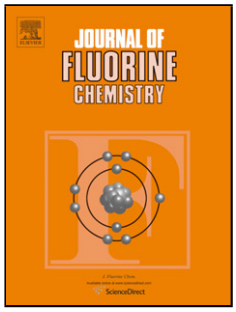

Title: Convenient synthesis of aliphatic $(CF_3)_2N$-compounds

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Convenient synthesis of aliphatic $(CF_3)_2N$-compounds

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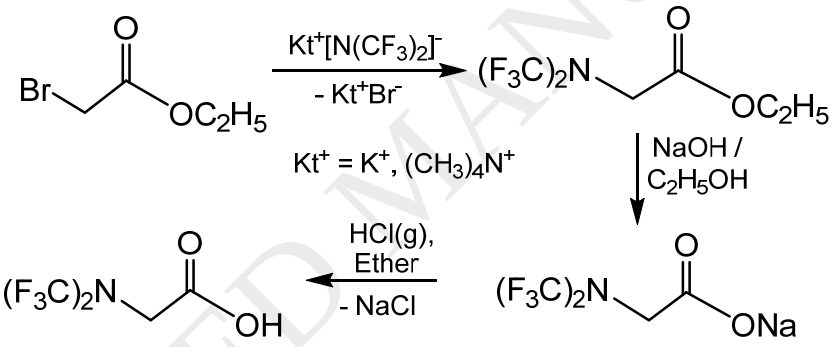
Dedicated to Professor Helge Willner on the occasion of his 70th birthday.

Keywords: nucleophilic substitution; $[N(CF_3)_2]^-$ anion; *N*,*N*-bis(trifluoromethyl)glycine; fluorinated amino acids; acidity; ionic liquids in organic synthesis

Graphical Abstract



***N,N*-bis(trifluoromethyl)glycine**

Highlights

1. $[N(CF_3)_2]^-$ anion can be easily generated from $CF_3SO_2N(CF_3)_2$.
2. $(CF_3)_2N$-derivatieves are accessible via nucleophilic substitution.
3. Previously unknown *N*,*N*-bis(trifluoromethyl)glycine is prepared in high yield.

Abstract.

Convenient syntheses of organic compounds bearing the $(CF_3)_2N$ group by means of nucleophilic substitution reactions with the $[N(CF_3)_2]^-$ anion were developed. The syntheses and properties of previously unknown *N*,*N*-bis(trifluoromethyl)glycine $(CF_3)_2NCH_2C(O)OH$ and its derivatives are described.

1. Introduction

The $[N(CF_3)_2]^-$ anion can be regarded as an analogue to well-known bis(trifluoromethylsulfonyl)imide anion, $[(CF_3SO_2)_2N]^-$ (DesMarteau anion [1]). Both anions are conjugated bases of the corresponding acids, namely bis(trifluoromethyl)amine, $(CF_3)_2NH$ (**1**), and bis(trifluoromethylsulfonyl)imide, $(CF_3SO_2)_2NH$. Although the $(CF_3SO_2)_2NH$ [1,2] was synthesised much later than bis(trifluoromethyl)amine (**1**) [3,4], the chemistry of the $[(CF_3SO_2)_2N]^-$ anion is far better developed in comparison to the chemistry of the $[N(CF_3)_2]^-$ anion. Currently, the bis(trifluoromethylsulfonyl)imide, $(CF_3SO_2)_2NH$, and its salts are available from various companies or can be prepared from trifluoromethylsulfonyl fluoride, CF_3SO_2F, by previously reported protocols [1,2]. The acid $(CF_3SO_2)_2NH$ and its alkali metal salts $(CF_3SO_2)_2NM$ (M = Li, Na, K) [5] are convenient starting materials for the preparation of hydrophobic ionic liquids with the bis(trifluoromethylsulfonyl)imide anion [6].

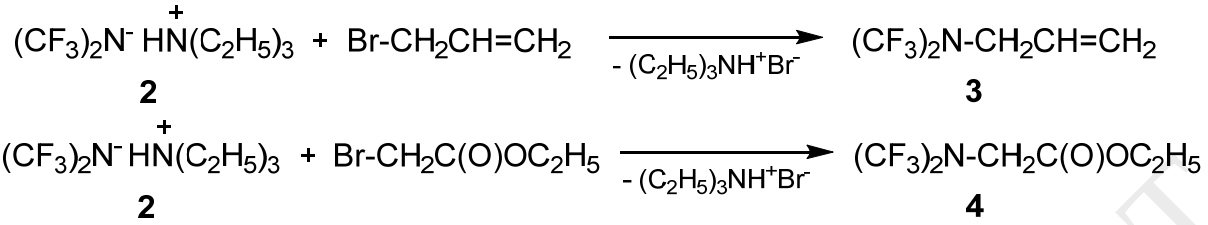
Apparently, $(CF_3)_2NH$ (**1**) is a much weaker base in comparison to $(CH_3)_2NH$. However, bis(trifluoromethyl)amine (**1**) can be protonated by the action of super acids, like anhydrous HF (aHF) acidified with AsF_5 [7,8].

The acidity of $(CF_3SO_2)_2NH$ (p*K*a = 1.7 [1]) is much higher than the acidity of $(CF_3)_2NH$. Nevertheless, $(CF_3)_2NH$ can be deprotonated by action of strong bases, for instance by triethylamine (Scheme 1) [9]. Salt **2** was isolated and characterized by ^1H and ^{19}F NMR and elemental analysis [9].

$$\underset{\mathbf{1}}{(CF_3)_2NH} \xrightarrow{N(C_2H_5)_3} \underset{\mathbf{2}}{(CF_3)_2N^- \overset{+}{H}N(C_2H_5)_3}$$

Scheme 1. Deprotonation of the $(CF_3)_2NH$ with triethylamine [9].

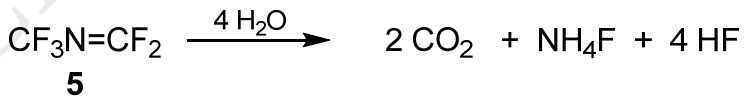
The reactions of salt **2** with allylbromide or α-bromo-ethylacetate resulted in the formation of the corresponding substituted products **3** and **4** (Scheme 2) [9]. Presumably, these reactions proceeded via a S_N1 mechanism.



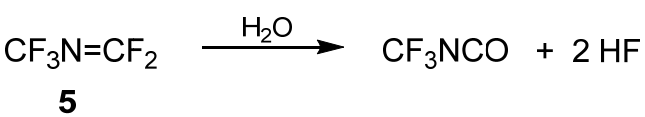
Scheme 2. Nucleophilic substitution reactions of the $(CF_3)_2N$-anion [9].

Bis(trifluoromethyl)amine (**I**) can be prepared by various methods as described in the literature [3, 4, 10]. $(CF_3)_2NH$ is a gas with a b.p. of -6.7 °C and it is extremely moisture sensitive [4]. Due to these properties, compound **1** is not an ideal starting material for the generation of the $[N(CF_3)_2]^-$ anion. More conveniently, the salts $(CF_3)_2NM$ (M = Cs, K) can be prepared by addition of CsF or KF to perfluoroazapropene, CF_3-N=CF_2 (**5**) [11,12]. $Cs[N(CF_3)_2]$ was isolated as a solid and characterized by NMR, infrared and Raman spectroscopy [13]. $Cs[N(CF_3)_2]$ reacts with allylbromide or α-bromoethylacetate similarly to the salt **2** giving access to the compounds **3** and **4** [11,12]. Gaseous **5** does not react with NaF [14]. The CF_3-N=CF_2 (**5**) has a b.p. of -33.7 °C [15]. It hydrolyses upon contact with moisture (Scheme 3) [4, 16]. The final products of the hydrolysis of CF_3-N=CF_2 (**5**) are carbon dioxide, ammonium fluoride, and HF (Scheme 3, A) [4]. Controlled hydrolysis of **5** gave trifluoromethylisocyanate, CF_3NCO (Scheme 3, B) [16].

A) Complete hydrolysis of perfluoroazapropene (**5**) [4]

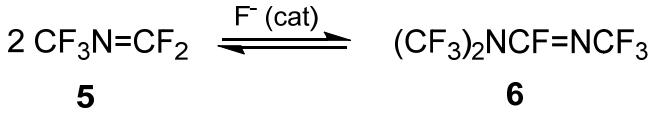


B) Controlled hydrolysis of perfluoroazapropene (**5**) [16]



Scheme 3. Hydrolysis of the CF_3-N=CF_2 (**5**) [4, 16].

Perfluoroazapropene (**5**) undergoes dimerization in the presence of fluoride anions (Scheme 4) [7,13,14].

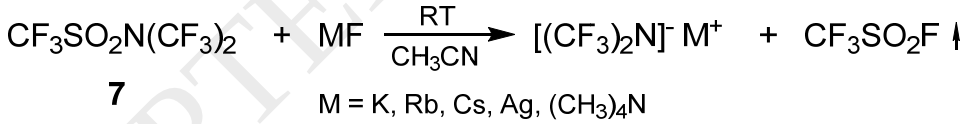


Scheme 4. Dimerization of the CF_3-N=CF_2 (**5**) [7,13,14].

This reaction is reversible, that enables the usage of the dimer **6** (b.p. 39 °C) [17] instead of gaseous **5** for the generation of the $[N(CF_3)_2]^-$ anion [13]. Perfluoroazapropene (**5**) is not commercially available, but it can be prepared by various methods as described in the literature. The synthesis and chemistry of perfluoroazapropene (**5**) and fluorinated aza-methines were reviewed several times [18 – 20].

Due to its properties and difficulties in the preparation, perfluoroazapropene (**5**) and dimer **6** are not convenient starting materials for the generation of the $(CF_3)_2$N-anion.

More than 20 years ago, we have described the synthesis of $(CF_3)_2$N-salts starting from $CF_3SO_2N(CF_3)_2$ (**7**) [21]. *N*,*N*-Bis(trifluoromethyl)trifluoromethane sulfonamide (**7**); b.p. 55-56 °C) is a convenient reagent for the preparation of organic and inorganic salts with the $[N(CF_3)_2]^-$ anion (Scheme 5) [22 – 25]. Compound **7** is stable at ambient conditions and can be stored for a long time.

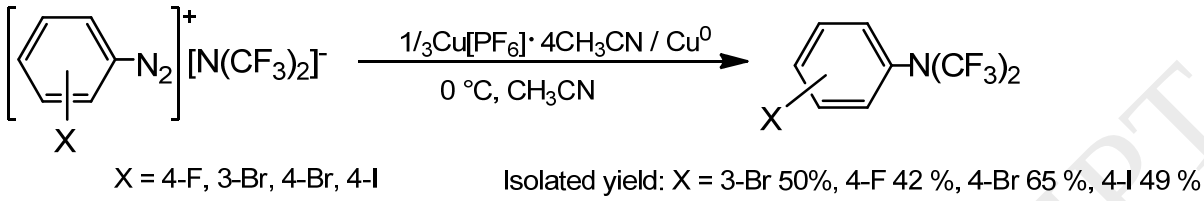


Scheme 5. Preparation of the $(CF_3)_2$N-salts starting from *N*,*N*-bis(trifluoromethyl)-trifluoromethanesulfonamide, $CF_3SO_2N(CF_3)_2$ (**7**) [22-25].

The gaseous by-product, CF_3SO_2F, can be trapped with solution of dimethyl amine to produce $CF_3SO_2N(CH_3)_2$, which is the starting material for the preparation of the $CF_3SO_2N(CF_3)_2$ (**7**) by electrochemical fluorination (Simons process) [21]. This technology offers a convenient route to use inexpensive dimethylamine for the synthesis of $(CF_3)_2$N-compounds [26].

Various organic salts of the $[N(CF_3)_2]^-$ anion were prepared by metathesis reactions of tetrafluoroborates with $Rb[N(CF_3)_2]$ [22-24]. These organic and inorganic salts are sources of the nucleophilic $[N(CF_3)_2]^-$ anion. For example, aromatic $(CF_3)_2$N-

compounds were prepared in one-step procedure starting from the corresponding diazonium salts [27]. Decomposition of these salts in the presence of a suitable Cu(I) catalyst resulted in the formation of the corresponding $(CF_3)_2N$-aromatic compounds in reasonable to good yields (Scheme 6) [28].



Scheme 6. Synthesis of Ar-$N(CF_3)_2$ compounds via diazonium salts [28].

Halogen containing *N*,*N*-bis(trifluoromethyl)anilines are useful starting material for further derivatisations of the aromatic ring.

However, only a limited number of aliphatic $(CF_3)_2N$-compounds prepared by means of nucleophilic substitution reactions with the $[N(CF_3)_2]^-$ anion have been reported in the literature [11,12,22,23,29].

Here, we present the convenient synthesis of previously unknown *N*,*N*-bis(trifluoromethyl)-α-aminoacetic acid (**8**), $(CF_3)_2NCH_2C(O)OH$ (*N*,*N*-bis(trifluoromethyl)glycine) and its derivatives. With this contribution, we demonstrate a practical methodology to introduce the $(CF_3)_2N$ group at primary and secondary carbon atoms by nucleophilic substitution reactions. Furthermore, the synthesized $(CF_3)_2N$-compounds are useful building blocks providing access to a variety of key synthons for organic synthesis.

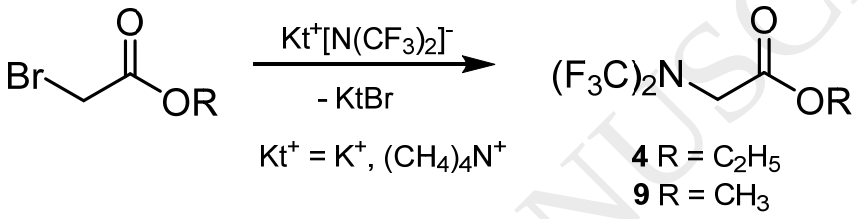
2. Results & Discussion

Despite the structural similarity to the dimethylamino group $N(CH_3)_2$, the bis(trifluoromethyl)amino group $N(CF_3)_2$, differs strongly in its electronic properties and sterically. The Hammett constant σ_p is -0.83 for $N(CH_3)_2$) [30] and +0.50 for $N(CF_3)_2$ [31] reflects higher electronegativity of bis(trifluoromethyl)amino group. This strongly influences the acid-base properties of the compounds bearing the $(CF_3)_2N$ group. For instance, *N*,*N*-dimethylaniline $C_6H_5N(CH_3)_2$ is a fairly strong base. In contrast, *N*,*N*-bis(trifluoromethyl)aniline, $C_6H_5N(CF_3)_2$, is not a base, at all. Moreover, it does not dissolve even in concentrated hydrochloric acid [31]. Another example is

the acidity of *N*,*N*-dimethylglycine $(CH_3)_2NCH_2C(O)OH$, in comparison to *N*,*N*-bis(trifluoromethyl)glycine $(CF_3)_2NCH_2C(O)OH$ (**8**). While the amino acid dimethylglycine exhibits two pK_a values (pK_a1 = 2.04, pK_a2 = 10.47) [32], titration of *N*,*N*-bis(trifluoromethyl)glycine revealed only one deprotonation step (pK_a = 2.94; this study).

2.1. Introduction of the $(CF_3)_2N$ group into aliphatic carbonyl compounds

Ethyl-*N*,*N*-bis(trifluoromethyl)glycine (**4**) was prepared by the interaction of $(CF_3)_2N$-salts with ethyl-α-bromoacetate (Scheme 7).



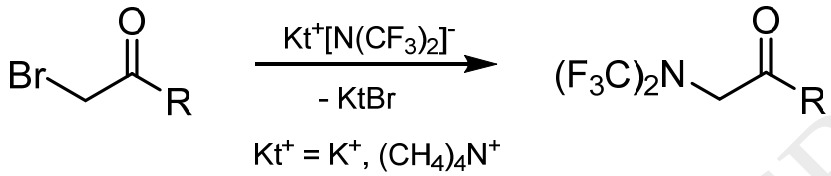
Scheme 7. Syntheses of ethyl- (**4**) and methyl *N*,*N*-bis(trifluoromethyl)glycine (**9**).

The reaction of $K[N(CF_3)_2]$ generated in dimethylacetamide (DMA) with ethyl-α-bromoacetate results in the formation of the compound **4** in 90% yield. The yield was increased up to 96% by changing the $(CF_3)_2N$-reagent to $[(CH_3)_4N][N(CF_3)_2]$ ($TMA[N(CF_3)_2]$) and using the ionic liquid bmpl FAP (bmpl = *N*-butyl-*N*-methylpyrrolidinium; FAP = tris(pentafluoroethyl)trifluorophosphate) as reaction media. The ionic liquid was recycled by washing of used bmpl FAP with water followed by drying *in vacuo*. It was reused several times (>10) without loss in the yield of **4**. In a similar manner, the reaction of methyl-α-bromoacetate with $K[N(CF_3)_2]$ in DMA gave the *N*,*N*-bis(trifluoromethyl)-α-aminoacetic acid methyl ester **9** in 91 % isolated yield. The above described procedures are more convenient and largely improve the yield of the compounds **4** and **9** in comparison to previously reported methods [22,25,29].

The essential drawback in the use of $[(CH_3)_4N][N(CF_3)_2]$ and $Rb[N(CF_3)_2]$ as reagents [22,29] for the syntheses of the compounds **4** and **9** is the formation of small quantities of mono-fluoroacetic acid esters as side products (**Caution! mono-fluoroacetic acid esters are volatile compounds and should be considered as highly toxic substances, similar to mono-fluoroacetic acid, and must be**

handled with all necessary safety measures). However, the formation of mono-fluoroacetic acid esters was not observed, when $K[N(CF_3)_2]$ was used as reagent for the syntheses of **4** and **9**. This finding is an important increase in reaction safety without loss in yield.

α-Bromoketones are possessing similar reactivity as ethyl-α-bromoacetate towards the $[N(CF_3)_2]^-$ anion. Various $(CF_3)_2N$-substituted ketones were prepared by this protocol (Scheme 8).



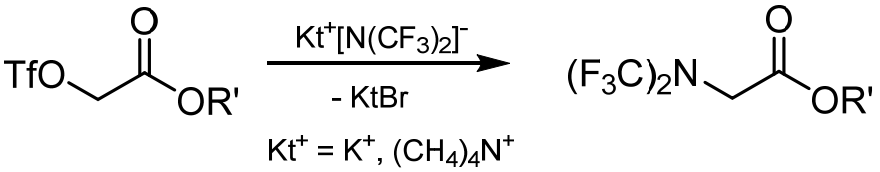
10a R = phenyl
10b R = 3,4,5-trimethoxyphenyl
10c R = *t*-Bu

11a Yield: 92%, 96%
11b Yield: 92%
11c Yield: 72%

Scheme 8. Synthesis of $N(CF_3)_2$ substituted ketones.

The yield of α-bis(trifluoromethyl)aminoacetophenone (**11a**) in the reaction of bromoacetophenone (**10a**) with *in situ* generated $K[N(CF_3)_2]$ is 92%. It can be increased to 96% by using $TMA[N(CF_3)_2]$. Bis(trifluoromethyl)aminomethyl-trimethoxyphenyl ketone (**11b**) was synthesised in 92% yield by the reaction of **10b** with $K[N(CF_3)_2]$, and $(CF_3)_2N$-pinacolone (**11c**) was prepared in 72% yield by reaction of bromomethyl-*tert*-butyl ketone **10c** with $TMA[N(CF_3)_2]$.

For a successful substitution at secondary carbon atoms, the reactivity of bromide as a leaving group is not sufficient. Since the $[N(CF_3)_2]^-$ anion can act as a weak base, elimination of HBr and formation of a double bond becomes the predominant reaction in this case. To overcome this problem, we used starting compounds having the better leaving triflate group, TfO. The corresponding triflates were prepared by literature known methods [33]. This approach allowed the preparation of compounds **13a,b** having the $(CF_3)_2N$ group bonded to secondary carbon atom (Scheme 9). The main drawback of this method is the inherent instability of the triflates **12a,b** above 0 °C due to their tendency to split off the triflate group. This is the main reason for the moderate yields achieved for **13a** (40%) and **13b** (44%). The elimination reaction and formation of ethyl acrylate was still a noticeable side reaction in the case of **12a**, but nevertheless, the main product in this reaction was the desired ethyl *N*,*N*-bis(trifluoromethyl)alanine (**13a**).



12a R = CH_3; R' = C_2H_5
12b R = C_6H_5; R' = CH_3

13a Yield: 40%
13b Yield: 44%

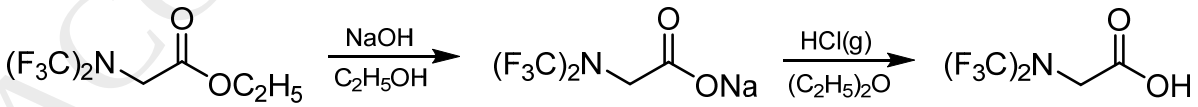
Scheme 9. Synthesis of α-$N(CF_3)_2$ substituted carboxylates.

The substitution at a tertiary carbon atom was investigated with the examples ethyl-2-methyl-2-bromopropanoate $(CH_3)_2CBrC(O)OEt$, and ethyl-2-methyl-2-mesylpropanoate $(CH_3)_2C(OSO_2CH_3)C(O)OEt$. However, only elimination of HBr and CH_3SO_2OH resulting in the formation of ethyl methacrylate could be observed during the substitution reactions with the $[N(CF_3)_2]^-$ anion. Replacement of the mesyl group with the triflate group as a leaving group did not give encouraging results. It appears, that ethyl-2-methyl-2-triflylpropanoate $(CH_3)_2C(OSO_2CF_3)C(O)OEt$, is not stable under the reaction conditions. Ethyl methacrylate was the only product in this reaction.

However, the "triflate-route" was successfully used for the introduction of the $N(CF_3)_2$ group into a non-activated position. For instance, methyl-ε-$N(CF_3)_2$-hexanoate (**14**) was prepared in 92% yield from methyl-6-(trifluoromethylsulfoxy)hexanoate $CF_3SO_2O(CH_2)_5C(O)OCH_3$, by reaction with *in situ* generated $Rb[N(CF_3)_2]$ (Table 3).

2.2. Derivatisation of the initial building blocks

Ethyl 2-bis(trifluoromethyl)aminoacetate (**4**) undergoes saponification in ethanol/NaOH to give the sodium salt **15** (Scheme 10).



4 **15** **8** Yield: 86%

Scheme 10. Synthesis of *N*,*N*-bis(trifluoromethyl)glycine (**8**) and its sodium salt **15**.

The sodium salt **15** can be protonated with dry gaseous HCl in diethyl ether to form the highly volatile acid **8** as colourless solid in 86% yield over two steps (Scheme 10). A pK_a value of 2.94 was determined for 2-bis(trifluoromethyl)aminoacetic acid (**8**) by

potentiometric titration in water at 25 °C (Table 1). As expected, 2-bis(trifluoromethyl)aminoacetic acid (**8**) is a stronger acid than acetic acid, but it is weaker as monofluoro- and trifluoro-acetic acids. The pK_a value of 2.94 is comparable to values determined for chloroacetic acid (pK_a = 2.87) [34,35] and trifluoropropionic acid (pK_a = 3.02) [36, 37] (Table 1). It is interesting to compare the acidity of *N*,*N*-bis(trifluoromethyl)glycine (**8**), *N*,*N*-dimethylglycine and glycine. The pK_a value of **8** is higher than the pK_a of glycine (2.31) [32,34] and of dimethylglycine (2.04) [32]. Hence, *N*,*N*-bis(trifluoromethyl)glycine (**8**) is a weaker acid than *N*,*N*-dimethylglycine. The higher acidity of glycine and *N*,*N*-dimethylglycine is due to the formation of zwitterions. The positively charged amino functionality increases the acidity of the adjacent carboxylic acid function. On the contrary, *N*,*N*-bis(trifluoromethyl)glycine is not able to form a zwitterion due to the low basicity of the $(CF_3)_2N$ group. Two CF_3 groups efficiently withdraw electron density from the nitrogen atom restricting protonation of the $(CF_3)_2N$-group, which hinders the formation of a zwitterionic structure. Thus, during the titration of *N*,*N*-bis(trifluoromethyl)glycine (**8**) only one deprotonation step was observed (pK_a = 2.94; this study), while the amino acid *N*,*N*-dimethylglycine exhibits two pK_a values (pK_{a1} = 2.04, pK_{a2} = 10.47) [32]. This observation proves the differences in the properties of the $N(CH_3)_2$ and the $N(CF_3)_2$ group. The comparison of the acidity of the *N*,*N*-bis(trifluoromethyl)glycine (**8**) and trifluoropropionic acid (Table 1) shows that the $(CF_3)_2N$ group in the aliphatic chain exerts a similar electron withdrawing effect like a CF_3 group or a Cl atom. This similarity is also evident from the comparison of inductive σ_I constants: 0.49, 0.49 and 0.40 (determined by ^{19}F NMR spectroscopic method) for $N(CF_3)_2$, CF_3, and Cl, respectively [31].

Table 1. Acidity of acetic acid and its substituted analogues

Acid	pK_a (in water at 25° C)	Ref.
H$CH_2C(O)OH$	4.76	[34, 35]
Cl$CH_2C(O)OH$	2.87	[34, 35]
$(CF_3)_2N$ $CH_2C(O)OH$	2.94	this study
CF_3 $CH_2C(O)OH$	3.02	[36, 37]
F$CH_2C(O)OH$	2.59	[34]
$(CH_3)_2N$ $CH_2C(O)OH$	2.04	[32]

CF_3C(O)OH	0.23	[35, 37]

N,*N*-bis(trifluoromethyl)glycine (**8**) was prepared in its protic form, $(CF_3)_2NCH_2C(O)O$**H**, and in its deuterated form, $(CF_3)_2NCH_2C(O)O$**D**. The IR spectra of these two forms of the compound **8** are presented in the Figure 1. The H form of the acid shows a broad absorption around 3000 cm^{-1} as expected for dimeric carboxylic acids. The spectrum is dominated by the strong ν_{as} (C=O) at 1724 cm^{-1} followed by strong C-F and C-O absorptions at 1100–1400 cm^{-1}. Isotopic labelling with deuterium strongly affected some bands, e.g. 1425 (ν_{COH}), 1254 (ν_{C-O}), and 889 ($\nu_{OH\cdots O}$). Two new broad bands arise at 2257 cm^{-1} and 2086 cm^{-1} upon deuteration and are clearly associated with OD vibrations. It is known that, strength of the H bonded network is in most cases associated with the acidity of the investigated compound [38]. Strong acids show a strong H bonded network, whereas medium strong acids show H bonded networks of medium strength. *N*,*N*-bis(trifluoromethyl)glycine cannot form a zwitterion due to the low basicity of the nitrogen atom. This explains the differences of the IR spectra (Table 2) compared to IR spectra of non-fluorinated amino acids. The IR spectrum (Fig. 1) of the *N*,*N*-bis(trifluoromethyl)aminoacetic acid (**8**) is more closely correlated to IR spectra of aliphatic carboxylic acids.

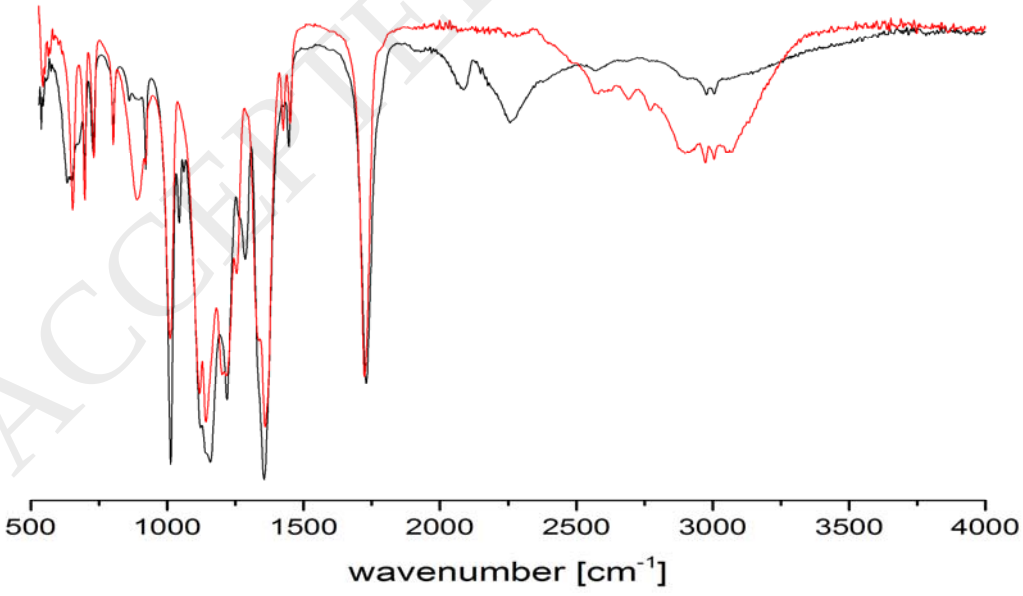
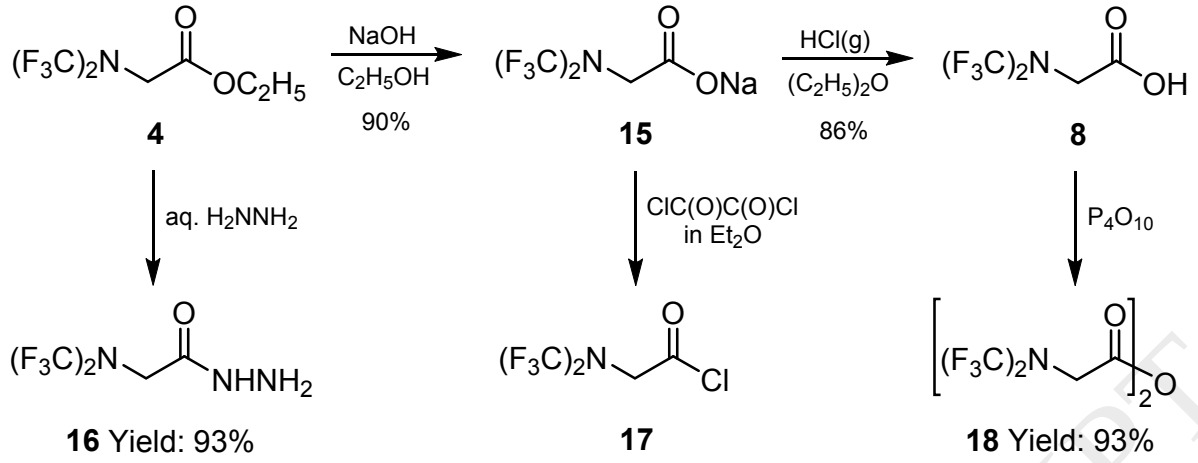


Figure 1. IR spectra of *N*,*N*-bis(trifluoromethyl)aminoacetic acid (**8**) as H (red) and D (black) isotopologue. For a better visibility, the spectra were scaled to similar transmission values.

Table 2. IR frequencies of deuterated and non-deuterated *N*,*N*-bis(trifluoromethyl)acetic acid (**8**). Frequencies marked with asterisks are strongly affected by the isotope effect.

ν $(CF_3)_2NCH_2C(O)O$**H**, cm^{-1}	ν $(CF_3)_2NCH_2C(O)O$**D**, cm^{-1}
3070*m, 3005m, 2973m, 2904*m, 2772w, 2691w, 2581w, 1724st, 1451w, 1425*w, 1359st, 1336*sh, 1254*m, 1218st, 1202st, 1142st, 1119st, 1011st, 921sh, 889*m br, 802w, 731w, 698m, 652m, 544w	3006w, 2977w, 2906w, 2769vw, 2683vw, 2572w, 2257*m, 2086*m, 1730st, 1446m, 1355st, 1286*m, 1219st, 1158st, 1122sh, 1061*vw, 1044*m, 1013st, 922m, 861w, 802w, 728m, 699m, 672*sh, 652m, 644*m, 633*m, 538w

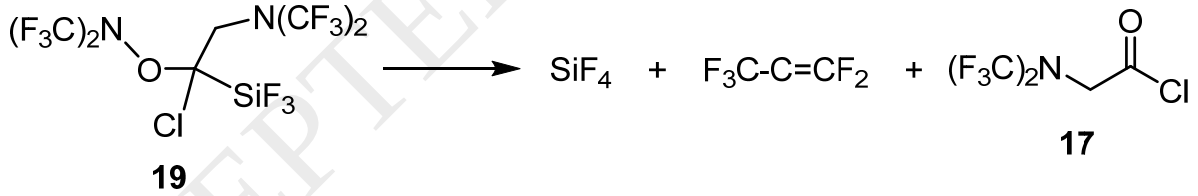
Reaction of the ester **4** with hydrazine hydrate to give the corresponding $(CF_3)_2$N-acetyl hydrazide (**16**) proceeds very slow in organic solvents typically used for this reaction, e.g. isopropanol (yield 31 % after 72 h boiling), DMF (yield 41 % in 26.5 h at RT), and DMSO (yield 78 % after 40 h at RT) (Scheme 11). Isolation of the hydrazide **16** from these solvents was difficult and resulted in loss of product due to its volatility. The use of the ionic liquid, *N*-butyl-*N*-methylpyrrolidinium triflate (bmpl OTf) as a solvent in this reaction increased the yield to 93 % after 24 h reaction time at room temperature. The product **16** was separated from the ionic liquid by sublimation. This procedure lets to avoid the time-consuming removal of organic solvents from the reaction mixture and enhances the isolation of the product **16**, significantly. The ionic liquid bmpl OTf can be recycled and reused without purification and loss in product yield.



Used *in situ* for further derivatization

Scheme 11. Syntheses of *N*,*N*-bis(trifluoromethyl)amino acetic acid hydrazide (**16**), chloride **17**, and anhydride **18**.

The sodium salt **15** reacted with oxalyl dichloride in diethyl ether to the acid chloride **17**, which was not fully separated from residual solvent by distillation. According to ^{1}H and ^{19}F NMR data, the conversion of **15** to **17** was quantitative (Scheme 11). A solution of the acid chloride **17** in diethyl ether was stored and used for further derivatisations without separation from Et_2O. The acid chloride **17** has been described in the literature previously [39]. It was detected as a side product of the decomposition of compound **19** according to the following equation (Scheme 12).

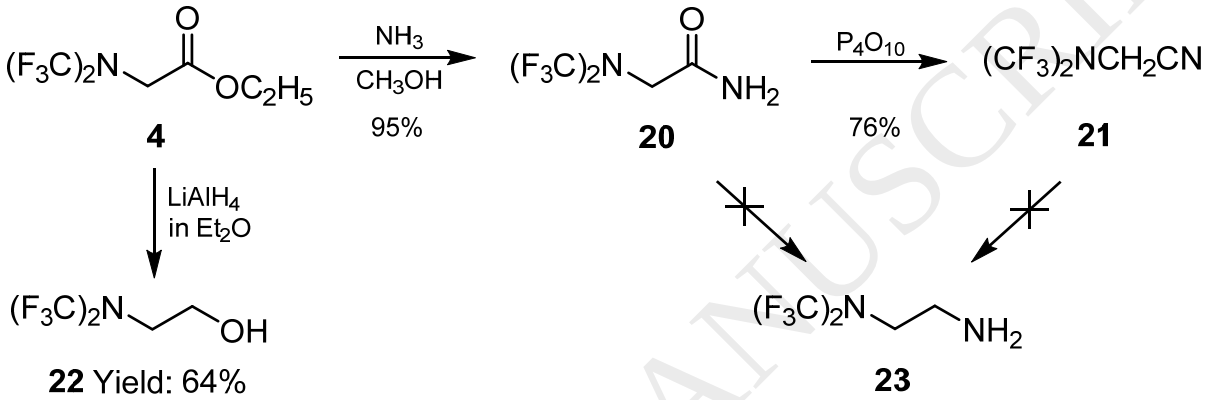


Scheme 12. Formation of the *N*,*N*-bis(trifluoromethyl)amino acetic acid chloride (**17**) as a side product, according to the literature [39].

The literature procedure depicted in Scheme 12 is not the method of choice for the preparation of compound **17**. The synthesis of the *N*,*N*-bis(trifluoromethyl)amino acetic acid chloride (**17**) starting from the sodium salt of *N*,*N*-bis(trifluoromethyl)glycine (**8**) according to Scheme 11 is much more practical and convenient. This remarkable example demonstrates the advantages of the new methodology based on the use of $(CF_3)_2N$-salts for nucleophilic substitution reactions in the syntheses of $(CF_3)_2N$ containing aliphatic organic compounds.

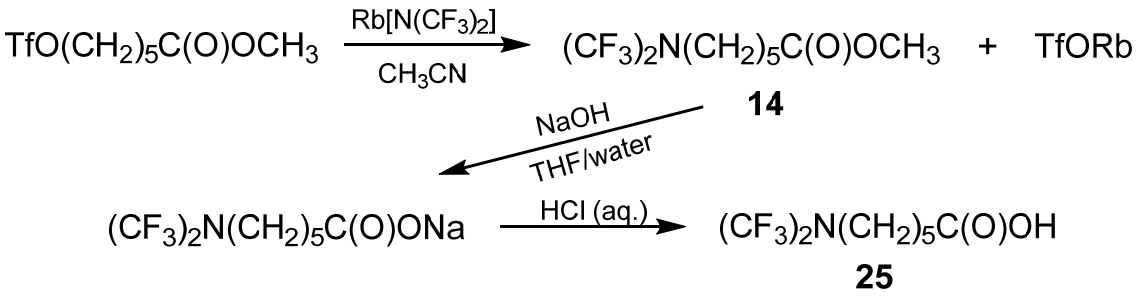
The *N*,*N*-bis(trifluoromethyl)glycine (**8**) was dehydrated by phosphorous(V)-oxide under solvent free condition to the corresponding acid anhydride **13**, which can be easily separated by sublimation under reduced pressure (Scheme 11). The anhydride **13** is a very reactive compound. We obtained single crystals of the *N*,*N*-bis(trifluoromethyl)glycine (**8**) by slow hydrolysis of the anhydride (**18**).

The ethyl ester of *N*,*N*-bis(trifluoromethyl)glycine (**4**) reacts not only with hydrazine hydrate, but in the presence of ammonia it is converted to $(CF_3)_2N$-substituted acetamide **20** in 95 % yield (Scheme 13).



Scheme 13. Preparation of the *N*,*N*-bis(trifluoromethyl)amino acetamide (**20**), 2-(bis(trifluoromethyl)amino)acetonitrile (**21**), and 2-(bis(trifluoromethyl)amino)ethanol (**22**).

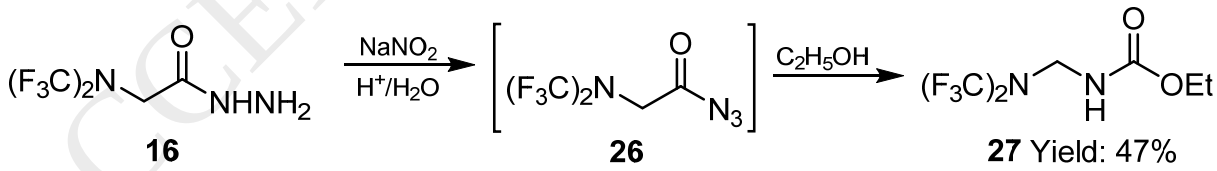
The subsequent dehydration of compound **20** with P_4O_{10} results in the formation of 2-(bis(trifluoromethyl)amino)acetonitrile (**21**) as a colourless liquid in 76% yield (Scheme 13). The alcohol **22** was synthesized in 64 % yield by reduction of ester (**IV**) at 0 °C using $LiAlH_4$ (Scheme 13). In a similar reaction, methyl-ε-N$(CF_3)_2$-hexanoate (**14**), $(CF_3)_2N(CH_2)_5C(O)OCH_3$, can be reduced by DIBAl-H in CH_2Cl_2 to the corresponding aldehyde **24** in a very good yield. The obtained aldehyde **24** was found to be highly sensitive against oxygen (air) and it is easily oxidized to $(CF_3)_2N$-substituted hexanoic acid **25**. This acid was independently obtained in 86 % yield by saponification of the methyl-ε-N$(CF_3)_2$-hexanoate (**14**) with aqueous NaOH followed by acidic workup.



Scheme 14. Preparation of the methyl-ε-N$(CF_3)_2$-hexanoate (**14**) and $(CF_3)_2$N-substituted hexanoic acid (**25**).

The reduction of the amide **20** or the nitrile **21** to the amine **23** (Scheme 13) was investigated by different reactions including reduction with $LiAlH_4$, BH_3, $NaBH_4$, and Pd/C/H_2, but no pure product **23** was isolated in these experiments. Several side products were observed in the reaction mixtures. The desired 2-[bis(trifluoromethyl)amino]ethylamine (**23**) was detected in the NMR-spectra of the reaction mixtures as a minor species. The difficulties in synthesizing this simple amine remain up to now unclear. A synthetic route to compound **23** by the Gabriel-synthesis was attempted, but it was also unsuccessful.

Hydrazide **16** was converted to the corresponding azide **26**, which was not isolated due to its instability above 0 °C. NMR spectroscopy showed full conversion of the hydrazide **16** within 30 min at 0 °C. Formation of any side products was not detected during this reaction. The carbamate **27** was synthesised in 47% yield by the Curtius rearrangement from azide **26** in the presence of ethanol (Scheme 14) by a method adapted from the literature [40].

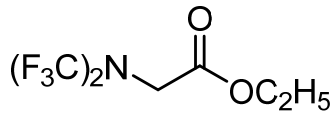
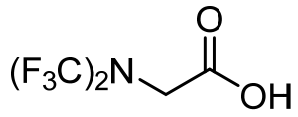
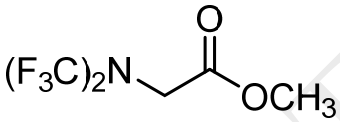
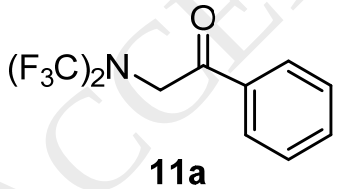


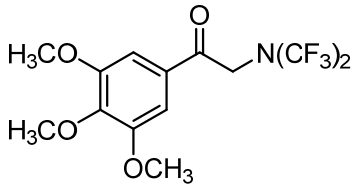
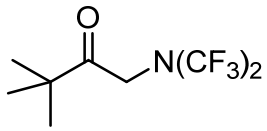
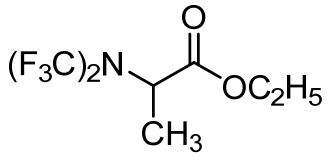
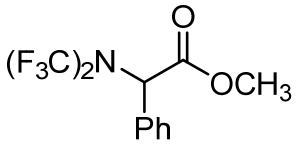
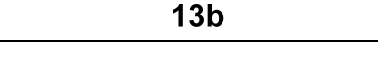
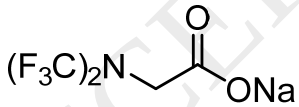
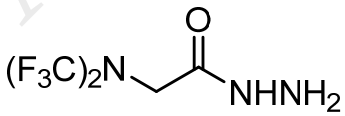
Scheme 15. Preparation of the *N*,*N*-bis(trifluoromethyl)amino acetazide (**26**) and its conversion to carbamate **27**.

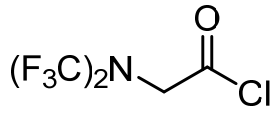
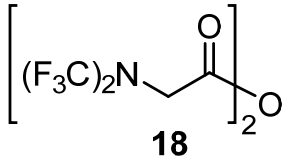
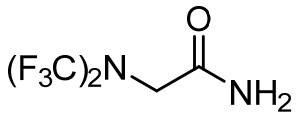
When the Curtius rearrangement was performed in *tert*-butanol instead of ethanol, the Boc-protected $(CF_3)_2$N-methylamine (**28**) was obtained. However, despite all efforts the deprotected amine was not isolated as pure compound.

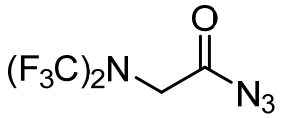
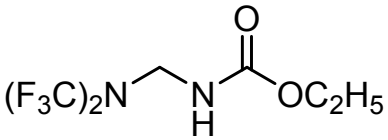
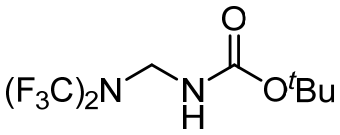
The product yields and the properties of the compounds synthesised, including their NMR spectra are presented in the Table 3.

Table 3. Syntheses and characterization of $N(CF_3)_2$ containing compounds

Product	Yield %	Boiling (Melting) point, °C (Pressure)	NMR (Solvent), δ, ppm
 **4**	90[a], 99[b]	125-126	**^{1}H NMR** (CD_3CN): 4.22 (q, *J* = 7 Hz, 2H, -O-**CH_2**CH_3), 4.13 (sept, *J* = 1.6 Hz, 2H, CH_2), 1.25 (t, *J* = 7 Hz, 3H, CH_3). **^{19}F-NMR** (CD_3CN): -57.70 (t, J = 1.6 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 167.24 (s, C=O), 120.30 (q, $^1J_{C,F}$ = 263 Hz, CF_3), 61.76 (s, -O-**CH_2**CH_3), 44.41 (s, CH_2), 13.23 (s, -O-CH_2**CH_3**).
 **8**	86	low melting solid	**^{1}H NMR** (CD_3CN): 9.63 (br. s, 1H, O**H**), 4.12 (sept, 2H, $^4J_{F,H}$ = 1.5 Hz, CH_2) **^{19}F NMR** (CD_3CN): -57.69 (t, $^4J_{F,H}$ = 1.5 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 167.8 (s, C=O), 120.3 (q, $^1J_{C,F}$ = 261 Hz, CF_3), 43.9 (s, CH_2).
	91[c]	114-115	**^{1}H-NMR** ($CDCl_3$): 3.96 (sept, J = 1.4 Hz, 2H, CH_2), 3.79 (s, 3H, O-CH_3) **^{19}F-NMR** ($CDCl_3$): -57.35 (t, J = 1.4 Hz).
 **11a**	92[k], 96[l]	33-34 (0.2 Pa; $1.5 \cdot 10^{-3}$ mm Hg)	**^{1}H NMR** (CD_3CN): 7.98 (d, J = 7.6 Hz, 2H, H^2+H^6), 7.69 (t, J = 7.6 Hz, 1H, H^4), 7.56 (t, J = 7.6 Hz, 2H, H^3+H^5), 4.94 (sept, $^4J_{F,H}$ = 1.6 Hz, 2H, CH_2). **^{19}F NMR** (CD_3CN): -57.06 (t, $^4J_{F,H}$ = 1.6 Hz). **^{13}C{^{1}H} NMR** ($CDCl_3$): 190.7 (C=O), 134.3 (s), 129.0 (s), 127.8 (s), 120.2 (q, $^1J_{C,F}$ = 262 Hz, CF_3), 49.3 (s).

 **11b**	92[m]	low melting solid	**^{1}H NMR** (CD_3CN): 7.26 (s, 2H, arom. CH), 4.94 (sept, $^4J_{F,H}$ = 1.7 Hz, 2H, CH_2), 3.89 (s, 6H, $2OCH_3$), 3.82 (s, 3H, OCH_3), **^{19}F NMR** (CD_3CN): -57.05 (t, $^4J_{F,H}$ = 1.7 Hz).
 **11c**	72[n]		**^{1}H NMR** ($CDCl_3$): 4.20 (sept, $^4J_{F,H}$ = 1.5 Hz, 2H, CH_2), 1.2 (s, 9H, $3CH_3$). **^{19}F NMR** ($CDCl_3$): -56.88 (t, $^4J_{F,H}$ = 1.5 Hz).
 **13a**	40[d]	132-135	**^{1}H NMR** ($CDCl_3$): 4.21 (m, 2H+1H, O-C**H$_2$**CH_3 + CH_3C**H**C=O), 1.56 (d, 3H, $^3J_{H,H}$ = 7 Hz, C**H$_3$**CHC=O), 1.25 (t, 3H, $^3J_{H,H}$ = 7 Hz, O-CH_2C**H$_3$**) **^{19}F NMR** ($CDCl_3$): -53,63 (br. s).
 **13b**	44[e]	26-30 (0.5 Pa; $3.8\cdot10^{-3}$ mm Hg)	**^{1}H NMR** ($CDCl_3$): 7.39 (m, 5H arom), 5.45 (br. s, 1H, C**H**C=O) 3.89 (s, 3H, OCH_3). **^{19}F NMR** ($CDCl_3$): -53.58 (br. s).
 **14**	92[i]	60.5-62.0 (500 Pa; 3.75 mm Hg)	**^{1}H NMR** (CD_3CN): 3.61 (s, 3H, OCH_3), 3.30 (br t, J = 7.6 Hz, 2H, 6-CH_2), 2.30 (t, J = 7.4 Hz, 2H, 2-CH_2), 1.61 (m, 4H, 3-,5-CH_2), 1.33 (m, 2H, 4-CH_2). **^{19}F NMR** (CD_3CN): -57.83 (br. s). **^{13}C{^{1}H} NMR** (CD_3CN): 174.7 (s), 122.3 (q, $^1J_{C,F}$ = 261 Hz, CF_3), 52.0 (s), 45.8 (s), 34.5 (s), 30.2 (s), 26.7 (s), 25.4 (s).
 **15**	90		**^{1}H NMR** (DMSO-d_6): 3.58 (sept, 2H, $^4J_{F,H}$ = 1.7 Hz, CH_2) **^{19}F NMR** (DMSO-d_6): -53.41 (t, $^4J_{F,H}$ = 1.7 Hz). **^{13}C{^{1}H} NMR** (DMSO-d_6): 170.1 (s), 121.0 (q, $^1J_{C,F}$ = 257 Hz, CF_3), 47.2 (s).
 **16**	31[f], 78[g], 93[h]	(98-100)	**^{1}H NMR** (CD_3CN): 7.81 (br. s, 1H, N**H**), 3.93 (sept, 2H, $^4J_{F,H}$ = 1.5 Hz, CH_2), 3.86 (br. s, 2H, N**H$_2$**). **^{19}F NMR** (CD_3CN): -58.08 (t, $^4J_{F,H}$ = 1.5 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 166.1 (s), 120.5 (q, *J* = 262 Hz, CF_3), 44.6 (s).

 **17**			**^{19}F NMR** (CD_3CN): -58.6 (t, J = 1.3 Hz).
 **18**	65		**^{1}H NMR** (CD_3CN): 4.37 (sept, 4H, $^{4}J_{F,H}$ = 1.6 Hz, 2x CH_2). **^{19}F NMR** (CD_3CN): -56.05 (t, $^{4}J_{F,H}$ = 1.6 Hz)
 **20**	95	(119.7) (DSC)	**^{1}H NMR** (CD_3CN): 6.46 (br. s, 1H, N**H**$_a$), 6.09 (br. s, 1H, N**H**$_b$), 3.96 (sept, 2H, $^{4}J_{F,H}$ = 1.5 Hz, CH_2). **^{19}F NMR** (CD_3CN): -58.13 (t, $^{4}J_{F,H}$ = 1.5 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 168.0 (s), 120.5 (q, $^{1}J_{C,F}$ = 260 Hz, CF_3), 45.4 (s),
$(CF_3)_2NCH_2C\equiv N$ **21**	76	108-112	**^{1}H NMR** (CD_3CN): 4.42 (sept, 2H, $^{4}J_{F,H}$ = 1.0 Hz). **^{19}F NMR** (CD_3CN): -59.09 (t, $^{4}J_{F,H}$ = 1.0 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 121.1 (q, *J* = 262 Hz, CF_3), 115.5 (s, **CN**), 32.8 (s, **CH_2**),
$(CF_3)_2NCH_2CH_2OH$ **22**	64	117-118	**^{1}H NMR** (CD_3CN): 3.61 (dt, 2H, $^{3}J_{H,H}$ = 6.0, $^{3}J_{H,OH}$ = 6.0 Hz, C**H_2**OH), 3.40 (t sept, 2H, $^{3}J_{H,H}$ = 6.0, $^{4}J_{F,H}$ = 1.4 Hz, C**H_2**), 3.10 (t, 1H, $^{3}J_{H,OH}$ = 6.0 Hz, O**H**). **^{19}F NMR** (CD_3CN): -57.77 (t, $^{4}J_{F,H}$ = 1.4 Hz). **^{13}C{^{1}H} NMR** (CD_3CN): 120.9 (q, $^{1}J_{C,F}$ = 261 Hz, CF_3), 59.6 (s, CH_2), 46.3 (s, CH_2OH).
$(CF_3)_2N(CH_2)_5C(O)H$ **24**	85[j]	69.5-70 (1500 Pa; 11.25 mm Hg)	**^{1}H NMR** (CD_3CN): 9.69 (t, J = 1.6 Hz, 1H, C(O)**H**), 3.30 (t hept, J = 7.6, 1.5 Hz, 2H, 6-CH_2), 2.42 (td, J = 7.3, 1.6 Hz, 2H, 2-CH_2), 1.62 (m, 4H, 3-, 5-CH_2), 1.33 (m, 2H, 2-CH_2). **^{19}F NMR** (CD_3CN): -57.92 (br. s). **^{13}C{^{1}H} NMR** (CD_3CN): 203.6, 122.1 (q, $^{1}J_{C,F}$ = 261 Hz, CF_3), 45.6 (s), 44.2 (s), 30.1 (s), 26.5 (s), 22.2 (s).
			^{1}H NMR (CD_3CN): 9.49 (s, 1H, O**H**), 3.30 (t hept, J = 7.7, 1.5 Hz, 2H, 6-CH_2), 2.30

$(CF_3)_2N(CH_2)_5C(O)OH$ **25**	86	67.5-68.5 (20 Pa; 0.15 mm Hg)	(t, J = 7.4 Hz, 2H, 2-CH_2), 1.62 (m, 4H, 3-, 5-CH_2), 1.35 (m, 2H, 4-CH_2). **^{19}F NMR** (CD_3CN): -57.88 (br. s). **^{13}C{^{1}H} NMR** (CD_3CN): 176.5 (s), 122.1 (q, $^1J_{C,F}$ = 261 Hz, CF_3), 45.6 (s), 34.1 (s), 30.0 (s), 26.4 (s), 25.0 (s).
 **26**		**Caution!** Compound may be explosive	**^{1}H NMR** (CD_3CN): 4.23 (sept, 2H, $^4J_{F,H}$ = 1.7 Hz, CH_2). **^{19}F NMR** (CD_3CN): -57.49 (t, $^4J_{F,H}$ = 1.7 Hz).
 **27**	47	colourless oil	**^{1}H NMR** ($CDCl_3$): 5.33 (br. s, 1H, N**H**), 4.80 (d, 2H, $^3J_{N,H}$ = 5.7 Hz, CH_2), 4.14 (q, 2H, $^3J_{H,H}$ = 7.2 Hz, OCH_2), 1.23 (t, 3H, $^3J_{H,H}$ = 7.2 Hz, CH_3). **^{19}F NMR** ($CDCl_3$): -56.62 (br. s). **^{13}C{^{1}H} NMR** ($CDCl_3$): 155.3 (C=O), 120.4 (q, $^1J_{C,F}$ = 262 Hz, CF_3), 61.7 (s, OCH_2), 50.6 (s, CH_2), 14.3 (s, CH_3).
 **28**	53	low melting solid	**^{1}H NMR** (CD_3CN): 6.18 (br. s, 1H, N**H**), 4.76 (d sept, 2H, $^3J_{N,H}$ = 7.0 Hz, $^4J_{F,H}$ = 1.3 Hz, CH_2), 1.42 (s, 9H, t-Bu). **^{19}F NMR** (CD_3CN): -56.71 (br. s). **^{13}C{^{1}H} NMR** (CD_3CN): 155.9 (s), 121.7 (q, $^1J_{C,F}$ = 263 Hz, CF_3), 80.9 (s), 51.9 (s, CH_2), 28.5 (s).

Conditions: [a] $BrCH_2C(O)OEt$ + KF/**7** in DMA (RT, 19 h); [b] $BrCH_2C(O)OEt$ + TMAF/**8** in bmpl FAP (80 °C, 16 h); [c] $BrCH_2C(O)OMe$ + KF/**7** in DMA (RT, 19 h); [d] **12a** + RbF/**7** in CH_3CN (RT, 18 h); [e] **12b** + $[Et_4N][N(CF_3)_2]$ in CH_2Cl_2 (RT, 24 h); [f] **4** + $NH_2NH_2{\cdot}H_2O$ in *i*-PrOH (82 °C, 72h); [g] **4** + $NH_2NH_2{\cdot}H_2O$ in DMSO (RT, 40 h); [h] **4** + $NH_2NH_2{\cdot}H_2O$ in bmpl OTf (RT, 24 h); [i] $CF_3SO_2O(CH_2)_5C(O)OCH_3$ + RbF/**7** in CH_3CN (RT, 15 min); [j] **14** + Di-*i*-BuAlH in CH_2Cl_2 (-50 °C, 3 h); [k] **10a** + KF/**7** in DMA (RT, 10 h); [l] **10a** + TMAF/**7** in bmpl FAP (50 °C, 18 h); [m] **10b** + KF/**7** in DMA (50 °C, 5 h); [n] **10c** + TMAF/**7** in bmpl FAP (70 °C, 20 h).

Summary

Organic compounds having the $(CF_3)_2N$ group are accessible by nucleophilic substitution reactions of $(CF_3)_2N$-salts with readily available starting materials. Aliphatic compounds, carboxylic acid esters, and ketones bearing the $(CF_3)_2N$ group at primary and secondary carbon atoms were prepared in good to excellent yields. A convenient method for the efficient introduction of the $N(CF_3)_2$ group using potassium fluoride for *in situ* generation of $(CF_3)_2N$-anion was developed. This method restricts

the formation of monofluorinated side products and thus increases the safety in the described syntheses. Syntheses of $(CF_3)_2N$-containig building blocks having various functional groups like carboxylic acids and its esters, acid hydrazide, acid anhydride, acid chloride and amide, ketone, and aldehyde functionalities, primary nitriles and alcohols are described. Derivatization of these new building blocks provide access to a variety of organic compounds using well-known chemical reactions. The remarkable stability of the $(CF_3)_2N$ group against strong acids (H_2SO_4), reducing agents (Di-*i*-BuAlH), and strong bases (NaOH) was demonstrated.

Acknowledgments

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3. Experimental Part

3.1. Materials and methods

All reactions were performed in a dry and inert atmosphere. All solvents were dried with 3 Å molecular sieve before using. Ionic liquids, 1-butyl-1-methylpyrrolidinium tris(pentafluoroethyl)trifluorophosphate (bmpl FAP) and 1-butyl-1-

methylpyrrolidinium trifluoromethanesulfonate (bmpl OTf), were dried *in vacuo* at 40 - 60 °C for several hours prior to use.

Anhydrous potassium fluoride, dimethylformamide (DMF), ω-bromoacetophenone, methyl bromoacetate, ethyl bromoacetate, bromopinacolone and toluene have been purchased from Sigma-Aldrich. Dimethylacetamide (DMA), ethanol, methanol, sodium nitrite, $LiAlH_4$, and hydrazine hydrate have been purchased from Merck / VWR. Gaseous ammonia (3.8) was delivered by Air Liquide and methyl mandelate, phosphorous(V)-oxide and sodium azide by Acros Organics. Oxalylchloride was purchased from Fluka. All chemicals were used as received unless otherwise noted. ω-Bromoacetophenone was purified by sublimation prior to use. Tetramethylammonium fluoride (TMAF) was synthesized by a known method [41] from tetramethylammonium tetrafluoroborate and sodium fluoride in methanol. Commercial potassium and rubidium fluorides were dried additionally in high vacuum at 80 – 100 °C for several hours and stored in the glovebox. Ionic liquid bmpl OTf was provided by Merck KGaA (Darmstadt, Germany) free of charge. Ionic liquid bmpl FAP was prepared according to literature known procedure [42] from 1-butyl-1-methylpyrrolidinium chloride and potassium tris(pentafluoroethyl)trifluorophosphate (KFAP) in water. Currently, bmpl OTf and bmpl FAP can be bought from Merck Millipore company; product Nrs. are 491029 and 491084 correspondingly.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 25 °C either in CD_3CN, $(CD_3)_2SO$, or in $CDCl_3$ on a Bruker Avance III 400 MHz spectrometer operating at 400.17, 100.62, 376.54 for ^{1}H, ^{13}C, ^{19}F nuclei, respectively. NMR signals were referenced against TMS (^{1}H, ^{13}C), and $CFCl_3$ (^{19}F) as external standards.

Elemental analysis (C, H, N, S) were performed with a Euro EA3000 instrument (HEKA-Tech, Germany).

Infrared spectra were measured on crystalline samples at room temperature on an Excalibur FTS 3500 spectrometer (Digilab, Germany) with a resolution of 4 cm^{-1}. IR spectra were recorded in the attenuated total reflection (ATR) mode in the region of 4000–530 cm^{-1}.

Potentiometric titration of *N*,*N*-bis(trifluoromethyl)glycine (**8**) was carried out for a 0.018 M solution in bidistilled water at 25 °C using 0.1 M KOH as titrant. The pH values during the titration experiment were measured with a Metrohm 780 pH-Meter using a glass electrode. The pK_a value of the *N*,*N*-bis(trifluoromethyl)glycine (**8**) was calculated using the Henderson-Hasselbalch equation.

Caution! Highly volatile mono-fluoroacetic acid esters can undergo hydrolysis resulting in the formation of volatile (5300 Pa; 39.75 mm Hg, 36°C) and highly toxic mono-fluoroacetic acid (LD_{50} = 7 mg/kg, oral/mouse; source: the National Institute for Occupational Safety and Health - NIOSH, *https://www.cdc.gov/niosh/rtecs/AH5ACA30.html*). By this reason mono-fluoroacetic acid esters should be considered as toxic as mono-fluoroacetic acid itself.

3.2. Introduction of the bis(trifluoromethyl)amino, $(CF_3)_2N$ group

Melting, boiling points, and the NMR spectroscopic data for the products described below are given in the Table 3.

Ethyl 2-bis(trifluoromethyl)aminoacetate; ethyl *N*,*N*-bis(trifluoromethyl)glycine, $(CF_3)_2NCH_2C(O)OEt$ (4)

Method A.

Anhydrous tetramethylammonium fluoride (5.82 g, 62.5 mmol) was suspended in 30 mL bmpl FAP in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide, $CF_3SO_2N(CF_3)_2$ (**7**) (18.84 g, 66.1 mmol) was slowly added within 10 minutes at room temperature, resulting in evolution of trifluoromethylsulfonylfluoride, CF_3SO_2F. The reaction mixture was stirred for 1 hour and then dry-ice/ethanol reflux-condenser was let to warm up to room temperature to release the rest of the CF_3SO_2F (b.p. -21.5 °C). Trifluoromethylsulfonyl fluoride, CF_3SO_2F can be trapped as a side product with dry-ice condenser and converted to $CF_3SO_2N(CH_3)_2$ by reaction with dimethylamine. $CF_3SO_2N(CH_3)_2$ is the starting material for the production of $CF_3SO_2N(CF_3)_2$ by means of electrochemical fluorination process [21]. After removal of the CF_3SO_2F from the reaction mixture, ethyl-α-bromoacetate, $BrCH_2C(O)OEt$ (8.22 g, 49.2 mmol) was added and the mixture was heated for 16 hours to 80 °C. The product was isolated by condensation into a trap, cooled with liquid nitrogen, at 0.1 Pa ($0.75 \cdot 10^{-3}$ mm Hg) at 80 °C as a clear colourless liquid in 99 % yield (11.7 g). The composition of the product is 97 mol% ethyl-2-bis(trifluoromethyl)aminoacetate and 3 mol% ethyl-2-fluoroacetate.

Method B.

Anhydrous potassium fluoride (10.0 g, 172 mmol) was suspended in 100 mL of dry DMA in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide (**7**) (52.0 g, 182 mmol) was slowly added at room temperature, which resulted in evolution of trifluoromethylsulfonylfluoride, CF_3SO_2F, and the formation of a biphasic mixture in the reaction vessel. The reaction mixture was stirred 4 hours. After evaporation of the CF_3SO_2F (dry-ice/ethanol reflux-condenser was let to warm up to room temperature), ethyl-α-bromoacetate (23.0 g, 138 mmol) was added at room temperature resulting in the formation of KBr precipitate. The mixture was stirred for 19 h at room temperature and the slurry was poured into 300 mL of ice water. The lower organic phase was separated, extracted two times with 100 mL of ice-cooled water, and dried with magnesium sulfate yielding the product in high purity as colourless liquid. The volatile product was over-condensed *in vacuo* onto calcium hydride and distilled. Yield: 29.7 g (90%). Elemental analysis: Calcd. for $C_6H_7F_6NO_2$, %: C 30.14, H 2.95, N 5.86, Found, %: C 29.38, H 2.90, N 5.97.

Methyl 2-bis(trifluoromethyl)aminoacetate, $(CF_3)_2NCH_2C(O)OMe$ (9) was obtained in 91 % yield as colourless liquid from methyl-α-bromoacetate as starting material.

1-Bis(trifluoromethyl)amino-2-phenyl-ethan-2-one, $(CF_3)_2NCH_2C(O)Ph$ (11a)

Method A.

In a two-neck flask equipped with a dry-ice/ethanol reflux-condenser, anhydrous tetramethylammonium fluoride (6.65 g, 71.4 mmol) was suspended in 30 mL of dry bmpl FAP. In twenty minutes, $CF_3SO_2N(CF_3)_2$ (**7**) (22.6 g, 79.2 mmol) was added, that resulted in a strong evolution of gaseous CF_3SO_2F. The reaction mixture was stirred for two hours under constant cooling, and then dry-ice/ethanol reflux-condenser was let to warm up to room temperature to release the rest of the CF_3SO_2F (b.p. -21.5 °C). After removal of the CF_3SO_2F from the reaction mixture, 1-bromo-2-phenyl-ethan-2-one, $BrCH_2C(O)Ph$ (**10a**) (11.4 g, 57.5 mmol) was added as a solid and the reaction mixture was heated at 50 °C for 18 h. The product was isolated by condensation into a trap, cooled with liquid nitrogen, at 0.1 Pa ($0.75 \cdot 10^{-3}$ mm Hg) and 80 °C as a colourless liquid in 99% (15.5 g,) yield. The isolated $(CF_3)_2NCH_2C(O)Ph$ (**11a**) contained 3 mol% of 1-fluoro-2-phenyl-ethan-2-one, $FCH_2C(O)Ph$ as a by-product.

Method B.

Anhydrous potassium fluoride (0.92 g, 15.9 mmol) was suspended in 10 mL of dry DMA in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide (**7**) (4.59 g, 16.1 mmol) was slowly added at room temperature, that resulted in evolution of CF_3SO_2F and the formation of a biphasic mixture in the reaction vessel. The reaction mixture was stirred for 1 hour and after evaporation of the CF_3SO_2F (the dry-ice/ethanol reflux condenser was let to warm up to room temperature), 1-bromo-2-phenyl-ethan-2-one (**10a**) (2.59 g, 13.0 mmol) was added at room temperature resulting in the precipitation of KBr. The mixture was stirred for 10 h at room temperature and the slurry was poured into 50 mL of ice water. After addition of 30 mL of dichloromethane, the lower organic phase was separated, extracted two times with 50 mL of ice water, and dried with magnesium sulphate. Evaporation of the solvent under reduced pressure yielded the product as a pale yellow, oily liquid that solidified upon standing. $(CF_3)_2NCH_2C(O)Ph$ (**11a**) was obtained in 92% yield (3.25 g).

Elemental analysis: Calcd. for $C_{10}H_7F_6NO$, %: C 44.29, H 2.60, N 5.17, Found, %: C 44.44, H 2.48, N 5.17.

1-Bis(trifluoromethyl)amino-2-(3,4,5-trimethoxyphenyl)-ethan-2-one (11b)

Anhydrous potassium fluoride (0.66 g, 11.4 mmol) was suspended in 10 mL of dry DMA in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide (**7**) (3.58 g, 12.6 mmol) was added slowly at room temperature resulting in the evolution of trifluoromethylsulfonylfluoride. The reaction mixture was stirred for 1 hour. After evaporation of the CF_3SO_2F (the dry-ice/ethanol reflux condenser was let to warm up to room temperature), 1-bromo-2-(3,4,5-trimethoxyphenyl)-ethan-2-one (**10b**) (2.59 g, 13.0 mmol) was added at room temperature resulting in the formation of KBr precipitate. The mixture was stirred for 5 h at 50°C and the slurry was poured into 150 mL of ice water. The resulting precipitate was isolated by filtration, dissolved in 20 mL dichloromethane, and dried with magnesium sulphate. Evaporation of the solvent under reduced pressure yielded the product **11b** (3.8 g, 92% yield) as a pale-yellow oil that solidified upon standing.

1-Bis(trifluoromethyl)amino-3,3-dimethylbutan-2-one (11c)

In a two-neck flask equipped with a dry-ice/ethanol reflux-condenser, anhydrous tetramethylammonium fluoride (1.01 g, 10.9 mmol) was suspended in 7 mL of dry bmpl FAP. $CF_3SO_2N(CF_3)_2$ (**7**) (3.49 g, 12.25 mmol) was added, that resulted in a strong gas (CF_3SO_2F) evolution. The mixture was stirred for 1 hour with constant cooling and then dry-ice/ethanol reflux-condenser was let to warm up to room temperature to remove the rest of the CF_3SO_2F. 1-Bromo-3,3-dimethylbutan-2-one (**10c**) (1.48 g, 8.26 mmol) was added and the reaction mixture was heated to 70 °C for 20 h. NMR analysis of the reaction mixture indicated full conversion of the starting material. The product was isolated by condensation at 0.3 Pa ($2.25 \cdot 10^{-3}$ mm Hg) and 80 °C into a trap cooled with liquid nitrogen. The obtained colourless liquid (2.0 g) contained 86 mol% of 1-bis(trifluoromethyl)amino-3,3-dimethylbutan-2-one (**11c**) and 14 mol% of 1-fluoro-3,3-dimethylbutan-2-one, $FCH_2C(O)C(CH_3)_3$, as a by-product. The yield of 1-bis(trifluoromethyl)amino-3,3-dimethylbutan-2-one, $(CF_3)_2NCH_2C(O)C(CH_3)_3$ (**11c**) is 72%.

Ethyl 2-[*N,N*-bis(trifluoromethyl)amino]propanoate (13a)

Step 1.

Pyridine (7.26 g, 92.0 mmol) was dissolved in 200 mL of dry dichloromethane, cooled to 0 °C, and triflic anhydride (25.0 g, 88.7 mmol) was added. After stirring of the resulting suspension for 1 h at 0 °C, ethyl 2-hydroxypropanoate (10.0 g, 84.7 mmol) was added. The initially formed precipitate dissolved and finally a fine, less voluminous solid formed. After stirring the reaction mixture for 1h at 0 °C the solvent was removed under reduced pressure (1200 Pa; 9.0 mm Hg) and the residue was extracted with dry pentane (5 x 20 mL). The pentane phases were combined and the solvent was distilled off. The product, ethyl-2-(trifluoromethylsulfoxy)propanoate, $CF_3SO_2OCH(CH_3)C(O)OEt$, was purified by fractional condensation at 50 °C under reduced pressure (2 Pa; $1.5 \cdot 10^{-2}$ mm Hg) into two traps, at –10 °C and –196 °C. Ethyl-2-(trifluoromethylsulfoxy)propanoate (**12a**) was isolated as a colourless clear liquid in 87 % yield (18.45 g). ^{1}H NMR ($CDCl_3$) δ, ppm: 5.19 (q, $^3J_{H,H}$ = 7.0 Hz, 1H, $CH_3C\mathbf{H}C=O$), 4.26 (q, $^3J_{H,H}$ = 7.0 Hz, 2H, O-C$\mathbf{H_2}CH_3$), 1.66 (d, $^3J_{H,H}$ = 7.0 Hz, 3H, C$\mathbf{H_3}$CHC=O), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, -O-$CH_2\mathbf{CH_3}$). ^{19}F NMR ($CDCl_3$, 25 °C) δ, ppm: -74.05 (s, $\mathbf{CF_3}$).

Step 2.

Dry rubidium fluoride (4.58 g, 43.8 mmol) was suspended in 46 mL of dry acetonitrile in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide (**7**) (14.5 g, 50.8 mmol) was added slowly at room temperature, that resulted in evolution of gaseous CF_3SO_2F. The reaction mixture was stirred for 1 hour and after evaporation of the CF_3SO_2F (dry-ice/ethanol reflux-condenser was let to warm up to room temperature), ethyl-2-(trifluoromethylsulfoxy)propanoate (**12a**) (10.1 g 40.5 mmol) was added. After stirring for 18 h at room temperature, all volatile compounds were condensed into a trap cooled with liquid nitrogen. The condensate was poured into 150 mL of water, the organic phase was separated, and distilled to yield 4.05 g (40%) of ethyl-2-bis(trifluoromethyl)aminopropanoate, $(CF_3)_2NCH(CH_3)C(O)OEt$ (**13a**).

Methyl 2-bis(trifluoromethyl)amino-2-phenylacetate (13b)

Step 1.

Triflic anhydride (20.11 g, 71.3 mmol) was added to a solution of collidine (9.48 g, 78.3 mmol) and methyl 2-hydroxy-2-phenylacetate (10.78 g, 64.8 mmol) in 100 mL of dry dichloromethane at –78 °C. The mixture was stirred for 90 minutes at –78 °C and the solvent was removed under reduced pressure. A slightly yellow residue was extracted at 0 °C 10 times with each of 20 mL pentane. After evaporation of the solvent from the combined pentane phases, 13.2 g of methyl 2-phenyl-2-(trifluoromethylsulfoxy)acetate (**12b**) was isolated as a colourless solid (yield 68 %). The solid slowly decomposes at temperatures above 0 °C.

^{1}H NMR ($CDCl_3$) δ, ppm 7.50 (s, 5H, arom. H), 6.06 (s, 1H, C**H**C=O), 3.87 (s, 3H, OCH_3). ^{19}F NMR ($CDCl_3$) δ, ppm: -75.49 (s, CF_3).

Step 2.

A solution of methyl 2-phenyl-2-(trifluoromethylsulfoxy)acetate (**12b**) (3.12 g, 10.5 mmol) in 5 mL of dry dichloromethane was added to a solution of $[Et_4N][N(CF_3)_2]$ (3.30 g, 11.8 mmol) in 10 mL of dry dichloromethane at room temperature. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure. The residue, a yellow to brown oil, was extracted with pentane. After

evaporation of the pentane, methyl 2-bis(trifluoromethyl)amino-2-phenylacetate (**13b**) was isolated by distillation as a colourless liquid in 44% yield.

Sodium 2-bis(trifluoromethyl)aminoacetate, $(CF_3)_2NCH_2C(O)ONa$ (15)

Sodium hydroxide (2.14 g, 53.5 mmol) was dissolved in 30 mL of dry ethanol and ethyl 2-bis(trifluoromethyl)aminoacetate (**4**) (13.28 g, 55.5 mmol) was added. The mixture was heated to 60 °C for 20 h. After removal of the solvent *in vacuo*, the product **15** was obtained as a colourless solid, which was purified by recrystallization from ethyl acetate/hexane (3:4). Yield: 11.3 g (90%).

Elemental analysis: Calcd. for $C_4H_2F_6NNaO_2$, %: C 20.62, H 0.87, N 6.01, Found, %: C 20.75, H 0.80, N 6.06.

2-Bis(trifluoromethyl)aminoacetic acid; *N*,*N*-bis(trifluoromethyl)glycine, $(CF_3)_2NCH_2C(O)OH$ (8)

Sodium 2-bis(trifluoromethyl)aminoacetate (**15**) (4.4 g, 18.9 mmol) was suspended in 20 mL of dry diethyl ether and dry gaseous HCl was bubbled through the mixture. The resulting slurry was stirred for one hour at room temperature. The solvent was removed *in vacuo.* After purification by sublimation, the product **8** was obtained as a colourless solid. Yield: 3.4 g (86 %).

Elemental analysis: Calcd. for $C_4H_3F_6NO_2$, %: C 22.76, H 1.43, N 6.64, Found, %: C 22.78, H 1.55, N 6.68.

The deuterated form of *N*,*N*-bis(trifluoromethyl)glycine (**8**) was synthesized by interaction of the sodium salt with gaseous DCl in diethyl ether.

2-*N*,*N*-Bis(trifluoromethyl)aminoacethydrazide, $(CF_3)_2NCH_2C(O)NHNH_2$ (16)

Method A.

Ethyl 2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**4**) (2.75 g, 11.5 mmol) was dissolved in 10 mL of dry, degassed 2-propanol. Distilled hydrazine hydrate (0.89 g, 17.8 mmol) was added to this solution and the reaction mixture was refluxed for 72 hours. The solvent was removed under reduced pressure. The residue was recrystallized twice from 10 mL of benzene yielding 2-*N*,*N*-bis(trifluoromethyl)aminoacethydrazide (**16**) (0.80 g, 31%) as thin, crystalline plates.

Method B.

Ethyl 2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**4**) (5.06 g, 21.2 mmol) was dissolved in 25 mL of DMSO and distilled hydrazine hydrate (2.46 g, 49.2 mmol) was added to the solution. The reaction mixture was stirred for 40 h at room temperature and the solvent was removed under reduced pressure. The resulting orange to yellow solid was recrystallized from 30 mL of benzene. The product, 2-*N*,*N*-bis(trifluoromethyl)aminoacethydrazide (**16**) was isolated as thin crystalline plates in 78% (4.0 g) yield.

Method C.

Ethyl-2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**4**) (10.2 g, 42.8 mmol) was added to dry bmpl OTf followed by addition of distilled hydrazine hydrate (5.8 g, 117 mmol). The initially biphasic reaction mixture was stirred for 24 h at room temperature and excess of hydrazine hydrate was removed *in vacuo*. The product, $(CF_3)_2NCH_2C(O)NHNH_2$ (**16**), was isolated in 93% (8.9 g) yield as a colourless solid by sublimation.

Elemental analysis: Calcd. for $C_4H_5F_6N_3O$, %: C 21.34, H 2.24, N 18.67, Found, %: C 21.34, H 2.08, N 18.67.

2-*N*,*N*-Bis(trifluoromethyl)aminoacetyl chloride, $(CF_3)_2NCH_2C(O)Cl$ (17)

Sodium 2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**15**) (1.2 g, 5 mmol) was suspended in 10 mL of dry diethylether and oxalyl dichloride (0.8 g, 6.4 mmol) was added dropwise. The resulting slurry was refluxed for 1h, filtrated and used after filtration for further experiments without additional purification.

The protons of the CH_2-group in the ^1H NMR-spectrum overlap with the signal of the diethyl ether.

2-*N*,*N*-Bis(trifluoromethyl)aminoacetic acid anhydride, $[(CF_3)_2NCH_2C(O)]_2O$ (18)

Solid 2-*N*,*N*-bis(trifluoromethyl)aminoacetic acid (**8**) (0.9 g, 4.4 mmol) was mixed with phosphorous(V)-oxide (0.8 g, 5.5 mmol). The reaction mixture was stirred and heated at 50 °C in a sealed flask for 3 h. The product **18** was isolated in 65 % yield (0.58 g) as a colourless solid by sublimation.

2-*N*,*N*-Bis(trifluoromethyl)amino-acetamide, $(CF_3)_2NCH_2C(O)NH_2$ (20)

Ethyl 2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**4**) (9.5 g, 39.8 mmol) was dissolved in 50 mL of a 3 M solution of NH_3 in methanol. The reaction mixture was stirred at 40 °C for 45 h. The solvent was removed yielding the product (**20**) as a colourless solid in 95% (7.9 g); m.p. 119.7 °C (DSC).

Elemental analysis: Calcd. for $C_4H_4F_6N_2O$, %: C 22.87, H 1.92, N 13.33, Found, %: C 22.83, H 1.94, N 13.51.

2-*N*,*N*-Bis(trifluoromethyl)amino-acetonitrile, $(CF_3)_2NCH_2C\equiv N$ (21)

2-*N*,*N*-Bis(trifluoromethyl)aminoacetamide (**20**) (5.6 g, 26.6 mmol) was heated with phosphorous(V)-oxide (1.9 g, 13.4 mmol) at 160 °C for 1h. The product was isolated in 76% (3.9 g) yield as a colourless liquid by distillation.

2-*N*,*N*-Bis(trifluoromethyl)amino-ethanol, $(CF_3)_2NCH_2CH_2OH$ (22)

Ethyl-2-*N*,*N*-bis(trifluoromethyl)aminoacetate (**4**) (14.7 g, 61 mmol) was added dropwise within 30 min to 40 mL of a 1 M solution of $LiAlH_4$ in diethyl ether cooled to 0 °C. The reaction mixture was stirred for 40 min at 0 °C and then slowly poured into ice-cold water. The organic phase was separated, dried and the product was isolated in 64% (7.7 g) yield by distillation.

Elemental analysis: Calcd. for $C_4H_5F_6NO$,%: C 24.38, H 2.56, N 7.11, Found, %: C 24.35, H 2.62, N 6.93.

Ethyl-*N*,*N*-bis(trifluoromethyl)aminomethyl carbamate, $(CF_3)_2NCH_2NHC(O)OEt$ (27)

Step 1.

***Safety note**: The intermediate 2-N,N-bis(trifluoromethyl)aminoacetyl azide was not isolated and kept constantly at 0 °C or below. Although above 0 °C we observed only slow decomposition, azides have the tendency to undergo spontaneous violent decomposition. The reaction should be performed only after application of additional safety precautions, for instance protecting shield.*

2-*N*,*N*-bis(trifluoromethyl)aminoacethydrazide (**16**) (1.1 g, 5.1 mmol) was dissolved in ice-cooled water by adding concentrated hydrochloric acid until a final pH = 1 was reached. A solution of $NaNO_2$ (0.4 g, 6.1 mmol) in 2 mL of water was added dropwise to the solution of the hydrazide **16** and the reaction mixture was stirred at 0 °C in an ice bath until the formed precipitate had dissolved (ca. 10 min). The reaction mixture

separated into two phases; the product 2-*N*,*N*-bis(trifluoromethyl)aminoacetyl azide (**16**) had concentrated in the bottom phase. For NMR spectra see Table 3.

Step 2.

The bottom phase was separated at 0 °C and mixed with 15 mL of dry ethanol. The reaction mixture was refluxed for 10 h. The solvent was removed and the product **17** was isolated as colourless oil in 47% (0.6 g) yield.

Elemental analysis: Calcd. for $C_6H_8F_6N_2O_2$, %: C 28.36, H 3.17, N 11.02, Found, %: C 28.44, H 3.06, N 10.85.

tert-Butyl-*N*,*N*-bis(trifluoromethyl)aminomethyl carbamate, $(CF_3)_2NCH_2NHC(O)O$-*t*-Bu (28)

2-*N*,*N*-bis(trifluoromethyl)aminoacethydrazide (**16**) (2.7 g, 12 mmol) was dissolved in ice-cold water by adding concentrated hydrochloric acid to reach a final pH of 1 and 10 mL of toluene was added. $NaNO_2$ (0.89 g, 12.9 mmol) in 5 mL of water was added dropwise to the solution of the hydrazide **16** and the reaction mixture was stirred at 0 °C in an ice bath until the formed precipitate had dissolved again. The lower phase was separated, *tert*-butanol (1.16 g, 15.7 mmol) was added and the mixture was refluxed for one hour. The solvent was removed under reduced pressure yielding 1.8 g (53%) of the product **28** as a slightly yellow oil that solidifies to give colourless needles.

ε-*N*,*N*-Bis(trifluoromethyl)aminohexanoic acid, $(CF_3)_2N(CH_2)_5C(O)OH$ (25),

Step 1.

ε-Caprolacton (19.5 g, 171 mmol) was dissolved in 200 of methanol and 11 drops of concentrated H_2SO_4 were added from a Pasteur pipette. The mixture was stirred for 40 minutes at room temperature and 200 mL water were added. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The product, methyl-ε-hydroxyhexanoate, was isolated in 78% (19.5 g) yield after distillation (b.p. 67.5-68.5 °C at 50 Pa; 0.38 mm Hg).

Step 2.

Triflic anhydride (20.6 g, 73 mmol) was added dropwise to an ice-cold solution of pyridine (5.46 g, 69 mmol) in 100 mL of dry CH_2Cl_2. A colourless solid formed. The

mixture was stirred for 40 min at 0 °C and methyl-ε-hydroxyhexanoate (9.3 g, 63.6 mmol) was added within 20 min to this slurry. The reaction mixture turned orange. After stirring for one hour at 0 °C, 100 mL of hexane were added and the precipitate was removed by filtration under argon. The orange filtrate was concentrated *in vacuo* yielding ca. 19 g of methyl-ε-(trifluoromethylsulfoxy)hexanoate as orange oil. This oil was used in the next step without purification.

Step 3.

Dry rubidium fluoride (7.40 g, 70.8 mmol) was suspended in 75 mL of dry acetonitrile in a two-neck flask equipped with a dry-ice/ethanol reflux-condenser. Under vigorous stirring, *N*,*N*-bis(trifluoromethyl)trifluoromethanesulfonamide (**8**) (22.5 g, 78.8 mmol) was slowly added at room temperature to the suspension resulting in evolution of CF_3SO_2F. The reaction mixture was stirred for 1 hour, dry-ice/ethanol reflux-condenser was let to warm up to room temperature, and the methyl-ε-(trifluoromethylsulfoxy)hexanoate (19.0 g, 68.3 mmol), obtained in step 2 as an orange oil, was added slowly to the reaction mixture. The reaction proceeded very fast. After 15 minutes, the reaction mixture was poured into 350 mL of ice water. The organic phase was separated, washed with water and distilled *in vacuo* yielding 16.5 g (92%) of methyl-ε-*N*,*N*-bis(trifluoromethyl)aminohexanoate, $(CF_3)_2N(CH_2)_5C(O)OMe$ (**14**).

Elemental analysis: Calcd. for $C_9H_{13}F_6NO_2$, %: C 38.44, H 4.66, N 4.98, Found, %: C 38.91, H 4.74, N 4.98.

Step 4.

A solution of NaOH (1.8 g, 45.0 mmol) in 9 mL of water was added to a solution of methyl-ε-*N,N*-bis(trifluoromethyl)aminohexanoate (**14**) (5.9 g, 21.2 mmol) in 45 mL THF. The mixture was heated to 70 °C (temperature in the bath) with reflux condenser for 18 h and then, the reaction mixture was concentrated *in vacuo*. 100 mL of water were added to the residue and the solution was acidified to pH 1 by adding of concentrated hydrochloric acid. The reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was distilled in vacuum yielding ε-*N*,*N*-bis(trifluoromethyl)aminohexanoic acid, $(CF_3)_2N(CH_2)_5C(O)OH$ (**25**) as a clear, colourless oil in 86% yield (4.8 g).

Elemental analysis: Calcd. for $C_8H_{11}F_6NO_2$, %: C 35.96, H 4.15, Found, %: C 35.85, H 4.37.

ε-*N*,*N*-Bis(trifluoromethyl)aminohexanal (24)

5 mL of the Di-*iso*-Butyl Aluminium Hydride (DIBAl-H; 1M in CH_2Cl_2) was added dropwise to a solution of methyl-ε-*N*,*N*-bis(trifluoromethyl)aminohexanoate (**14**) (1.19 g, 4.2 mmol) in 20 mL of dry CH_2Cl_2 at -78 °C. Evolution of a gas was observed. The mixture was stirred for 3 h (T < -50 °C) and 5 mL of methanol were slowly added to quench the reaction mixture. The mixture was poured into 100 mL of vigorously stirred 1 M aqueous solution of potassium-sodium tartrate. After 2 h of stirring, the organic phase was separated. The solvent was removed under reduced pressure and the colourless liquid residue was distilled yielding 0.90 g (85%) pure ε-*N*,*N*-bis(trifluoromethyl)aminohexanal, $(CF_3)_2N(CH_2)_5C(O)H$ (**24**). The aldehyde was very sensitive against oxidation by ambient oxygen, that resulted in the formation of ε-*N*,*N*-bis(trifluoromethyl)aminohexanoic acid (**25**).

Elemental analysis: Calcd for $C_8H_{11}F_6NO$, %: C 38.26, H 4.41, N 5.58, Found, %: C 38.12, H 4.26, N 6.10.

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