Syntheses and Reactions of 2-Halo-5-thiazolecarboxylates

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A variety of 2-halo-5-thiazolecarboxylates was prepared from substituted-3-aminoacrylates and 3-ketoesters. Selective reduction of 2-chloro-5-thiazolecarboxylates **4a**, **4i** and **4j** with sodium borohydride in ethanol provided the corresponding 2-halo-5-thiazolemethanols **27-29**. Nucleophilic displacements on [2-chloro-4-(trifluoromethyl)-5-thiazolyl]methyl methanesulfonate (**32c**) occurred selectively at the 5-substituent to provide 2-chloro-4-(trifluoromethyl)-5-(heteroatom-substituted-methyl)thiazoles **32d-f**.

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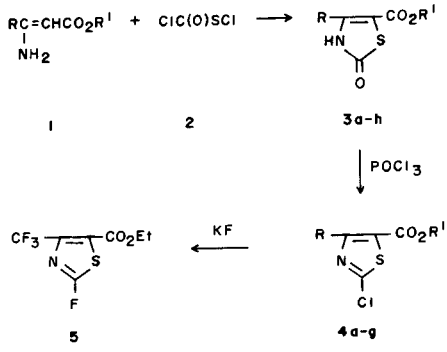
Although 5-thiazolecarboxylates are reported in the literature [1], surprisingly few 2-halo derivatives had been described [2] prior to the beginning of our investigation and only after the completion of our work [3] were 2-halo-5-thiazolecarboxylates with 4-alkyl substituents other than methyl reported [4]. Since we required various 5-thiazolecarboxylates for biological evaluation as agricultural chemicals, we decided to do a systematic study on the syntheses and reactions of 2-halo-5-thiazolecarboxylates. This account reports the results of our investigation.

The synthesis of 2-halo-5-thiazolecarboxylates are depicted in Schemes I and II.

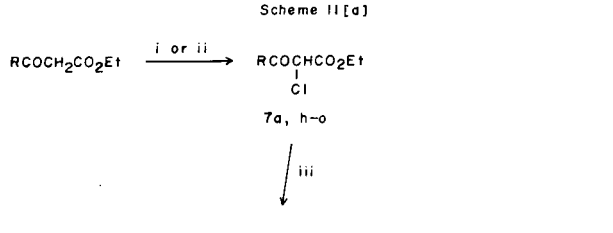
Scheme I



a, R = CF_3, R' = Et
b, R = CF_3CF_2, R' = Et
c, R = $CF_3CF_2CF_2$, R' = Me
d, R = CCl_3, R' = Et
e, R = C_6H_5, R' = Et
f, R = 3-$CF_3C_6H_4$, R' = Et
g, R = Me, R' = Et
h, R = Et, R' = Et
i, R = i-Pr, R' = Et

Reactions of substituted-3-aminoacrylates **1a-h** with chlorocarbonylsulfenyl chloride (**2**) afforded 2,3-dihydro-2-oxo-5-thiazolecarboxylates **3a-h**. The 2-chloro-5-thiazolecarboxylates **4a-g** were obtained by treatment of **3a-g** with phosphorus oxychloride. Generally, the reaction rate could be accelerated and the yields of **4a-g** could be improved by adding one equivalent of organic base such as pyridine

Scheme II[a]

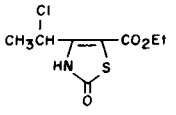


a, R = CF_3
b, R = CF_3CF_2
c, R = $CF_3CF_2CF_2$
d, R = CCl_3
e, R = C_6H_5
f, R = 3-$CF_3C_6H_4$
g, R = Me
h, R = Et
i, R = i-Pr
j, R = t-Bu
k, R = 2-ClC_6H_4
l, R = 4-ClC_6H_4
m, R = 4-FC_6H_4
n, R = 3-$CH_3C_6H_4$
o, R = 4-$NO_2C_6H_4$

[a] Reagents: i, SO_2Cl_2; ii, Cl_2; iii, $NH_2C(S)NH_2$; iv, HNO_2; v, CuCl; vi, t-BuONO, $CuCl_2$; vii, CuBr; viii, NaI.

to the reaction mixture. Reaction of 3-aminoacrylates **1** with **2** have been reported by Grohe and Heitzer [5]; however, Grohe and Heitzer's study was limited to **1** containing 3-methyl, -trichloromethyl and -carbethoxy substituents. We found that although the reaction of **1g** with **2** gave **3g** in good yield, reactions of **1a-f** with **2** gave **3a-f** only in modest yields (41-58%). In addition, the reaction of **1h** with **2** gave **3h** in poor yield (10%) accompanied by an α-chlorinated product **11** (12% yield). Furthermore, two by-products, **12** and **13**, were isolated from the reaction of **1a** with **2** in a total yield of 10%. The structural assignments of **12** and **13** were confirmed by spectral data and elemental analyses as well as by independent syntheses of **12** from reaction of **1a** with sulfur dichloride and **13** from reaction of **12** with triethylamine [6]. The chemistry in Scheme I was further complicated by the difficulties encountered in obtaining 3-aminoacrylates containing bran-

ched alkyl groups at the 3-position in good yields. For instance, **1i** was obtained only in low yields from 3-ketoester **6i** by literature methods [7,8]. These difficulties prompted us to synthesize other 2-halo-5-thiazolecarboxylates **4h-o** by the Hantzsch method [9] as shown in Scheme II.



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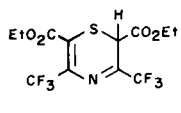

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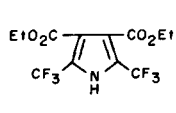

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The 2-amino-5-thiazolecarboxylates **8a** and **8h-o** were obtained simply by reactions of 2-chloro-3-ketoesters **7a** and **7h-o**, respectively, with thiourea in refluxing ethanol.

The 2-chloro and -bromo-5-thiazolecarboxylates **4h-o** and **9** were prepared by Sandmeyer reactions whereas the 2-iodo derivative **10** was prepared by treatment of the diazonium salt from **8a** with sodium iodide. We found that **4i, 4j,** and **4l** could be obtained in better yields (Table 3) using the *t*-butyl nitrite-cupric chloride reagent system of Doyle *et al.* [10]. This procedure not only utilizes a solvent (acetonitrile) which dissolves the starting compounds **8** but also eliminates by-products such as **14**, resulting in higher yields of the desired products **4**. Compounds **3a-h** are listed in Table 1, compounds **8a** and **8h-o** are listed in Table 2, and compounds **4a-o, 5, 9,** and **10** are listed in Table 3.

Table 1

Physical Data of 4-Substituted 2,3-Dihydro-2-oxo-5-thiazolecarboxylates **3a-h**

Compound No.	Mp (°C) (Solvent)	Yield %	Molecular Formula	Analysis % Calcd./(Found) C	H	N
3a	121-123 (hexane-ether)	55	$C_7H_6F_3NO_3S$	34.85 (34.84)	2.51 (2.54)	5.81 (5.85)
3b	95-97 (hexane-ether)	46	$C_8H_6F_5NO_3S$	32.99 (32.71)	2.08 (1.96)	4.81 (4.86)
3c	113-116 (hexane-ether)	41	$C_8H_4F_7NO_3S$	29.36 (29.15)	1.23 (1.25)	4.30 (4.39)
3d	109-110 (hexane-ether)	55	$C_7H_6Cl_3NO_3S$ [a]	28.96 (28.98)	2.08 (2.09)	4.82 (4.82)
3e	199-201 [b]	48	$C_{12}H_{11}NO_3S$ [c]			
3f	168-171 (benzene)	58	$C_{13}H_{10}F_3NO_3S$	49.20 (49.26)	3.18 (3.20)	4.44 (4.39)
3g	176-178 [d]	60	$C_7H_9NO_3S$ [c]			
3h	120-123	10	$C_8H_{11}NO_3S$	47.74 (47.59)	5.51 (5.50)	6.96 (6.87)

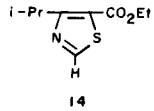
[a] *Anal.* Calcd. for Cl: 36.61. Found: 36.62. [b] Lit mp 202° [11]. [c] Not analyzed. [d] Lit mp 177-178° [5].

Table 2

Physical Data of 4-Substituted 2-Amino-5-thiazolecarboxylates **8a,h-o**

Compound No.	Mp (°C) (Solvent)	Yield %	Molecular Formula	Analysis % Calcd./(Found) C	H	N
8a	168-171 [a]	72	$C_7H_7F_3N_2O_2S$ [b]			
8h	177-179 (ethanol)	75	$C_8H_{12}N_2O_2S$	47.97 (47.92)	6.04 (6.04)	13.90 (14.00)
8i	174-178 [c] (ethanol-water)	82	$C_9H_{14}N_2O_2S$	50.44 (50.47)	6.58 (6.61)	13.08 (13.07)
8j	105-107 [d] (hexane)	53	$C_{10}H_{16}N_2O_2S$	52.60 (52.66)	7.06 (7.06)	12.27 (12.21)
8k	165-166 (toluene)	31	$C_{12}H_{11}ClN_2O_2S$	50.96 (50.96)	3.92 (3.96)	9.90 (9.91)
8l	198-200	80	$C_{12}H_{11}ClN_2O_2S$	50.96 (50.88)	3.92 (3.93)	9.90 (9.90)
8m	205-208 (ethanol)	76	$C_{12}H_{12}FNO_2S$	54.11 (54.12)	4.16 (4.16)	10.52 (10.52)
8n	185-187 (ethanol)	61	$C_{13}H_{14}N_2O_2S$	59.52 (59.55)	5.38 (5.31)	10.68 (10.55)
8o	259-261 [e]	81	$C_{12}H_{11}N_3O_4S$ [b]			

[a] Lit mp 168-170° [12]. [b] Not analyzed. [c] Lit mp 176-178° [4b]. [d] Lit mp 108-109° [4b]. [e] Lit mp 258° [13].



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Hydrolysis of **4a** gave the corresponding acid **15**, which was converted to the acid chloride **17**. Esters **19a-j** (Table 4) were prepared in good yields simply by heating various alcohols and phenols with **17** at reflux. In contrast, heating 2-chloro-4-methyl-5-thiazolecarbonyl chloride (**18**) with alcohols at reflux yielded the corresponding alkyl 2,3-dihydro-4-methyl-2-oxo-5-thiazolecarboxylates **22j-l** as the major products. We attribute the formation of **22j-l** to the hydrogen chloride catalyzed displacement of chlorine in the initial products **20j-l** by alcohols followed by dealkylation of the resulting 2-alkoxy derivatives **24j-l** by hydrogen chloride (Scheme III). We were able to obtain **20k** in good yield when triethylamine was used to scavange hydrogen chloride. Compounds **19a-j** are weaker bases than **20j-l** due to the electron-withdrawing trifluoromethyl group and are therefore more stable under acidic conditions. As a result, no observable by-products **21a-j** are formed.

Ester **4a** reacts readily with good nucleophiles to give the corresponding derivatives **25a-c**. For instance, reaction of **4a** with one equivalent of sodium ethoxide at 0°

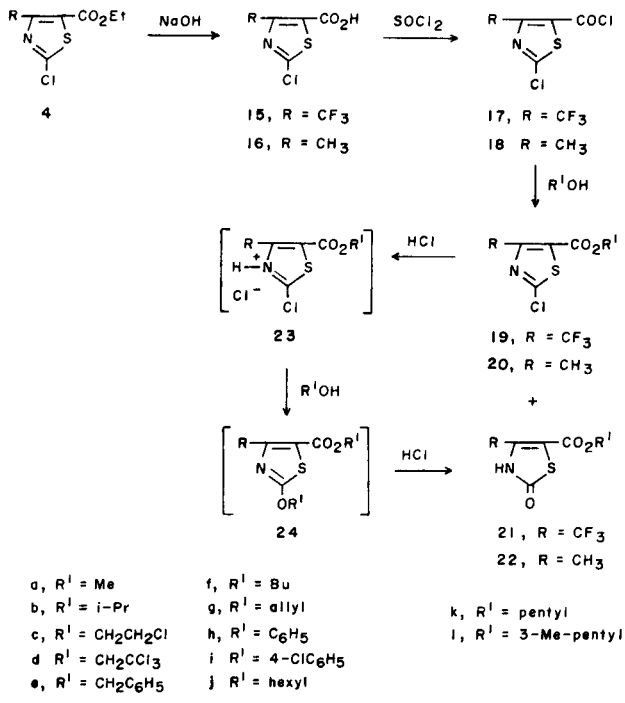
Table 3

Physical Data of 2-Halo-5-thiazolecarboxylates **4a-o**, **5**, **9** and **10**

Compound No.	Mp (°C) (Solvent) or n_D^{25}	Yield %	Molecular Formula	Analysis % Calcd./(Found) C	H	N	Cl
4a	58-59 (hexane)	92 [b,c]	$C_7H_5ClF_3NO_2S$	32.38 (32.33)	1.94 (1.98)	6.40 (6.35)	[d]
4b	1.4660	21 [b,e] 71 [b,f]	$C_6H_5ClF_5NO_2S$	31.03 (30.62)	1.63 (1.18)	4.52 (5.08)	[d]
4c	1.4353	10 [b,e] 69 [b,f]	$C_6H_3ClF_7NO_2S$	27.80 (27.42)	0.87 (0.87)	4.05 (4.03)	[d]
4d	42.5-43.5 [g]	14 [b,h]	$C_7H_5Cl_4NO_2S$	27.18 (27.27)	1.62 (1.66)	4.53 (4.53)	45.86 (45.87)
4e	56-57 (hexane)	68 [b,c]	$C_{12}H_{10}ClNO_2S$	53.83 (53.86)	3.76 (3.78)	5.23 (5.21)	13.24 (13.14)
4f	26.5-27 [g]	67 [b,c]	$C_{13}H_{19}ClF_3NO_2S$	46.50 (46.61)	2.70 (2.71)	4.17 (4.19)	10.56 (10.70)
4g	46-47.5 [i]	91 [b,c]	$C_7H_8ClNO_2S$ [d]				
4h	1.5189 [g]	52 [j-l]	$C_8H_{10}ClNO_2S$	43.73 (43.88)	4.59 (4.62)	6.38 (6.34)	[d]
4i	1.5145	49 [g,j-l] 86 [j,m]	$C_9H_{12}ClNO_2S$	46.24 (46.40)	5.18 (5.22)	5.99 (6.06)	[d]
4j	1.5138	41 [g,j-l] 79 [j,m]	$C_{10}H_{14}ClNO_2S$	48.48 (48.41)	5.70 (5.72)	5.56 (6.06)	[d]
4k	150 [n] (0.3 torr)	15 [j,k,o]	$C_{12}H_9Cl_2NO_2S$	47.69 (47.61)	3.00 (3.02)	4.63 (4.62)	23.43 (23.45)
4l	119-120 (ethanol)	37 [j,k,o] 70 [j,m]	$C_{12}H_9Cl_2NO_2S$	47.69 (47.71)	3.00 (2.97)	4.63 (4.55)	[d]
4m	113-114 (ethanol)	77 [j-l]	$C_{12}H_9ClFNO_2S$	50.44 (50.42)	3.17 (3.18)	4.90 (4.90)	[d]
4n	41-42 (ethanol)	34 [j,k,o]	$C_{13}H_{12}ClNO_2S$	55.42 (55.38)	4.29 (4.33)	4.97 (4.99)	12.58 (12.53)
4o	146-148 (acetone-chloroform)	23 [j-l]	$C_{12}H_9ClN_2O_4S$	46.09 (46.08)	2.90 (2.92)	8.95 (8.95)	11.34 (11.23)
5	1.4344	38 [p]	$C_7H_5F_4NO_2S$	34.57 (34.31)	2.07 (1.80)	5.76 (5.76)	[d]
9	75.5-76.5 (petroleum ether)	51 [q]	$C_7H_5BrF_3NO_2S$	27.64 (27.65)	1.66 (1.65)	4.61 (4.61)	26.28 [r] (26.27) [r]
10	75-76 (hexane)	26 [s]	$C_7H_5F_3INO_2S$	23.94 (23.94)	1.44 (1.44)	3.99 (3.95)	36.15 [t] (36.08) [t]

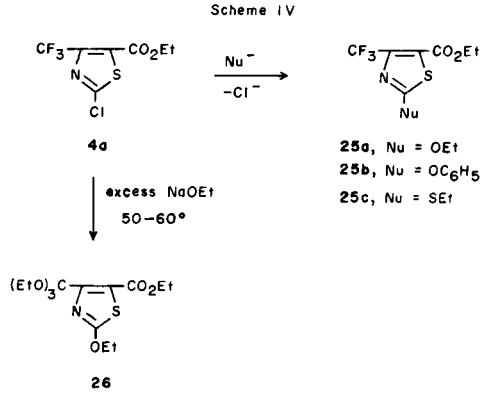
[a] For methods of preparation see Experimental. [b] Yield based from **3** according to Scheme I. [c] Prepared by Method D. [d] Not analyzed. [e] Prepared by Method E. [f] Prepared by Method F, pyridine was used as base. [g] Purified by column chromatography. [h] Prepared by reacting **3d** with a mixture of phosphorus pentachloride and phosphorus oxychloride. [i] Lit mp 48-51° [2a]. [j] Yield based from **8** according to Scheme II. [k] Reagents *iv* and *v* were used. [l] Prepared by Method I. [m] Reagent *vi* was used, prepared by Method K. [n] Bp, purified by preparative tlc. [o] Prepared by Method J. [p] Prepared from **4a** according to Scheme I. [q] Prepared from **8a** according to Scheme II; reagents *iv* and *vii* were used. [r] Analysis of bromine. [s] Prepared from **8a** according to Scheme II; reagents *iv* and *viii* were used. [t] Analysis of iodine.

Scheme III



gave **25a** in 78% yield. However, if the reaction was carried out with excess sodium ethoxide at 50-60°, the 2-ethoxy-4-(triethoxymethyl) derivative **26** was obtained (Scheme IV).

Scheme IV



Reduction of **4a** with sodium borohydride in ethanol gave the 5-hydroxymethyl derivative **27** in good yield (74%). This selective reduction of the ester group was extended to 2-chloro-4-alkyl-5-thiazolecarboxylates **4i** and **4j**

Table 4

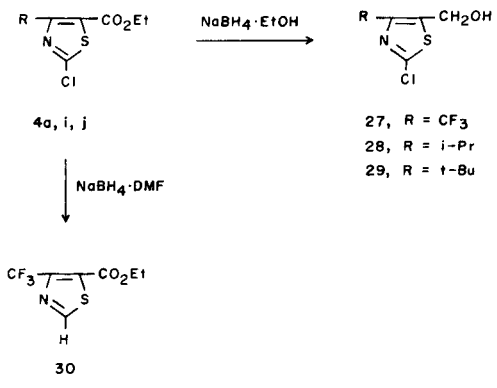
Physical Data of Compounds **19a-j**, **20k** and **22j-l**

Compound No.	Mp (°C) (Solvent) or n_D^{25}	Yield %	Molecular Formula	Analysis % Calcd./(Found) C	H	N	Cl
19a	32-34 (hexane)	95 [b]	$C_6H_3ClF_3NO_2S$	29.33 (29.23)	1.23 (1.24)	5.70 (5.74)	14.44 (14.43)
19b	1.4655	86 [b]	$C_8H_7ClF_3NO_2S$	35.10 (35.15)	2.58 (2.62)	5.12 (5.11)	12.96 (12.90)
19c	1.4965	91 [b]	$C_7H_4Cl_2F_3NO_2S$	28.59 (28.67)	1.37 (1.40)	4.76 (4.76)	24.11 (24.06)
19d	1.5094	87 [b]	$C_7H_2Cl_4F_3NO_2S$	23.16 (23.24)	0.56 (0.62)	3.86 (3.92)	38.95 (38.96)
19e	56-58 (hexane)	53 [b]	$C_{12}H_7ClF_3NO_2S$	44.80 (44.86)	2.19 (2.19)	4.35 (4.34)	11.02 (11.09)
19f	1.4685	75 [b]	$C_9H_9ClF_3NO_2S$	37.57 (37.54)	3.15 (3.17)	4.87 (4.90)	[c]
19g	1.4816	85 [b]	$C_8H_5ClF_3NO_2S$	35.37 (35.50)	1.86 (1.93)	5.16 (5.22)	[c]
19h	1.5389	58 [d]	$C_{11}H_5ClF_3NO_2S$	42.94 (42.97)	1.64 (1.67)	4.55 (4.58)	[c]
19i	1.5522	85 [d]	$C_{11}H_4ClF_3NO_2S$	38.60 (39.08)	1.17 (1.00)	4.09 (4.09)	[c]
19j	1.4657	87 [b]	$C_{11}H_{13}ClF_3NO_2S$	41.84 (41.86)	4.15 (4.15)	4.44 (4.43)	[c]
20k	110 [e] (0.05 torr)	90 [f]	$C_{10}H_{14}ClNO_2S$	48.48 (48.46)	5.70 (5.74)	5.65 (5.65)	[c]
22j	92.5-94 [g]	40 [h]	$C_{11}H_{17}NO_3S$	54.30 (54.29)	7.04 (7.04)	5.76 (5.72)	[c]
22k	92-94 [i]	50 [h]	$C_{10}H_{15}NO_3S$	52.38 (52.35)	6.59 (6.59)	6.11 (6.10)	[c]
22l	94-95 (ethanol)	40 [h]	$C_{11}H_{17}NO_3S$	54.30 (54.35)	7.04 (7.08)	5.76 (5.76)	[c]

[a] For methods of preparation see Experimental. [b] Yield based from **17** prepared by Method L. [c] Not analyzed. [d] Yield based from **17**, prepared by Method M. [e] Bp. [f] Yield based from **18**, triethylamine was used as hydrogen chloride scavanger. [g] Lit mp 94° [14]. [h] Yield based from **18**, prepared by Method N. [i] Lit mp 99° [14].

to provide the corresponding 2-chloro-5-thiazolemethanols **28** and **29**, respectively. Reduction of **4a** with sodium borohydride in dimethylformamide, however, proceeded differently giving **30** as the major product (Scheme V).

Scheme V



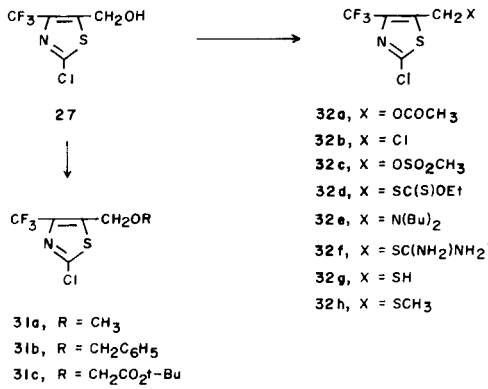
4a, i, j

27, R = CF_3
28, R = i-Pr
29, R = t-Bu

30

Carbinol **27** could be alkylated under phase transfer conditions to give the corresponding ethers **31a-c**. Upon treatment with acetic anhydride, thionyl chloride, or methanesulfonyl chloride, **27** is transformed into the corresponding acetate **32a**, chloride **32b**, or mesylate **32c**, respectively. Nucleophilic displacement of **32c** occurred selectively at the 5-substituent to provide 5-heteroatom-substituted-methyl derivatives **32d-f**. Hydrolysis of **32f** gave thiol **32g** which was alkylated *in situ* to provide the methylthiomethyl derivative **32h** (Scheme VI).

Scheme VI



27

32a, X = $OCOCH_3$
32b, X = Cl
32c, X = OSO_2CH_3
32d, X = SC(S)OEt
32e, X = $N(Bu)_2$
32f, X = $SC(NH_2)NH_2^+$ $^-SO_2CH_3$
32g, X = SH
32h, X = SCH_3

31a, R = CH_3
31b, R = $CH_2C_6H_5$
31c, R = CH_2CO_2t-Bu

The 2-halothiazoles described above possess herbicide antidote activity for α-chloroacetanilide herbicides [3,15]. Compound **19e** is a commercial safener (flurazole; Screen ®) for 2-chloro-2',6'-diethyl-*N*-(methoxymethyl)acetanilide (alachlor; Lasso ®) in sorghum.

EXPERIMENTAL

Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. The pmr spectra were recorded on a Varian T-60 (60 MHz) and EM-360L (60 MHz) spectrometers. The cmr (proton decoupled) spectra were measured at 25.05 MHz with a JEOL FX-100 spectrometer. The pmr and cmr spectra were recorded in deuteriochloroform unless otherwise noted and are expressed in parts per million (ppm) downfield from tetramethylsilane. The H-F and C-F coupling constants are expressed as $^nJ_{HF}$ and $^nJ_{CF}$ where n is the number of bonds between either hydrogen and fluorine or carbon and fluorine. Mass spectra were determined with a Varian Mat 311A instrument operating in either electron impact (EI) or field ionization (FI) mode. Infrared spectra were recorded on a Perkin Elmer 727B spectrometer. Column chromatography was performed with 60-200 μm silica gel 60 (EM Reagents). Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. Unless otherwise noted, the organic layers were dried over magnesium sulfate and concentration *in vacuo*. The flash distillations were performed using a Kugelrohr distillation apparatus, and the recorded temperature for a specific fraction was the temperature of the Kugelrohr pot. The 3-aminoacrylates **1a-f** and **1h** were prepared according to the literature procedures [6-8,16-18]; **1g** was purchased from Aldrich Chemical Company. The 3-ketoesters **6a** and **6i-o** were either commercially available or prepared by known procedures [19,20].

Ethyl 3-Amino-4-methyl-2-pentenoate (**1i**). (a) Method A.

This compound was prepared by the procedure of Takaya *et al.* [8]. A mixture of 15.8 g (0.10 mole) of **6i**, 8.9 g (0.10 mole) of ethyl urethane, 0.8 g of *p*-toluenesulfonic acid, and 70 ml of toluene was held at reflux for 63 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate, dried, and concentrated. The residue was distilled at reduced pressure (93-96°/1 torr) through a 6 inch Vigreux column. The distillate (10.3 g) was purified by chromatography using petroleum ether (30-75°): ether (19:1 v/v) as eluent to give 9.2 g (40%) of a colorless liquid; n_D^{25} 1.4785; pmr: δ 10.7 (s, NH, 1H), 5.0 (s, HC=C, 1H), 3.5-4.3 (m, OCH_2 and CH, 5H), 1.0-1.3 (m, CH_3, 12H).

A 2.1 g (9.16 mmoles) sample of the above liquid was added to a solution of sodium ethoxide, prepared from 0.7 g of sodium and 30 ml of ethanol, under nitrogen. The solution was held at reflux for 18 hours, cooled, and poured into 200 ml of water. The mixture was extracted with 200 ml of ether. The ether solution was dried and concentrated. The residue was flash distilled (80-100°/1 torr) to give 1.2 g (83%) of **1i** as a colorless liquid; n_D^{25} 1.4919; lit bp 100°/4 torr [21]; pmr (carbon tetrachloride): δ 6.3 (broad s, NH_2, 2H), 4.40 (s, HC=C, 1H), 4.00 (q, CH_2, 2H, J = 7 Hz), 2.26 (h, CH, 1H, J = 7 Hz), 1.1-1.4 (m, CH_3, 9H).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.06; H, 9.66; N, 8.88.

Method B.

Compound **1i** was prepared also form **6i** in 28% yield by the procedure of Prelog and Szpilfogel [7].

General Procedure for Preparation of **3a-h**. Method C.

A mixture of **1** (0.1 mole), **2** (0.11 mole), and chlorobenzene (50 ml) was heated at 80-135° for 2 hours, cooled and triturated with petroleum ether (200 ml). The light yellow precipitate was recrystallized from an appropriate solvent to give pure **3a-h** (Table 1).

Ethyl 2,3-Dihydro-2-oxo-4-(trifluoromethyl)-5-thiazolecarboxylate (**3a**).

A mixture of 17.0 g (0.0928 mole) of **1a** [18], 13.0 g (0.0992 mole) of **2**, and 50 ml of chlorobenzene was heated at 135° for 2 hours, cooled, and triturated with petroleum ether. The light yellow precipitate was recrystallized from hexane-ether to give 12.7 g (55%) of white prisms; see Table 1; ir (chloroform): 2500-3200 (NH), 1720 (OC=O), 1660-1700 cm^{-1} (NC=O); pmr: δ 9.4 (broad s, NH, 1H), 4.32 (q, OCH_2, 2H, J = 7 Hz), 1.32 (t, CH_3, 3H, J = 7 Hz).

Ethyl 2,3-Dihydro-4-ethyl-2-oxo-5-thiazolecarboxylate (**3h**) and Ethyl 4-(α-Chloroethyl)-2,3-dihydro-2-oxo-5-thiazolecarboxylate (**11**).

To a solution of 15.2 g (0.116 mole) of **2** in 25 ml of chlorobenzene at 10° was added dropwise 14.9 g (0.104 mole) of **1h** [7] in such a way that temperature of the reaction mixture did not exceed 20°. After complete addition of **1h**, the reaction mixture was stirred at 60-70° for 1 hour and

cooled. Chlorobenzene was removed *in vacuo*. The residue was dissolved in ether and the ether solution was filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed using petroleum ether: ether (9:1 v/v) as eluent. The first fraction was 0.5 g of an unidentified oil. The second fraction was 4.3 g of solid which was recrystallized from heptane to give 3.0 g (12%) of **11** as a light yellow solid, mp 128-130°; pmr: δ 10.86 (s, NH, 1H), 6.17 (q, CHCl, 1H, J = 7 Hz), 4.37 (q, OCH_2, 2H, J = 7 Hz), 1.83 (d, CH_3, 3H, J = 7 Hz), 1.37 (t, CH_3, 3H, J = 7 Hz); cmr: δ 173.53, 160.88, 144.28, 106.20, 61.96, 47.41, 23.97, 14.21.

Anal. Calcd. for $C_6H_{10}ClNO_3S$: C, 40.76; H, 4.28; N, 5.94; Cl, 15.04. Found: C, 40.71; H, 4.28; N, 5.96; Cl, 14.98.

The third fraction contained 0.6 g of an unidentified oil. The fourth fraction contained 3.0 g of a solid-liquid mixture, which was crystallized from heptane to give 2.0 g of pink solid, mp 115-116°. A portion (0.3 g) of this material was purified by preparative thin-layer chromatography on silica gel using petroleum ether:ether (1:1 v/v) as eluent to give pure **3h**; see Table 1; pmr: δ 11.06 (s, NH, 1H), 4.03 (q, OCH_2, 2H, J = 7 Hz), 3.0 (q, CH_2, 2H, J = 7 Hz), 1.2-1.5 (m, CH_3, 6H).

Genreal Procedure for Preparation of **4** from **3**. (a) Method D. Reaction of **3** with Phosphorus Oxychloride.

A mixture of **3** (0.025 mole) and excess phosphorus oxychloride (30 ml) was held at reflux for 16-60 hours and concentrated *in vacuo*. The residue was stirred with water (100 ml). The aqueous mixture was extracted with ether (2 × 100 ml). The combined ether extracts were dried and concentrated to a residue which was purified by crystallization from an appropriate solvent or by column chromatography.

(b) Method E. Reaction of **3** with Phosphorus Oxychloride and a Catalytic Amount of Dimethylformamide.

A mixture of **3** (0.01-0.05 mole), 30 ml of phosphorus oxychloride and a few drops of dimethylformamide was held at reflux for 30-87 hours and concentrated *in vacuo*. The residue was treated with ice water and extracted with ether (2 × 50 ml). The combined ether extracts were washed with 5% aqueous sodium hydroxide (2 × 50 ml), dried, and concentrated. The residue was purified by recrystallization or flash distillation *in vacuo*.

(c) Method F. Reaction of **3** with Phosphorus Oxychloride and One Equivalent of Pyridine.

A mixture of **3** (0.03 mole), 50 ml of phosphorus oxychloride, and 0.03 mole of pyridine was held at reflux for 18 hours and concentrated *in vacuo*. The residue was poured into water. The organic was taken into ether. The ether extract was dried and concentrated. The residue was purified by flash distillation *in vacuo*.

Ethyl 2-Chloro-4-(trichloromethyl)-5-thiazolecarboxylate (**4d**).

A mixture of 14.5 g (0.05 mole) of **3d**, 10.4 g (0.05 mole) of phosphorus pentachloride, and 100 ml of phosphorus oxychloride was held at reflux for 7 days. Excess phosphorus oxychloride was removed *in vacuo*. The residue was treated with ice water, and the aqueous mixture was extracted with ether. The ether solution was extracted with 10% aqueous sodium hydroxide, dried over calcium sulfate and concentrated *in vacuo*. The residue was chromatographed using ethyl acetate:petroleum ether (19:1 v/v) as eluent to give 2.27 g of solid. Recrystallization from petroleum ether at low temperature gave 2.13 g (14%) of solid, mp 42.5-43.5°, see Table 3; ir (chloroform): 1730, 1700 cm^{-1} [22].

Ethyl 2-Fluoro-4-(trifluoromethyl)-5-thiazolecarboxylate (**5a**).

A mixture of 26 g (0.10 mole) of **4a**, 0.26 g of 18-crown-6, 104 g (1.78 moles) of potassium fluoride, and 150 ml acetonitrile was held at reflux for 87 hours. Gas chromatographic analysis of the reaction mixture indicated that reaction was only 20% complete. Acetonitrile was distilled off and the reaction mixture was heated at 150-200° for 22 hours. The reaction mixture was cooled, diluted with 300 ml of acetonitrile, and filtered. The filtrate was concentrated and the residue (18 g) was distilled through a spinning band column to give 9.2 g (38%) of colorless liquid, bp 95-99°/15 torr, see Table 3; pmr: δ 4.43 (q, OCH_2, 2H, J = 7 Hz), 1.43 (t, CH_3, 3H, J = 7 Hz); cmr: δ 170.2 (d, $^1J_{CF}$ = 291 Hz), 158.1, 140.4 (dq, $^2J_{CF}$ = 39.7 Hz, $^3J_{CF}$ = 14.0 Hz), 127.4 (broad), 119.3 (q, $^1J_{CF}$ = 272.8 Hz), 63.4, 14.0.

Ethyl *p*-Chlorobenzoylacetate (**6l**).

This compound was prepared by the procedure of Thorp and Brunskill [20a]. To a cold (5°) vigorously stirred mixture of 121.9 g (0.936 mole) of ethyl acetoacetate, 314 ml of benzene, 626 ml of water, and 41.3 ml of 33% aqueous sodium hydroxide was added simultaneously in two dropping funnels 177 g (1.01 moles) of *p*-chlorobenzoyl chloride and 189 ml of 33% aqueous sodium hydroxide in 2 hours. The reaction mixture was heated at 35° for 1 hour, cooled, and filtered to give 170 g of solid. Part (150 g) of this solid was added to a mixture of 39.0 g (0.729 mole) of ammonium chloride and 78 ml of concentrated ammonium hydroxide in 780 ml of water. The mixture was stirred at 40-50° for 3 hours and cooled in an ice bath. The precipitate was filtered to give 116 g of solid which was flash distilled at 1 torr to give 76 g (38%) of crude **6l**; pmr: δ 7.2-8.0 (m, aromatic, 4H), 5.56 (s, enol C=CH, 0.3H), 4.0-4.4 (m, OCH_2, 2H), 3.93 (s, keto CH_2, 1.7H), 1.1-1.4 (m, CH_3, 3H).

Ethyl *o*-Chlorobenzoylacetate (**6k**).

Compound **6k** was prepared in 15% yield from ethyl acetoacetate and *o*-chlorobenzoyl chloride by the procedure described for **6l** and isolated as an oil; pmr: δ 7.2-7.5 (m, aromatic, 4H), 5.53 (s, enol C=CH, 0.4H), 4.0-4.4 (m, OCH_2, 2H), 4.0 (s, keto CH_2, 1.6H), 1.1-1.4 (m, CH_3, 3H).

Ethyl *m*-Toluoylacetate (**6n**).

Compound **6n** was prepared in 17% yield from ethyl acetoacetate and *m*-tolyl chloride by the procedure described for **6l** and isolated as an oil after flash distillation (95-98°/0.5 torr); pmr: δ 7.2-7.8 (m, aromatic, 4H), 5.60 (s, enol C=CH, 0.2H), 4.0-4.4 (m, OCH_2, 2H), 3.93 (s, keto CH_2, 1.8H), 2.20 (s, CH_3, 3H), 1.1-1.4 (m, CH_3, 3H).

General Procedure for Preparation of **7**. Method G.

Compound **7a** was prepared from **6a** by the procedure of Walborsky and Baum [23]. Compounds **7h-o** were prepared by chlorination of **6h-o** with sulfuryl chloride according to the procedure of Bankowski and Zadrozna [24] and purified by distillation *in vacuo*.

General Procedure for Preparation of **8a,h-o**. Method H.

An equimolar mixture of **7a,h-o** (0.05-0.1 mole) and thiourea in 40-180 ml of ethanol was held at reflux for 16 hours and concentrated *in vacuo*. The residue was stirred with saturated aqueous sodium bicarbonate. The precipitate was collected and recrystallized from an appropriate solvent to give pure **8a,h-o** (Table 2).

General Procedure for Preparation of **4h-o**. (a) Method I.

To a solution of **8** (0.01-0.04 mole) and 0.2 g of cupric sulfate in 60 ml of concentrated hydrochloric acid was added a solution of 1.5-2.0 equivalents of sodium nitrite in 10-20 ml of water in 15 minutes. In the cases of **8j** and **8m**, chloroform (30 ml) was added to the reaction mixture to dissolve the insoluble amine. The reaction mixture was stirred for 0.25-1 hour and poured into a solution of one equivalent of cuprous chloride in concentrated hydrochloric acid. After vigorous gas evolution subsided, the mixture was extracted wtih ether (2 × 100 ml). The combined ether extracts were washed successively with water, dilute ammonium hydroxide, and brine, dried, and concentrated *in vacuo*. The residue was purified by column chromatography using petroleum ether:ether (97:3 v/v) as eluent to give pure **4** (Table 3).

(b) Method J.

To a cold (−5°) mixture of **8** (0.015-0.04 mole), 80 ml of 85% phosphoric acid, and 40 ml of 70% nitric acid was added 1.1 equivalents of sodium nitrite in 20 minutes. The mixture was stirred at −5° to 0° for 10 minutes and poured into a mixture of one equivalent of cuprous chloride and 40 ml of 6 *N* hydrochloric acid. After gas evolution subsided (30 minutes), the mixture was extracted with ether (2 × 100 ml). The combined

ether extracts were washed successively with 100 ml of water, 100 ml of dilute ammonium hydroxide, and brine, dried, and concentrated. The residue was flash distilled at reduced pressure. The distillate was purified either by crystallization from an appropriate solvent or by column chromatography.

(c) Method K.

To a mixture of 1.5 equivalents of *t*-butyl nitrite, 1.2 equivalents of cupric chloride, and 400 ml of acetonitrile was added 1 equivalent (0.1-0.25 mole) of **8** in 1 hour. The reaction mixture was stirred at room temperature for 2 hours then at 65° for 1 hour and filtered. The filtrate was poured into 400 ml of 6 *N* hydrochloric acid and extracted with ether (2 × 100 ml). The combined ether extracts were dried and concentrated. The residue was flash distilled to give the pure product. No column chromatographic purification of the product was required when this procedure was used.

Ethyl 2-Chloro-4-*i*-propyl-5-thiazolecarboxylate (**3i**) and Ethyl 4-*i*-Propyl-5-thiazolecarboxylate (**14**).

To solution of 2.14 g (0.01 mole) of **8i** and 0.1 g of cupric sulfate in 40 ml of concentrated hydrochloric acid was added dropwise a solution of 1.0 g of sodium nitrite in 10 ml of water in 15 minutes. The reaction mixture was stirred for 5 minutes. Cuprous chloride (1.0 g, 0.01 mole) was added to the above solution. After vigorous gas evolution subsided, the reaction mixture was extracted into ether (2 × 50 ml). The ether extracts were washed successively with water, saturated aqueous sodium bicarbonate, and brine, dried, and concentrated. The residual oil was chromatographed on silica gel. The first fraction, eluted with petroleum ether:ether (99:1 v/v) gave 1.15 g (49%) of **4i** as a colorless liquid, see Table 3; pmr: δ 3.7-4.6 (m, CH and OCH_2, 3H), 1.2-1.5 (m, CH_3, 9H). The second fraction, eluted with petroleum ether:ether (19:1 v/v), gave 0.1 g (5%) of **14** as a colorless liquid; n_D^{25} 1.5040 (lit bp 93-95°/0.8 torr [4b]); pmr: δ 8.4 (s, N=CH, 1H), 3.8-5.6 (m, CH and OCH_2, 3H), 1.2-1.5 (m, CH_3, 9H).

Anal. Calcd. for $C_9H_{13}NO_2S$: C, 54.24; H, 6.57. Found: C, 54.40; H, 6.65.

Ethyl 2-Bromo-4-(trifluoromethyl)-5-thiazolecarboxylate (**9**).

To a mixture of 4.5 g (0.0187 mole) of **8a** [12], 50 m l of 85% phosphoric acid, and 25 ml of 70% nitric acid at −10° was added a solution of 4.0 g (0.0579 mole) of sodium nitrite in 20 ml of water in 30 minutes. The mixture was stirred at −10° to −5° for 10 minutes and poured into a solution of 2.70 g (0.0187 mole) of cuprous bromide in 20 ml of hydrobromic acid. After the vigorous gas evolution subsided, the reaction mixture was diluted with water. The solid suspension was filtered and air-dried to give 4.8 g of solid which was purified by column chromatography using petroleum ether:ether (4:1 v/v) as eluent to give 2.9 g (51%) of white needles; see Table 3; pmr: δ 4.40 (q, CH_2, 2H, J = 7 Hz), 1.37 (t, CH_3, 3H, J = 7 Hz).

Ethyl 2-Iodo-4-(trifluoromethyl)-5-thiazolecarboxylate (**10**).

To a cold mixture of 4.0 g (0.0166 mole) of **8a**, 30 ml of 85% phosphoric acid, and 30 ml of 70% nitric acid was added a solution of 1.26 g (0.0166 mole) of sodium nitrite in 10 ml of water in 10 minutes. The reaction mixture was stirred for 10 minutes and poured into a solution of 10 g of potassium iodide in 100 ml of water. The mixture was stirred overnight and extracted with ether (100 ml). The ether extract was washed with aqueous sodium thiosulfate, dried and concentrated. The residual oil (3.7 g) was purified by column chromatography using petroleum ether:ether (19:1 v/v) as eluent to give 1.5 g (26%) of a light yellow solid, see Table 3; pmr: δ 4.33 (q, CH_2, 2H, J = 7 Hz), 1.33 (t, CH_3, 3H, J = 7 Hz).

Isolation of Diethyl 3,5-Bis(trifluoromethyl)-2*H*-1,4-thiazine-2,6-dicarboxylate (**12**) and Diethyl 2,5-Bis(trifluoromethyl)-3,4-pyrroledicarboxylate (**13**).

To a cold (−5°) solution of 120 g (0.921 mole) of chlorocarbonylsulfenyl chloride in 100 ml of chlorobenzene was added 169 g (0.921 mole) of **1a** in 30 minutes. The reaction mixture was stirred at 70° for 17 hours, then at 80° for 2 hours and finally at 90° for 2 hours. The reaction mixture was cooled to room temperature and triturated with 200 ml of hexane. The insoluble solid was collected and washed with water to give 154 g (69%) of **3a**, mp 121-123°.

The hexane filtrate was concentrated *in vacuo* and the residue was stirred with ether (100 ml) and filtered to remove 1.3 g of sulfur. The ether filtrate was concentrated *in vacuo* and the residue was tirturated with hexane and filtered to give additional 5.1 g (1.5%) of **3a**. The hexane filtrate was concentrated *in vacuo* and the residue was flash distilled (1 torr, 110°) to give 36 g of oil which was purified by column chromatography using petroleum ether:ethyl acetate (19:1 v/v) as eluent. After removal of an earlier fraction (3.2 g), the second fraction was 5.9 g of oil which was *ca.* 86-96% pure **12**. The third fraction was 18.3 g (10%) of **12** as a yellow oil; n_D^{25} 1.4396; pmr (carbon tetrachloride): δ 4.55 (s, CH, 1H), 4.0-4.5 (m, CH_2, 4H), 1.1-1.6 (m, CH_3, 6H); cmr: δ 163.9, 161.2, 138.4 (q, $^2J_{CF}$ = 38.3 Hz), 134.5 (q, $^2J_{CF}$ = 37.5 Hz), 124.7, 120.1 (q, $^1J_{CF}$ = 273.5 Hz), 118.9 (q, $^1J_{CF}$ = 277.2 Hz), 63.8, 34.8, 13.8; ir (film): 1740 cm^{-1}; ms, m/e (relative intensity): 379 (M^+, 4), 307 (65), 306 (62), 279 (42), 278 (16), 259 (17), 234 (96), 69 (100).

Anal. Calcd. for $C_{12}H_{11}F_6NO_4S$: C, 38.00; H, 2.92; N, 3.69. Found: C, 38.50; H, 3.01; N, 3.72.

The yellow oil obtained above was found to be identical to the product derived from the reaction of **1a** with sulfur dichloride [6]. The cmr spectrum indicated that the above described yellow oil contained a minor impurity with chemical shifts identical to **13** obtained by the following procedure.

To 3.79 g (0.01 mole) of **12** was added 1.01 g (0.01 mole) of triethylamine. After the initial exotherm subsided, the reaction mixture was diluted with 20 ml of toluene, stirred for 30 minutes, and filtered. The filtrate was concentrated *in vacuo*. The residue was flash distilled (1 torr, 130°) to give 3.1 g of oil which was chromatographed on silica gel using petroleum ether:ethyl acetate (19:1 δ/δ) as eluent to give 2.3 g of oil. Crystallization from petroleum ether at low temperature gave 2.0 g (57%) of **13**, mp 55-57°; pmr: δ 10.67 (broad s, NH, 1H), 4.37 (q, CH_2, 4H, J = 7 Hz), 1.30 (t, CH_3, 6H, J = 7 Hz); cmr: δ 162.3, 122.5 (q, $^2J_{CF}$ = 41.2 Hz), 119.2 (q, $^1J_{CF}$ = 269.1 Hz), 118.2 (q, $^3J_{CF}$ = 1.2 Hz), 62.2, 13.8.

Anal. Calcd. for $C_{12}H_{11}F_6NO_4$: C, 41.51; H, 3.19; N, 4.03. Found: C, 41.51; H, 3.19; N, 4.01.

2-Chloro-4-(trifluoromethyl)-5-thiazolecarboxylic Acid (**15**).

A mixture of 116 g (0.45 mole) of **4a**, 8 g (0.45 mole) of sodium hydroxide, 200 ml of water, and 400 ml of tetrahydrofuran was stirred at room temperature for 16 hours and made acidic with 50 ml of concentrated hydrochloric acid. The reaction mixture was extracted twice with 200 ml of ether. The combined ether extracts were dried and concentrated *in vacuo*. The residual solid was recrystallized from hexane-benzene to give 76 g (73%) of white solid, mp 131-135°; ir (chloroform): 3400, 3200-2600, 1680 cm^{-1}.

Anal. Calcd. for $C_5HClF_3NO_2S$: C, 25.92; H, 0.47; Cl, 15.31; N, 6.05. Found: C, 26.07; H, 0.52; Cl, 15.64; N, 6.10.

2-Chloro-4-(trifluoromethyl)-5-thiazolecarbonyl Chloride (**17**).

A mixture of 36.0 g (0.155 mole) of **15** and 171 g (1.437 mole) of thionyl chloride was held at reflux for 6 hours and concentrated *in vacuo* to give 38.1 g (98%) of an oil.

Anal. Calcd. for $C_5Cl_2F_3NOS$: C, 24.02; N, 5.60. Found: C, 24.00; N, 5.61.

2-Chloro-4-methyl-5-thiazolecarbonyl Chloride (**18**).

The crude acid chloride was prepared from **16** [2b] and thionyl chloride by the procedure described above.

General Procedure for Preparation of **19**. (a) Method L. Reaction of **17** with Alcohols.

A mixture of 5.0 g (0.02 mole) of **17** and an excess of an appropriate alcohol was held at reflux or at 130-140° for 6 hours and concentrated. The residue was either crystallized from an appropriate solvent or flash distilled under reduced pressure.

(b) Method M. Reaction of **17** with Phenols.

An equimolar mixture of **17** and an appropriate phenol was held at 130-140° for 6 hours, cooled, and diluted with ether. The ether solution was washed with 20% aqueous sodium hydroxide, dried, and concentrated *in vacuo*. The residue was flash distilled at reduced pressure to give the pure ester.

The esters prepared from **17** are summarized in Table 4.

General Procedures for Preparation of **22**. Method N.

A mixture of **18** and an excess of an appropriate alcohol was held at reflux for 4 hours and concentrated *in vacuo*. The residue, which contained both **20** and **22**, was crystallized from hexane to give a solid. Recrystallization from an appropriate solvent provided pure **22** (Table 4).

Pentyl 2-Chloro-4-methyl-5-thiazolecarboxylate (**20k**).

To a mixture of 1.20 g (0.14 mole) of pentanol and 1.02 g (0.01 mole) of triethylamine cooled in an ice bath was added a solution of 1.64 g (0.01 mole) of **18** in 10 ml of ether. The reaction mixture was stirred for 2 hours and filtered. The filtrate was washed with saturated aqueous sodium bicarbonate, dried, and concentrated. The residue was flash distilled (110°/0.5 torr) to give 2.2 g (90%) of a colorless liquid, see Table 4; pmr: δ 4.33 (t, OCH_2, 3H, J = 7 Hz), 2.67 (s, CH_3, 3H), 0.8-2.0 (m, CH_2 and CH_3, 9H).

Ethyl 2-Ethoxy-4-(trifluoromethyl)-5-thiazolecarboxylate (**25a**).

To a cold (0°) solution of sodium ethoxide, prepared from 0.46 g (0.02 mole) of sodium and 40 ml of dry ethanol, was added 5.2 g (0.02 mole) of **4a**. The reaction mixture was heated to 80° and then poured into ice water. The precipitate was collected to give 4.2 g (78%) of a white solid, mp 30.5-31.5°; pmr: δ 4.1-4.7 (m, CH_2, 4H), 1.2-1.7 (m, CH_3, 6H).

Anal. Calcd. for $C_9H_{10}F_3NO_3S$: C, 40.15; H, 3.74; N, 5.20. Found: C, 40.11; H, 3.75; N, 5.19.

Ethyl 2-Phenoxy-4-(trifluoromethyl)-5-thiazolecarboxylate (**25b**).

A mixture of 5.2 g (0.02 mole) of **4a**, 1.88 g (0.02 mole) of phenol, 2.76 g (0.02 mole) of potassium carbonate and 50 ml of acetone was held at reflux for 3 days and concentrated *in vacuo*. The residue was treated with water and extracted with ether. The ether extract was dried and concentrated *in vacuo*. The residual solid was heated in hexane, cooled, and filtered to give 4.8 g (78%) of solid, mp 52-54°; pmr: δ 7.2-7.5 (m, aromatic, 5H), 4.43 (q, CH_2, 2H, J = 7 Hz), 1.37 (t, CH_3, 3H, J = 7 Hz).

Anal. Calcd. for $C_{13}H_{10}F_3NO_2S$: C, 49.21; H, 3.18; N, 4.41. Found: C, 49.27; H, 3.19; N, 4.38.

Ethyl 2-Ethylthio-4-(trifluoromethyl)-5-thiazolecarboxylate (**25c**).

To a sodium ethoxide solution, prepared from 0.6 g (0.026 mole) of sodium and 23 ml of dry ethanol, was added a solution of 1.8 g (0.029 mole) of ethanethiol in 10 ml of ethanol. To the above solution was added 6.5 g (0.025 mole) of **4a**. The reaction mixture was stirred for 20 minutes and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in ether. The ether solution was washed with 5% aqueous sodium hydroxide, dried, and concentrated to 6.55 g of oil which was crystallized from petroleum ether at low temperature to give 6.0 g (84%) of white solid, mp 52.5-53.5°; pmr: δ 4.37 (q, OCH_2, 2H, J = 7 Hz), 3.26 (q, SCH_2, 2H, J = 7 Hz), 1.2-1.7 (m, CH_3, 6H); ir (chloroform): 1720 cm^{-1}.

Anal. Calcd. for $C_9H_{10}F_3NO_2S_2$: C, 37.89; H, 3.53; N, 4.91; S, 22.48. Found: C, 37.88; H, 3.54; N, 4.90; S, 22.47.

Ethyl 2-Ethoxy-4-(triethoxymethyl)-5-thiazolecarboxylate (**26**).

To a warm (55-65°) solution of sodium ethoxide, prepared from 2.0 g (0.0869 mole) of sodium and ethanol, was added 5.2 g (0.02 mole) of **4a**. The reaction mixture was stirred for 4 hours and concentrated *in vacuo*. The residue was treated with water and extracted with ether. The ether extract was dried and concentrated. The residue was flash distilled (115°/0.1 torr) to give 2.2 g (32%) of oil; n_D^{25} 1.4776; pmr: δ 4.1-4.7 (m, CH_2, 4H), 3.55 (q, CH_2, 6H, J = 7 Hz), 1.0-1.6 (m, CH_3, 15H).

Anal. Calcd. for $C_{15}H_{25}NO_6S$: C, 51.86; H, 7.25; N, 4.03. Found: C, 51.36; H, 7.03; N, 4.57.

2-Chloro-4-(trifluoromethyl)-5-thiazolemethanol (**27**).

To a solution of 25.9 g (0.1 mole) of **4a** in 100 ml of ethanol was added 3.78 g (0.1 mole) of sodium borohydride. The reaction was exothermic causing the reaction temperature to rise to 50° in 5 minutes. The reaction mixture was cooled to 28° and stirred at 28° for 30 minutes before being poured into 300 ml of ice water. The aqueous mixture was extracted twice with 150 ml of ether. The combined ether extracts were dried over calcium sulfate and concentrated *in vacuo*. The residual oil (20.5 g) was crystallized from hexane at low temperature to give 18.3 g (84%) of solid, mp 39-45°; pmr: δ 5.0 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 3.4 (broad s, OH, 1H); ir (chloroform): 3600, 3400 cm^{-1}.

Anal. Calcd. for $C_5H_3ClF_3NOS$: C, 27.60; H, 1.39; N, 6.44; Cl, 16.29. Found: C, 27.61; H, 1.41; N, 6.44; Cl, 16.25.

2-Chloro-4-*i*-propyl-5-thiazolemethanol (**28**).

To a mixture of 8.0 g (0.034 mole) of **4i** and 20 ml of ethanol was added 1.3 g (0.034 mole) of sodium borohydride in 10 minutes. The reaction mixture was stirred for 30 minutes and concentrated *in vacuo*. The residue was chromatographed on silica gel using petroleum ether:ether (9:1 v/v) as eluent. The first fraction was 2.2 g of recovered **4i**. The second fraction (3.4 g) was flash distilled (95°/0.5 torr) to give 2.7 g (40%) of a colorless liquid; n_D^{25} 1.5425; pmr: δ 4.73 (s, CH_2, 2H), 2.8-3.4 (m, OH and CH, 2H), 1.3 (d, CH_3, 6H, J = 7 Hz).

Anal. Calcd. for $C_7H_{10}ClNOS$: C, 43.86; H, 5.63; N, 7.31; Cl, 18.50. Found: C, 43.86; H, 5.60; N, 7.28; Cl, 18.48.

2-Chloro-4-*t*-butyl-5-thiazolemethanol (**29**).

To a cold (5°) mixture of 24.8 g (0.1 mole) of **4j** and 60 ml of ethanol was added portionwise 3.79 g (0.1 mole) of sodium borohydride in 30 minutes. The reaction temperature rose spontaneously to 35°. The reaction mixture was stirred for 2 hours and concentrated *in vacuo* to give a residue which was treated with water and extracted with ether. The ether extracts were dried and concentrated to give 22.9 g of oil which was chromatographed on silica gel using petroleum ether:ether (19:1 v/v) as eluent. The first fraction was 13.0 g of recovered **4j**. The second fraction was 6.6 g of an oil which was flash distilled (102°/0.7 torr) to give 6.4 g (31%) of oil; n_D^{25} 1.5436; pmr: δ 4.87 (broad s, CH_2, 2H), 2.80 (broad s, OH, 1H), 1.33 (s, CH_3, 9H).

Anal. Calcd. for $C_8H_{12}ClNOS$: C, 46.70; H, 5.88; N, 6.81; Cl, 17.24. Found: C, 46.68; H, 5.89; N, 6.81; Cl, 17.23.

Ethyl 4-(Trifluoromethyl)-5-thiazolecarboxylate (**30**).

To a cold (10°) solution of 2.6 g (0.01 mole) of **4a** in 20 ml of dimethylformamide was added 0.58 g (0.015 mole) of sodium borohydride. The reaction temperature rose spontaneously to 45°. The reaction mixture was cooled to 0° and stirred at 0° for 20 minutes before being poured into water. The aqueous mixture was extracted with petroleum ether (4 × 50 ml). The combined petroleum ether extracts were dried and concentrated *in vacuo*. The residue (1.6 g) was chromatographed on silica gel using petroleum ether:ether (19:1 v/v) as eluent. The first fraction was 1.21 g of oil which was crystallized from petroleum ether at low temperature to give 0.75 g (31%) of white needles, mp 38.5-39.5; pmr: δ 8.9 (s, N=CH, 1H), 4.40 (q, CH_2, 2H, J = 7 Hz), 1.40 (t, CH_3, 2H, J = 7 Hz); ir (chloroform): 1700 cm^{-1}.

Anal. Calcd. for $C_7H_6F_3NO_2S$: C, 37.33; H, 2.69; N, 6.22. Found: C, 37.33; H, 2.70; N, 6.19.

2-Chloro-5-(methoxymethyl)-4-(trifluoromethyl)thiazole (**31a**).

To a well stirred mixture of 4.32 g (0.02 mole) of **27**, 38.8 g (0.273 mole) of methyl iodide, 0.1 g of Aliquat 336 [25], and 25 ml of hexane was added 13 ml of 50% aqueous sodium hydroxide and 13 ml of water. The reaction mixture was held at reflux for 3 hours. The hexane layer was separated, dried, and concentrated *in vacuo* to give a residue (5.4 g) which was flash distilled (80°/2 torr) to give 4.16 g (68%) of a colorless liquid; n_D^{25} 1.4694; pmr: δ 4.76 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 3.5 (s, CH_3, 3H).

Anal. Calcd. for $C_6H_5ClF_3NOS$: C, 30.98; H, 2.27; N, 6.02. Found: C, 31.11; H, 2.18; N, 6.05.

2-Chloro-5-[(benzyloxy)methyl]-4-(trifluoromethyl)thiazole (**31b**).

A mixture of 4.32 g (0.02 mole) of **27**, 14.1 g (0.0825 mole) of benzyl bromide, 0.1 g of Aliquat 336, 25 ml of hexane, 15 ml of 50% aqueous sodium hydroxide and 15 ml of water was held at reflux for 30 minutes. The hexane layer was separated, dried, and concentrated *in vacuo* to a residue (6.8 g) which was flash distilled (120-130°/2 torr) to give 5.0 g (81%) of a colorless liquid; n_D^{25} 1.5215; pmr: δ 7.3 (s, aromatic, 5H), 4.77 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 4.60 (s, CH_2Ar, 3H).

Anal. Calcd. for $C_{12}H_9ClF_3NOS$: C, 46.83; H, 2.95; N, 4.35. Found: C, 46.88; H, 2.97; N, 4.56.

t-Butyl [2-Chloro-5-(trifluoromethyl)-5-thiazolyl]methoxyacetate (**31c**).

A mixture of 4.32 g (0.02 mole) of **27**, 0.1 g of Aliquat 336, 3.9 g (0.02 mole) of *t*-butyl bromoacetate, 10 g (0.25 mole) of sodium hydroxide, 24 ml of water, and 50 ml of hexane was held at reflux for 1 hour and filtered. The hexane layer was separated, dried, and concentrated *in vacuo* to a residue (1.6 g) which was chromatographed on silica gel using petroleum ether:ether (50:1 v/v) as eluent to give 1.1 g (16.5%) of an oil; n_D^{25} 1.4607; pmr: δ 4.90 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 4.03 (s, CH_2, 2H), 1.33 (s, CH_3, 9H); ir (film): 1720 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}ClF_3NO_3S$: C, 39.82; H, 3.95; N, 4.22; Cl, 10.69. Found: C, 39.91; H, 4.00; N, 4.20; Cl, 10.64.

[2-Chloro-4-(trifluoromethyl)-5-thiazolyl]methyl Acetate (**32a**).

To a solution of 6.53 g (0.03 mole) of **27**, 5.72 g (0.056 mole) of acetic anhydride in 20 ml of ether was added 2.7 g (0.034 mole) of pyridine. The reaction mixture was stirred for 2 hours, washed successively with water, saturated aqueous sodium bicarbonate, and diluted hydrochloric acid, then was dried and concentrated *in vacuo*. The residue was flash distilled (80-90°/1.5 torr) to give 6.2 g (86%) of a colorless liquid; n_D^{25} 1.4631; pmr: δ 5.3 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 2.10 (s, CH_3, 3H); ir (film): 1740 cm^{-1}.

Anal. Calcd. for $C_7H_5ClF_3NO_2S$: C, 32.38; H, 1.97; N, 5.40. Found: C, 32.48; H, 1.97; N, 5.42.

2-Chloro-5-chloromethyl-4-(trifluoromethyl)thiazole (**32b**).

A mixture of 6.73 g (0.031 mole) of **27** and 15 ml of thionyl chloride was heated on a steam bath for 5 minutes. Excess thionyl chloride was removed *in vacuo* and the residue was flash distilled to give 6.9 g of a yellow oil. This material was chromatographed on silica gel using petroleum ether:ether (19:1 v/v) as eluent to give 5.9 g of oil. Distillation at 6 torr gave 5.28 g (72%) of a colorless liquid; bp 80-82°; n_D^{25} 1.4886; pmr; δ 4.8 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz).

Anal. Calcd. for $C_5H_2Cl_2F_3NS$: C, 25.44; H, 0.86; N, 5.93. Found: C, 25.50; H, 0.89; N, 5.92.

[2-Chloro-4-(trifluoromethyl)-5-thiazolyl]methyl Methanesulfonate (**32c**).

To a cold (0°) solution of 34.7 g (0.161 mole) of **27** in 150 ml of toluene was added 18.2 g (0.18 mole) of triethylamine in 30 minutes. To the above mixture was added 20.5 g (0.18 mole) of methanesulfonyl chloride. The reaction mixture was stirred at room temperature for 2 hours and was allowed to stand in the refrigerator for 4 days. The insoluble salt was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and the ether solution was washed with water, dried, and concentrated *in vacuo* to give 43.8 g (92%) of crude product which was used without further purification.

S-[2-Chloro-4-(trifluoromethyl)-5-thiazolyl]methyl *O*-Ethyl Carbonodithioate (**32d**).

To a solution of 5.5 g (0.019 mole) of **32c** in 50 ml of acetone was added 2.0 g (0.017 mole) of potassium xanthogenate. The reaction mixture was stirred for 2 hours at room temperature and filtered. The acetone filtrate was concentrated *in vacuo* to give 6.9 g of yellow oil which was chromatographed on silica gel using petroleum ether:ether (9:1 v/v) as eluent. The earlier fraction was 4.1 g (70%) of a yellow oil, n_D^{25} 1.5497; pmr: δ 4.5-4.9 (m, OCH_2 and SCH_2, 4H), 1.43 (t, CH_3, 3H, J = 7 Hz).

Anal. Calcd. for $C_8H_7ClF_3NOS_3$: C, 29.86; H, 2.19; N, 4.35; S, 29.89. Found: C, 29.86; H, 2.19; N, 4.34; S, 29.94.

N,N-Dibutyl-2-chloro-4-(trifluoromethyl)-5-thiazolemethanamine (**32e**).

To a cold (−65°) solution of 6.0 g (0.02 mole) of **32c** in 20 ml of ether was added a solution of 2.57 g (0.02 mole) of dibutylamine in 10 ml of ether in 10 minutes. The reaction mixture was stirred at room temperature for 18 hours and washed with saturated aqueous sodium bicarbonate, dried, and concentrated *in vacuo*. The residue (6.3 g) was chromatographed on silica gel using petroleum ether:ether (30:1 v/v) as eluent. The first fraction was 2.7 g (41%) of an oil; n_D^{25} 1.4687; pmr: δ 3.8 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 2.53 (s, CH_2, 4H, J = 7 Hz), 0.9-1.8 (m, CH_2 and CH_3, 14H).

Anal. Calcd. for $C_{13}H_{20}ClF_3N_2S$: C, 47.48; H, 6.13; N, 8.52. Found: C, 47.58; H, 6.15; N, 8.48.

S-[2-Chloro-4-(trifluoromethyl)-5-thiazolyl]methyl Carbaminidothioate Methanesulfonic Acid Salt (**32f**).

A mixture of 6.0 g (0.02 mole) of **32c**, 1.36 g (0.018 mole) of thiourea, and 50 ml of ethanol was held at 75° for 10 minutes and concentrated *in vacuo*. The residue was triturated with ether and filtered to give 6.6 g (84%) of white powder, mp 164-166°.

Anal. Calcd. for $C_7H_9ClF_3N_3O_2S_3$: C, 22.61; H, 2.44; N, 11.30. Found: C, 22.73; H, 2.44; N, 11.30.

2-Chloro-4-(trifluoromethyl)-5-thiazolemethanethiol (**32g**).

A mixture of 7.42 g (0.02 mole) of **32c**, 2.4 g (0.06 mole) of sodium hydroxide, 0.1 g of benzyltriethylammonium chloride, 24 ml of hexane, and 24 ml of water was stirred for 3.5 hours and filtered. The filtrate was extracted with ether. The ether extracts were dried and concentrated *in vacuo* to give 1.8 g of oil which was flash distilled (95°/2 torr) to give 0.6 g of **32g** as an oil; n_D^{25} 1.5173. The aqueous layer was neutralized with concentrated hydrochloric acid and extracted with ether. The ether extracts were dried and concentrated *in vacuo* to give 2.1 g of an oil. The oil was flash distilled at 2 torr to give two fractions. The second fraction (bp 90°) was an additional 0.9 g of **32g**. The first fraction (0.7 g, bp 50-70°) was chromatographed on silica gel using petroleum ether:ethyl acetate (9:1 v/v) as eluent to give 0.45 g of **32g**; n_D^{25} 1.5169; pmr: δ 3.93 (dq, CH_2, 2H, J = 8 Hz, $^5J_{HF}$ = 1.5 Hz), 2.20 (t, SH, 1H, J = 8 Hz). Total yield of **32g** was 41%.

Anal. Calcd. for $C_5H_3ClF_3NS_2$: C, 25.70; H, 1.29; N, 6.01. Found: C, 25.68; H, 1.32; N, 5.95.

2-Chloro-5-[(methylthio)methyl]-4-(trifluoromethyl)thiazole (**32h**).

A mixture of 3.72 g (0.01 mole) of **32f**, 2.0 g of calcium carbonate, 1 g of sodium metabisulfite, 0.1 g of benzyltriethylammonium chloride, 5.2 g (0.03 mole) of methyl iodide, 50 ml of water, and 25 ml of methylene chloride was stirred for 13 hours and filtered. The methylene chloride solution was dried and concentrated *in vacuo* to give 2.4 g of an oil which was flash distilled (90°/2 torr) to give 2.1 g of distillate. This material was chromatographed on silica gel using petroleum ether:ethyl acetate (30:1 v/v) as eluent. The first fraction was 1.77 g (71%) of a colorless oil; n_D^{25} 1.5115; pmr: δ 3.93 (q, CH_2, 2H, $^5J_{HF}$ = 1.5 Hz), 2.16 (s, CH_3, 3H).

Anal. Calcd. for $C_6H_5ClF_3NS_2$: C, 29.09; H, 2.03; N, 5.66. Found: C, 28.85; H, 1.69; N, 5.61.

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