no preparative methods appeared to be fully satisfactory to prepare carbamoyl fluorides. In that context, we thus decided to first develop our own method to easily, safely and cheaply obtain the expected carbamoyl fluorides from the corresponding amines.

Recently, we described an efficient preparation of a stable solution of trifluoromethoxide anion (**1**) from inexpensive 2,4-dinitrotrifluoromethoxybenzene (**DNTFB**).[14] This anion is known to be able to collapse into difluorophosgene upon losing the fluoride anion. Therefore, we hypothesized that the N-H of the amines could help to promote such a dissociation, thereby

generating, in situ, $C(O)F_2$ which could then react with amines to ultimately provide the expected carbamoyl fluorides.

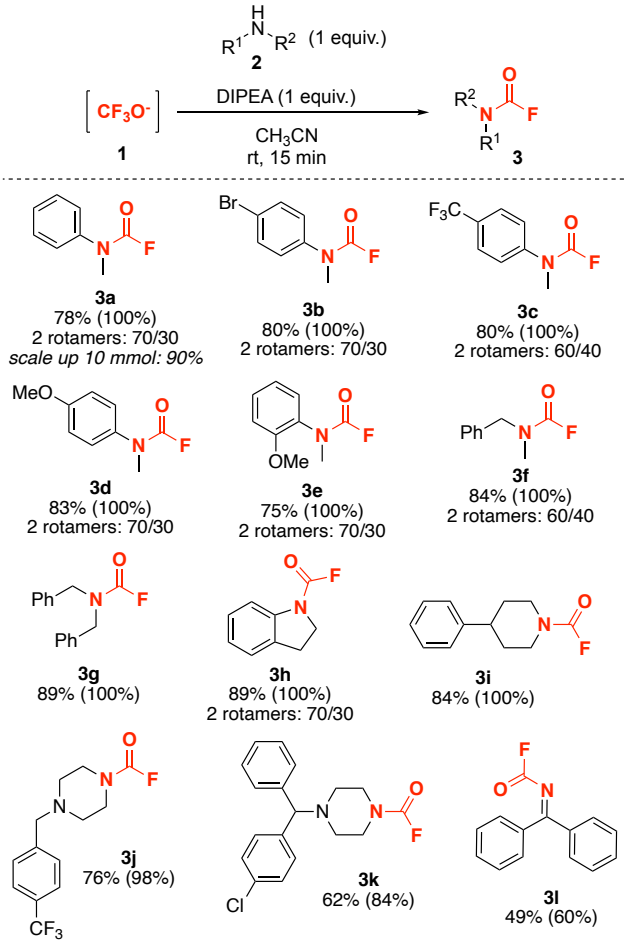
When piperazine **2j** was added to the preformed solution of **1**, the expected carbamoyl fluoride **3j** was obtained with excellent yield within 20 h at room temperature (Scheme 1a). Since HF is formally formed during the reaction, the addition of diisopropylethylamine (DIPEA) was considered. The yield remained similar but with a significantly shortened reaction time to only 15 min (Scheme 1b).



Scheme 1. Reaction of **1** with piperazine **2j.**

This excellent result led us to consider the latter conditions (Scheme 1b) as a very efficient preparative method to form carbamoyl fluorides easily and safely. In order to confirm the efficiency of this method, other amines were then assessed in this reaction (Scheme 2).

Excellent yields were also observed with anilines, regardless of the electronic character of the substituents (**3a-e**). Moreover, no specific steric hindrance effect was observed with an ortho-substituent (**3e**). Benzylamines gave equally excellent results (**3f-g**). With cyclic amines such as indoline (**3h**), piperidine (**3i**) or piperazines (**3j-k**), very good yields were also obtained. More interestingly (and less usual), carbamoyl fluoride from an imine was successfully formed as well with satisfactory yield (**3l**). Finally, this method was scaled-up to 10 mmol scale without detrimental influence onto the yield (**3a**). Of note, in case of unsymmetric amines ($R^1 \neq R^2$), 2 rotamers were observed (ratio 60/40 to 70/30), as previously observed in literature.[9a, 9b]



Scheme 2. Synthesis of carbamoyl fluorides. Isolated yields. In parentheses, yields determined by ^{19}F NMR with $PhOCF_3$ as internal standard.

In the case of primary amines, expected carbamoyl fluorides were observed by ^{19}F NMR with only low yields and a degradation was observed over time (e.g. with benzylamine, yields of 12% within 2h and 6% within 5h were obtained). This in accordance with literature, describing the formation of isocyanates from carbamoyl fluorides arising from primary amines.[7e]

These results highlight the efficiency of the method and its wide range of application in terms of substrates. Therefore, bioactive, and more sophisticated, amines were also considered (Figure 1). With such substrates, the reaction gave also good to excellent yields. Free NH moieties do not seem to interfere with the reaction (**3n**, **3r**). It also seemed compatible with the ester function in the case of tetracaine (**3o**). With sildenafil (**3r**), the reaction showed tolerance to the sulfonamide and amide functional groups. In the case of ciprofloxacin (**3p**), with only 1 equiv. of **1**, a mixture of carbamoyl fluorides with either the carboxylic function (**3p**, X=OH) or the corresponding acyl fluoride (**3p**, X=F) was obtained. As the acyl fluoride resulted from the reaction between the carboxylic acid and difluorophosgene,[15] the reaction was carried out with 2 equiv. of **1** and only the carbamoyl fluoride with the acyl fluoride group (**3p**, X=F) was then formed.

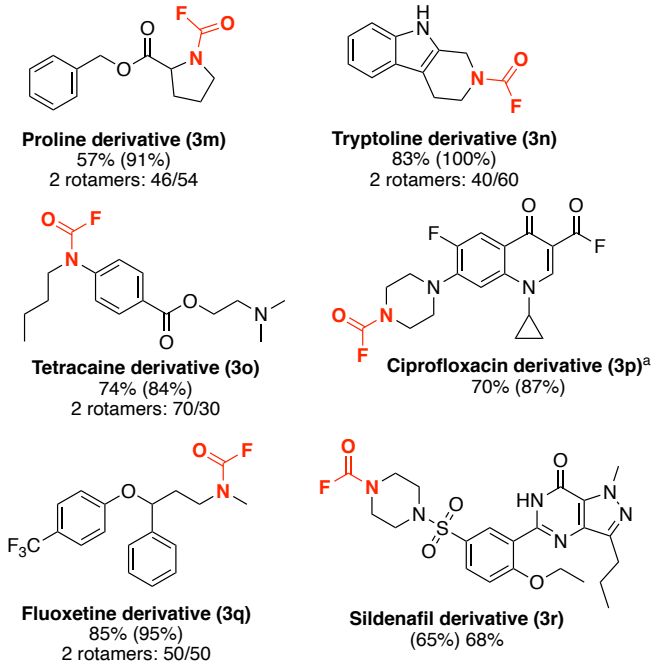


Figure 1. Carbamoyl fluoride arising from bioactive amines. Isolated yields. In parentheses, yields determined by ^{19}F NMR with $PhOCF_3$ as internal standard. [a] with 2 equiv. of CF_3O^- solution **1**.

Having in hand an efficient synthesis method to obtain carbamoyl fluorides, we then turned our attention on their properties, starting with the study of the stability of these compounds, especially in conditions close to physiological ones.

First, stability in various media, especially aqueous ones, was studied with compound **1a** as model substrate (Figure 2).

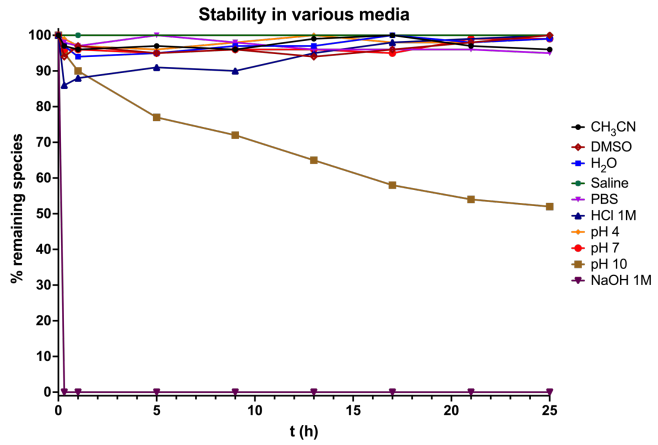


Figure 2. Stability of carbamoyl fluoride **1a** in various media (T = 28°C). PBS: phosphate-buffered saline (pH =7.4).

Carbamoyl fluorides appeared to be stable in both organic solvents (DMSO, CH_3CN) and water. The same stability was also observed in more physiological media such as saline or PBS (phosphate-buffered saline). Carbamoyl fluorides are also compatible with a wide pH range, since hydrolysis was only observed from pH = 10. Nevertheless, a rapid hydrolysis was observed in strong alkaline solution (NaOH 1M).

To confirm and reinforce this stability observed in a medium close to physiological one, an incubation at 37°C in PBS, and for a longer time was also considered (Figure 3). A good stability was observed over 100 h as more than 80% of the initial amount of carbamoyl fluoride was recovered.

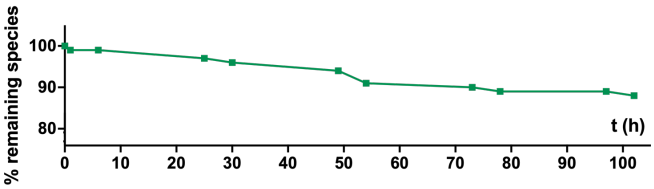


Figure 3. Incubation of carbamoyl fluoride **1a** in PBS at 37°C.

These interesting stabilities prompted us to further investigate the compatibility of carbamoyl fluorides in environments mimicking physiological one.

Stability studies in the presence of various nucleophilic amino-acids were then performed (Figure 4). Again, a very good compatibility was observed. A similar tolerance was also noted in the presence of serum albumin.

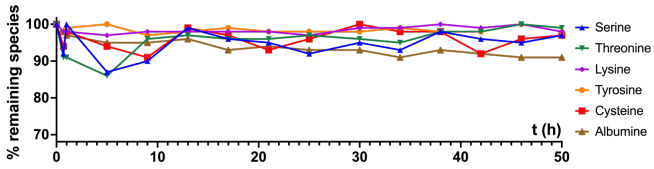


Figure 4. Stability of carbamoyl fluoride **1a** in presence of various nucleophilic amino-acids and serum albumin (T = 28°C).

All these results demonstrated an excellent stability of carbamoyl fluorides in conditions close to the physiological environment and suggest a potential use of this fluorinated moiety in medicinal chemistry.

To pursue our study on carbamoyl fluoride properties, the impact of carbamoyl fluoride on the lipophilicity of molecules, an important parameter in drug design, was determined (Figure 5).[16] It appeared that the exchange of a hydrogen with a C(O)F group on the nitrogen of the amines does not significantly alter the lipophilicity of the corresponding molecules (Figure 5). This suggests that the introduction of a carbamoyl fluoride in place of an amino group on molecules should not disturb their physicochemical properties too much.

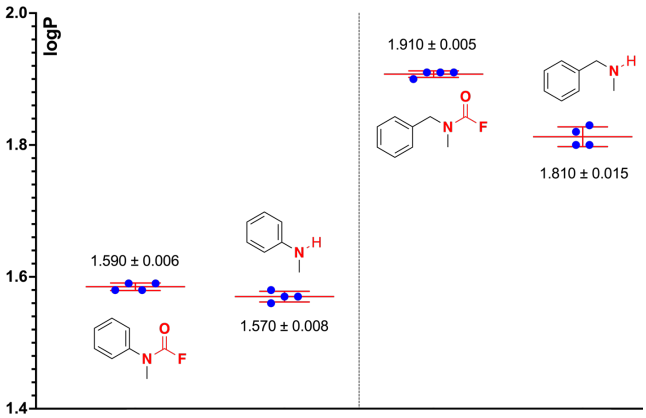


Figure 5. Lipophilicity of carbamoyl fluorides and corresponding amines.

With these properties in hand, we then considered the application of carbamoyl fluorides.

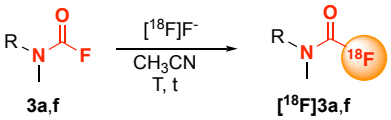
Some chemical reactivities of carbamoyl fluorides have been described in the literature with heteronucleophiles to access ureas, carbamates or thiocarbamates.[9c, 10-11, 13] In the case of N-CF_3 carbamoyl fluorides, reaction with Grignard reagents and Ni-catalyzed coupling have also been described to obtain the corresponding amides.

On our side, we have considered the potential use of carbamoyl fluoride in PET radiochemistry.

Radiolabeled molecules with fluorine-18 are used in PET imaging for various applications ranging from drug design, pharmacological studies to medical diagnosis.[5a, 17] Many radiolabeling approaches have been described these last years.[5c, 18] One of these approaches uses fluorinated tags that can be easily introduced onto organic molecules and then radiolabeled at a late-stage by $^{18}F/^{19}F$ isotopic exchange. Recently, SuFEx chemistry has been applied to obtain fluorosulfonates and sulfamoyl fluorides that were radiolabeled by $^{18}F/^{19}F$ isotopic exchange.[19] Based on these results, we hypothesized that carbamoyl fluorides could also be used in a similar labeling strategy. Therefore, $^{18}F/^{19}F$ isotopic exchange was performed with carbamoyl fluorides **3a** as model to establish the proof-of-concept of such a labeling (Table 1).

With carbamoyl fluoride from aniline (**3a**), radiolabeling under standard conditions, at 80°C, resulted primarily in hydrolysis of **3a**, with only a very small amount of labeled product being observed (entry 1). Under standard conditions, cyclotron-produced $[^{18}F]F^-$ is trapped on an anion-exchanger cartridge and is then eluted inside the reactor with K_2CO_3 / Kryptofix 222 in CH_3CN/H_2O eluent. Due to the sensitivity of carbamoyl fluorides under strongly basic conditions (Figure 2), the presence of K_2CO_3 could explain the observed degradation of **3a**. To confirm this hypothesis, a new eluent was prepared by replacing potassium carbonate with potassium triflate. In this case, the radiolabeling worked well to produce **[^{18}F]3a** with good radiochemical yield (entry 2). Interestingly, radiolabeling could also be performed at 28°C, with even a better radiochemical yield (entry 3). Finally, in only 3 min (instead of 10 min), the radiochemical yield remains satisfactory (entry 4). The optimal conditions of entry 3 were applied to the aliphatic carbamoyl fluoride **3f** (entry 5). Surprisingly, a disappointing result was observed. Assuming that aliphatic carbamoyl fluorides may be less reactive than the aromatics, heating was considered (entries 6-7) and 60°C appeared to be the best conditions to obtain a satisfactory radiochemical yield (entry 6).

Table 1. $^{18}F/^{19}F$ isotopic exchange with carbamoyl fluorides.



3a,**f** **[^{18}F]3a**,**f**

Entry	$[^{18}F]F^-$ eluent[a]	3	T (°C)	t (min)	RCY (%)[b]
1	K_2CO_3 / Kryptofix 222	**3a**	80	10	2
2	TfOK / Kryptofix 222	**3a**	80	10	33
3	TfOK / Kryptofix 222	**3a**	28	10	44
4	TfOK / Kryptofix 222	**3a**	28	3	35
5	TfOK / Kryptofix 222	**3f**	28	10	4
6	TfOK / Kryptofix 222	**3f**	60	10	27
7	TfOK / Kryptofix 222	**3f**	80	10	16

[a] Solvent: CH_3CN/H_2O, 50/50. [b] Radiochemical yields (RCY) were estimated from $[^{18}F]F^-$ within the reactor and are decay-corrected from end of elution of $[^{18}F]F^-$ inside reactor.

With these two conditions in hand, the scope of this radiolabeling method was explored (Figure 6).

Labeling gave globally satisfactory to good yields. In general, the radiochemical purity (RCP) was excellent (> 95%). It is interesting to note that the chemical purity (CP), observed without further purification, was often already satisfactory, certainly due to the mild conditions.

Molar activity (A_m) of **[^{18}F]3a** was found to be 1.2 GBq/µmol. This value is higher than those obtained with labeling of Aryl-SCF_3, Aryl-OCF_3 or Aryl-CF_3 previously described[20] but remains modest. Even if high A_m is not systemically required, depending on the radiotracer,[21] at this stage, such value appears best suited to support drug development studies. This modest value of A_m is not surprising because a large excess of precursor **3a** (6.5 mmol vs 0.277 nmol of ^{18}F) was used. We can then reasonably suppose that by using an automatic synthesizer more adapted to work with smaller reaction volume, allowing to use a lower precursor quantity, a higher A_m should be achieved, as demonstrated with SuFEx radiolabelings.[19]

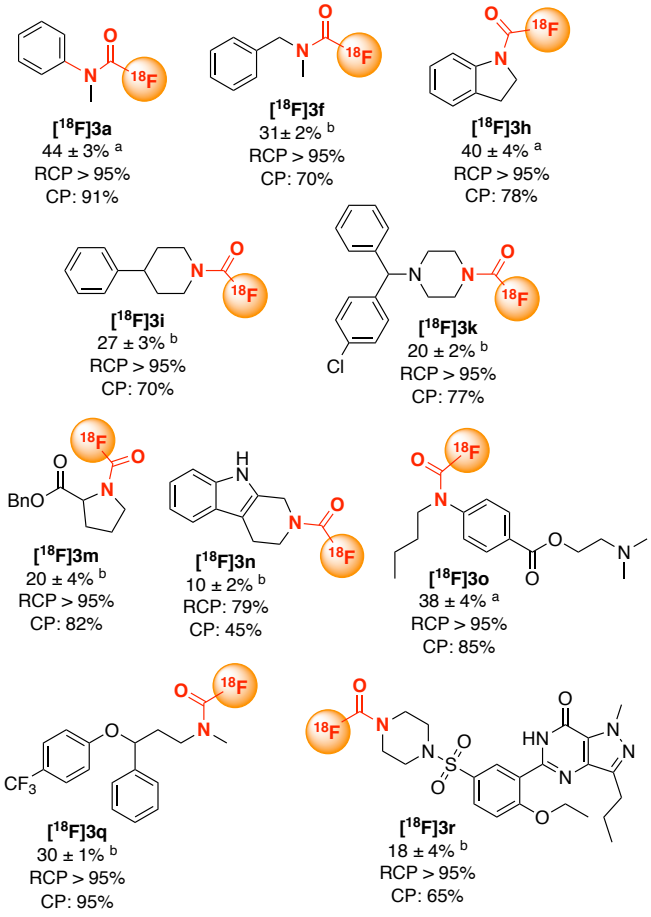


Figure 6. Scope of radiolabeling of carbamoyl fluorides. Radiochemical yields are expressed as average ± SD (n = 2-3) and estimated from $[^{18}F]F^-$ within the reactor and decay-corrected from end of elution of $[^{18}F]F^-$ inside reactor. RCP: radiochemical purity, determined by HPLC. CP: chemical purity, determined by HPLC. [a] 28°C. [b] 60°C.

This labeling is compatible with certain functional groups as ester (**[^{18}F]3m**,**o**), sulfonamide (**[^{18}F]3r**), amide (**[^{18}F]3r**) or chloride (**[^{18}F]3k**). It was also found to be tolerant to free NH (**[^{18}F]3n**,**r**), with the observed radiochemical yields not being too much affected; the main impact concerned the chemical purity. Elaborated molecules such as Prozac (**[^{18}F]3q**), Tetracaine (**[^{18}F]3o**) or Viagra (**[^{18}F]3r**), could be labeled with good results.
Compared to sulfamoyl fluorides previously described in the literature,[19a] the labeling of carbamoyl fluorides by $^{18}F/^{19}F$ isotopic exchange seems to be competitive.

Conclusion

In this study, the little explored carbamoyl fluorides have been better described in order to bring relevant information to the whole community of chemists for other applications. Stability studies have been carried out, demonstrating their resistance in conditions close to physiological requirements. Their impact on lipophilicity has also been determined. To promote the future uses of this fluorinated group, an easy, safe, inexpensive and metal-free synthesis method has also been proposed to complement the few existing methods. Finally, a first possible application of carbamoyl fluorides was described by demonstrating the efficiency of their radiolabeling by $^{18}F/^{19}F$ isotopic exchange. This proof of concept opens the way to further developments to use carbamoyl fluorides as a potential fluorine-18 tag.
All these results have led to a better understanding of carbamoyl fluorides and should help to add this promising fluorinated group to the toolbox of synthetic chemists, medicinal chemists and radiochemists.

Experimental Section

Typical procedure: Synthesis of Carbamoyl fluoride. To a flask equipped with a magnetic stirrer, DMAP (1 mmol, 1 equiv.), **DNTFB** (1 mmol, 1 equiv.) and anhydrous MeCN (3 mL) were added. The reaction mixture was stirred for 2 h at 20 °C. N,N-Diisopropylethylamine (1 mmol, 1 equiv.) and the amine (1 mmol, 1 equiv.) were then added to the mixture at 20 °C. The flask was sealed and the reaction mixture was stirred for 15 min. Conversion was determined by ^{19}F NMR with $PhOCF_3$ as an internal standard. The reaction mixture was partitioned in between Et_2O and water. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to dryness. The crude residue was purified by flash chromatography to produce the desired product.

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Keywords: Fluorine • Carbamoyl fluoride • Dinitrotrifluoromethoxybenzene • Trifluoromethoxide • Radiochemistry

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