Chemistry of Heterocyclic Compounds, Vol. 42, No. 2, 2006

NEW DATA ON THE ALKYLATION OF CYCLIC THIOUREAS WITH α-HALO-CARBOXYLIC ACIDS AND THEIR ESTERS. 1. ALKYLATION OF ETHYLENE THIOUREA

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The detailed scheme of reactions, occurring on interacting ethylene thiourea with chloroacetic acid and its esters, has been supplemented with a series of new reactions. The whole spectrum of products formed on interaction of ethylene thiourea with 2-bromobutyric acid has been obtained.

Keywords: ethylene thiourea (2-imidazolidinethione), interaction with 2-bromobutyric acid, interaction with chloroacetic acid and its esters.

The alkylation products of cyclic thioureas with α-halocarboxylic acids and their esters are of interest as substances with possible biological activity due to affinity towards NO synthase [1] and GABA receptors [2]. Although the considered reactions of individual representatives of this series of compounds have been studied in some detail, their synthetic possibilities are far from being exhausted. In addition there has been no systematic consideration of the character of the conversions as a function of the size of the heterocycle of cyclic thioureas. The present work is the first step on the route of such consideration and suggests a continuation to examples of six- and seven-membered cyclic thioureas.

Alkylation of the five-membered cyclic thiourea, ethylene thiourea (2-imidazolidinethione, **1**), with α-halocarboxylic acids and their esters has been studied in [3-10], most thoroughly in [3]. We have added to the data obtained in these studies, pertaining to chloroacetic acid and its esters, with a series of new reactions, and also have obtained all the possible products formed on interacting ethylene thiourea (**1**) with 2-bromobutyric acid, an alkylating agent not used previously.

None of the mentioned studies reported the preparation of [(4,5-dihydro-2-imidazolyl)thio]acetic acid hydrochloride (**2a**) in one step, directly by the interaction of compound **1** with chloroacetic acid. Only a two-step procedure for obtaining this compound was proposed. First the corresponding free base, the zwitter-ion [(4,5-dihydroimidazol-3-ium-2-yl)thio]acetate (**3a**) (pathway *a*), was obtained by the action of chloroacetic acid on compound **1** in the presence of sodium acetate in boiling ethanol. Compound **3a** was then converted into the desired hydrochloride **2a** (pathway *b*) [3]. Attempts to alkylate compound **1** with chloroacetic acid under the "usual" conditions, i.e. in boiling ethanol or water, gave not the expected amino acid hydrochloride **2a** but the hydrochloride of 3-(2-aminoethyl)-2,4-thiazolidinedione (**4a**) (pathway *c*) [3]. We succeeded in developing a one-step method of obtaining compound **2a** by the interaction of compound **1** with chloroacetic acid in anhydrous acetone at room temperature (pathway *d*).

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0009-3122/06/4202-0221

The preparation of ethyl [(4,5-dihydro-2-imidazolyl)thio]acetate hydrochloride (**5**) by the interaction of compound **1** with ethyl chloroacetate on boiling in ethanol (pathway *e*) or pyridine was described in [3]. The use of anhydrous solvent was obviously linked with the fear of the possible formation of thiazolidinedione **4a** in place of the desired compound **5** by hydrolysis of the C=N double bond in the product of cyclization of compound **5**, the hydrochloride of 5,6-dihydroimidazo[2,1-*b*][1,3]thiazol-3(2H)-one (**6a**).

We have established that such a precaution is excessive, since ester derivative **5** may be obtained not only by the method indicated but also on boiling compound **1** with ethyl chloroacetate in 96% ethanol (pathway *f*), and the transformation of compound **5** into thiazolidinedione **4a** expected in the latter case does not occur. Ester derivative **5** may also be obtained by maintaining the reactants mentioned in anhydrous acetone at room temperature (pathway *g*). However to obtain the butyl analog of compound **5** by treating ethylene thiourea **1** with butyl chloroacetate in boiling alcohol was unsuccessful, only thiazolidinedione **4a** was isolated from the reaction mixture (pathway *h*).

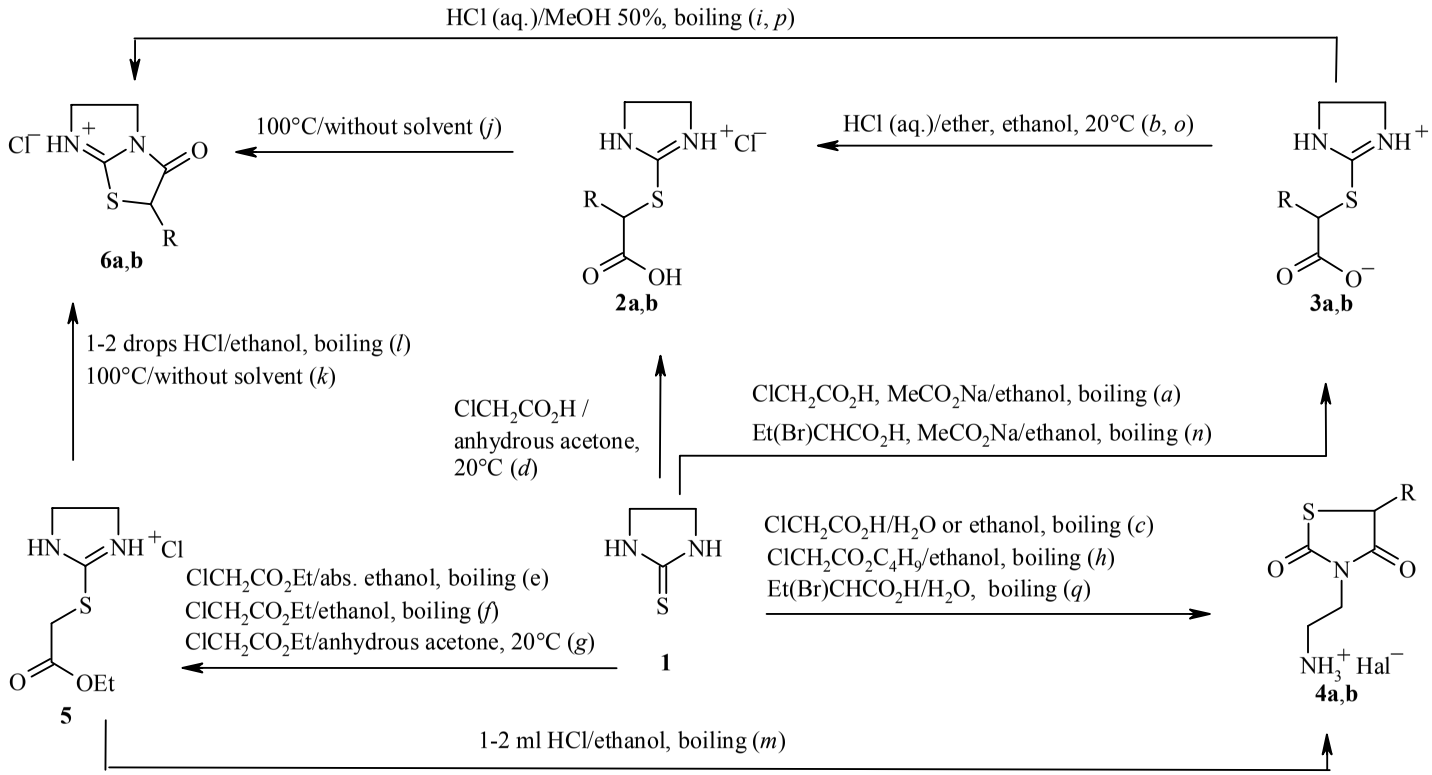
"Discrepant" results on the alkylation of compound **1** with chloroacetic acid and its esters in boiling ethanol may be explained in the following way. Probably compound **1** is alkylated by chloroacetic acid more rapidly than by its esters, i.e. amino acid **2a** is formed more rapidly than ester derivative **5**. Compound **2a**, in turn, is cyclized into bicyclic compound **6a** more rapidly than compound **5**. The resulting bicyclic compound **6a** is subject to hydrolysis to thiazolidinedione **4a**. As a result, at the same time in the reaction, substrate **1** interacts with chloroacetic acid and "succeeds" in being transformed into thiazolidinedione **4a**, and with ethyl chloroacetate gives only ester derivative **5**. The ease of cyclization of amino acid **2a** compared with its ester **5** may be caused not only by structural factors but also by the higher acidity of the medium generated by amino acid **2a**, since such cyclizations are usually catalyzed by acids. The different course of the reaction in the case of the acid and its ethyl ester may also be linked with the different solubility of the monocyclic derivatives **2a** and **5** in the reaction medium. Amino acid hydrochloride **2a** is possibly more soluble in ethanol than the hydrochloride of its ester **5**. As a result the first succeeds in being cyclized in solution to be precipitated from it, and the second does not.

It is possible that on alkylation of ethylene thiourea **1** with butyl chloroacetate the reaction mixture is additionally acidified due to the relative ease of hydrolysis of the ester group in the alkylating agent and/or the intermediately formed butyl analog of compound **5** [11]. Compound **2a** formed in this or any procedure is relatively rapidly cyclized into bicyclic compound **6a** (more rapidly than the hypothetical butyl analog of compound **5**), which in turn is hydrolyzed to thiazolidinedione **4a**. Additional acidification of the reaction mixture (as a result of hydrolysis) favors the acid-catalyzed cyclization.

Previously, only one preparative method was known for obtaining the bicyclic compound **6a**, *viz*. by boiling zwitter-ion **3a** in aqueous methanolic HCl (pathway *i*) [3]. This compound is also obtained on heating compound **1** with chloroacetic acid in glacial acetic acid. However this method may not be considered as preparative since a significant amount of thiazolidinedione **4a** is formed in addition to the desired compound [9]. We have developed simple and efficient methods for obtaining 5,6-dihydroimidazo[2,1-*b*][1,3]thiazol-3(2H)-one hydrochloride (**6a**) by heating amino acid hydrochloride **2a** or its ethyl ester hydrochloride **5** without solvent at 100°C (pathways *j* and *k* respectively). We have also found one further method for obtaining bicyclic compound **6a**, by boiling ester derivative **5** in 96% ethanol in the presence of a catalytic amount of HCl (1-2 drops hydrochloric acid) (pathway *l*). On adding a larger amount of the same acid (1-2 ml) only thiazolidinedione **4a**, the product of hydrolysis of compound **6a**, may be isolated from the reaction mixture (pathway *m*). Two further methods are known for obtaining thiazolidinedione **4a**, from compound **1** and chloroacetyl chloride in acetone, and also by extended treatment of zwitter-ion **3a** with saturated ethanolic HCl solution [4].

All the possible products of interaction of ethylene thiourea **1** with 2-bromobutyric acid were successfully obtained by the procedures given in [3]. These were zwitter-ionic 2-[(4,5-dihydroimidazol-3-ium-2-yl)thio]butyrate (**3b**), 2-[(4,5-dihydro-2-imidazolyl)thio]butyric acid hydrochloride (**2b**), 2-ethyl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazol-3(2H)-one hydrochloride (**6b**), and 3-(2-aminoethyl)-5-ethyl-2,4-

Reactions occurring on interacting 2-imidazolidinethione (**1**) with α-halocarboxylic acids and their esters



2-4, 6 a R = H, **b** R = Et; **4 a** Hal = Cl, **b** Hal = Br

thiazolidinedione hydrobromide (**4b**) (pathways *n-q* respectively). It should be noted that the methyl analog of the bicyclic compound **6b** was not successfully obtained in the reaction of compound **1** with ethyl α-bromopropionate according to the authors of [10].

EXPERIMENTAL

The ^{1}H NMR spectra were obtained in DMSO-d_6 on a Bruker DPX-300 (300 MHz) spectrometer, chemical shifts were determined relative to the signal of the solvent. The chemical shifts for multiplet signals are given for their geometric centers. TLC was carried out on Silufol UV-254 plates, eluting with butyl acetate–ethanol–chloroform, 1:10:100. Anhydrous acetone was prepared by the procedure of [12].

2-Imidazolidinethione (1) was obtained by the method of [13]; mp 197-198°C (lit.198°C [10]). ^{1}H NMR spectrum, δ, ppm: 4.0 (4H, 4-, 5-CH_2); 10.4 (2H, s, $N_{(1)}H$, $N_{(3)}H$).

[(4,5-Dihydroimidazol-3-ium-2-yl)thio]acetate (3a) was obtained by the action of chloroacetic acid on compound **1** in ethanol in the presence of sodium acetate as described in [3] (pathway *a*); mp 181-184°C (lit. 183°C [3]). ^{1}H NMR spectrum, δ, ppm: 3.6 (4H, 4-, 5-CH_2); 4.0 (2H, s, SCH_2); 11.2 (2H, s, $N_{(1)}H$, $N_{(3)}H$).

2-[(4,5-Dihydroimidazol-3-ium-2-yl)thio]butyrate (3b) was obtained analogously to compound **3a** (pathway *n*). Compound **1** (1.02 g, 10 mmol) was dissolved in ethanol (20 ml) with stirring and moderate heating. 2-Bromobutyric acid (2.50 g, 1.6 ml, 15 mmol) and sodium acetate (1.0 g, 12 mmol) were added to the obtained solution and stirring was continued for 2.5 h. The solvent was removed in vacuum, and the resulting residue was twice recrystallized from 20% ethanol. Yield 0.90 g (48%); mp 135-137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.1 (3H, t, *J* = 8, $CHCH_2C\underline{H}_3$); 2.0 (2H, m, $CHC\underline{H}_2CH_3$); 3.6 (4H, NCH_2); 4.0 (1H, t, *J* = 7, $C\underline{H}CH_2CH_3$); 11.2 (2H, s, $N_{(1)}H$, $N_{(3)}H$). Found. %: C 44.66; H 6.48; N 14.86. $C_7H_{12}N_2O_2S$. Calculated, %: C 44.66; H 6.43; N 14.88.

[(4,5-Dihydro-2-imidazolyl)thio]acetic Acid Hydrochloride (2a). A (pathway *d*). Chloroacetic acid (1.42 g, 15 mmol) was added with vigorous stirring to compound **1** (1.02 g, 10 mmol) in anhydrous acetone (20 ml) and the reaction mixture was left at ~20°C for 8 h. The resulting solid was filtered off, and washed with anhydrous acetone. Yield 1.17 g (59%); mp 128-129°C (lit. mp 129°C [3]). ^{1}H NMR spectrum, δ, ppm: 4.0 (4H, 4-, 5-CH_2); 4.4 (2H, s, SCH_2); 8.2 (2H, s, $N_{(1)}H$, $N_{(3)}H$).

B. Compound **2a** was obtained by the action of aqueous HCl in ether on compound **3a** as described in [3] (pathway *b*); mp 128-129°C.

2-[(4,5-Dihydro-2-imidazolyl)thio]butyric Acid Hydrochloride (2b) was obtained analogously to compound **2a** by procedure B (pathway *o*). Conc. HCl (1 ml) was added dropwise with vigorous stirring to a suspension of compound **3b** (0.56 g, 3.0 mmol) in ether (25 ml) at ~20°C. As a result of the reaction a colorless oil formed on the bottom of the flask, and crystallized after adding ethanol (25 ml). The resulting solid was recrystallized from 20% ethanol. Yield 0.40 g (59%); mp 112-114°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.2 (3H, t, *J* = 8, $CHCH_2C\underline{H}_3$); 2.0 (2H, m, $CHC\underline{H}_2CH_3$); 4.0 (4H, 4-, 5-CH_2); 4.4 (1H, t, *J* = 7, $C\underline{H}CH_2CH_3$); 8.2 (2H, s, $N_{(1)}H$, $N_{(3)}H$). Found, %: C 37.45; H 5.83; N 12.40. $C_7H_{12}N_2O_2S{\cdot}HCl$. Calculated, %: C 37.41; H 5.83; N 12.47.

Ethyl [(4,5-Dihydro-2-imidazolyl)thio]acetate Hydrochloride (5). A. Compound **5** was obtained by the action of ethyl chloroacetate on compound **1** in absolute ethanol as described in [3] (pathway *e*)); mp 143-144°C (lit. 144°C [3]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.3 (3H, t, *J* = 7, $CH_2C\underline{H}_3$); 3.9 (4H, 4-, 5-CH_2); 4.2 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 4.4 (2H, s, SCH_2); 11.0 (2H, s, $N_{(1)}H$, $N_{(3)}H$).

B (pathway *f*). Compound **1** (2.04 g, 20 mmol) was dissolved by heating in ethanol (15 ml). Ethyl chloroacetate (3.67 g, 3.17 ml, 30 mmol) was added to the obtained solution, and the reaction mixture boiled for 2 h. The solvent was removed in vacuum, and the residue recrystallized from acetonitrile. Yield 3.10 g (69%); mp 142-144°C.

C (pathway *g*). Ethyl chloroacetate (1.84 g, 1.6 ml, 15 mmol) was added with vigorous stirring to compound **1** (1.02 g, 10 mmol) in anhydrous acetone (20 ml) and the mixture left at ~20°C for 10 h. The resulting solid was filtered off, washed with anhydrous acetone, and recrystallized from acetonitrile. Yield 0.77 g (34%); mp 143-144°C.

3-(2-Aminoethyl)-2,4-thiazolidinedione Hydrochloride (4a). A. Compound **4a** was obtained as described in [3] by the action of chloroacetic acid on compound **1** in water (pathway *c*); mp 225-227°C (lit. mp 227°C [3]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.0 (2H, t, *J* = 6, $N_{(3)}C\underline{H}_2CH_2$); 3.8 (2H, t, *J* = 6, $N_{(3)}CH_2C\underline{H}_2$); 4.1 (2H, s, 5-$CH_2$); 8.9 (3H, s, NH_3).

B (pathway *c*). This method was mentioned in [3] but no description was given. Compound **1** (1.02 g, 10 mmol) in 96% ethanol (5 ml) was heated until complete solution of the substrate. A solution of chloroacetic acid (1.04 g, 11 mmol) in 96% ethanol (5 ml) was added to the obtained solution, and the mixture was boiled for 1 h. The solvent was removed in vacuum, and the residue recrystallized from ethanol. Yield 0.84 g (43%); mp 224-225°C.

C (pathway *h*). Compound **1** (1.02 g, 10 mmol) in 96% ethanol (10 ml) was heated until the substance had completely dissolved. Butyl chloroacetate (1.70 g, 1.54 ml, 11 mmol) was added to the obtained solution, and the reaction mixture was boiled for 3 h. The solvent was removed in vacuum, the oily residue was treated with heptane, and the resulting solid was recrystallized from ethanol. Yield 0.19 g (10%); mp 225-227°C.

D (pathway *m*). Compound **5** (0.90 g, 4.0 mmol) was dissolved in 96% ethanol (20 ml) by heating. Conc. HCl (1 ml) was added dropwise to the obtained solution, and the reaction mixture boiled for 3 h. The solvent was removed in vacuum, and the residue recrystallized from ethanol. Yield 0.47 g (60%); mp 224-226°C.

3-(2-Aminoethyl)-5-ethyl-2,4-thiazolidinedione Hydrobromide (4b) (pathway *q*). Compound **1** (1.12 g, 11 mmol) in water (20 ml) was heated until complete solution of the substrate. 2-Bromobutyric acid (2.39 g, 1.60 ml, 14 mmol) was added to the obtained solution, and the reaction mixture boiled for 12 h. The solvent was removed in vacuum, the oily residue was treated with ethyl acetate, and the resulting solid was recrystallized from ethanol. Yield 2.48 g (84%); mp 178-179°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.0 (3H, t, *J* = 8, 5-$CH_2C\underline{H}_3$); 1.9 (1H, m, 5-$C\underline{H}_AH_BCH_3$); 2.1 (1H, m, 5-$CH_A\underline{H}_BCH_3$); 3.0 (2H, t, *J* = 5, $N_{(3)}C\underline{H}_2CH_2$); 3.8 (2H, t, *J* = 5, $N_{(3)}CH_2C\underline{H}_2$); 4.4 (1H, m, H-5); 8.2 (3H, s, NH_3). Found, %: C 31.27; H 4.91; N 10.36. $C_7H_{12}N_2O_2S\cdot HBr$. Calculated, %: C 31.24; H 4.87; N 10.41.

5,6-Dihydroimidazo[2,1-*b*][1,3]thiazol-3(2H)-one (6a). A. Compound **6a** was obtained by the action of HCl on zwitter-ion **3a** as described in [3] (pathway *i*); mp 205-206°C (lit. 206°C [3]). ^{1}H NMR spectrum, δ, ppm: 4.4 (2H, 5-CH_2); 4.5 (2H, 6-CH_2); 4.8 (2H, s, 2-CH_2); 10.5 (1H, s, NH).

B (pathway *j*). A weighted portion of compound **2a** (0.20 g, 1.0 mmol) was heated in vacuum at 100°C for 6 h. Yield 0.18 g (100%); mp 204-206°C.

C (pathway *k*). A weighted portion of compound **5** (0.22 g, 1.0 mmol) was heated in vacuum at 100°C for 6 h. Yield 0.18 g (100%); mp 204-205°C.

D (pathway *l*). Compound **5** (0.90 g, 4.0 mmol) was dissolved in 96% ethanol (20 ml) by heating. Conc. HCl (2 drops) was added to the obtained solution, and the reaction mixture was boiled for 3 h. The solvent was removed in vacuum, and the residue was crystallized from 2-propanol–ethanol, 1:1. Yield 0.43 g (60%); mp 205-206°C.

2-Ethyl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazol-3(2H)-one (6b) (pathway *p*). Compound **3b** (0.56 g, 3.0 mmol) was dissolved in 50% methanol (2 ml) by heating. Conc. HCl (2.5 ml) was added dropwise to the obtained solution, and the reaction mixture boiled for 10 min. The solvent was removed at atmospheric pressure, and the residue recrystallized from isopropyl alcohol. Yield 0.25 g (40%); mp 198-201°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.2 (3H, t, *J* = 8, $CH_2C\underline{H}_3$); 2.0 (1H, m, 2-$C\underline{H}_AH_BCH_3$); 2.1 (1H, m, 2-$CH_A\underline{H}_BCH_3$); 4.2 (2H, 5-CH_2); 4.6 (2H, 6-CH_2); 4.8 (1H, t, *J* = 7, 2-CH); 12.4 (1H, s, NH). Found, %: C 40.68; H 5.36; N 13.57. $C_7H_{10}N_2OS\cdot HCl$. Calculated, %: C 40.68; H 5.36; N 13.55.

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