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SYNTHESIS AND STRUCTURAL STUDIES OF 3-ACYLAMINO-4-AMINO-2,3-DIHYDRO-2-IMINOTHIAZOLE-5-CARBOXYLATES AND 4-ACYLHYDRAZINO-2-AMINOTHIAZOLE-5-CARBOXYLATES

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Abstract – The preparation of thiazole derivatives through reactions of ethyl 3-amino-3-acylhydrazinopropenoates (**1**)with inorganic thiocyanates and thiourea was investigated. The reaction of **1** with sodium thiocyanate, in acetic acid in the presence of bromine, afforded ethyl 3-acylamino-4-amino-2,3-dihydro-2-iminothiazole-5-carboxylates (**3**) selectively. On reacting the same compounds (**1**) with thiourea, in acetic acid and in the presence of bromine, 4-acylhydrazino-2-aminothiazole-5-carboxylates (**4**) were yielded. The structure of the representative compound (**3c**), ethyl 4-amino-3-benzoyl-amino-2,3-dihydro-2-iminothiazole-5-carboxylate has been solved by means of X-Ray crystallographic data analysis.

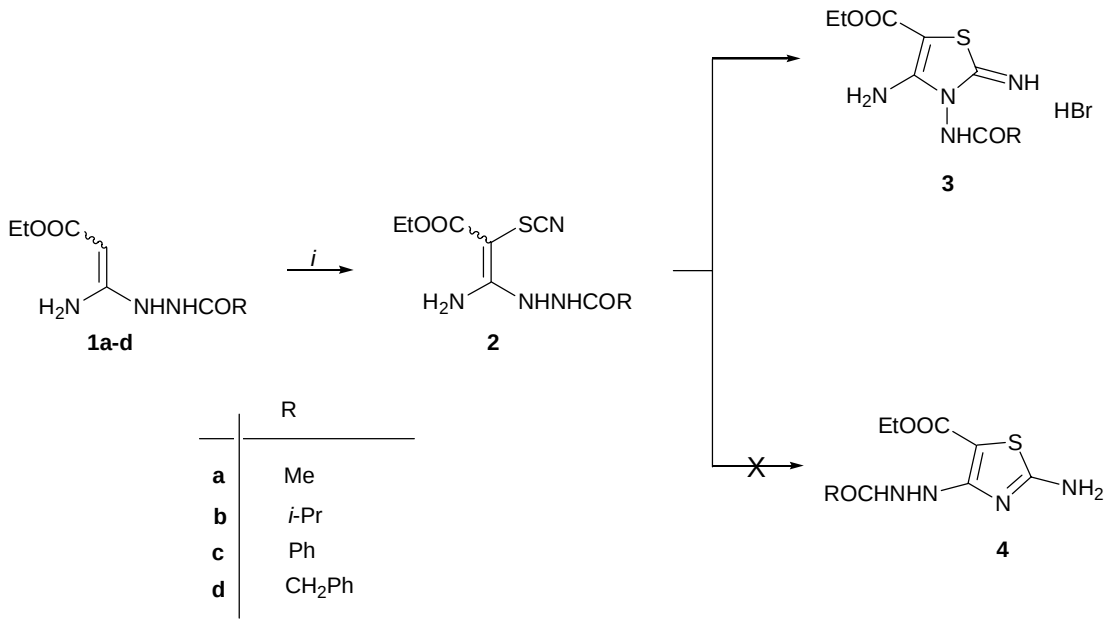
INTRODUCTION

2-Aminothiazole-5-carboxylates have attracted much attention because they have been utilized in the preparation of biologically active molecules such as angiotensin II antagonist,[1] DNA minor groove binding analogs of netropsin, [2] in addition to many others.[3-7] In spite of the enormous amount of literature reported for synthesis of aminothiazole derivatives relatively few successful preparation methods for diamino-thiazole derivatives have been described.[8-16] The few published methods for the preparation of 2,4-diaminothiazole derivatives have involved the reaction of 1-alkyl- or 1-aryl-3-amidinothioureas with α-halo ketones[14] or two step condensation of *N*-phenylthiocarbamoyltrichloroacetamidines with phenacyl

bromide in presence of a strong base as DBU.[16] On scanning literature no report can be found on 3-acylamino-2-imino- or 4-acylhydrazinothiazole derivatives. During the course of a research program devoted to the synthesis of aminoazoles we have reported an efficient route for 2-amino-5-cyano-4-dialkylaminothiazoles.[17] With the aim to synthesize acylhydrazinothiazoles we have investigated the details of reaction of ethyl 3-amino-3-acylhydrazinopropenoates (**1**) with thiocyanate salts and thiourea. The compounds (**1**) are versatile building blocks due to their facile preparation and to their functionalities. The utility of these intermediates in heterocyclic synthesis has been demonstrated in our laboratories.[18]

RESULTS AND DISCUSSION

First, we have investigated the reactions of **1** with sodium thiocyanate. Bromine was added to the suspension of compounds (**1**) and sodium thiocyanate (1:2 molecular ratio) in acetic acid at 5 °C. After few minutes reaction product precipitated as white solid. Analytical and spectral data of the isolated compounds account for the formation of aminothiazole derivatives, however it is possible to obtain two different thiazole derivatives: namely ethyl 3-acylamino-4-amino-2,3-dihydro-2-iminothiazole-5-carboxylates (**3**) and ethyl 4-acylhydrazino-2-aminothiazole-5-carboxylates (**4**) (Scheme 1). The obtained compounds were isolated as hydrobromides salts and were purified by repeated washing with hot ethanol.



Scheme 1. *Reagents and conditions*: *i*, NaSCN / Br_2/ AcOH, 0 - 5 °C

Attempts to isolate the corresponding free bases proved to be quite disappointing, resulting in poor recovery and/ or extensive decomposition. Only the reaction product of amidrazones (**1a**) and (**1b**) can be obtained as free base when treated with 20% sodium carbonate solution. Presumably amidrazones (**1**) react with thiocyanogen, generated *in situ* by action of bromine on inorganic thiocyanate, to give

2-thiocyanato-3-amino-3-acylhydrazinopropenoates (**2**). The latter readily undergo ring closure giving thiazole derivatives (**3**) or (**4**). Since IR, NMR and MS spectroscopic data do not allow us to distinguish between the two possible products (**3**) or (**4**), we performed an X-Ray crystallographic analysis of thiazole (**3c**) bearing as acyl substituent a benzoyl group. Figure 1 shows the ORTEP drawing for this compound and Table 1 reports the crystal data. X-Ray crystallographic data accounted for the 3-benzoylamino-4-amino- 2-imino-2,3-dihydrothiazole-5-carboxylic acid ethyl ester structure (**3c**). In the crystal unit there are two molecules of **3c**, reported as A and B, and two HBr molecules. Both molecules A and B have non planar configuration and can be described in terms of three nearly planar parts: P1 (N2 C8 N4 S1 C9 C10 N3 O2 O3 C11), P2 (N1 C7 O1) and P3 (C1…C6). Only atoms C12 and C13 lie out of the P1 plane, while in the plane the maximum deviation is for the O3 atom -0.076 (5) Å for A and 0.052 (5) Å for B molecule. The dihedral angle between the P1 and P2 plane is 82.4(2)° in A and 85.2(1)° in B, that between P2 and P3 is 13.0(2)° for A and 30.2(2)° for B and between P1 and P3 the angle is 69.7(2)° and 55.3(2)° for A and B molecules respectively. The lengthening of the S1-C9 1.745 (5)Å for A and 1.737 (5) Å for B molecule bond distance versus the S1-C8 (1.705) (5) and 1.695 (5) Å for A and B), may be described in terms of strain of the substituents at C8 and C9. The further crystallographic difference between the two molecules is in the orientation of the phenyl and thiazole rings; the dihedral angles formed by these systems, are 70.5(2)° and 54.5(2)° for the A and B molecule respectively. The comparison of the molecules with the aid of the program (PARST) reveals only a pseudotraslation. In both molecules, the packing contacts of major relevance are intra and intermolecular hydrogen bonds, in particular N3b-H…O1a^{i} (i = 1-x, 1-y, 2- z) with N…O 2.890(7) Å, H…O1a 2.155(5) Å and N3b-H…O1a 162.2(4)°.

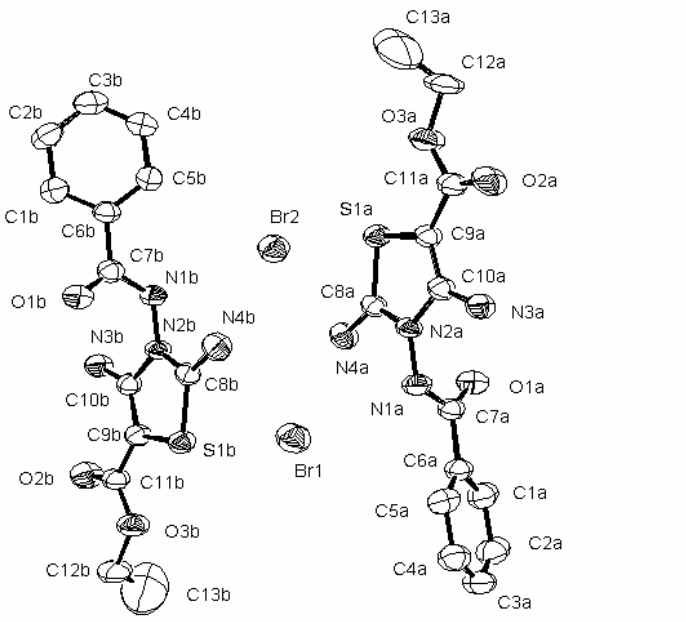


Figure 1. Crystal structure of thiazole (**3c**)

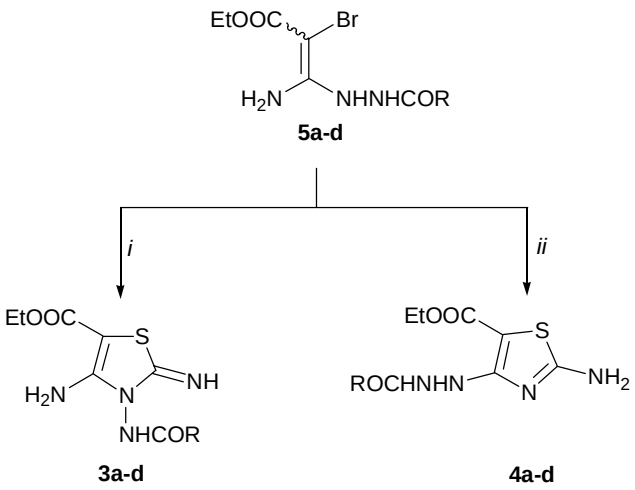
Table 1. Crystal data for thiazole (**3c**)

Formula	$C_{26}H_{28}Br_2N_8O_6S_2$
Fw	772.5
Space group	*P*-1
a (Å)	12.176(9)
b (Å)	13.681(8)
c (Å)	9.707(10)
α (°)	98.92(6)
β (°)	95.28(7)
γ (°)	91.27(5)
V (Å ^{3})	1590(2)
Z	2
ρ (g cm^{-3})	1.614
μ (mm^{-1})	0.492
Crystal size (mm^3)	0.22 x 0.31 x 0.39
θ range(°)	3.65 to 70.01
N° of independent Reflections	5932 [R(int) = 0.0131]
Data / restraints / parameters	5924 / 0 / 405
R [$I>2\sigma(I)$]	0.0749
wR_2	0.1887

From the reaction of **1a** and NaSCN, 2-thiocyanatepropenoate (**2a**) was obtained in addition to **3a**. Characteristic absorption band of SCN group at 2060 cm^{-1} in IR spectrum of **2a** was diagnostic for the assigned structure. In order to isolate the products (**2a-d**) we have investigated the reaction between all ethyl 3-amino-3-acylhydrazinopropenoates (**1a-d**) and ammonium thiocyanate in acetic acid and in the presence of bromine. As matter of fact, as we have previously reported, this salt allowed us to isolate the open chain intermediates.[17] The reaction of ethyl 3-amino-3-isobutyrylhydrazinopropenoate (**1b**) with ammonium thiocyanate at 5 °C for 15 min produced the thiocyanated compound (**2b**) in 65% yield. Ethyl 3-amino-3-acetylhydrazinopropenoate (**1a**) gave a mixture of **2a** and 2-aminothiazole (**3a**). Compounds (**2a**) and (**3a**) were separated each other by treatment of the reaction mixture with water. Adduct (**2a**) precipitated while thiazole (**3a**) was recovered in 35% yield as free base when treated with 20% sodium carbonate solution. The substrates (**1c**) and (**1d**) yielded the corresponding thiazole derivatives (**3c**) and (**3d**) as exclusively products. The structure of **2** was determined by microanalyses and spectral data. The IR spectra of **2** show absorption bands in the 2050-2080 cm^{-1} region and in the 1715 - 1685 cm^{-1} region due to the SCN group and the ester moiety respectively. The ^{1}H-NMR spectra do not contain high-field signals relative to C-2 (methine) protons. This information indicates that these compounds have the enaminic structure showed in Scheme 1. The ^{1}H-NMR spectra show three deuterium oxide exchangeable signals at about 7, 10 and 11 ppm attributable to NH_2, NH and NHCOR groups respectively as well as a splitting of the signal at about 10 ppm, as consequence of possible formation of intramolecular hydrogen bond between N-2 protons and ester moiety. This assumption is further confirmed by ^{13}C-NMR spectra that display two signals attributable to carbonyl carbon atom of COOEt group. Furthermore ^{13}C-NMR spectra exhibit

single signals relative to C-2, C-3 and SCN carbon atoms and this fact indicate that the isolable adducts (**2**) exist exclusively in a single isomeric form. Spectral data clearly indicate that isolated adducts (**2**) have *E*-configuration. *E*-Isomers are more stable compounds as pointed out by their chemical inertia. As matter of fact in all attempts to cyclize **2** the unreacted starting material was recovered. Thus we can presume that thiocyanation of **1** afford the formation of **2** in *E/Z* isomeric mixture, whose ratio is related to substitution pattern of **1**. Furthermore only *Z*-isomers participate in intramolecular heterocyclization reaction to give thiazoles (**3**) while *E*-isomers remain unaffected.

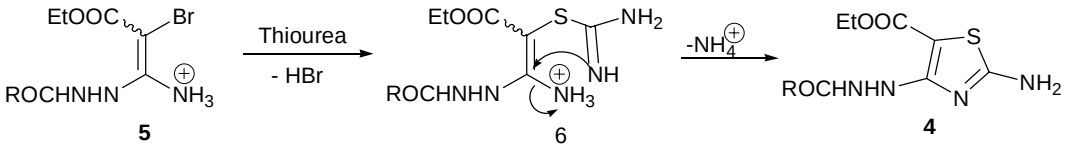
Successively we have examined the reaction of sodium thiocyanate with ethyl 3-amino-3-acylhydrazino-2-bromopropenoates (**5**). These were easily prepared from the reaction of the corresponding compounds (**1**) and bromine in acetic acid at 5 °C. 2-Bromopropenoates (**5**) were obtained at almost pure state and can be utilized in the successive reaction without further purification. As revealed by their NMR spectra, registered in DMSO-d_6 solution, compounds (**5**) exist in tautomeric species amide hydrazone, hydrazide imide and enaminic, and each tautomer can display geometric isomerism. Treatment of compounds (**5**) with equimolecular amounts of sodium thiocyanate, in acetic acid at 5 °C, led to formation of thiazoles (**3**) as shown in Scheme 2.



Scheme 2. *Reagents and conditions*: *i*, NaSCN / AcOH, rt; *ii*, thiourea / AcOH, rt.

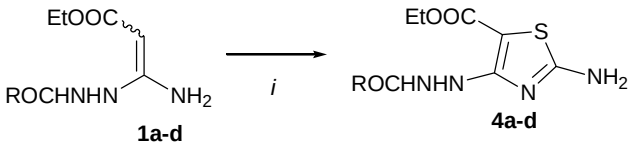
By performing the reaction in acetone solution under reflux we obtained lower yields of thiazoles (**3**). The formation of thiazoles (**3**) can be interpreted as arising from nucleophilic displacement of the bromine atom of **5** by sulphur atom of thiocyanate, followed by intramolecular addition of N-2 nitrogen onto the carbon nitrogen triple bond. Chemical characteristics of **5** suggest their further exploitation as substrates in the reaction with thiourea for the synthesis of aminothiazole derivatives through Hantzsch synthesis. It was recently reported that condensation of thiourea with β-chloro-β-ethoxycarbonylenamines[19] and α-chloroximes[20] afforded 2-amino-5-ethoxycarbonylthiazoles and 2-aminothiazoles respectively. The reaction of **5** with thiourea afforded new thiazole derivatives which were identified as ethyl

4-acylhydrazino-2-aminothiazole-5-carboxylates (**4**). The structure of **4** was confirmed by analytical data and mainly on the basis of the comparison of their IR and ^{1}H-NMR spectra with those of thiazoles (**3**). Several reaction conditions were investigated utilizing as sample compound (**5c**). The reaction of **5c** with thiourea, performed in acetone solution under reflux, afforded 4-acylhydrazinothiazole (**4c**) in low yields. The addition of a base such as potassium carbonate led to an increase in the yield of **4c**. However, we found that reaction of **5** with an equivalent of thiourea was most effective in acetic acid solution at 5 °C, providing excellent yields of **4**. The observation that the best yields of **4** are obtained in acid solution leads to support a mechanism involving initial protonation of N-3 nitrogen, followed by nucleophilic attack of thiourea to form intermediate (**6**) (Scheme 3).



Scheme 3. Proposed mechanism of formation of thiazoles (**4**).

The formation of **6** has been greatly facilitated by presence of the strongly electron-withdrawing ammonium function. The internal cyclization culminates with extrusion of ammonia affording thiazoles (**4**). Attempts to isolate open chain intermediates did not succeed even under mild reaction conditions, as they readily undergo in situ cyclization. On the other hand high yields of 4-acylhydrazinothiazoles (**4**) were obtained in the one step reaction of equimolecular amounts of compounds (**1**), thiourea and bromine in cold acetic acid (Scheme 4).



Scheme 4. *Reagents and conditions*: *i*, thiourea / Br_2/ AcOH, 0 - 5 °C.

We can assume that also in this reaction the ethyl 3-amino-3-(2-acylhydrazino)-2-bromopropenoate (**5**) is initially formed, then it reacts with thiourea as above described. Table 2 summarizes yields of **2**, **3** and **4** obtained following the above described synthetic procedures.

The comparison of spectral data of the isomeric thiazoles (**3**) and (**4**) reveals some differences. IR spectra of thiazoles (**3**) display a band at 1692-1735 cm^{-1}. These frequencies are characteristic of a free uncoordinated carbonyl group. The presence of a free uncoordinated carbonyl group was further confirmed by X-Ray data. The IR spectra of thiazoles (**4**) are quite different and they show a wide band at about 1650 cm^{-1} that signifies the presence of a C=O- -HN- hydrogen bond chelate structure. ^{1}H-NMR spectra of thiazole (**3**) and (**4**) show significant differences for deuterium oxide exchangeable signals only. As matter of fact thiazoles (**3a-d**) display 4-NH_2 signal at about 7.00-7.20 ppm, while in the compounds (**4a-d**) 2-NH_2 group resonates

at 7.80-8.00 ppm. MS spectra of compounds (**3**) are characterized by the presence of several peaks due to extensive fragmentation of the molecular ion, on the contrary those of compounds (**4**) show very few fragments.

Table 2. Yields of Products (**2**, **3**, and **4**).

Substrate	Products (yields %)				
	Method A *	Method B #	Method C §	Method D @	Method E °
1a	**2a** (15), **3a** (70)	**2a** (55), **3a** (30)	**4a** (90)		
1b	**3b** (87)	**2b** (85)	**4b** (65)		
1c	**3c** (98)	**3c** (96)	**4c** (70)		
1d	**3d** (80)	**3d** (77)	**4d** (98)		
5a				**3a** (55)	**4a** (75)
5b				**3b** (60)	**4b** (50)
5c				**3c** (82)	**4c** (55)
5d				**3d** (65)	**4d** (72)

* NaSCN, Br_2, AcOH, rt; # NH_4SCN, Br_2, AcOH, rt; § Thiourea, Br_2, AcOH, rt; @ NaSCN, AcOH, rt; °Thiourea, AcOH, rt

EXPERIMENTAL

All reagents were purchased from Aldrich or Merck. All chemicals were reagent grade and used without further purification; all solvents were freshly distilled before use. Melting points were determined on a Stuart Scientific Melting point SMP1 and are uncorrected. ^{1}H-NMR spectra were recorded in DMSO-d_6 solution with a Varian Unity 300 spectrometer. The chemical shift are reported in part per million (δ, ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. IR spectra were obtained in Nujol mull with a Bruker Vector22 spectrophotometer. MS spectra were determined with a Fisons QMD 1000 spectrometer in EI mode at 70 eV. Elemental analyses were carried out with a Carlo Erba model 1106 Elemental Analyzer. Ethyl 3-amino-3-acylhydrazinopropenoates (**1**) were prepared by previously described procedures.[21]

General Procedure for the Synthesis of Thiazoles 3 (Method A). A mixture of compounds (**1**) (10 mmol) and NaSCN (1.62 g, 20 mmol) in AcOH (5 mL) was cooled at 0 – 5 °C. Bromine (0.5 mL, 10 mmol) was added and the mixture was stirred at rt. After few min a white solid precipitated, the stirring is continued for further 15 min and then the reaction mixture was diluted with ethyl acetate (20 mL). The

precipitate was filtered and purified by recrystallization in the cases of **3a** and **3b** and by washings with hot EtOH in the cases of **3c** and **3d.** Compound (**1a**) gave a mixture of 2-iminothiazole (**3a**) and (**2a**). Compounds (**2a**) and (**3a**) were separated each other by treatment of the reaction mixture with water (20 mL). Adduct (**2a**) precipitated (0.37 g, 15%) while thiazole (**3a**) was recovered in 70% yield (1.70 g) by treatment of the mother liquors with 20% aqueous sodium carbonate (10 mL).

Ethyl 3-Acetylamino-4-amino-2,3-dihydro-2-iminothiazole-5-carboxylate (3a). Yield 1.70 g, 70%, mp 215- 217 °C (2-PrOH). IR cm^{-1}: 3490, 3470, 3320, 3150, 1725, 1670, 1610. ^1H NMR δ: 1.12 (t, *J* = 7.3 Hz, 3H, CH_3), 1.91 (s, 3H, CH_3), 4.04 (q, *J* = 7.3 Hz, 2H, CH_2), 7.12 (s, 2H, NH_2), 8.32 (s, 1H, NH), 10.39 (s, 1H, NH). MS m/z (%): 244 (M^+, 50), 198 (23), 187 (11), 174 (24), 157 (3), 145 (10), 130 (40), 100 (100). Anal. Calcd for $C_8H_{12}N_4O_3S$: C, 39.34; H, 4.95; N, 22.94. Found C, 39.39; H, 4.96; N, 22.90.

Ethyl 4-Amino-3-*iso*-butyrylamino-2,3-dihydro-2-iminothiazole-5-carboxylate (3b). Yield 2.40 g, 87%, mp 110-111 °C (Benzene). IR cm^{-1}: 3445, 3395, 3345, 1735, 1610. ^1H NMR δ: 1.04 (d, *J* = 6.8 Hz, 6H, CH_3), 1.13 (t, *J* = 6.8 Hz, 3H, CH_3), 2.31 (m, 1H, CH), 4.03 (q, *J* = 6.8 Hz, 2H, CH_2), 7.04 (s, 2H, NH_2), 8.31 (s, 1H, NH), 10.03 (s, 1H, NH). MS m/z (%): 272 (M^+, 14), 229 (44), 187 (15), 182 (14), 172 (10), 128 (23), 70 (22), 43 (100). *Anal.* Calcd for $C_{10}H_{16}N_4O_3S$: C, 44.01; H, 5.92; N, 20.57. Found C, 44.04; H, 5.93; N, 20.60.

Ethyl 4-Amino-3-benzoylamino-2,3-dihydro-2-iminothiazole-5-carboxylate Hydrobromide (3c). Yield 3.79 g, 98%; mp 260 °C (decomp). IR cm^{-1}: 3391, 3299, 1692, 1653, 1600. ^1H NMR δ: 1.22 (t, *J* = 6.9 Hz, 3H, CH_3), 4.16 (q, *J* = 6.9 Hz, 2H, CH_2), 7.56- 7.98 (m, 7H, Ar and NH_2), 10.53, 12.03 (br s, 3H, NH). MS *m/z* (%): 306 (M-HBr, 19), 162 (65), 105 (100), 77 (48). *Anal.* Calcd for $C_{13}H_{14}N_4O_3S \cdot HBr$: C, 40.32; H, 3.90; N, 14.47. Found C, 40.36; H, 3.89; N, 14.44.

Ethyl 4-Amino-2,3-dihydro-3-phenylacetylamino-2-iminothiazole-5-carboxylate Hydrobromide (3d). Yield 3.20 g, 80%, mp 250 °C (decomp). IR cm^{-1}: 3379, 3296, 3089, 1715, 1686, 1658, 1621. ^1H NMR δ: 1.19 (t, *J* = 7.0 Hz, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.17 (q, *J* = 7.0 Hz, 2H, CH_2), 7.26 (m, 5H, Ar), 7.79 (s, 2H, NH_2), 10.49 (s, 1H, NH), 11.62 (s, 1H, NH). MS *m/z* (%): 320 (M-HBr, 21), 275 (4), 229 (79), 176 (15), 159 (11), 91 (100). *Anal.* Calcd for $C_{14}H_{16}N_4O_3S \cdot HBr$: C, 41.90; H, 4.27; N, 13.96. Found C, 41.85; H, 4.29; N, 14.00.

Reactions between Compounds (1) and Ammonium Thiocyanate (Method B). A mixture of compound (**1**) (10 mmol) and NH_4SCN (1.5 g, 20 mmol) in AcOH (5 mL) was cooled at 0 - 5 °C. Bromine (0.5 mL, 10 mmol) was added and the mixture was stirred at rt. After few min a white solid precipitate, the stirring is

continued for further 15 min and then the reaction mixture was diluted with ethyl acetate (20 mL). The precipitate was filtered off. In the reaction of **1b**, **1c** and **1d** were respectively produced the thiocyanated compound (**2b**), thiazole derivatives (**3c**) and (**3d**) as exclusively products. Compound (**1a**) gave a mixture of **2a** and 2-iminothiazole (**3a**). Compounds (**2a**) and (**3a**) were separated each other by treatment of the reaction mixture with water (20 mL). Adduct (**2a)** precipitated while thiazole (**3a**) was recovered in 30% yield by basification of the mother liquors with 20% aqueous sodium carbonate (10 mL).

Ethyl 3-Acetylhydrazino-3-amino-2-thiocyanatopropenoate (2a). Yield 1.30 g, 55 %; mp 200-202 °C (2-PrOH). IR cm^{-1}: 3360, 3280, 3240, 3150, 2060, 1715, 1680, 1660, 1630. ^{1}H NMR δ: 1.15 (t, *J* = 6.3 Hz, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.15 (q, *J* = 6.3 Hz, 2H,CH_2), 7.78 (s, 2H, NH_2), 10.38 (s, 1H, NH), 11.43 (s, 1H, NH). ^{13}C NMR δ: 14.76, 21.39 (CH_3), 60.48 (CH_2), 70.76 (C-2), 130.26 (SCN), 148.75 (C-3), 161.65, 166.54 (COOEt), 169.19 (CONH). *Anal.* Calcd for $C_8H_{12}N_4O_3S$: C, 39.34; H, 4.95; N, 22.94. Found C, 39.29; H, 4.93; N, 22.98.

Ethyl 3-Amino-3-*iso*-butyrylhydrazino-2-thiocyanatopropenoate (2b). Yield 2.31 g, 85%. mp 162-163°C (2-PrOH). IR cm^{-1}: 3380, 3300, 3260, 3100, 2080, 1705, 1685, 1605. ^{1}H NMR δ: 1.12 (d, *J* = 6.8 Hz, 6H, CH_3), 1.19 (t, *J* = 7.3 Hz, 3H, CH_3), 3.37 (m, 1H, CH), 4.18 (q, *J* = 7.3 Hz, 2H, CH_2), 7.59 (s, 2H, NH_2), 10.25 (s, 1H, NH), 11.29 (s, 1H, NH). ^{13}C NMR δ: 14.53, 18.64 (CH_3), 32.83 (CH), 60.55 (CH_2), 71.15 (C-2), 130.17 (SCN), 148.68 (C-3), 161.62, 166.59 (COOEt), 175.21 (CONH). *Anal.* Calcd for $C_{10}H_{16}N_4O_3S$: C, 44.10; H, 5.92; N, 20.57. Found C, 44.15; H, 5.91; N, 20.55.

General Procedure for the Synthesis of Thiazoles (4) (Method C). A mixture of compound (**1**) (10 mmol) and thiourea (0.76 g, 10 mmol) in AcOH (5 mL) was cooled at 0 – 5 °C. Bromine (0.5 mL, 10 mmol) was added and the mixture was stirred at rt for 1 h. Then the reaction mixture was diluted with ethyl acetate (20 mL). The formed precipitate was filtered and purified by washings with hot EtOH. Thiazole (**4b**) was purified by recrystallization from EtOH.

Ethyl 4-Acetylhydrazino-2-aminothiazole-5-carboxylate (4a). Yield 2.20g, 90%; mp 295-297 °C (decomp). IR cm^{-1}: 3321, 3300, 3116, 1686, 1650, 1617, 1567, 1531. ^{1}H NMR δ: 1.15 (t, *J* = 7.0 Hz, 3H, CH_3), 1.77 (s, 3H, CH_3), 4.05 (q, *J* = 7.0 Hz, 2H, CH_2), 7.91 (s, 2H, NH_2), 8.16 (s, 1H, NH), 9.92 (s, 1H, NH). MS *m/z* (%): 244 (M^+, 19), 202 (7), 156 (100). *Anal.* Calcd for $C_8H_{12}N_4O_3S$: C, 39.34; H, 4.95, N, 22.94. Found C, 39.29; H, 4.94; N, 22.97.

Ethyl 4-*iso*-Butyrylhydrazino-2-aminothiazole-5-carboxylate (4b). Yield 1.80 g, 65%; mp 219-220 °C (EtOH). IR cm^{-1}: 3401, 3320, 3288, 3059, 1645, 1575, 1557. ^{1}H NMR δ: 0.97 (d, *J* = 7.0 Hz, 6H, CH_3), 1.14

(t, J = 7.0 Hz, 3H, CH_3), 2.34 (hept, J = 7.0 Hz, 1H, CH), 4.05 (q, J = 7.0 Hz, 2H, CH_2), 7.82 (s, 2H, NH_2), 8.14 (s, 1H, NH), 9.88 (s, 1H, NH). MS *m/z* (%): 272 (M^+, 19), 202 (25), 156 (100), 70 (40). *Anal.* Calcd for $C_{10}H_{16}N_4O_3S$: C, 44.10; H, 5.92; N 20.57. Found C, 44.14; H, 5.93; N, 20.54.

Ethyl 4-Benzoylhydrazino-2-aminothiazole-5-carboxylate (4c). Yield 2.10 g, 70%; mp 238-239 °C (decomp). IR cm^{-1}: 3353, 3304, 3284, 3115, 1673, 1652, 1626, 1558. ^{1}H NMR δ: 1.16 (t, J = 7.0, 3H, CH_3), 4.09 (q, J = 7.0, 2H, CH_2), 7.44, 7.83 (m, 5H, Ar), 7.89 (s, 2H, NH_2), 8.36 (s, 1H, NH), 10.59 (s, 1H, NH). MS *m/z* (%): 307 (M^+, 20), 306 (17), 201 (3), 105 (100), 77 (49). *Anal.* Calcd for $C_{13}H_{14}N_4O_3S$: C, 50.97; H, 4.61; N, 18.29. Found C, 51.00; H, 4.60; N, 18.27.

Ethyl 4-Phenylacetylhydrazino-2-aminothiazole-5-carboxylate (4d). Yield 3.14 g, 98%; mp 267 °C (decomp). IR cm^{-1}: 3393, 3333, 3301, 3065, 1648, 1569, 1534. ^{1}H NMR δ: 1.13 (t, J = 7.1 Hz, 3H, CH_3), 3.40 (s, 2H, CH_2), 4.02 (q, J = 7.1Hz, 2H, CH_2), 7.23 (m, 5H, Ar), 7.99 (s, 2H, NH_2), 8.02 (s, 1H, NH), 10.24 (s, 1H, NH). MS *m/z* (%): 321 (M^+, 17), 320 (23), 202 (44), 156 (100), 91 (26), 90 (41). *Anal.* Calcd for $C_{14}H_{16}N_4O_3S$: C, 52.49; H, 5.03; N, 17.49. Found C, 52.45; H, 5.05; N, 17.46.

General Procedure for the Synthesis of 2-Bromopropenoates (5). A mixture of **1** (10 mmol) in AcOH (5 mL) was cooled at 0 – 5 °C. Bromine (0.5 mL, 10 mmol) was added and the mixture was stirred at rt. After 1 h the reaction mixture was diluted with ethyl acetate (20 mL). The formed precipitate was filtered, dried and used for the successive reactions without further purification.

Ethyl 3-Acetylhydrazino-3-amino-2-bromopropenoate (5a). Yield 1.60 g, 60%; mp 112-113 °C. IR cm^{-1}: 3473, 3289, 3226, 1746, 1659, 1618, 1594, 1573. ^{1}H NMR δ: 1.21 (t, J = 6.9 Hz, 3H, CH_3), 1.80, 1.87 (s, 3H, CH_3), 4.20 (q, J = 6.9 Hz, 2H, CH_2), 6.61 (s, 2H, NH_2), 9.56, 9.69 (s, 1H, NH). *Anal.* Calcd for $C_7H_{12}N_3O_3Br$: C, 31.60; H, 4.55; N, 15.79. Found C, 31.56; H, 4.56; N, 15.81.

Ethyl 3-Amino-3-*iso*-butyrylhydrazino-2-bromopropenoate (5b). Yield 1.80 g, 60%; mp 159-160°C. IR cm^{-1}: 3346, 3291, 3104, 1740, 1709, 1681, 1626. ^{1}H NMR δ: 0.96 (m, 6H, $CH(C\underline{H}_3)_2$), 1.16 (m, 3H, CH_2 $C\underline{H}_3$), 2.35, 3.01 (2m, 1H, CH), 3.65, 5.12 (2s, 1H, $C\underline{H}$ $(CH_3)_2$), 4.10 (m, 2H, OCH_2), 6.26, 6.51 (2s, 2H, NH_2), 9.46, 9.53, 10.44 (3s, 3H, NH). *Anal.* Calcd for $C_9H_{16}N_3O_3Br$: C, 36.75; H, 5.48; N, 14.29. Found C, 36.80; H, 5.49; N, 14.25.

Ethyl 3-Amino-3-benzoylhydrazino-2-bromopropenoate (5c). Yield 3.20 g, 98%; mp 150-153 °C. IR cm^{-1}: 3306, 3173, 3059, 1733, 1683, 1606. ^{1}H NMR δ: 1.22 (t, J = 7.2 Hz, 3H, CH_3), 4.23 (q, J = 7.2 Hz, 2H, CH_2), 5.64 (s, 1H, CH), 7.68 (m, 5H, Ar), 9.75 (s, 2H, NH), 11.13 (s, 1H, NH). *Anal.* Calcd for $C_{12}H_{14}N_3O_3Br$: C, 43.92; H, 4.30; N, 12.80. Found C, 43.88; H, 4.31; N, 12.83.

Ethyl 3-Amino-3-phenylacetylhydrazino-2-bromopropenoate (5d). Yield 2.46 g, 72%; mp 134-135 °C. IR cm^{-1}: 3435, 3224, 1753, 1653, 1621, 1596. ^1H NMR δ: 1.18 (t, *J* = 7.3 Hz, 3H, CH_3), 3.64 (s, 2H, CH_2), 4.19 (q, *J* = 7.3 Hz, 2H, CH_2), 6.61 (s, 2H, NH_2), 7.20 (m, 5H, Ar), 9.80 (s, 1H, NH), 9.85 (s, 1H, NH). *Anal.* Calcd for $C_{13}H_{16}N_3O_3Br$: C, 45.63; H, 4.71; N, 12.28. Found C, 45.68; H, 4.70; N, 12.30.

Alternative Preparation of Thiazoles (3) (Method D). A mixture of **5** (10 mmol) and NaSCN (0.81 g, 10 mmol) in AcOH (5 mL) was stirred at rt for 1 h. Then the reaction mixture was diluted with ethyl acetate (20 mL). The formed thiazole (**3**) was isolated and purified as above described. Compounds (**3a**), (**3b**), (**3c**) and (**3d**) were obtained in 55, 60, 82 and 65% yields respectively.

Alternative Preparation of Thiazoles (4) (Method E). A mixture of **5** (10 mmol) and thiourea (0.76 g, 10 mmol) in AcOH (5 mL) was stirred at rt for 1 h. Then the reaction mixture was diluted with ethyl acetate (20 mL). The formed thiazole (**4**) was isolated and purified as above described. Compounds (**4a**), (**4b**), (**4c**) and (**4d**) were obtained in 75, 50, 55 and 72% yields respectively.

Collection of X-Ray Diffraction Data and Structure Analysis of 3c.

Suitable crystals for X-Ray analysis were obtained by recrystallization from EtOH. A crystal of **3c** was mounted on a CAD4 Enraf-Nonius diffractometer and was used to measure cell dimensions and diffraction intensities. The crystal belongs to the triclinic system, space group P-1. The unit-cell dimensions were obtained from the setting angles of 24 accurately measured reflections with θ>30°. No decay in the intensity of standard reflections was noticed over the course of data collections. The intensity data were corrected for Lorentz, polarization effects but not for absorption. Crystal data: the structure was solved by direct methods using SIR92[22] program and refined by full-matrix least-squares techniques based on F^2 using SHELXL97.[23] Anisotropic thermal parameters were employed for non-hydrogen atoms. The hydrogen atoms were located from ΔF maps and included in the refinement with isotropic parameters, except those belonging to ethyl and phenyl groups, which were added to calculated positions and allowed to ride on associated carbon atoms. Neutral scattering factors[24] were employed and the anomalous dispersion terms for all atoms were included in F_C. The calculations, were performed on computers using SHELXL,[23] PARST[25] and ORTEP3[26] programs. CCDC-211205 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

REFERENCES

1. J. Pratt, H. S. Jae, S. Rosemberg, K. Spina, M. Winn, S. Buchner, E. Novosad, D. Kerkman, K. Shiosaki, T. Opgenorth, and J. DeBernardis, *Bioorg. Med. Chem. Lett*., 1994, **4**, 169.
2. B. Plouvier, C. Bailly, R. Houssin, and J. P. Henichart, *Heterocycles*, 1991, **32**, 693.
3. T.E. Lehmann, W. A. Greenberg, D. A. Liberles, C. K. Wada, and P. B. Dervan, *Helv. Chim. Acta*,1997, **80**, 2002.
4. E. C. Roberts and Y. F. Shealy, *J. Med. Chem*., 1972, **15**, 1310
5. W. Knauf, P. Strehlke, and E. Woelk, *Eur. J. Med. Chem. Chim. Ther*., 1975, **10**, 533.
6. P. V. Plazzi, F. Bordi, C. Silva, G. Morini, P. L. Castellani, G. Vaona, and M. Impiacciatore, *Farmaco*, 1989, **44**, 1011.
7. P. J. Islip, M. D. Closier, M. R. Johnson, and M. C. Neville, *J. Med. Chem*., 1972, **15**, 101.
8. W. Daries, J. A. MacLaren, and L. R. Wilkinson, *J. Chem. Soc*., 1950, 3491.
9. R. M. Dodson and H. W. Turner, *J. Am. Chem. Soc*., 1951, **73**, 4517.
10. K. Gewald, P. Blauschmidt, and R. Mayer, *J. Prakt. Chem.*, 1967, **35**, 97.
11. K. Hirai, H. Sugimoto, and T. Ishiba, *J. Org. Chem*., 1980, **45**, 253.
12. M. Yokoyama, M. Kurauchi, and T. Imamoto, *Tetrahedron Lett*., 1981, **22**, 2285.
13. W. Ried, G. W. Broft, and J. W. Batz, *Chem. Ber*., 1983, **116**, 1547.
14. K. N. Rajasekharan, K. P. Nair, and G. C. Jenardanan, *Synthesis*, 1986, 353.
15. F. Freeman and D. S. H. L. Kim, *J. Org. Chem*., 1991, **56**, 4645.
16. M. Romero-Ortega, A. Aviles, R. Cruz, A. Fuentes, R. M. Gomez, and A. Plata, *J. Org. Chem*., 2000, **65**, 7244.
17. M. T. Cocco and V. Onnis, *Synthesis*, 1993, 199.
18. M. T. Cocco, C. Congiu, and V. Onnis, *Trends in Heterocyclic Chemistry*, 1995, **4**, 13.
19. H. Bohme and R. Brown, *Liebigs Ann. Chem*., 1971, **744**, 27.
20. J. Beger and P. D. Thong, Ger. (East), 127,813 (Cl. C07D277/12), 04 Nov. 1986, Appl. 280,132, 30 Aug. 1985 (*Chem. Abstr*., 1987, **107**, 154324).
21. M. T. Cocco, C. Congiu, V. Onnis, and A. Maccioni, *J. Heterocycl. Chem*, 1991, **28**, 797.
22. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, and M. Camalli, *J. Appl. Cryst.*, 1994, **27**, 435.
23. G. M. Sheldrick, SHELXL97, Universität Göttingen, 1997.
24. International Tables for X-Ray Crystallography, Vol 4, Kynoch Press, Birmingham, UK, 1974.
25. M. Nardelli, *Comput. Chem.*, 1983, **7**, 95.
26. L. J. Faruggia, ORTEP3 for Windows *J. Appl. Cryst.*, 1997, **30**, 565.