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Short communication

SHORT COMMUNICATION

Novel one-pot process for the synthesis of ethyl 2-imino-4--methyl-2,3-dihydrothiazole-5-carboxylates

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Abstract: A facile one-pot, two-step process for the synthesis of ethyl 2-imino--4-methyl-2,3-dihydrothiazole-5-carboxylates *via* the cyclocondensation of ethyl 3-oxo-2-thiocyanatobutanoate with a variety of hydrazine and hydrazide derivatives was developed. Ethyl 3-oxo-2-thiocyanatobutanoate itself was synthesized as an intermediate from the reaction of ethyl 2-chloroacetoacetate with potassium thiocyanate (KSCN). The molecular structures of these newly synthesized compounds were elucidated based on elemental analysis and spectral data.

Keywords: three-component reaction; thiocyanation; thiazole derivatives; cyclocondensation; hydrazines; hydrazides.

INTRODUCTION

Thiazoles are of eminent importance because of their potential as bioactive compounds[1,2] and versatile building blocks for natural products and pharmaceuticals.[3,4] Thiazole heterocycles are important subunits in many complex natural compounds and drugs, *e.g.*, vitamin B_1, epothilones, thiostrepton, nizatidine (ulcer therapeutic), ritonavir (a potent inhibitor of HIV protease, Fig. 1) and thiamine pyrophosphate (TPP, a coenzyme that is part of the Krebs cycle in the process of cellular respiration).[3–6] A tetrahydrothiazole also appears in the skeleton of penicillin, which is one of the first and most important broad spectrum antibiotics. Thiazole derivatives display a wide range of biological activities, such as cardiotonic, fungicidal, sedative, anesthetic, bactericidal and anti--inflammatory.[7–12] Furthermore, there are many other applications of thiazole derivatives, for example in liquid crystals or cosmetics (sunscreens).[13,14]

The synthesis of thiazole derivatives is important because of their wide range of pharmaceutical and biological properties. Many methods have been developed

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for the construction of thiazole ring systems. One classical and widely used method is the condensation of α-haloketones with thioamide derivatives, which is known as the Hantzsch reaction.[15–17] Another efficient method is the introduction of substituents onto a thiazole core structure through Stille coupling, which involves the use of organostannane intermediates.[18] In recent years, a new and frequently encountered method for thiazole synthesis is the conversion of thiazoline derivatives through the use of dehydrogenating reagents, such as sulfur, $KMnO_4$, Cu(I)/Cu(II)/peroxide oxidation, MnO_2, NaH/DBU, etc.[19–26]

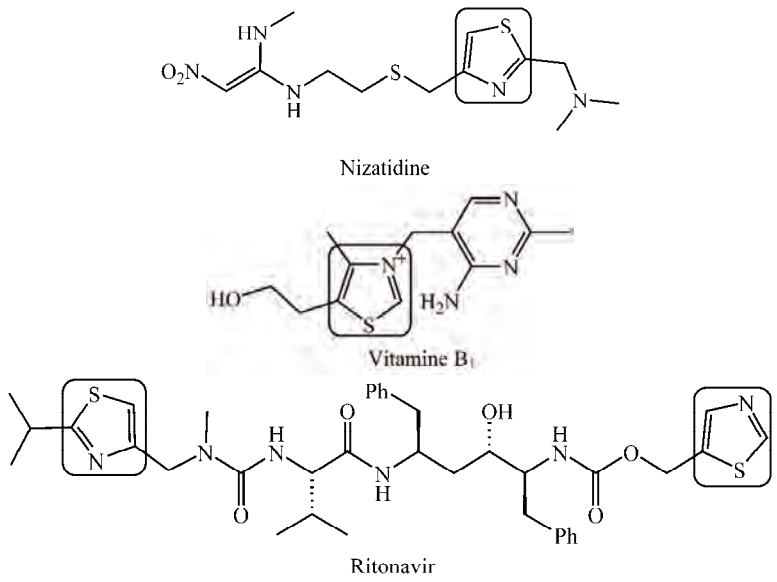


Fig. 1. Thiazoles as part of some natural compounds and drugs.

These findings prompted the present synthesis of new ethyl 2-imino-4--methyl-2,3-dihydrothiazole-5-carboxylates. These synthesized compounds were characterized by NMR and IR spectral data, and elemental analysis data.

EXPERIMENTAL

All chemicals and solvents were purchased from Merck and TCI Chemical Companies and were used without purification. All yields refer to isolated products and are expressed in %. Melting points were recorded on a Kruss type KSP1N melting point meter and are uncorrected. The IR spectra of the products in the range 400–4,000 cm^{-1} were recorded on a Bruker Tensor-27 FT-IR spectrometer and only noteworthy absorptions are listed. The ^1H- and ^{13}C-NMR spectra of DMSO-d_6 solutions were recorded on a Bruker FT-NMR Ultra Shield-400 spectrometer with residual protons of the solvent as internal standard (2.50 ppm for ^1H and 39.48 ppm for ^{13}C). Elemental analyses were performed for C, H, N and S on a Thermo Finnigan Flash EA microanalyzer. Monitoring of the progress of the reactions and the

purity of the products were affected by TLC on alufoil plates pre-coated with silica gel (60, Merck); the eluent was $CHCl_3$:CH_3OH, 9:1 and visualization was with I_2 vapor.

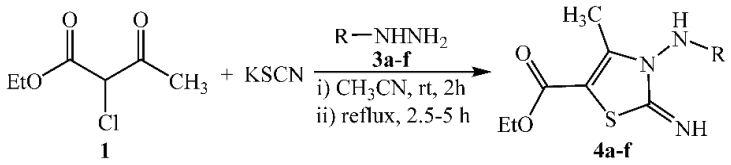
Physical, analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

*General procedure for the synthesis of ethyl 2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylates (**4a**–**f**)*

A suspension of ethyl 2-chloroacetoacetate (**1**, 1.65 g, 10 mmol) and potassium thiocyanate (KSCN) (0.97 g, 10 mmol) in acetonitrile (10 mL) was stirred at room temperature for 2 h. Then, hydrazine or hydrazide derivatives **3a**–**f** were added dropwise to the reaction mixture and the mixture was stirred for a further 1 h at the same temperature before it was heated under reflux for 2.5–5 h (2.5 h for **4a** and **b**; 4 h for **4c** and 5h for **4d**–**f**). The reaction mixture was cooled to room temperature, the precipitate was filtered off, and washed with water (10 mL) and ethanol (10 mL), dried in air, and recrystallized from methanol, to give the pure products **4a**–**f** as white, yellow or red crystals.

RESULTS AND DISCUSSION

Ethyl 2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylates **4a**–**f** were prepared in a simple and facile one-pot, two-step procedure. First, ethyl 2-chloroacetoacetate (**1**) was reacted with potassium thiocyanate (KSCN) in acetonitrile as a solvent at room temperature for 2 h to give ethyl 3-oxo-2-thiocyanatobutanoate (**2**) as an intermediate. Then, treatment of this compound with various hydrazine or hydrazide derivatives (**3a**–**f**) under reflux for 2.5–5 h gave new thiazoles **4a**–**f** in 48–83 % yields after recrystallization from methanol (Scheme 1). The structures of all products are presented in Table I.



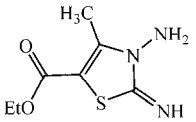
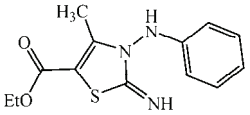
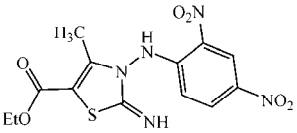
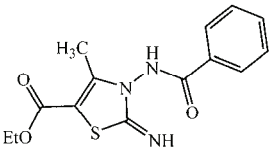
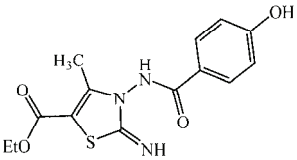
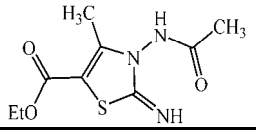
1 **4a-f**

R = H; C_6H_5; 2,4-$[NO_2]_2$-C_6H_3; C_6H_5CO; 4-OH-C_6H_4CO; CH_3CO

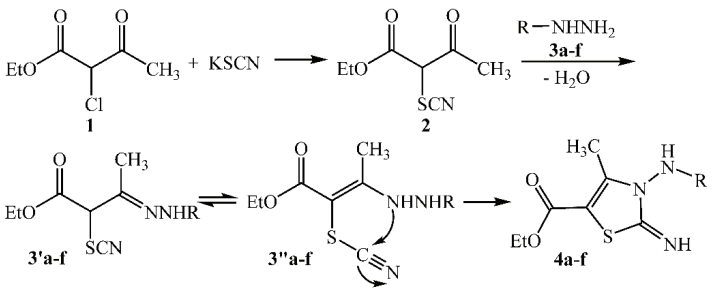
Scheme 1. Total synthesis of thiazole derivatives **4a**–**f**.

A plausible mechanism is depicted in Scheme 2 for the formation of these compounds. As shown, first, ethyl 3-oxo-2-thiocyanatobutanoate (**2**) as an intermediate was probably produced from the substitution reaction between ethyl 2-chloroacetoacetate (**1**) and potassium thiocyanate (KSCN). Then, condensation of compound **2** with hydrazine and hydrazide derivatives **3a**–**f** generated intermediates **3′a**–**f** or **3″a**–**f**. Finally, ethyl 2-imino-4-methyl-2,3-dihydrothiazole-5--carboxylates **4a**–**f** were afforded from intramolecular addition reactions of intermediates **3″a**–**f** by attack of the NH group to the carbon atom of the C≡N bond. Note that in this multistep synthesis, none of the likely key intermediates was isolated.

TABLE I. Synthesis of thiazole derivatives **4a**–**f**

No.	Product	R	Reagent **3a**–**f**	Yield, %	M.p., °C
4a		H	Hydrazine	50	285–286
4b		C_6H_5	Phenylhydrazine	55	280–281 (Decomp.)
4c		2,4-$[NO_2]_2$-C_6H_3	2,4-Dinitrophenylhydrazine	83	218–219 (Decomp.)
4d		C_6H_5CO	Benzhydrazide	68	200–201
4e		4-OH-C_6H_4CO	4-Hydroxybenzhydrazide	48	185–186
4f		CH_3CO	Acetohydrazide	60	179–180

The structural assignments of compounds **4a**–**f** were based on their analytical and spectral data. The ^{1}H-NMR spectra of compounds **4a**–**f** showed triplet and quartet signals due to methyl and methylene protons included in the ethoxy group within δ 1.23–1.30 and 4.15–4.27 ppm ($J \approx 7.1$ Hz), signals due to the methyl and –NH– groups of the thiazole ring within δ 1.91–2.55 and 10.02–11.44



Scheme 2. The proposed mechanism of formation of products **4a**–**f**.

ppm, respectively, and signals within δ 7.81–11.00 ppm belonging to the –NNH– groups of compounds **4b**–**f**. The ^{13}C-NMR spectra of the products exhibited signals within δ 14.00–14.44, 59.67–62.81 and 162.44–169.91 ppm attributed to methyl, methylene and carbonyl carbons, respectively, included in the $-CO_2Et$ group, signals within δ 11.31–22.41, 106.08–107.95, 161.35–163.03 and 157.06––161.58 ppm, attributed to the $-C=C\mathbf{C}H_3$, $-\mathbf{C}=CCH_3$, $-C=\mathbf{C}CH_3$ and –C=NH carbons, respectively, signals within δ 165.11–167.73 ppm belonging to the carbonyl carbons adjacent to the –NH– groups of compounds **4d**–**f**. The FT-IR spectra of **4a**–**f** in KBr disks showed absorption bands within ν 3305–3467 cm^{-1} corresponding to –NH– groups, 1647–1715 cm^{-1} belonging to carbonyl groups, 1601–1666 cm^{-1} belonging to imine groups and 1406–1611 cm^{-1} attributed to the –C=C– bonds. All this evidence plus microanalytical data strongly supports the formation of all products.

CONCLUSIONS

In summary, several new ethyl 2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylates were synthesized in a one-pot, two-step process from the cyclocondensation of ethyl 3-oxo-2-thiocyanatobutanoate as an intermediate with various hydrazines and hydrazides, which constitute potential precursors for the synthesis of various biological and pharmaceutical compounds.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgments. The authors would like to thank Mrs. Marzieh Akbari for recording the NMR spectra.

ИЗВОД

НОВ ПОСТУПАК СИНТЕЗЕ ЕТИЛ-2-ИМИНО-4-МЕТИЛ-2,3-ДИХИДРОТИАЗОЛ-5--КАРБОКСИЛАТА У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ

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Развијен је нов поступак синтезе етил-2-имино-4-метил-2,3-дихидротиазол-5-карбоксилата, у једном реакционом кораку циклокондензације етил-3-оксо-2-тиоцијанатобутаноата и хидразина или хидразинских деривата. Полазно једињење етил-3-оксо-2--тиоцијанатобутаноат синтетисан је из етил-2-хлорацетата и калијум-тиоцијаната (KSCN). Структура добијених једињења одређена је на основу резултата спектроскопске и елементалне анализе.

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SUPPLEMENTARY MATERIAL TO

Novel one-pot process for the synthesis of ethyl 2-imino-4--methyl-2,3-dihydrothiazole-5-carboxylates

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PHYSICAL, ANALYTICAL AND SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

Ethyl 3-amino-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate ***(4a)***. Yield: 50 %; white crystals; m.p.: 285–286 °C; Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.78; H, 5.51; N, 20.88; S, 15.93 %. Found: C, 41.82; H, 5.56; N, 20.86, S, 15.85 %; IR (KBr, cm^{-1}): 1585 (C=C stretching of thiazole ring), 1623 (C=N stretching of imine group), 1693 (C=O stretching of CO_2Et group), 3467, 3434 (NH stretching of imine and primary amine groups); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.24 (3H, *t*, *J* = 7.1 Hz, CH_3), 2.07 (3H, *s*, =CCH_3), 4.16 (2H, *q*, *J* = 7.1 Hz, OCH_2), 7.91 (2H, *s*, NH_2, D_2O exchangeable), 10.16 (1H, *s*, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 169.91 (C=O), 161.32 (=**C**CH_3), 159.99 (C=NH), 106.65 (**C**=CCH_3), 59.73 (OCH_2), 19.91 (C=C**C**H_3), 14.44 (CH_2**C**H_3).

Ethyl 2-imino-4-methyl-3-(phenylamino)-2,3-dihydrothiazole-5-carboxylate ***(4b)***. Yield: 55 %; white crystals; Decomp. 280–281 °C; Anal. Calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56 %. Found: C, 56.24; H, 5.52; N, 15.18, S, 11.48 %; IR (KBr, cm^{-1}): 1406, 1545 (C=C stretching of aromatic ring), 1611 (C=C– stretching of thiazole ring), 1666 (C=N stretching of imine group), 1709 (C=O stretching of CO_2Et group), 3349 (NH stretching of imine and secondary amine); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.30 (3H, *t*, *J* = 7.1 Hz, CH_3), 2.09 (3H, *s*, =CCH_3), 4.27 (2H, *q*, *J* = 7.1 Hz, OCH_2), 7.43, 7.72 (3H, *m*, 2H, *d*, *J* = 10.1 Hz, aromatic), 7.81 (1H, *s*, N**H**Ph, D_2O exchangeable), 10.06 (1H, *s*, C=NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 162.44 (C=O), 161.44 (=**C**CH_3), 157.06 (C=NH), 145.85, 130.72, 123.05, 115.79 (aromatic), 106.93 (**C**=CCH_3), 60.96 (OCH_2), 17.31 (=C**C**H_3), 14.13 (CH_2**C**H_3).

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*Ethyl 3-((2,4-dinitrophenyl)amino)-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4c**)*. Yield: 83 %; red crystals; Decomp. 218–219 °C; Anal. Calcd. for $C_{13}H_{13}N_5O_6S$: C, 42.51; H, 3.57; N, 19.07; S, 8.73 %. Found: C, 42.55; H, 3.53; N, 19.14, S, 8.67 %; IR (KBr, cm^{-1}): 1338, 1427 (N–O stretching of NO_2 group), 1498, 1594 (C=C stretching of aromatic and thiazole rings), 1613 (C=N stretching of imine group), 1715 (C=O stretching of CO_2Et group), 3089, 3305 (NH stretching of imine and secondary amine); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.26 (3H, *t*, *J* = 7.1 Hz, CH_3), 2.55 (3H, *s*, =CCH_3), 4.26 (2H, *q*, *J* = 7.1 Hz, OCH_2), 8.30, 8.33, 9.03 (1H, *d*, *J* = 2.6 Hz, 1H, *d*, *J* = 2.6 Hz, 1H, *d*, *J* = 9.3 Hz, aromatic), 8.95 (1H, *s*, N**H**Ph, D_2O exchangeable), 11.44 (1H, *s*, C=NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 168.65 (C=O), 161.83 (C=**C**CH_3), 159.11 (C=NH), 148.99, 143.07, 138.47, 130.25, 122.79, 116.27 (aromatic), 107.95 (**C**=CCH_3), 62.81 (OCH_2), 14.00 (CH_2**C**H_3), 11.31 (=C**C**H_3).

*Ethyl 3-benzamido-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4d**)*. Yield: 68 %; white crystals; m.p.: 200–201 °C; Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50 %. Found: C, 55.00; H, 5.01; N, 13.79, S, 10.45 %; IR (KBr, cm^{-1}): 1463, 1509 (C=C stretching of aromatic and thiazole rings), 1601 (C=N stretching of imine group), 1647 (C=O stretching of CONH group), 1669 (C=O stretching of CO_2Et group), 3442 (NH stretching of imine and amide); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.23 (3H, *t*, *J* = 7.0 Hz, CH_3), 2.12 (3H, *s*, =CCH_3), 4.15 (2H, *q*, *J* = 7.0 Hz, OCH_2), 7.53–7.98 (5H, *m*, aromatic), 10.72 (1H, *s*, C=NH, D_2O exchangeable), 11.00 (1H, *s*, CONH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 168.47 (CO_2Et), 165.11 (CONH), 161.35 (=**C**CH_3), 159.72 (C=NH), 132.14, 131.92, 128.53, 127.60 (aromatic), 106.08 (**C**=CCH_3), 59.67 (OCH_2), 16.96 (=C**C**H_3), 14.44 (CH_2**C**H_3).

*Ethyl 3-(4-hydroxybenzamido)-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4e**)*. Yield: 48 %; yellow crystals; m.p.: 185–186 °C; Anal. Calcd. for $C_{14}H_{15}N_3O_4S$: C, 52.33 %; H, 4.71; N, 13.08; S, 9.98 %. Found: C, 52.39; H, 4.66; N, 13.15, S, 9.90 %; IR (KBr, cm^{-1}): 1472, 1506 (C=C– stretching of aromatic and thiazole rings), 1609 (C=N stretching of imine group), 1674 (C=O stretching of CONH group), 1702 (C=O stretching of CO_2Et group), 3419 (NH stretching of imine and amide); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.24 (3H, *t*, *J* = 7.0 Hz, CH_3), 2.16 (3H, *s*, =CCH_3), 4.17 (2H, *q*, *J* = 7.0 Hz, OCH_2), 6.93, 7.80 (2H, *d*, *J* = 8.2 Hz, 2H, *d*, *J* = 8.2 Hz, aromatic), 8.15 (1H, *s*, OH, D_2O exchangeable), 10.13 (1H, *s*, C=NH, D_2O exchangeable), 10.59 (1H, *s*, CONH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 169.85 (CO_2Et), 167.73 (CONH), 163.03 (=**C**CH_3), 161.58 (C=NH), 159.73, 132.32, 129.41, 114.93 (aromatic), 106.63 (**C**=CCH_3), 60.40 (OCH_2), 22.41 (=C**C**H_3), 14.35 (CH_2**C**H_3).

*Ethyl 3-acetamido-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4f**)*. Yield: 60 %; white crystals; m.p.: 179–180 °C; Anal. Calcd. for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27; S, 13.18 %. Found: C, 44.39; H, 5.37; N, 17.33, S, 13.14 %; IR (KBr, cm^{-1}): 1590 (C=C stretching of aromatic and thiazole rings), 1616 (C=N stretching of imine group), 1673 (C=O stretching of CONH group), 1703 (C=O stretching of CO_2Et group), 3253, 3382 (NH stretching of imine and amide); ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.23 (3H, *t*, J = 7.1 Hz, CH_3), 1.91 (3H, *s*, $=CCH_3$), 2.43 (3H, *s*, $COCH_3$), 4.16 (2H, *q*, J = 7.1 Hz, OCH_2), 10.02 (1H, *s*, C=NH, D_2O exchangeable), 10.39 (1H, *s*, CONH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 168.99 (CO_2Et), 167.72 (CONH), 161.79 ($=\mathbf{C}CH_3$), 161.49 (C=NH), 106.86 ($\mathbf{C}=CCH_3$), 60.03 (OCH_2), 20.45 ($=C\mathbf{C}H_3$), 17.29 ($CO\mathbf{C}H_3$), 14.24 ($CH_2\mathbf{C}H_3$).