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Tailored approaches towards the synthesis of L-*S*-trifluoromethylcysteine and L-trifluoromethionine containing peptides

Charlène Gadais,[a] Nathalie Saraiva-Rosa,[a] Evelyne Chelain,[a] Julien Pytkowicz,*[a] Thierry Brigaud*[a]

Abstract: Among the fluorinated noncanonical amino acids, *L*-trifluoromethionine (TFM) and *L*-S-trifluoromethylcysteine (TfmCys), fluorinated analogs of methionine and cysteine, are of particular interest because of their ability to locally increase the hydrophobicity of peptides. We report herein the synthesis of Boc/Benzyl protected TFM and TfmCys using a cheap and user friendly radical trifluoromethylation. The benzyl protecting group of these fluorinated amino acids can be conveniently removed by hydrogenolysis circumventing troublesome saponification reactions. For the first time, TfmCys was inserted in a peptide sequence by liquid or solid phase peptide synthesis. Finally, a late trifluoromethylation strategy using Togni's reagent on disulfide bridged peptides was also efficient to incorporate TFM or TfmCys at both *N*-terminal and internal positions.

In the last decades, unnatural fluorinated amino acids have proven to be efficient tools to advantageously modulate the biophysical and biochemical properties of peptides or proteins.[1] Moreover, due to its nearly total absence in biological media, fluorine is an outstanding bioorthogonal atom useful as NMR probe to explore conformational changes in peptides and proteins and their interactions with other biological molecules.[2–4] Among the fluorinated noncanonical amino acids successfully designed for such purpose, L-trifluoromethionine (L-*S*-trifluoromethylhomocysteine; TFM), the fluorinated analog of methionine, was the subject of many relevant studies.[5] The TFM was bioincorporated into bacteriophage lysozyme (LaL),[6,7] DNA polymerase[8] or a green fluorescent protein (M2-EGFP)[9] and used as a potential ^{19}F reporter. More recently, the kinetic and the presence of intermediate oligomeric species during the formation of amyloid fibrils from IAPP or $A\beta_{1-40}$ was demonstrated by ^{19}F NMR.[10,11] Moreover, various amide derivatives of TFM showed antimicrobial properties[12] and a small TFM containing peptides increased the chemotactic activity of the tripeptide TFM-Leu-Phe.[13] Methionine is frequently involved in hydrophobic interactions and the authors often invoked the increases of the fluorinated peptide hydrophobicity and the strengthening of the interaction with the hydrophobic pocket of the receptor to explain their results. In 2006, the axial ligand methionine 121 from a blue copper protein involved in electron transfer (Pseudomonas aeruginosa azurin: Az) has been replaced by isostructural unnatural amino acid analogues including a TFM one. A linear correlation was established between the hydrophobicity of the side chains and the diminution of protein reduction potential.[14] Recently, TFM was used as lysine hydrophobic isostere in short peptides inhibitors of histone methyltransferase PRC2 and was found to inhibit the enzyme better than methionine containing peptides.[15] However, data concerning the hydrophobicity of methionine and its trifluoro analogue are scarce and most of them obtained from fragment methods. Although several example of TFM containing peptides or proteins can be found in the literature, the incorporation of the *S*-trifluoromethyl analogue of cysteine has been scarcely reported. Two octreotide analogues containing L-*S*-trifluoromethylcysteine (TfmCys) were synthesized in 2008 by Seebach, Togni and co-workers but unfortunately showed a lower affinity towards the receptor than Octreotide itself.[16,17]

In the course of our ongoing studies dealing with the measurement of the hydrophobic contribution of unnatural trifluoromethylated amino acids (TfmAA's) we are developing their incorporation into short peptide sequences. Due to their biological relevance, we turned our attention to TFM but also to TfmCys that is, to our opinion, underused as cysteine fluorinated analogue or NMR probe. Although several examples have been reported in the literature for the bioincorporation[5-9] or the solution phase[13] incorporation of TFM into peptides, its integration by means of solid phase peptide synthesis (SPPS) is very scarcely documented.[10] Because of the high leaving group propensity of the SCF_3 group, the direct incorporation of TfmCys into peptides is much more challenging and, to our knowledge, has never been reported so far neither by solution nor by solid phase peptide synthesis. However its indirect incorporation into peptides has been successfully achieved by late electrophilic *S*-trifluoromethylation of sulfanyl group or cystine containing peptides.[16] Today, an important panel of methods to obtain SCF_3 compounds is found in the literature.[18,19] In the particular case of TfmCys and TFM syntheses, the majority of developed strategies involves trifluoromethylation of available chiral thiols (L-cysteine and L-homocysteine) or the dimeric disulfide precursor (L-cystine and L-homocystine). Since the seminal work of Taborsky et al[20] using very toxic reagents, more user friendly syntheses have been developed. The CF_3 moiety can be delivered from trifluoromethyl iodide using anionic[21] or radical chemistry under irradiation.[22,23] Langlois and co-workers published an interesting alternative to generate the CF_3 radical from sodium trifluoromethanesulfinate and applied it to the synthesis of TfmCys and TFM from L-cystinate and DL-homocystinate methyl ester.[24] Alternatively, TfmCys derivatives could also be obtained from photolysis of an intermediate trifluorothioacetate. [25] However a mixture was obtained from

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which the desired product was not easily separated from side products. Recently, Togni and co-worker described a direct cysteine trifluoromethylation using an electrophilic hypervalent iodine(III) trifluoromethylated reagent. [26] These conditions were successfully applied to synthesis of the Fmoc protected trifluoromethionine[10] and more interestingly to the late stage trifluoromethylation of dipeptides, β-dipeptides and even an acyclic Octreotide analogue containing two cysteines.[17] In the latter case however the authors obtained a mixture of mono, di and tri-trifluoromethylated product since the reagent could also attack the indol moiety of tryptophan.

We report herein the synthesis of four model SCF_3 group containing tripeptides especially designed for probing the consequences of the introduction of this fluorinated group on peptides hydrophobicity. The fluorinated amino acids TfmCys and TFM are positioned at the *N*-terminal position for peptides **1a** and **1b** and in the internal position for peptides **2a** and **2b** (scheme 1). we developed three different approaches towards the synthesis of these target peptides i) liquid synthesis from conveniently protected TfmCys or TFM residues ii) solid phase synthesis (SPPS) under microwave conditions iii) late stage trifluoromethylation of dimeric cystine and homocystine derivatives using Togni's reagent.

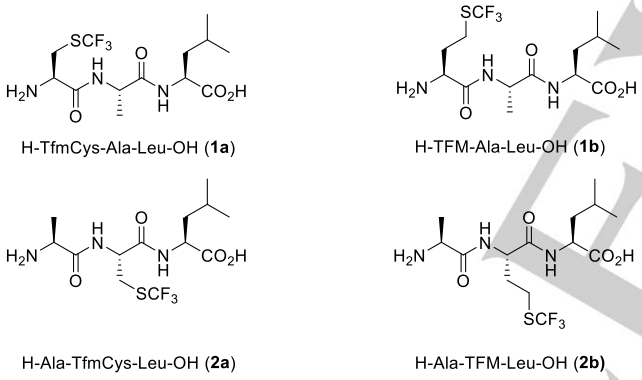
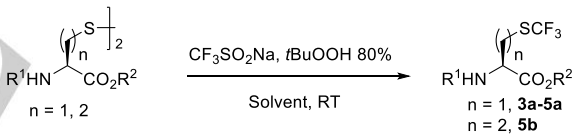


Figure 1. TfmCys and TFM target peptides.

We first devoted our efforts to the synthesis of conveniently protected TfmCys and TFM. The electrophilic *S*-trifluoromethylation using Togni's reagent seemed very attractive because of its compatibility with Fmoc and Boc protecting groups.[10,26] In order to obtain the most versatile synthon for liquid peptide coupling, we decided to start from Boc/Bn protected cystine and homocystine. First, we tested the electrophilic trifluoromethylation on the isolated cysteine generated by reduction of the corresponding disulfides in classical conditions. But unfortunately the reaction was unpaired by a difficult separation of the desired product from the reagent derived byproduct. Considering the moderate results obtained via the electrophilic trifluoromethylation we decided to introduce the trifluoromethyl group via a radical substitution reaction on the disulfide group. Although the reaction developed by Langlois et al. requires at least a twofold excess of trifluoromethylsulfinate and *tert*-butylhydroperoxide, these reagents are quite cheap. The results are summarized in table 1. No conversion of the fully deprotected cystine occurred presumably because of its low solubility (entry 1). Even the *N*-Boc protected substrates in an acetonitrile/methanol mixture proved to be unreactive (entries 2 and 3). As already noticed by Langlois et al., once the carboxylic acid group is protected as an ester, the reaction proceeds in pure acetonitrile to give the trifluoromethyl cysteine hydrochloride **3a** (entry 4). In the same conditions, the *N*-acetyl cysteine methyl ester gave the expected trifluoromethyl cysteine **4a** in 84% yield (entry 5).

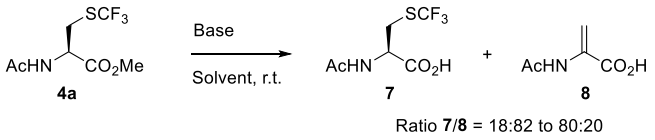
In order to incorporate such SCF_3 group containing amino acids in a peptide chain, both amino and carboxylic protecting groups should be selectively removed. We first try to perform the saponification reaction of the cysteine methyl ester derivative **4a**. Unfortunately, even in mild basic conditions [27] the β-elimination reaction of the SCF_3 group could not be avoided and a significant amount of the elimination product **8** [28,17] was always obtained beside the expected amino acid **7** (Scheme 1). In order to obtain TfmCys and TFM ready to use for peptide synthesis, we decided to prepare the orthogonally protected Boc/Bn substrates which should provide the corresponding carboxylic acid derivatives by hydrogenolysis. The S-trifluoromethylation of the cystine and the DL-homocystine derivatives gave the corresponding trifluoromethylthiolated amino acids in 33% and 42% yield respectively (Table 1, entries 6 and 7).

Table 1. Radical trifluoromethylation of cystine and homocystine derivatives.



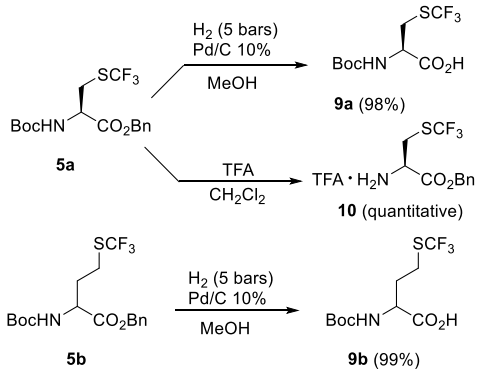
Entry	n	R^1, R^2	Conditions	Product	Yield (%)[a]
1	1	H, H	A[b]	-	-
2	1	Boc, H	B[c]	-	-
3	2	Boc, H	B[c]	-	-
4	1	HCl, Me	B[c]	**3a**	24
5	1	Ac, Me	B[c]	**4a**	84
6	1	Boc, Bn	C[d]	**5a**	33
7[e]	2	Boc, Bn	D[f]	**5b**[g]	42

[a] Isolated yields. [b] Conditions A : *t*BuOOH (3 equiv) / CF_3SO_2Na (3 equiv) / H_2O. [c] Conditions B : *t*BuOOH (4.5 equiv) / CF_3SO_2Na (3 equiv) / MeCN or MeCN/MeOH. [d] Conditions C : *t*BuOOH (9.5 equiv) / CF_3SO_2Na (6 equiv) / MeCN. [e] Reaction from Boc-DL-homocystine benzyl ester. [f] Conditions D : *t*BuOOH (6 equiv) / CF_3SO_2Na (4.5 equiv) / MeCN. [g] Racemic mixture.



Scheme 1. Saponification reaction of the methyl ester **4a** leading to the SCF_3 β-elimination as a side reaction.

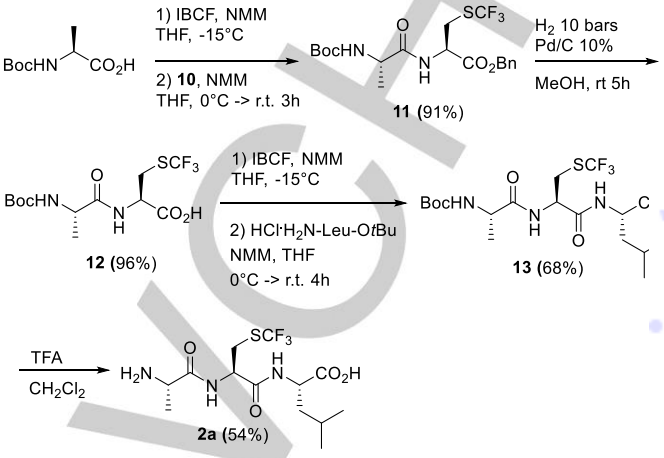
The benzyl esters **5a** and **5b** were submitted to hydrogenolysis in the presence of palladium to give the free carboxylic acids **9a** and **9b** in excellent yields. The Boc protection of TfmCys **5a** could also be removed quantitatively in classical acidic condition to give the benzyl ester **10** (scheme 2).



Scheme 2. TfmCys and TFM target peptides.

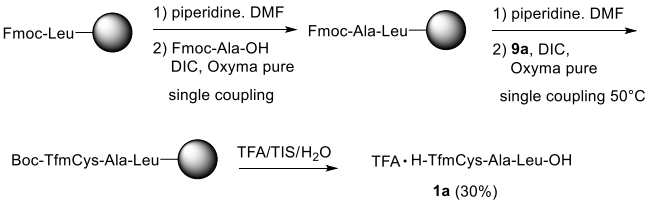
Even if the electrophilic trifluoromethylation using Togni's reagent is known to proceed in better yields than the radical one, the price of the reagents and the ease of purification made the radical addition a method of choice to prepare sufficient quantities of Boc-TfmCys-OH (**9a**), Boc-TFM-OH (**9b**) and H-TfmCys-OBn (**10**) appropriate for liquid or SPPS coupling.

Since the benzyl ester protection is orthogonal to Boc and *tert*-Butyl ester protections, the amino acid H-TfmCys-OBn (**10**) is suitably designed for its incorporation into a short peptide chain by liquid phase peptide synthesis. We chose the hydrophobic H-Ala-TfmCys-Leu-OH peptide **2a** as a model (Scheme 3). For the liquid phase peptide coupling at the *N*-terminal position of **10**, we chose the mixed anhydride activation because of the reduced basicity of *N*-methyl morpholine (NMM) compared to Hunig's base, typically used with other coupling reagents. In these conditions, the dipeptide **11** resulting from the coupling of **10** with the Boc-protected alanine, was obtained in very good yield (91%) without any traces of SCF_3 elimination side products. The hydrogenolysis of the benzyl ester proceeded smoothly to give the *C*-terminal unprotected dipeptide **12** that was submitted to a coupling reaction in the same conditions with the *tert*-butyl ester protected leucine to give the tripeptide **13** in 68% yield. To our great satisfaction, no SCF_3 elimination side product was detected at this step either. After a standard silica gel purification, the protecting groups of **13** were removed using TFA in dichloromethane (scheme 3) to yield the tripeptide **3** in 54% yield. To our knowledge this synthesis constitutes the first introduction of the TfmCys in a peptide using the classical liquid phase coupling methodology.



Scheme 3. Liquid phase synthesis of tripeptide **2a**.

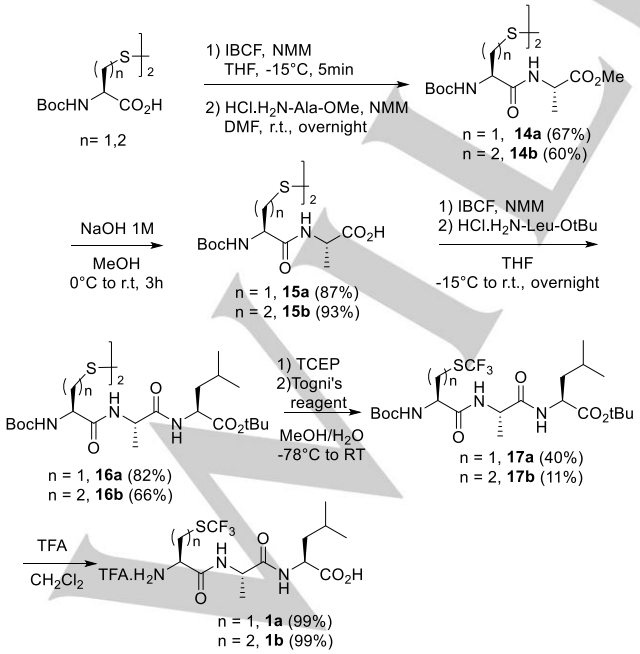
In other respect, the use of the Boc-TfmCys-OH amino acid **9a** in Solid Phase Peptide Synthesis (SPPS) was investigated. However because of the acidic lability of the Boc protection, the Tfm-cysteine could only be inserted at the peptide *N*-terminus. Thus the synthesis of the tripeptide **1a** was investigated by manual SPPS on a high loaded Wang Resin using HATU and DIPEA as coupling mix. Unfortunately, in these conditions the coupling reaction of the fluorinated amino acid occurred with a very low yield. The microwave technology is known to increase the yield of difficult peptide coupling and reduce the amount of side-reactions often observed with unusual amino acids. Thus the synthesis of **1a** was investigated with an automated microwave peptide synthesizer using DIC and oxyma pure as coupling reagents, a standard procedure for microwave activation. In these conditions, the expected tripeptide **1a** was obtained in 30% yield from a single coupling of Boc-TfmCys-OH **9a** at 50°C (scheme 4). To our knowledge, this result validates for the first time, the incorporation of TfmCys in a peptide by SPPS.



Scheme 4. Automated microwave activation SPPS of **1a.**

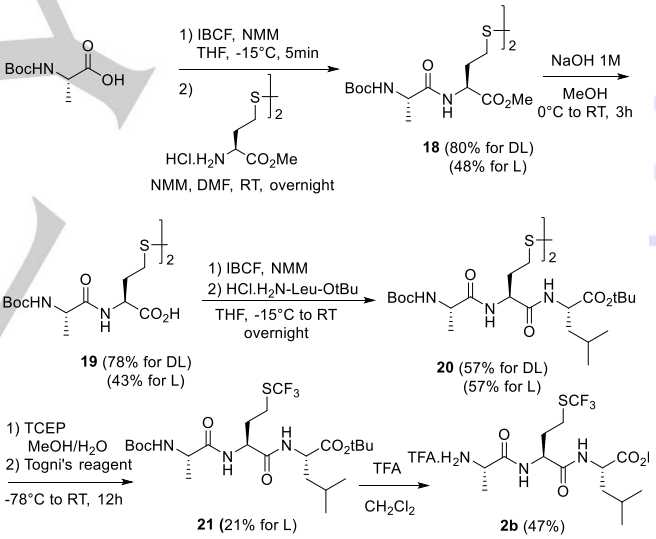
In parallel to the direct introduction of TfmCys and TFM by solution of solid phase peptide synthesis, we developed an alternative strategy based on a late stage trifluoromethylation

reaction using Togni's reagent. This strategy inspired by the pioneer works of Seebach, Togni et al.[17] allowed the synthesis of tripeptides incorporating the trifluoromethylated amino acid in *N*-terminal or central position. The strategy consists in the introduction of the trifluoromethyl group at the end of synthesis via the electrophilic trifluoromethylation reaction of dimeric hexapeptides obtained from commercial cystine or homocystine. As shown in the scheme **5**, this method provided the trifluoromethylated tripeptides **1a,b** with TfmCys and TFM in *N*-terminal position. After a classical Boc protection of the amine functions of L-cystine or L-homocystine, the coupling reaction of alanine methyl ester hydrochloride was performed through a mixed anhydride activation of the two carboxylic acid functions with isobutylchloroformate in the presence of *N*-methylmorpholine. The corresponding diBoc protected dimethyl ester dipeptides **14a** and **14b** were obtained in 67% and 60% respectively. After saponification of the methyl ester functions, the diBoc protected diacids **15a** and **15b** were obtained in very good yields. The two diacids were then engaged in a last coupling with hydrochloride leucine *tert*-butylester using the mixed anhydride activation, and the corresponding peptide dimers **16a** and **16b** were obtained in quite good yields. The last step before deprotection of the peptides is the electrophilic *S*-trifluoromethylation using Togni's reagent after reduction of the disulfide bridges. The disulfide derivatives were cleaved by treatment with tris(2-carboxyethyl)phosphine hydrochloride (TCEP) at room temperature. The addition of Togni's reagent at -78°C on the resulting thiols gave the trifluoromethylated *N*-protected tert-butylester tripeptides **17a** and **17b** in moderate 40% and 11% yield respectively after purification by silica gel chromatography. After simultaneous removal of the Boc and the *tert*-butyl ester protecting groups with a large excess of TFA in dichloromethane, the expected H-TfmCys-Ala-Leu-OH (**1a**) and H-TFM-Ala-Leu-OH (**1b**) were quantitatively obtained as their TFA salts.



Scheme 5. Synthesis of H-TfmCys-Ala-Leu-OH (**1a**) and H-TFM-Ala-Leu-OH (**1b**).

As presented in scheme **6**, the synthesis of the tripeptide **2b** incorporating the trifluoromethionine in the central position has also been achieved by electrophilic late trifluoromethylation of a homocystine based hexapeptide. The first steps of this pathway were initially tested from the DL-homocystine before being carried out on enantiopure L-homocystine. The coupling reaction between the Boc-protected L-alanine and homocystine methyl ester hydrochloride was performed through the mixed anhydride activation of alanine with isobutylchloroformate in the presence of *N*-methylmorpholine to yield the corresponding di-Boc protected dimethyl ester **18**. After saponification of the ester functions, the second coupling was carried out in the same conditions with leucine *tert*-butyl ester hydrochloride to yield the precursor of the trifluoromethylated tripeptide **20** in 57%. After reduction of the disulfide, the trifluoromethylation reaction using the electrophilic hypervalent iodine (III) trifluoromethylated reagent leaded to the protected tripeptides **21** with a moderate yield (21%). After removal of the protecting groups, the peptide was purified by semi-preparative HPLC to provide the peptide **2b** as its TFA salt in 47% yield.



Scheme 6. Synthesis of H-Ala-TFM-Leu-OH (**2b**)

In conclusion, we developed the synthesis of enantiopure L-*S*-trifluoromethylcysteine and L-trifluoromethionine suitably protected for peptide synthesis using a cheap radical trifluoromethylation of disulfide precursors. Circumventing the elimination of SCF_3 moiety by hydrogenolysis of the benzyl ester protected TfmCys, we were able to perform the liquid phase and the solid phase synthesis of TfmCys containing peptides. We also performed the late stage trifluoromethylation of dimeric disulfide bridged hexapeptides derived from cystine or homocystine. If this strategy was already described for TfmCys, we demonstrated that it is also transposable for the synthesis of

TFM containing peptides. These synthetic progresses will be of major interest considering the relevant incorporation of these two unnatural amino acids in peptides for biological issues. The application of these short fluorinated peptides in terms of hydrophobicity measurements will be reported in due course.

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Keywords: Fluorinated amino acids • (L)-*S*-trifluoromethyl cysteine • (L)-trifluoromethionine • Fluorinated peptides • Solid phase and solution phase peptide synthesis

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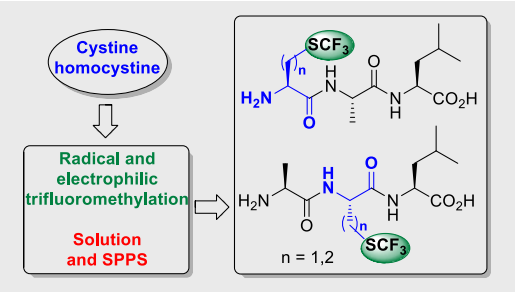
COMMUNICATION

L-trifluoromethionine (TFM) and *L*-S-trifluoromethylcysteine (TfmCys) are synthesized using a cheap and user friendly radical trifluoromethylation. TfmCys is inserted for the first time in a peptide sequence by liquid or solid phase peptide synthesis. A late trifluoromethylation strategy using Togni's reagent on disulfide bridged peptides is also efficient for the incorporation of TFM or TfmCys at both *N*-terminal and internal positions.



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