Synthesis of *S*-trifluoromethyl-containing α-amino acids from sodium trifluoromethanesulfinate and dithio-amino acids

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Abstract

N-Protonated or *N*-acetylated dimethyl cystinates and homocystinates react with sodium trifluoromethanesulfinate and t-butyl hydroperoxide to yield the corresponding derivatives of methyl *S*-trifluoromethyl cysteinate and homocysteinate in a stereospecific manner. Methyl *S*-trifluoromethyl-*N*-acetyl cysteinate and homocysteinate are readily saponified, without racemization, by sodium hydrogen carbonate in a water/methanol mixture.

Introduction

A recent paper described the synthesis of enantiomerically pure *S*-trifluoromethylated α-amino acids from iodotrifluoromethane and the corresponding thiolated amino acids ((L)-cysteine, (L)-homocysteine, (D)-penicilamine) [1], using typical SET conditions which are now routinely used to reach perfluoroalkyl thioethers from aliphatic [2–5], aromatic [2, 5–8] and heterocyclic thiols [9, 10]:

$$H\text{–}S\text{–}(CR_2)_n\text{–}CH(NH_2)COOH \xrightarrow[2.H^+]{1.CF_3I/liq.NH_3/h\nu} CF_3\text{–}S\text{–}(CR_2)_n\text{–}CH(NH_2)COOH$$

(R = H, n = 1,2; R = CH_3, n = 1)

This publication has prompted us to report upon our own preparation of the same biologically-active compounds.

Results and discussion

Recently, we published a synthesis of trifluoromethyl thioethers from disulfides using sodium trifluoromethanesulfinate and 63% aqueous t-butyl hydroperoxide as the trifluoromethylating agent [11]:

$$CF_3SO_2^- + Bu^tOOH \longrightarrow CF_3SO_2\cdot + Bu^tO\cdot + OH^-$$

$$CF_3SO_2\cdot \longrightarrow \cdot CF_3 + SO_2$$

$$\cdot CF_3 + RS\text{–}SR \longrightarrow RS\text{–}CF_3 + RS\cdot \ (\xrightarrow{Bu^tO\cdot}$$

over-oxidized products)

$$SO_2 + HO^- \longrightarrow HSO_3^-$$

$$HSO_3^- + Bu^tOOH \longrightarrow HSO_4^- + Bu^tOH$$

In the present paper, we illustrate this reaction with derivatives of (L)-cystine (**1a,b**) and (D,L)-homocystine (**1c,d**) as substrates:

$$[-S-(CH_2)_n-\underset{\displaystyle NHR}{\underset{|}{CH}}-COOMe]_2 \xrightarrow[CH_3CN \text{ or } H_2O,\ 20\ ^\circ C]{CF_3SO_2Na\ /\ Bu^tOOH}$$

(**1a**) (L): n = 1, R = H_2^+
(**1b**) (L): n = 1, R = $COCH_3$
(**1c**) (D, L): n = 2, R = H_2^+
(**1d**) (D, L): n = 2, R = $COCH_3$

$$CF_3\text{—}S\text{—}(CH_2)_n\text{—}\underset{\displaystyle NHR}{\underset{|}{CH}}\text{—}COOMe$$

(**2a–2d**)

This reaction cannot be performed with unprotected cystine and homocystine, which are barely soluble in water or acetonitrile, but proceeds smoothly, under very mild conditions, with *N,N'*-diprotonated or *N,N'*-diacetylated dimethyl (L)-cystinate and dimethyl (D,L)-homocystinate. Compounds **1a** and **1c** can be simply trifluoromethylated in water, in which they are soluble, whereas compounds **1b** and **1d** must be treated in pure acetonitrile. This reaction offers medium yields but involves safe, easy-to-handle and readily available re-

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agents, since sodium trifluoromethanesulfinate results, in one step, from bromotrifluoromethane and sodium dithionite [12]. Reaction conditions and results are summarized in Table 1 (yields expressed as (mol $RSCF_3$/mol RSSR) × 100 since one thiyl moiety of the disulfide is used to produce the trifluoromethyl thioether).

The initially neutral medium becomes acidic as the reaction proceeds, hence no epimerization of the chiral centres can occur. Thus, the trifluoromethylation of the pure dimethyl (L)-cystinate derivatives **1a,b** was completely stereoselective and afforded the enantiomerically pure methyl *S*-trifluoromethyl-(L)-cysteinate derivatives **2a,b**.

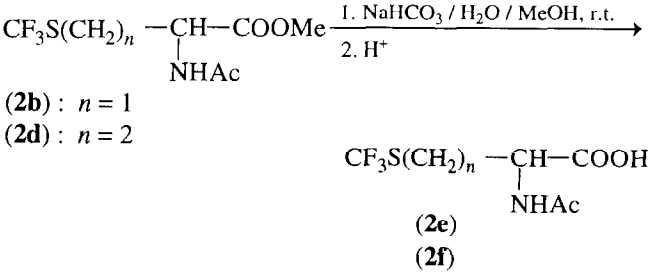
N,N'-Bis(trifluoroacetyl)dimethyl cystinate, which was not soluble in acetonitrile, was treated in ethyl acetate with the trifluoromethylating system, since this is also a good solvent for sodium trifluoromethanesulfinate, but surprisingly the initial amino acid was recovered unchanged. It is possible that in this case the sulfinate anion was too tightly bound to the electrophilic trifluoroacetyl moiety and was thus shielded from oxidation.

The experiments reported in Table 1 led to two types of *S*-trifluoromethylated α-amino acids:

(i) Those with a free amino group and a protected carboxy group (**2a**, **2c**), which are useful for peptidic syntheses starting from the amino moiety.

(ii) Those where both the amino and carboxy groups are protected (**2b**, **2d**). Mild saponification of the ester moiety in such compounds could lead to *N*-protected amino acids suitable for peptidic syntheses starting from the carboxy group.

Usually, the selective saponification of *N*-acetylated and *O*-esterified peptides is performed with caesium carbonate in a hydromethanolic medium in order to prevent any racemization [13]. In fact, compound **2b** yields *S*-trifluoromethyl-*N*-acetyl-(L)-cysteine, $CF_3SCH_2CH(NHAc)COOH$(**2e**), in 70% yield when treated for 24 h at room temperature with caesium carbonate in a water/methanol (50:50 v/v) mixture. Surprisingly, however, we observed that the same ester **2b** was readily saponified at room temperature (up to 65% within 30 min) by a hydromethanolic solution of sodium hydrogen carbonate, although it has been reported [13] that alkaline hydrogen carbonates are two-times less efficient for this purpose than carbonates. Furthermore, **2d** (racemic mixture) was hydrolyzed even faster on simple washing with sodium hydrogen carbonate, and afforded *S*-trifluoromethyl-*N*-acetyl-(D,L)-homocysteine, $CF_3S(CH_2)_2CH(NHAc)COOH$ (**2f**), quantitatively.



In conclusion, several derivatives of *S*-trifluoromethylated α-amino acids can be synthesized stereospecifically in two to four steps from commercial cystine or homocystine and simple or readily available reagents, and in such forms that they can be incorporated into peptides in several ways.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ or D_2O at 60 MHz on a Varian EM 360 spectrometer or at 300 MHz on a Bruker AM 300 apparatus. Chemical shifts (δ) are given in ppm from tetramethylsilane, chosen as the internal standard, and coupling constants (*J*) are given in Hz. ^{19}F NMR spectra were recorded in $CDCl_3$, D_2O or DMSO at 56.4 MHz on a Varian EM 360 apparatus or at 75.38 MHz on a Bruker WP 80 spectrometer. Chemical shifts (Φ_F) are given in ppm from fluorotrichloromethane which is the internal standard.

TABLE 1. Trifluoromethylation of dimethyl cystinate and homocystinate derivatives

Substrate No.	Solvent	Molar ratio	Product		
			No.	Yield (%)	$[\alpha]_D^{25}$
1a	H_2O	CF_3SO_2Na (3 equiv.) Bu^tOOH (4.5 equiv.)	**2a**	48	11.7 (c = 0.5; MeOH)
1b	MeCN	CF_3SO_2Na (2 equiv.) Bu^tOOH (3 equiv.)	**2b**	46	41.2 (c = 1.15; CH_2Cl_2)
1c	H_2O	CF_3SO_2Na (2 equiv.) Bu^tOOH (3 equiv.)	**2c**	56	0
1d	MeCN	CF_3SO_2Na (2 equiv.) Bu^tOOH (3 equiv.)	**2d**	37	0

Melting points (m.p,) were determined on a Köfler apparatus. Optical rotation $[\alpha]_D^{25}$ values were measured on a Perkin-Elmer 141 polarimeter fitted with a 6.2 ml trough (length 10 cm). Concentrations are given in g $(100\ ml)^{-1}$.

Starting materials

Dimethyl (L)-cystinate bis-hydrochloride (**1a**) is commercially available. Dimethyl (D,L)-homocystinate bis-hydrochloride (**1c**) was obtained, following the method previously reported [14], by treating (D,L)-cystine in methanol with thionyl chloride. Dimethyl *N,N'*-diacetyl-(L)-cystinate (**1b**) and dimethyl *N,N'*-diacetyl-(D,L)-homocystinate (**1d**) were prepared, following ref. 14, by treatment of **1a** and **1c** with acetyl chloride and triethylamine. Dimethyl *N,N'*-bis(trifluoroacetyl)-(L)-cystinate resulted from the action of trifluoroacetic anhydride on **1a**, following ref. 15.

Dimethyl (D,L)-homocystinate bis-hydrochloride (**1c**): Yield, 93%. ^1H NMR (60 MHz, D_2O) δ: 2.4 (t, $J=7$, 4H, CH_2CH); 2.9 (t, $J=7$, 4H, SCH_2); 3.9 (s, 6H, OCH_3); 4.3 (t, $J=7$, 2H, CH); 4.8 (s, 6H, NH_3^+) ppm.

Dimethyl *N,N'*-diacetyl-(L)-cystinate (*Ib*): Yield, 45%; m.p. 94 °C (lit. value, 96 °C [14]). ^1H NMR (60 MHz, $CDCl_3$) δ: 2.0 (s, 6H, $COCH_3$); 3.1 (d, $J=6$, 4H, CH_2); 3.7 (s, 6H, OCH_3); 4.8 (m, 2H, CH); 6.8 (d, $J=8$, 2H, NH) ppm.

Dimethyl *N,N'*-diacetyl-(D,L)-homocystinate (**1d**): Yield, 43%; m.p. 105 °C. ^1H NMR (60 MHz, $CDCl_3$) δ: 1.9–2.3 (m, 10H, CH_2CH and $COCH_3$ (at 2.0 ppm)); 2.7 (m, 4H, SCH_2); 3.6 (s, 6H, OCH_3); 4.7 (m, 2H, CH); 6.8 (d, 2H, NH) ppm.

Dimethyl *N,N'*-bis(trifluoroacetyl)-(L)-cystinate: Yield, 90%; m.p. 154 °C (lit. value, 152–154 °C [15]); $[\alpha]_D^{25} = -185°$ ($c=1.01$; MeOH) (lit. value $-183°$ ($c=2.5$; MeOH) [15]). ^1H NMR (60 MHz, $CDCl_3$) δ: 2.9–3.3 (m, 4H, CH_2); 3.7 (s, 6H, OCH_3); 4.3–5.0 (m, 2H, CH); 10 (s(broad), 2H, NH) ppm. ^{19}F NMR (75.38 MHz, $CDCl_3$) Φ: -74 (s, $COCF_3$) ppm.

Synthesis of methyl esters of S-trifluoromethylated α-amino acids

Methyl S-trifluoromethyl-(L)-cysteinate hydrochloride (2a)

Dimethyl (L)-cystinate bis-hydrochloride (**1a**) (1.5 g, 4.4 mmol) and 2.18 g (13.3 mmol) of sodium trifluoromethanesulfinate were dissolved in 70 ml of water. A 63% aqueous solution of t-butyl hydroperoxide (19.7 mmol) (3 ml) was added over 1.75 h to this efficiently stirred mixture by means of a syringe pump, the whole being maintained at 20 °C by means of a water bath. The mixture was held at room temperature under stirring for 2.5 h then excess hydroperoxide, if present (potassium iodide test), was destroyed by the addition of an aqueous solution of sodium metabisulfite (final pH = 1). The reaction mixture was extracted with 35 ml of petroleum ether (in order to remove non-ionic impurities) then brought to pH = 9 (phenolphthalein) with 1 N NaOH solution and extracted twice with 30 ml of diethyl ether. A solution of hydrogen chloride in ether (0.68 N) was dropped on to the combined ethereal extracts until complete precipitation occurred. In this way 0.5 g (2.09 mmol) of **2a** was obtained, after filtration, as a pearly white solid: yield, 48%; m.p. 70 °C; $[\alpha]_D^{25} = 11.7$ ($c=0.5$; MeOH). ^1H NMR (300 MHz, D_2O) δ: 3.54 (dd, $^2J_{H_aH_b}=15.8$, $^3J_{H_aH_c}=7.1$, 1H, $S-CH_aH_b-CH_c=$); 3.67 (dd, $^2J_{H_bH_a}=15.8$, $^3J_{H_bH_c}=4.8$, 1H, $S-CH_aH_b-CH_c=$); 3.85 (s, 3H, OCH_3); 4.53 (dd, $^3J_{H_aH_c}=7.1$, $^3J_{H_bH_c}=4.8$, 1H, $CH_c=$); 4.77 (s, 3H, NH_3^+) ppm. ^{19}F NMR (75.38 MHz, DMSO) Φ: -43.9 (s, CF_3) ppm.

Methyl S-trifluoromethyl-(D,L)-homocysteinate hydrochloride (2c)

Compound **2c** (0.38 g, 1.5 mmol) was obtained as a white solid using the same procedure and starting from an aqueous solution (60 ml) consisting of 1.0 g (2.7 mmol) of dimethyl (D,L)-homocystinate bis-hydrochloride (**1c**) and 0.9 g (5.4 mmol) of sodium trifluoromethanesulfinate treated with 1.23 ml (8.12 mmol) of t-butyl hydroperoxide solution: yield, 56%; m.p. 94 °C. ^1H NMR (300 MHz, D_2O) δ: 2.25–2.52 (m, 2H, $S-CH_2-CH_2-CH=$); 3.08–3.25 (m, 2H, $S-CH_2-CH_2-CH=$); 3.87 (s, 3H, OCH_3); 4.33 (t, $J=7$, 1H, $CH_2-CH=$); 4.8 (s, 3H, NH_3^+) ppm. ^{19}F NMR (75.38 MHz, D_2O) Φ: -43.5 (s, CF_3) ppm.

Methyl N-acetyl-S-trifluoromethyl-(L)-cysteinate (2b)

Dimethyl *N*-acetyl-(L)-cystinate (**1b**) (0.85 g, 2.4 mmol) and 0.81 g (4.8 mmol) of sodium trifluoromethanesulfinate were dissolved in 50 ml of acetonitrile. A 63% aqueous solution of t-butyl hydroperoxide (7.2 mmol) (1.1 ml) was added over 45 min to this efficiently stirred mixture by means of a syringe pump, the whole being maintained at 20 °C by means of a water bath. The mixture was held at room temperature under stirring for 2.5 h then excess hydroperoxide, if present (potassium iodide test), was destroyed by the addition of an aqueous solution of sodium metabisulfite (final pH = 1). The reaction mixture was poured into 100 ml of water and extracted twice with 50 ml of ethyl ether. The combined ethereal phases were dried over $MgSO_4$ and evaporated to provide 0.59 g of crude **2b** as an oil which crystallized slowly and was purified by chromatography on silica (20 g) using a mixture of petroleum ether and acetone (60:40 v/v) as eluant. Pure crystalline **2b** (0.29 g) was thus obtained (some traces of t-butanol, which could remain in **2b** after chromatography, may be evaporated under vacuum (1 Torr) or eliminated by recrystallization from cyclohexane): yield, 46%; m.p.

72 °C; $[\alpha]_D^{25} = 41.2$ ($c = 1.15$; CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.03 (s, 3H, CO−CH_3); 3.35 (dd, $^2J_{H_aH_b} = 14.3$, $^3J_{H_aH_c} = 4.7$, 1H, S−CH_aH_b−CH_c=); 3.52 (dd, $^2J_{H_bH_a} = 14.3$, $^3J_{H_bH_c} = 4.7$, 1H, S−CH_aH_b−CH_c=); 3.80 (s, 3H, OCH_3); 4.90 (m, 1H, −CH_c=); 6.59 (d, $^3J_{H_cNH} = 4.7$, 1H, NH) ppm. ^{19}F NMR (75.38 MHz, $CDCl_3$) Φ: −41.4 (s, CF_3) ppm.

Methyl N-acetyl-S-trifluoromethyl-(D,L)-homocysteinate (2d)

Compound **2d** (0.23 g, 0.89 mmol) was obtained as a crystalline solid after chromatography, using the same procedure starting from a solution consisting of 0.89 g (2.34 mmol) of dimethyl *N,N'*-diacetyl-(D,L)-homocystinate (**1d**) and 0.78 g (4.78 mmol) of sodium trifluoromethanesulfinate in 60 ml of acetonitrile. This mixture was treated with 1.1 ml (7.23 mmol) of t-butyl hydroperoxide solution: yield, 37%. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.08 (s, 3H, CO−CH_3); 2.22–2.38 (m, 2H, S−CH_2−CH_2−CH=); 2.87–3.00 (m, 2H, CF_3S−CH_2); 3.79 (s, 3H, OCH_3); 4.65–4.78 (m, 1H, CH_2−CH=); 6.68 (m, 1H, =CH−NH) ppm. ^{19}F NMR (75.38 MHz, $CDCl_3$) Φ: −42.1 (s, CF_3) ppm.

Hydrolysis of methyl esters of N-acetyl α-amino acids

Formation of N-acetyl-S-trifluoromethyl-(L)-cysteine (2e)

From 2b and caesium carbonate – Methyl *N*-acetyl-*S*-trifluoromethyl cysteinate (**2b**) (150 mg, 0.61 mmol) and 400 mg (1.22 mmol) of caesium carbonate were stirred for 24 h in a mixture of water (5 ml) and methanol (5 ml). The solution was acidified to pH = 1 with 10 N aqueous hydrochloric acid and then evaporated to dryness. The residue was treated with 20 ml of ethyl acetate. After filtration, the organic phase was evaporated to dryness to yield 100 mg of *N*-acetyl-*S*-trifluoromethyl cysteine as white needles: yield, 70%; $[\alpha]_D^{25} = 24.2$ ($c = 1.2$; MeOH). ^1H NMR (300 MHz, D_2O) δ: 2.03 (s, 3H, CO−CH_3); 3.32 (dd, $^2J_{H_aH_b} = 14.0$, $^3J_{H_aH_c} = 8.0$, 1H, S−CH_aH_b−CH_c=); 3.51 (dd, $^2J_{H_bH_a} = 14.0$, $^3J_{H_bH_c} = 5.0$, 1H, S−CH_aH_b−CH_c=); 4.70 (dd, $^3J_{H_aH_c} = 8.0$, $^3J_{H_bH_c} = 5.0$, 1H, −CH_c=); 4.92 (s, 2H, CO_2H and NH, mean position) ppm. ^{19}F NMR (75.38 MHz, D_2O) Φ: −40.15 (s, CF_3) ppm.

From 2b and sodium hydrogen carbonate – Methyl *N*-acetyl-*S*-trifluoromethyl-(L)-cysteinate (**2b**) (50 mg, 0.20 mmol) and 18 mg of sodium hydrogen carbonate were stirred for 30 min in a mixture of water (2 ml) and methanol (2 ml). The solution was acidified to pH = 1 with 10 N aqueous hydrochloric acid and then evaporated to dryness. The residue was treated with 5 ml of ethyl acetate. After filtration, the organic phase was evaporated to dryness to yield 30 mg of *N*-acetyl-*S*-trifluoromethyl cysteine as a white solid: yield, 65%; $[\alpha]_D^{25} = 20.1$ ($c = 0.5$; MeOH).

Formation of N-acetyl-S-trifluoromethyl-(D,L)-homocysteine (2f) from 2d and sodium hydrogen carbonate

Methyl *N*-acetyl-*S*-trifluoromethyl-(D,L)-homocysteinate (**2d**), dissolved in ethyl ether, was washed with a saturated aqueous solution of sodium hydrogen carbonate. The reaction medium was acidified to pH = 1 with hydrochloric acid and the resulting precipitate extracted with ethyl acetate. After evaporation, *N*-acetyl-*S*-trifluoromethyl-(D,L)-homocysteine was obtained in quantitative yield. ^1H NMR (300 MHz, D_2O) δ: 2.04 (s, 3H, CO−CH_3); 2.06–2.38 (m, 2H, S−CH_2−CH_aH_b−CH_c=); 2.92–3.16 (m, 2H, CF_3S−CH_2); 4.52 (dd, $^3J_{H_cH_a} = 4.7$, $^3J_{H_cH_b} = 9.4$, 1H, CH_c=); 4.80 (s, 2H, CO_2H and NH, mean position) ppm. ^{19}F NMR (75.38 MHz, D_2O) Φ: −40.6 (s, CF_3) ppm.

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