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Robust synthesis of trifluoromethionine and its derivatives by reductive trifluoromethylation of amino acid disulfides by CF_3I/Na/Liq.NH_3 system

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ABSTRACT

We disclose the reductive trifluoromethylation of chemically stable homocystine and cystine to provide corresponding trifluoromethyl ethers by the CF_3I/Na/Liq.NH_3 system. Both non-protected and protected homocystines can be nicely converted into trifluoromethylated methionines under the same condition. The method described offers a robust synthesis of pharmaceutically important trifluoromethionine, suitable for multigram synthesis. Pentafluoroethylation of homocystine was also achieved by the CF_3CF_2I/Na/Liq.NH_3 system.

1. Introduction

Amebiasis is an infectious disease caused by the enteric protozoan parasite *Entamoeba histolytica* and is the second leading cause of death from parasitic diseases after malaria. Metronidazole and related compounds are commonly used against invasive intestinal and extraintestinal amebiasis [1,2]. Although clinical resistance against metronidazole has not yet been demonstrated, sporadic cases of treatment failure have been reported [1]. In addition, it has been shown that this parasite easily adapts to therapeutic levels of metronidazole *in vitro* [3]. Resistance to metronidazole is also acquired easily by many bacterial species as well as *Giardia intestinalis* and *Trichomonas vaginalis* [1]. Therefore, the development of a novel antiamebic drug is urgently required. Trifluoromethionine (**1a**, *S*-trifluoromethyl-L-homocysteine), a trifluorinated analogue of the amino acid methionine, has emerged as a promising lead for amebiasis due to its high toxicity against bacteria highly related to amebiasis [4]. Recently, Nozaki and co-workers within our group reported an efficient cytotoxic effect of amide derivatives of trifluoromethionine against the enteric protozoan parasite *E. histolytica* (Fig. 1) [4b,5].

Another importance aspect of trifluoromethionine is its utility as a probe to elucidate the biochemistry of methionine residues in proteins [6]. Honek and co-workers studied the incorporation of trifluoromethionine into peptides and proteins, and gained conformational information of protein structure, side chain dynamics as well as ligand binding using ^{19}F NMR spectroscopy [7]. As a part of our continuous research program in the development of effective drugs for amebiasis [4], we required a large amount of trifluoromethionine (**1a**) to start the clinical study. Although several methods for the synthesis of **1** have been reported [8], they require several synthetic steps difficult to perform in a multi-gram scale, and are expensive with chemically unstable homocysteine being required as a starting material. In this paper, we report the facile synthesis of trifluoromethionine (**1a**) by direct reductive trifluoromethylation of chemically stable homocystine (**2a**) under the combinatorial condition, CF_3I/Na/Liq.NH_3. This method is robust and can be perform at a large scale. Direct reductive trifluoromethylation of protected homocystine **2b** and cystine (**2c**) also proceeded nicely by this method in good to high yields (Scheme 1(b)).

2. Results and discussion

Among several synthetic methods available [8], the most straightforward way to prepare **1a** is the direct trifluoromethylation of homocysteine using trifluoromethyl iodide (CF_3I) in liquid NH_3 under ultraviolet (UV) irradiation reported by Soloshonok et al. (Scheme 1(a)) [8b]. Enantiomerically pure trifluoromethionine can be easily obtained in a single step from homocysteine

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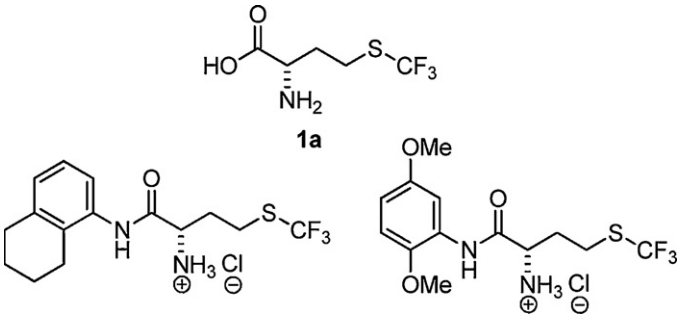
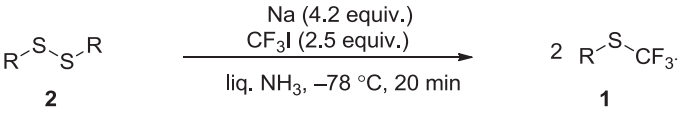


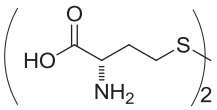
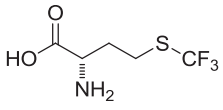
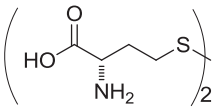
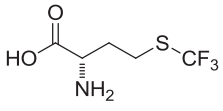
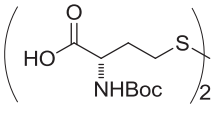
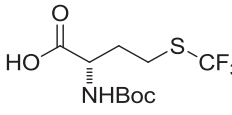
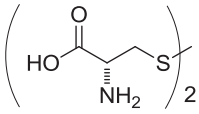
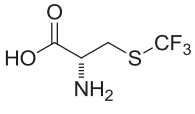
Fig. 1. Trifluoromethionine and its derivatives as promising drug candidates against protozoan parasites [5].

without protection by the method. However, when we performed this method in a large scale for a pre-clinical study of **1a** [5], we often suffered from difficulties of removing a by-product, homocystine (**2a**), through the use of ion-exchange chromatography. Moreover UV-irradiation is also somewhat tedious in large-scale synthesis. The instability of homocysteine is another disadvantageous point of this transformation. To overcome these problems, a different synthetic approach was executed. Robust preparative methods are especially important for large-scale synthesis, which must be highly reproducible. We attempted to find out direct trifluoromethylation from chemically stable homocystine (**2a**) instead of homocysteine into **1a** without UV-irradiation. Incidentally, trifluoromethyl thioethers can be synthesized from disulfides by reaction of the trifluoromethyl anion [9]; however, the method suffers from the fact that half of the disulfide is wasted in the process. In 1991, Wakselman and co-workers reported the reductive trifluoromethylation of disulfides with CF_3Br (4 bar) in the presence of dithionite or hydroxymethanesulfinate salts in DMF-H_2O medium leads to the formation of aliphatic and aromatic trifluoromethyl sulfides [10]. However, this method is less efficient when using alkane–disulfides as substrates and to make matters worse, CF_3Br is known as an ozone depletion chemical that could destruct ozone dramatically. For this reason, substitute chemicals such as CF_3I must be selected for consideration to replace CF_3Br. In 2004, Dolbier and co-workers reported an atom-economic procedure for preparation of trifluoromethyl thioethers from disulfide using CF_3I in DMF in the presence of tetrakis(dimethylamino)ethylene (TDAE) as the organic reducing agent [11]. However, using expensive TDAE is a problem for large-scale synthesis, and in fact, we failed to convert homocystine into **1a** by CF_3I/TDAE in the DMF system. After many attempts, we were pleased to find that a combination of Birch reduction condition, Na/Liq.NH_3 with CF_3I, efficiently produced **1a** from homocystine. Actually, as shown in Table 1, the use of Na (4.2 equiv.), CF_3I (2.5 equiv.) in liquid NH_3 at −78 °C gave **1a** in 80% yield from homocystine (Entry 1). Furthermore, we successfully carried out this reaction on a 10 g scale (Entry 2). It should be noted that *N*-Boc-protected homocystine **2b** is well-tolerated under this condition to provide the desired *N*-Boc-protected trifluoromethionine **1b** in 70% yield (Entry 3). This method was also applicable for the direct trifluoromethylation of cystine (**2c**) to trifluoromethyl cysteine (**1c**) in 65% yield (Entry 4).

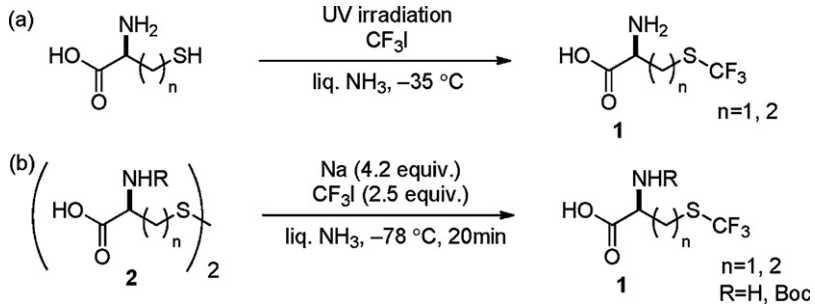
It is interesting to note that when we used pentafluoroethyl iodide (C_2F_5I) instead of CF_3I, pentafluoroethionine **3** was obtained from **2a** in 67% yield (Scheme 2). The Birch condition was used for reductive alkylation of disulfides, as reported more than 20 years ago [12], but this method had not been applied to the fluoroalkylation reaction of disulfides. As far as we know, this is the first

Table 1
Reductive trifluoromethylation of disulfides of amino acids, homocystine and cystine.

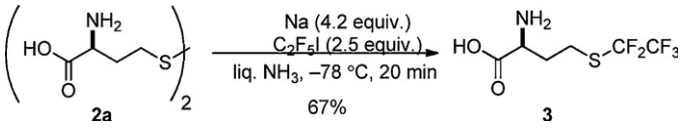


Entry	Substrate **2**	Product **1**	Yield (%)
1	 **2a**	 **1a**	80
2[a]	 **2a**	 **1a**	93
3	 **2b**	 **1b**	70
4	 **2c**	 **1c**	65

[a] The experiment was performed on a 10 g scale.



Scheme 1. Synthesis of trifluoromethionine and its derivatives. (a) Trifluoromethylation of thiols by CF_3I under UV irradiation reported by Soloshonok et al. (b) Reductive trifluoromethylation of disulfide by CF_3I/Na/Liq.NH_3 (this work).



Scheme 2. Reductive pentafluoroethylation of homocystine **2a** to pentafluoroethionine **3**.

example of reductive fluoroalkylation reaction of disulfides under the Birch condition.

3. Conclusion

In conclusion, extremely facile synthesis of trifluoromethionine (**1a**) from readily available and chemically stable homocystine (**2a**) was developed by direct trifluoromethylation using CF_3I/Na/Liq.NH_3. The described method offers a robust synthesis of trifluoromethionine (**1a**), suitable for multigram synthesis. The methodology described here seems to be the simplest one for the synthesis of these compounds and can be extended to the perfluoroalkylation of disulfides such as the pentafluoroethylation reaction.

4. Experimental

4.1. General

^1H, ^{13}C and ^{19}F NMR spectra were recorded with Varian 200 or 300 spectrometers in $CDCl_3$ or D_2O solutions. TMS, residual chloroform and $CFCl_3$ were used as internal references for ^1H, ^{13}C and ^{19}F NMR in $CDCl_3$ solution, respectively. Residual H_2O was used as an internal reference for ^1H NMR in D_2O solution. TFA-*d* was used as an internal reference for ^{13}C and ^{19}F NMR in D_2O solution. Chemical shifts are expressed in ppm (δ). Coupling constants (J) values are in Hz. Optical rotations were measured on a HORIBA SEPA-300. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. Mass spectra were recorded on a SHIMAZU LCMS-2010EV (ESI-MS). HRMS was recorded on a WATERS ESI/Synapt G2 HDMS (ESI-MS).

4.2. General experimental procedure for the reductive trifluoromethylation of amino acid disulfides

The disulfide **2** was dissolved in liquid ammonia in a flask cooled to −78 °C, and sodium was slowly added in small pieces until the reaction mixture turned blue. Trifluoromethyl iodide or pentafluoroethyl iodide was then slowly added with a balloon. After stirring for 20 min at this temperature, the cooling bath was removed to evaporate the ammonia completely. The residue was dissolved in 1 M sodium hydroxide aqueous solution. The resulting mixture was applied to Dowex 50W (H^+), the resin was washed well with pure water, and the compound was eluted with 2% ammonia. After evaporating all solvent, the pure product was afforded as a white solid.

L-Trifluoromethionine (**1a**): reaction of L-homocystine (**2a**, 37 mmol, 10 g), sodium (160 mmol, 3.7 g) and CF_3I (93 mmol, 18 g) in about 150 mL of liquid ammonia gave **1a** (14 g, 93%); m.p. 227–228 °C (H_2O/methanol) [lit. 227–230 °C [8b]]; $[\alpha]_D^{24}$ = +25.3 (c 2.01, 4 N HCl) [lit. $[\alpha]_D^{25}$ = +24.1 (c 0.1, 4 N HCl) [8b]]; ^1H NMR (200 MHz, D_2O) δ 4.09 (t, J = 6.6 Hz, 1H), 3.03 (t, J = 8.2 Hz, 2H), 2.40 − 1.95 (m 2H); ^{19}F NMR (188 MHz, D_2O) δ −41.3 (s, 3F); ^{13}C NMR (75.5 MHz, D_2O) δ 171.0, 130.6 (q, J = 306 Hz), 51.2, 30.2, 25.1; IR (KBr) 2917, 2849, 1557, 1506, 1417, 1101, 919 cm^{-1}; MS (ESI) m/z 204 $(M+H)^+$.

N-Boc-*S*-trifluoromethyl-L-homocysteine (**1b**): *N*-Boc-L-Homocystine (**2b**, 4.0 mmol, 1.87 g), sodium (16.8 mmol, 385 mg) and CF_3I (10.0 mmol, 1.96 g) reacted in about 30 mL of liquid ammonia. After removed the ammonia, the residue was dissolved in 10 mL of water. The aqueous solution was adjusted to pH 3.0. The mixture was extracted with ethyl acetate (3× 30 mL). The combined organic layer was washed with 4 N NaS_2O_3 aq., brine, and then dried over Na_2SO_4. After removing all solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 9/1) gave the pure product in 70% yield (5.60 mmol, 1.70 g); m.p. 53–54 °C (EtOAc/hexane); $[\alpha]_D^{24}$ = +14.2 (c 0.52, $CHCl_3$) [lit. $[\alpha]_D^{25}$ = +16.2 (c 2.0, $CHCl_3$) [13]]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (br, 2/5H, rotamer), 5.11 (d, J = 6.9 Hz, 3/5H, rotamer), 4.45 (br, 3/5H, rotamer), 4.32 (br, 2/5H, rotamer), 2.98 (t, J = 7.5 Hz, 2H), 2.32 (br, 1H), 2.09 (br, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ −41.6, (s, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.9, 174.9, 157.0, 155.7, 130.9 (q, 306 Hz), 82.6, 80.7, 53.2, 52.3, 33.3, 33.0, 28.1, 30.0, 25.7; IR (KBr) 2917, 2849, 1717, 1654, 1541, 1458, 1386, 1108, 670 cm^{-1}; MS (ESI) m/z 302 $(M-H)^-$.

S-Trifluoromethyl-L-cysteine (**1c**): reaction of L-cystine (**2c**, 4.0 mmol, 961 mg), sodium (16.8 mmol, 385 mg) and CF_3I (10.0 mmol, 1.96 g) in about 30 mL of liquid ammonia gave **1c** (983 mg, 65%); m.p. 232–234 °C (H_2O) [lit. 230–232 °C [8b]]; $[\alpha]_D^{25}$ = −24.3 (c 0.52, H_2O) [lit. $[\alpha]_D^{25}$ = +52.3 (c 0.1, H_2O) [8b]]. Since the value of specific rotation observed here was very different from the value reported in Ref. [8b]], we prepared **1c** by the procedure described in Ref. [8b]] to confirm this issue. The specific rotation of **1c** by the method [8b]] was ascertained to be $[\alpha]_D^{26}$ = −25.0 (c 0.21, H_2O), which is very close to our observed value; ^1H NMR (300 MHz, D_2O) δ 4.33 (dd, J = 4.5, 7.2 Hz, 1H), 3.63 (dd, J = 4.5, 15.6 Hz, 1H), 3.48 (dd, J = 7.2, 15.6 Hz, 1H); ^{19}F NMR (282 MHz, D_2O) δ −41.4 (s, 3F); ^{13}C NMR (150.9 MHz, D_2O) δ 171.9, 130.7 (q, J = 306 Hz), 54.3, 30.3; IR (KBr) 3427, 2926, 2855, 1615, 1505, 1403, 1346, 1094, 845, 759, 721 cm^{-1}; MS (ESI) m/z 190 $(M+H)^+$.

S-Pentafluoroethyl-L-homocysteine (**3**): reaction of L-homocystine (**2a**, 3.73 mmol, 1.0 g), sodium (15.7 mmol, 359 mg) and C_2F_5I (9.33 mmol, 2.29 g) in about 30 mL of liquid ammonia gave **3**

(1.27 g, 67%); m.p. 208–209 °C (H_2O/methanol); $[\alpha]_D^{24}$ = +23.2 (c 1.60, 4 N HCl); ^{1}H NMR (200 MHz, D_2O) δ 4.03 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 7.4 Hz, 2H), 2.34 – 2.03 (m, 2H); ^{19}F NMR (188 MHz, D_2O) δ −83.3 (s, 3F), −91.8 (s, 2F); ^{13}C NMR (75.5 MHz, D_2O) δ 170.8, 121.4 (qt, J = 40.9, 286 Hz), 118.1 (tq, J = 36.5, 286 Hz), 51.1, 30.5, 23.8; IR (KBr) 2918, 2850, 1584, 1214, 1097, 984, 755 cm^{-1}; MS (ESI) m/z 254 $(M+H)^+$; HRMS (ESI) calcd for $C_6H_9NO_2F_5S$ m/z 254.0274 $(M+H)^+$, found: 254.0279. The fluorine signals deriving from **1c** in ^{19}F NMR spectra exhibit little vicinal coupling, and they appear as two singlet signals, as is exemplified by the fluorine NMR spectrum of CF_3CF_2I [14].

Acknowledgements

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