Reactions of 4-Chloroacetoacetic Esters with Thioureas (1)

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Several heterocyclic acetic acids and esters were synthesized by allowing the appropriate thiourea, ethylenethiourea or trimethylenethiourea to react with 4-chloroacetoacetic esters, followed by acid hydrolysis to the hydrochlorides of the free acids. Both esters and acids of 2-aminothiazole-4-acetic acid, 5,6-dihydroimidazo[2,1-*b*]thiazole-3-acetic acid and 6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-3-acetic acid were obtained.

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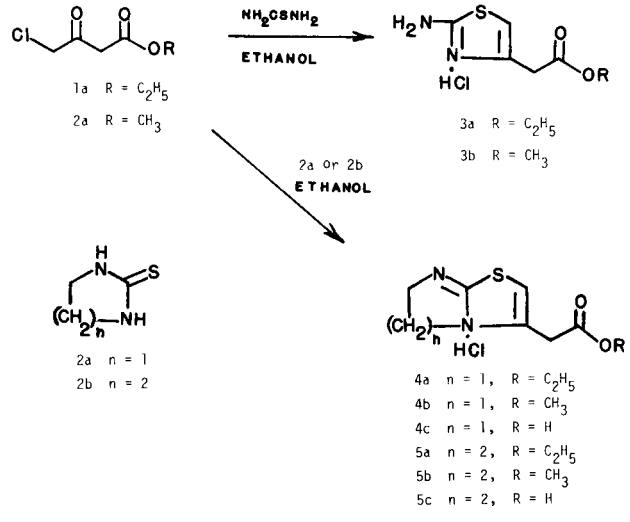
In previous publications (3-6), we demonstrated that ethyl 4-chloroacetoacetate (**1a**), a γ-haloketo ester, could be successfully reacted with "thiocarbamate" containing species such as thiosemicarbazides, thiosemicarbazones, thiopyrimidines, and thiotriazoles to yield ethyl acetate substituted thiazoles. A number of these thiazoleacetic acid esters were hydrolyzed to the corresponding acids. However, decarboxylation occurred quite readily in some instances (6-11).

SCHEME I



Esters of thiazole-4-acetic acids are formed by condensation of γ-haloacetoacetic esters with acyclic and cyclic thioureas, and hydrolysis of these esters leads to acids of varying stability, depending on the substituents present. The general results are discussed by Elderfield (8). In connection with another problem, we needed samples of certain thiazole-4-acetic acid derivatives, and therefore reexamined this reaction, using both ester **1a** and its methyl analog, methyl 4-chloroacetoacetate (**1b**) with acyclic and cyclic thioureas. Following a modified procedure of Campaigne and Rogers (12), ester **1b** was prepared by Grignard reaction of methyl chloroacetate, as described in the experimental procedure.

Condensations of esters **1a** and **1b** with thiourea in absolute ethanol gave the hydrochlorides of the appropriate 2-aminothiazole-4-acetates (**3a** and **b**) (Scheme 1). Heating ethylenethiourea (imidazolidine-2-thiol, **2a**) with esters **1a** and **1b** in ethanol generated the hydrochlorides of ethyl and methyl 5,6-dihydroimidazo-[2,1-*b*]thiazole-3-acetate, (**4a** and **b**), while the hydrochlorides of ethyl (**5a**) and methyl (**5b**) 6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-4-acetate were formed after reacting trimethylenethiourea (3,4,5,6-tetrahydropyrimidine-2-thiol, **2b**) with esters **1a** and **1b** (Scheme 1). Typical carbonyl absorptions between 1730 and 1720 cm^{-1} were observed in the ir (potassium bromide) of the hydrochlorides. Other spectral data was in agreement with the assigned structures (Tables 1 and 2).

Free bases of hydrochlorides **3a, 3b, 4a, 4b,** and **5a, 5b** were obtained after neutralizing with sodium bicarbonate and melting points of the recrystallized free bases are recorded in Table 1. The free bases of **3a** (m.p. 93°, lit. m.p. 92°) (13a,b) and **4a** (m.p. 129°, lit. m.p. 128°) (14) were previously prepared. Hydrolysis of compounds **4a** and **5a** in concentrated hydrochloric acid yielded the acids 4,5-dihydroimidazo[2,1-*b*]thiazole-3-acetic acid hydrochloride (**4c**) and 6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-5-acetic acid hydrochloride (**5c**). Spectral data of acids **4c** and **5c** are given in Tables 1 and 2. 2-Aminothiazole-4-acetic acid has previously been reported (15).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137-B infrared spectrometer using potassium bromide pellets unless stated otherwise. With trifluoroacetic acid as the solvent or other solvents as noted, and tetramethylsilane (TMS) as an internal standard, nuclear magnetic resonance spectra were determined on a Varian Model T60 spectrometer. Elemental analyses were performed at Midwest Micro Labs Inc., Indianapolis, Indiana. At 70 eV, a Varian Mat CH-7 spectrometer recorded the mass spectrum. Usually based on the first crystallization, the % yields are not considered optimum. Free bases were obtained by neutralizing hydrochlorides at room temperature with 10% sodium bicarbonate.

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Table 1

Thiazole Acetic Ester Derivatives

Compound No.	% Yield	M.p. (HCl)	M.p. (freebase)	Formula	Calcd. % C	H	Cl	N	S	Found % C	H	Cl	N	S
3a (a)	61	157°	93° (d)	$C_7H_{11}ClN_2O_2S$	37.74	4.99	15.93	12.58	14.38	37.68	5.11	16.17	12.51	14.13
3b (a)	83	174°	120°	$C_6H_9ClN_2O_2S$	34.51	4.36	16.99	13.43	15.37	34.75	4.20	17.14	13.25	15.38
4a (b)	88	211°	129° (e)	$C_8H_{12}ClN_2O_2S$	43.45	5.28	14.26	11.26	12.87	43.23	5.25	14.36	11.46	13.08
4b (b)	78	196°	182°	$C_8H_{12}ClN_2O_2S$	40.92	4.74	15.11	11.94	13.64	41.17	4.57	15.10	11.87	13.86
5a (c)	88	196°	118°	$C_{10}H_{15}ClN_2O_2S$	45.70	5.77	13.50	10.66	12.19	45.24	5.73	13.83	10.85	12.39
5b (c)	50	199°	180°	$C_9H_{13}ClN_2O_2S$	43.45	5.28	14.26	11.26	12.87	43.35	5.31	14.50	11.15	12.72

(a) Prepared by Method A. (c) Prepared by Method B. (c) Prepared by Method C. (d) J. Hamel, *Bull. Soc. Chim. France*, **29**, 390 (1921). (e) R. B. Blackshire and C. J. Sharpe, *J. Chem. Soc.*, 3603 (1971).

Table 2

Spectral Data

Compound No.	Ir (potassium bromide) cm^{-1} NH⁺	C=O	Pmr (Trifluoroacetic Acid) Chemical Shift, ppm (δ)
3a	3200-2500	1725	1.42 (t, 3H, CH_3) 3.95 (s, 2H, CH_2CO_2), 4.45 (q, 2H, OCH_2), 6.70 (s, 1H, C-5 thiazole proton)
3b	3200-2600	1725	3.85-4.05 (m, 5H, CH_2CO_2, OCH_3), 6.85 (s, 1H, C-5 thiazole proton)
4a	3200-2700	1725	1.42 (t, 3H, CH_3), 3.90 (s, 2H, CH_2CO), 4.20-4.75 (m, 6H, NCH_2CH_2N, OCH_2), 6.70 (s, 1H, C-2 thiazole proton)
4b	3200-2700	1725	3.90-4.10 (m, 5H, CH_2CO_2, CH_3), 4.60 (broad s, 4H, NCH_2CH_2N), 6.70 (s, 1H, C-2 thiazole proton)
5a	3200-2600	1725	1.45 (t, 3H, CH_3), 2.20-2.55 (m, 2H, CH_2), 3.65-4.70 (m, 8H, NCH_2, CH_2N, CH_2CO_2, OCH_2), 6.75 (s, 1H, C-2 thiazole proton)
5b	3200-2600	1725	2.25-2.55 (m, 2H, CH_2), 3.55-4.30 (m, 9H, CH_2N, CH_2N, CH_2CO_2, OCH_3), 6.70 (s, 1H, C-2 thiazole proton).

Methyl 4-Chloroacetoacetate (**1b**).

Ester **1b** (16,17) was prepared by a modification of the method of Campaigne and Rogers (12); the modification consisted of substitution of tetrahydrofuran for ether and the inverse mode of addition while preparing the Grignard reagent.

To a stirred solution of methyl chloroacetate (325 g., 3.0 moles) in tetrahydrofuran (500 ml.) in a three necked, round bottom flask equipped with a condenser with nitrogen inlet, a stirrer, and funnel, was added magnesium (24.3 g., 1.0 mole) in 2.4 g. portions at 20 minute intervals (total time was 7 hours). The reaction was kept at 30-35°. After standing overnight, the reaction was refluxed for two hours. The reaction mixture was poured into one liter of ice water and sufficient cold, 50% sulfuric acid was added to give *p*H 2-3. The phases were separated and the aqueous phase was extracted with ether. The combined organic phases were washed successively with water, saturated sodium bicarbonate solution, saturated sodium chloride solution, then dried over magnesium sulfate. The ether solution was concentrated under reduced pressure to give 173 g. of light orange liquid. Distillation through an 80 cm column of glass helixes gave 97.0 g. of methyl chloroacetate, b.p. 27° (9 torr), and 55.0 g. of **1b** as a colorless liquid, b.p. 65-68° (2.5-3.0 torr). Also, distilling the residue through a Bantamware Vigreux column yielded 2.7 g. of **1b** (b.p. 53-85°; 0.7 torr). The material balance was 97 g. (0.90 mole; 30% recovery) of methyl chloroacetate and 62.0 g. (0.41 mole; 41%) of **1b**; ir (mull): 3000-2800 (alkyl), 1730-1720 (C=O), 1450, 1370 cm^{-1}; pmr (deuteriochloroform): δ 3.75 (s, 2H, $COCH_2CO_2$), 3.85 (s, 3H, OCH_3), 4.35 (s, 2H, $ClCH_2CO$); m.s. (70 eV): 150 m/e (M^+), m.w. 150.

Method A, General Procedure for Preparing 2-Aminothiazole-4-acetic Esters.

To 2.0 g. (25.0 mmoles) of thiourea suspended in 75 ml. of ethanol, an equimolar amount of 4-chloroacetoacetate (**1a**, Aldrich Chemicals or **1b**) was added at room temperature and the whole refluxed with constant stirring for 4 hours, a colorless solution gradually evolved. On cooling, the hydrochloride (**3a** or **b**) precipitate was filtered, washed with ethanol, dried, and recrystallized from 2-propanol. The free base was obtained after neutralizing the hydrochloride with 10% sodium bicarbonate and recrystallizing from benzene.

Method B, General Procedure for Preparing 5,6-Dihydroimidazo[2,1-*b*]-thiazole-3-acetic Esters.

The 4-chloroacetoacetate (**1a** or **1b**) was added to an equimolar amount of ethylenethiourea (imidazolidine-2-thiol, **2a**) (2.5 g., 25.0 mmoles) suspended in 70 ml. of ethanol at room temperature and refluxed for 4 hours with constant stirring as a clear solution. Upon cooling, the hydrochloride (**4a** or **b**) precipitated and was filtered, washed with ethanol, dried and recrystallized from ethanol. Neutralizing the hydrochloride with 10% sodium bicarbonate gave the free base which was recrystallized from ethanol.

Method C, General Procedure for Preparing 6,7-Dihydro-5*H*-thiazolo-[3,2-*c*]pyrimidine-3-acetic Esters.

In 70 ml. of ethanol, 3.0 g. (25.0 mmoles) of trimethylenethiourea (3,4,5,6-tetrahydropyrimidine-2-thiol, **2b**) was refluxed with an equimolar amount of 4-chloroacetoacetate (**1a** or **1b**) for 5 hours with constant stirring as a clear solution. After concentrating under reduced pressure and cooling, the hydrochloride (**5a** or **5b**) precipitated and was filtered, washed with ethanol, dried, and recrystallized from ethanol. The free base was obtained after neutralizing the hydrochloride with 10% sodium bicarbonate and recrystallizing from ethanol.

5,6-Dihydroimidazo[2,1-*b*]thiazole-3-acetic Acid Hydrochloride (**4c**).

In a 500 ml. Erlenmeyer flask, 16.0 g. (0.064 mole) of hydrochloride **4a** was dissolved in 50 ml. of concentrated hydrochloric acid by heating on a

steam bath with occasional stirring. After warming 20 minutes as a clear solution, the flask was chilled in an ice bath and 10 ml. of 2-propanol added, precipitating white crystals. The flask was allowed to set in an ice bath for 30 minutes before and after adding an excess of 2-propanol (125 ml.) to the resulting white suspension. Filtering, washing with 2-propanol, and drying yielded 11.0 g. (78%) of hydrochloride **4c** which browned 10° prior to decomposing at 258-61° after crystallizing from aqueous 2-propanol; ir (potassium bromide): 3300-2700 (-$\dot{N}H^+$, -CO_2H), 1725 (-$\dot{C}$=O), 1600, 1550 (-$\dot{C}$=N-) cm^{-1}; pmr (trifluoroacetic acid): δ 4.00 (s, 2H, -CH_2CO-), 4.65 (broad s, 4H, -$\dot{N}CH_2CH_2N$=); 6.70 (s, 1H, thiazole ring proton).

Anal. Calcd. for $C_7H_9ClN_2O_2S$: C, 38.10; H, 4.12; N, 12.70. Found: C, 38.34; H, 4.14; N, 12.43.

6,7-Dihydro-5*H*-thiazolo[3,2-c]pyrimidine-3-acetic Acid Hydrochloride (**5c**).

By heating on a steam bath with occasional stirring, 25.0 g. (0.0952 mole) of ester hydrochloride **5a** was gradually dissolved in 45 ml. of concentrated hydrochloric acid. The clear yellow solution was warmed for 25 minutes and then chilled in an ice bath. 2-Propanol (150 ml.) was added to the solution, which was allowed to set until white hydrochloride (**5c**) precipitated. An excess of ethyl ether (100 ml.) was then slowly added to increase precipitation of **5c** (11.0 g., 49%), which melted at 209-211° after filtering, washing with 2-propanol, and drying; ir (potassium bromide): 3300-2500 (-$\dot{N}H^+$, -CO_2H), 1725-1715 (-$\dot{C}$=O), 1625-1600 (-$\dot{C}$=N-) cm^{-1}; pmr (trifluoroacetic acid): δ 2.60-2.20 (m, 2H, C-6 methylene), 4.40-3.60 (m, 6H, -CH_2CO-, $CH_2\dot{N}$-, CH_2N=), 6.75 (s, 1H, thiazole ring proton), 8.20 (broad s, 1H, -$\dot{N}H^+$).

Anal. Calcd. for $C_8H_{11}ClN_2O_2S$: C, 40.93; H, 4.74; N, 11.94. Found: C, 41.17; H, 4.67; N, 12.00.

REFERENCES AND NOTES

(1) Contribution No. 3525. This work was partially supported by Grant GM-10366, General Medical Sciences, U.S. Public Health Service, to Indiana University.

(2) Taken in part from a thesis submitted by T. P. S. in partial fulfillment of the requirements for the Ph.D. degree at Indiana University, May, 1979.

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(17) The methyl 4-chloroacetoacetate (**1b**) was prepared in this laboratory by Dr. Paul Krieger. Since completion of these experiments, **1b** has become available commercially.