# Fluorinations with sulfur tetrafluoride and HF. 2. Preparation of trifluoromethylated thiazoles and isothiazoles

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## Abstract

Several new trifluoromethylated thiazoles and isothiazoles have been prepared using $SF_4$ on precursor carboxylic acids. This chemistry demonstrates the usefulness and applicability of the sulfur tetrafluoride fluorination to the preparation of novel thiazoles and isothiazoles.

## Introduction

As a part of a program designed to evaluate new areas of chemistry for a broad range of biological activities, we designed and built a reactor [1] which gave us the opportunity to study fluorinations using HF and $SF_4$. Of particular interest to us were trifluoromethylated heterocycles which, in theory, could be prepared from the action of sulfur tetrafluoride on carboxylic acid derivatives. The results of these reactions and the new molecules prepared are described here.

## Experimental

All $^1H$ and $^{13}C$ NMR spectra were recorded on either a Bruker WM360 or Varian XL 300 spectrometer while $^{19}F$ NMR spectra were taken using Varian EM-360L and XL-300 spectrometers. Spectra were referenced to TMS (tetramethylsilane) for proton and carbon and $CFCl_3$ for fluorine with upfield chemical shifts reported as negative values. Mass spectra were typically recorded on a Hewlett–Packard bench top GC–EI instrument. Reagents used were all commercial grade and boiling points and melting points are all uncorrected.

*4.-Bromo-2-thiazole carboxylic acid (2)*

A solution of 2,4-dibromothiazole [2] (3.6 g, 15 mmol) in ether (25 ml) was added to n-BuLi (7.2 ml, 18 mmol) in ether (50 ml) over 30 min at a rate such that the temperature did not exceed −73 °C [3]. The resulting

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colored solution was stirred for 1 h at −78 °C when $CO_2$ (>1 g) gas was introduced for 3 min. This was followed by solid $CO_2$ (2 g solid) and the mixture was allowed to warm to 10–20 °C when $H_2O$ (50 ml) was added and the layers separated. The water was washed with ether (1×25 ml), acidified with conc. HCl (2 ml), and extracted again with ether (3×100 ml). The ethers were combined, dried ($MgSO_4$), filtered and concentrated to 2.7 g of a colored solid. Crystallization from hexane/ether gave 1.7 g (55%) of **2** as a solid: m.p., 114–115 °C; $^1$H NMR (acetone-$d_6$): $\delta$ 8.15 (s, H-5); $^{13}$C NMR ($CDCl_3$): $\delta$ 125.9, 127.2, 160.0, 160.2 (all singlets).

*4,5-Dichloro-2-thiazole carboxylic acid (3)*

A flask, charged with n-BuLi (2.5 M in hexane, 40 ml), ether (150 ml) and pentane (80 ml) was cooled to −100 °C and treated with 2-bromo-4,5-dichlorothiazole (17.5 g, 75.4 mmol) [8] in ether (30 ml) at a rate such that the internal temperature did not exceed −95 °C. The resulting dark solution was stirred for 30 min at −100 °C when $CO_2$ (>5 g) gas was added over a 5-min period. The color turned very dark and the temperature rose to −60 °C. Additional $CO_2$ (9 g) was added as a solid and the reaction was allowed to warm to 0 °C over 40 min. The final solution was poured into water (400 ml). Layers were separated and the water was washed with ether (200 ml). The aqueous was acidified with 6 N HCl (25 ml) and a brown solid was filtered. This material was slurried with light petroleum ether and filtered to give 8.1 g of **3** (54%): m.p., 98–101 °C; $^{13}$C NMR (acetone-$d_6$): $\delta$ 127.5, 139.4, 156.6, 160.0 (all singlets); MS (EI): 200.8 (M+4, 14.0%), 198.8 (M+2, 68.8%), 196.8 ($M^+$, 100%).

*A general procedure for the fluorination with $SF_4$*

A 300 ml autoclave [1] was charged with acid (0.1 mol), evacuated, cooled to −60 °C, and subsequently charged with HF (30 g) and $SF_4$ (33 g, 0.3 mol). The reaction was heated to 40 °C for 20 h* with stirring at 400–600 rpm. Afterward, the volatiles were vented and the reaction was diluted with ether (100 ml). The organic solution was stored over NaF as a precaution and was later washed with water (1×200 ml), 10% NaOH (1×200 ml) and distilled to give pure product.

*2-Chloro-4-methyl-5-(trifluoromethyl)thiazole (6)*

2.6 g (54%), b.p., 85 °C/10 mmHg; $^1$H NMR ($CDCl_3$): $\delta$ 2.58 (q, $J$=2 Hz, 3H); $^{19}$F NMR ($CDCl_3$): $\delta$ −59.4 (q, $J$=2 Hz). Analysis: Calcd. for $C_5H_3ClF_3NS$: C, 29.79; H, 1.50; N, 6.95%. Found: C, 29.87; H, 1.55; N, 6.88%.

*4-Bromo-2-(trifluoromethyl)thiazole (7)*

18.4 g (76%), b.p., 101–105 °C/150 mmHg; $^1$H NMR ($CDCl_3$): $\delta$ 7.46 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 118.5 (q, $J$=269 Hz, $CF_3$), 120.5 (s, C-5),

*We have lengthened the reaction time for several substrates, increased the stoichiometry of HF and $SF_4$, and heated to 90 °C without any obvious adverse effects on the outcome of the reaction.

126.6 (s, C-4), 155.9 (q, $J$=41.6 Hz, C-2); $^{19}$F NMR ($CDCl_3$): $\delta$ −66.5; MS (GC/EI): 231 ($M^+$, 94.2%), 233 (M+2, 100%). Analysis: Calcd. for $C_4HBrF_3NS$: C, 20.71; H, 0.43; N, 6.04; Br, 34.44%. Found: C, 21.32; H, 0.67; N, 6.12; Br, 34.49%.

*4,5-Dichloro-2-(trifluoromethyl)thiazole (8) [4]*

2.8 g (64%), light yellow liquid; $^{13}$C NMR ($CDCl_3$): $\delta$ 118.1 (q, $J$=273 Hz, $CF_3$), 125.1 (q, $J$=2.5 Hz, C-5),138.9 (s, C-4), 151.3 (q, $J$=46 Hz, C-2); $^{19}$F NMR ($CDCl_3$): $\delta$ −62.8 (s); MS (CI): 222 (M+1, 100%), 224 (M+3, 82.4%), 226 (M+5,17.1%).

*3,4-Dichloro-5-(trifluoromethyl)isothiazole (9)*

20.7 g (83%), b.p., 76–79 °C/150 mmHg; $^{13}$C NMR ($CDCl_3$): $\delta$ 119.9 (q, $J$=270 Hz, $CF_3$), 123.7 (q, $J$=2.9 Hz, C-4), 149.3 (q, $J$=39 Hz, C-5), 150.3 (s, C-3); $^{19}$F NMR ($CDCl_3$): $\delta$ −59.9. Analysis: Calcd. for $C_4Cl_2F_3NS$: C, 21.64; H, 0.00; N, 6.31; Cl, 31.94%. Found: C, 21.86; H, 0.00; N, 6.37; Cl, 31.72%.

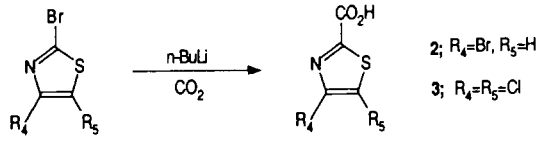
*4,5-Dibromo-3-(trifluoromethyl)isothiazole (10)*

4.1 g (93% estimated at 95% pure); $^{13}$C NMR ($CDCl_3$): $\delta$ 111.4 (s, C-4), 118.4 (q, $J$=274.5 Hz, $CF_3$), 139.5 (s, C-5), 155.1 (q, $J$=39.5 Hz, C-3); $^{19}$F NMR ($CDCl_3$): $\delta$ −66.6.

## Results and discussion

Two encompassing reviews on the synthetic use of sulfur tetrafluoride have appeared in the literature [5, 6]. Despite all the work that has been done, there are only scattered reports describing the preparation of trifluoromethylated heterocycles from their precursor carboxylic acids using $SF_4$. To the best of our knowledge, there is only one report of the reaction of $SF_4$ with a thiazole-2-carboxylic acid [4] which does not cite a yield. Furthermore, examples of 5-trifluoromethyl thiazoles and any trifluoromethyl isothiazoles are scarce [7, 8] and their preparations do not lend themselves to synthetic programs where gram quantities of the compounds are needed. We felt that it would be of value to develop convenient routes to 2- and 5-trifluoromethylthiazoles, and 3- and 5-trifluoromethylisothiazoles, using this reaction. Since 4-trifluoromethylthiazoles are easy to prepare from ethyl trifluoroacetoacetate [9], we chose not to work with this system.

The parent carboxylic acids were easily prepared from readily available materials [2] or by literature methods [10–12]. Equation (1) shows the role metalation chemistry played in obtaining **2** and **3** in 55 and 74% yield respectively.




2; $R_4$=Br, $R_5$=H

3; $R_4$=$R_5$=Cl

(1)

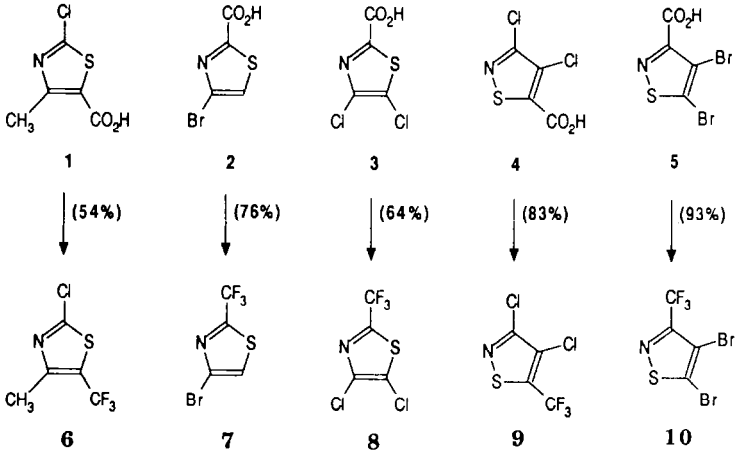



Fig. 1.

Based on the literature [4] we believed that these fluorinations should work. What was not certain was how well these substrates would survive the reaction conditions. In all five cases, fluorination went smoothly to give the desired trifluoromethyl derivatives **6–10** in modest to excellent yields overnight at 40 °C. Residual starting acid or acid fluoride products were never detected. Each product was a stable, distillable liquid that was fully characterized by $^{1}H$ and $^{19}F$ NMR spectroscopy and elemental analysis (see experimental) or mass spectrometry. In the case of **9**, as much as 40 g could be prepared in one reaction using our 300 ml reactor [1]. It is also interesting to observe that the literature which describes the formation of **8** [4] also reports the presence of an additional fluorinated product. After very careful examination of the crude product from our study, we saw no evidence for other characterizable materials. It may be that the appearance of this extra product was related to the initial synthesis of the starting carboxylic acid which was not well defined. It is now apparent that thiazole and isothiazole carboxylic acids undergo clean fluorinations with $SF_4$ under fairly mild conditions. Our results are summarized in Fig. 1.

In conclusion, fluorination of 2- and 5-thiazole carboxylic acids, and 3- and 5-isothiazole carboxylic acids, with $SF_4$ in anhydrous HF is an excellent method for obtaining their trifluoromethylated derivatives. Both heterocyclic systems are extremely tolerant toward the strongly acidic reaction conditions. Because of the evident synthetic utility of this method to obtain substantial quantities of novel intermediates, we have studied other heterocyclic systems which will be reported later [13].

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