

## Facile one-pot synthesis of thiazol-2(3*H*)-imine derivatives from $\alpha$ -active methylene ketones

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### 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  $\alpha$ -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  $\alpha$ -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.

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## 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  $\alpha$ -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  $\alpha$ -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; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 1.39 (br. s, 3H, CH<sub>3</sub>-C4), 2.02 (s, 3H, CH<sub>3</sub>C=O), 3.13 (d, 1H, *J*=12.0 Hz, *HCH*), 3.27 (d, 1H, *J*=12.0 Hz, 1H, *HCH*), 4.52 (d, 1H, *J*=15.7 Hz, *HCH*-Ph), 4.94 (d, 1H, *J*=15.7 Hz, *HCH*-Ph), 6.62 (br. s, 1H, OH), 7.03–7.28 (m, 3H, Ar-H), 7.28–7.53 (m, 2H, Ar-H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): 25.86 (CH<sub>3</sub>-C4), 27.41 (CH<sub>3</sub>C=O), 39.77 (C5), 46.05 (CH<sub>2</sub>), 90.76 (C5), 126.82, 127.27, 128.23, 138.31, (C<sub>arom</sub>), 169.56 (C=N), 181.29 (C=O); EI MS: *m/z*

=245 (100%), 264 (M<sup>+</sup>, 60%). Elemental analysis for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (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  $\alpha$ -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  $\alpha$ -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(3*H*)-imine (**5**)

The  $\alpha$ -active methylene ketone was acetone and the primary amine was *p*-toluidine; yield 80%; m.p. 116–118 °C. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 2.21 (s, 3H, CH<sub>3</sub>-C4), 2.24 (s, 3H, CH<sub>3</sub>-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); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): 17.42 (CH<sub>3</sub>C4), 20.33 (CH<sub>3</sub>Ar), 101.68 (C5), 116.83 (C4), 129.25, 129.72, 138.95, 147.93 (C<sub>arom</sub>), 163.20 (C=NH); EI MS: *m/z*=204 [M<sup>+</sup>] (100%). Elemental analysis for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>S (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(3*H*)-imine (**6**)

A mixture of **5** (0.5 g, 2.4 mmol), *N*-bromosuccinimide (0.46 g, 2.6 mmol) 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; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 2.18 (s, 3H, CH<sub>3</sub>-Ar), 2.24 (s, 3H, CH<sub>3</sub>-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); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): 15.55 (CH<sub>3</sub>C4), 20.37 (CH<sub>3</sub>Ar), 89.38 (C5), 117.33, 129.40, 130.63, 138.20 (C<sub>arom</sub>), 146.81 (C4), 162.30 (C=NH); EI MS: *m/z*=283 [M<sup>+</sup>] (36%), 284 [M+2] (100%). Elemental analysis for C<sub>11</sub>H<sub>11</sub>BrN<sub>2</sub>S (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(3*H*)-imine (**7a**)

The  $\alpha$ -active methylene ketone was cyclohexane and the primary amine was *o*-toluidine; yield 65%; as white crystals; m.p. 330–332 °C; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 1.50–2.06 (m, 8H, 4 CH<sub>2</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 7.11–7.35 (m, 4H, Ar-H), 9.51 (br. s, 1H, NH); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): 16.61 (CH<sub>3</sub>), 18.73 (2CH<sub>2</sub>), 28.13 (2CH<sub>2</sub>), 85.39 (C5), 126.78, 129.12, 130.64, 131.52, 134.91, 139.51 (C<sub>arom</sub>), 174.43 (C4), 180.80 (C=NH); EI MS: *m/z* = 244 [M<sup>+</sup>] (100%). Elemental analysis for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>S (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(3*H*)-imine (**7b**)

The  $\alpha$ -active methylene ketone was cyclohexane and the primary amine was *p*-toluidine; yield 70%; as white crystals; m.p. 288–290 °C; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): 1.30–1.88 (m, 8H, 4CH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 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); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): 17.48 (CH<sub>3</sub>), 20.74 (2CH<sub>2</sub>), 28.70 (2CH<sub>2</sub>), 83.96 (C5), 129.36,

129.63, 133.25, 137.57 ( $C_{\text{arom}}$ ), 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  $\alpha$ -active methylene ketone was cyclohexane and the primary amine was *p*-aminophenol; yield 58%; as white crystals; m.p. 278–280 °C;  $^1H$ -NMR (DMSO- $d_6$ ): 1.65–1.86 (m, 4H, 2CH<sub>2</sub>), 2.57 (s, 4H, 4CH<sub>2</sub>), 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<sub>2</sub>), 115.04 (C5), 133.60 (C4), 115.31, 118.84, 145.08, 151.85 ( $C_{\text{arom}}$ ), 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  $\alpha$ -active methylene ketone was cyclohexane and the primary amine was *o*-chloroaniline; yield 50%; as white crystals; m.p. 292–294 °C;  $^1H$ -NMR (DMSO- $d_6$ ): 1.32–1.94 (m, 8H, 4 CH<sub>2</sub>), 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<sub>2</sub>), 84.65 (C5), 153.73 (C4), 129.46, 132.25, 135.23, 165.43 ( $C_{\text{arom}}$ ), 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  $\alpha$ -active methylene ketone was acetoacetanilide and the primary amine was benzylamine; yield 80%; as white solid; m.p.

192–194 °C;  $^1H$ -NMR (DMSO- $d_6$ ): 2.42 (s, 3H, CH<sub>3</sub>), 4.49 (d, 2H,  $J=5.9$  Hz, CH<sub>2</sub>), 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- $d_6$ ): 17.57 (CH<sub>3</sub>), 47.46 (CH<sub>2</sub>), 112.40 (C5), 120.30, 123.23, 127.09, 127.31, 128.39, 128.45, 138.53, 139.15 ( $C_{\text{arom}}$ ), 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  $\alpha$ -active methylene ketone was acetoacetanilide and the primary amine was *p*-aminophenol; yield 60%; as white crystals; m.p. 238–240 °C;  $^1H$ -NMR (DMSO- $d_6$ ): 2.48 (s, 3H, CH<sub>3</sub>), 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- $d_6$ ): 17.58 (CH<sub>3</sub>), 112.62 (C5), 115.53 (C4), 120.42, 120.69, 123.39, 128.51, 132.29, 139.10, 153.35, 154.24 ( $C_{\text{arom}}$ ), 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  $\alpha$ -active methylene ketone was acetoacetanilide and the primary amine was 2,4,6-trimethylphenol; yield 55%; as white crystals; m.p. 198–200 °C;  $^1H$ -NMR (CDCl<sub>3</sub>): 2.13–2.19 (m, 6H, 2CH<sub>3</sub>-Ar), 2.20–2.25 (m, 3H, CH<sub>3</sub>-Ar), 2.32 (s, 3H, CH<sub>3</sub>-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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 17.53 (2CH<sub>3</sub>Ar), 18.21 (CH<sub>3</sub>Ar), 18.91 (CH<sub>3</sub>C4), 119.75 (C5), 120.10, 121.85, 123.55, 128.84, 129.01, 134.03, 135.25, 137.30 (C<sub>arom</sub>), 138.51 (C4), 169.06 (C=NH), 169.87(C=O); EI MS: *m/z*=55 (100%), 351 [M<sup>+</sup>] (20%). Elemental analysis for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>OS (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  $\alpha$ -active methylene ketone was ethyl acetoacetate and the primary amine was benzylamine; yield 75%; as white crystals; m.p. 103–105 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.22 (t, *J*=7.1 Hz, 3H, CH<sub>3</sub>-CH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>-C4), 4.15 (q, 2H, *J*=7.1 Hz, CH<sub>2</sub>-CH<sub>3</sub>), 4.46 (d, 2H, *J*=5.9 Hz, CH<sub>2</sub>-Ar), 7.21–7.45 (m, 5H, Ar-H), 8.83 (br. s, 1H, NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): 14.33 (CH<sub>3</sub>CH<sub>2</sub>), 17.32 (CH<sub>3</sub>C4), 47.54 (CH<sub>2</sub>CH<sub>3</sub>), 59.38 (CH<sub>2</sub>Ar), 107.33 (C5), 127.21, 127.39, 128.44, 138.11 (C<sub>arom</sub>), 159.37 (C4), 161.90 (C=NH), 169.86 (C=O); EI MS: *m/z*=91 (100%), 276 [M<sup>+</sup>] (50%). Elemental analysis for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (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<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S; formula weight 264.34; monoclinic; space group P2<sub>1</sub>/c; *a* = 5.3087(2) Å, *b* = 14.2598(5) Å, *c* = 16.7855(6) Å,  $\alpha = \gamma = 90^\circ$ ,  $\beta = 95.0810(10)^\circ$ ; *V* = 1265.69(8); *Z* = 4; *D*<sub>calcd</sub> = 1.387 Mg m<sup>-3</sup>;  $\lambda$  = 0.71073 Å; absorption coefficient = 0.251 mm<sup>-1</sup>; *F*(000) = 560; *T* = 100 (2) K; crystal size = 0.144 x 0.111 x 0.037 mm<sup>3</sup> [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**). <sup>1</sup>H-NMR spectrum showed the existence of CH<sub>2</sub> 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 <sup>13</sup>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.

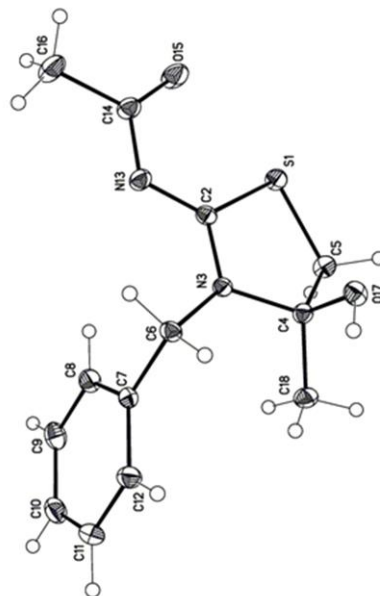


Fig. 1. X-ray crystal structure of compound **2**

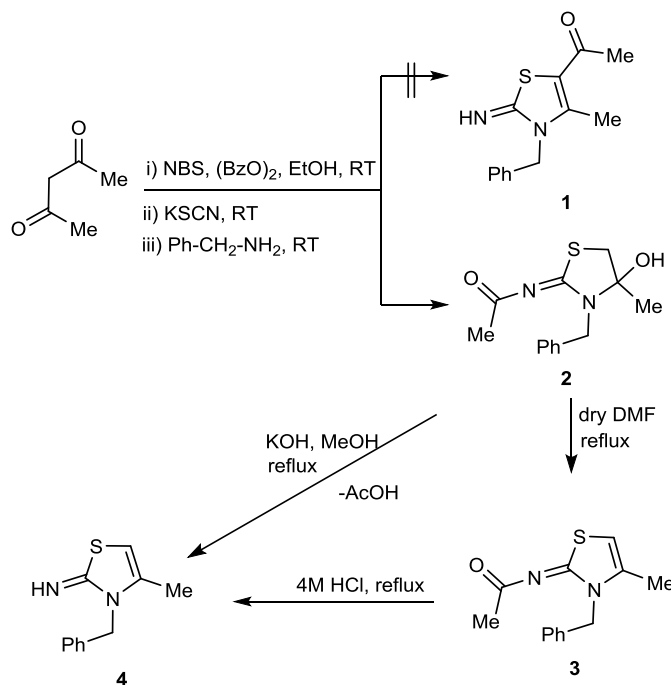
The mechanism for the one-pot formation of compound **2** is postulated as shown in scheme 2.

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**.

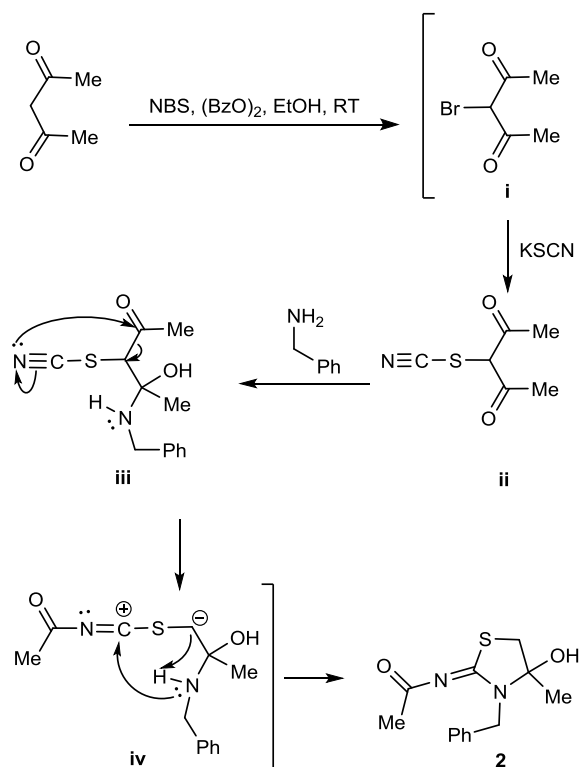
Dehydration of compound **2** to *N*-(3-benzyl-4-methylthiazol-2(3*H*)-ylidene)acetamide **3** was achieved to the unsaturated thiazole ring by refluxing compound **2** in anhydrous dimethylformamide. Compound **3** was also synthesized directly by the same procedure used for the synthesis of compound **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**).

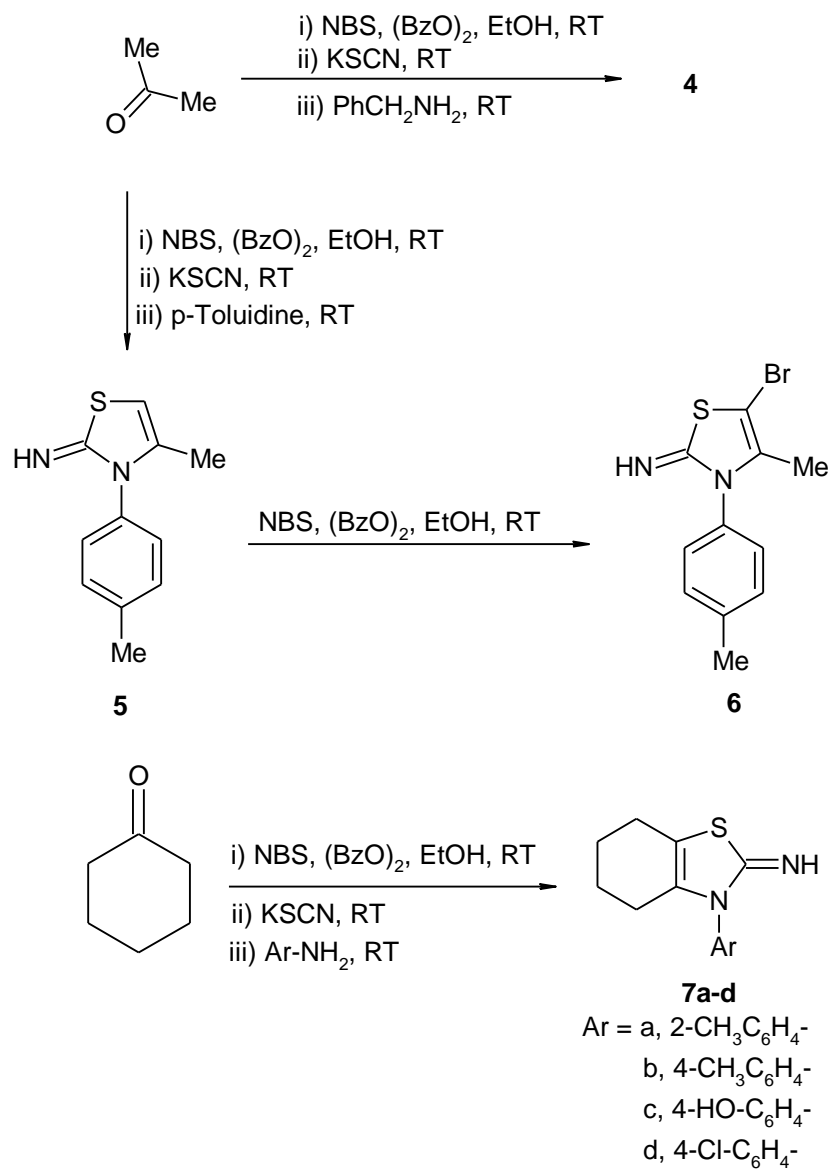
This procedure was used as a general method for the one-pot four-steps synthesis of thiazol-2(3*H*)-imine derivatives from different  $\alpha$ -active methylene ketones and different amino compounds; the  $\alpha$ -active methylene ketone was brominated by NBS in ethanol in the presence of few crystals 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  $\alpha$ -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**). <sup>1</sup>H NMR for compound **6** showed the disappearance of the H5 signal at  $\delta$  6.39 ppm which is a significant signal for compound **5**. The expected products 3-arylamino-4,5,6,7-

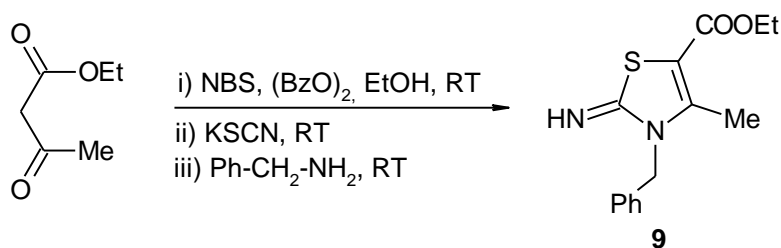
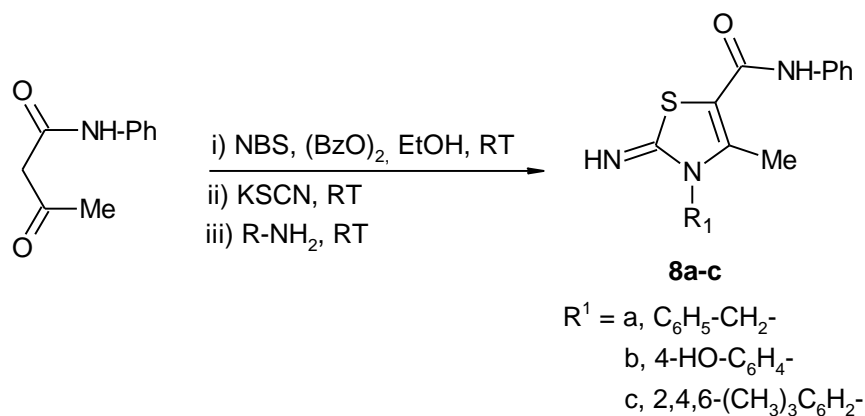
tetrahydrobenzo[*d*]thiazol-2(3*H*)-imine (**7a-d**) were obtained when the general method was applied on cyclohexanone as  $\alpha$ -active methylene

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  $\alpha$ -active methylene ketones such as ethyl acetoacetate and acetoacetanilide. Benzylamine was the primary amine in the case of using ethyl acetoacetate as  $\alpha$ -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  $\alpha$ -active methylene ketones, NBS, potassium thiocyanate, and a primary amine. The  $\alpha$ -active methylene ketones were symmetrical and asymmetrical ketones. The primary amines

were mostly aromatic amines and also benzylamine was used.

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### Supporting Information

Full experimental detail, <sup>1</sup>H, and <sup>13</sup>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.

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