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## SYNTHETIC AND THEORETICAL APPROACH TOWARDS SPIROTHIAZOLIDINONE SYSTEMS

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**Abstract** – A convenient synthesis of spirothiazolidinones by nucleophilic cyclocondensation of intermediate imine with mercaptoacetic acid is described. Computational studies have been performed to substantiate the proposed mechanism as well as to ascertain transition state of the system.

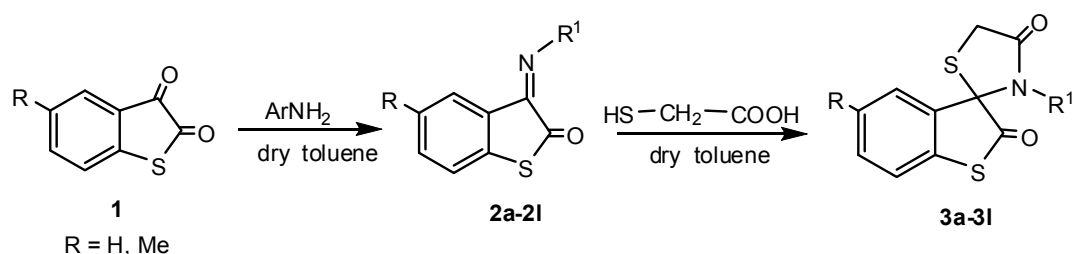
### INTRODUCTION

Thiazolidinone derivatives have long been known for a wide spectrum of pharmaceutical activities.<sup>1</sup> It is a core constituent of many pharmacologically important synthetic and naturally occurring drugs,<sup>2</sup> in which fused benzene ring substituted at various positions have been found to be more potent.<sup>3</sup> Because of their structure activity relationship, it is a privileged objective in combinatorial library synthesis.<sup>4</sup> The research on the chemistry of thioisatins has continued unabated due to their wide spread occurrence in thiodrugs and biological activities.<sup>5,6</sup> The presence of –N–C–S– linkage in thiazolidinones account for the fungicidal, antibacterial and antiviral activities.<sup>7,8</sup> They are also known to possess amoebicidal and anticonvulsant activities.<sup>9</sup> In continuation to our investigations on new reactions and scaffolds, we have explored readily available building blocks useful for the dynamic combinatorial chemistry.<sup>10</sup> To further explore the potential of this protocol and in connection with earlier work on the synthesis of spirothiazolidinones,<sup>11,12</sup> herein we now report the reactions of benzo[*b*]thiophene-2,3-diones with derivatives of aromatic/aliphatic amines and mercaptoacetic acid to produce a series of spirothiazolidinone derivatives (52-71%) containing benzothiophene nucleus which may act as structural motifs for spiroannulated system. The theoretical assay of such type of moieties has not been well studied yet and merited detailed investigation. The optimized geometries of transition states and product moieties

have been well analyzed theoretically and thus the mechanism involved is explored with the help of B3LYP<sup>13</sup> level in 6-31G\*<sup>14</sup> basis set using Gaussian 03 suite of programs.

## RESULTS AND DISCUSSION

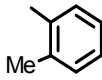
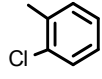

The first step in the synthesis of spirothiazolidinones involved condensation between the thioisatins **1** and aromatic/aliphatic amines in toluene to yield imino intermediates (Schiff bases) **2a-2l** in 58-64% yield after recrystallisation from ethanol at room temperature. In the second step cyclocondensation of imino intermediates **2a-2l** with mercaptoacetic acid in refluxing toluene produced spirothiazolidinones **3a-3l** in 52-71% yield (Scheme 1). All these reactions were carried out by use of “Dean Stark apparatus” and stoichiometric amounts of water were removed azeotropically.

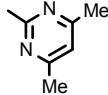
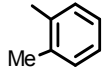
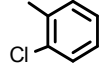
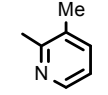
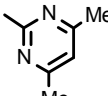


**Scheme 1**

The imino intermediates were readily characterized by appearance of  $>C=N$  stretching in the range 1570-1650  $\text{cm}^{-1}$  in the IR spectra as well as by presence of a signal at 150-158 ppm due to imino carbon in the <sup>13</sup>C NMR spectra. The formation of spirothiazolidinones was ascertained by disappearance of  $>C=N$  in the range 1570-1650  $\text{cm}^{-1}$ , appearance of methylene proton ( $>CH_2$ ) in the <sup>1</sup>H NMR spectrum at ~ 3.5 ppm (singlet), appearance of additional  $>C=O$  signal at ~164 ppm in the <sup>13</sup>C NMR spectra. The mass spectrum of product **3f** showed the following peaks:  $m/z$  (%) 296 ( $M^+$ , 62), 268 (100), 222 (48), 194 (39).

**Table 1.** Spirothiazolidinones (**3a-3l**)

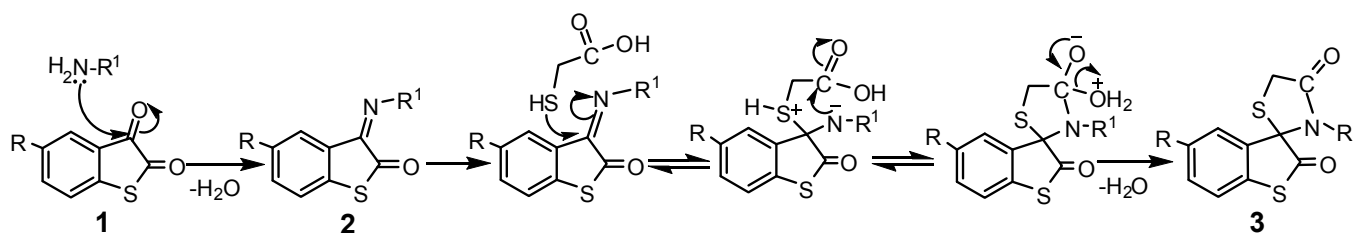
Entry	Product	R	R <sup>1</sup>	Time /hr	Mp/°C	Yield/%
1	<b>3a</b>	Me	C <sub>6</sub> H <sub>5</sub>	7	169-171	68
2	<b>3b</b>	Me		6	148-152	67
3	<b>3c</b>	Me		9	183	71
4	<b>3d</b>	Me		7	188-190	56

5	<b>3e</b>	Me		8	180	52
6	<b>3f</b>	H	C <sub>6</sub> H <sub>5</sub>	6	169	68
7	<b>3g</b>	H		7	159-162	67
8	<b>3h</b>	H		8	151-154	71
9	<b>3i</b>	H		10	170-174	58
10	<b>3j</b>	H		9	185-188	52
11	<b>3k</b>	Me	Et-	5	173-176	74
12	<b>3l</b>	Me	<i>i</i> -Pr-	4	180-181	65

All these data were conclusively indicative of products as spirothiazolidinones **3a-3l**. The physical properties of spirothiazolidinones are given in Table 1.

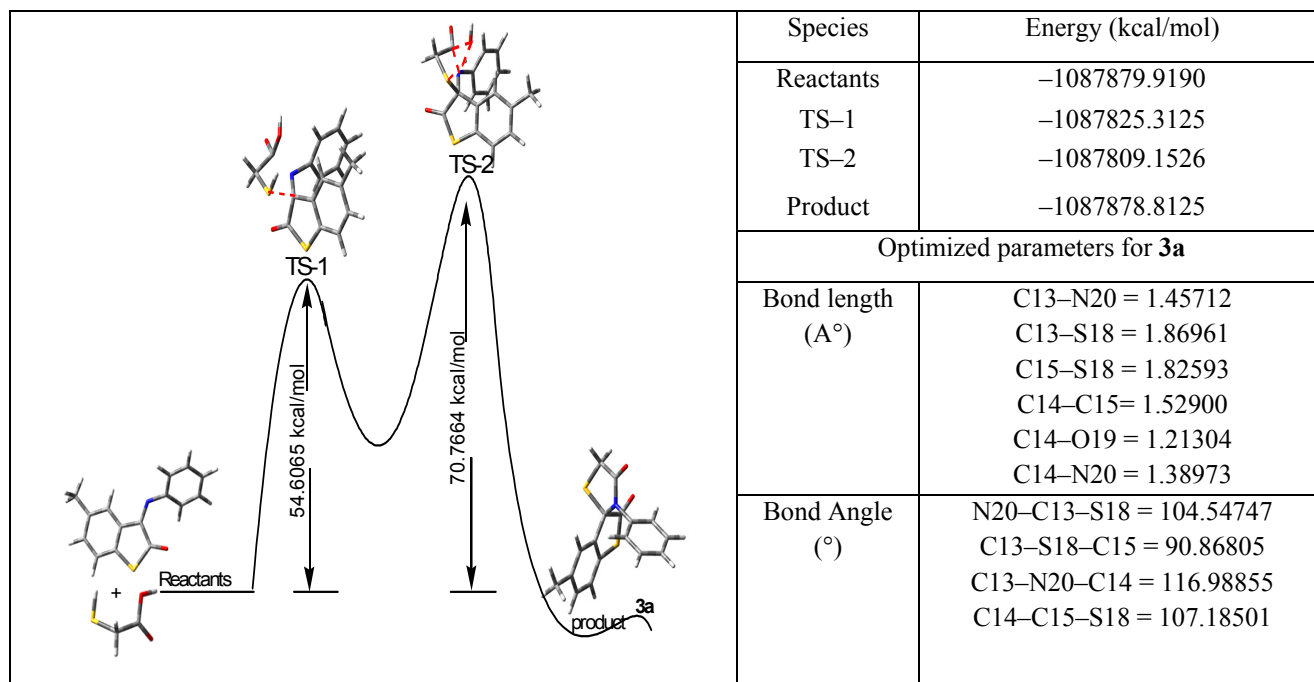
### MECHANISM OF CYCLOCONDENSATION REACTION

First step involves the nucleophilic addition of aromatic/aliphatic amines to  $\beta$ -carbonyl group of thioisatin leading to imino intermediates **2**. Subsequently, attack of sulphur lone pair of mercaptoacetic acid on the imino carbon followed by attack of nitrogen lone pair on carbonyl carbon of mercaptoacetic acid results the cyclocondensation for the formation of spirothiazolidinones. The mechanism of cyclocondensation reaction is represented in Figure 1.



**Figure 1.** Mechanism of cyclocondensation reaction

The mechanism suggested and transition states interpreted are supported by theoretical calculations on the basis of density functional approach in 6-31G\* basis set. The transition states have first order saddle point in frequency calculations confirming these interpretations. According to the mechanism, there should be two consecutive transition states in the mechanistic pathway which would facilitate the reaction. In the first transition state there is a bond formation between sulphur lone pair and the imino carbon.



**Figure 2.** Energy profile diagram and transition states for the mechanism suggested for **3a**

In the second transition state, there is a bond formation between carbonyl carbon of mercaptoacetic acid and the imino nitrogen with subsequent removal of H<sub>2</sub>O. The energy profile diagram and corresponding transition state structures for **3a** are depicted in Figure 2.

## CONCLUSION

A convenient synthesis of spirothiazolidinones has been accomplished. The mechanism has been favored by location of transition state studies and delocalization studies.

## EXPERIMENTAL

Melting points were determined in an open glass capillary and are uncorrected. The solvents were purified by standard procedures.<sup>15</sup> The IR spectra were recorded on Nicolet Magna IR TM model 550 in KBr pellets. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a JEOL AL-300 instrument at 300 and 75 MHz using CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ ppm. The mass spectra was recorded on JEOL-AccuTOF JMS-T100LC having DART (Direct analysis in Real Time). Elemental analyses were performed using a Perkin Elmer series C, H, N and S analyser-2400. Thin layer chromatography (TLC) was performed on alumina foil on Merck's Kiesel gel 60 F<sub>254</sub> sheets; visualization was achieved at ultra fluorescence on Indian Equipment Corporation equipment, IEC-312 at 354 nm. Column chromatography was carried over silica gel 60-120 mesh as adsorbent, using solvents of rising polarity. The theoretical calculations of the title moieties were performed using the Gaussian 03 suite of program.<sup>16</sup>

## GENERAL PROCEDURE

### *Synthesis of benzothiazolidinone derivatives:*

A mixture of substituted thioisatin (5 mmol) and aryl/aliphatic amines (5 mmol) was refluxed in absolute EtOH (25 mL) for 4-6 h. The completion of the reaction was confirmed by TLC (MeOH/EtOAc, 1:4), the reaction mixture was then cooled to room temperature, followed by removal of solvent under vacuum. The crude solid was recrystallized from EtOH to afford pure imino derivatives as white or yellow crystalline solids. For the formation of benzothiazolidinone; the corresponding imino derivative (2 mmol) was refluxed with mercaptoacetic acid (0.184 g, 2 mmol) in toluene (25 mL) in a Dean-Stark Apparatus. After 6 h, colour of the reaction mixture changed from reddish to light yellow. The products **3** separated out were filtered, washed with cold petroleum ether and recrystallised from MeOH/EtOH (3:1).

### *Physical and analytical data of benzothiazolidinone derivatives:*

#### **3'-(Phenyl)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3a)**

Yellowish solid, Yield: 290 mg (68%), Mp 169-171 °C. IR (KBr) ( $V_{\max}$ ,  $\text{cm}^{-1}$ ): 3124-3000 (Ar-H), 1738 (C=O), 1718 (C=O), 1600 (C=C), 608 (C-S).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.15-6.21 (8H, m, H-Ar), 3.49 (2H, s,  $\text{CH}_2$ ), 2.20 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 20.21 ( $\text{CH}_3$ ), 84.2 (spiroC), 124.20-137.90 (Ar-C), 162.5 (C=O), 188.5 (C=O). (Anal. Calcd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_2\text{S}_2$ : C, 62.36; H, 4.00; N, 4.28; S, 19.59%. Found: C, 61.98; H, 3.56; N, 4.01; S, 19.62%).

#### **3'-(2-Methylphenyl)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3b)**

Pale yellowish solid, Yield: 299 mg (62%), Mp 148-152 °C. IR (KBr) ( $V_{\max}$ ,  $\text{cm}^{-1}$ ): 3132-3000 (Ar-H), 1738 (C=O), 1722 (C=O), 1608 (C=C), 609 (C-S).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.52-6.21 (7H, m, ArH), 3.56 (2H, s,  $\text{CH}_2$ ), 2.10 (3H, s,  $\text{CH}_3$ ), 1.92 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.2 ( $\text{CH}_3$ ), 82.2 (spiro C) 121.20-142.20 (Ar-C), 161.4 (C=O), 184.2 (C=O). (Anal. Calcd. for  $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{S}_2$ : C, 63.32; H, 4.43; N, 4.10; S, 18.78%. Found: C, 63.36; H, 4.20; N, 4.25; S, 19.22%).

#### **3'-(2-chlorophenyl)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3c)**

Dirty white solid, Yield: 321 mg (71%), Mp 183 °C. IR (KBr) ( $V_{\max}$ ,  $\text{cm}^{-1}$ ): 3134-3000 (Ar-H), 1740 (C=O), 1720 (C=O), 1600 (C=C), 608 (C-S).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.35-6.21 (8H, m, H-Ar), 3.52 (2H, s,  $\text{CH}_2$ ), 2.21 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 20.1 ( $\text{CH}_3$ ), 85.4 (spiro C), 123.20-135.90 (Ar-C), 162.5 (C=O), 185.5 (C=O). (Anal. Calcd. for  $\text{C}_{17}\text{H}_{12}\text{ClNO}_2\text{S}_2$ : C, 56.42; H, 3.34; Cl, 9.80; N, 3.87; S, 17.72%. Found: C, 56.21; H, 3.43; Cl, 9.67; N, 3.75; S, 17.88%).

#### **3'-(3-Picoline)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3d)**

Yellow solid, Yield: 421 mg (56%), Mp 188-190 °C. IR (KBr) ( $V_{\max}$ ,  $\text{cm}^{-1}$ ): 3140-3010 (Ar-H), 1745 (C=O), 1720 (C=O), 1600 (C=C), 610 (C-S).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.57-6.21 (6H, m, H-Ar), 3.54 (2H, s,  $\text{CH}_2$ ), 2.19 (3H, s,  $\text{CH}_3$ ), 1.98 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 15.9 ( $\text{CH}_3$ ), 21.70 ( $\text{CH}_3$ ), 85.60 (spiro C), 124.20-145.90 (Ar-C), 155.50 (C=N), 163.5 (C=O), 186.5 (C=O). (Anal. Calcd.

for  $C_{17}H_{14}N_2O_2S_2$ : C, 59.63; H, 4.12; N, 8.18; S, 18.73%. Found: C, 59.55; H, 4.01; N, 8.32; S, 18.63%.

**3'-(4,6-Dimethylpyrimidine)spiro[3*H*-5-methylbenzo[*b*]thiophene-3,2'-thiazolidine]-2,4'-dione (3e)**

White solid, Yield: 221 mg (52%), Mp 180 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3132-3008 (Ar-H), 1738 (C=O), 1720 (C=O), 1600 (C=C), 608 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 8.57-6.25 (5H, m, H-Ar), 3.50 (2H, s,  $CH_2$ ), 2.17 (3H, s,  $CH_3$ ), 1.98 (3H, s,  $CH_3$ ).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta_C$ : 15.9 ( $CH_3$ ), 21.20 ( $CH_3$ ), 81.6 (spiro C), 123.20-145.90 (Ar-C), 154.50 (C=N), 162.5 (C=O), 190.5 (C=O). (Anal. Calcd. for  $C_{17}H_{15}N_3O_2S_2$ : C, 57.12; H, 4.23; N, 11.76; S, 17.94%. Found: C, 56.95; H, 4.11; N, 11.88; S, 17.86%.)

**3'-(Phenyl)spiro[3*H*-benzo[*b*]thiophene-3,2'-thioazolidine]-2,4'-dione (3f)**

Cream solid, Yield: 280 mg (62%), Mp 169 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3124-3000 (Ar-H), 1740 (C=O), 1710 (C=O), 1600 (C=C), 608 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 7.25-6.20 (9H, m, H-Ar), 3.48 (2H, s,  $CH_2$ ).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta_C$ : 83.1 (spiro C), 122.25-130.90 (Ar-C), 160.50 (C=O), 185.60 (C=O). MS:  $m/z$  (%) = 313 ( $M^+$ , 62), 268 (100), 222 (48), 194 (39). (Anal. Calcd. for  $C_{16}H_{11}NO_2S_2$ : C, 61.32; H, 3.54; N, 4.47; S, 20.46%. Found: C, 61.11; H, 3.36; N, 4.57; S, 20.49%.)

**3'-(2-Methylphenyl)spiro[3*H*-benzo[*b*]thiophene-3,2'-thiazolidine]-2,4'-dione (3g)**

Light yellowish solid, Yield: 301 mg (67%), Mp 159-162 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3138-3010 (Ar-H), 1742 (C=O), 1725 (C=O), 1600 (C=C), 609 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 7.57-6.25 (8H, m, H-Ar), 3.52 (2H, s,  $CH_2$ ), 1.98 (3H, s,  $CH_3$ ).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta_C$ : 20.10 ( $CH_3$ ), 83.5 (spiro C), 122.20-145.90 (Ar-C), 163.5 (C=O), 186.40 (C=O). (Anal. Calcd. for  $C_{17}H_{13}NO_2S_2$ : C, 62.36; H, 4.00; N, 4.28; S, 19.59%. Found: C, 62.12; H, 4.06; N, 4.34; S, 19.51%.)

**3'-(2-Chlorophenyl)spiro[3*H*-benzo[*b*]thiophene-3,2'-thiazolidine]-2,4'-dione (3h)**

Brownish solid, Yield: 324 mg (68%), Mp 151-154 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3125-3015 (Ar-H), 1728 (C=O), 1710 (C=O), 1600 (C=C), 608 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 7.25-6.20 (9H, m, H-Ar), 3.62 (2H, s,  $CH_2$ ).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta_C$ : 82.5 (spiro C), 122.21-136.80 (Ar-C), 161.6 (C=O), 183.2 (C=O). (Anal. Calcd. for  $C_{16}H_{10}ClNO_2S_2$ : C, 55.25; H, 2.90; Cl, 10.19; N, 4.03; S, 18.44%. Found: C, 55.17; H, 2.98; Cl, 10.11; N, 4.12; S, 18.38%.)

**3'-(3-Picoline)spiro[3*H*-benzo[*b*]thiophene-3,2'-thiazolidine]-2,4'-dione (3i)**

Yellow solid, Yield: 262 mg (58%), MP 170-174 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3138-3000 (Ar-H), 1742 (C=O), 1722 (C=O), 1600 (C=C), 610 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 8.27-6.25 (7H, m, H-Ar), 3.50 (2H, s,  $CH_2$ ), 1.98 (3H, s,  $CH_3$ ).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta_C$ : 15.20 ( $CH_3$ ), 83.6 (spiro C), 123.20-145.90 (Ar-C), 166.5 (C=O), 187.5 (C=O). (Anal. Calcd. for  $C_{16}H_{12}N_2O_2S_2$ : C, 58.52; H, 3.68; N, 8.53; S, 19.53%. Found: C, 58.46; H, 3.62; N, 8.44; S, 19.59%.)

**3'-(4,6-Dimethylpyrimidine)spiro[3*H*-benzo[*b*]thiophene-3,2'-thiazolidine]-2,4'-dione (3j)**

Chocolate brown solid, Yield: 211 mg (56%), Mp 185-188 °C. IR (KBr) ( $V_{max}$ ,  $cm^{-1}$ ): 3112-3000 (Ar-H), 1738 (C=O), 1729 (C=O), 1600 (C=C), 608 (C-S).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta_H$ : 8.52-6.32 (5H, m, H-

Ar), 3.62 (2H, s, CH<sub>2</sub>), 1.89 (3H, s, CH<sub>3</sub>), 1.92 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 15.2 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 82.9 (spiro C), 121.22-142.50 (Ar-C), 161.3 (C=O), 191.6 (C=O). (Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 55.96; H, 3.82; N, 12.24; S, 18.67%. Found: C, 55.91; H, 3.88; N, 12.18; S, 18.71%).

### 3'-(Ethyl)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3k)

Fade yellow solid, Yield: 413 mg (74%), Mp 173-176 °C. IR (KBr) (V<sub>max</sub>, cm<sup>-1</sup>): 3025-3000 (Ar-H), 1745 (C=O), 1735 (C=O), 1615 (C=C), 615 (C-S). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.21-6.91 (3H, m, H-Ar), 3.55 (2H, s, CH<sub>2</sub>), 3.41 (2H, m, CH<sub>2</sub>), 1.73 (3H, s, CH<sub>3</sub>), 1.31 (3H, t, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 15.1 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>), 34.7 (CH<sub>2</sub>), 83.5 (spiro C), 126.22-138.50 (Ar-C), 165.6 (C=O), 181.3 (C=O). (Anal. Calcd. for C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub>S<sub>2</sub>: C, 55.89; H, 4.69; N, 5.01; S, 22.96%. Found: C, 55.51; H, 4.29; N, 4.68; S, 23.21%).

### 3'-(2-Propyl)spiro[3H-5-methylbenzo[b]thiophene-3,2'-thiazolidine]-2,4'-dione (3l)

Dark brown solid, Yield: 381 mg (65%), Mp 180-181 °C. IR (KBr) (V<sub>max</sub>, cm<sup>-1</sup>): 3030-3010 (Ar-H), 1736 (C=O), 1733 (C=O), 1610 (C=C), 615 (C-S). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.11-6.68 (3H, m, H-Ar), 3.76 (1H, m, CH), 3.54 (2H, s, CH<sub>2</sub>), 2.04 (3H, s, CH<sub>3</sub>), 1.41 (6H, d, 2CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 12.2 (2CH<sub>3</sub>), 18.1 (CH<sub>3</sub>), 33.1 (CH), 84.5 (spiro C), 125.22-135.40 (Ar-C), 161.3 (C=O), 191.6 (C=O). (Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>2</sub>S<sub>2</sub>: C, 57.31; H, 5.15; N, 4.77; S, 21.86%. Found: C, 57.03; H, 5.38; N, 4.65; S, 22.16%).

## ACKNOWLEDGEMENT

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