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Toward the Synthesis of the Rare *N*-(Trifluoromethyl)amides and the *N*-(Difluoromethylene)-*N*-(trifluoromethyl)amines [$RN(CF_3)CF_2R'$] Using BrF_3

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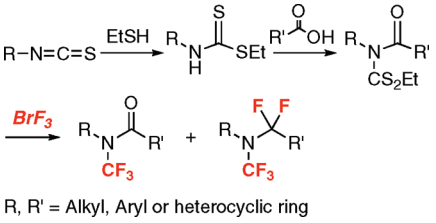

A synthesis of a wide range of different aliphatic, aromatic, and heterocyclic *N*-(trifluoromethyl)-amides along with aromatic *N*-(difluoromethylene)-*N*-(trifluoromethyl)amine derivatives has been developed. The starting materials are the easily available isothiocyanates, and the fluorinating reagent is the commercially available bromine trifluoride. The reaction is performed under mild conditions, and the fluorinated amides and amines are produced in moderate to high yields.

Introduction

Fluoro-organic compounds, whose chemistry is being continuously developed at an unparallel rapid pace, have an important role in our daily life. Among the major players on this subject are the trifluoromethyl (CF_3) and the difluoromethylene (CF_2) groups. These moieties influence significantly the physiological, physical, and chemical properties of numerous compounds used, among others, in material sciences and medicinal and agricultural chemistry.[1] Yet, *N*-(trifluoromethyl)amide derivatives are rare despite the fact that some of them have high antifungal properties,[2] show potential activity for HIV therapy,[3] and are useful electrolyte additives for batteries.[4] Only a few tailor-made syntheses are reported for their preparation, and they are centered around the reaction of perfluoro *N*-alkylamines with oleum,[5] on attaching the $F_2C{=}NCF_3$ group to different acids,[2,6] and the electrochemical fluorination of *N*,*N*-dimethylperfluoroacrylamides.[7] We report here a general and facile route for the preparation of *N*-(trifluoromethyl)amides based on the use of BrF_3 along with an option of constructing the corresponding unknown pentafluoroamines (mainly for aromatic derivatives) by changing the reaction conditions.

Although commercial, bromine trifluoride is not a common reagent in every organic laboratory, and many chemists do not feel at ease with it because of its high reactivity. However, under the right conditions, it can be used as a fluorinating agent for various heteroatoms,[8] for forming

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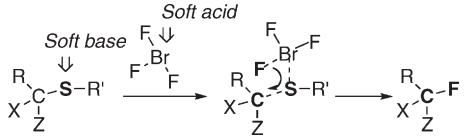
hexafluorocyclopentadiene,[9] producing modern anesthetics such as desflurane,[10] for transforming carbonyls to the CF_2 moiety,[11] and for converting either alkyl halides or carbonyls to the CHF_2 group.[12] It was also used for synthesizing the novel OCF_2Cl,[13] OCF_2H,[14] and OCF_2O[15] moieties, for achieving difficult to obtain aromatic brominations[16] and for other transformations.[17]

The major reason for the highly reactive nature of bromine trifluoride is its weak Br−F bonds encouraging indiscriminate radical reactions.[18] In order to avoid such pathways, a soft base (usually a sulfur or a nitrogen atom) has to be present in the target molecule in order to form a complex with the soft acidic bromine atom and thus place its fluorides near the site where a substitution is planned (Scheme 1).[17] It should be emphasized that this proximity and the fact that the fluorides are nonsolvated are responsible for a very fast substitution (usually less than a minute), which is quite uncharacteristic for reactions involving a nucleophilic fluorination.

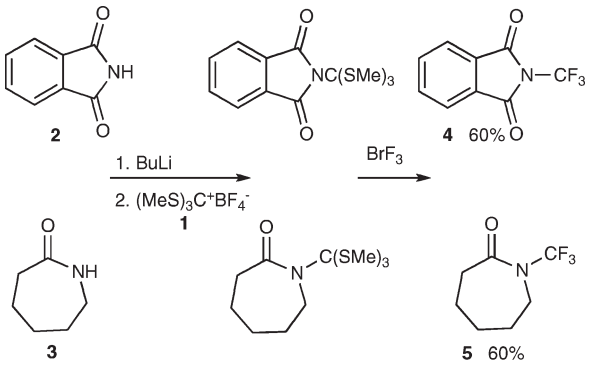
SCHEME 1. General Mechanism for Selective Reactions with BrF_3



Results and Discussion

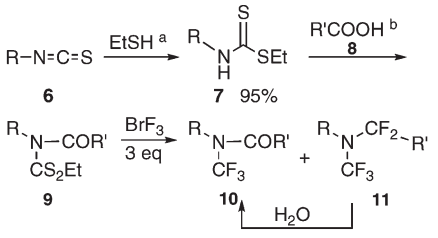
Our initial strategy for the preparation of *N*-(trifluoromethyl)amides was to react amides with strong bases such as butyllithium followed by addition of carbon disulfide and methyl iodide[1d,19] in order to obtain the *N*-trismethylthioamides (RC(O)N(R)CSSMe) in hope that they would be suitable substrates for reaction with BrF_3. However, when we tried this approach with phtalimide and other amides, very low yields (< 20%) of the dithiocarbamates were obtained. A more promising approach was to react different imides or amides with tris(methylthio)methyl tetrafluoroborate (**1**).[20] Indeed, when **1** was reacted with the anion of phtalimide (**2**) or caprolactam (**3**) we obtained the corresponding $NC(SMe)_3$ derivatives which, when treated with bromine trifluoride produced the *N*-(trifluoromethyl)phthalimide (**4**)[21] and *N*-(trifluoromethyl)caprolactam (**5**)[4] both in 60% yield (Scheme 2).

SCHEME 2. Formation of *N*-(Trifluoromethyl)amides with $(MeS)_3C^+BF_4^-$



The synthesis of **1**, however, is somewhat problematic since it is very moisture sensitive, and what is more, many amides did not give satisfactory results. We turned our attention therefore to the family of isothiocyanates (**6**), which proved to be the best general entry to the family of *N*-(trifluoromethyl)amides and, if desired, also to the novel family of aromatic *N*-(difluoromethylene)-*N*-(trifluoromethyl)amines. The isothiocyanate derivatives (**6**) were reacted with ethanethiol to form ethyl alkyldithicarbamates (**7**) in almost quantitative yield (Scheme 3). The next step involved treating compounds **7** with carboxylic acids **8** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) forming a variety of respective ethyl alkyl(alkanoyl)dithiocarbamate derivatives (**9**) in good yields. These readily obtained compounds could then complex the bromine atom of the BrF_3 and as a result the nearby fluorides efficiently substituted the sulfur atoms forming the desired *N*-(trifluoromethyl) compounds (**10**) in good yields (Scheme 3).

SCHEME 3. Aliphatic *N*-(Trifluoromethyl)amides (10)



	Yield **9**	Yield **10** [c]
a. R = C_4H_9 ; R' = C_5H_{11}	75%	85%
b. R = C_4H_9 ; R' = $C_{10}H_{21}$	95%	85%
c. R = C_4H_9 ; R' = $Cl(CH_2)_4$	75%	65%
d. R = C_4H_9 ; R' = $MeCH_2CH(Me)$	90%	85%
e. R = C_4H_9 ; R' = $MeOOC(CH_2)_3$	95%	85%
f. R = C_2H_5 ; R' = $CH(CH_2CH_2CH_3)_2$	90%	90%
g. R = C_6H_{11} ; R' = C_7H_{15}	95%	85%

a) Et_3N, THF, reflux 20h; b) DCC/DMAP; c) after hydrolysis

Thus, when ethyl butyl(hexanoyl)dithiocarbamate (**9a**), prepared from **7a**,[22] was treated with 3 mol/equiv of bromine

(9) For example, it has been used to make hexafluorocyclopentadiene: Soelch, R. R.; Mauer, G. W.; Lemal, D. M. *J. Org. Chem.* **1985**, *50*, 5845-5852.
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trifluoride, the product, obtained in a few seconds, proved to be the desirable *N*-butyl-*N*-(trifluoromethyl)hexanamide (**10a**) accompanied by another somewhat surprising compound found to be *N*-butyl-*N*-1,1-difluorohexyl-*N*-(trifluoromethyl)amine (**11a**). However, **11a** was hydrolytically unstable and in the presence of moisture was fully hydrolyzed to the desired **10a** for a total yield of 85% in a few minutes.[15,23]

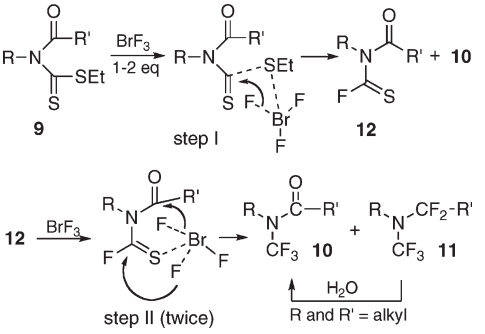
Similarly, ethyl butyl(dodecanoyl)dithiocarbamate (**9b**) served as a starting material for *N*-butyl-*N*-(trifluoromethyl)-dodecanamide (**10b**) obtained in 85% yield with parallel formation of *N*-butyl-*N*-(1,1-difluorododecyl)-*N*-(trifluoromethyl)amine (**11b**), which again could be readily, and practically quantitatively, hydrolyzed back to **10b** (Scheme 3).

The scope of this reaction is quite wide. While it is known that BrF_3 can substitute chlorine with fluorine,[24] we found that the reaction at the sulfur center is much faster so a chlorine atom is not much affected. Ethyl butyl(5-chloropentanoyl)dithiocarbamate (**9c**) was thus converted to the desired *N*-butyl-5-chloro-*N*-(trifluoromethyl)pentanamide (**10c**), although in 65% yield, somewhat lower than usual. Branched aliphatic compounds were not susceptible to eliminations or substitutions at the tertiary center,[25] and *N*-butyl-2-methyl-*N*-(trifluoromethyl)butanamide (**10d**) was formed in 85% yield by applying bromine trifluoride to ethyl butyl-(2-methylbutanoyl)dithiocarbamate (**9d**). Another common functionality, the ester group, also does not affect the outcome of the reaction as evident from the case of methyl 5-(butyl(ethylthiocarbonothioyl)amino)5-oxopentanoate (**9e**). The product, which was obtained in seconds, was identified to be methyl 5-(butyl(trifluoromethyl)amino)-5-oxopentanoate (**10e**) in 85% yield. It should be noted that unlike the cases in which the nearby ester's carbonyl was located close to the complexed BrF_3 and converted to the CF_2 group, the remote ester with its hard basic oxygens cannot complex the reagent, and therefore, no reaction around this region was noted.

The reaction goes well with an array of isothiocyanates. Ethyl ethyl(2-propylpentanoyl)dithiocarbamate (**9f**) was prepared in 90% yield from ethyl ethyldithiocarbamate (**7f**),[26] which in itself was made from ethyl isothiocyanate (**6f**). When **9f** was reacted with bromine trifluoride, the result, after hydrolysis, was found to be *N*-ethyl-2-propyl-*N*-(trifluoromethyl)pentanamide (**10f**) in high yield. An additional secondary cyclic isothiocyanate **6g** was smoothly converted to ethyl cyclohexyldithiocarbamate (**7g**)[27] and again successfully transformed to **10g** in 85% yield.

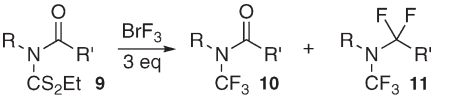
For a full conversion and best yields for the construction of the CF_3 group, about 3 mol/equiv of bromine trifluoride was used. If less of the reagent is employed the yields were affected, but we were able to identify a major type of product found to be alkyl(alkanoyl)thiocarbamoic fluoride (**12**) obtained in about 50% yield. We believe that compounds **12** are intermediates for both final products **10** and **11** where in the aliphatic series the latter was eventually quantitatively hydrolyzed back to **10**. The formation of the somewhat unusual **11** was made possible when centers susceptible to nucleophilic attacks such as carbonyls are in close proximity to the complexed reagent. One molecule of BrF_3 could then offer one fluoride to the sulfur bonded carbon and another to the carbonyl resulting in molecules of type **11** (Scheme 4).

SCHEME 4. Stepwise Formation of 10 and 11



Unlike the aliphatic series the stability of **11** increases with the presence of aromatic substituents (either R or R'). In general, the presence of aromatic rings, especially ones activated toward electrophilic attacks, can pose a problem when reactions with BrF_3 are involved, since the strongly electrophilic bromine could lead to aromatic brominations which are mostly avoided with deactivated aromatics.[13,28] Ethyl butyl (4-nitrophenylcarbonyl)dithiocarbamate (**9h**) prepared from ethyl butyldithiocarbamate (**7a**) and 4-nitrobenzoic acid (**8h**), was reacted with 3 mol/equiv of BrF_3 to form the new *N*-butyl-*N*-(difluoro(4-nitrophenyl)methyl)-*N*-(trifluoromethyl)amine (**11h**) in 65% yield along with *N*-butyl-*N*-(trifluoromethyl)-4-nitro benzamide (**10h**) obtained in 30% yield (Scheme 5). The aromatic derivative **11h** was hydrolytically stable and could be isolated and purified. It should be noted that when **10h** itself served as a substrate, the carbonyl remained intact, emphasizing the necessity of the sulfur complexation center for transforming the amide's carbonyl to the CF_2 moiety.

SCHEME 5. Aromatic 10 and 11



	Yield 10	Yield 11
h. R = C_4H_9 ; R' = *p*-$NO_2C_6H_4$	30%	65%
i. R = C_4H_9 ; R' = 3-Py	40%	55%
j. R = *p*-$NO_2C_6H_4$; R' = C_5H_{11}	30%	60%
k. R = R' = *p*-$NO_2C_6H_4$;	traces	75%

The instability of the CF_2 group toward hydrolysis in the aliphatic series as well as its stability in the aromatic one may be explained by fluorine hyperconjugation. In the aliphatic domain this phenomenon is encouraged both by the nitrogen lone pair and the positive inductivity of the alkyl group, which makes the difluoromethylene carbon susceptible to attack by the water nucleophilic oxygen. In contrast to the series containing aromatic rings **11h** − **11k** the electron

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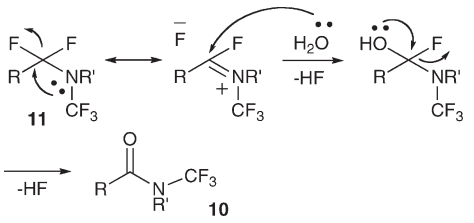
accepting ability of the aromatic rings, discourages fluorine hyperconjugation necessary for the hydrolysis of the difluoromethylene moiety (Scheme 6). In the past we have witnessed somewhat similar behavior.[15]

SCHEME 6. Hydrolysis of *N*-(Difluoromethylene)-*N*- (trifluoromethyl)amine 11



Since the pyridine ring does not react readily with bromine trifluoride, we hoped to widen the scope of the reaction to compounds that possess this heterocyclic. When 3 mol/equiv of BrF_3 were reacted with ethyl butyl(pyridine-3-carbonyl)-dithiocarbamoate (**9i**), obtained from **7a**[22] and nicotinic acid (**8i**), both *N*-butyl-*N*-(trifluoromethyl)pyridine-3-carboxamide (**10i**) and *N*-(difluoro(pyridin-3-yl)methyl)-*N*-(trifluoromethyl)butan-1-amine (**11i**) were formed in 40% and 55% yields respectively (Scheme 5). Here too, when **10i** itself was reacted with BrF_3 the carbonyl resisted any transformation again supporting the notion that a presence of soft base such as sulfur is essential.

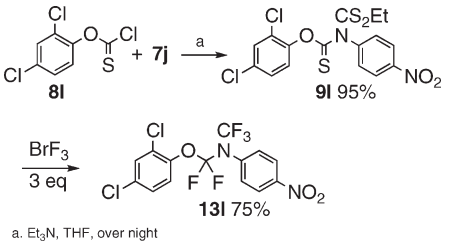
In order to show that it is of no consequence on which side of the molecule the aromatic ring is located, we reacted ethyl 4-nitrophenyldithiocarbamate (**7j**)[29] with hexanoic acid (**8a**) and subjected the product **9j** to a reaction with BrF_3 resulting in *N*-(4-nitrophenyl)-*N*-(trifluoromethyl)hexanamide (**10j**) and *N*-(1,1-difluorohexyl)-4-nitro-*N*-(trifluoromethyl)aniline (**11j**) in 30% and 60% yields. As with the case of dialkyl derivatives when less than 3 mol/equiv of BrF_3 was applied, the selectivity of the reaction was reduced and **10j** was found to be the major product.

When bis-aromatic precursor such as ethyl 4-nitrophenyl-(4-nitrophenylcarbonyl)dithiocarbamate (**9k**) was reacted with 3 mol/equiv of BrF_3 the stable *N*-(difluoro(4-nitrophenyl)methyl)-4-nitro-*N*-(trifluoromethyl)aniline (**11k**) was successfully produced in 75% yield with only traces of **10k** (Scheme 5). Using about 2 mol/equiv of the fluorinating agent reversed the distribution and **10k** was obtained in a 60% yield with not much of the pentafluoro derivative **11k**.

In order to increase the amount of the pentafluoroamine derivatives, we have constructed molecules containing two separate sulfur centers starting from the easily made *O*-2,4-dichlorophenyl chloridothiocarbonate (**8l**)[15] and ethyl 4-nitrophenyldithiocarbamate (**7j**). The desired product *O*-2,4-dichlorophenyl ethylthiocarbonothioyl(4-nitrophenyl)thiocarbamate (**9l**) was obtained in 95% yield (Scheme 7). When this compound was reacted with BrF_3, the novel *N*-((2,4-dichlorophenoxy)-difluoromethyl)-4-nitro-*N*-(trifluoromethyl)aniline (**13l**) was successfully formed in 75% yield (the balance seems to be brominated **13l**). Although the location of the CF_2 moiety is between oxygen and nitrogen atoms, which usually encourage hydrolysis, the presence of the aromatic rings decreases the hyperconjugation thus increases the stability toward hydrolysis.

(29) Zsolnai, T. *Arzneim.-Forsch.* **1966**, *16*, 1092–1099.

SCHEME 7. Formation of 13l



In conclusion, bromine trifluoride should not be suspiciously looked upon any longer. This work adds another layer to its rich but relatively hidden synthetic potential as we have demonstrated here its role in the preparation of a wide variety of the rare or unknown *N*-(trifluoromethyl)amide and *N*-(difluoromethylene)-*N*-(trifluoromethyl)amine derivatives. The fluorination step is usually completed in seconds, and the fluorinated products are obtained under remarkably mild conditions.

Experimental Section

General Procedure for the Preparation of Ethyl Alkyl/Aryl Dithiocarbamate Derivatives (7). A solution of the different aliphatic isothiocyanates (**6**) (26.0 mmol) was reacted with 3.3 mL (39.0 mmol) of ethanethiol in the presence of Et_3N (0.3 mL, 26.0 mmol) in 40 mL of dry THF and was refluxed for 20 h to form **7** in about 95% yields. In the case of aromatic dithiocarbamates the reaction was carried out under the same conditions with toluene as a solvent and in the presence of catalytic amount of dibutyltin dilaurate. In both cases, evaporation of the solvent followed by flash chromatography yielded the desired product. Some general procedures and description of representative experiments may be found below. The rest of the experimental procedures can be found in the Supporting Information.

Ethyl butyldithiocarbamate (7a)[22] was prepared as described in the general procedure, in 95% yield (4.4 g, colorless oil). In alkyl dithiocarbamate derivatives, some tautomerization of hydrogen atom occurred, and it distribute on both nitrogen and sulfur atoms. This fact was demonstrated in the NMR spectrum, where two different types of molecules may be seen: ^{1}H NMR 8.22 and 7.31 (1 H, s), 3.75−3.68 and 3.48−3.38 (2 H, m), 3.34−3.20 (2 H, m), 1.65 (2 H, quint, J = 7.7 Hz), 1.45−1.29 (5 H, m), 0.88 ppm (3 H, t, J = 7.7 Hz); ^{13}C NMR 200.4 and 197.6, 46.8 and 46.1, 30.5 and 30.3, 29.5, 20.1, 14.2, 13.6 ppm.

General Procedure for the Preparation of Ethyl Bis-aliphatic, Aliphatic/Aromatic, or Bis-aromatic Dithiocarbamate Derivatives 9. When 11 mmol of alkyl or 4-nitrophenyl dithiocarbamate (**7**) was reacted with 11 mmol of different acids **8** in the presence of 3.5 g (16.9 mmol) of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 134 mg (1.1 mmol) of 4-(dimethylamino)pyridine (DMAP) in 50 mL of dichloromethane, the corresponding dithiocarbamate derivatives (**9**) were formed in 70−95% yields. Evaporation of the solvent followed by flash chromatography yielded the desired products that were used, without further purification, as precursors for the next fluorination step.

Ethyl butyl(hexanoyl)dithiocarbamate (9a) was prepared from ethyl butyldithiocarbamate (**7a**) (2.0 g) and hexanoic acid (**8a**) (1.3 g) as described in the general procedure, in 75% yield: 2.3 g, orange oil; ^{1}H NMR 4.08 (2 H, t, J = 7.0 Hz), 3.14 (2 H, q, J = 7.0 Hz), 2.70 (2 H, t, J = 7.0 Hz), 1.70−1.59 (4 H, m), 1.34−1.26 (9 H, m), 0.89−0.84 ppm (6 H, m); ^{13}C NMR 208.3, 174.9, 50.9, 36.9, 32.4, 31.1, 30.2, 25.2, 22.3, 19.9, 13.7, 13.5, 11.9 ppm.

General Procedure for the Preparation of the *N*-(Trifluoromethyl)amide (10) and *N*-Difluoro-*N*-(trifluoromethyl)amine (11) Derivatives with BrF_3. A dithiocarbamate derivative (3 mmol) was dissolved in 25 mL of $CHCl_3$ or $CFCl_3$ in a glass flask and cooled to 0 °C. The best results were achieved when BrF_3 (3 molar equiv, 9 mmol) was dissolved in a few milliliters of $CFCl_3$, cooled to 0 °C, and added dropwise to the reaction mixture using a glass dropping funnel also at 0 °C. The reaction mixture was then washed with aqueous Na_2SO_3 until colorless, extracted with CH_2Cl_2, and dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography yielded the desired fluorinated compounds.

***N*-Butyl-*N*-(trifluoromethyl)hexanamide (10a)** was prepared from **9a** (830 mg) as described in the general procedure for the reaction with BrF_3, in 85% yield (610 mg): oil; ^{1}H NMR 3.54−3.49 (2 H, m), 2.45 (2 H, t, J = 7.0 Hz), 1.67−1.59 (2 H, m), 1.51−1.48 (2 H, m), 1.31−1.22 (6 H, m), 0.90−0.88 ppm (6 H, m); ^{13}C NMR 172.5, 122.1 (q, J = 265 Hz), 43.3, 34.9, 31.3, 31.1, 24.5, 22.4, 19.8, 13.8, 13.5 ppm; ^{19}F NMR −51.8 ppm (3 F, s); IR 1703.2 cm^{-1}; MS (CI) m/z 240.2 $(MH)^+$. Anal. Calcd for $C_{11}H_{20}F_3NO$: C, 55.22; H, 8.42; N, 5.85. Found: C, 54.92; H, 8.37; N, 5.76.

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Supporting Information Available: Additional experimental details, NMR's spectra of all *N*-(trifluoromethyl)amide and *N*-(difluoromethylene)-*N*-(trifluoromethyl)amine derivatives and their novel precursors described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.