Reactions of a 4-(Trifluoromethyl)thiazole Dianion

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Treatment of 2-trifluoroacetamido-4-(trifluoromethyl)thiazole with two equivalents of *n*-butyllithium at −78° produced the thiazole dianion **5** *in situ*, which reacted preferentially at the 5-position with a variety of electrophiles. These electrophiles include: an aldehyde, ketone, chloroformate, acid chloride, phosphorus oxychloride, silicon chloride, and disulfide. Dianion **5** also combined with dibromodifluoromethane at −98° to give the corresponding 5-(bromodifluoromethyl)thiazole **7**, which is an unusual reaction for an aromatic or heteroaromatic system. Compound **7** was converted to a 4,5-*bis*-(trifluoromethyl)thiazole **8** using tetrabutylammonium fluoride.

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Thiazole heterocycles have received much attention in the past due to their unique biological activity [1-4]. We have an interest in 4-trifluoromethyl substituted thiazoles since they serve as safeners (herbicide antidotes) for the acetanilide class of herbicides [2-4]. Previously we reported the preparation and reactions of a variety of 4-trifluoromethyl-5-nitrogen substituted thiazoles [5-6]. Our needs dictated that we explore not only the 5-nitrogen substitutions, but also as many other functionalities as possible at this position. Ester and ketone functionalities at the 5-position of a thiazole are common and are derived from the reaction of a 2-halo-1,3-dicarbonyl compound with a thiourea [7]. A few heteroatom functionalities were introduced into the 5-position of a thiazole *via* displacement of a fluorine with nucleophiles [8-11].

In most of the above reports each time a new functionality is desired at the 5-position of a thiazole a different linear synthesis is completed. In principle it woluld be more efficient to prepare these 5-position derivatives in a divergent fashion from a common thiazole intermediate. We also sought to retain an amino functionality at the 2-position of the thiazole. We proposed that treatment of the 2-trifluoroacetamidothiazoles **3** or **4** with a strong base such as *n*-butyllithium would lead to the dianion **5**, Scheme I. Studies of a dianion such as **5** have not appeared in the literature, but various metallation reactions have been performed in the thiazole area [1,12]. A dianion such as **5** should be protected from further reaction with a strong nucleophile at the 2-position of the thiazole or the acetamide carbonyl since the amide moiety exists as a salt. This situation allows for the 2-trifluoroacetamido moiety to function as a protecting group during the reaction while alkylation takes place at the more reactive 5-position of the thiazole. Combination of **5** with a number of different electrophiles would lead to the desired compounds and we have indeed found this to be the case.

A convenient source of 2-amino-4-(trifluoromethyl)thiazole **2** was found *via* the reaction of bromopropanone **1** with thiourea [13]. Treatment of **2** with trifluoroacetic anhydride led to the 2-trifluoroacetamide **3** in 94% yield. Compound **3** served as a precursor to **5** upon treatment with two equivalents of *n*-butyllithium at −78° in tetrahydrofuran. Reaction of **2** with *N*-bromosuccinimide followed by trifluoroacetic anhydride gave the 2-trifluoroacetamide **4** in 85% yield, which also served as a precursor to **5** upon treatment with two equivalents of *n*-butyllithium using the same conditions as above. Quenching solutions of **5** with deuterium oxide resulted in deuterium incorporation at the 5-position of the molecule to an extent of 98% as judged by nmr and mass spectral analysis. The next step was to explore the reaction of **5** with differnt types of electrophiles.

Treatment of **3** with two equivalents of *n*-butyllithium at −78° in tetrahydrofuran generated dianion **5** *in situ* which was reacted with a variety of electrophiles, Table 1. Dianion **5** combined with *N,N*-dimethylformamide to give the aldehyde (entry 1) and with benzophenone or benzaldehyde to produce the corresponding alcohols (entries 2 and 3). Dianion **5** also reacted with a chloroformate, acid chloride, phosphorous chloride, silicon chloride, and a disulfide to give the corresponding derivatives shown in entries 4-8. In general, yields were moderate to good.

We also sought to introduce fluorinated methyl groups into the 5-position of the thiazole *via* the above dianion chemistry, Scheme II. We were surprized to find that this ploy was successful when dichlorodifluoromethane or dibromodifluoromethane were utilized as the electrophiles for the alkylation of dianion **5**. When a solution of **5** was treated with dichlorodifluoromethane at −95° in tetrahydrofuran the 5-difluoromethyl substituted thiazole **6** was isolated after work up in 29% yield along with the starting material **3** in 18% yield. However, when solutions of **5** maintained at −98° in tetrahydrofuran were treated with dibromodifluoromethane the reaction took a different course and gave the bromodifluoromethyl substituted thiazole **7** in 80% yield along with **4** in 9% yield and the starting material **3** in 4% yield. When this reaction was

Scheme I

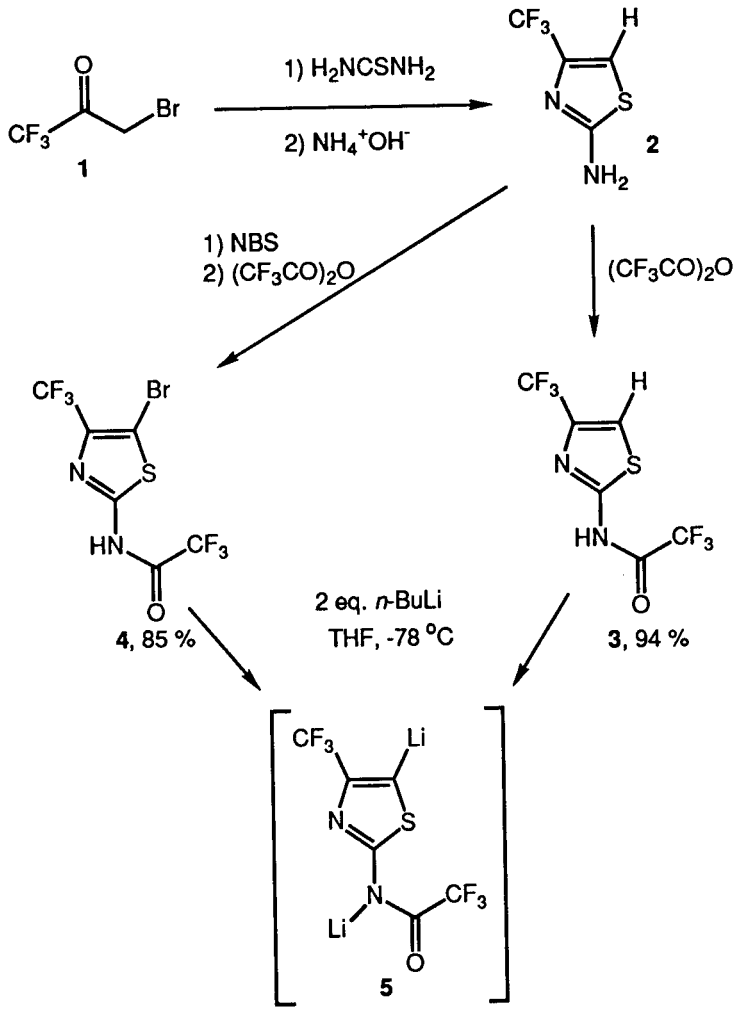
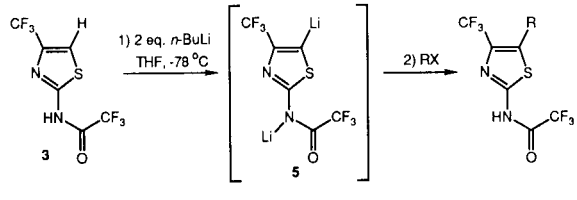


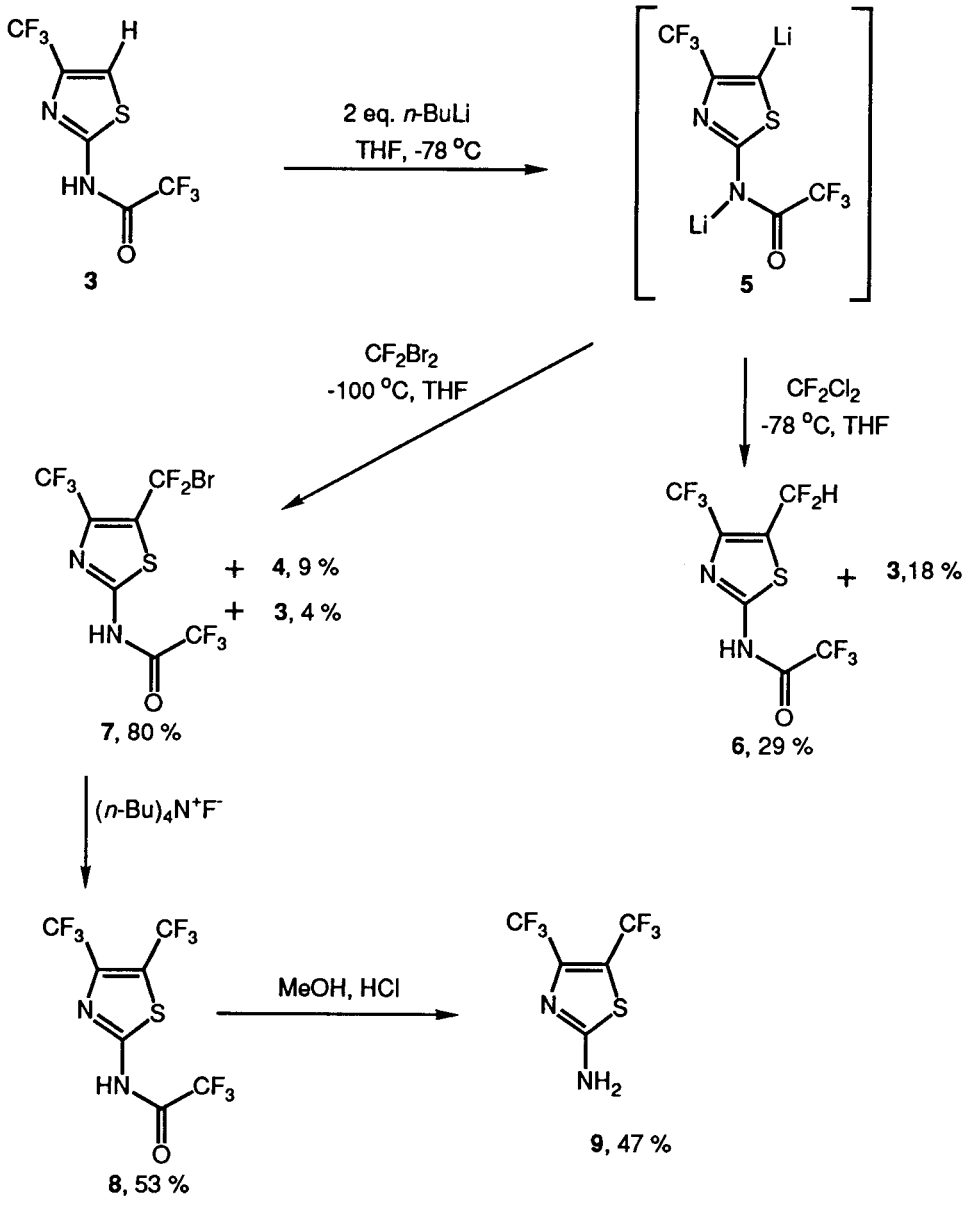
Table 1.



Entry	RX	R	% Yield	Formula	Analysis % Calcd./Found C	H	N
1	$HCON(CH_3)_2$	COH	37 [a, b]	$C_5H_3F_3N_2OS$	30.62 30.68	1.54 1.59	14.28 14.03
2	PhCOPh	$C(OH)(Ph)_2$	58	$C_{19}H_{12}F_6N_2O_2S$	51.12 51.01	2.71 2.28	6.28 6.02
3	HCOPH	CH(OH)Ph	71	$C_{13}H_8F_6N_2O_2S$	42.17 41.75	2.18 2.19	7.57 7.57
4	$ClCO_2CH_2CCl_3$	$CO_2CH_2CCl_3$	47	$C_9H_3Cl_3F_6N_2O_3S$	24.59 24.82	0.69 0.67	6.37 6.40
5	ClCOPh	COPh	40	$C_{13}H_6F_6N_2O_2S$	42.40 42.36	1.64 1.38	7.61 7.26
6	$ClPO(OEt)_2$	$PO(OEt)_2$	49	$C_{10}H_{11}F_6N_2O_4PS$	30.01 30.08	2.77 2.83	7.00 7.10
7	$ClSi(CH_3)_2$	$Si(CH_3)_2$	49	$C_9H_{10}F_6N_2OSSi$	32.14 31.97	3.00 3.07	8.33 7.84
8	CF_3SSCF_3	SCF_3	76 [b]	$C_5H_2F_6N_2S_2$	22.39 22.47	0.75 0.75	10.44 10.40

[a] Compound 4 was used for the starting material. [b] In this case the yield of the amine is given after hydrolysis of the amide.

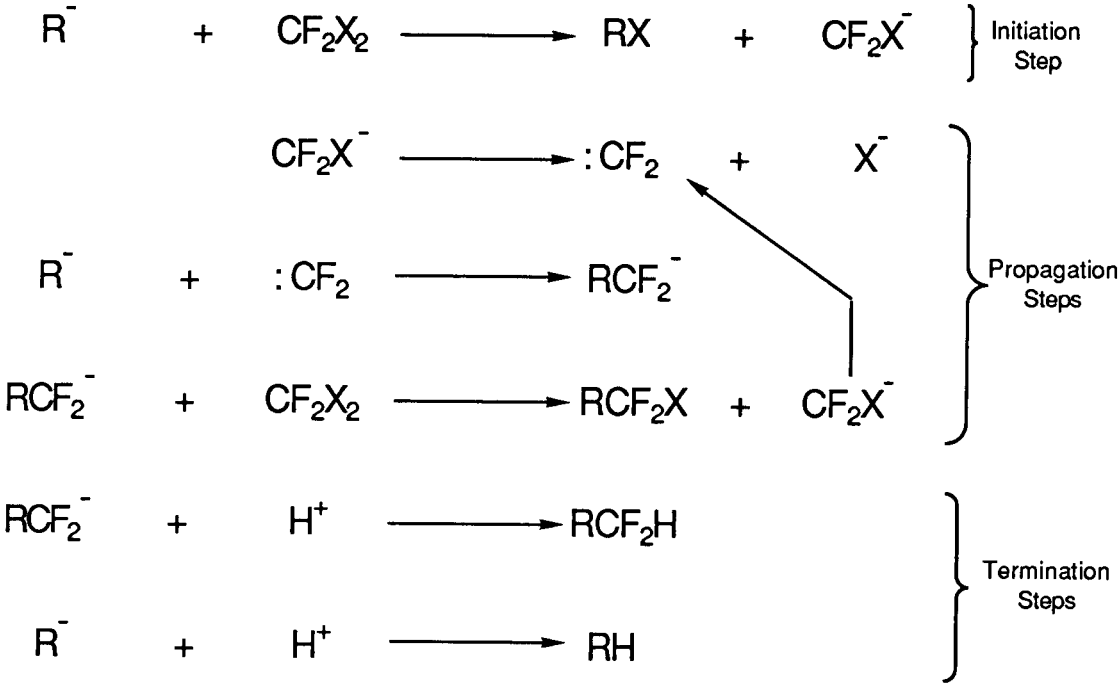
Scheme II



performed on a larger scale the temperature was more difficult to control and rose to −91° upon addition of the electrophile. After work up we found that the ratio of **3** (27% yield) and **4** (28% yield) to **7** (45% yield) had increased. This mixture could not be separated until after the bromodifluoromethyl group of **7** was converted to a trifluoromethyl group with tetrabutylammonium fluoride in 53% yield [14]. Compound **8** was then hydrolyzed and purified to give the amine **9** in 47% yield.

A mechanism that explains the difference in the products observed above in the alkylation of **5** with halogenated methanes is given in Scheme III. The reaction may proceed *via* a carbene chain mechanism [15-17] where the initiation step is attack of the anion on the dihalodifluoromethane generating a 5-halothiazole which corresponds to **4** above and a halodifluoromethyl anion. The first of the propagation steps involves fragmentation of the halodifluoromethyl anion to give difluorocarbene and halide. The difluorocarbene then combines with another molecule of the anion to give a thiazole difluoromethyl anion which in turn reacts with another molecule of dihalodifluoromethane. This generates the desired halodifluoromethyl substituted thiazole which corresponds to compound **7** and another halodifluoromethyl anion. Fragmentation of this second halodifluoromethyl anion to difluorocarbene continues to propagate the carbene chain. Termination of

Scheme III



the carbene chain occurs when the thiazole difluoromethyl anion or the starting anion comes in contact with a proton source. This gives the difluoromethyl thiazole or the starting material.

When dibromodifluoromethane was used as the electrophile all of the possible products involved in the carbene chain mechanism were observed except the 5-difluoromethyl substituted thiazole. The main product in the reaction was the desired 5-bromodifluoromethylthiazole **7** and the minor products were the 5-bromo compound **4** and the starting material **3**. These results would tend to indicate that the carbene chain was indeed propagated since the initiation and termination products were present in only small amounts. In the reaction involving dichlorodifluoromethane the only products that were isolated were the 5-difluoromethyl substituted thiazole **6** and the starting material **3**. Both of these compounds were obtained in poor yield and correspond to the products of the termination reactions which would indicate that a carbene chain reaction was not propagated to any extent in this case.

Carbene chain reactions with halogenated methanes have been reported mainly for non-aromatic systems such as 1,3-dicarbonyl compounds [15-16] and thiols [17]. In general, the reactions of aromatic lithium compounds with dihalodifluoromethane result only in metal-halogen exchange to give the corresponding arylhalide [18]. Our reactions with thiazole dianion **5** are somewhat unusual in that they parallel the reactivity pattern of the non-aromatic systems. It is not entirely clear why the thiazole dianion **5** gave the carbene chain products upon treatment with dibromodifluoromethane rather than metal-halogen exchange. Perhaps the electron dificient nature of the thiazole in combination with the low temperature (−98°) slows the rate of the metal-halogen exchange reaction [19]. This then allows the carbene chain reaction to take place. However, when this reaction was performed on a larger scale the temperature rose to −91° and more of the 5-bromothiazole **4** and the starting material **3** were noted relative to the desired 5-bromodifluoromethylthiazole **7**. It is possible that a portion of **4** that is formed at the higher temperature is the result of a metal-halogen exchange. This may also be true at the lower temperatures, but to a lesser extent. Regardless of the mechanism of this reaction it is clear that the electron deficient nature of the thiazole and the temperature play an important role.

In summary, the thiazole dianion **5** combined with a variety of electrophiles to give moderate to good yields of the corresponding 5-substituted thiazoles. Dianion **5** was also found to combine with dibromodifluoromethane or dichlorodifluoromethane to give the corresponding 5-bromodifluoromethylthiazole **7** or the 5-difluoromethylthiazole **6** respectively. Compound **7** was converted to the 4,5-*bis*-trifluoromethylthiazole **9** by treatment with tetrabutylammonium fluoride.

EXPERIMENTAL

General Methods.

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The 60 MHz ^{1}H nmr and ^{19}F nmr were obtained on a Varian EM-360 at 1.4 tesla. The 90 MHz ^{13}C nmr and 360 MHz ^{1}H nmr were obtained on a Bruker WM-360 at 8.4 tesla. The 100 MHz ^{13}C nmr and 400 MHz ^{1}H nmr were taken on a Varian XL-400. Absorptions are expressed in parts per million (δ) with tetramethylsilane, the deuterated solvent, or 1,1,1-benzotrifluoride as internal reference. Infrared spectra were recorded on a Perkin-Elmer 781 spectometer, and absorptions are reported in wavenumbers (cm^{-1}). Low-resolution electron impact mass spectra and chemical ionization mass spectra were obtained on a Finnegan MAT CH7A instrument by a direct probe insertion at 70 eV. All mass spectra are electron impact unless noted otherwise. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Preparative separations were effected using a Waters Prep-500 instrument (refractive index detection) or a Harrison Research Chromatotron (uv visualization). All solvents were reagent grade and were obtained from Fisher Scientific. The solvents were used without further drying or purification except for tetrahydrofuran which was purchased dry from Aldrich Chemical Co. All commercially available chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI or Fairfield Chemical Co., Blythwood, South Carolina.

2,2,2-Trifluoro-*N*-[4-(trifluoromethyl)-2-thiazolyl]acetamide (**3**).

To a stirred suspension of **2** (100 g, 595 mmoles) in 200 ml of methylene chloride was added trifluoroacetic anhydride (137.5 g, 654 mmoles). The mixture was stirred at room temperature and then a gentle reflux began. After 20 minutes all of the starting material had gone into solution. The mixture was stirred another 20 minutes and was then evaporated *in vacuo* to give a crude oil. This oil was distilled through a short path (65-70°, 0.1 torr) to give 147.7 g (94% yield) of **3** as a clear oil; ^{1}H nmr (400 MHz, deuteriochloroform): δ 11.20-10.80 (bs, 1-H), 7.54 (s, 1-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 159.68, 157.71 (q, J = 40.89 Hz), 142.29 (q, J = 38.62 Hz), 121.96 (q, J = 270.26 Hz), 119.35 (q, J = 3.45 Hz), 117.00 (q, J = 286.59); ^{19}F nmr (57 MHz, acetone-d_6): δ −65.0 (s, 3-F), −75.7 (s, 3-F); ms: m/z (relative intensity) 264 (M$^+$, 100), 245 (15.01), 216 (6.89), 195 (23.46), 175 (29.65), 167 (9.94), 126 (26.17), 69 (83.29).

Anal. Calcd. for $C_6H_2F_6N_2OS$: C, 27.28; H, 0.76; N, 10.61. Found: C, 27.34; H, 0.80; N, 10.69.

2,2,2-Trifluoro-*N*-[4-(trifluoromethyl)-5-bromo-2-thiazolyl]acetamide (**4**).

Compound **2** (100 g, 59.5 mmoles) and *N*-bromosuccinimide (127.1 g, 71.4 mmoles) were stirred in 1.5 liters of acetonitrile under nitrogen and heated gently to about 60°. At this point the mixture became exothermic and the temperature was controlled with an ice-bath. After the exotherm had subsided (15 minutes) the mixture was refluxed for 3 hours. The mixture was then cooled and the solvents were removed *in vacuo*. The mixture was dissolved in ethyl acetate and filtered through a pad of silica gel. The filtrate was evaporated to dryness and the residue was recrystallized from cyclohexane/ethyl acetate to give 125 g of 2-amino-4-(trifluoromethyl)-5-bromothiazole as a brown solid, 85% yield, mp = 125-126°; ^{13}C nmr (100 MHz, deuteriochloroform): δ 170.92, 139.36 (q, J = 35.76 Hz), 122.23 (q, J = 271.78 Hz), 98.18 (q, J = 2.94 Hz); ms: m/z (relative intensity) 248 (M$^+$ + 2, 67.90), 246 (M$^+$, 62.42), 167 (100), 147 (55.41), 125 (29.16), 106 (13.81), 69 (20.95).

Anal. Calcd. for $C_4H_2BrF_3N_2S$: C, 19.45; H, 0.82; N, 11.34. Found: C, 19.53; H, 0.85; N, 11.38.

To 2-amino-4-(trifluoromethyl)-5-bromothiazole (100 g, 405 mmoles) in 250 ml of methylene chloride at 0° was added with stirring trifluoroacetic anhydride (93.5 g, 445 mmoles) over 5 minutes. The mixture was allowed to warm to room temperature and the solvent was removed *in vacuo* to give 160 g of a brown oily residue. The crude oil was kuglerohr distilled (90-105°, 0.1 torr) to give 139 grams of **4** as a colorless oil, 100% yield; ^{19}F nmr (57 MHz, acetone-d_6): δ −62.6 (s, 3-F), −75.5 (s, 3-F); ^{13}C nmr (100 MHz, deuteriochloroform): δ 159.64, 158.03 (q, J = 41.65 Hz), 139.22 (q, J = 37.62 Hz), 121.81 (q, J = 272.36 Hz), 116.86 (q, J = 286.51 Hz), 109.34 (q, J = 2.52 Hz); ms: m/z (relative intensity) 344 (M$^+$ + 2, 77.31), 342 (M$^+$, 80.29), 263 (15.23), 215 (6.96), 166 (25.96), 125 (20.90), 106 (10.28), 69 (100).

Anal. Calcd. for $C_6HBrF_6N_2OS$: C, 21.01; H, 0.29; N, 8.17. Found: C, 20.83; H, 0.20; N, 8.24.

2,2,2-Trifluoro-*N*-[4-(trifluoromethyl)-5-deuterio-2-thiazolyl]acetamide.

To compound **3** (1.0 g, 3.7 mmoles) dissolved in 25 ml of dry tetrahydrofuran at −78° under nitrogen was added dropwise with stirring *n*-butyllithium (3.0 ml of a 2.6 *N* solution in hexane, 7.8 mmoles). The mixture was allowed to stir for 20 minutes at −78° and then 5 ml of deuterium oxide was added and the mixture was allowed to warm to room temperature. The mixture was then treated with 10 ml of 1.2 *N* hydrochloric acid and extracted several times with ether. The organic layer was washed with saturated sodium chloride and evaporated *in vacuo*. The residue was a colorless oil (1.0 grams, 100% yield) that was the desired 5-deuteriothiazole as evidenced by ^{19}F nmr. The ^{1}H nmr indicated that there were no signals in the 8.0-6.0 ppm region. Mass spectral analysis indicated that deuterium incorporation was 98%.

2-Amino-4-(trifluoromethyl)-5-thiazolecarboxaldehyde (Entry 1, Table 1).

Compound **3** (5.0 g, 14.6 mmoles) was stirred in 50 ml of tetrahydrofuran at −78° under nitrogen while *n*-butyllithium (12.0 ml, 31.2 mmoles, 2.6 *N* in hexane) was added dropwise over 15 minutes. During this time the temperature was maintained below −60°. The solution was stirred for 20 minutes at −78° and then dry *N,N*-dimethylformamide (1.1 g, 15.1 mmoles) was added and the mixture was allowed to warm to room temperature and was quenched with 50 ml of water. The mixture was acidified to *p*H 1 with concentrated hydrochloric acid and extracted with 150 ml of ether. The organic phase was dried with sodium sulfate, filtered through silica gel, and the filtrate was concentrated *in vacuo*. The solid residue was recrystallized from ethyl acetate/hexane to yield 0.9 g of a bright yellow crystalline solid, mp >240°. A second crop gave another 0.15 g for a total yield of 1.05 g, 37% yield; ir (nujol): cm^{-1} 3380, 3260, 3100, 1640, 1620, 1500, 1375, 1260, 1200, 1120; ^{19}F nmr (57 MHz, acetone-d_6): δ −61.7 (s, 3-F); ^{1}H nmr (360 MHz, acetone-d_6): δ 9.95 (s, 1-H), 7.80 (bs, 2-H); ^{13}C nmr (90 MHz, acetone-d_6): δ 180.6, 173.0, 146.0 (q, J = 34.0 Hz), 128.0, 120.0 (q, J = 271.7); ms: m/z (relative intensity) 196 (M$^+$, 63.31), 195 (29.23), 167 (11.25), 147 (16.86), 126 (6.88), 106 (5.61), 69 (4.66).

Anal. Calcd. for $C_5H_3F_3N_2OS$: C, 30.62; H, 1.54; N, 14.28. Found: C, 30.68; H, 1.59; N, 14.03.

General Procedure for the Preparation of 5-Substituted Thiazoles (Entries 2-7, Table 1).

2,2,2-Trifluoro-*N*-[5-(hydroxydiphenylmethyl)-4-(trifluoromethyl)-2-thiazolyl]acetamide (Entry 2, Table 1). Compound **3** (4.5 g, 17.0 mmoles) was stirred in 225 ml of dry tetrahydrofuran at −78° under nitrogen while *n*-butyllithium (15.0 ml, 36.0 mmoles, 2.4 *N* in hexane) was added dropwise over 15 minutes. The temperature was maintained below −60° during the addition. The mixture was stirred for 20 minutes at −78° and then added *via* cannula to a solution of benzophenone (3.4 g, 18.7 mmoles) in 40 ml of dry tetrahydrofuran. The mixture was stirred for 5 minutes at −78° and was allowed to warm to room temperature. The solution was quenched with 100 ml of 1.2 *N* hydrochloric acid and was extracted with 250 ml of ether. The ether layer was washed with 75 ml of brine, dried with sodium sulfate, and filtered through silica gel. The filtrate was evaporated *in vacuo* and the residue was chromatographed on a Prep-500 instrument to give a solid which was recrystallized from ethyl acetate/hexane to give 4.4 grams (58% yield) of white crystals, mp 114.5-115°; ir (chloroform): cm^{-1} 3590, 3360, 1730, 1550, 1445, 1350, 1270, 1170; ^{19}F nmr (57 MHz, acetone-d_6): δ −58.0 (s, 3-F), −74.5 (s, 3-F); ^1H nmr (60 MHz, acetone-d_6): δ 7.5-7.2 (m, 10-H), 6.0 (bs, 1-H). The amide proton was not observed; ms: m/z (relative intensity) 446 (M^+, 23.50), 369 (22.70), 349 (27.11), 341 (32.41), 183 (31.57), 155 (21.20), 105 (100), 77 (71.95), 69 (20.50), 43 (85.93).

Anal. Calcd. for $C_{19}H_{12}F_6N_2O_2S$: C, 51.12; H, 2.71; N, 6.28. Found: C, 51.01; H, 2.28; N, 6.02.

2,2,2-Trifluoro-*N*-[5-(hydroxyphenylmethyl)-4-trifluoromethyl)-2-thiazolyl]acetamide (Entry 3, Table 1).

Prepared from **3** and benzaldehyde as white crystals (71% yield) following separation on a Prep-500 and recrystallization from ethyl acetate/hexane, mp 148-148.5°; ir (chloroform): cm^{-1} 3580, 3360, 1725, 1550, 1360, 1265, 1160, 1135; ^{19}F nmr (57 MHz, acetone-d_6): δ −60.9 (s, 3-F), −75.6 (s, 3-F); ^1H nmr (360 MHz, acetone-d_6): δ 12.4 (bs, 1-H), 7.6-7.2 (m, 5-H), 6.45 (s, 1-H), 5.85 (bs, 1-H); ^{13}C nmr (90 MHz, acetone-d_6): δ 156.6, 156.0 (q, J = 34.0 Hz), 144.5, 143.7, 133.0 (q, J = 34.0 Hz), 129.4, 128.9, 127.1, 122.0 (q, J = 271.7), 116.0 (q, J = 288.7), 69.4; ms: m/z (relative intensity) 370 (M^+, 87.05), 353 (15.35), 273 (22.03), 265 (87.77), 195 (17.07), 105 (45.84), 79 (100), 69 (83.85).

Anal. Calcd. for $C_{13}H_8F_6N_2O_2S$: C, 42.17; H, 2.18; N, 7.57. Found: C, 41.75; H, 2.19; N, 7.57.

2,2,2-Trichloroethyl 2-[(Trifluoroacetyl)amino]-4-(trifluoromethyl)-5-thiazolecarboxylate (Entry 4, Table 1).

Prepared from **3** and trichloroethyl chloroformate; white crystals were obtained (47% yield) following separation on a Prep-500 and recrystallization from hexane, mp 121-121.5°; ir (chloroform): cm^{-1} 3360, 3200, 2960, 1740, 1540, 1445, 1370, 1275, 1175, 1050, 915; ^1H nmr (60 MHz, acetone-d_6): δ 12.0 (bs, 1-H), 5.1 (s, 2-H); ^{19}F nmr (57 MHz, acetone-d_6): δ −62.0 (s, 3-F), −75.6 (s, 3-F); ms: m/z (relative intensity) 442 (M^+ + 4, 7.18), 440 (M^+ + 2, 20.21), 438 (M^+, 19.85), 403 (4.87), 291 (100), 269 (4.74), 243 (9.30), 221 (11.43), 166 (12.40), 125 (12.81), 106 (6.56), 69 (26.44).

Anal. Calcd. for $C_9H_3Cl_3F_6N_2O_3S$: C, 24.59; H, 0.69; N, 6.37. Found: C, 24.82; H, 0.67; N, 6.40.

2,2,2-Trifluoro-*N*-[5-benzoyl-4-(trifluoromethyl)-2-thiazolyl]acetamide (Entry 5, Table 1).

Prepared from **3** and benzoyl chloride; white crystals were obtained (40% yield) following separation on a Prep-500 and recrystallization from ethyl acetate/hexane, mp 121-121.5°; ir (nujol): cm^{-1} 3210, 2900, 1720, 1630, 1565, 1355, 1270, 1175, 1145; ^1H nmr (60 MHz, acetone-d_6): δ 12.0 (bs, 1-H), 8.1-7.4 (m, 5-H); ^{19}F nmr (57 MHz, acetone-d_6): δ −62.9 (s, 3-F), −73.7 (s, 3-F); ms: m/z (relative intensity) 368 (M^+, 21.97), 349 (2.31), 291 (5.03), 105 (100), 77 (46.84), 69 (19.58).

Anal. Calcd. for $C_{13}H_6F_6N_2O_2S$: C, 42.40; H, 1.64; N, 7.61. Found: C, 42.36; H, 1.38; N, 7.26.

Diethyl [2-[(Trifluoroacetyl)amino]-4-(trifluoromethyl)-5-thiazolyl]-phosphonate (Entry 6, Table 1).

Prepared from **3** and diethyl chlorophosphate; white crystals were obtained (49% yield) following recrystallization from ethyl acetate/hexane, mp 189.5-190°; ir (nujol): cm^{-1} 2900, 1715, 1550, 1450, 1210, 1175, 1140, 1070, 1020; ^{19}F nmr (57 MHz, acetone-d_6): δ −63.0 (d, J = 2.0 Hz, 3-F), −66.4 (s, 3-F); ^1H nmr (360 MHz, acetone-d_6): δ 4.3-4.2 (m, 4-H); 1.35 (t, J = 7.2 Hz, 6-H); ms: m/z (relative intensity) 400 (M^+, 20.15), 372 (16.44), 344 (84.32), 327 (16.69), 291 (36.05), 264 (22.23), 243 (17.24), 125 (18.38), 105 (21.37), 81 (14.54), 69 (37.73), 40 (100).

Anal. Calcd. for $C_{10}H_{11}F_6N_2O_4PS$: C, 30.01; H, 2.77; N, 7.00. Found: C, 30.08; H, 2.83; N, 7.10.

2,2,2-Trifluoro-*N*-[5-(trimethylsilyl)-4-(trifluoromethyl)-2-thiazolyl]acetamide (Entry 7, Table 1).

Prepared from **3** and trimethylsilyl chloride as a colorless oil (49% yield) following purification on a Prep-500; ir (chloroform): cm^{-1} 3380, 3180, 2950, 1730, 1550, 1505, 1455, 1350, 1260, 1150, 1040, 920, 850: ^{19}F nmr (57 MHz, acetone-d_6): δ −60.8 (s, 3-F), −75.7 (s, 3-F); ^1H nmr (60 MHz, acetone-d_6): δ 0.40 (s, 9-H), the amide proton was not observed; ms: m/z (relative intensity) 336 (M^+, 18.79), 321 (100), 251 (10.80), 231 (20.27), 163 (8.90), 106 (20.06), 77 (87.04), 69 (46.11).

Anal. Calcd. for $H_9H_{10}F_6N_2OSSi$: C, 32.14; H, 3.00; N, 8.33. Found: C, 31.97; H, 3.07; N, 7.84.

4-(Trifluoromethyl)-5-[(trifluoromethyl)thio]-2-thiazoleamine (Entry 8, Table 1).

Compound **3** (10 g, 37.9 mmoles) was stirred in 115 ml of dry tetrahydrofuran at −78° under nitrogen while *n*-butyllithium (30.6 ml of 2.6 *N* in hexane, 79.6 mmoles) was added dropwise *via* syringe. After the addition the mixture was stirred at −78° for 15 minutes. *Bis*-(trifluoromethyl)disulfide (16.1 g, 79.6 mmoles) was then introduced into the mixture slowly by delivering the compound from an inverted lecture bottle through a long cannula. The cannula was removed after the correct amount of disulfide was delivered. The mixture was then allowed to warm to room temperature and quenched with dilute aqueous hydrochloric acid. The mixture was partitioned between ether and dilute aqueous hydrochloric acid and the organic layer was dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo* to give the trifluoroacetamide; ^{19}F nmr (57 MHz, deuteriochloroform): δ −47.0 (s, 3-F), −64.5 (s, 3-F), −78.5 (s, 3-F); ms: m/z (relative intensity) 364 (M^+, 20.82), 315 (44.91), 295 (36.17), 249 (18.54), 236 (20.41), 145 (38.55), 69 (72.22). The amide was cleaved to the amine by refluxing the crude mixture in 100 ml of 1:1 methanol/1.2 *N* hydrochloric acid for 30 minutes. The mixture was made basic with ammonium hydroxide and extracted three times with 100 ml of ether. After removal of volatiles 7.7 g of the amine were recovered as a brown solid, 76% yield. This amine could be recrystallized from cyclohexane, mp 109-111°; ir (chlo-

roform): cm^{-1} 3480, 3400, 3290, 3010, 1625, 1605, 1500, 1370, 1180, 1150, 1110; ms: m/z (relative intensity) 268 (M^+, 61.38), 249 (5.07), 199 (100), 157 (21.10), 140.07 (33.06), 113 (10.47), 69 (13.79).

Anal. Calcd. for $C_5H_2F_6N_2S_2$: C, 22.39; H, 0.75; N, 10.44. Found: C, 22.47; H, 0.75; N, 10.40.

2,2,2-Trifluoro-*N*-[5-(difluoromethyl)-4-(trifluoromethyl)-2-thiazolyl]acetamide (**6**).

To a solution of **3** (5.0 g, 18.9 mmoles) in 250 ml of tetrahydrofuran at −78° was added dropwise with stirring *n*-butyllithium (16.0 ml of a 2.5 *N* solution in hexane, 40 mmoles) over 10 minutes. The mixture was stirred an additional 20 minutes at −78° and then transferred *via* cannula to a solution of dichlorodifluoromethane (15.0 g, 124 mmoles) in 250 ml of tetrahydrofuran maintained at −95°. The addition took 10 minutes and the mixture was maintained at −90° during the transfer. The mixture turned dark brown over the course of the transfer. The mixture was stirred at −95° for another 10 minutes and was then allowed to warm to room temperature. The mixture was quenched with 100 ml of 1.2 *N* hydrochloric acid and then extracted with 300 ml of ether. The organic phase was washed with 100 ml of brine, dried over sodium sulfate and filtered through a pad of silica gel. The filtrate was evaporated *in vacuo* to give 5.5 grams of a dark brown oil. The oil was kugelrohr distilled (60-75°, 0.07 torr) to give 3.6 g of a colorless oil. This oil was then chromatographed on a Prep-500 to give 1.7 grams of **6** (29% yield) as a colorless oil and 0.9 grams of **3** (18% yield).

Data for **6**.

This compound had ^{19}F nmr (57 MHz, acetone-d_6): δ −62.8 (td, J = 3.8, 1.9 Hz, 3-F), −75.9 (s, 3-F), −104.6 (dq, J = 54.0, 3.8 Hz, 2-F); ms: m/z (relative intensity) 314 (M^+, 79.66), 295 (16.71), 266 (4.81), 245 (22.15), 225 (29.50), 176 (28.56), 69 (100).

Anal. Calcd. for $C_7H_2F_8N_2OS$: C, 26.76; H, 0.64; N, 8.92. Found: C, 26.37; H, 0.64; N, 8.65.

2,2,2-Trifluoro-*N*-[5-(bromodifluoromethyl)-4-(trifluoromethyl)-2-thiazolyl]acetamide (**7**).

To a solution of **3** (5.0 g, 18.9 mmoles) in 250 ml of dry tetrahydrofuran at −78° was added dropwise with stirring *n*-butyllithium (16.0 ml of a 2.5 *N* solution in hexane, 40 mmoles) over 10 minutes. The mixture was stirred another 20 minutes at −78° and was then cooled to −98°. To this solution was added *via* cannula a solution of dibromodifluoromethane (11.9 g, 56.7 mmoles) in 250 ml of dry tetrahydrofuran maintained at −78°. The addition took 25 minutes and a dark brown color was evident during this time along with an exotherm to −94°. The mixture was stirred at −98° for another 10 minutes and was then allowed to warm to 0° and was quenched with 100 ml of 1.2 *N* hydrochloric acid. The mixture was extracted with 300 ml of ether and the organic layer washed with 100 ml of brine. The organic layer was dried over magnesium sulfate, filtered, and the filtrate was evaporated *in vacuo* to give 6.7 g of an orange-brown oil. This oil was an inseparable mixture of **7** (80% yield), **4** (9% yield), and **3** (4% yield) in a ratio of 88:9:3 as judged by ^{19}F nmr.

Data for **7**.

This compound had ^{19}F nmr (57 MHz, acetone-d_6): δ −34.6 (q, J = 10.5 Hz, 2-F), −61.5 (t, J = 10.5 Hz, 3-F), −76.6 (s, 3-F); ^{13}C nmr (90 MHz, acetone-d_6): δ 157.5, 156.0 (q, J = 34.0 Hz), 137.0 (q, J = 34 Hz), 131.0 (t, J = 34 Hz), 120.0 (q, J = 272.0 Hz), 115.0 (q, J = 272.0 Hz), 11.0 (t, J = 306 Hz); gcms: m/z (relative intensity) M^+ was not observed, 375 [(M^+ + 2) − 19, 1.35], 373 (M^+ − 19, 1.32), 313 (M^+ − 79, 50.38), 265 (11.26), 243 (17.89), 190 (8.69), 166 (8.80), 147 (11.11), 106 (9.77), 69 (100).

2,2,2-Trifluoro-*N*-[4,5-*bis*-(trifluoromethyl)-2-thiazolyl]acetamide (**8**).

To **7**, which was a mixture with **3** and **4** from above (1.3 g, 4.9 mmoles) dissolved in 30 ml of methylene chloride was added tetrabutyl ammonium fluoride (1.4 g, 5.36 mmoles, this material was dried at 90°, 0.1 torr for 24 hours prior to use). The mixture was stirred at room temperature for 10 minutes and an aliquot was removed for ^{19}F nmr, which indicated that the conversion was complete. The mixture was partitioned between ether and 1.2 *N* hydrochloric acid followed by brine. The organic layer was dried over sodium sulfate, filtered through silica gel, and the filtrate was evaporated *in vacuo* to give 1.5 g of a yellow-brown oil. The oil was chromatographed on a chromatotron and then kuglerohr distilled (35-45°, 0.03 torr) to give 0.6 g of **8**, 53% yield.

Data of **8**.

This compound had ^{19}F nmr (57 MHz, acetone-d_6): δ −53.1 (q, J = 8.6 Hz, 3−F), −62.8 (q, J = 8.6 Hz, 3-F); −75.7 (s, 3-F); ms: m/z (relative intensity) 332 (M^+, 27.88), 313 (7.64), 263 (8.99), 236 (7.50), 194 (23.84), 166 (14.20), 125 (14.34), 69 (100).

Anal. Calcd. for $C_7HF_9N_2OS$: C, 25.31; H, 0.30; N, 8.43. Found: C, 24.95; H, 0.32; N, 8.31.

4,5-*Bis*-(trifluoromethyl)-2-thiazoleamine (**9**).

To a solution of **8** (0.6 g, 2.6 mmoles) in 25 ml of methanol was added acetyl chloride (1 ml). The mixture was then refluxed under nitrogen for 2 hours and the solvent was removed *in vacuo*. The residue was partitioned between ether and aqueous *p*H 9.0 buffer. The organic layer was washed with additional *p*H 9.0 buffer followed by brine. The ether layer was dried over sodium sulfate, filtered through a pad of silica gel, and the filtrate was evaporated *in vacuo*. The residue was recrystallized from hexane to give 0.2 g of **9** (47% yield) as white crystals, mp 79-79.5°; ir (nujol): cm^{-1} 3500, 3280, 3150, 1630, 1525, 1455, 1370, 1300, 979, 910; ^{19}F nmr (57 MHz, acetone-d_6): δ −52.3 (q, 8.6 Hz, 3-F), −63.3 (q, 8.6 Hz, 3-F); ^{13}C nmr (90 MHz, acetone-d_6): δ 170.64, 140.00 (q, J = 33.3 Hz), 122.05 (q, J = 268.5), 120.50 (q, J = 271.34), 133.10 (q, J = 33.3 Hz); ms: m/z (relative intensity) 236 (M^+, 100), 217 (35.70), 194 (60.49), 167 (10.11), 147 (18.18), 125 (41.04), 106 (15.11), 69 (38.70).

Anal. Calcd. for $C_5H_2F_6N_2S$: C, 25.43; H, 0.85; N, 11.86. Found: C, 25.33; H, 0.87; N, 11.84.

Large Scale Preparation of 2,2,2-Trifluoro-*N*-[5-(bromodifluoromethyl)-4-(trifluoromethyl)-2-thiazolyl]acetamide (**7**), 2,2,2-Trifluoro-*N*-[4,5-*bis*-(trifluoromethyl)-2-thiazolyl]acetamide (**8**), and 4,5-*Bis*-(trifluoromethyl)-2-thiazoleamine (**9**).

To a solution of **3** (20.0 g, 75.76 mmoles) in 500 ml of dry tetrahydrofuran at −78° under nitrogen was added dropwise with stirring *n*-butyllithium (63.6 ml of a 2.5 *N* solution in hexane, 159 mmoles). The addition took 25 minutes and the mixture was stirred for another 20 minutes at −78°. The resulting suspension was cooled to −100° and to the mixture was added *via* cannula a solution of dibromodifluoromethane (47.7 g, 227 mmoles) in 250 ml of tetrahydrofuran maintained at −78°. The transfer took 30 minutes and the mixture was allowed to stir at −100° for 10

minutes before allowing to warm to 0°. During the transfer the mixture turned dark brown and an exotherm was observed to −91°. After warming to 0° the mixture was quenched with 200 ml of 1.2 *N* hydrochloric acid. The resulting mixture was washed with 200 ml of brine. The ether layer was dried over magnesium sulfate, filtered, and the filtrate was evaporated *in vacuo* to give 30.8 g of an orange-yellow oil. The ^{19}F nmr indicated that **7** (45% yield), **4** (28% yield), and **3** (27% yield) were present in this mixture (see above for the spectral data for each of these compounds). The mixture was used in the next step below.

To a solution of tetrabutylammonium fluoride (33.0 g, 126 mmoles, dried at 90°, 0.1 torr for 24 hours) in 200 ml of methylene chloride was added **7** (30 g of the mixture from above) in 100 ml of methylene chloride. The mixture was stirred at room temperature for 20 minutes. The solution was diluted with 300 ml of ether and washed with 4 x 125 ml of 1.2 *N* hydrochloric acid followed by brine. The organic phase was dried over magnesium sulfate, filtered through silica gel, and the filtrate was evaporated *in vacuo* to give 25.1 g of an orange-brown oil which contained **8** as evidenced by ^{19}F nmr. This oil was dissolved in 100 ml of methanol and the resulting solution was added to a solution made by adding 10 ml of acetyl chloride to 200 ml of methanol. The mixture was stirred and heated to reflux for 15 hours. The solvent was removed *in vacuo* to give a yellow solid which was partitioned between ether and *p*H 9.0 buffer three times. The organic phase was dried over sodium sulfate, filtered through silica gel, and the filtrate was evaporated *in vacuo*. The residue was purified on the Prep-500 to give 3.0 g of **9** (17% overall yield from **3**) as a white solid, mp 79.5-80°. See above for spectral data.

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