Archives of Pharmaceutical Sciences Ain Shams University 2020; Vol. 4(2):237-248

OPEN ACCESS

Pharmaceutical Chemistry

Research Article

Facile one-pot synthesis of thiazol-2(3*h*)-imine derivatives from α-active methylene ketones

Dalia E. El-Sawah[a], Yasser M. Loksha[a], Eman Z. Elrazaz[*b], Khalil A. Abboud[c], Bradley Russell-Webster[c], Khaled A. M. Abouzid[b,d]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sinai University, Al-Arish, North Sinai, Egypt*
[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt*
[c]*Department of Chemistry, University of Florida, Gainesville, FL 32611, USA*
[d]*Department of Organic & Medicinal Chemistry, Faculty of Pharmacy, University of Sadat City, Menoufia, Egypt*

ABSTRACT

The synthesis of thiazol-2(3*H*)-imine derivatives was achieved by using a facile and efficient One-pot procedure through the bromination of some α-active methylene ketones followed by treatment with potassium thiocyanate and condensation with various primary amines in ethanol as a one-pot four-step process. The α-active methylene ketones were symmetrical and asymmetrical ketones. The primary amines were mostly aromatic amines and also benzylamine was used. This proposed method does not require techniques such as extraction and chromatography. Surprisingly, the product from the reaction of 3-thiocyanoacetylacetone and benzylamine was elucidated to be *N*-(3-benzyl-4-hydroxy-4-methylthiazolidin-2-ylidene)acetamide (**2**) and not the expected compound 1-(3-benzyl-2-imino-4-methyl-2,3-dihydrothiazol-5-yl)ethan-1-one (**1**), which was proved based on the existence of the methylene group in the compound. The mechanism of the novel compound **2** was confirmed by subsequent chemical reactions, spectroscopic data, and X-ray crystallography. The molecular structure of all newly synthesized thiazol-2(3*H*)-imine derivatives were elucidated based on spectroscopic data and elemental analysis.

Keywords: *thiazole; anti-bacterial; anti-fungal; NBS; active methylene ketones.*

***Correspondence** | Eman Z. Elrazaz; Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt. Email: eman_elrazaz@pharma.asu.edu.eg

Citation | El-Sawah D, Loksha YM, Elrazaz EZ, Abboud KA, Russell-Webster B, Abouzid KAM, 2020. Facile one-pot synthesis of thiazol-2(3H)-imine derivatives from α-active methylene ketones. Arch Pharm Sci ASU 4(2): *237-248*

DOI: 10.21608/aps.2020.47968.1045

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 06 November 2020. **Accepted** 16 December 2020.

Published by: Ain Shams University, Faculty of Pharmacy

1. INTRODUCTION

The development of novel methods for the improvement of the synthetic procedures of important moieties in medicinal chemistry is still in demand to save time, increase yield, and facilitate the pathways **[1-6]**. Thiazole is an efficient moiety in the drug discovery process as thiazole derivatives play an extensive role in medicinal chemistry due to its broad range of biological activities that include anticonvulsant activities **[7]**, antiviral **[8]**, anti-inflammatory **[9]**, antifungal, and antibacterial activity **[10]**. Also, the thiazole nucleus is present in a large number of drugs like antibiotics (penicillin, cephalosporin, and micrococcin), Abafungin and Ravuconazole as antifungal drugs, Ritonavir as an anti-HIV drug, and Sulfathiazole as an antimicrobial drug **[11]**. Several methods for the synthesis of thiazoles and their derivatives were developed by various catalysts, conditions, and strategies **[12-21]**. From these methods, we were interested in the synthesis of thiazoles by condensation of α-halo ketones with thioamides

[22-28]. Beyzaei *et al.* reported the one-pot synthesis of thiazol-2(3*H*)-imines through nucleophilic substitution of chloride in 3-chloroacetylacetone with thiocyanate group followed by cyclo condensation with various hydrazine or hydrazide derivatives.

Based on the above information and different methods of synthesis, we demonstrate an efficient one-pot procedure for the synthesis of thiazole-2(3*H*)-imines starting from α-active methylene ketones. The mechanism of thiazole ring formation was confirmed by X-ray crystallography of compound **2** in addition to spectroscopic analyses for all compounds.

2. METHODS AND MATERIALS

2.1.Chemistry

2.1.1. Method for preparation of *N*-(3-Benzyl-4-hydroxy-4-methylthiazolidin-2-ylidene)acetamide (2)

A mixture of acetylacetone (5.14 mL, 0.05 moles), *N*- bromosuccinimide (9.79 g, 0.055 moles) and benzoyl peroxide (0.05 g) in ethanol (15 mL) was stirred for 30 minutes at room temperature then potassium thiocyanate (4.85 g, 0.05 moles) was added with continuous stirring of the mixture for an additional hour. Benzylamine (5.3 mL, 0.05 moles) was added portion wise and after 2 h of stirring, the obtained solid product was filtered off and crystallized from ethanol to give 12.5 g of the pure white crystals of compound **2**; yield 95%; m.p. 144–146°C;^{1}H-NMR (DMSO-d6):1.39 (br. s, 3H, CH_3-C4), 2.02 (s, 3H, CH_3C=O), 3.13 (d, 1H, *J*=12.0 Hz, *H*CH), 3.27 (d, 1H, *J*=12.0 Hz, 1H, HC*H*), 4.52 (d, 1H, *J*=15.7 Hz, *H*CH-Ph), 4.94 (d, 1H, *J*=15.7 Hz, HC*H*-Ph), 6.62 (br. s, 1H, OH), 7.03–7.28 (m, 3H, Ar-H), 7.28–7.53 (m, 2H, Ar-H);^{13}C-NMR (DMSO-d_6): 25.86 (*C*H_3-C4), 27.41 (*C*H_3C=O), 39.77 (C5), 46.05 (CH_2), 90.76 (C5), 126.82, 127.27, 128.23, 138.31, (C_{arom}), 169.56 (C=N), 181.29 (C=O);EI MS:*m/z* =245 (100%), 264 (M^+, 60%). Elemental analysis for $C_{13}H_{16}N_2O_2S$ (264.34). Calcd: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.30; H, 6.16; N, 10.91.

2.1.2. Methods for preparation of *N*-(3-Benzyl-4-methylthiazol-2(3*H*)-ylidene) acetamide (3):

2.1.2.1. Method (1)

Compound **2** (2.64 g, 0.01 mol) was refluxed in (15 mL) anhydrous DMF for 2 h. The reaction mixture was poured onto ice-cold water (25 mL) with continuous stirring. The obtained solid product was filtered off and crystallized from ethanol to give 1.6 g of compound **3**; yield 66%; m.p. 118–119 °C. Lit. **[29]** m.p. 119.5 °C.

2.1.2.2. Method (2)

The same procedure was used for the synthesis of compound **2** in a slight difference that stirring after addition of benzylamine was continued to complete five hours.

2.1.3. Methods for preparation of 3-Benzyl-4-methylthiazol-2(3*H*)-imine (4)

2.1.3.1. Method (1)

Compound **2** (0.53 g, 0.002 moles) was added to a stirred solution of potassium hydroxide (0.15 g, 2.2 mmol) in methanol (30 mL). The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured onto cold water (50 mL) and the obtained solid product was filtered off and dried to afford 0.25 g of compound **4**; yield 60%; m.p. 128–129 °C **[30]**.

2.1.3.2. Method (2)

Compound **3** (1.23 g, 0.005 mol) was refluxed in 4M HCl (10 mL) and ethanol (10 mL) for 3 h. The reaction mixture was left to reach room temperature and then was neutralized by sodium bicarbonate. The obtained crystallized product was filtered off and dried to afford 0.7 g of compound **4**; yield 70%.

2.1.3.3. Method (3)

The following general method was used to obtain compound **4** in 90% yield in which the α-active methylene ketone was acetone and the primary amine was benzylamine.

2.1.4. General procedure for one-pot synthesis of thiazol-2(3*H*)-imines (4, 5, 6,7a-d, 8a-c, 9)

A mixture of the α-active methylene ketone (0.02 mol), *N*-bromosuccinimide (3.91 g, 0.022 moles), and benzoyl peroxide (0.05 g) in ethanol (15 mL) was stirred for 1 h at room temperature. Potassium thiocyanate (1.94 g, 0.02 moles) was added with continuous stirring of the mixture and after 1 h, the primary amine (0.02 moles) was added portion-wise with stirring. After 2 h the product began to separate. Stirring was continued for an additional 3 h and the obtained solid product was filtered off and crystallized from ethanol to give the desired derivative of thiazol-2(3*H*)-imine.

4-Methyl-3-(p-tolyl)thiazol-2(3H)-imine (5)

The α-active methylene ketone was acetone and the primary amine was *p*-toluidine; yield 80%; m.p. 116–118 °C. ^{1}H-NMR (DMSO-d6):2.21 (s, 3H, CH_3-C4), 2.24 (s, 3H, CH_3-Ar), 6.39 (s, 1H, CH), 7.09 (d, 2H, *J*=8.5 Hz, Ar-H), 7.48 (d, 2H, *J*=8.5 Hz, Ar-H), 9.95 (s, 1H, NH); ^{13}C-NMR (DMSO-d6):17.42 (*C*H_3C4), 20.33 (CH_3Ar), 101.68 (C5), 116.83 (C4), 129.25, 129.72, 138.95, 147.93 (C_{arom}), 163.20 (C=NH); EI MS: *m/z*=204 [M^+] (100%). Elemental analysis for $C_{11}H_{12}N_2S$ (204.29). Calcd: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.64; H, 6.22; N, 14.01.

5-Bromo-4-methyl-3-(p-tolyl)thiazol-2(3H)-imine (6)

A mixture of **5** (0.5 g, 2.4 mmoles), *N*-bromosuccinimide (0.46 g, 2.6 mmoles) and benzoyl peroxide (0.005 g) in ethanol (15 mL) was stirred for 30 min. at room temperature. Excess ethanol was evaporated under reduced pressure then ice-cold water (30 mL) was added to the residual material with stirring. The solid product was filtered off and crystallized from ethanol to give 0.48 g of compounds 6; yield 70%; m.p. 126–128°C; ^{1}H-NMR (DMSO-d6):2.18 (s, 3H, CH_3-Ar), 2.24 (s, 3H, CH_3-C4), 7.11 (d, *J*=8.2 Hz, 2H, Ar-H), 7.44 (d, *J*=8.2 Hz, 2H, Ar-H), 10.15 (br. s, 1H, NH); ^{13}C-NMR (DMSO-d6):15.55 (CH_3C4), 20.37 (CH_3Ar), 89.38 (C5), 117.33, 129.40, 130.63, 138.20 (C_{arom}), 146.81 (C4), 162.30 (C=NH); EI MS: *m/z* =283 [M^+] (36%), 284 [M+2] (100%). Elemental analysis for $C_{11}H_{11}BrN_2S$ (283.19). Calcd: C, 46.66; H, 3.92; Br, 28.22; N, 9.89. Found: C, 46.89; H, 3.96; N, 10.09.

3-(o-Tolyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2(3H)-imine (7a)

The α-active methylene ketone was cyclohexane and the primary amine was *o*-toluidine; yield 65%; as white crystals; m.p. 330–332 °C; ^{1}H-NMR (DMSO-d6):1.50–2.06 (m, 8H, 4 CH_2), 2.29 (s., 3H, CH_3), 7.11–7.35 (m, 4H, Ar-H), 9.51 (br. s, 1H, NH); ^{13}C-NMR (DMSO-d6):16.61 (CH_3), 18.73 ($2CH_2$), 28.13 ($2CH_2$), 85.39 (C5), 126.78, 129.12, 130.64, 131.52, 134.91, 139.51 (C_{arom}), 174.43 (C4), 180.80 (C=NH); EI MS: *m/z* = 244 [M^+] (100%). Elemental analysis for $C_{14}H_{16}N_2S$ (244.36). Calcd:C, 68.82; H, 6.60; N, 11.46. Found: C, 68.99; H, 6.83; N, 11.65.

3-(p-Tolyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2(3H)-imine (7b)

The α-active methylene ketone was cyclohexane and the primary amine was *p*-toluidine; yield 70%; as white crystals; m.p. 288–290 °C; ^{1}H-NMR (DMSO-d6):1.30–1.88 (m, 8H, $4CH_2$), 2.37 (s, 3H, CH_3), 7.14 (d,2H, *J*=7.7 Hz,Ar-H), 7.28 (d,2H, *J* = 7.7 Hz, Ar-H), 9.63 (s, 1H, NH); ^{13}C-NMR (DMSO-d6):17.48 (CH_3), 20.74 ($2CH_2$), 28.70 ($2CH_2$), 83.96 (C5), 129.36,

129.63, 133.25, 137.57 (C_{arom}), 181.06 (C=NH); EI MS: *m/z*=244 [M^+] (100%). Elemental analysis for $C_{14}H_{16}N_2S$ (244.36). Calcd: C, 68.82; H, 6.60; N. 11.46. Found: C, 68.70; H, 6.79; N, 11.63.

4-(2-Imino-4,5,6,7-tetrahydrobenzo[d]thiazol-3(2H)-yl)phenol (7c)

The α-active methylene ketone was cyclohexane and the primary amine was *p*-aminophenol; yield 58%; as white crystals; m.p. 278–280 °C;^{1}H-NMR (DMSO-d6):1.65–1.86 (m, 4H, $2CH_2$), 2.57 (s, 4H, $4CH_2$), 6.69 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.36 (d, *J* = 8.6 Hz, 2H, Ar-H), 9.53 (s , 1H, NH), 11.06 (br. s, 1H, OH); ^{13}C-NMR(DMSO-d_6): 22.41, 22.69, 23.13, 26.49 ($4CH_2$), 115.04 (C5), 133.60 (C4), 115.31, 118.84, 145.08, 151.85 (C_{arom}), 179.39 (C=NH); EI MS: *m/z*=246 [M^+] (100%). Elemental analysis for $C_{13}H_{14}N_2OS$ (246.33). Calcd: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.25; H, 5.95; N, 11.53.

3-(4-Chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2(3H)-imine (7d)

The α-active methylene ketone was cyclohexane and the primary amine was *o*-chloroaniline; yield 50%; as white crystals; m.p. 292–294 °C;^{1}H-NMR (DMSO-d6):1.32–1.94 (m, 8H, 4 CH_2), 7.29 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.57 (d, 2H, *J* = 8.8 Hz, Ar-H), 9.83 (br. s, 1H, NH); ^{13}C-NMR(DMSO-d_6): 17.88, 20.41, 21.08, 29.12 ($4CH_2$), 84.65 (C5), 153.73 (C4), 129.46, 132.25, 135.23, 165.43 (C_{arom}), 181.53 (C=NH); EI MS: *m/z*=169 (100%), 264 [M^+] (17%), 265 [M+2] (6%). Elemental analysis for $C_{13}H_{13}ClN_2S$ (264.77). Calcd: C, 58.97; H, 4.95; N, 10.58. Found: C, 59.20; H, 5.11; N, 10.82

3-Benzyl-2-imino-4-methyl-N-phenyl-2,3-dihydrothiazole-5-carboxamide (8a)

The α-active methylene ketone was acetoacetanilide and the primary amine was benzylamine; yield 80%; as white solid; m.p. 192–194 °C;^{1}H-NMR (DMSO-d6):2.42 (s, 3H, CH_3), 4.49 (d, 2H, *J*=5.9 Hz, CH_2), 6.88–7.17 (m, 1H, Ar-H), 7.21–7.48 (m, 7H, Ar-H), 7.61 (d, 2H, *J*=8.1 Hz, Ar-H), 8.61 (s, 1H, NH-Ph), 9.48 (s, 1H, C=NH); ^{13}C-NMR (DMSO-d6):17.57 (CH_3), 47.46 (CH_2), 112.40 (C5), 120.30, 123.23, 127.09, 127.31, 128.39, 128.45, 138.53, 139.15 (C_{arom}), 154.30 (C4), 160.66 (C=NH), 168.02 (C=O); EI MS: *m/z*=91 (100%), 323 [M^+] (15%). Elemental analysis for $C_{18}H_{17}N_3OS$ (323.41). Calcd: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.59; H, 5.43; N, 13.21

3-(4-Hydroxyphenyl)-2-imino-4-methyl-N-phenyl-2,3-dihydrothiazole-5-carboxamide (8b)

The α-active methylene ketone was acetoacetanilide and the primary amine was *p*-aminophenol; yield 60%; as white crystals; m.p. 238–240 °C;^{1}H-NMR (DMSO-d6):2.48 (s, 3H, CH_3), 6.78 (d, 2H, *J*=8.8 Hz, Ar-H), 7.06 (m, 1H, Ar-H), 7.31 (t, 3H, *J*=7.0 Hz, Ar-H), 7.37 (d, *J*=7.8 Hz, 2H, Ar-H), 7.63 (d, 2H, *J*=7.8 Hz, Ar-H), 9.28 (br. s, 1H, C=NH), 9.58 (s, 1H, OH), 10.17 (s, 1H, NH-Ph), ^{13}C-NMR (DMSO-d6):17.58 (CH_3),112.62 (C5), 115.53 (C4), 120.42, 120.69, 123.39, 128.51, 132.29, 139.10, 153.35, 154.24 (C_{arom}), 160.57 (C=NH), 164.69 (C=O); EI MS: *m/z*=233 (100%), 325 [M^+] (35%). Elemental analysis for $C_{17}H_{15}N_3O_2S$ (325.39). Calcd: C, 62.75; H, 4.65; N, 12.91. Found: C, 63.01; H, 4.76; N, 13.17.

2-Imino-3-mesityl-4-methyl-N-phenyl-2,3-dihydrothiazole-5-carboxamide (8c)

The α-active methylene ketone was acetoacetanilide and the primary amine was 2,4,6-trimethylphenol; yield 55%; as white crystals; m.p. 198–200 °C; ^{1}H- NMR ($CDCl_3$): 2.13–2.19 (m, 6H, $2CH_3$-Ar), 2.20–2.25 (m, 3H, CH_3-Ar), 2.32 (s, 3H, CH_3-C4), 6.85–7.00 (m, 2H, Ar-H), 7.00–7.20 (m, 1H, Ar-H), 7.20–7.46 (m, 2H, Ar-H), 7.46–7.64 (m, 2H, Ar-H), 8.79 (s,

1H, C=NH), 12.28 (s, 1H, NH-Ph); ^{13}C-NMR ($CDCl_3$): 17.53 ($2CH_3Ar$), 18.21 (CH_3Ar), 18.91 (CH_3C4), 119.75 (C5), 120.10, 121.85, 123.55, 128.84, 129.01, 134.03, 135.25, 137.30 (C_{arom}), 138.51 (C4), 169.06 (C=NH), 169.87(C=O); EI MS: *m/z*=55 (100%), 351 [M^+] (20%). Elemental analysis for $C_{20}H_{21}N_3OS$ (351.47). Calcd: C, 68.35; H, 6.02; N, 11.96. Found: C, 68.09; H, 6.21; N, 12.19.

Ethyl 3-benzyl-2-imino-4-methyl-2,3-dihydrothiazole-5-carboxylate (9)

The α-active methylene ketone was ethyl acetoacetate and the primary amine was benzylamine; yield 75%; as white crystals; m.p. 103–105 °C; ^{1}H-NMR (DMSO-d6):1.22 (t, *J*=7.1 Hz, 3H, CH_3-CH_2), 2.41 (s, 3H, CH_3-C4), 4.15 (q, 2H, *J*=7.1 Hz, CH_2-CH_3), 4.46 (d, 2H, *J*=5.9 Hz, CH_2-Ar), 7.21–7.45 (m, 5H, Ar-H), 8.83 (br. s, 1H, NH);^{13}C-NMR (DMSO-d6):14.33 (CH_3CH_2), 17.32 (CH_3C4), 47.54 (CH_2CH_3), 59.38 (CH_2Ar), 107.33 (C5), 127.21, 127.39, 128.44, 138.11 (C_{arom}), 159.37 (C4), 161.90 (C=NH), 169.86 (C=O); EI MS: *m/z*=91 (100%), 276 [M^+] (50%). Elemental analysis for $C_{14}H_{16}N_2O_2S$ (276.35). Calcd: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.48; H, 6.00; N, 10.22.

2.2 X-ray crystal data

Crystal data for compound **2** was preformed to ensure the formation of the novel compound **2** : empirical formula $C_{13}H_{16}N_2O_2S$; formula weight 264.34; monoclinic; space group $P2_1/c$; a = 5.3087(2) Å, b=14.2598(5) Å, c=16.7855(6) Å, $\alpha = \gamma = 90°$, β = 95.0810(10)°; V=1265.69(8); Z=4; D_{calcd} =1.387 Mg m^{-3}; λ=0.71073 Å; absorption coefficient=0.251 mm^{-1}; F(000)=560; T=100 (2) K; crystal size=0.144 x 0.111 x 0.037 mm^3 **[31]**.

3. RESULTS AND DISCUSSION

A facile One-pot four-steps procedure for the synthesis of thiazole-2(3*H*)-imine was used in an attempt to synthesize 1-(3-benzyl-2-imino-4-methyl-2,3-dihydrothiazol-5-yl)ethan-1-one (**1**) through the bromination of acetylacetone by *N*-bromosuccinimide in ethanol at room temperature then by the addition of potassium thiocyanate to the reaction, followed by the addition of benzylamine to the reaction mixture and stirring was continued for another two hours. The product from the reaction was elucidated to be *N*-(3-benzyl-4-hydroxy-4-methylthiazolidin-2-ylidene)acetamide (**2**) and not the expected compound **1**. The formation of the novel compound **2** was elucidated by subsequent chemical reactions, spectroscopic analysis, and X-ray crystallography **(Fig. 1)**. ^{1}HNMR spectrum showed the existence of CH_2 in position 5 at 3.13 and 3.27 ppm as two doublets with coupling constant of 12.0 Hz and also hydroxyl group was detected as a broad singlet at 6.62 ppm. In addition to the previous observations, the appearance of C5 at 90.76 ppm in ^{13}C-NMR confirm the structure **2** rather than **1** in which the signal has to be shifted to the low field with a higher chemical shift value.

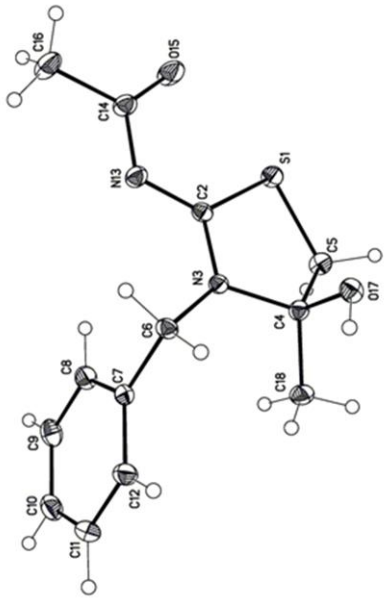


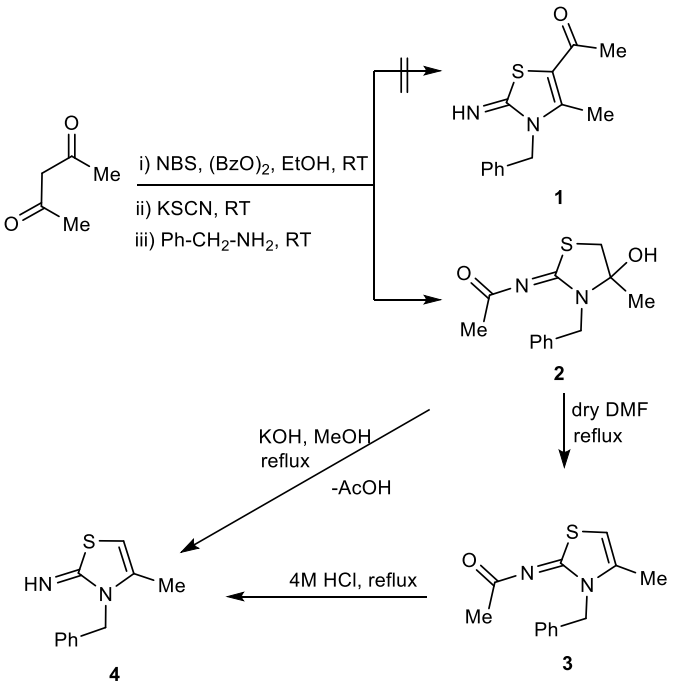
Fig. 1. X-ray crystal structure of compound 2

The mechanism for the one-pot formation of compound **2** is postulated as shown in scheme 2.

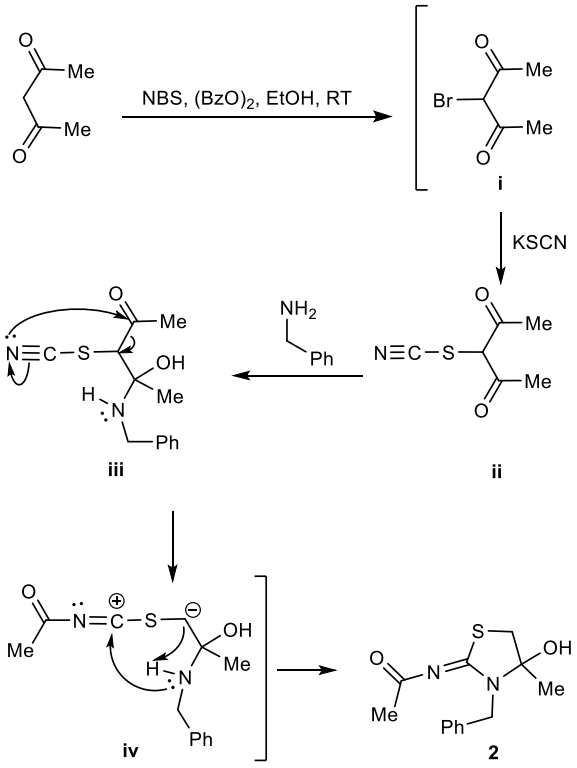
The first step is the free-radical bromination of acetylacetone to form 3-bromoacetylacetone (**i**) which was not isolated from the reaction. The second step is the nucleophilic substitution of the bromide ion in structure (**i**) by thiocyanate group to afford 3-thiocyanateacetylacetone (**ii**) which also was not isolated from the reaction. The addition of benzylamine to the reaction mixture enhanced the addition reaction on the carbonyl group of compound **(ii)** to afford the intermediate (**iii)**. Rearrangement reaction was taken place by nucleophilic attack at the carbonyl of the acetyl group by the lone pair of electron on the nitrogen atom of SCN to furnish the intermediate (**iv)** which was cyclized to compound **2**.

Dehydration of compound **2** to *N*-(3-benzyl-4-methylthiazol-2(3*H*)-ylidene)acetamide **3** was achieved to the unsaturated thiazole ring by refluxing compound **2** in anhydrous dimethylformamide. Compound **3** was also synthesized directly by the same procedure used for the synthesis of compound **2** in a slight difference that stirring after addition of benzylamine was continued to complete five hours. Compound **3** has previously been synthesized by D'hooghe *et al* **[29]** through a different pathway by treatment of 1-benzyl-2-(thiocyanomethyl)aziridine with acetyl chloride and a catalytic amount of titanium(IV) chloride in dichloromethane and subsequent heating the product with potassium *tert*-butoxide in dimethylsulphoxide.

Interestingly, compound 4 has been prepared by various methods. Refluxing compound **2** in methanolic potassium hydroxide afforded the deacetylated thiazole derivative **4** in 60% yield. The second method for synthesis of compound **4** in 70% yield is refluxing compound **3** in a mixture of 4M hydrochloric acid in ethanol. Boga et *al*.**[30]** have published the synthesis of compound **4** by a different pathway through heating *N*-benzylthiourea with chloroacetone in a mixture of DMSO-HCl followed by neutralization of the hydrochloride product.



Scheme 1: Synthesis of compound **4**



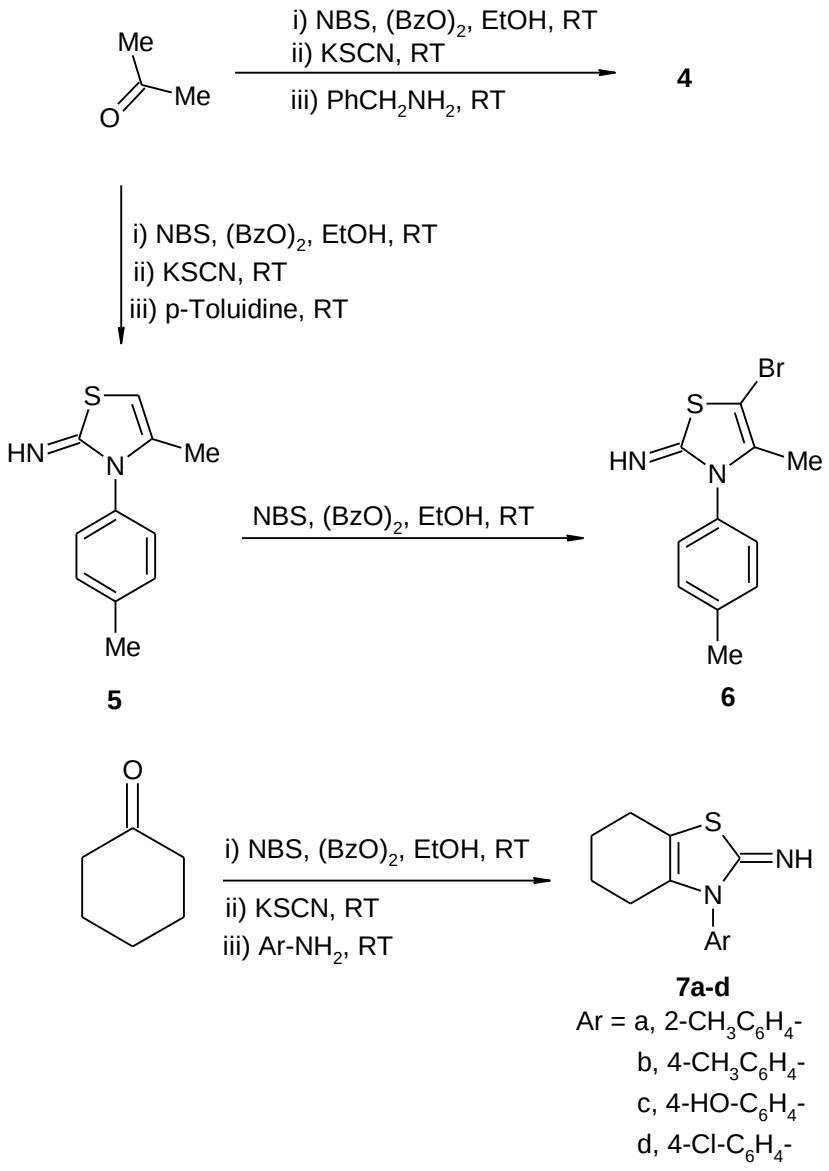
Scheme 2: Postulated mechanism for the formation of compound **2**

The third method for synthesis of 4-methyl-3-(propane-2-ylideneamino)thiazol-2(3*H*)-imine **4** in 90% yield was carried out by bromination of acetone using *N*-bromosuccinimide in absolute ethanol at room temperature then nucleophilic substitution of the bromo derivative with thiocyanate group through the addition of potassium thiocyanate to the reaction mixture. Cyclization to compound **4** was completed by the addition of benzylamine with continuous stirring for 4 h **(Scheme 3).**

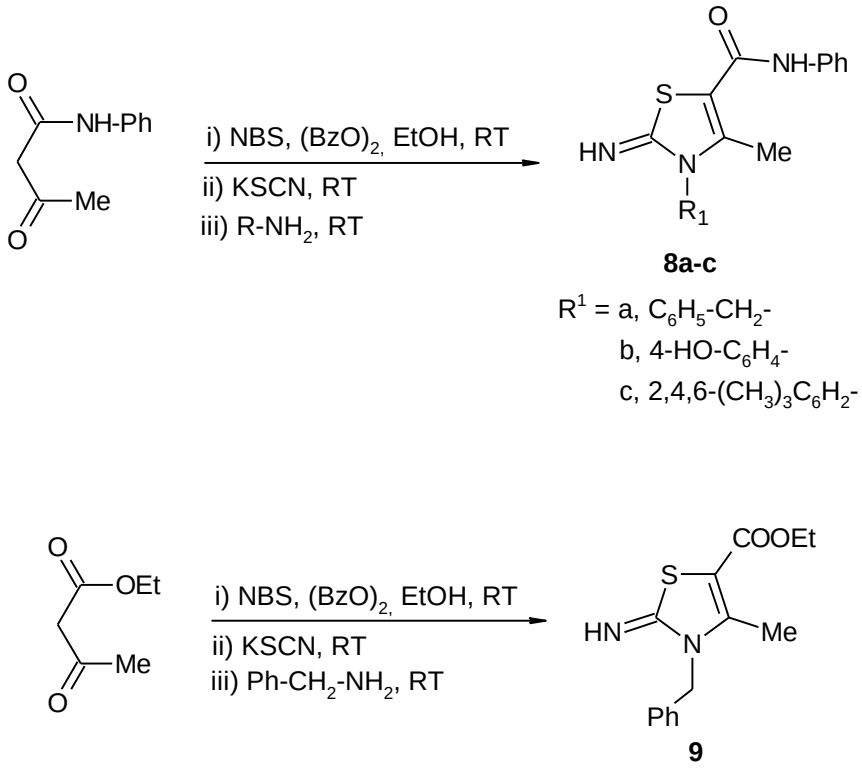
This procedure was used as a general method for the one-pot four-steps synthesis of thiazol-2(3*H*)-imine derivatives from different α-active methylene ketones and different amino compounds; the α-active methylene ketone was brominated by NBS in ethanol in the presence of few crystals of benzoyl peroxide as an initiator for free radical reaction followed by addition of potassium thiocyanate at room temperature and subsequent addition of the primary amine.

The method was carried out using different α-active methylene ketones and different primary amines. Acetone and cyclohexanone were selected as symmetrical ketones included only one carbonyl group and two symmetrical active methylene groups. By carrying out the general method on acetone using *p-toluidine* as primary aromatic amine, the product from the reaction was 4-methyl-3-(p-tolyl)thiazol-2(3*H*)-imine (**5**) as expected. Bromination of compound **5** by NBS in the presence of few crystals of benzoyl peroxide in ethanol as a solvent afforded 5-Bromo-4-methyl-3-(*p*-tolyl)thiazol-2(3*H*)-imine (**6**). ^{1}H NMR for compound **6** showed the disappearance of the H5 signal at δ 6.39 ppm which is a significant signal for compound **5**. The expected products 3-arylamino-4,5,6,7-

tetrahydrobenzo[*d*]thiazol-2(3*H*)-imine (**7a-d**) were obtained when the general method was applied on cyclohexanone as α-active methylene ketone and some selected aromatic amines (o-toluidine, p-toluidine, *p*-hydroxyphenyl, and *p*-chlorophenol) **(Scheme 3)**.



Scheme 3



Scheme 4

The general method was also applied on unsymmetrical α-active methylene ketones such as ethyl acetoacetate and acetoacetanilide. Benzylamine was the primary amine in the case of using ethyl acetoacetate as α-active methylene ketone. In the case of acetoacetanilide, the selected primary amines were benzylamine, *p*-aminophenol, and 2,4,6-trimethylamine. The products from the reactions were elucidated by spectroscopic analyses to be the expected 3-arylamino-2-imino-4-methyl-*N*-phenyl-2,3-dihydrothiazole-5-carboxamide (**8a-c**) **(Scheme 4)**.

Conclusion

A facile one-pot synthesis of thiazol-2(3*H*)-imine derivatives was provided by stepwise reaction of α-active methylene ketones, NBS, potassium thiocyanate, and a primary amine. The α-active methylene ketones were symmetrical and asymmetrical ketones. The primary amines were mostly aromatic amines and also benzylamine was used.

Acknowledgment

The National Science Foundation and the University of Florida for funding of the purchase of the X-ray equipment.

Supporting Information

Full experimental detail, ^{1}H, and ^{13}C NMR spectra, X-ray Data. This material can be found via the “Supplementary Content” section of this article’s webpage.’

Declarations

Consent to publish

Not applicable

Availability of data and materials

The data generated or analyzed during this study are included in the main manuscript and the

additional supplementary data.

Competing interests

There are no competing interests

Funding Statement

No funding source was received

Authors' contributions

All authors contributed to the design of the study, collection, analysis, interpretation of data, and writing of the manuscript. All authors read and approved the final manuscript.

Acknowledgment

The National Science Foundation and the University of Florida for funding of the purchase of the X-ray equipment.

4. REFERENCES

1. Mekky, A. E. M.; Sanad, S. M. H.;& Ahmed, A. A. M. Microwave-assisted three-component one-pot synthesis of bis(aminoazolo[1,5-a]pyrimidines) and bis(aminoazino[1,2-a]benzimidazoles) bearing thiazole moiety. Chemistry Select. 2019, 4(33), 9710–9715. DOI:10.1002/slct.201902828

2. Wu, S. J.; Zhao, Z. Q.; Gao, J. S.; Chen, B. H.;Chen, G. F. Efficient one-pot synthesis of 2,3-dihydro quinazoline-4(1H)-ones promoted by FeCl3/ neutral Al2O3. Res. Chem. Intermed.2019, 45, 2327–2339.DOI:10.1007/s11164-018-03732-w

3. Zhu, Z.; Tang, X.; Cen, J.; Li, J.; Wu, W.;& Jiang, H. Copper-catalyzed synthesis of thiazol-2-yl ethers from oxime acetates and xanthates under redox-neutral conditions. Chemical Communications. 2018, 54, 3767–3770. DOI: 10.1039/c8cc00445e

[4. Beyzaei, H.; Beygi, A. Aryan, R. One-pot synthesis and characterization of highly functionalized thiazoles. Iran. J. Chem. Chem. Eng.2016, 35, 31–37.

5. Loksha, Y. M.; Pedersen, E. B.; La Colla, P.; Loddo, R. Facile synthesis of the NNRTI microbicide MC-1220 and synthesis of its phosphoramidite prodrugs. Org. Biomol. Chem.2016, 14, 940–946.DOI:10.1039/c5ob02055g

6. Riyadh, S.; Khalil, K.;& Aljuhani, A. Chitosan-MgO Nanocomposite: one-pot preparation and

It's utility as an eco-friendly biocatalyst in the synthesis of thiazoles and [1, 3, 4]thiadiazoles.

Nanomaterials. 2018, 8, 928. DOI: 10.3390/nano8110928

7. Mishchenko, M.; Shtrygol, S.; Kaminskyy, D.; & Lesyk, R. Thiazole-bearing 4-thiazolidinediones as new anticonvulsant agents. Scientia Pharmaceutica. 2020, 88, 16.

DOI: 10.3390/scipharm88010016

8. Singh, I. P.; Gupta, S.; & Kumar, S. Thiazole compounds as antiviral agents: an update. Medicinal Chemistry. 2020, 16, 4–23.DOI: 10.2174/1573406415666190614101253

9. Sinha, S.; Doble, M.; & Manju, S. L.Design, synthesis and identification of novel substituted 2-amino thiazole analogs as potential anti-inflammatory agents targeting 5-lipoxygenase. European Journal of Medicinal Chemistry. 2018, 158, 34–50.DOI: 10.1016/j.ejmech.2018.08. 098

10. Adole, V. A.; More, R. A.; Jagdale, B. S.; Pawar, T. B.;& Chobe, S. S. Efficient synthesis, antibacterial, antifungal, antioxidant and cytotoxicity study of 2-(2-hydrazineyl)thiazole derivatives. ChemistrySelect. 2020, 5, 2778–2786. DOI:10.1002/slct.201904609

11. Ayati, A.; Emami, S.; Asadipour, A.; Shafiee, A.;& Foroumadi, A. Recent applications of

1,3-thiazole core structure in the identification of new lead compounds and drug discovery. European Journal of Medicinal Chemistry.2015, 97, 699–718.DOI: 10.1016/j.ejmech.2015.04.015

12. Reddy, G. T.; Kumar, G.;& Reddy, N. C. G. Water-mediated one-pot three-component synthesis of hydrazine-thiazoles catalyzed by copper oxide nanoparticles dispersed on titanium dioxide support: a green catalytic process. Advanced Synthesis & Catalysis.2018, 360, 995–1006. DOI:10.1002/adsc.201701063

13. Parvizi, J.;Mahmoodi, N. O.;& Ghanbari Pirbasti, F. Ultrasound and water-mediated synthesis of bis-thiazoles catalyzed by Fe(SD)3 as Lewis acid-surfactant-combined catalyst. Journal of Sulfur Chemistry. 2017, 39, 140–150. DOI:10.1080/17415993.2017.1400033

14. Uzelac, E. J.;& Rasmussen, S. C. Synthesis of brominated thiazoles via sequential bromination–debromination methods. The Journal of Organic Chemistry. 2017, 82, 5947–5951. DOI:10.1021/acs.joc.7b00495

15. Pathania, S.;& Rawal, R. K. Green synthetic strategies toward thiazoles: a sustainable approach. Chemistry of Heterocyclic Compounds.2020, 56, 445–454.DOI: 10.1007/s10593-020-02679-4

16. De Andrade, V. S. C.;& de Mattos, M. C. S. One-pot synthesis of 4-aryl-2-aminothiazoles from styrenes and thioureas promoted by tribromoisocyanuric acid. Tetrahedron Letters. 2020, 61, 152-164 DOI:10.1016/j.tetlet.2020.152164

17. Ni, P.; Tan, J.; Li, R.; Huang, H.; Zhang, F.;& Deng, G.-J. Brønsted acid-promoted thiazole synthesis under metal-free conditions using sulfur powder as the sulfur source. RSC Advances. 2020, 10, 3931–3935. DOI: 10.1039/c9ra09656f

18. Srivastava, A.; Shukla, G.; Yadav, D.;& Singh, M. S. Access to fully substituted thiazoles and 2,3-dihydrothiazoles via copper-catalyzed [4 + 1] heterocyclization of α-(n-hydroxy/aryl)imino-β-oxodithioesters with α-diazocarbonyls. The Journal of Organic Chemistry. 2017, 82, 10846–10854. DOI: 10.1021/acs.joc.7b01601

19. Abu-Zaied, M. A.;& Elgemeie, G. H. Thiazoles in glycosylation reactions: Novel synthesis of thiazole thioglycosides. Heteroatom Chemistry. 2017, 28, 21404. DOI:10.1002/hc.21404

20. Liu, Y.; Du, Y.; Li, Z.; Xie, Y.; He, P.; Qiao, J.;& Fan, X. Efficient one-pot synthesis of 2,4-disubstituted thiazoles and dimeric thiazoles directly from acyl chlorides and β-azido Disulfides. Synthesis. 2017, 49, 4876–4886. DOI: 10.1055/s-0036-1590810

21. Narasimhamurthy, K. H.; Sajith, A. M.; Joy, M. N.;& Rangappa, K. S. An overview of recent developments in the synthesis of substituted thiazoles. ChemistrySelect. 2020, 5, 5629–5656. DOI:10.1002/slct.202001133

22. Zhang, Q., Wu, J., Pan, Z., Zhang, W., & Zhou, W. A one-pot synthesis of 2-aminothiazoles via the coupling of ketones and thiourea using I2/dimethyl sulfoxide as a catalytic oxidative system. Journal of Chemical Research.2020,00, 1-6. DOI: 10.1177/1747519820930961

23. Alsharif, Z. A.; & Alam, M. A. Modular synthesis of thiazoline and thiazole derivatives by using a cascade protocol. RSC Advances. 2017, 7, 32647–32651. DOI: 10.1039/c7ra05993k

24. De Mattos, M.;& de Andrade, V. One-pot telescoped synthesis of thiazole derivatives

from β-keto esters and thioureas promoted by tribromoisocyanuric acid. Synthesis. 2018,50, 4867–4874. DOI: 10.1055/s-0037-1610243

25. Prevost, J. R. C.; Kozlova, A.;Saadi, B. E.; Yildiz, E.; Modaffari, S.; Lambert, D. M.; Frédérick, R. Convenient one-pot formation of highly functionalized 5-Bromo-2-aminothiazoles, potential endocannabinoid hydrolase MAGL inhibitors. Tetrahedron Letters. 2018, 59, 4315-4319. DOI:10.1016/j.tetlet.2018.10.055

26. De Andrade, V.;& de Mattos, M. N-halo reagents-mediated greener protocols for heterocyclic synthesis: safe chemistry and pot-economy approaches to azoles and quinoxalines. Current Green Chemistry. 2018,5, 68-85. DOI: 10.2174/2452273202666180719124023

27. Jiang, J.; Huang, H.;& Deng, G.-J. Four-component thiazole formation from simple chemicals under metal-free conditions. 2019, 21, 986-990. Green Chemistry. DOI: 10.1039/c8gc03895c

28. Sun, J.; Ge, H.; Zhen, X.; An, X.; Zhang, G.; Zhang-Negrerie, D.; Zhao, K.TBHP/AIBN-mediated synthesis of 2-amino-thioazoles from active methylene ketones and thiourea under metal-free conditions. Tetrahedron.2018, 74, 2107–2114. DOI:10.1016/j.tet.2018.02.064

29. D'hooghe, M.; Waterinckx, A.; Kimpe, N.A novel entry toward 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines by ring transformation of 2-(thiocyanomethyl)aziridines.J. Org. Chem. 2005, 70, 227–232.DOI: 10.1021/jo048486f

30. Boga, C.; Forlani, L.; Silvestroni, C.; Corradi, B. A.; Sgarabotto, P. Condensation of thiourea derivatives with carbonyl compounds: one-pot synthesis of N-alkyl-1,3-thiazol-2-amines and of 3-alkyl-1,3-thiazolimines.J. Chem. Soc. Perkin Trans.1.1999, 1, 1363–1368. DOI: 10.1039/a809086f

31. Spek, A. L. What makes a crystal structure report valid? Inorganica Chimica Acta. 2018, 470, 232–237. DOI:10.1016/j.ica.2017.04.036