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A synthesis of 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole and 2,5-dichloro-5-isocyanatothiazole is described *via* the "Curtius Rearrangement" performed under anhydrous conditions. The synthetic procedure described allows for the isolation, storage, and manipulation of these highly reactive isocyanates. A number of derivatives of the above isocyanates were prepared. These include: carbamates, thiocarbamates, ureas, amines, amidines, and amides.

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In the past, compounds within the area of thiazole chemistry have been shown to exhibit a wide variety of biological activity [1-4]. Much effort has been devoted to the synthesis of thiazoles with nitrogen substitution at the 2-position, but comparatively few examples with nitrogen substitution at the 4- and 5-positions have appeared [3-9]. A number of these compounds have traditionally been prepared *via* the reduction of a nitro group [10-11], the "Beckman Rearrangement" [12], the "Curtius Rearrangement" [12-17], the reaction of a 2-haloacetonitrile with thiourea [18-19], the reduction of an azide [6-9], or the displacement of a fluoro group with a nitrogen nucleophile [6-9]. Many of these methods suffer from low yields or inconvenient starting materials and in some cases the intermediates could not be isolated or manipulated for the study of a variety of reactions. Our interests centered around 4- and 5-nitrogen substituted thiazoles that were highly halogenated, since these compounds may serve as intermediates to new agricultural herbicides and/or herbicide safeners (herbicide antidotes) [2-4]. We wish to report the synthesis (*via* the "Curtius Rearrangement" performed under anhydrous conditions) and reactions of 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole and 2,5-dichloro-4-isocyanatothiazole that allows for the isolation, storage, and manipulation of these highly reactive isocyanates.

The synthesis of 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole was completed as outlined in Scheme I. The preparation of acid chloride **3** was accomplished from ethyl 2-chloro-4,4,4-trifluoroacetoacetate and thiourea [2] (70% yield from ethyl 4,4,4-trifluoroacetoacetate). The acid chloride **3** was then converted to the acyl azide **4** by slowly adding **3** to a solution of sodium azide in water/acetone maintained at 0°. The "Curtius Rearrangement" was performed in dry, refluxing carbon tetrachloride and the resulting isocyanate **5** was purified by distillation (87% yield from **3**). The isocyanate decomposed readily in the presence of moist air, but was stable when stored at 0° under a nitrogen atmosphere.

A small amount of a second product was isolated from the distillation residue of **5** (1% yield) and was identified

as the *bis*-thiazolylurea **6**. This compound was probably formed from traces of water in the system. The water probably reacted with **5** to form an unstable carbamic acid which readily lost carbon dioxide to give a thiazole amine. This amine could then yield **6** upon intermolecular attack of a molecule of isocyanate **5** (*vide infra*).

The 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole was found to be a versatile and highly reactive intermediate. Compound **5** combined with alcohols, thiols, and amines to give the corresponding carbamates, thiocarbamates, and ureas, Table 1. The reaction was usually carried out at 0° in methylene chloride, although diethylamine would react with **5** even at -30°. The transformations were usually complete in a few minutes.

The unusual reactivity of isocyanate **5** was further demonstrated when **5** was treated with *N,N*-dimethylformamide, Scheme II. The mixture became exothermic and gas evolution occurred immediately. After workup, the product was identified as the thiazole amidine **7**. This reaction has been described for highly activated isocyanates such as chlorosulphonylisocyanate [20] and was proposed to proceed through a 4-membered ring intermediate. The unusual reactivity of **5** is probably due to the electron deficient nature of the thiazole ring. This effect undoubtedly is enhanced by the presence of the strongly electron withdrawing trifluoromethyl group.

The isocyanate **5** was hydrolyzed to the amine **8** (Scheme II) in a water/ether mixture utilizing high dilution techniques (the concentration of the isocyanate with respect to the ether was maintained at 0.1 molar, 71% yield). Attempts to hydrolyze **5** in more concentrated systems yielded a significant amount of the urea dimer **6**. The amine **8** was stable at room temperature and could be converted to the acetamide **9** by heating the amine with acetic anhydride in toluene (54% yield).

The synthesis of 2,5-dichloro-4-isocyanatothiazole was accomplished by a sequence of reactions similar to that used for 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole, Scheme III. Ethyl 2-amino-4-thiazolecarboxylate **11** was prepared according to the procedure of Dickey, Towne,

## Scheme I

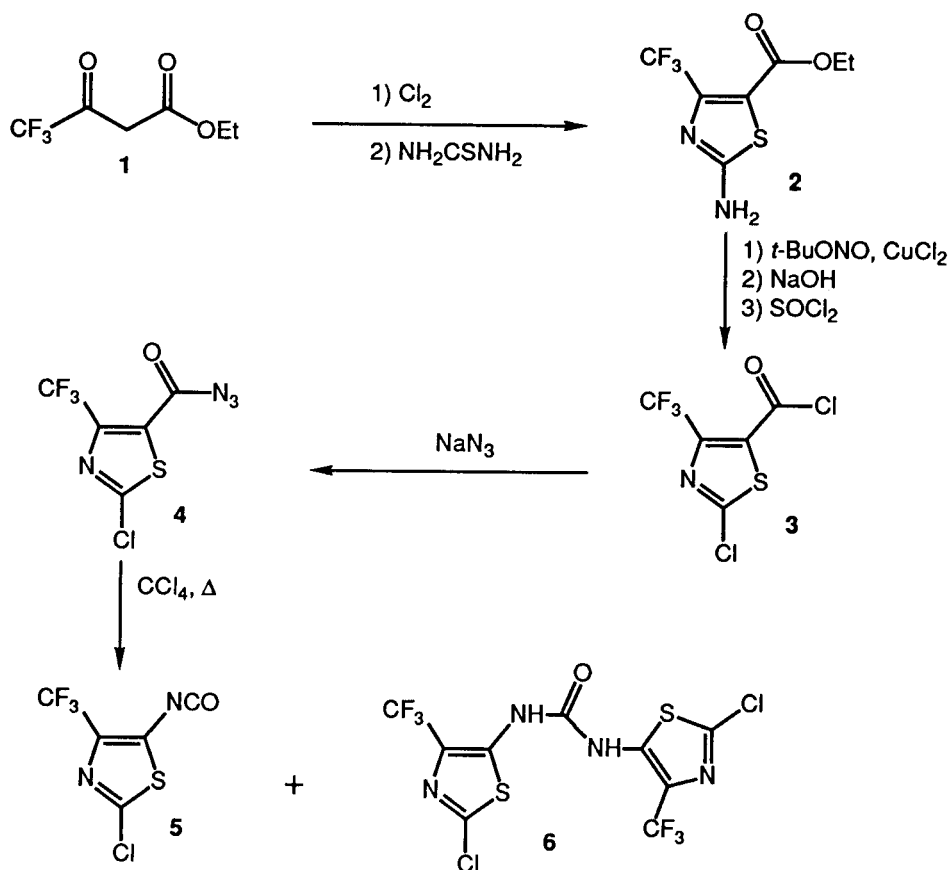
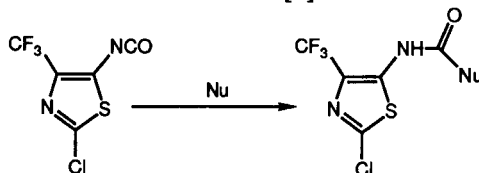


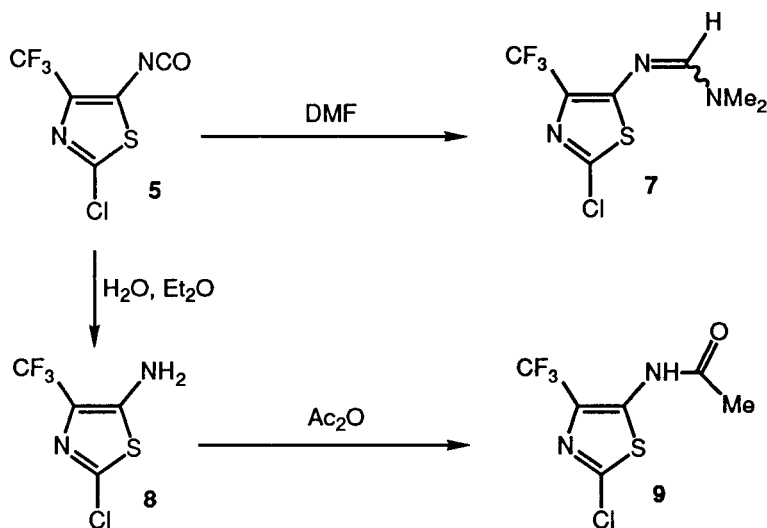
Table 1. [a]



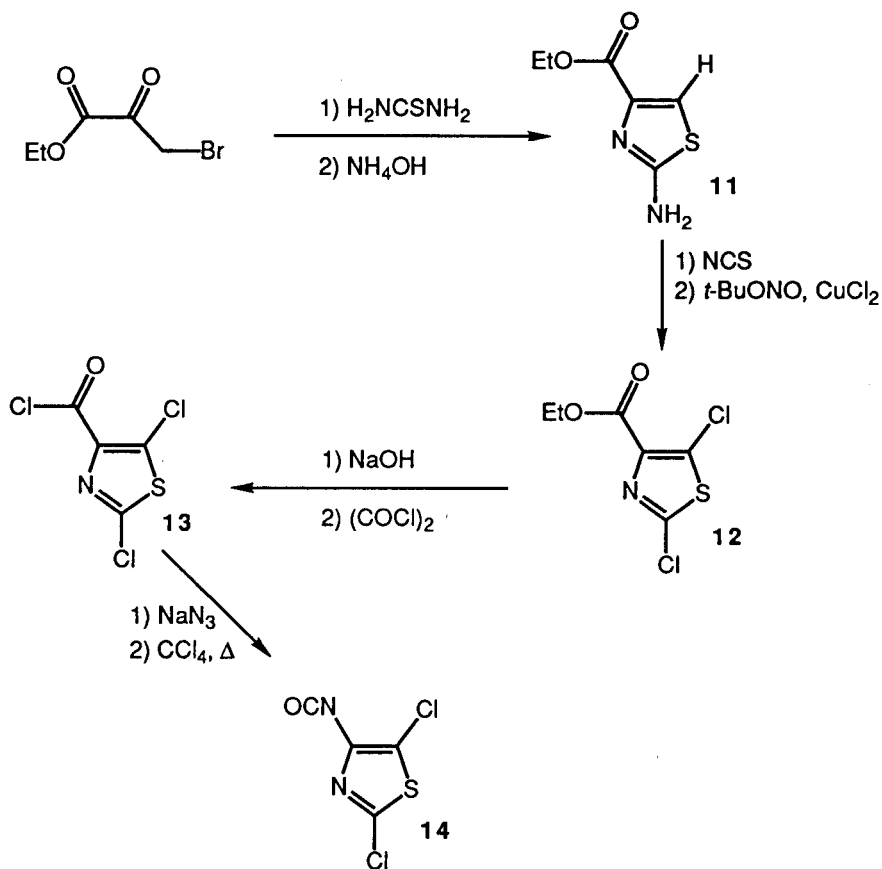
Entry	Nu	% Yield	Formula	Analysis %		
				Calcd./	Found	N
1	(Et) <sub>2</sub> NH	76 [d]	C <sub>9</sub> H <sub>11</sub> ClF <sub>3</sub> N <sub>3</sub> OS	35.83	3.67	13.93
				35.82	3.68	13.98
2	2-NH <sub>2</sub> -4,6-di-CH <sub>3</sub> -Pyrimidine	50	C <sub>11</sub> H <sub>9</sub> ClF <sub>3</sub> N <sub>5</sub> OS	37.56	2.58	19.91
				37.55	2.61	19.87
3	<i>t</i> -BuOH	46	C <sub>9</sub> H <sub>10</sub> ClF <sub>3</sub> N <sub>2</sub> O <sub>2</sub> S	35.71	3.33	9.25
				35.67	3.36	9.26
4	<i>o</i> -CF <sub>3</sub> -Phenol	84 [b]	C <sub>12</sub> H <sub>5</sub> ClF <sub>6</sub> N <sub>2</sub> O <sub>2</sub> S	36.89	1.29	7.17
				36.92	1.32	7.14
5	(CF <sub>3</sub> ) <sub>2</sub> CHOH	94 [b]	C <sub>8</sub> H <sub>2</sub> ClF <sub>9</sub> N <sub>2</sub> O <sub>2</sub> S	24.23	0.51	7.06
				24.38	0.56	7.03
6	CH <sub>3</sub> SH	87 [b, c]	C <sub>6</sub> H <sub>4</sub> ClF <sub>3</sub> N <sub>2</sub> OS <sub>2</sub>	26.04	1.46	10.12
				26.12	1.50	10.12
7	PhSH	61	C <sub>11</sub> H <sub>6</sub> ClF <sub>3</sub> N <sub>2</sub> OS <sub>2</sub>	39.00	1.79	8.27
				39.13	1.80	8.23

[a] Reactions were performed at 0° in methylene chloride with one equivalent of the nucleophile. [b] Catalytic triethylamine was added. [c] Excess methanethiol was utilized. [d] The reaction was cooled to -30°.

Scheme II



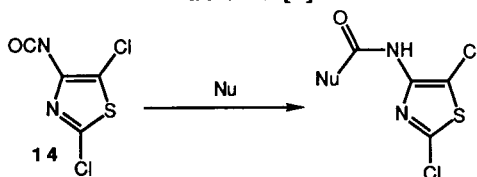
Scheme III



and Wright [21] from ethyl bromopyruvate and thiourea (87% yield). Chlorination at the 5-position with *N*-chlorosuccinimide (98% yield) followed by diazotization and chlorination at the 2-position gave the thiazole ester **12** (65% yield). Ester hydrolysis with sodium hydroxide (94% yield) and acid chloride formation with oxalyl

chloride gave **13** (94% yield). The "Curtius Rearrangement" was performed as before by converting the acid chloride to the azide followed by heating the azide in carbon tetrachloride. The resulting isocyanate **14** was purified by distillation (73% yield).

Table 2. [a]



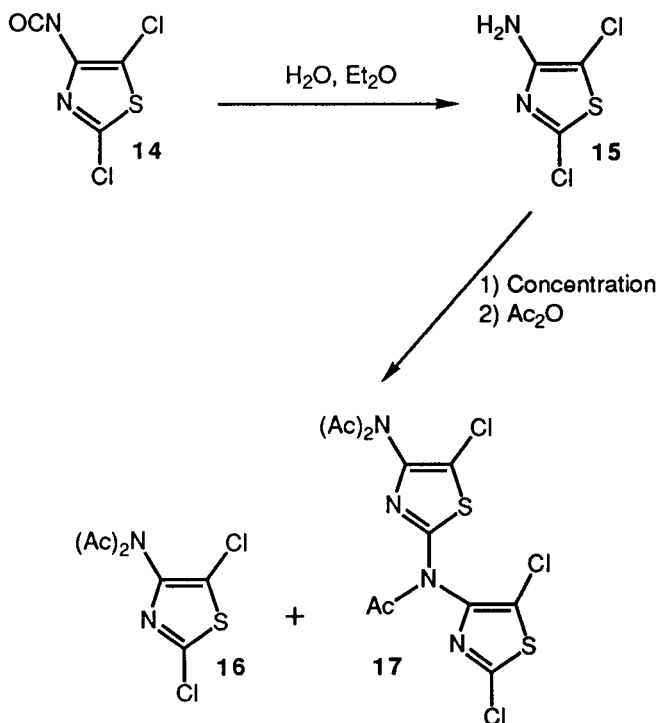
Entry	Nu	% Yield	Formula	Analysis %		
				Calcd./	Found	
			C	H	N	
1	(CH <sub>3</sub> ) <sub>2</sub> CHNH <sub>2</sub>	65 [c]	C <sub>7</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> OS	33.08 33.02	3.57 3.61	16.53 16.54
2	<i>m</i> -CF <sub>3</sub> -Aniline	90	C <sub>11</sub> H <sub>6</sub> Cl <sub>2</sub> F <sub>3</sub> N <sub>3</sub> OS	37.00 37.00	1.70 1.73	11.80 11.76
3	CH <sub>3</sub> OH	98 [c]	C <sub>5</sub> H <sub>4</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S	26.45 26.39	1.78 1.81	12.34 12.32
4	<i>m</i> -CF <sub>3</sub> -Phenol	41 [b]	C <sub>11</sub> H <sub>5</sub> Cl <sub>2</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub> S	36.99 37.07	1.41 1.43	7.84 7.84
5	(CF <sub>3</sub> ) <sub>2</sub> CHOH	85 [b]	C <sub>7</sub> H <sub>2</sub> Cl <sub>2</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub> S	23.16 23.29	0.56 0.60	7.72 7.71
6	CH <sub>3</sub> SH	92 [b, c]	C <sub>5</sub> H <sub>4</sub> Cl <sub>2</sub> N <sub>2</sub> OS <sub>2</sub>	24.70 24.82	1.66 1.69	11.52 11.47
7	<i>p</i> -Cl-Thiophenol	74 [b]	C <sub>10</sub> H <sub>5</sub> Cl <sub>3</sub> N <sub>2</sub> OS <sub>2</sub>	35.36 35.25	1.48 1.50	8.25 8.17

[a] Reactions were performed at room temperature in methylene chloride with one equivalent of the nucleophile. [b] Catalytic triethylamine was added.  
[c] Excess nucleophile was used.

The 2,5-dichloro-4-isocyanatothiazole also decomposed upon exposure to moist air, but was stable in a tightly capped bottle. Treatment of **14** with alcohols, thiols and amines gave good yields of the corresponding carbamates, thiocarbamates, and ureas shown in Table 2. The reac-

tions of isocyanate **14** were usually less vigorous than with isocyanate **5** and required several hours of reaction time at room temperature. Isocyanate **14** did not yield an amidine when treated with *N,N*-dimethylformamide. No isolable products were present upon workup after 24 hours.

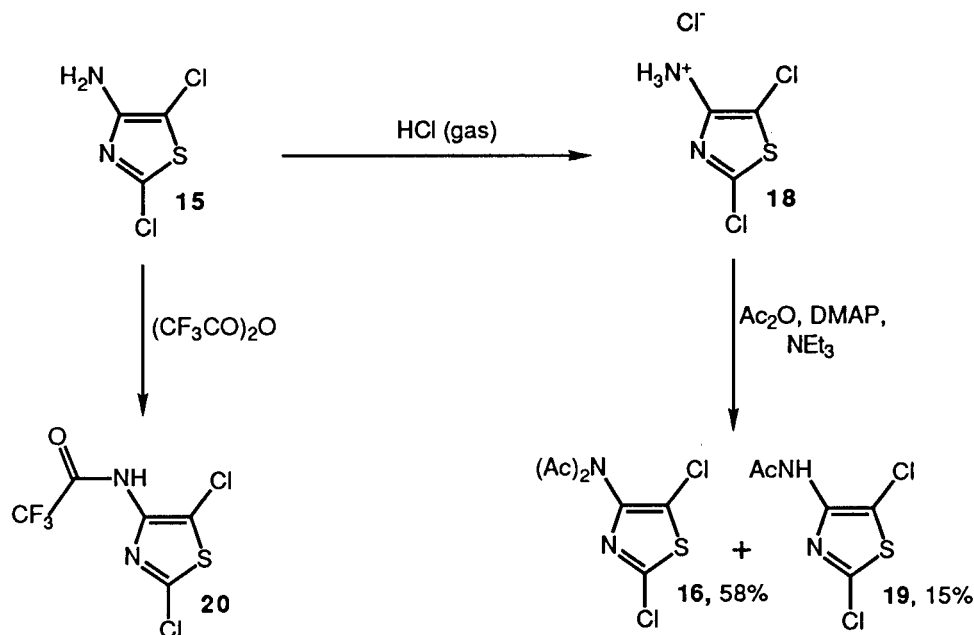
Scheme IV



An unusual transformation was encountered when an attempt to hydrolyze **14** was made, Scheme IV. Treatment of **14** with water and ether (0.1*M* with respect to the ether) appeared to produce the amine **15**. Upon concentration of solutions of **15**, a mixture of products was present which gradually decomposed to a black tar. In order to understand what was taking place the above mixture was treated with acetic anhydride immediately after the solution was concentrated to dryness. Two products were isolated after chromatography: a diacetylthiazole **16** (4% yield) and a triacetyl thiazole dimer **17** (45% yield). Apparently the amine **15** was formed, but on concentration intermolecular attack at the 2-position of another thiazole molecule occurred to give a dimer [22]. This dimer was probably also susceptible to further attack by other thiazole amines which resulted in polymerization. This reaction was stopped by trapping with acetic anhydride.

The above isolation problem was solved by treating dilute ether solutions of **15** with gaseous hydrochloric acid, Scheme V. The amine hydrochloride salt **18** precipitated from the solution (92% yield) and was stored without decomposition. The amine hydrochloride was liberated and acylated with triethylamine, catalytic 4-(dimethylamino)pyridine, and acetic anhydride at room

Scheme V



temperature to give a mixture of the imide **16** (58% yield) and the amide **19** (15% yield). Alternatively, dilute solutions of **15** were treated with reactive acylating agents such as trifluoroacetic anhydride. This ploy gave the trifluoroacetamide **20** in 85% yield.

In summary the 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole was more reactive toward nucleophiles than the 2,5-dichloro-4-isocyanatothiazole. This difference was reflected in the formation of amidine **7** from isocyanate **5**. The amine **15** was more nucleophilic than amine **8** as evidenced by the formation of dimer **17**. In both cases these differences were probably due to the presence or absence of the electron withdrawing trifluoromethyl group. Work is continuing in this area and other interesting reactions have been discovered which will be reported at a future date; see also the following papers in this journal [23-24].

## EXPERIMENTAL

### General Methods.

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. 60 MHz  $^1H$  nmr were obtained on a Varian EM-360 at 1.4 tesla. The  $^{13}C$  nmr and 360 MHz  $^1H$  nmr were obtained on a Bruker WM-360 at 8.4 tesla. Absorptions are expressed in parts per million ( $\delta$ ) with tetramethylsilane or the deuterated solvent as internal reference. Infrared spectra were recorded on a Perkin-Elmer 781 spectrometer, 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. Mass spectra are electron impact unless

specified 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. All commercially available chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI. Ethyl-4,4,4-trifluoroacetate was obtained from Fairfield Chemical Co.

### 2-Chloro-4-(trifluoromethyl)-5-isocyanatothiazole **5**.

Sodium azide (27.4 g, 42.2 mmoles), water (200 ml), and acetone (200 ml) were added to a 1 liter round-bottomed flask. This mixture was cooled to  $0^\circ$  while 2-chloro-4-(trifluoromethyl)-5-chlorocarbonylthiazole (100 g, 40.2 mmoles) was added dropwise to the vigorously stirred solution over 1 hour. After the addition was complete the mixture was allowed to warm to room temperature and stirring was continued for an additional 1 hour. Water was then added and the mixture was extracted 3 x 200 ml with carbon tetrachloride. The combined organic layers were dried (magnesium sulfate), filtered, and the total volume was adjusted to 1.5 liters with additional dry carbon tetrachloride. The carbon tetrachloride solution was then brought slowly to reflux under nitrogen and the mixture was kept there for 5 hours. The solvent was removed *in vacuo* and the residue was distilled through a 6 inch vigreux column collecting between  $35-40^\circ$  @ 0.1 mm of Hg. The isocyanate was obtained as a clear oil (80 g, 87% yield). The isocyanate decomposed in the presence of moist air and was best stored under nitrogen in a tightly capped bottle at  $0^\circ$ ; ir (neat):  $cm^{-1}$  2280, 1605, 1460, 1375, 1150;  $^{13}C$  nmr (deuteriochloroform):  $\delta$  145.8 (s), 133.3 (q,  $J = 37.4$  Hz), 133.0 (s), 125.6 (s), 119.5 (q,  $J = 271.9$  Hz); ms:  $m/z$  (relative intensity), 230 ( $M^+ + 2$ , 12), 228 ( $M^+$ , 29), 202 (100), 182 (53), 147 (71). The bis-thiazolyl urea **6** was isolated from the distillation residue of **5** by chromatography on a Prep-500 instrument (20% ethyl acetate,

80% cyclohexane) to give 0.17 g of **6** (1% yield) as a white solid, mp 228-230° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3275 (br), 1695, 1565, 1405, 1220;  $^1\text{H}$  nmr (60 MHz, dimethyl sulfoxide- $d_6$ ):  $\delta$  10.0 (bs); ms:  $m/z$  (relative intensity), 432 ( $M^+ + 2$ , 8), 430 ( $M^+$ , 11), 228 (16), 202 (100), 182 (32), 147 (28).

*Anal.* Calcd. for  $\text{C}_9\text{H}_2\text{Cl}_2\text{F}_6\text{N}_4\text{O}_2\cdot 0.75\text{H}_2\text{O}$ : C, 24.31; H, 0.79; N, 12.60. Found: C, 24.30; H, 0.82; N, 12.60.

General Procedure for the Synthesis of 5-Substituted Thiazolyl Ureas, Carbamates, and Thiocarbamates (Table 1).

Methylene chloride (50 ml), **5** (3.0 g, 13.1 mmoles), the appropriate amine, alcohol, or thiol (14.4 mmoles), and 4 drops of triethylamine (entries 4, 5, and 6 only; Table 1) were added to a 100 ml round bottomed flask maintained at 0°. An initial exotherm was usually noted. The mixture was stirred under nitrogen for 2 hours. The solvent was removed *in vacuo* and the crude product was recrystallized, chromatographed, or kuglerohr distilled where appropriate. Pertinent analytical data is given below.

*N*-2-Chloro-4-(trifluoromethyl)-5-thiazolyl-*N',N'*-diethylurea (Entry 1, Table 1).

This compound was obtained as a clear oil; ir (neat):  $\text{cm}^{-1}$  3460, 3325 (br) 1680, 1570, 1510, 1410, 1200;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.5 (bs, 1-H), 3.35 (q,  $J = 8$  Hz, 4-H), 1.22 (t,  $J = 8$  Hz, 6-H); ms:  $m/z$  (relative intensity), 303 ( $M^+ + 2$ , 13), 301 ( $M^+$ , 36), 100 (100), 72 (75).

*Anal.* Calcd. for  $\text{C}_9\text{H}_{11}\text{ClF}_3\text{N}_3\text{O}_2\text{S}$ : C, 35.83; H, 3.67; N, 13.93. Found: C, 35.82; H, 3.68; N, 13.98.

*N*-2-Chloro-4-(trifluoromethyl)-5-thiazolyl-*N'*-4,6-dimethyl-2-pyrimidinylurea (Entry 2, Table 1).

This compound was obtained as a white solid, mp 217-218°; ir (chloroform):  $\text{cm}^{-1}$  3400, 2880, 1685, 1595, 1575, 1455;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  13.0 (bs, 1-H), 10.5 (bs, 1-H), 6.80 (s, 1-H), 2.35 (s, 6-H); ms:  $m/z$  (relative intensity) 353 ( $M^+ + 2$ , 14), 351 ( $M^+$ , 37), 150 (100), 123 (87), 96 (28), 67 (25).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_9\text{ClF}_3\text{N}_5\text{O}_2\text{S}$ : C, 37.56; H, 2.58; N, 19.91. Found: C, 37.55; H, 2.61; N, 19.87.

1,1-Dimethylethyl 2-Chloro-4-(trifluoromethyl)-5-thiazolylcarbamate (Entry 3, Table 1).

This compound was obtained as a yellow oil; ir (neat):  $\text{cm}^{-1}$  3440, 3275 (br), 1720, 1570, 1410, 1255, 1160;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.50 (bs, 1-H), 1.50 (s, 9-H); ms:  $m/z$  (relative intensity) 304 ( $M^+ + 2$ , 13), 302 ( $M^+$ , 34), 246 (63), 229 (30), 202 (41), 57 (100).

*Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{ClF}_3\text{N}_2\text{O}_2\text{S}$ : C, 35.71; H, 3.33; N, 9.25. Found: C, 35.67; H, 3.36; N, 9.26.

3-(Trifluoromethyl)phenyl 2-Chloro-4-(trifluoromethyl)-5-thiazolylcarbamate (Entry 4, Table 1).

This compound was obtained as a yellow oil; ir (neat):  $\text{cm}^{-1}$  3425, 3275 (bd), 1740, 1580, 1485, 1455, 1330, 1240;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.90 (bs, 1-H), 7.60-6.90 (m, 4-H); ms:  $m/z$  (relative intensity), 392 ( $M^+ + 2$ , 13), 390 ( $M^+$ , 36), 229 (45), 162 (100).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_5\text{ClF}_6\text{N}_2\text{O}_2\text{S}$ : C, 36.89; H, 1.29; N, 7.17. Found: C, 36.92; H, 1.32; N, 7.14.

2,2,2-Trifluoro-1-(trifluoromethyl)ethyl 2-Chloro-4-(trifluoromethyl)-5-thiazolylcarbamate (Entry 5, Table 1).

This compound was obtained as a white solid, mp 85-86° (ethyl

acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3410, 2975, 1769, 1580, 1220;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.10 (bs, 1-H), 5.80-5.30 (m, 1-H); ms:  $m/z$  (relative intensity) 398, ( $M^+ + 2$ , 23), 396 ( $M^+$ , 58), 378 (3), 357 (8), 228 (22), 174 (17), 151 (48), 69 (100).

*Anal.* Calcd. for  $\text{C}_8\text{H}_2\text{ClF}_6\text{N}_2\text{O}_2\text{S}$ : C, 24.23; H, 0.51; N, 7.06. Found: C, 24.38; H, 0.56; N, 7.03.

*S*-Methyl 2-Chloro-4-(trifluoromethyl)-5-thiazolylcarbamate (Entry 6, Table 1).

This compound was obtained as a white solid, mp 71-73° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3400, 2925, 1670, 1560, 1390, 1150;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.30 (bs, 1-H), 2.40 (s, 3-H); ms:  $m/z$  (relative intensity), 278 ( $M^+ + 2$ , 33), 276 ( $M^+$ , 80), 248 (29), 75 (100).

*Anal.* Calcd. for  $\text{C}_6\text{H}_4\text{ClF}_3\text{N}_2\text{O}_2\text{S}_2$ : C, 26.04; H, 1.46; N, 10.12. Found: C, 26.12; H, 1.50; N, 10.12.

*S*-Phenyl 2-Chloro-4-(trifluoromethyl)-5-thiazolylcarbamate (Entry 7, Table 1).

This compound was obtained as a white solid, mp 91-92° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3380, 3000, 1665, 1565, 1450, 1140;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.00 (bs, 1-H), 7.60-7.40 (m, 5-H); ms:  $m/z$  (relative intensity), 340 ( $M^+ + 2$ , 15), 338 ( $M^+$ , 36), 310 (8), 228 (22), 137 (38), 109 (100).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_6\text{ClF}_3\text{N}_2\text{O}_2\text{S}_2$ : C, 39.00; H, 1.79; N, 8.27. Found: C, 39.13; H, 1.80; N, 8.23.

2-Chloro-*N*-dimethylaminomethylene-4-(trifluoromethyl)-5-thiazoleamine (**7**).

To a 100 ml round-bottomed flask were added *N,N*-dimethyl formamide (50 ml) and **5** (2.7 g, 11.8 mmoles). Vigorous gas evolution occurred and the mixture was stirred at room temperature for 1 hour. The solution was poured into 300 ml of water and extracted with ether, 3 x 100 ml. The organic layer was dried (magnesium sulfate), filtered, and the solvent was removed *in vacuo*. The crude solid was chromatographed on the Prep-500 (20% ethyl acetate/80% cyclohexane) to give 2.5 g of **7** as a white solid (82% yield), mp 81-82° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  2925, 1635, 1545, 1390, 1115;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.40 (s, 1-H), 3.00 (s, 6-H); ms:  $m/z$  (relative intensity) 259 ( $M^+ + 2$ , 33), 257 ( $M^+$ , 87), 222 (97), 202 (28), 181 (23), 44 (100).

*Anal.* Calcd. for  $\text{C}_7\text{H}_7\text{ClF}_3\text{N}_3\text{S}$ : C, 32.63; H, 2.74; N, 16.31. Found: C, 32.72; H, 2.79; N, 16.29.

2-Chloro-4-(trifluoromethyl)-5-thiazoleamine (**8**).

Dry ether (1.75 liters) and **5** (40 g, 175 mmoles) were added to a 3 liter round-bottomed flask. The mixture was vigorously stirred and water (500 ml) was added in one portion. Gas evolution occurred and the mixture was vigorously stirred for 1 hour. The organic layer was evaporated dried (magnesium sulfate), and the solvent was removed *in vacuo*. The crude solid was recrystallized from ethyl acetate/cyclohexane to give 25 g of **8** as a white solid (71% yield), mp 111-112°; ir (chloroform):  $\text{cm}^{-1}$  3460, 3375, 1610, 1550, 1480, 1405, 1150; ms:  $m/z$  relative intensity), 204 ( $M^+ + 2$ , 25), 202 ( $M^+$ , 75), 182 (65), 147 (100).

*Anal.* Calcd. for  $\text{C}_4\text{H}_2\text{ClF}_3\text{N}_2\text{S}$ : C, 23.72; H, 1.00; N, 13.83. Found: C, 23.64; H, 1.00 N, 13.83.

*N*-2-Chloro-4-(trifluoromethyl)-5-thiazolylacetamide (**9**).

Compound **8** (15 g, 74.3 mmoles), acetic anhydride (21 ml, 223 mmoles), and toluene (100 ml) were added to a 200 ml round-bottomed flask. The mixture was allowed to reflux under nitrogen for 4 hours. The solution was treated with decolorizing carbon and filtered through a pad of silica gel with ether. The solvent was removed *in vacuo* and the crude solid was recrystallized from ethyl acetate/cyclohexane to give 9.7 g of **9** as a white solid (54% yield), mp 90-92°; ir (chloroform):  $\text{cm}^{-1}$  3425, 3000, 1690, 1565, 1395, 1255;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.30 (bs, 1-H), 2.25 (s, 3-H); ms:  $m/z$  (relative intensity), 246 ( $\text{M}^+ + 2$ , 4), 244 ( $\text{M}^+$ , 12), 202 (45), 182 (10), 147 (11), 43 (100).

Anal. Calcd. for  $\text{C}_6\text{H}_4\text{ClF}_3\text{N}_2\text{OS}$ : C, 29.46; H, 1.65; N, 11.45. Found: C, 29.43; H, 1.65; N, 11.41.

#### Ethyl 2,5-Dichloro-4-thiazolecarboxylate (**12**).

Ethyl 2-amino-4-thiazolecarboxylate **9** (200 g, 1160 mmoles), *N*-chlorosuccinimide (170.8 g, 1280 mmoles), and acetonitrile (2 liters) were added to a 4 liter round-bottomed flask. The mixture was heated to reflux under nitrogen and an initial exotherm was controlled by removing the heating mantle from the flask. The mixture was allowed to reflux under nitrogen for 3 hours, while monitoring the loss of starting material by gc. The mixture was allowed to cool and the solvent was removed *in vacuo*. The crude amine was then heated gently in 2 liters of ethyl acetate and treated with decolorizing carbon. The mixture was filtered through a large pad of silica gel contained in a sintered glass funnel. After removal of volatiles, 235 g of ethyl 2-amino-5-chloro-4-thiazolecarboxylate was recovered as a light brown solid (98% yield). The thiazole was of sufficient purity for further transformations; ir (chloroform):  $\text{cm}^{-1}$  3505, 3410, 3020, 1725, 1620, 1550, 1345;  $^1\text{H}$  nmr (360 MHz, dimethyl sulfoxide- $d_6$ ):  $\delta$  7.51 (bs, 2-H), 4.24 (q,  $J = 7.1$  Hz, 2-H), 1.28 (t,  $J = 7.1$  Hz, 3-H);  $^{13}\text{C}$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  164.0, 160.3, 136.6, 118.6, 60.5, 14.0; ms:  $m/z$  (relative intensity), 208 ( $\text{M}^+ + 2$ , 9), 206 ( $\text{M}^+$ , 29), 161 (20), 134 (27), 99 (94), 56 (100).

Ethyl 2-amino-5-chloro-4-thiazolecarboxylate (240 g, 1160 mmoles), anhydrous cupric chloride (234 g, 1750 mmoles), and acetonitrile (2 liters) were added to a 3 liter round-bottomed flask. The slurry was mechanically stirred under nitrogen at room temperature while *t*-butyl nitrite (180 g, 1750 mmoles) was added dropwise over 2 hours. During this time the solution became slightly exothermic and nitrogen gas was evolved. After the addition was complete the mixture was stirred for 1 hour. The mixture was then added to 4 liters of water and 4 liters of chloroform and made acidic with 12*N* hydrochloric acid. The aqueous layer was separated and extracted 2 x 500 ml with additional chloroform. The combined organic layers were dried (magnesium sulfate) and treated with decolorizing carbon. The mixture was filtered through a large pad of silica gel contained in a sintered glass funnel. The solvents were removed *in vacuo* to give 170.5 g, (65% yield) of **12** as a yellow oil. The product was of sufficient purity for further transformations, but could be kuglerohr distilled if necessary, bp 75-80° @ 0.5 mm of Hg; ir (neat):  $\text{cm}^{-1}$  3000, 1730, 1500, 1455, 1310, 1210, 1160;  $^1\text{H}$  nmr (360 MHz, deuteriochloroform):  $\delta$  4.45 (q,  $J = 7.3$  Hz, 2-H), 1.44 (t,  $J = 7.3$  Hz, 3-H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  158.6, 147.3, 139.5, 134.2, 61.3, 13.6; ms:  $m/z$  (relative intensity), 227 ( $\text{M}^+ + 2$ , 20), 225 ( $\text{M}^+$ , 28), 197 (41), 180 (95), 153 (100), 91 (65), 79 (72).

Anal. Calcd. for  $\text{C}_6\text{H}_5\text{Cl}_2\text{NO}_2\text{S}$ : C, 31.88; H, 2.23; N, 6.20. Found: C, 31.99; H, 2.24; N, 6.17.

#### 2,5-Dichloro-4-chlorocarbonylthiazole (**13**).

Compound **12** (64 g, 280 mmoles), sodium hydroxide (12.13 g, 300 mmoles), tetrahydrofuran (500 ml), and water (500 ml) were added to a 2 liter round-bottomed flask. The mixture was stirred at room temperature for 3 hours. The mixture was made acidic with 12 *N* hydrochloric acid and extracted 3 x 400 ml with ethyl acetate. The organic layer was dried (magnesium sulfate), filtered, and the solvents were removed *in vacuo* to give 52.7 g of 2,5-dichloro-4-thiazolecarboxylic acid as a light brown solid (94% yield), mp 195-196° (ethyl acetate). This product was of sufficient purity for further transformations; ir (chloroform):  $\text{cm}^{-1}$  3050, 2900 (br), 1715, 1515, 1475, 1070;  $^{13}\text{C}$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  160.3, 147.1, 140.8, 133.8; ms:  $m/z$  (relative intensity), 199 ( $\text{M}^+ + 2$ , 53), 197 ( $\text{M}^+$ , 77), 161 (57), 153 (44), 79 (96), 45 (100).

Anal. Calcd. for  $\text{C}_4\text{HCl}_2\text{NO}_2\text{S}$ : C, 24.26; H, 0.51; N, 7.07. Found: C, 24.35; H, 0.53; N, 7.05.

2,5-Dichloro-4-thiazolecarboxylic acid (125 g, 634.5 mmoles), chloroform (500 ml), oxalyl chloride (111 ml, 1270 mmoles), and 10 drops of *N,N*-dimethylformamide were added to a 1 liter round bottomed flask. An initial vigorous gas evolution occurred. The mixture was stirred for 6 hours at room temperature under nitrogen. The solvents were removed *in vacuo* and 128 g of **13** were obtained as a brown solid (94% yield). This product was of sufficient purity for further reactions; ir (chloroform):  $\text{cm}^{-1}$  1770, 1455, 1085, 995.

#### 2,5-Dichloro-4-isocyanatothiazole (**14**).

Sodium azide (39.2 g, 603.7 mmoles), water (550 ml), and acetone (250 ml) were added to a 1 liter round-bottomed flask. The mixture was cooled to 0° and vigorously stirred under nitrogen while **13** (118 g, 549 mmoles) was added dropwise (as a solution in 250 ml of dry acetone) over 30 minutes. The mixture was allowed to warm to room temperature and stir for 1 hour. The mixture was then extracted 2 x 500 ml with carbon tetrachloride. The organic layer was back extracted 2 x 300 ml with water. The organic layer was dried (magnesium sulfate), and filtered through a pad of silica gel. The carbon tetrachloride volume was adjusted to 2 liters with additional dry carbon tetrachloride. The mixture was brought slowly to reflux under nitrogen and held there for 4 hours. The solvent was removed *in vacuo* and the crude oil was distilled through a 6 inch vigreux column collecting between 58-60° @ 0.5 mm of Hg. The isocyanate was obtained as a yellow oil (77.9 g, 73% yield). The isocyanate decomposed in moist air, but was stable when stored under nitrogen in a tightly capped bottle at 0°; ir (carbon tetrachloride):  $\text{cm}^{-1}$  2265, 1590, 1072, 1062;  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  147.7, 137.4, 129.4, 114.8.

General Procedure for the Synthesis of 4-Substituted Thiazole Carbamates, Thiocarbamates and Ureas (Table 2).

Methylene chloride (50 ml), **14** (2.0 g, 10.3 mmoles), the appropriate alcohol, thiol, or amine (10.3 mmoles), and 4 drops of triethylamine (entries 4, 5, and 7 only, Table 2) were added to a 100 ml round-bottomed flask. The mixture was stirred under nitrogen at room temperature for 4 hours. An initial exotherm was usually noted. The solvents were removed *in vacuo* and the crude products were recrystallized or chromatographed where appropriate. Pertinent analytical data is given below.

*N*-2,5-Dichloro-4-thiazolyl-*N'*-1-methylethylurea (Entry 1, Table 2).

This compound was obtained as a white solid, mp 168-169° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3420, 3350, 3005, 1680, 1545;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.15 (bs, 1-H), 6.60 (bs, 1-H), 4.20-3.50 (m, 1-H), 1.20 (d,  $J = 7$  Hz, 6-H); ms:  $m/z$  (relative intensity, chemical ionization), 256 ( $M^+ + 2$ , 61), 254 ( $M^+$ , 100), 220 (33), 113 (79).

*N*-2,5-Dichloro-4-thiazolyl-*N'*-3-(trifluoromethyl)phenylurea (Entry 2, Table 2).

This compound was obtained as a white solid, mp 200-202° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3410, 3300, 3010, 1700, 1560, 1335;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  9.20 (bs, 1-H), 8.60 (bs, 1-H), 8.10-7.90 (m, 1-H), 7.80-7.30 (m, 3-H); ms:  $m/z$  (relative intensity, chemical ionization) 358 ( $M^+ + 2$ , 78), 356 ( $M^+$ , 100), 322 (25), 162 (66), 135 (55), 113 (94).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_6\text{Cl}_2\text{F}_3\text{N}_2\text{O}_2\text{S}$ : C, 37.00; H, 1.70; N, 11.80. Found: C, 37.00; H, 1.73; N, 11.76.

Methyl 2,5-Dichloro-4-thiazolylcarbamate (Entry 3, Table 2).

This compound was obtained as a white solid, mp 105-106° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3420, 3005, 1745, 1445, 1215;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.20 (bs, 1-H), 3.80 (s, 3-H); ms:  $m/z$  (relative intensity), 228 ( $M^+ + 2$ , 69), 226 ( $M^+$ , 100), 194 (40), 147 (19), 120 (37), 79 (100).

*Anal.* Calcd. for  $\text{C}_5\text{H}_4\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ : C, 26.45; H, 1.78; N, 12.34. Found: C, 26.39; H, 1.81; N, 12.32.

3-(Trifluoromethyl)phenyl 2,5-Dichloro-4-thiazolylcarbamate (Entry 4, Table 2).

This compound was obtained as a white solid, mp 112-113°; ir (chloroform):  $\text{cm}^{-1}$  3420, 3010, 1770, 1330, 1195;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  7.70-7.40 (m, 4-H), 7.35 (bs, 1-H); ms:  $m/z$  (relative intensity, chemical ionization) 359 ( $M^+ + 2$ , 43), 357 ( $M^+$ , 59), 195 (100), 161 (33).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_5\text{Cl}_2\text{F}_3\text{N}_2\text{O}_2\text{S}$ : C, 36.99; H, 1.41; N, 7.84. Found: C, 37.07; H, 1.43; N, 7.84.

2,2,2-Trifluoro-1-(trifluoromethyl)ethyl 2,5-Dichloro-4-thiazolylcarbamate (Entry 5, Table 2).

This compound was obtained as a white solid, mp 134-135° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3410, 3020, 1780, 1435, 1235;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  10.50 (bs, 1-H), 6.20-5.60 (m, 1-H); ms:  $m/z$  (relative intensity), 364 ( $M^+ + 2$ , 84), 362 ( $M^+$ , 94), 194 (84), 151 (64), 106 (79), 69 (100).

*Anal.* Calcd. for  $\text{C}_7\text{H}_2\text{Cl}_2\text{F}_6\text{N}_2\text{O}_2\text{S}$ : C, 23.16; H, 0.56; N, 7.72. Found: C, 23.29; H, 0.60; N, 7.71.

*S*-Methyl 2,5-Dichloro-4-thiazolylcarbamothioate (Entry 6, Table 2).

This compound was obtained as a white solid, mp 99-101°; ir (chloroform):  $\text{cm}^{-1}$  3400, 3010, 1690, 1430, 1215, 1075;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.20 (bs, 1-H), 2.40 (s, 3-H); ms:  $m/z$  (relative intensity), 244 ( $M^+ + 2$ , 50), 242 ( $M^+$ , 68), 214 (57), 194 (47), 168 (53), 75 (100).

*Anal.* Calcd. for  $\text{C}_5\text{H}_4\text{Cl}_2\text{N}_2\text{OS}_2$ : C, 24.70; H, 1.66; N, 11.52. Found: C, 24.82; H, 1.69; N, 11.47.

*S*-4-Chlorophenyl 2,5-Dichloro-4-thiazolylcarbamothioate (Entry 7, Table 2).

This compound was obtained as a white solid, mp 155-157° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3400, 3015, 1695, 1480, 1215;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  1030 (bs, 1-H), 7.70-7.20 (m, 4-H); ms:  $m/z$  (relative intensity), 194 (86), 144 (100), 133 (86), 109 (85).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_5\text{Cl}_3\text{N}_2\text{OS}_2$ : C, 35.36; H, 1.48; N, 8.25. Found: C, 35.25; H, 1.50; N, 8.17.

2,5-Dichloro-4-thiazoleamine Hydrochloride (**18**).

Dry ether (516 ml) and **14** (10 g, 51.6 mmoles) were added to a 1 liter round-bottomed flask. The mixture was vigorously stirred at room temperature was water (100 ml) was added in one portion. Vigorous stirring was continued until no carbon dioxide evolution was noted, 1 hour. The ether layer was separated, dried (magnesium sulfate), and filtered. Anhydrous hydrogen chloride was bubbled through the solution until no more thiazole hydrochloride precipitated, 15 minutes. The thiazole **16** was collected by filtration and dried to give 9.7 g of a white powder (92% yield), mp 120° dec. This material was not soluble in any common nmr solvent; ir (nujol):  $\text{cm}^{-1}$  1455, 1175, 1050; ms:  $m/z$  (relative intensity) 170 ( $M^+ + 2$  (minus HCl), 55.91, 168 ( $M^+$  (minus HCl), 89.97, 107 (100), 79 (33.94), 72 (56.96).

*Anal.* Calcd. for  $\text{C}_5\text{H}_3\text{Cl}_3\text{N}_2\text{S}$ : C, 17.53; H, 1.47; N, 13.63. Found: C, 17.56; H, 1.50; N, 13.63.

*N*-Acetyl-*N*-2,5-dichloro-4-thiazolylacetamide (**16**) and *N*-2,5-dichloro-4-thiazolylacetamide (**19**).

Compound **18** (3.2 g, 15.7 mmoles), chloroform (100 ml), acetic anhydride (4.8 g, 47.1 mmoles), triethylamine (10.9 ml, 78.5 mmoles), and 4-dimethylaminopyridine (0.2 g, 1.6 mmoles) were added to a 250 ml round-bottomed flask. The mixture was stirred at room temperature under nitrogen for 24 hours. The solution was then diluted with ether and extracted 3 x 50 ml with water. The organic layer was dried (magnesium sulfate), filtered through a pad of silica gel, and the solvents were removed *in vacuo*. The crude residue was separated on a chromatotron using ethyl acetate/cyclohexane mixtures to give 2.3 g (58% yield) of imide **16** and 0.5 g (15% yield) of the amide **19**.

Analytical Data for **16**.

This compound was obtained as a white solid, mp 68-70° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3010, 1730, 1530, 1370, 1220;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  2.20 (s); ms:  $m/z$  (relative intensity), 255 ( $M^+ + 2$ , 13), 253 ( $M^+$ , 18), 210 (69), 168 (69), 44 (100).

*Anal.* Calcd. for  $\text{C}_7\text{H}_6\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ : C, 33.22; H, 2.39; N, 11.07. Found: C, 33.25; H, 2.41; N, 11.07.

Analytical Data for **19**.

This compound was obtained as a white solid, mp 124-125° (ethyl acetate/cyclohexane); ir (chloroform):  $\text{cm}^{-1}$  3420, 3260, (br), 3005, 1700, 1435, 1215;  $^1\text{H}$  nmr (60 MHz, deuteriochloroform):  $\delta$  8.20 (bs, 1-H), 2.10 (s, 3-H); ms:  $m/z$  (relative intensity), 212 ( $M^+ + 2$ , 27), 210 ( $M^+$ , 39), 168 (100), 107 (51), 79 (31).

*Anal.* Calcd. for  $\text{C}_5\text{H}_4\text{Cl}_2\text{N}_2\text{OS}$ : C, 28.45; H, 1.91; N, 13.27. Found: C, 28.36; H, 1.94; N, 13.23.

Imide **16** and *N*-Acetyl-*N*-2-acetyl-2,5-dichloro-4-thiazolylamino-5-chloro-4-thiazolylacetamide **17**.

The isocyanate **14** (2.0 g, 10.3 mmoles) was hydrolyzed to the amine as described above utilizing high dilution techniques (ether, 100 ml and water, 50 ml). The organic layer was dried



(magnesium sulfate), filtered and the solvent was removed *in vacuo*. Upon concentration the thiazole amine reacted with itself. The product was then heated with acetic anhydride (50 ml) at 120° for 30 minutes to stop any further reactions from occurring. The acetic anhydride was removed *in vacuo* and the mixture was chromatographed on a Prep-500 (20% ethyl acetate, 80% cyclohexane) to give 20 g of the dimer **17** (45% yield) as a white solid and 0.1 g of the imide **16** (4% yield) as a white solid.

#### Analytical Data for **17**.

This compound was obtained as a white solid, mp 145-146° (ethyl acetate/cyclohexane); ir (methylene chloride):  $\text{cm}^{-1}$  3050, 2980, 1725, 1700, 1530, 1485, 1290, 1225;  $^1\text{H}$  nmr (360 MHz, acetone- $d_6$ ):  $\delta$  2.22 (s);  $^{13}\text{C}$  nmr (acetone- $d_6$ ):  $\delta$  172.0, 171.1, 154.0, 149.7, 141.9, 140.4, 126.8, 118.9, 25.8, 22.1; ms:  $m/z$  (relative intensity), 431 ( $\text{M}^+ + 4$ , 1), 429 ( $\text{M}^+ + 2$ , 4), 427 ( $\text{M}^+$ , 4), 385 (36), 343, (56), 325 (49), 301 (56), 44 (100).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_9\text{Cl}_3\text{N}_4\text{O}_3\text{S}_2$ : C, 33.70; H, 2.12; N, 13.10. Found: C, 33.46; H, 2.18; N, 12.91.

#### *N*-2,5-Dichloro-4-thiazolyl-2,2,2-trifluoroacetamide (**20**).

The isocyanate **14** (3.0 g, 15.5 mmoles) was hydrolyzed to the free amine as described above using high dilution techniques (155 ml of ether, 50 ml of water). The resulting ether solution of the amine was treated with 10 ml of trifluoroacetic anhydride at room temperature and stirred under nitrogen for 1 hour. The solvents were removed *in vacuo* and the crude solid was recrystallized from ethyl acetate/cyclohexane to give 3.5 g of **20** (85% yield) as a white solid, mp 95-97°; ir (chloroform):  $\text{cm}^{-1}$  3400, 3020, 1755, 1540, 1440, 1215, 1165; ms:  $m/z$  (relative intensity), 266 ( $\text{M}^+ + 2$ , 83), 264 ( $\text{M}^+$ , 100), 229 (64), 195 (83), 106 (37), 79 (43).

*Anal.* Calcd. for  $\text{C}_5\text{HCl}_2\text{F}_3\text{N}_2\text{OS}$ : C, 22.66; H, 0.38; N, 10.57. Found: C, 22.53; H, 0.40; N, 10.55.

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