

One-pot Synthesis and Characterization of Highly Functionalized Thiazoles

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ABSTRACT: A facile and efficient one-pot three-step process for the synthesis of 5-acetyl-2-imino-4-methylthiazoles via the cyclocondensation of 3-thiocyanatoacetylacetone with various hydrazine or hydrazide derivatives in EtOH has been developed. 3-Thiocyanatoacetylacetone itself has been synthesized as the intermediate from substitution reaction of thiocyanate with 3-chloroacetylacetone. Better results were obtained by three-step procedures vs one-step reaction. The proposed method does not required techniques such as extraction and chromatography. Surprisingly, 3,5-dimethyl-4-thiocyanato-1H-pyrazoles were not produced in this reaction, it was proved based on the existence of the acetyl group in the products. The molecular structures of newly synthesized compounds were elucidated on the basis of elemental analysis and spectral data.

KEYWORDS: One-pot synthesis; Thiazole; Cyclocondensation; Hydrazine; Hydrazide.

INTRODUCTION

Thiazole derivatives are appeared in many natural and synthetic products with a wide range of pharmacological activities. For example, thiazole ring is present in vitamin B₁ and its coenzyme, which play in the electron sink and the decarboxylation of α -keto acids, respectively [1]. They are also helpful in the normal function of the nervous system due to their role in the synthesis of acetylcholine (a neurotransmitter).

Thiazole ring system occurs in the antibiotics bacitracin, penicillin and in numerous synthetic drugs. Synthetic drugs belonging to the thiazole family include the antimicrobial agents sulfathiazole and acinitrazole [2], anti-HIV drug ritonavir [3], the antidepressant pramipexole [4], antineoplastic agents bleomycin and tiazofurin [5], the antiasthmatic drug cinalukast [6], antiulcer agent nizatidine [7]. Thiazole derivatives such as the non-steroidal anti-inflammatory drug meloxicam [8]

and fanetizole [9] were also used in wide range. Thiazole derivatives containing 1,3,4-thiadiazole, 1,3,4-oxadiazole and 1,2,4-triazole substituents have showed the distinct antibacterial and antifungal activities [10]. Thiazole is known as a ligand of estrogen receptors [11] and the novel class of antagonists for adenosine receptors [12].

Commercial significant thiazoles are found in many fungicides and dyes. Thifluzamide, tricyclazole, and thiabendazole are marked for control of various agricultural pests [13, 14]. Red and yellow dyes of rhodanine and primuline are some examples of the thiazole derivatives [15, 16].

According to the emerging importance of thiazoles and their derivatives, several methods for their synthesis were developed by using the various catalysts [17-21], conditions [22-27] and strategies [28-34]. The development of novel methods for the improvement of time, yield,

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1021-9986/2016/4/31

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and reaction conditions is still in demand. In this study, highly functionalized thiazoles were synthesized in moderate to good yields *via* an efficient method, without necessity of using the toxic and expensive solvents and catalysts. Besides, the products were purified in a simple and quick process.

Based on the above information and our interest in thiazole as a biologically active pharmacophore [35-39] and the widespread application of one-pot processes in the synthesis of heterocyclic compounds [40-44], we have developed a one-pot procedure for the synthesis of highly functionalized thiazoles, starting from 3-chloroacetylacetone and potassium thiocyanate (KSCN) without isolation of the intermediate 3-thiocyanatoacetylacetone. The synthesized compounds are characterized by NMR, IR spectral data, and elemental analysis.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from Merck and TCI chemical companies and were used without purification. All yields refer to isolated products. Melting points were recorded on a Kruss type KSP1N melting point meter and are uncorrected. The IR spectra of products were determined as KBr pellets on Bruker Tensor-27 FT-IR spectrometer. 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 reactions and the purity of the products were effected by TLC on alufoil plates pre-coated with silica gel (60, Merck), eluent was $\text{CHCl}_3\text{-CH}_3\text{OH}$, 9:1, visualization with I_2 vapor.

General procedure for the preparation of 5-acetyl-2-imino-4-methylthiazoles (3a-f)

A suspension of 3-chloroacetylacetone (**1**) (1.35 g, 10 mmol) and potassium thiocyanate (KSCN) (0.97 g, 10 mmol) in absolute ethanol (10 mL) was mixed at room temperature for 2h. Then, hydrazine or hydrazide derivatives **2a-f** were added dropwise to the reaction mixture. The mixture was stirred for a further 3h at the same temperature before it was heated under reflux

for 6-8 h (8 h for **3a,b**; 6 h for **3c,d,f** and 7 h for **3e**). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and poured gradually onto crashed ice. The slurry was filtered off, dried, and recrystallized from various ratios of ethanol-water mixtures to provide the pure products **3a-f**.

1-(3-Amino-2-imino-4-methyl-2,3-dihydrothiazol-5-yl)ethan-1-one (3a)

Bright orange powder, Yield 0.82 g, 48%, m.p 188–189 °C. IR (KBr): 3467, 3340, 1693, 1623, 1506, 1471, 1278, 1243, 1106, 774, 513 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): 2.14 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.31 (s, 3H, CH_3CO), 8.00 (s, 2H, NH_2), 12.53 (b, 1H, C=NH). ^{13}C NMR (100 MHz, DMSO- d_6): 14.2 ($\underline{\text{C}}\text{H}_3\text{-C=C}$), 29.3 ($\underline{\text{C}}\text{H}_3\text{CO}$), 106.4 ($\text{CH}_3\text{-C=C}$), 158.1 (C=NH), 170.0 ($\text{CH}_3\text{-C=C}$), 186.1 (C=O). Anal. Calcd for $\text{C}_6\text{H}_9\text{N}_3\text{OS}$: C, 42.09; H, 5.30; N, 24.54; S, 18.72. Found: C, 42.02; H, 5.26; N, 24.61; S, 18.75.

1-(3-((2,4-Dinitrophenyl)amino)-2-imino-4-methyl-2,3-dihydrothiazol-5-yl)ethan-1-one (3b)

Dark orange powder, Yield 1.85 g, 55%, m.p 111–112 °C. IR (KBr): 3325, 2987, 1707, 1618, 1505, 1448, 1380, 1341, 1317, 1256, 1100, 922, 836, 759, 742 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): 2.12 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.32 (s, 3H, CH_3CO), 8.07, 8.64 (d, 1H, $J = 8.2$ Hz, m, 2H, Ph), 8.91 (s, 1H, NNH), 12.49 (s, 1H, C=NH). ^{13}C NMR (100 MHz, DMSO- d_6): 12.2 ($\underline{\text{C}}\text{H}_3\text{-C=C}$), 29.3 ($\underline{\text{C}}\text{H}_3\text{CO}$), 107.8 ($\text{CH}_3\text{-C=C}$), 121.2 (C-3), 128.6 (C-1), 130.1 (C-6), 133.0 (C-5), 146.4 (C-2), 154.1 (C-4), 156.0 (C=NH), 170.2 ($\text{CH}_3\text{-C=C}$), 186.3 (C=O). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_5\text{S}$: C, 42.67; H, 3.32; N, 20.82; S, 9.45. Found: C, 42.73; H, 3.29; N, 20.76; S, 9.50.

N-(5-Acetyl-2-imino-4-methylthiazol-3(2H)-yl)benzamide (3c)

Bright yellow powder, Yield 2.2 g, 80%; m.p 217–218 °C. IR (KBr): 3199, 3011, 1701, 1632, 1578, 1535, 1488, 1447, 1339, 1279, 989, 933, 784, 689 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): 2.12 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.31 (s, 3H, CH_3CO), 7.51 (s, 1H, H-4), 7.54 (d, 2H, $J = 7.6$ Hz, H-3,5), 7.93 (d, 2H, $J = 7.0$ Hz, H-2,6), 10.52 (s, 1H, C=NH), 12.67 (b, 1H, NNH). ^{13}C NMR (100 MHz, DMSO- d_6): 13.3 ($\underline{\text{C}}\text{H}_3\text{-C=C}$), 29.2 ($\underline{\text{C}}\text{H}_3\text{CO}$), 117.1 ($\text{CH}_3\text{-C=C}$), 127.4 (C-2,6), 128.4 (C-3,5), 130.7 (C-4), 131.8 (C-1), 154.4 (C=NH), 165.8 (NHCO), 170.3 ($\text{CH}_3\text{-C=C}$),

186.2 ($\text{CH}_3\text{C}=\text{O}$). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$: C, 56.75; H, 4.82; N, 15.28; S, 11.57. Found: C, 56.71; H, 4.76; N, 15.26; S, 11.64.

***N*-(5-Acetyl-2-imino-4-methylthiazol-3(2*H*)-yl)-4-hydroxybenzamide (3*d*)**

Dark yellow powder, Yield 1.89 g, 65%, m.p 182–183 °C. IR (KBr): 3409, 3258, 2360, 1717, 1616, 1541, 1508, 1457, 1324, 1291, 922, 781, 669 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 2.14 (s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 2.31 (s, 3H, CH_3CO), 6.90 (d, 2H, $J = 8.5$ Hz, H-3,5), 7.89 (d, 2H, $J = 8.5$ Hz, H-2,6), 8.06 (s, 1H, OH), 10.14 (s, 1H, $\text{C}=\text{NH}$), 12.50 (s, 1H, NNH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 13.0 ($\text{CH}_3\text{-C}=\text{C}$), 29.2 (CH_3CO), 110.6 ($\text{CH}_3\text{-C}=\text{C}$), 114.8 (C-3,5), 129.4 (C-1), 134.1 (C-2,6), 153.6 ($\text{C}=\text{NH}$), 162.0 (C-4), 166.5 (NHCO), 170.2 ($\text{CH}_3\text{-C}=\text{C}$), 186.3 ($\text{CH}_3\text{C}=\text{O}$). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$: C, 53.64; H, 4.55; N, 14.37; S, 10.93. Found: C, 53.60; H, 4.50; N, 14.42; S, 11.00.

***N*-(5-Acetyl-2-imino-4-methylthiazol-3(2*H*)-yl)acetamide (3*e*)**

Dark yellow powder, Yield 1.09 g, 51%, m.p 198–199 °C. IR (KBr): 3287, 3179, 2372, 1745, 1611, 1506, 1418, 1372, 1336, 1273, 984, 961, 670 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 2.10 (s, 3H, NHCOCH_3), 2.13 (s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 2.30 (s, 3H, CH_3CO), 10.24 (s, 1H, $\text{C}=\text{NH}$), 12.60 (b, 1H, NNH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 14.2 ($\text{CH}_3\text{-C}=\text{C}$), 17.2 (CH_3CONH), 29.3 (CH_3CO), 109.2 ($\text{CH}_3\text{-C}=\text{C}$), 160.1 ($\text{C}=\text{NH}$), 168.6 (NHCO), 170.1 ($\text{CH}_3\text{-C}=\text{C}$), 186.0 ($\text{CH}_3\text{C}=\text{O}$). Anal. Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_2\text{S}$: C, 45.01; H, 5.15; N, 19.78; S, 14.99. Found: C, 45.06; H, 5.20; N, 19.70; S, 15.03.

***N*-(5-Acetyl-2-imino-4-methylthiazol-3(2*H*)-yl)furan-2-carboxamide (3*f*)**

White powder, Yield 1.91 g, 72%, m.p 278–279 °C (dec). IR (KBr): 3433, 3297, 2367, 1687, 1607, 1558, 1500, 1462, 1348, 1290, 1030, 954, 878, 784, 600 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 2.13 (s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 2.31 (s, 3H, CH_3CO), 7.95 (d, 1H, $J = 3.6$ Hz, H-5), 8.18 (m, 1H, H-3), 8.83 (m, 1H, H-4), 10.37 (s, 1H, $\text{C}=\text{NH}$), 12.43 (s, 1H, NNH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 13.3 ($\text{CH}_3\text{-C}=\text{C}$), 29.2 (CH_3CO), 107.1 ($\text{CH}_3\text{-C}=\text{C}$), 112.8 (C-3), 124.6 (C-4), 144.5 (C-5), 149.2 (C-2), 155.5 (NHCO), 159.9 ($\text{C}=\text{NH}$), 170.3 ($\text{CH}_3\text{-C}=\text{C}$), 186.3

($\text{CH}_3\text{C}=\text{O}$). Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$: C, 49.73; H, 4.23; N, 15.88; S, 12.04. Found: C, 49.80; H, 4.18; N, 15.84; S, 12.09.

RESULTS AND DISCUSSION

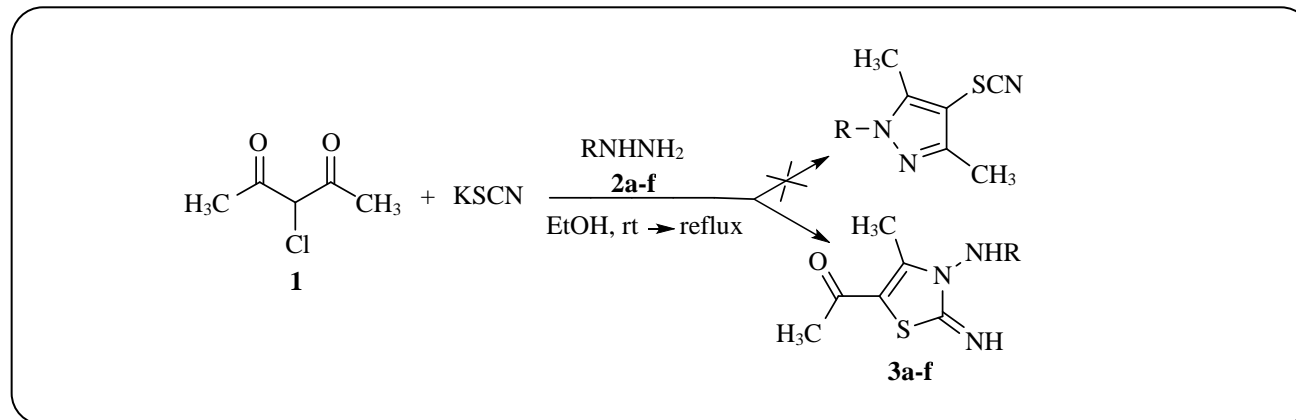
Highly functionalized thiazoles **3a-f** were prepared in a simple and facile one-pot three-step procedure. Initially, 3-chloroacetylacetone (**1**) was reacted with potassium thiocyanate (KSCN) in ethanol at room temperature for 2 h to give 3-thiocyanatoacetylacetone as intermediate. Then, this compound was reacted with various hydrazine or hydrazide derivatives **2a-f** under the same conditions for another 3 h to complete the ketone-amine condensation reaction. Finally, the reaction mixture was refluxed for 6-8 h before being poured into crashed ice to precipitate out new thiazoles **3a-f** as white or colored solids in 48–80% yields after recrystallization from ethanol-water (Scheme 1). The structure of all products are presented in Table 1.

The one-step reaction between reagents led to various unidentified by-products which resulted in the lower yield of the desired products. Therefore, a three-step process was preferably used. During this process, 3,5-dimethyl-4-thiocyanato-1*H*-pyrazoles were not produced, it can be easily proved by the presence of acetyl group in products. A plausible mechanism is depicted for the formation of thiazoles (**3a-f**) (Scheme 2). As shown, the nucleophilic substitution of chloride by thiocyanate led to formation of intermediate **1'** as an unstable solid [45], although its analogues have been successfully prepared [46]. Then, compound **2** was condensed with hydrazine and hydrazide derivatives **3a-f** to generate intermediates **2'a-f**. Finally, intramolecular nucleophilic addition of the NH group to the carbon atom of the $\text{C}=\text{N}$ bond were afforded thiazoles **3a-f**.

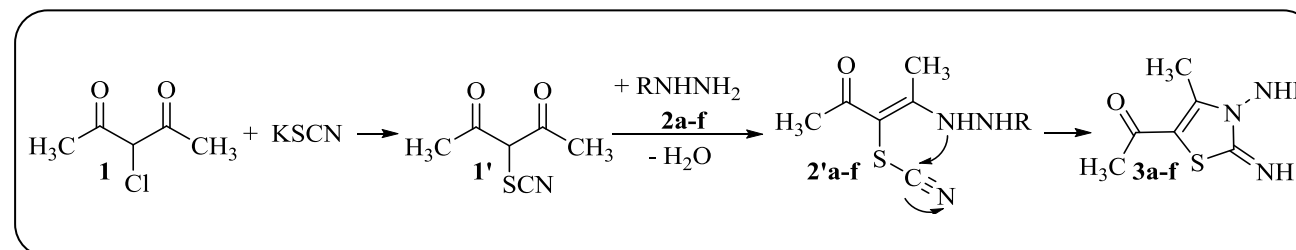
The structural assignments of compounds **3a-f** were based on their analytical and spectral data. The ^1H NMR spectra of compounds **3a-f** showed singlet signals due to methyl protons of acetyl group within $\delta = 2.30\text{--}2.32$ ppm, signals of methyl and -NH- groups of the thiazole ring within $\delta = 2.12\text{--}2.14$ ppm and $\delta = 10.14\text{--}12.53$ ppm respectively, and singlet or broad signals appeared within $\delta = 8.91\text{--}12.67$ ppm belonging to -NNH- groups. The ^{13}C NMR spectra of the products exhibited signals within $\delta = 29.2\text{--}29.3$ ppm and $\delta = 186.0\text{--}186.3$ ppm attributed to methyl and carbonyl carbons included in acetyl group,

Table 1: One-pot synthesis of highly functionalized thiazoles 3a-f.

Entry	R	Product
3a	H	
3b	2,4-[NO ₂] ₂ -C ₆ H ₃	
3c	C ₆ H ₅ CO	
3d	4-OH-C ₆ H ₄ CO	
3e	CH ₃ CO	
3f	2-C ₄ H ₃ O-CO	



Scheme 1: Synthesis of thiazole derivatives 3a-f.



Scheme 2: Proposed mechanism.

signals within $\delta = 12.2\text{--}14.2$ ppm, $\delta = 106.4\text{--}117.2$ ppm, $\delta = 170.0\text{--}170.3$ ppm and $\delta = 153.6\text{--}160.1$ ppm attributed to the $\underline{\text{C}}\text{H}_3\text{-C}=\underline{\text{C}}$ -, $\text{-S-}\underline{\text{C}}=\underline{\text{C}}$ -, $\text{-S-C}=\underline{\text{C}}$ - and $\text{-C}=\text{NH}$ carbons respectively, signals appeared within $\delta = 155.5\text{--}168.6$ relating to carbonyl carbons adjacent to the -NH- groups of compounds **3c-f**. The FT-IR spectra of **3a-f** in KBr disk showed the absorption bands within $\nu = 3179\text{--}3467$ cm^{-1} corresponding to -NH- groups, within $\nu = 1687\text{--}1715$ cm^{-1} belonging to carbonyl groups, within $\nu = 1607\text{--}1632$ cm^{-1} belonging to imine groups and within $\nu = 1505\text{--}1578$ cm^{-1} attributed to the endocyclic $\text{-C}=\underline{\text{C}}$ -. Also absence of absorption band of nitrile group around 2200 cm^{-1} plus microanalytical data strongly support the formation of all products.

CONCLUSIONS

In summary, an efficient protocol for the one-pot synthesis of highly functionalized thiazoles have been described from the cyclocondensation of 3-thiocyanatoacetylacetone as intermediate with various hydrazines or hydrazides, which constitute potential precursors for the synthesis of various biological and pharmaceutical compounds.

Acknowledgement

The authors appreciate the University of Zabol for their support and assistance of this project.

Received: Aug. 28, 2015; Accepted: Aug. 23, 2016

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