



## Synthesis and reactions of (Z)-2-imino-5-(3,4,5-trimethoxy benzylidene)thiazolidin-4(H)one

Mahmoud Refae Mahmoud\*, Hassan Mohamed Fawzy Madkour,  
Eman Abd El-Fattah El-Bordany and El-Sayed Ahmed Soliman

Chemistry Department, Faculty of Science, Ain Shams University, Cairo, 11566, Egypt

\*Corresponding author at: Chemistry Department, Faculty of Science, Ain Shams University, Cairo, 11566, Egypt. Tel.: +2.202.4821096; fax: +2.202.831836.  
E-mail address: [mrefae2000@yahoo.com](mailto:mrefae2000@yahoo.com) (M.R. Mahmoud).

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### ABSTRACT

5-Arylmethylene-2-imino-4-oxo-2-thiazolidine **3** was obtained as the sole product from the reaction of  $\alpha$ -cyano-3,4,5-trimethoxy cinnamionitrile and/or ethyl- $\alpha$ -cyano-3,4,5-trimethoxy cinnamate (**1a,b**) with 2-imino-4-oxo-2-thiazolidine **2**. The reaction of **3** with benzyl amine gave the imidazolidin-4(H)one derivative **4** while with hydrazine hydrate afforded the dimeric product **5**. Also, reaction of thiazolidinone derivative **3** with piperidine gave thiazol-4(5H)one derivative **6** which on treatment with Grignard reagent and active methylene compounds afforded thiazolidin-4-one derivatives **7-9**, respectively. Compound **6** was converted to the potassium salt **10** which treated with acetic acid, ethyl chloroacetate and furoyl chloride to give the compounds **11-13**, respectively. The structures of all new compounds were evidenced by microanalytical data and spectral data.

### 1. Introduction

In connection with our program of preparing heterocyclic compounds which might have potential biological activities [1-7]. The reaction of activated nitriles with 2-thiazolidine derivatives has previously claimed to afford the thiazolopyrimidine derivatives in moderate yield [8,9]. We report here that no thiazolopyrimidine **3'** could be isolated in the reaction of  $\alpha$ -cyano-3,4,5-trimethoxy cinnamionitrile and/or ethyl- $\alpha$ -cyano-3,4,5-trimethoxy cinnamate (**1a,b**) with 2-imino-4-oxo-2-thiazolidine **2** and instead we have found that the reaction product in all cases was 5-arylmethylene-2-imino-4-oxo-2-thiazolidine **3**.

### 2. Experimental

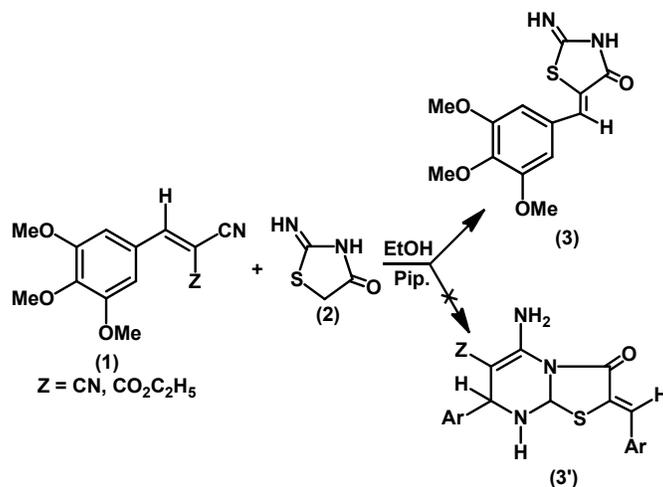
All melting points are uncorrected. The infrared spectra are recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. The  $^1\text{H}$  NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift ( $\delta$ ) expressed in ppm downfield from TMS. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC was run using TLC aluminum sheets silica gel F<sub>254</sub> (Merck).

(Z)-2-Imino-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-4-one (**3**): A mixture of iminothiazolidinone **2** (1.16 g, 10 mmole), 0.5 mL piperidine,  $\alpha$ -cyano-3,4,5-trimethoxy cinnamionitrile **1a** and/or ethyl- $\alpha$ -cyano-3,4,5-trimethoxy cinnamate **1b** (10 mmole) was refluxed in 30 mL absolute ethanol for 6h. The solid product deposited on hot was filtered off, washed with hot water, dried and recrystallized from *n*-butanol as yellow crystals (Scheme 1). Yield: 48%. M.p.: 263-265 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3171  $\nu(\text{NH})$ , 3076  $\nu(\text{C-H}_{\text{arom}})$ , 2936, 2860  $\nu(\text{C-H}_{\text{alkyl}})$ , 1678  $\nu(\text{CO})$ , 1638  $\nu(\text{C=N})$ .  $^1\text{H}$  NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm):

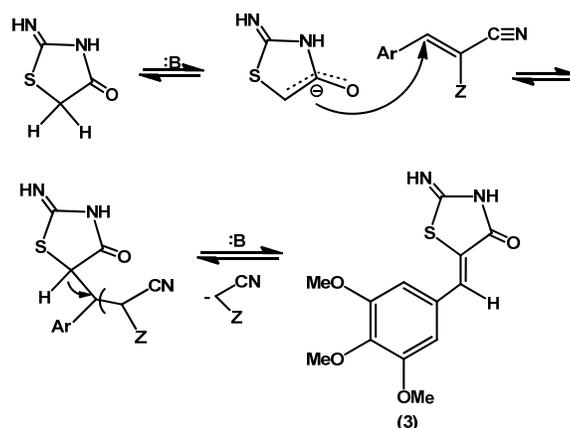
9.36 (s, 1H, NH, exchangeable with D<sub>2</sub>O), 8 (s, 1H, NH, exchangeable with D<sub>2</sub>O), 7.3 (s, 1H, =CH), 6.7 (br.s, 2H<sub>arom.</sub>), 3.9 (s, 6H, 2OMe), 3.85 (s, 3H, OMe).  $^{13}\text{C}$  NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm): 159.3 (C<sub>4</sub>), 155.2 (C<sub>3'</sub>, C<sub>5'</sub>), 146.7 (C<sub>2</sub>), 142.7 (C<sub>4'</sub>), 138.9 (C<sub>6</sub>), 128.6 (C<sub>1'</sub>), 128.6 (C<sub>1'</sub>), 114.2 (C<sub>5</sub>), 111.2 (C<sub>2'</sub>), 58.2 (C<sub>4'</sub>-OMe) 55.4 (C<sub>3'</sub>-OMe). MS (EI, *m/z* (%)): 294 (M, 75.9), 224 (M-HCN, HNCO. 91.4), 209 (base, 100), 196 (76.8), 181 (61.8). Anal. calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S (294.31): C, 53.05; H, 4.78; N, 9.51. Found: C, 52.83; H, 5.1; N, 10.0%.

(2E, 5Z)-1-benzyl-2-benzylimino-5-(3,4,5-trimethoxybenzylidene)-imidazolidin-4(H)one (**4**): A mixture of **3** (1.47 g, 5 mmole) and benzyl amine (0.53 mL, 5 mmole) was boiled in ethanol (20 mL) for 4 h (TLC). The excess solvent was removed and the crude oil triturated with petroleum-ether (B.p.: 40-60 °C). The solid separated was filtered off, dried and then recrystallized from light petroleum-ether (B.p.: 80-100 °C) to give yellow crystals (Scheme 3). Yield: 30%. M.p.: 120-122 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3420  $\nu(\text{NH})$ , 3062  $\nu(\text{C-H}_{\text{arom.}})$ , 2938, 2840  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1724  $\nu(\text{CO})$ , 1652  $\nu(\text{C=N})$ , 1590  $\nu(\text{C=C})$ .  $^1\text{H}$  NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm): 7.64 (s, 1H, NH, exchangeable with D<sub>2</sub>O), 7.5 (m, 10H<sub>arom.</sub>), 7.1 (s, 1H, =CH), 6.9 (s, 2H<sub>arom.</sub>), 4.6 (br.s, 4H, -NCH<sub>2</sub>Ph), 3.92 (s, 6H, 2OMe), 3.79 (s, 3H, OMe). MS (EI, *m/z* (%)): 457 (M, 22.6), 384 (30.3), 224 (base, 100), 210 (57.8), 91 (25.3). Anal. calcd. for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> (457.49): C, 70.88; H, 5.94; N, 9.18. Found: C, 70.36; H, 5.8; N, 8.77%.

(5Z,5'Z)-2,2'-(hydrazin-1,2-diyl)bis[5-(3,4,5-trimethoxybenzylidene)-thiazol-4(5H)one (**5**): A mixture of **3** (1.47 g, 5 mmole) and hydrazine hydrate (5 mL, 10 mmole) was refluxed in 20 mL *n*-butanol for 0.5 h (TLC). The separated solid was filtered off, and washed with butanol and recrystallized from dioxane to give yellow powder (Scheme 3). Yield: 30%. M.p.: 316-318 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3230  $\nu(\text{NH})$ , 3060  $\nu(\text{C-H}_{\text{arom.}})$ , 2928, 2851  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1707  $\nu(\text{CO})$ .



Scheme 1



Scheme 2

<sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm): 7.4 (s, 2H), 6.9 (m, 4H<sub>arom.</sub>), 3.92 (s, 12H, 4OMe), 3.8 (s, 6H, 2OMe), 3.1 (br.s, 2H, 2NH, exchangeable with D<sub>2</sub>O). MS (EI, *m/z* (%)): 586 (M, 12.7), 294 (16.2), 252 (7.3), 224 (base, 100), 209 (base-Me, 47.6), 181 (30.1). Anal. calcd. for C<sub>26</sub>H<sub>26</sub>N<sub>4</sub>O<sub>8</sub>S<sub>2</sub> (586.6): C, 53.23; H, 4.46; N, 9.55. Found: C, 53.42; H, 3.96; N, 9.16%.

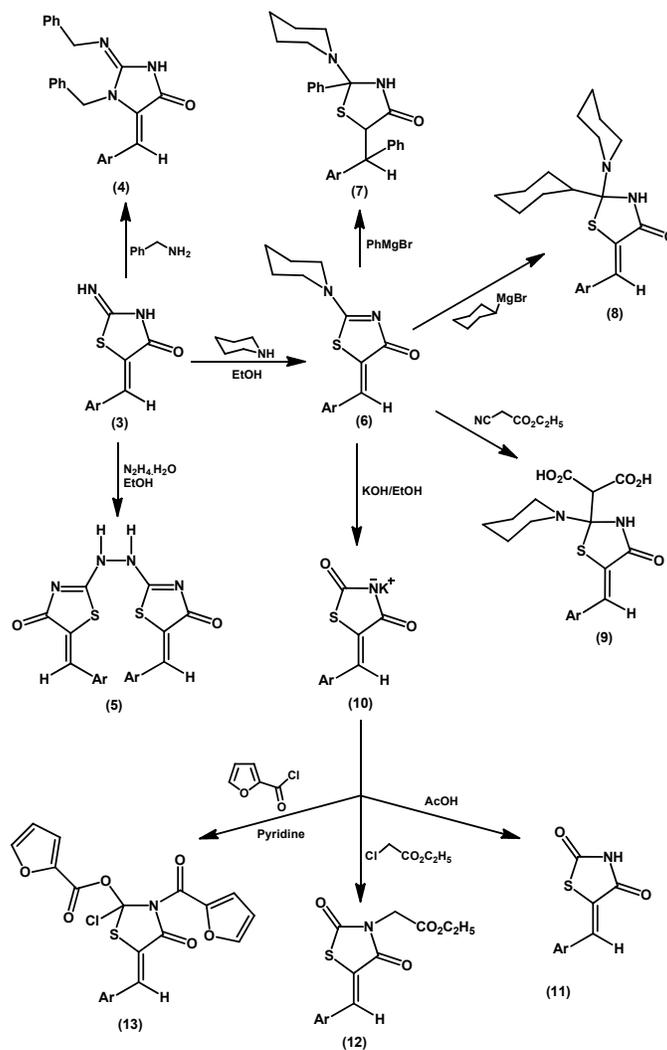
(*Z*)-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-thiazol-4(5H) one (**6**): A mixture of **3** (1.47 g, 5 mmole) with 0.5 mL of piperidine was refluxed in 20 mL ethanol for 3h. The reaction mixture was concentrated, left to cool, acidified with cold dilute hydrochloric acid. The solid that separated was collected, washed with water, dried and then recrystallized from benzene as yellow crystals (Scheme 3). Yield: 45%. M.p.: 156-158 °C. FT-IR (KBr, cm<sup>-1</sup>): 3060 ν(C-H<sub>arom.</sub>), 2931, 2863 ν(C-H<sub>alkyl</sub>), 1678 ν(CO). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm): 7.7 (s, 1H, =CH), 6.8 (s, 2H<sub>arom.</sub>), 3.91 (s, 6H, 2OMe), 3.83 (s, 3H, OMe), 2.3-1.5 (br.m, 10H, C<sub>5</sub>H<sub>10</sub>N). <sup>13</sup>C NMR (200 MHz, DMSO-*d*<sub>6</sub>, ppm): 177 (C<sub>4</sub>), 155 (C<sub>2</sub>), 154.2 (C<sub>3</sub>', C<sub>5</sub>'), 143.8 (C<sub>6</sub>), 140.1 (C<sub>4</sub>'), 131.3 (C<sub>5</sub>), 128.1 (C<sub>1</sub>'), 104.8 (C<sub>2</sub>', C<sub>6</sub>'), 60.1, 56.1, 55.3 (3OMe), 46, 25.3, 24 (piperidyl carbons). MS (EI, *m/z* (%)): 362 (M, 1.5), 348 (M-Me, 18.3), 331 (base, 100), 330 (M-S, 98.2), 111 (52.9). Anal. calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S (362.41): C, 59.65; H, 6.11; N, 7.72. Found: C, 60.03; H, 5.87; N, 7.26%.

A solution of phenyl magnesium bromide or cyclohexyl magnesium bromide (15 mmole) in anhydrous ether (100 mL) was added dropwise while shaking to a warm solution of

4-oxo-2-thiazoline **6** (1.81 g, 5 mmole) in anhydrous benzene (100 mL). The whole mixture warmed over a water-bath for 10 hours and left standing at room temperature for 24 hours. The Grignard complex was decomposed with a saturated solution of ammonium chloride (200 mL) and extracted with ether (200 mL). The combined ether-benzene extract was washed thoroughly with water, dried over anhydrous sodium sulphate and evaporated. The viscous oil which remained was triturated several times with light petroleum-ether (B.p.: 40-60 °C) and the remain insoluble fraction was dissolved in a suitable solvent to give **7** and **8**, respectively.

2-Phenyl-5-[phenyl(3,4,5-trimethoxyphenyl)methyl]-2-(piperidin-1-yl)-thiazolidin-4-one (**7**): Recrystallized from light petroleum-ether (B.p.: 80-100 °C) as pink crystals (Scheme 3). Yield: 36%. M.p.: 160-162 °C. FT-IR (KBr, cm<sup>-1</sup>): 3404 ν(br. NH), 3072 ν(C-H<sub>arom.</sub>), 2936, 2858 ν(C-H<sub>alkyl</sub>), 1667 ν(CO). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, ppm): 8.0 (s, 1H, NH, exchangeable with D<sub>2</sub>O), 7.4-6.6 (m, 12H<sub>arom.</sub>), 5.1 (d, *J* = 5.8 Hz, 1H<sub>benzylic</sub>), 4.4 (d, 1H, *J* = 5.6 Hz, C<sub>5</sub>-H), 3.88 (s, 9H, 3OMe), 2.21-1.34 (two m, 10H, C<sub>5</sub>H<sub>10</sub>). MS (EI, *m/z* (%)): 518 (M, 3.7), 502 (M-Me, 3.4), 469 (4.4), 257 (base, 100), 243 (base-Me, 37.9), 166 (base-3CH<sub>2</sub>O, 20.2). Anal. calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>S (518.63): C, 69.47; H, 6.59; N, 5.40. Found: C, 70.09; H, 6.42; N, 5.00%.

(*Z*)-2-Cyclohexyl-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-4-one (**8**): Recrystallized from light petroleum-ether (B.p.: 80-100 °C) as white crystals (Scheme 3).



Scheme 3

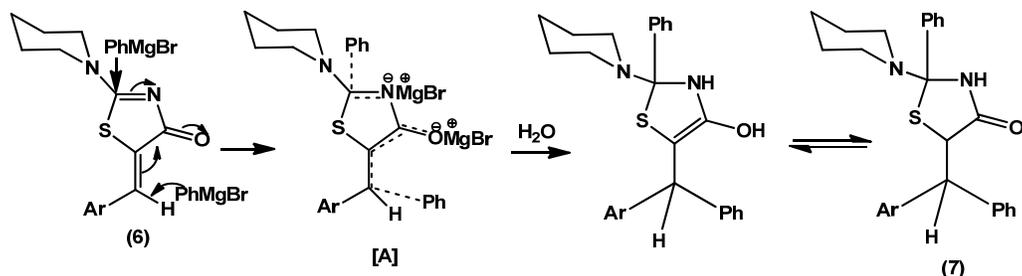
Yield: 22%. M.p.: 176-178 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3420  $\nu(\text{NH})$ , 3064  $\nu(\text{C-H}_{\text{arom.}})$ , 2929  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1688  $\nu(\text{CO})$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 7.8 (br.s, 1H, NH, exchangeable with  $\text{D}_2\text{O}$ ), 7.2 (s, 1H, =CH), 6.9 (s, 2H<sub>arom.</sub>), 3.89 (s, 9H, 30Me), 2.1-1.6 (two m, 10H,  $\text{C}_5\text{H}_{10}$ ), 1.49-1.08 (m, 11H,  $\text{C}_6\text{H}_{11}$ ). MS (EI,  $m/z$  (%)): 446 (M, 22.7), 432 (M-Me, 31.9), 349 (27.7), 249 (12.8), 184 (base, 100). Anal. calcd. for  $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{S}$  (446.61): C, 64.54; H, 7.66; N, 6.27. Found: C, 64.56; H, 7.43; N, 5.91%.

(*Z*)-2-[4-oxo-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-2-yl] malonic acid (**9**): To a stirred mixture of **6** (1.81 g, 5 mmole), ethylcyanoacetate (0.56 g, 5 mmole) and 20 mL dry benzene, sodium hydride (0.24 g, 10 mmole) was added portion wise and the whole mixture was refluxed for 3 hrs until no more substrate (TLC). The excess solvent was evaporated. The reaction mixture was treated with cold dilute hydrochloric acid. The separated solid was collected by suction, washed with water, dried and then recrystallized from benzene to give compound **9** as orange crystals (Scheme 3). Yield: 32%. M.p.: 164-166 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): br. centered at 3446  $\nu(\text{NH, OH})$ , 2935, 2846  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1694  $\nu(\text{CO})$ , 1583  $\nu(\text{C=C})$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 10.2 (s, 2H, 2COOH, exchangeable with  $\text{D}_2\text{O}$ ), 7.53 (s, 1H, exchangeable with  $\text{D}_2\text{O}$ ), 7.15 (s, 1H, CH=), 6.8 (s, 2H<sub>arom.</sub>), 4.77 (s, 1H), 3.9-3.8 (two s, 9H, 30Me), 1.6-1.07 (m, 10H,  $\text{C}_5\text{H}_{10}\text{N}$ ). MS (EI,  $m/z$  (%)): 466 (M, 10.2), 462 (M-2H,

23.6), 323 (base, 100), 224 (17.6), 210 (16.9). Anal. calcd. for  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_8\text{S}$  (466.48): C, 54.18; H, 5.4; N, 6.01. Found: C, 54.6; H, 5.34; N, 5.92%.

(*Z*)-5-(3,4,5-trimethoxybenzylidene)-3H-thiazolidin-2,4-dione potassium salt (**10**): A mixture of **6** (5 mmole) and 25 mL 10% ethanolic potassium hydroxide solution was refluxed for 1h. After concentration the separated potassium salt was collected by suction as white crystals (Scheme 3). Yield: 80%. M.p.: >300 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3077  $\nu(\text{C-H}_{\text{arom.}})$ , 2946  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1652  $\nu(\text{CO})$ .  $^1\text{H NMR}$  (200 MHz,  $\text{DMSO}-d_6$ , ppm): 7.84 (s, 2H<sub>arom.</sub>), 7.66 (s, 1H, CH=), 3.9-3.8 (two s, 9H, 30Me).

(*Z*)-5-(3,4,5-trimethoxybenzylidene)-3H-thiazolidin-2,4-dione (**11**): The potassium salt **10** was dissolved in water with stirring then acidified with acetic acid. The solid deposited was filtered off, washed several times with water, dried and then recrystallized from dilute ethanol as pale yellow crystals (Scheme 3). Yield: 90%. M.p.: 207-208 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3127  $\nu(\text{NH})$ , 2931, 2852  $\nu(\text{C-H}_{\text{alkyl.}})$ , 1737, 1680  $\nu(\text{CO})$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ , ppm): 10.7 (s, 1H, exchangeable with  $\text{D}_2\text{O}$ ), 8.03 (s, 1H, CH=), 6.78 (s, 2H<sub>arom.</sub>), 3.9-3.8 (two s, 9H, 30Me). MS (EI,  $m/z$  (%)): 295 (M, 32.3), 224 (base, 100), 134 (base-3CH<sub>2</sub>O, 16.8), 91 (11.7), 77 (28.6), 65 (55.3). Anal. calcd. for  $\text{C}_{13}\text{H}_{13}\text{NO}_5\text{S}$  (295.29): C, 52.87; H, 4.43; N, 4.74. Found: C, 53.42; H, 4.4; N, 4.66%.



Scheme 4

(*Z*)-ethyl-2-[2,4-dioxo-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-3-yl]acetate (**12**): A mixture of **10** (1.67 g, 5 mmole) and ethylchloroacetate (0.62 g, 5 mmole) was refluxed in 30 mL ethanol for 6 hrs (TLC). The separated solid was filtered off, dried and then recrystallized from ethanol to give compound **12** as pale yellow crystals (Scheme 3). Yield: 23%. M.p.: 119 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3072  $\nu$ (C-H<sub>arom.</sub>), 2940, 2862  $\nu$ (C-H<sub>alkyl.</sub>), 1741, 1717, 1682  $\nu$ (CO).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ , ppm): 7.6 (s, 1H, =CH), 6.6 (s, 2H<sub>arom.</sub>), 4.6 (d, d, 2H), 4.2 (q, 2H,  $J = 6.4$  Hz), 3.9-3.85 (two s, 9H, 3OMe), 1.36 (t, 3H,  $J = 6.4$  Hz). MS (EI,  $m/z$  (%)): 381 (M, 23.9), 335 (M-EtOH, 24.2), 308 (M-C<sub>2</sub>H<sub>4</sub>, CO<sub>2</sub>, 17.7), 224 (base, 100), 134 (base-3CH<sub>2</sub>O, 7.2), 77 (56.2). Anal. calcd. for C<sub>17</sub>H<sub>19</sub>NO<sub>7</sub>S (381.37): C, 53.53; H, 5.01; N, 3.67. Found: C, 53.0; H, 5.17; N, 4.07%.

(*Z*)-5-(3,4,5-trimethoxybenzylidene)-2-chloro-3-(furan-2-carbonyl)-4-oxothiazolidin-2-yl furan-2-carboxylate (**13**): A mixture of **10** (1.67 g, 5 mmole) and furoyl chloride (0.65 g, 5 mmole) was refluxed in 30 mL dry pyridine for 4hrs (TLC). After concentration, cold dilute hydrochloric acid was added. The separated solid was filtered off, washed with water, dried and then recrystallized from a mixture of benzene/ethanol to give compound **13** as yellow crystals (Scheme 3). Yield: 13%. M.p.: 185-188 °C. FT-IR (KBr,  $\text{cm}^{-1}$ ): 3072  $\nu$ (C-H<sub>arom.</sub>), 2935, 2843  $\nu$ (C-H<sub>alkyl.</sub>), 1717  $\nu$ (CO<sub>ester</sub>), 1687  $\nu$ (CO), 1588  $\nu$ (C=C). MS (EI,  $m/z$  (%)): 521 (M+2, 9.7), 520 (M, 27.8), 298 (43.1), 252 (54.9), 224 (base, 100), 209 (base-Me, 96.9). Anal. calcd. for C<sub>23</sub>H<sub>18</sub>ClNO<sub>9</sub>S (519.89): C, 53.13; H, 3.48; N, 2.69. Found: C, 53.42; H, 3.08; N, 3.30%.

### 3. Results and discussion

5-Arylmethylene-2-imino-4-oxo-2-thiazolidine **3** obtained as the sole product in a good yield upon treatment of 2-imino-4-oxo-2-thiazolidine (**2**) with  $\alpha$ -cyano-3,4,5-trimethoxy cinnamonnitrile and/or ethyl- $\alpha$ -cyano-3,4,5-trimethoxy cinnamate (**1a,b**) in refluxing ethanol in the presence of catalytic amount of piperidine (Scheme 1). Structure of compound **3** was substantiated from microanalytical data and was confirmed by infrared,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectra (c.f. Exp.).

The configuration assigned to the exocyclic C=C double bond in compound **3** (*Z*-configuration) has been proven by  $^1\text{H}$  NMR calculations [10] which are compatible with the observed data given in the experimental part. Furthermore, the negative field of the carbonyl oxygen suffers from the repulsive forces with the  $\pi$ -cloud of the aromatic ring in case of *E*-configuration and hence the compound favours the formation of the structure shown in Scheme 1.

The formation of **3** was assumed to proceed via nucleophilic addition of the thiazolidinyl-C-5 to the  $\beta$ -carbon of the activated double bond of **1** forming the 1:1 adduct followed by removal of malononitrile or ethylcyanoacetate molecule (Scheme 2).

When (*Z*)-2-imino-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-4(*H*)-one (**3**) was subjected to react with benzyl amine in refluxing ethanol, H<sub>2</sub>S released during the reaction period

and a sulfur free compound with molecular formula C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> is produced which indicates the incorporation of two molecules of benzyl amine. This compound was identified to be (*2E*, 5*Z*)-1-benzyl-2-benzylimino-5-(3,4,5-trimethoxy benzylidene)-imidazolidin-4(*H*)-one (**4**) from microanalytical data and spectroscopic analysis (Scheme 3).

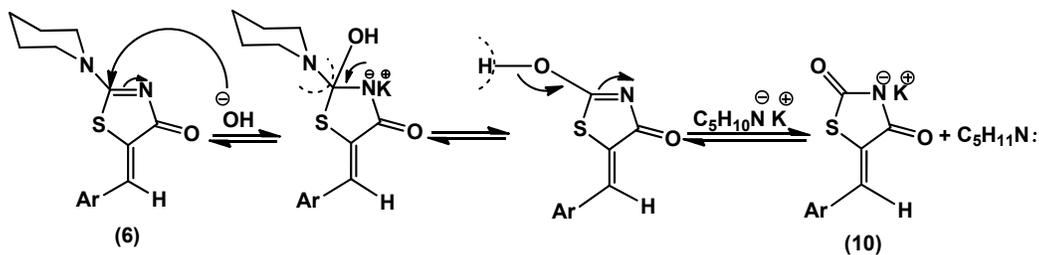
Differing accounts dealing with action of hydrazine hydrate on thiazolidinone derivatives were reported [11-13]. Omer and Rauof et al. [12] reported the cleavage of 5-arylmethylene-2,4-dioxo-1,3-thiazolidines with hydrazines and afforded the respective triazinones. Here in, hydrazinolysis of compound **3** in refluxing *n*-butanol afforded the dimeric product **5** (Scheme 3).

Several authors reported the formation of piperidino and morpholino salts of 5-arylmethylene-4-oxo-2-thioxo-thiazolidines by reacting 3*H*-thiazolinones with the required secondary amine in acetone or methyl acetate solution [11,12]. Treatment of (*Z*)-2-imino-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-4-one (**3**) with piperidine afforded the compound **6** which assigned as (*Z*)-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)thiazol-4(*5H*)-one (c.f. Exp.).

The reaction of Grignard reagents with various 5-arylidene-1,3-thiazolidines and its piperidino salts have been reported [14]. Actually, the majority of the products resulted from the action of cyclohexyl magnesium bromide and phenyl magnesium bromide on **6** represents some of the mentioned routes (1,2-addition at C=N, C=O and 1,4-addition to C=C-C=O and C=C-C=N). Thus, the reaction of **6** with phenyl magnesium bromide in refluxing ether-anhydrous benzene mixture afforded the adduct **7**.

The structure of **7** was evidenced by analytical data which infers the incorporation of two molar proportions of the Grignard reagent. The transformation of **6** to **7** was represented in scheme 4, it is supported that the reaction has occurred either through 1,2-addition to C=N group of the thiazolidine ring, or through the transition state [A] which resulted from the 1,4-addition to C=C-C=O ring system followed by rearrangement (Scheme 4).

Cyclohexyl magnesium bromide attacks 2-piperidino derivative **6** in refluxing ether-anhydrous benzene mixture through 1,2-addition at C=N to give (*Z*)-2-cyclohexyl-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-4-one (**8**). The structure of **8** is substantiated by microanalysis which infers the addition of one molecule of cyclohexane and confirmed by IR spectrum which exhibits the strong absorption bands characteristic for NH (br.), C-H (str.), and C=O of thiazolidine ring and was rigidly established by mass spectrum which shows fragmentation pattern consistent with the assigned structure **8** (c.f. Exp.). The carbanion which derived from ethyl cyanoacetate in anhydrous benzene upon treating with sodium hydride reacted with compound **6** to afford orange solid product from which it is possible to isolate (*Z*)-2-[4-oxo-2-(piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-2-yl]malonic acid (**9**).



Scheme 5

Conversion of **6** into the potassium salt **10** have been done on the basis of higher acidity of 3*H*-compound following the reported method [12] by treating **6** with ethanolic potassium hydroxide solution. Formation of the salt **9** infers that the substituent at the 2-position was replaced through the reaction (Scheme 5).

The IR spectrum of **10** show  $\nu_{C=O}$  at relative lower frequency ( $1652\text{ cm}^{-1}$ ) as compared with the extra conjugation performed by the newly formed negative charge. Furthermore,  $^1\text{H}$  NMR spectrum of **10** show only resonances of aromatic protons (2H) at  $\delta$  7.84 ppm together with olefinic proton at  $\delta$  7.66 ppm, and two singlets for three methoxy protons (9H) at  $\delta$  (ranged from 3.9-3.8 ppm which consistent with the proposed structure. (*Z*)-5-(3,4,5-trimethoxybenzylidene)-3*H*-thiazolidin-2,4-dione (**11**) was obtained upon treating the potassium salt **10** with dilute acetic acid.

Alkylation of **10** with ethyl chloroacetate in boiling ethanol affords the *N*-alkylation product (*Z*)ethyl-2-[2,4-dioxo-5-(3,4,5-trimethoxybenzylidene)-thiazolidin-3-yl]acetate (**12**). Acylation of **10** with furoyl chloride in pyridine gave a yellow crystals product **13** after reflux for four hours (TLC). Full analysis for **13** using spectroscopic methods indicates the incorporation of two moles of the acid chloride with loss of KCl.

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