



A Novel One-Pot Green Synthesis and Characterization of 5-Substituted Bis-Iminothiazolidinones

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Abstract: In this study, some new 5-substituted bis-iminothiazolidinone derivatives have been synthesized via one-pot green synthesis. The study comprises two steps. In the first step, bis-thioureas were prepared by the reaction of aryl isothiocyanates with substituted amines. In the second step, substituted bis-thioureas prepared beforehand and chloroacetic acid were condensed with substituted thiophene-2-carboxaldehydes and new 5-substituted bis-iminothiazolidinone compounds were obtained. The structures of all these synthesized compounds were determined and characterized by infrared, nuclear magnetic resonance and mass spectral data.

Keywords: 5-Substituted bis-iminothiazolidinone, bis-thiourea, one-pot reaction, green synthesis.

Submitted: July 03, 2018. **Accepted:** September 04, 2018.

Cite this: Tuğcu F. A Novel One-Pot Green Synthesis and Characterization of 5-Substituted Bis-Iminothiazolidinones. JOTCSA. 2018;5(3):1061-70.

DOI: <http://dx.doi.org/10.18596/jotcsa.440080>.

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INTRODUCTION

One-pot method without catalyst and solvent saves both time and energy since many intermediate products and final products do not need to be purified (1-2). Also, due to the growing concern for the influence of organic solvents on the environment as well as on the human body, development of solvent-free organic reactions have attracted the attention of synthetic organic chemists. These types of reactions are simple to handle, reduce pollution and comparatively cheaper to operate. For these reasons, solventless reaction complies with the fifth principle of green chemistry. It is believed that solvent-free synthesis is industrially useful and largely green. Green chemistry, also called sustainable chemistry, are processes that reduce or eliminate the use and generation of hazardous substances. From this point of view, one-pot solvent-free reactions are regarded as an ideal method of green synthesis (3).

Iminothiazolidinones have attracted much interest over the years since they are important and versatile scaffolds having engaged a pronounced position in medicinal chemistry. They

are well-known to possess an extensive spectrum of biological activities (4-10). There are many existing methods for the synthesis of 5-substituted iminothiazolidinones, but they are generally synthesized in two steps (11-15). In the first step, iminothiazolidinones are formed by the reaction of thioureas or N-substituted thioureas with α -chloroacetic acid or their acid esters or amides. In the second step, these compounds are reacted with aromatic aldehydes in basic medium to give 5-substituted iminothiazolidinone compounds. For example, Ottana et al. (12) synthesized the 2-imino-4-thiazolidinone compound as a result of the reaction of N-propyl-N'-phenylthiourea compound prepared from phenylisothiocyanate and propylamine with chloroacetyl chloride in triethylamine medium; this compound was then condensed with aromatic aldehydes in piperidine-containing medium to give 5-arylidene-2-imino-4-thiazolidinones.

There are few articles in the literature for bis-iminotiazolidinone (16) despite the many publications on the synthesis of 5-substituted iminotiazolidinone compounds. Therefore, in this article, reports the synthesis of new 5-substituted bis-iminothiazolidinone derivatives by the one-

pot solvent free green reaction from the corresponding substituted thiophene-2-carbaldehyde with bis-thiourea and chloroacetic acid at 70 °C. This article is consistent with the green chemistry approach because it describes a reaction which take place at low temperature and does not use solvents and catalysts, making it environmentally friendly, efficient and economic.

MATERIALS AND METHODS

Reagents purchased from Merck were as follows: dichloromethane, chloroform, ethyl acetate, n-hexane, chloroacetic acid, thiophene-2-carboxaldehyde, 3-methylthiophene-2-carboxaldehyde, phenyl isothiocyanate, p-tolyl isothiocyanate, 1,4-phenylenediamine, 4,4'-methylenedianiline, silica gel 60 (0.063-0.200 mm), and sea sand. All reagents were used as purchased from the manufacturer. Dichloromethane, chloroform, and n-hexane were used after purification for column chromatography. TLC was carried out on aluminum sheets pre-coated with silica gel 60 F254 purchased from Merck, and the spots were

visualized with UV light (254/366 nm) using a Camag UV lamp.

NMR (^1H and ^{13}C) spectra were saved on a Bruker 500 MHz NMR spectrometer at Yildiz Technical University and Erzurum Atatürk University, Department of Chemistry. CDCl_3 was used as a solvent. FTIR spectra were recorded on a Philips PU 9714 ATR spectrometer using a Perkin-Elmer Spectrum One program at Yildiz Technical University, Instrumental Analysis Laboratory. Melting points were obtained with a Gallenkamp Melting Point Apparatus in open capillaries with no correction.

Preparation of Bis-thiourea Derivatives (1a-d)

A mixture of the appropriate diamine (1 mmol) and substituted phenyl isothiocyanate (2.4 mmol) was stirred in CH_2Cl_2 at room temperature for 24 hours. The crude product was concentrated under vacuum and recrystallized from ethanol. General synthesis of bis-thioureas is summarized in Figure 1.

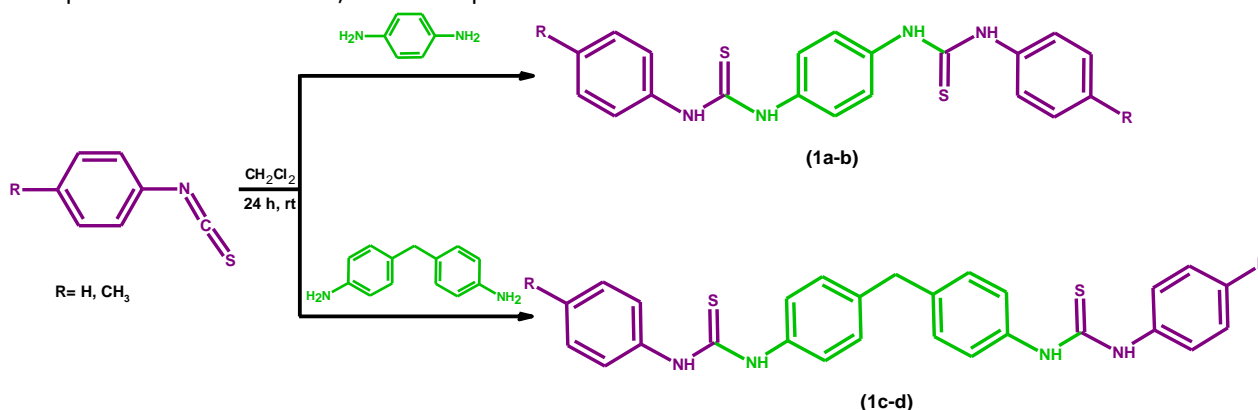


Figure 1. Synthesis of bis-thiourea derivatives.

Preparation of 5-Substituted Bis-Iminothiazolidinone Derivatives (2a-h)

To synthesize 5-substituted bis-iminothiazolidinone compounds, the appropriate bis-thiourea (1 mmol), chloroacetic acid (2.4 mmol) and substituted thiophene-2-carbaldehyde

(2 mmol) were stirred at room temperature for 4 hours and then heated at 70 °C for 6 hours. The product was purified by column chromatography. General synthesis of these compounds is summarized in Figure 2.

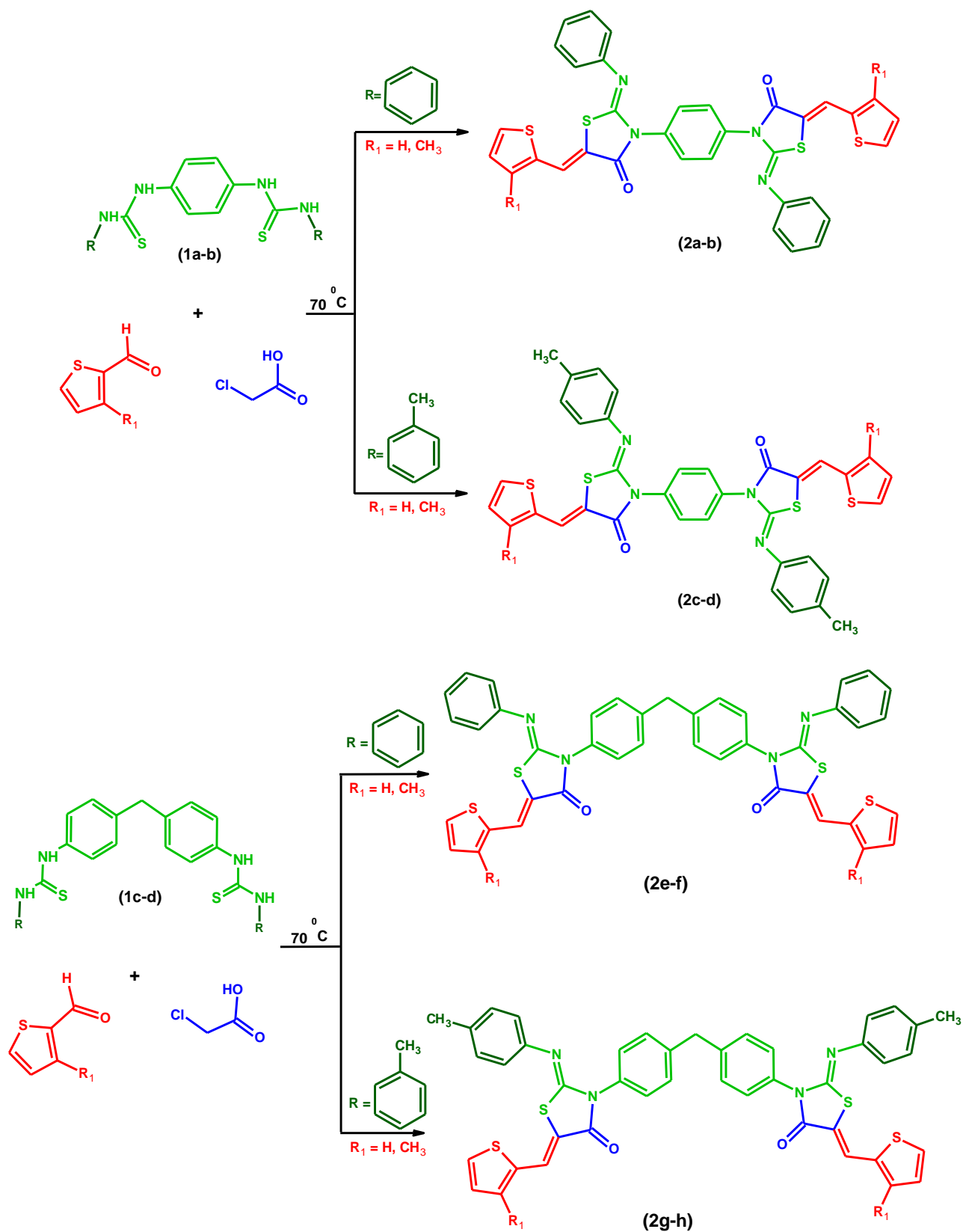


Figure 2. Synthesis of 5-substituted bis-iminothiazolidinone derivatives.

RESULTS AND DISCUSSION

The synthesis of bis-thiourea (**1a-d**) was done using diamine and substituted phenyl isothiocyanate in CH_2Cl_2 at room temperature.

They were recrystallized from hot ethanol and were characterized by recording their spectral data (Table 1). A mechanism for the reaction of bis-thiourea is shown in Figure 3 (17).

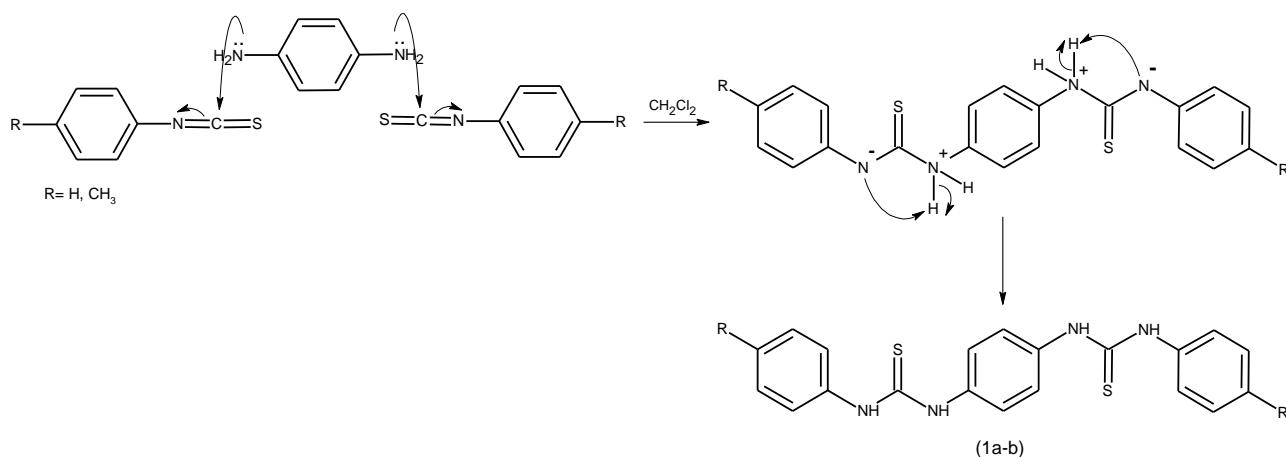


Figure 3. Proposed mechanism for the formation of bis-thiourea derivatives.

When the FTIR spectrum of bis-thioureas (**1a-d**) were analyzed, the conjugated C=C and C-N vibrations were observed in the ranges of 1600-1550 and 1540-1490 cm^{-1} , respectively. On the other hand, the N-H vibrations (3467-3438 and 3315-3360 cm^{-1}) of diamine used as reagents and the N=C=S stretching bands (2200-2000 cm^{-1}) of substituted isothiocyanate disappeared, which indicates that condensation had taken place.

Eight new 5-substituted bis-iminothiazolidinone derivatives (**2a-h**) were obtained from the second step of the present study. The synthesized crude products were obtained in varying yield depending on the structure and were purified by column chromatography. For the one-pot condensation method between bis-thiourea, thiophene-2-carboxaldehyde and chloroacetic acid, an estimated mechanism for the formation of 5-substituted bis-iminothiazolidinone was proposed by referring to the literature in Figure 4 (18-19). The structures of all synthesized compounds (**2a-h**) were explained based on the analysis of their spectroscopic data (Table 1).

When the infrared spectra of 5-substituted bis-iminothiazolidinones were analyzed, the conjugated C=C and C=N stretching vibrations that were distinctive for nitrogen having heterocyclic compounds are observed in the ranges of 1600-1500 and 1670-1600 cm^{-1} ,

respectively. Moreover, the N-H vibrations (3295-3190 cm^{-1}) of bis-thiourea, the C=O stretching ($\sim 1674 \text{ cm}^{-1}$) of heteroaromatic aldehyde and the -OH vibration bands (3400-2800 cm^{-1}) of chloroacetic acid disappeared, which indicates that cyclization and condensation reactions occurred. The characteristic absorption bands of C=O groups were observed at 1680-1722 cm^{-1} in the FTIR spectrum of the 5-substituted bis-iminothiazolidinone derivatives.

In the second step of clarifying the structures, when the ^1H NMR spectra of the initial substances and those of the products were compared, the singlet pertaining to the -CHO group observed at around 11.0 ppm in the spectra of substituted thiophene-2-carboxaldehydes and the singlet at around 9.8 and 9.3 ppm belonging to the -NH group in bis-thiourea were not encountered in ^1H NMR of the 5-substituted bis-iminothiazolidinone (**2a-h**), which is an evidence of the suggested structures. The multiple peaks seen between 6.8-7.7 ppm in the lower area of the spectra show the proton resonances of aromatic and the hetero aromatic bond. The H-atoms of -CH₂ and -CH₃ which belong to the compounds were observed in the ranges 4.03 ppm and 2.41-2.35 ppm respectively.

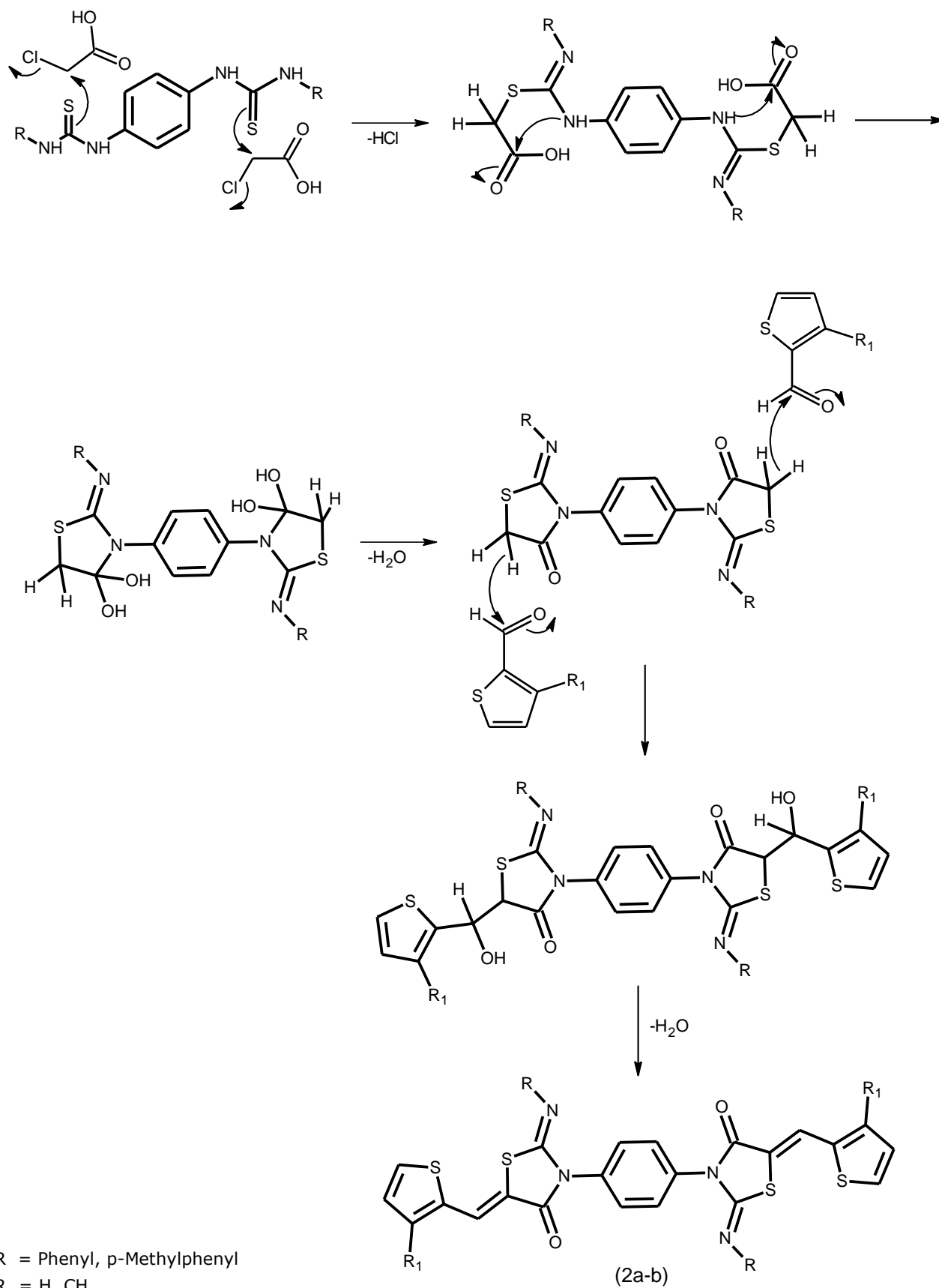


Figure 4. Proposed mechanism for the synthesis of 5-substituted bis-iminothiazolidinones.

Mass spectra of the products were obtained in order to give certainty to the determined structure. When the mass spectra of compounds

(2a-h) were examined, the observed molecular ion peaks confirmed the molecular weights of the products (Table 1).

Table 1. Physical, chemical, and spectral properties of all synthesized compounds.

Compound	Crystal structure	M.p (°C)	FTIR (ATR) ($\gamma_{\max}/\text{cm}^{-1}$)	^1H NMR (500MHz, <i>d</i> -DMSO) (δ ppm)	MS (m/z)
1,1'-(1,4-Phenylene)bis(3-phenylthiourea) (1a) (20)	White bar	205-6	3221 (N-H), 2922 (C-H), 1506 (N-H), 1072 (C-S), 746 (N-H)	7.13 (1H, t), 7.34 (2H, t), 7.44 (2H, s), 7.49 (2H, d), 9.80 (2H, s)	
1,1'-(1,4-Phenylene)bis(3-p-tolylthiourea) (1b) (21)	White powder	230-2	3295 (N-H), 2939 (C-H), 1509 (N-H), 1141 (C-S), 810 (N-H)	2.26 (6H, s), 6.52 (2H, d), 6.99 (2H, d), 7.10 (2H, d), 7.30 (2H, d), 9.31 (2H, s)	
1,1'-[4,4'-Methylenebis(1,4-phenylene)]bis(3-phenylthiourea) (1c) (22)	White bar	320-2	3190 (N-H), 2939 (C-H), 1509 (N-H), 1233 (C-S), 877 (N-H)	3.89 (2H, s), 7.12 (1H, t), 7.21 (2H, d), 7.32 (2H, t), 7.38 (2H, d), 7.47 (2H, d), 9.31 (2H, s)	
1,1'-[4,4'-Methylenebis(1,4-phenylene)]bis(3-p-tolylthiourea) (1d)	White powder	230-1	3195 (N-H), 2920 (C-H), 1586 (N-H), 1141 (C-S), 820 (N-H)	2.51(6H, s), 3.89 (2H, s), 7.21 (4H, t), 7.47 (4H, d), 9.31 (2H, s)	
3,3'-(1,4-Phenylene)bis[2-(phenylimino)-5-(thiophen-2-ylmethylene)thiazolidin-4-one] (2a)	Light yellow powder	161-2	3015 (=C-H), 1706 (C=O), 1626 (C=N), 1590 (C=C), 1352 (C-N), 827 (C-S)	6.57 (2H, d, <i>J</i> =7.0 Hz, Ar-H), 6.70 (2H, d, <i>J</i> =7.4 Hz, Ar-H), 7.10 (2H, d, <i>J</i> =7.0 Hz, Ar-H), 7.18 (1H, t, <i>J</i> =7.4 Hz, Ar-H), 7.28 (1H, t, <i>J</i> =4.9 Hz, Ar-H), 7.40 (2H, t, <i>J</i> =8.1 Hz, Ar-H), 7.65 (1H, d, <i>J</i> =3.7 Hz, Ar-H), 7.90 (1H, d, <i>J</i> =5.1 Hz, Ar H), 8.05 (1H, s, vinyl H)	647 (M+1), 646 (M ⁺), 645 (M-1), 563, 479, 443, 361, 329

3,3'-(1,4-Phenylene)bis{5-[(3-methylthiophen-2-yl)methylene]-2-(phenylimino)thiazolidin-4-one} (2b)	Light yellow layer	181-2	3082 (=C-H), 2917 (CH ₃), 1704 (C=O), 1624 (C=N), 1595 (C=C), 1352 (C-N), 823 (C-S)	2.37 (3H, s, CH ₃), 6.81 (2H, d, J=8.1 Hz, Ar-H), 7.20 (2H, d, J=8.1 Hz, Ar-H), 7.29 (1H, t, J=5.0 Hz, Ar-H), 7.38 (2H, d, J=8.4 Hz, Ar-H), 7.41 (2H, d, J=8.3 Hz, Ar-H), 7.64 (1H, d, J=3.5 Hz, Ar-H), 7.92 (1H, d, J=5.1 Hz, Ar-H), 8.05 (1H, s, vinyl H)	675 (M+1), 674 (M ⁺), 673 (M-1), 592, 508, 361, 329.
3,3'-(1,4-Phenylene)bis[5-(thiophen-2-ylmethylene)-2-(p-tolylimino)thiazolidin-4-one] (2c)	Light yellow bar	173-4	3082 (=C-H), 2917 (CH ₃), 1704 (C=O), 1622 (C=N), 1585 (C=C), 1361 (C-N), 827 (C-S)	2.38 (3H, s, CH ₃), 6.60 (2H, d, J=7.0 Hz, Ar-H), 6.95 (2H, bd, J=7.2 Hz, Ar-H), 7.09 (2H, d, J=7.0 Hz, Ar-H), 7.12 (1H, d, J=5.1 Hz, Ar-H), 7.18 (1H, t, J=7.4 Hz, Ar-H), 7.39 (2H, t, J=8.2 Hz, Ar-H), 7.82 (1H, d, J=5.1 Hz, Ar-H), 7.88 (1H, s, vinyl H)	675 (M+1), 674 (M ⁺), 673 (M-1), 576, 480, 361, 329
3,3'-(1,4-Phenylene)bis{5-[(3-methylthiophen-2-yl)methylene]-2-(p-tolylimino)thiazolidin-4-one} (2d)	Light yellow bar	186-7	3140 (=C-H), 2926 (C-H), 1722 (C=O), 1601 (C=N), 1502 (C=C), 1359 (C-N), 823 (C-S)	2.40 (3H, s, CH ₃), 2.49 (3H, s, CH ₃), 6.90 (2H, d, J=8.2 Hz, Ar-H), 7.13 (1H, d, J=4.9 Hz, Ar-H), 7.20 (2H, d, J=8.2 Hz, Ar-H), 7.35 (2H, d, J=8.6 Hz, Ar-H), 7.42 (2H, d, J=8.6 Hz, Ar-H), 7.86 (1H, d, J=4.9 Hz, Ar-H), 7.93 (1H, s, vinyl H)	704 (M+1), 703 (M ⁺), 702 (M-1), 605, 508, 402, 361, 329
3,3'-[4,4'-Methylene bis(4,1-phenylene)]bis[2-(phenylimino)-5-(thiophen-2-ylmethylene)thiazolidin-4-one] (2e)	Light yellow powder	205-6	3140 (=C-H), 2926 (C-H), 1682 (C=O), 1636 (C=N), 1591 (C=C), 1270 (C-N), 717 (C-S)	4.03 (2H, s, CH ₂), 6.94 (2H, d, J=8.2 Hz, Ar-H), 6.99-7.17 (3H, m, Ar-H), 7.21 (2H, t, J=8.2 Hz, Ar-H), 7.29 (2H, m, Ar-H), 7.37-7.58 (3H, m, Ar-H), 8.00 (1H, s, vinyl H)	738 (M+1), 737 (M ⁺), 736 (M-1), 643, 569, 375, 314, 242

3,3'-[4,4'-Methylenebis(4,1-phenylene)]bis{5-[(3-methylthiophen-2-yl)methylene]-2-(phenylimino)thiazolidin-4-one} (2f)	Yellow powder	198-9	3060 (=C-H), 2924 (C-H), 1687 (C=O), 1670 (C=N), 1592 (C=C), 1362 (C-N), 840 (C-S)	2.43 (3H, s, CH ₃), 3.97 (2H, s, CH ₂), 6.92 (2H, d, J=8.2 Hz, Ar-H), 6.99 (1H, d, J=5.0 Hz, Ar-H), 7.13 (2H, d, J=8.2 Hz, Ar-H), 7.46 (2H, dd, J=8.6;1,7 Hz, Ar-H), 7.50 (1H, d, J=5.0 Hz, Ar-H), 7.54(3H, t, J=7.9;7.4 Hz, Ar-H), 8.06 (1H, s, vinyl H)	766 (M+1), 765 (M ⁺), 764 (M-1), 569, 389, 314, 242
3,3'-[4,4'-Methylenebis(4,1-phenylene)]bis[5-(thiophen-2-ylmethylene)-2-(p-tolylimino)thiazolidin-4-one] (2g)	Light yellow powder	214-5	3024 (=C-H), 2910 (C-H), 1712 (C=O), 1630 (C=N), 1596 (C=C), 1352 (C-N), 819 (C-S)	2.41 (3H, s, CH ₃), 4.04 (1H, s, CH ₂), 6.88 (2H, brd, J=8.2 Hz, Ar-H), 6.93 (1H, dd, J=4.9;4.7 Hz, Ar-H), 7.14 (1H, d, J=4.9 Hz, Ar-H), 7.18 (2H, brd, J=8.4, Ar-H), 7.21 (2H, brd, J=8.2, Ar-H), 7.40 (2H, brd, J=8.4, Ar-H), 7.53 (1H, d, J=4.5, Ar-H), 8.00 (1H, s, vinyl H)	766 (M+1), 765 (M ⁺), 764 (M-1), 569, 389, 314, 242
3,3'-[4,4'-Methylenebis(4,1-phenylene)]bis{5-[(3-methylthiophen-2-yl)methylene]-2-(p-tolylimino)thiazolidin-4-one} (2h)	Yellow powder	207-8	3027 (=C-H), 2918 (C-H), 1712 (C=O), 1630 (C=N), 1596 (C=C), 1352 (C-N), 819 (C-S)	2.35 (3H, s, CH ₃), 2.41 (3H, s, CH ₃), 4.03 (1H, s, CH ₂), 6.88 (2H, brd, J=8.2 Hz, Ar-H), 6.94 (1H, dd, J=8.5 Hz, Ar-H), 7.13 (1H, d, J=5.0 Hz, Ar-H), 7.19 (2H, brd, J=8.2, Ar-H), 7.39 (2H, brd, J=8.4, Ar-H), 7.46 (1H, d, J=4.5, Ar-H), 8.01 (1H, s, vinyl H)	794 (M+1), 793 (M ⁺), 792 (M-1), 597, 389, 314, 242

CONCLUSION

In conclusion, this study reports an appropriate and reliable synthesis of 5-substituted bis-iminothiazolidinones (**2a-h**) starting from previously prepared bis-thioureas (**1a-d**), chloroacetic acid and substituted thiophene-2-carbaldehyde via one-pot green synthesis.

ACKNOWLEDGEMENTS

Thanks are due to Yıldız Technical University Scientific Research Projects Coordination's support in this study. Project Number: 2013-01-02-GEP03.

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