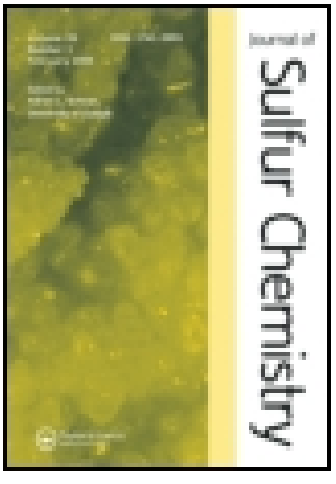

Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

3,4-Dimethyl-2,5-functionalized thieno[2,3-b]thiophenes: versatile precursors for novel bis-thiazoles

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Published online: 10 Nov 2014.

To cite this article: Osama M. Sayed, Ahmed E.M. Mekky, Ahmad M. Farag & Ahmad H.M. Elwahy (2014): 3,4-Dimethyl-2,5-functionalized thieno[2,3-b]thiophenes: versatile precursors for novel bis-thiazoles, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2014.975131

To link to this article: http://dx.doi.org/10.1080/17415993.2014.975131

Journal of Sulfur Chemistry, 2014
http://dx.doi.org/10.1080/17415993.2014.975131

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3,4-Dimethyl-2,5-functionalized thieno[2,3-*b*]thiophenes: versatile precursors for novel bis-thiazoles

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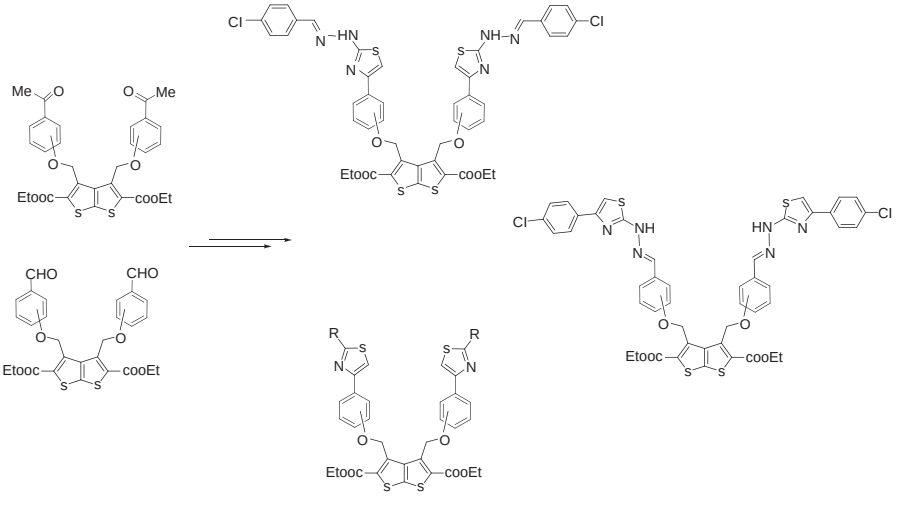
(*Received 2 September 2014; accepted 6 October 2014*)

Synthesis of novel bis(thiazoles) **19–22**, **24**, **25**, **30** and **31** is reported. Thus, reaction of the bis(α-bromoketones) **14** and **15** with the corresponding thioamide derivatives **16–18** in refluxing EtOH in the presence of triethylamine afforded **19–22** in good yields. On the other hand, the novel bis(thiazoles) **24** and **25** can be synthesized by the reaction of **14** and **15** with the corresponding *p*-chlorobenzaldehyde thiosemicarbazones **23** in refluxing EtOH. The novel isomeric bis(thiazoles) **30** and **31** can also be synthesized by a reaction of the corresponding bis(benzaldehyde thiosemicarbazones) **27** and **28** with *p*-chlorophenacyl bromide **29**. Compounds **27** and **28** were obtained by condensation of the corresponding bis(aldehydes) **12** and **13** with thiosemicarbazide **26**.



Keywords: bis(α-bromoketones); alkylation; cyclization; condensation; bis(thiazole); thieno[2,3-*b*]thiophene

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1. Introduction

Considerable attention has been focused on thienothiophenes due to their interesting biological activities. They have been tested as potential antitumor, antiviral, antibiotic and antiglaucoma drugs or as inhibitors of platelet aggregation.[1–5] In addition, thienothiophenes are of potential interest as π-electron donors and have potential applications in a wide variety of optical and electronic systems.[6–12]

Moreover, thiazole derivatives have attracted increasing attention due to their numerous pharmacological applications and biological activities, such as anti-inflammatory, analgesic, antimicrobial, anti-HIV , antihypertensive and herbicidal activity.[13–21]

Furthermore, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds in recent years, due to a wide array of diverse activities, especially, as antitumor and as antimicrobial agents.[22–40]

2. Results and discussion

Recently, a technologically convenient one-pot synthesis of 2,5-functionalized thieno[2,3-*b*]thiophenes **1** and **2** (Figure 1), starting from 1,3-diketones, has been reported. In this procedure, carbon disulfide and alkylating agents containing electron-withdrawing groups are used. The reaction proceeds in dry Dimethylformamide (DMF) in the presence of anhydrous potassium fluoride as a promoter for condensation.[41]

The latter compounds can be used as starting materials for the synthesis of interesting bis(heterocyces). In this respect, Mabkhot et al. reported the synthesis of 4,4'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)dithiazol-2-amine **4** from **1** firstly by bromination upon treatment with Br_2 in AcOH to give 1,1'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-bromoethanone) **3** followed by reaction with thiourea in refluxing EtOH in the presence of triethylamine (TEA) to give the corresponding bis-thiazole derivative **4** (Scheme 1).[42]

In continuation of these studies, we report herein on the synthesis of some novel (thieno[2,3-*b*]thiophen-3,4-diyl)bis(thiazoles) **19–22**, **24**, **25**, **30** and **31** in which the thiazoles are linked to the thieno[2,3-*b*]thiophene core via phenoxymethyl groups.

For this purpose, ethyl 3,4-bis(bromomethyl)-5-(propionyloxy)thieno[2,3-*b*]thiophene-2-carboxylate **5** was chosen as a key intermediate and could be readily obtained from the

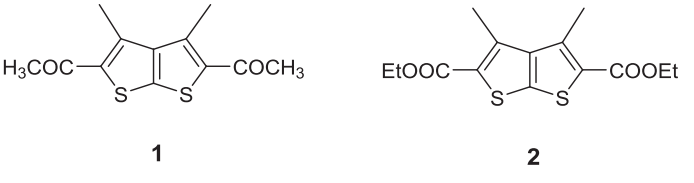
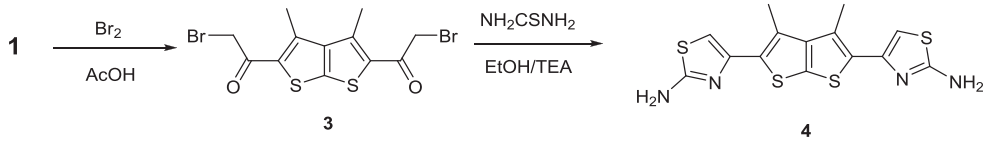
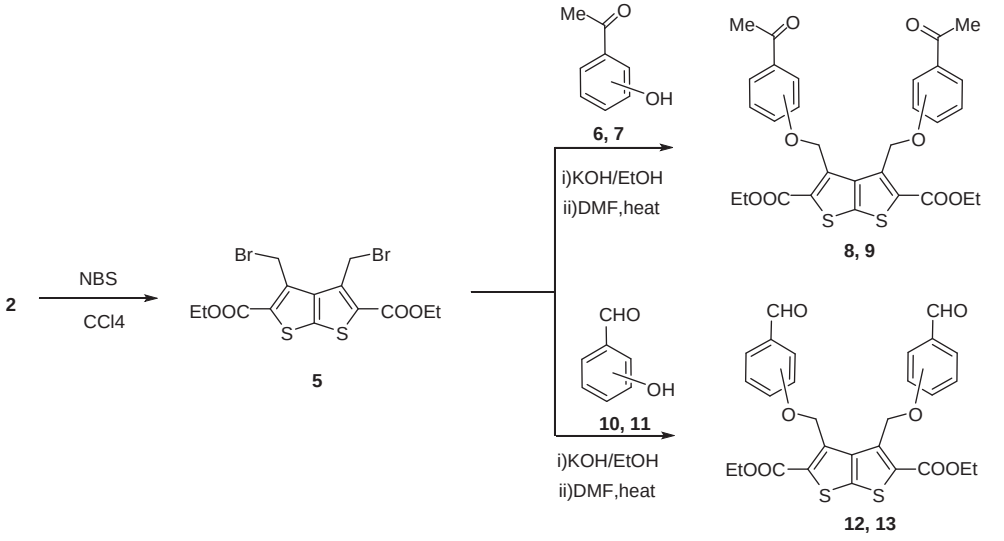


Figure 1. Structures of 2,5-functionalized thieno[2,3-*b*]thiophenes 1 and 2.



Scheme 1. Synthesis of 4,4′-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)dithiazol-2-amine 4 from 1.



Scheme 2. Synthesis of bis(acetophenones) 8 and 9 as well as bis(aldehydes)12 and 13.

corresponding diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate **2** by radical bromination using N-Bromosuccinimide (NBS)/dibenzoyl peroxide (Scheme 2).[43,44]

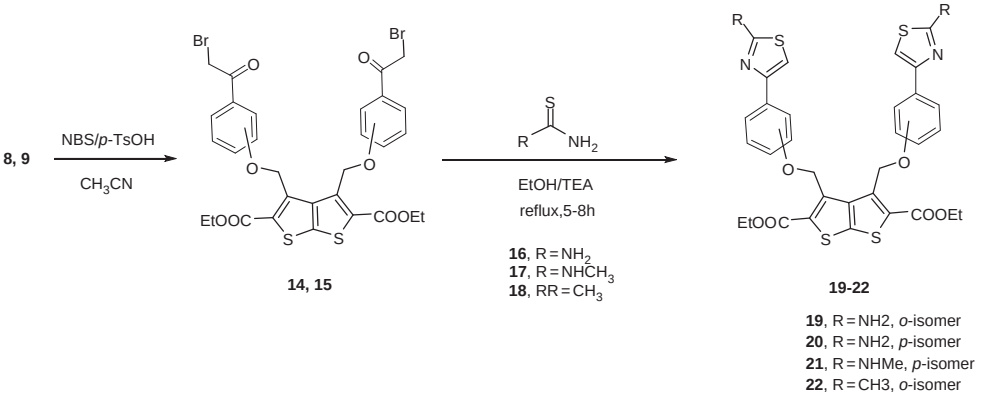
The synthetic utility of **5** as building blocks for novel bis(acetophenones) **8** and **9** as well as novel bis(aldehydes) **12** and **13** was investigated. Thus, the reaction of **5** with the potassium salt (obtained upon treatment of 2-hydroxyacetophenone **6** and 4-hydroxyacetophenone **7**, respectively, with ethanolic KOH), in boiling DMF afforded **8** and **9** in 83% and 78% yields, respectively. Similarly, the bis(aldehydes) **12** and **13** were prepared in 70% and 75% yields, respectively, by the reaction of **5** with the potassium salt (obtained upon treatment of salicylaldehyde **(10)** and 4-hydroxybenzaldehyde **(11)** with ethanolic KOH) (Scheme 2).

α-Bromination of the side chain of **8** and **9** with NBS in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in acetonitrile afforded the corresponding bis(α-bromoketones) **14** and **15** as single monobrominated ketones in most instances in high yield (Scheme 3). Reaction of the bis(α-bromoketones) **14** and **15** with the thioamide derivatives **16–18** in refluxing EtOH/TEA afforded the corresponding novel bis(thiazoles) **19–22** (Scheme 3). The reaction was completed within 5–8 h and the products were obtained in good yields.

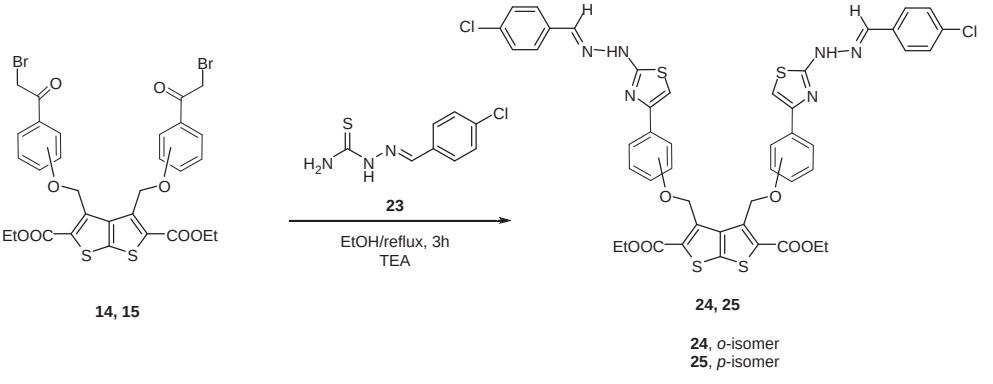
Our study was extended to include the synthesis of the new bis(thiazolylhydrazones) **24** and **25** as outlined in Scheme 4. Thus reaction of the corresponding bis(α-bromoketones) **14** and **15** with *p*-chlorobenzaldehyde thiosemicarbazone **23** [45,46] in refluxing EtOH in the presence of few drops of TEA as a catalyst afforded **24** and **25** in 82% and 83% yields, respectively.

The novel isomeric bis(thiazolylhydrazones) **30** and **31** were also successfully prepared, from **12** and **13** firstly by reaction with thiosemicarbazide **26** in refluxing EtOH containing few drops of AcOH to give the corresponding bis(benzaldehyde thiosemicarbazones) **27** and **28**. Subsequent reaction of the latter compounds with *p*-chlorophenacyl bromide **29** in refluxing ethanol in the presence of few drops of TEA afforded **30** and **31** in 81% and 78% yields, respectively (Scheme 5).

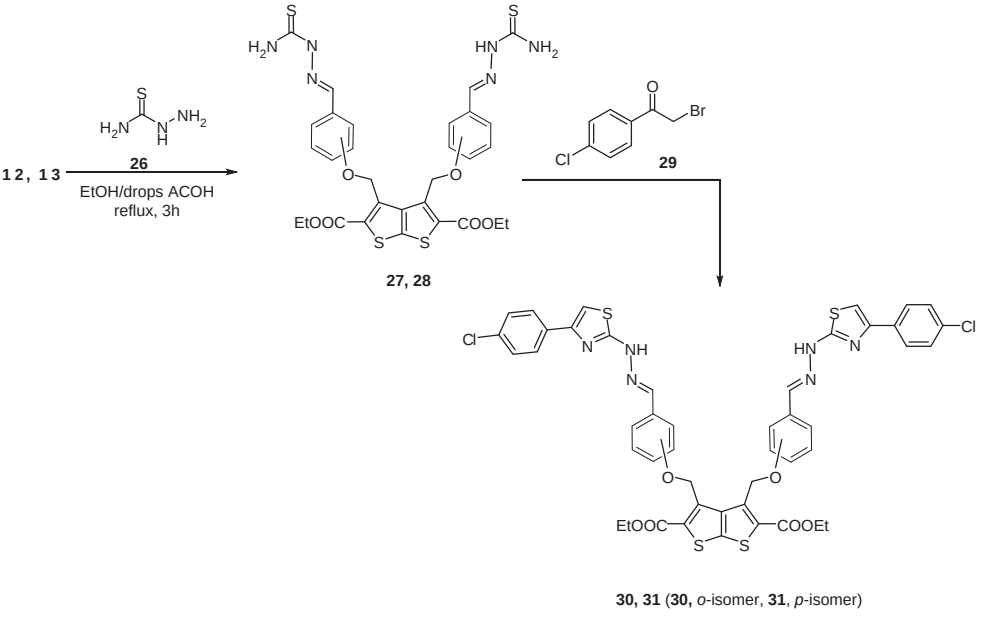
All of the isolated compounds were characterized by elemental analyses, as well as spectral data that agree with the proposed structures. The structures of bis(aminothiazoles) 19 and 20 were confirmed by IR, ^{1}H-NMR and mass spectral data. Thus, the IR spectrum of **19** as a representative example showed absorption bands at 3165 and 3058 cm^{-1} due to NH_2. Moreover, the absence of the absorption band corresponding to carbonyl stretching frequency of the parent



Scheme 3. Synthesis of bis(thiazoles) 19-22.



Scheme 4. Synthesis of bis(thiazolylhydrazones)24 and 25.



Scheme 5. Synthesis of bis(thiazolylhydrazones)30 and 31.

phenacyl bromide clearly confirmed the formation of bis(aminothiazole) **19**. The ^{1}H NMR spectrum of compound **19** showed a D_2O-exchangeable signal at δ 6.93–7.69 due to NH_2 protons and a sharp singlet at δ 6.65 attributed to the C-5 proton of the thiazole ring. All other protons were seen at the expected chemical shifts and integral values. The mass spectrum of compound **19** showed an intense molecular ion peak at *m/z* 693, in agreement with its molecular formulae.

On the other hand, the IR spectrum of bis(thiazolylhydrazone) **24** revealed an absorption band at 3167 cm^{-1} due to (NH). Its ^{1}H NMR spectrum showed the presence of a characteristic singlet at δ 7.98 due to one methine proton (−N=CH−). The mass spectrum of compound **24** showed a molecular ion peak at *m/z* 966 (M^+, 21.04%) in agreement with its respective molecular formula. The spectra of other bis(thiazoles) **25**, **30** and **31** exhibited similar spectral data which are listed in the experimental section.

3. Conclusions

We have developed an efficient synthesis of previously unreported bis(thiazoles) which are linked to the 3- and 4-positions of thieno[2,3-*b*]thiophene core via phenoxymethyl groups. Full characterization of these compounds is reported. The newly synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities. Due to the mild reaction condition, good yields, easily accessible starting material and straightforward product isolation, we think that this new synthetic approach discussed here should provide access for novel new bis(functionalized) heterocycles with potentially potent biological and pharmaceutical activities.

4. Experimental

4.1. *General*

Melting points were determined in open glass capillaries with a Gallenkamp apparatus and were not corrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined on a Varian Mercury VX 300 NMR spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV.

4.2. *Synthesis of the potassium salt of 6,7,10 and 11*

To a solution of KOH (0.57 g, 10 mmol) in methanol (10 mL) was added the appropriate hydroxyketones **6** and **7** or the appropriate hydroxyaldehydes **10** and **11** (10 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed *in vacuo*. The remaining solid was triturated with dry ether, collected, dried and used in the next step without further purification.

4.3. *Synthesis of 1,ω-bis(acetophenone) (8 and 9) and 1,ω-bis(aldehyed) (12 and 13)*

A solution of the appropriate potassium salt of **6, 7, 10** or **11** (20 mmol) and the dibromo compound **5** (10 mmol) in DMF (20 mL) was heated under reflux for 10 min, during which time, KBr precipitated. The solvent was then removed *in vacuo*, and the remaining material was washed with water (50 mL) and purified by crystallization from proper solvent.

4.3.1. *Diethyl 3,4-bis((2-acetylphenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**8**)*

Yield (78%, EtOH), mp. 150–152°C; IR (cm^{-1}): 1714, 1670 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.22 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 2.24 (s, 6H, CH_3CO), 4.29 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 5.65 (s, 4H), 6.93–7.55 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6): δ 14.32, 31.67, 61.55, 62.17, 113.45, 121.27, 128.29, 130.13, 134.13, 135.67, 135.81, 145.61, 145.97, 157.36, 161.62, 198.80; MS: *m/z* 581 (M^+, 28.51%); $C_{30}H_{28}O_8S_2$: Anal. Calcd C, 62.05; H, 4.86; S, 11.04. Found C, 62.08%; H, 4.81%; S, 11.01%.

4.3.2. *Diethyl 3,4-bis((4-acetylphenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**9**)*

Yield (83%, acetone), mp. 158–162°C; IR (cm^{-1}): 1712, 1672 (2 CO); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 2.5 (s, 6H, CH_3CO), 4.40 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 5.77 (s, 4H, OCH_2), 6.81 (d, 4H, ArH, $J = 8.7$ Hz), 7.76 (d, 4H, ArH, $J = 8.7$ Hz); ^{13}C NMR (DMSO-d_6): δ 14.35, 31.32, 61.32, 62.24, 114.47, 130.46, 130.86, 135.37, 136.14, 145.81, 146.17, 161.68, 161.84, 196.61; MS: *m/z* 581 (M^+, 1.46%); $C_{30}H_{28}O_8S_2$: Anal. Calcd C, 62.05; H, 4.86; S, 11.04. Found C, 62.08%; H, 4.81%; S, 11.01%.

4.3.3. *Diethyl 3,4-bis((2-formylphenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**12**)*

Yield (73%, Dioxane), mp. 224–226°C [Lit.[44], 224–226°C].

4.3.4. *Diethyl 3,4-bis((4-formylphenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**13**)*

Yield (65%, acetone), mp. 170–172°C; IR (cm^{-1}): 2848, 2728(CHO),1670 (CO);^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, CH_2CH_3, $J = 6.6$ Hz), 4.33 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 5.67 (s, 4H), 6.99 (d, 4H, ArH, $J = 8.4$ Hz), 7.62 (d, 4H, ArH, $J = 8.4$ Hz), 9.77 (s, 2H,CHO); ^{13}C NMR (DMSO-d_6): δ 14.40, 61.89, 62.12, 113.41, 124.61, 128.54, 135.71, 136.69, 143.41, 146.07, 160.38, 161.66, 189.66; MS: *m/z* 552 (M^+, 2.36%); $C_{28}H_{24}O_8S_2$: Anal. Calcd C, 60.86; H, 4.38; S, 11.60. Found C, 60.82%; H, 4.35%; S, 11.55%.

4.4. *Synthesis of bis(α-bromoacetophenones) 14 and 15*

4.4.1. *General procedure*

To a stirred solution of bis(acetophenone) derivatives **8** or **9** (l0 mmol) and *p*-TsOH (5.6 g, 20 mmol) in acetonitrile (50 mL), NBS (3.6 g, 20 mmol) was slowly added. After addition of NBS was complete, the reaction mixture was refluxed with stirring for 5 h. The solvent was then evaporated *in vacuo* and the residue was dissolved in chloroform (50 mL), washed with water (2×20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was recrystallized from acetonitrile to afford the corresponding bis(α-bromoketone) derivative **15** as white crystals. Compound **14** was used in the next step without further purification.

*4.4.1.1. Diethyl 3,4-bis((4-(2-bromoacetyl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**15**)* Yield (67%), mp. 148–150°C; IR (cm^{-1}): 1702, 1658 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 4.32 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 4.75 (s, 4H, CH_2Br), 5.68 (s, 4H, OCH_2), 6.85 (d, 4H, ArH, $J = 8.7$ Hz), 7.82 (d, 4H, ArH, $J = 8.7$ Hz); ^{13}C NMR (DMSO-d_6): δ 14.40, 61.37, 62.19, 65.36, 113.37, 125.49, 128.58, 130.10, 136.06, 145.80, 146.70, 161.67, 166.22, 195.34; MS: *m/z* 736 (M^+, 36.94%), 738 ($M+2$, 18.89%); $C_{30}H_{26}Br_2O_8S_2$: Anal. Calcd C, 48.79; H, 3.55; S, 8.68. Found C, 48.82%; H, 3.49%; S, 8.62%.

4.5. *Synthesis of bis(aminothiazole) derivatives (19–22)*

4.5.1. *General procedure*

A solution of the appropriate bis(α-bromoacetophenones) compound **14** or **15** (10 mmol) and the appropriate thioamide compound **16–18** (20 mmol) in ethanol, in the presence of TEA as a catalyst, was heated under reflux for 5–8 h. The reaction mixture was then cooled and the solvent was evaporated *in vacuo* and the solid residue was collected and recrystallized from ethanol to give the corresponding bis(aminothiazole) products **19–22** as white crystals.

*4.5.1.1. Diethyl 3,4-bis((2-(2-aminothiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**19**)* Yield (64%), mp. 188–190°C); IR (cm^{-1}): 3165, 3058, (NH_2), 1701 (CO), 1571 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 4.32 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 5.70 (s, 4H, OCH_2), 6.65 (s, 2H, thiazole-5-CH), 6.93–7.69 (m, 12H, ArH, NH_2); MS: *m/z* 693 (M^+, 78.23%); $C_{32}H_{28}N_4O_6S_4$: Anal. Calcd C, 55.47; H, 4.07; N, 8.09; S, 18.51. Found C, 55.47%; H, 4.07%; N, 8.09%; S, 18.51%.

*4.5.1.2. Diethyl 3,4-bis((4-(2-aminothiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**20**)* Yield (67%), mp. 230–235°C; IR (cm^{-1}): 3192, 3076 (NH_2), 1714 (CO), 1567 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 4.32 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 5.66 (s, 4H, OCH_3), 6.93 (s, 2H, thiazole-5-CH), 6.96–7.52 (m, 12H, ArH, NH_2); ^{13}C NMR (DMSO-d_6): δ 14.50, 61.25, 62.22, 115.24, 127.56, 127.70, 129.60, 135.15, 136.96, 145.82, 146.23, 157.87, 158.89, 161.73, 170.34; MS: *m/z* 693 (M^+, 10%); $C_{32}H_{28}N_4O_6S_4$: Anal. Calcd C, 55.47; H, 4.07; N, 8.09; S, 18.51.Found C, 55.4%2; H, 4.09%; N, 8.11%; S, 18.41%.

*4.5.1.3. Diethyl 3,4-bis((4-(2-(methylamino)thiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**21**)* Yield (62%), mp. 150–153°C; IR (cm^{-1}): 3118 (NH), 1708 (CO), 1587 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 2.99 (s, 6H, $NHCH_3$), 4.32 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 5.7 (s, 4H, OCH_2), 6.89 (s, 2H, thiazole-5-CH), 6.91–7.45 (m, 10H, ArH, NH); MS: *m/z* 721 (M^+, 79.31%); $C_{34}H_{32}N_4O_6S_4$: Anal. Calcd C, 56.65; H, 4.47; N, 7.77; S, 17.79.Found C, 56.60%; H, 4.50%; N, 7.70%; S, 17.82%.

*4.5.1.4. Diethyl 3,4-bis((2-(2-methylthiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**22**)* Yield (67%), mp. 148–150°C; IR (cm^{-1}): 1712 (CO), 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.18 (t, 6H, CH_2CH_3, $J = 6.3$ Hz), 2.60 (s, 6H, CH_3), 4.24 (q, 4H, CH_2CH_3, $J = 6.3$ Hz), 5.58 (s, 4H, OCH_2), 6.82–7.99 (m, 10H, ArH, thiazole-5-CH); MS: *m/z* 691 (M^+, 5.21%); $C_{34}H_{30}N_2O_6S_4$: Anal. Calcd C, 59.11; H, 4.38; N, 4.05; S, 18.56. Found C, 59.15%; H, 4.40%; N, 4.06%; S, 18.52%.

4.6. *Synthesis of bis(hydrazinylthiazol) derivatives 24 and 25*

4.6.1. *General procedure*

To a solution of the appropriate bis(α-bromoacetophenones) compound **14** or **15** (10 mmol) in ethanol (20 mL) containing few drops of TEA, *p*-chlorobenzaldehyde thiosemicarbazone **23** (20 mmol) was added. The reaction mixture was heated under reflux for 3 h. The solid obtained upon cooling was filtered, collected and recrystallized from *n*-butanol to give the corresponding bis(hydrazinylthiazol) products **24** and **25** as yellow crystals.

*4.6.1.1. Diethyl-3,4-bis((2-(2-((E)-2-(4-chlorobenzylidene)hydrazinyl)thiazol-4-yl)phenoxy) methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**24**)* Yield (83%), mp. 207–210°C; IR (cm^{-1}): 3167 (NH), 1706 (CO), 1567 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.16 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 4.20 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 4.85 (s, 2H, NH), 5.60 (s, 4H, OCH_2), 6.80–7.92 (m, 18H, ArH, thiazole-5-CH), 7.98 (s, 2H, CH=N); MS: *m/z* 966 (M^+, 21.04%), 968 (M + 2, 25.00%); $C_{46}H_{36}Cl_2N_6O_6S_4$: Anal. Calcd C, 57.08; H, 3.75; N, 8.68; S, 13.25. Found C, 57.10%; H, 3.72%; N, 8.65%; S, 13.22%.

*4.6.1.2. Diethyl-3,4-bis((4-(2-((E)-2-(4-chlorobenzylidene)hydrazinyl)thiazol-4-yl)phenoxy) methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**25**)* Yield (82%), mp. 220–224°C; IR (cm^{-1}): 3116 (NH), 1712 (CO), 1565 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 4.33 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 4.98 (s, 2H, NH), 5.64 (s, 4H, OCH_2), 6.86–770 (m, 18H, ArH, thiazole-5-CH), 8.06 (s, 2H, CH=N); MS: *m/z* 966 (M^+, 8.06%), 968 (M + 2, 10.17%); $C_{46}H_{36}Cl_2N_6O_6S_4$: Anal. Calcd C, 57.08; H, 3.75; N, 8.68; S, 13.25. Found C, 57.10%; H, 3.72%; N, 8.65%; S, 13.22%.

4.7. *Synthesis of the bis(thiocarbazone) derivatives 27 and 28*

4.7.1. *General procedures*

A solution of the appropriate bis(aldehydes) **13** or **14** (10 mmol) and thiosemicarbazide **26** (20 mmol) in absolute ethanol (25 mL), in the presence of few drops of acetic acid as a catalyst, was heated under reflux for 3 h. The reaction mixture was then cooled and the solid formed was collected and recrystallized from the appropriate solvent to give the corresponding bis(thiocarbazones) **27** and **28** as white crystals.

*4.7.1.1. Diethyl-3,4-bis((2-((E)-(2-carbamothioylhydrazono)methyl)phenoxy)methyl) thieno [2,3-b]thiophene-2,5-dicarboxylate (**27**)* Yield (70%, AcOH), mp. 240–242°C; IR (cm^{-1}): 3420, 3356, 3270 (NH_2, NH), 1706 (CO), 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.25 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 4.32 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 5.59 (s, 4H, OCH_2), 6.79–8.00 (m, 12H, ArH, NH_2), 8.27 (s, 2H, CH=N), 11.28 (s, 2H, NH); MS: *m/z* 699 (M^+, 9.66%); $C_{30}H_{30}N_6O_6S_4$: Anal. Calcd C, 51.56; H, 4.33; N, 12.03; S, 18.35. Found C, 51.56%; H, 4.31%; N, 12.05%; S, 18.32%.

*4.7.1.2. Diethyl-3,4-bis((4-((E)-(2-carbamothioylhydrazono)methyl)phenoxy)methyl) thieno [2,3-b]thiophene-2,5-dicarboxylate (**28**)* Yield (75%, AcOH), mp. 206–208°C; IR (cm^{-1}): 3410, 3397, 3318 (NH_2, NH), 1708 (CO), 1602 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 4.33 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 5.68 (s, 4H, OCH_2), 6.91–7.88 (m, 12H, ArH, NH_2), 7.95 (s, 2H, CH=N), 11.27 (s, 2H, NH); MS: *m/z* 699 (M^+, 2.42%);

$C_{30}H_{30}N_6O_6S_4$: Anal. Calcd C, 51.56; H, 4.33; N, 12.03; S, 18.35. Found C, 51.56%; H, 4.31%; N, 12.05%; S, 18.32%.

4.8. *Synthesis of bis(thiazolylhydrazones) 30 and 31*

4.8.1. *General procedures*

A solution of the appropriate bis(benzaldehydthiosemicarbazide) compounds **27** or **28** (10 mmol) and *p*-chlorophenacyl bromide **29** (20 mmol) in absolute ethanol (20 mL) containing few drops of TEA was heated under reflux for 5 h. The reaction mixture was then cooled and the solid formed was collected and recrystallized from the appropriate solvent to give the corresponding bis(thiazolylhydrazones) **30** and **31** as white crystals**.**

*4.8.1.1. Diethyl-3,4-bis((2-((E)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl) phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**30**)* Yield (78%, EtOH/DMF), mp. 186–188°C; IR (cm^{-1}): 3120 (NH), 1704 (CO), 1559 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.24 (t, 6H, CH_2CH_3, $J = 7.2$ Hz), 4.31 (q, 4H, CH_2CH_3, $J = 7.2$ Hz), 5.64 (s, 4H, OCH_2), 6.88–7.81 (m, 18H, ArH, thiazole-5-CH), 8.20 (s, 2H, CH=N), 11.92 (s, 2H, NH); MS: *m/z* 966 (M^+, 1.94%), 968 (M + 2, 15.20%); $C_{46}H_{36}Cl_2N_6O_6S_4$: Anal. Calcd C, 57.08; H, 3.75; N, 8.68; S, 13.25. Found C, 57.10; H, 3.77; N, 8.65; S, 13.22%.

*4.8.1.2. Diethyl-3,4-bis((4-((E)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl) phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**31**)* (81%, AcOH), mp. 208–210°C; IR (cm^{-1}): 3429 (NH), 1705 (CO);^{1}H NMR (DMSO-d_6): δ 1.29 (t, 6H, CH_2CH_3, $J = 6.9$ Hz), 4.34 (q, 4H, CH_2CH_3, $J = 6.9$ Hz), 5.62 (s, 4H, OCH_2), 6.72–7.77 (m, 18H, ArH, thiazole-5-CH), 7.91 (s, 2H, CH=N), 11.92 (s, 2H, NH); MS: *m/z* 966 (M^+, 1.94%), 968 (M + 2, 15.20%); $C_{46}H_{36}Cl_2N_6O_6S_4$: Anal. Calcd C, 57.08; H, 3.75; N, 8.68; S, 13.25. Found C, 57.10%; H, 3.77%; N, 8.65%; S, 13.22%.

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