

Utilization of 2-Ylidene-4-Thiazolidinones in the Synthesis of Heterocyclic Compounds Part (IV): Synthesis of Thiophene Derivatives

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Dedicated to the memory of the Late Prof. Dr. Mansour A. Makhlouf

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ABSTRACT: 3-Amino-2-thiophenecarboxamides (**3a-e**) were synthesized from 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile(**1**) and employed in the synthesis of a variety of thiophene derivatives. These 3-Amino-2-thiophenecarboxamides (**3a-c**) which when treated with aromatic aldehydes under relatively mild conditions produced the 3-arylideneamines (**6a-d**). Treatment of the carboxamide(**3d**) with triethylorthoformate gave the thiophene-3-ylformimidate (**7**). Reacting 3-aminothiophene-2-carboxamides (**3b,c**) with chloroacetyl chloride furnished 5-(2-chloro-N-phenylacetamido)-3-(2-chloroacetamido)-2-carboxamides (**8a,b**). The 3-amino-2-thiophene carboxamides (**3a-e**) on reacting with acetic anhydride yielded the thienooxazinone(**11**). Ethyl 4-cyano-3-[(ethoxymethylene)amino]-5-phenylaminothiophene-2-carboxylate (**12**) when treated with hydrazine, phenylhydrazine and hydroxylamine yielded some interesting unexpected thiophene derivatives (**13**), (**14**) and (**15**).

Key words: 3-arylideneaminothiophene-2-carboxamides, 3,5-(dichloroacetamido)-4-cyano-N-alkylthiophene-2-carboxamide derivatives, ethyl 4-cyano-3-[(ethoxymethylene)amino]-5-phenylaminothiophene-2-carboxylate, 3-amino-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbohydrazide, ethyl 2-substituted-5-(phenylaminothiophene)-3-ylformimidates.

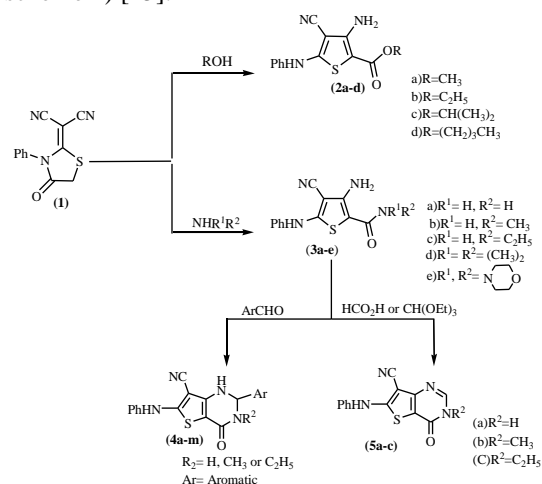
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I. INTRODUCTION:

Derivatives of thiophene have attracted tremendous interest mostly due to their chemical and pharmacological activities. An extensive variety of therapeutic applications of thiophene derivatives has been surveyed in the literature [1-5]. These compounds are reported to be used as anti-inflammatory [6-9], analgesic, and antiprotozoal agents [10,11]. Thiophene derivatives were also found to act as antitumor agents [12-14]. On the other hand, thiophene moiety and their derivatives are known as diabetes mellitus [15], antihypertensive [16], antimicrobial [17,18], cholesterol inhibitors [19] and antiviral [20]. In addition, fused thiophene derivatives were tested as templates for serine protease inhibition [21] and alternate substrate inhibitors of cholesterol esterase [22]. We have reported that the reactions of 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile (**1**) [23] with some alcohols gave the corresponding 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxylates (**2a-d**) [24]. Similarly, this 4-thiazolidinone (**1**) on reacting with a number of

amines produced 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**3a-e**) [24]. In addition, these carboxamides were transformed into a number of tetrahydrothienopyrimidinones (**4a-m**) and dihydrothienopyrimidinones (**5a-c**) as shown in (cf. scheme 1) [25].



Scheme 1

Encouraged by the above research results and in continuation of our studies on synthesis and transformations of 2-ylidene-4-thiazolidinones into other heterocyclic compounds, [23-26] we report herein the utility of both 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**3a-e**) and ethyl 4-cyano-3-[(ethoxymethylene)amino]-5-(phenylamino)thiophene-2-carboxylate (**12**) derived from ethyl 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxylate (**2b**) (cf. scheme 1) in the synthesis of a variety of thiophene derivatives that may possess biological activities.

Experimental:

General Remarks:

Melting points were recorded by Koffler melting points apparatus and are uncorrected. Infrared spectra were recorded on a Bruker FTIR laboratory in the frequency range of 3900-450 cm^{-1} using KB runless otherwise stated. Nuclear Magnetic Resonance spectra were recorded on a Bruker avance 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR using DMSO or CDCl_3 as solvent and tetramethylsilane (TMS) as the internal standard and given in δ scale ppm. The chemical shift (δ) values are expressed in parts per million (ppm). Legend: s = singlet, d = doublet, t = triplet and m = multiplet. The structures and names of all the compounds were generated using Chemdraw ultra 12.0.

Synthesis:

4-Amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**3a-e**) were synthesized according to our reported methods [24,25] by treatment of 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile (1) with ammonia, methyl amine, ethyl amine, dimethylamine or morpholine respectively. Ethyl 4-cyano-3-amino-5-(phenylamino)thiophene-2-carboxylate (**2b**) was synthesized by treatment of 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile (1) with ethanol in the presence of triethylamine (TEA) [24].

3-Arylideneamino-4-cyano-5-phenylaminothiophene-2-carboxamides (**6a-d**):

General procedure:

A solution of 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**3c,d**) (0.0017 mol), aromatic aldehyde (0.0017 mol) and sodium sulfate anhydrous (0.0017 mol) in ethanol (20 mL) containing a few drops of glacial acetic acid were stirred at varying reaction conditions. The reaction mixture was then cooled. The precipitated solid that formed was filtered off and recrystallized from ethanol.

3-(4-Nitrobenzylideneamino)-4-cyano-N-ethyl-5-(phenylamino)thiophene-2-carboxamide (**6a**):

Refluxing for 2 h.; Yield: 55%, red solid, mp. 204.206 °C; ν_{max} (neat) 3281(NH), 3173(NH), 2203(CN), 1617(C=O), 1595(C=N); δ_{H} DMSO 10.28 (br, 1H, PhNH), 9.04 (s, 1H, N=CH), 8.43-7.41 (m, 9H, arom. and br, 1H, NH), 3.38-3.24 (q, 2H, NCH_2), 1.09-1.04 (t, 3H, CH_3); δ_{C} DMSO 164.95(C=O), 161.65(C=N), 114.82 (CN), 160.58, 150.19, 146.39, 140.79, 140.40, 130.79, 130.08, 125.25, 124.75, 121.13, 83.81, 111.53 (C_{arom}), 34.53 (CH_2), 15.29 (CH_3).

3-(4-Methylbenzylideneamino)-4-cyano-N-ethyl-5-(phenylamino)thiophene-2-carboxamide (**6b**):

Refluxing for 2 h.; Yield: 50%, yellow crystalline solid, mp. 196-198 °C; ν_{max} (neat) 3388(NH), 3256(NH), 2206(CN), 1644(C=O), 1595(C=N); δ_{H} DMSO 10.21 (br, 1H, NH), 8.85 (s, 1H, N=CH), 7.917-7.14 (m, 9H, arom. and br, 1H, NH), 3.273-2.21 (q, 2H, CH_2), 2.27 (s, 3H, (CH_3 Ph)), 1.091-1.05 (t, 3H, CH_3); δ_{C} DMSO 166.29(C=O), 161.64(N=CH), 115.00(CN), 160.92, 146.99, 144.20, 140.04, 137.91, 132.45, 130.35, 129.27, 126.74, 125.02, 121.24, 83.33 (C_{arom}), 34.38 (CH_2), 21.76 (CH_3 Ph), 15.25 (CH_3).

3-(4-Nitrobenzylideneamino)-4-cyano-N,N-dimethyl-5-(phenylamino)thiophene-2-carboxamide (**6c**):

Refluxing for 2 h.; Yield: 70%, Orange crystalline solid, mp. 218-220 °C; ν_{max} (neat) 3310(NH), 2203(CN), 1617(C=O), 1578 (C=N); δ_{H} DMSO 10.13 (br, 1H, NH), 8.73 (s, 1H, N=CH), 8.41-7.12 (m, 9H, arom.), 2.85 (s, 6H, 2 CH_3); δ_{C} DMSO 164.18(C=O), 162.36(N=CH), 114.64 (CN), 160.16, 150.06, 146.74, 141.20, 140.67, 130.50, 130.05, 128.75, 124.74, 124.61, 120.31, 106.99, 85.77 (C_{arom}), 37.20 [$\text{N}(\text{CH}_3)_2$].

3-(4-Chlorobenzylideneamino)-4-cyano-N,N-dimethyl-5-(phenylamino)thiophene-2-carboxamide (**6d**): RT for 5 days. Yield: 54%, yellow crystalline solid. Mp 226-228 °C; ν_{max} (neat) 3227(NH), 2206(CN), 1600 (C=O), 1556(C=N); δ_{H} DMSO 9.98 (br, 1H, NH), 8.56 (s, 1H, N=CH), 7.98-7.12 (m, 9H, arom.), 2.86 (s, 6H, 2 CH_3); δ_{C} DMSO 164.56(CO), 162.60(N=CH), 114.61 (CN), 159.99, 147.31, 141.36, 140.67, 134.34, 130.49, 130.05, 128.75, 124.76, 120.31, 106.62, 86.40, (C_{arom}), 37.20 [$\text{N}(\text{CH}_3)_2$]. Ethyl N-4-cyano-2-(dimethylcarbamoyl)-5-(phenylamino)thiophene-3-yl-formimidate (**7**):

A solution of 3-amino-4-cyano-N,N-dimethyl-5-(phenylamino)thiophene-2-carboxamide (**3d**) (0.001 mol) and triethylorthoformate (20 mL) was refluxed for 3 h. The solid product that formed was filtered off, dried and recrystallized from benzene. Yield: 56% white crystals, mp. 160-162 °C; ν_{max} (neat) 3270 (NH), 2206(CN), 1645(C=O), 1594(C=N); δ_{H} DMSO

9.97 (br, 1H, NH), 7.96 (br, 1H, (CH=N)), 7.37-7.10 (m, 5H, arom.), 4.29-4.27 (q, 2H, (OCH₂)), 2.89 (s, 6H, (CH₃)₂), 1.34-1.29 (t, 3H, CH₃); δ_{C} DMSO 162.86 (CO), 159.35 (N=C), 159.20, 143.29, 141.27, 129.97, 124.37, 120.02, 105.43, 87.57 (Carom), 114.43 (CN), 70.09 (OCH₂), 63.27 (NCH₃)₂, 14.35 (CH₃).

5-(2-Chloro-N-phenylacetamido)-3-(2-chloroacetamido)-4-cyano-N-alkyl-thiophene-2-carboxamides (8a,b) General procedure: To a solution of 3-amino-4-cyano-N-alkyl-5-(phenylamino)thiophene-2-carboxamides (3b,c) (0.0020 mol) in dioxane (30 mL) was added chloroacetyl chloride (0.0040 mol) drop wise with stirring. The reaction mixture was then refluxed for 30 minutes and left to stand at RT overnight. The separated solid was collected by filtration, washed with (5%) sodium bicarbonate, dried and recrystallized from dioxane.

5-(2-Chloro-N-phenylacetamido)-3-(2-chloroacetamido)-4-cyano-N-methylthiophene-2-carboxamide (8a): Yield: 70%, white crystalline solid, mp. 202-204; ν_{max} (cm⁻¹) 3330 (NH), 3223 (NH), 2210 (CN), 1665 (br.) two (C=O), 1627 (CH₃-HNCO); δ_{H} DMSO 10.50 (br, 1H, (thienyl-NHCO)), 10.07 (CH₃-NHCO), 7.68-7.16 (m, 5H, arom.), 4.37 (s, 2H, (CH₂Cl)), 3.57 (s, 2H, (OCH₂Cl)), 2.71-2.70 (s, 3H, CH₃); δ_{C} 1 DMSO 65.93 (CO), 161.19 (CO), 159.88 (CO), 141.03, 135.04, 130.07, 124.96, 120.75, 121.10, 110.88, 89.66 (Carom), 113.92 (CN), 66.76 (CH₂Cl), 43.31 (CH₂Cl), 26.72 (CH₃).

5-(2-Chloro-N-phenylacetamido)-3-(2-chloroacetamido)-4-cyano-N-ethyl-thiophene-2-carboxamide (8b):

Yield: 53%, white solid, mp. 198-200 °C; ν_{max} (cm⁻¹) 3328 (NH), 3228 (NH), 2211 (CN), 1670 (br.) two (CO), 1620 (CH₃CH₂-HNCO); δ_{H} DMSO 10.54 (thienyl-NHCO), 10.07 (br, 1H, CONH), 7.74-7.14 (m, 5H, arom.), 4.37 (s, 2H, (OCH₂Cl)), 3.57 (s, 2H, (OCH₂Cl)), 3.21-3.15 (q, 2H, CH₂), 1.08-1.04 (t, 3H, CH₃); δ_{C} DMSO 165.85 (CO), 160.60 (CO), 159.90 (CO), 141.05, 135.21, 130.08, 124.98, 122.10, 120.79, 110.63, 89.57 (C_{arom}), 113.94 (CN), 113.92 (CN), 66.79 (CH₂Cl), 43.21 (CH₂Cl), 34.52 (CH₂), 15.16 (CH₃).

N-(7-cyano-2-methyl-4-oxo-4H-thieno[3,2-d][1,3]oxazin-6-yl)-N-phenyl-acetamide (11):

General procedure:

A solution of 3-amino-4-cyano-N-alkyl-5-(phenylamino)thiophene-2-carboxamide (3b-e) (0.0012 mol) in acetic anhydride (15 mL) was refluxed for 5 h. The reaction mixture was cooled and the precipitated solid was filtered off and recrystallized from benzene. Yields: 60% (b), 54% (c), 51% (d) and 33% (e) respectively; white

crystals. mp. 290-292 °C; (lit.²⁴ mp. 294-296; yield: 59 %).

Ethyl 4-cyano-3-[(ethoxy methylene)amino]-5-(phenylamino)thio-phene-2-carboxylate (12):

A solution of ethyl 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxylate (2b) (0.001 mol) and triethylorthoformate (25 ml) was refluxed for 3 h. The solid product that formed was filtered off, dried and recrystallized from ethanol.

Yield 54%; white crystal, mp. 162-164 °C, ν_{max} (cm⁻¹) 1701 (C=O), 2207 (CN), 3397 (NH); δ_{H} CDCl₃ 7.75 (s, 1H, PhNH), 7.37-7.06 (m, 5H arom. and N=CH), 4.38-4.33 (q, 2H, OCH₂), 4.18-4.13 (q, 2H, (OCH₂)), 1.46-1.33 (t, 3H, CH₃), 1.24-1.20 (t, 3H, CH₃); δ_{C} CDCl₃ 161.86 (CO), 159.00 (C=N), 157.20, 148.29, 140.21, 129.97, 124.37, 1129.52, 105.43, 87.57 (C_{arom}), 114.85 (CN), 68.29 (OCH₂), 65.27 (OCH₂), 14.25 (CH₃), 14.30 (CH₃).

3-Amino-4-oxo-6-(phenylamino)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbohydrazide (13):

A mixture of ethyl 4-cyano-3-(ethoxymethyleneamino)-5-(phenylamino)thiophene-2-carboxylate (12) (1g, 0.0029 mol), hydrazine hydrate (98%) (6 mL) and acetic acid (2.5 mL) in ethanol (25 mL) was heated under reflux for 1 h. The precipitated product was then filtered off, dried and recrystallized from ethanol. Yield 64%. Canary yellow crystalline solid, mp. 228-230 °C; IR (cm⁻¹) 3389-3316 (NH₂), 3204 (NH), 1669 (CO), 1635 (CO); δ_{H} DMSO 11.19 (NH), 8.40 (s, 1H, CONH), 8.25 (s, 1H, CH=N), 7.36-6.99 (m, 5H, arom), 5.73 (br, 2H, NH₂), 4.85 (br, 2H, NH₂); δ_{C} DMSO 163.90 (CO), 159.49 (CO), 156.97 (CH=N), 154.72, 151.49, 149.05, 129.74, 123.10, 121.16, 102.65, 89.23 (C arom.).

Ethyl N2(phenylcarbohydrazido)5(phenylamino)thiophene-3-ylform-imidate (14):

A mixture of ethyl 4-cyano-3-(ethoxymethyleneamino)-5-(phenylamino)thiophene-2-carboxylate (11), (0.4g, 0.0012 mol) phenylhydrazine (2.4 mL) and acetic acid (1 mL) in ethanol (15 mL) was heated under reflux for 5 h. The precipitated product was then filtered off, dried and recrystallized from ethanol.

Yield: 54 %, color?? mp. 220-222 °C; IR (cm⁻¹) 3376-3329 (NH), 1643 (CO), 1592 (C=N-); δ_{H} DMSO 10.87 (s, 1H, NHCO), 10.63 (s, 1H, N-HNPh), 9.36 (s, 1H, NHPh), 7.63 (s, 1H, N=CH), 6.71 (s, thienyl-H), 7.54-6.09 (m, 10H, arom.), 4.31-4.25 (q, 2H, OCH₂), 1.32-1.29 (t, 3H, CH₃); δ_{C} DMSO 162.31 (CO), 148.53, (CH=N), 146.38, 145.78, 140.43, 140.23, 130.55, 129.54, 123.95, 118.40, 118.14, 112.40, 103.17, 85.10 (C_{arom}),

60.49 (OCH₂), 14.95 CH₃.

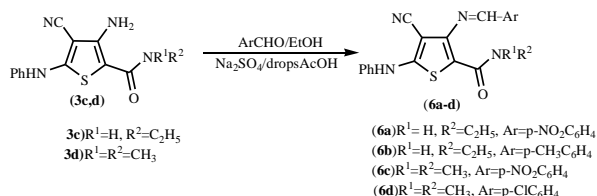
Ethyl N-(2-(hydroxycarbonyl)-5-(phenylamino)thiophene-3-ylformimide (15):

A solution of ethyl 4-cyano-3-(ethoxymethyleneamino)-5-(phenylamino)thiophene-2-carboxylate (**11**) (0.5 g, 0.0014 mol) and hydroxylamine hydrochloride (0.1 g, 0.0014 mol) in ethanol (20 mL) containing TEA (0.6 mL) was boiled under reflux for 5h. The reaction mixture was then cooled. The formed precipitate was filtered off washed with water, dried and recrystallized from dioxane.

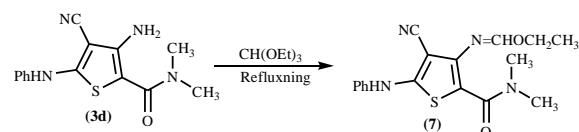
Yield: 44 %, brown solid, mp. 280 °C decompose; IR (cm⁻¹) 3342(NH), 3280(OH), 1642(CO); δ_HDMSO 11.07 (s, 1H, NH), 10.40 (br, 1H, OH), 9.77 (s, 1H, NPh), 7.55-7.12 (m, 6H, arom. and 1H, N=CH), 4.26-4.16 (q, 2H, OCH₂), 1.29-1.20 (t, 3H, CH₃); δ_CDMSO 161.39 (CO), 149.24, 147.53, (CH=N), 145.90, 140.13, 133.41, 130.36, 124.36, 120.74, 118.50 (C_{arom.}), 60.06 (OCH₂), 14.96 (CH₃).

II. RESULTS AND DISCUSSION:

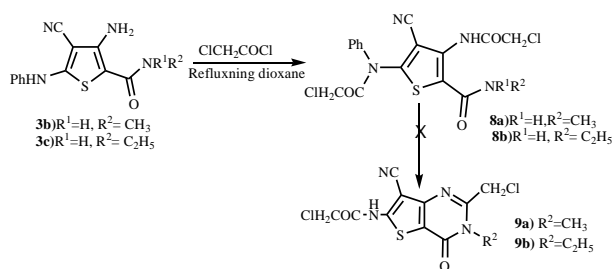
The presence of active amino groups in the synthesized multifunctional alkyl 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**3b-d**) would make them very versatile synthons. Hence, some new Schiff bases (**6a-d**) were synthesized by reacting these 3-aminothiophene-2-carboxamides (**3c,d**) with some various aromatic aldehydes. Although this type of condensation reactions was easily carried out when the tertiary carboxamide (**3d**) was used, it was, however, difficult to control when these carboxamides are primary or secondary, due to their tendency to cyclize to thienopyrimidinones (**4a-m**) [25]. Nevertheless, 3-arylideneamino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (**6a-d**) were successfully synthesized under controlled conditions from the 3-aminothiophene-2-carboxamides (**3c,d**) and aromatic aldehydes in ethanol containing a catalytic amount of glacial acetic acid.



IR spectra of the Schiff bases (**6a-d**) did not show any NH₂ and NH absorption bands. Bands at 2211-2203 and 1644-1600 are assigned for CN groups, and the amidic carbonyls respectively. The ¹H NMR of all Schiff bases (**6a-d**) spectra showed new signals at δ 9.04-7.42 ppm for azomethine protons and D₂O-exchangable singlet signals at δ 10.30-9.89 ppm for NPh protons. The signals at δ 7.91-6.72 ppm represent the aromatic protons together with the D₂O-exchangable amidic NH proton. ¹³C NMR spectrum showed signals at 166.83-164.18, 162.60-160.58 and 115.00-113.92 ppm which were assigned to the amidic, azomethine and cyano carbonyl carbons respectively. The ¹³C NMR spectra for all 3-arylideneamines (**6a-d**) revealed signals at δ 166.83-160.58 ppm which were assigned to amidic C=O and azomethine N=CH- carbons respectively. When 3-amino-4-cyano-5-(phenylamino)thiophene-2-N,N-dimethylcarboxamide (**3d**) was reacted with triethylorthoformate the expected ethyl N-(4-cyano-2-(dimethylcarbamoyl)-5-(phenylamino)thiophene-3-ylformimidate (**7**) was produced. This compound could be transformed into other useful compounds by some cycloaddition and nucleophilic reactions at the formimidate group.

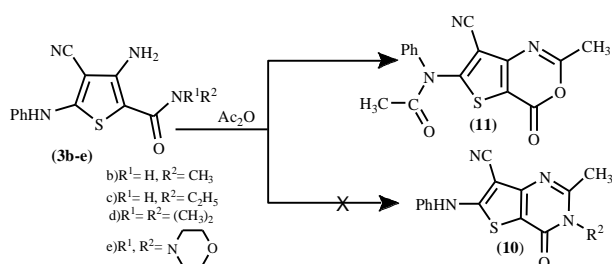


The IR spectrum of this compound did not show any NH₂ group absorption. ¹H NMR spectrum showed new signals a singlet at δ 7.96 ppm (N=CH) and a quartet at δ 4.30-4.27 ppm (OCH₂) and a triplet at δ 1.34-1.29 ppm (CH₃) indicating the presence of azomethine and ethoxy groups respectively. The ¹³C NMR spectrum revealed a carbonyl group at δ 162.86 ppm, and a new N=CH signal at δ 159.20 ppm. In addition, new signals at δ 63.27 ppm and at δ 14.35 ppm representing CH₂ and CH₃ of the ethoxy group. When 3-aminothiophene-2-carboxamides (**3b,c**), in which the amides are secondary, were subjected to reaction with chloroacetyl chloride two nucleophilic substitutions occurred by the amino groups at positions 3 and 5 of the thiophene ring resulting in the formation of 5-(2-chloro-N-phenylacetamido)-3-(2-chloroacetamido)-4-cyano-N-alkylthiophene-2-carboxamides (**8a,b**). The reaction did not proceed under the employed conditions to the expected dihydrothienopyrimidinones (**9a,b**), as shown in scheme 2. The spectral data of the products (**8a,b**) are in accordance with their proposed structures.



Scheme 2

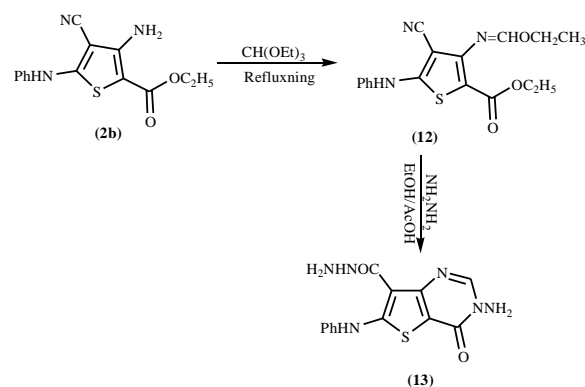
Their IR spectra revealed new bands at ν 3330-3223 cm⁻¹ for NH groups instead of the NH₂ groups. It also gave two new bands at ν 1670 and 1665 cm⁻¹ representing the chloroacetamido carbonyl groups. The ¹H-NMR spectrum lacked the NH₂ signal and showed new signals at δ 10.54 and 10.07 ppm indicating the presence of two NH protons. The ¹³C-NMR spectra also showed new carbonyl groups at δ 165.94-165.93 (COCH₂Cl), 161.19 and 160.66 ppm (CONH), and new CH₂ groups for (14b) at δ 66.79, 43.31 and 43.21 ppm which were clearly confirmed by DEPT technique. The presence of considered the good leaving chlorogroup in these types of compounds (8a,b) can be displaced easily by a number of nucleophiles opening the way to various synthetic routs. In an attempt to prepare 3-ethyl-2,6-bis(phenylamino)thieno[3,2d]pyrimidin-4(3H)ones (10), 3-aminothiophene-2-carboxamides (3a-e) were refluxed in acetic anhydride but the product of each reaction was the unexpected thienooxazinone (11) (cf. scheme 3). The carboxamide (3b) gave a slightly better reaction yield than the other three employed amides (3c-e) results are in agreement with our earlier report (24).



Scheme 3

Amino-2-thiophenecarboxamides (3a-c) were not the only versatile synthons employed in the synthesis of thiophene compounds, but also ethyl 4-cyano-3-amino-5-(phenylamino)-2-carboxylate (2b). This amino ester which was synthesized by reacting 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (1) with ethanol, as previously reported (24), gave ethyl 4-cyano-3[(ethoxymethylene)amino]5(phenylamino)thiophene-2-carboxylate (12) when reacted with triethylorthoformate. The IR spectrum of this

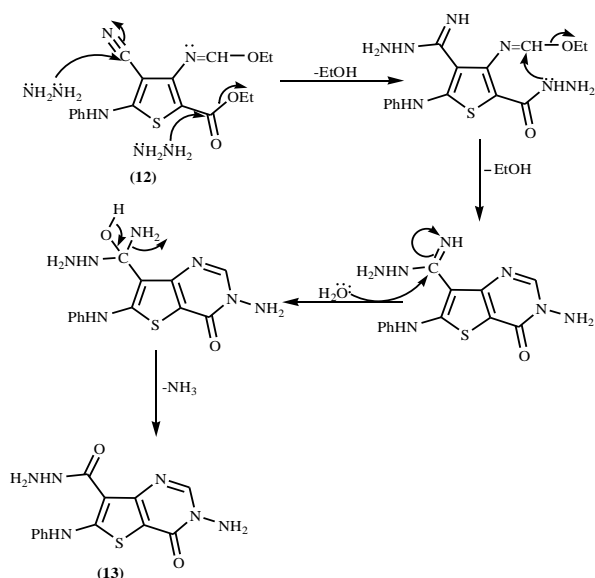
compound (12) did not show any NH₂ group absorption but showed new band at 1599 cm⁻¹ which was attributed to N=CH group. The ¹H-NMR spectra showed a CH proton as a singlet at 7.75 ppm and two ethoxy groups as two quartets 4.13-4.18 ppm and 4.33-4.38 ppm representing two OCH₂ protons and two triplets at 1.20-1.24 ppm and 1.33-1.46 ppm for two CH₃ groups. The aromatic protons together with NH protons appeared as multiplets at 7.06-7.37 ppm. ¹³C-NMR spectrum revealed the presence of the amidic CO at 161.86 ppm and a C=N signal at 159.00 ppm. Treatment of (12) with hydrazine hydrate in the presence of a catalytic amount of acetic acid in refluxing ethanol resulted in the formation of 3-amino-4-oxo-6-(phenylamino)-3,4-dihydrothieno-[3,2-d]-pyrimidine-7-carbohydrazide (13) (cf. scheme 4).



Scheme 4

The IR spectrum of this compound (13) revealed the disappearance of the cyano absorption and the presence of the absorption band at 3389 cm⁻¹ for NH group and at 33316-3204 cm⁻¹ representing NH₂ group. The absorption at 1668 cm⁻¹ indicated the carbonyl group of the pyrimidinone ring. In addition, the absorption at ν 1635 cm⁻¹ indicated the presence of a carbohydrazide carbonyl group. The ¹H-NMR spectrum lacked the signals of the ethoxy groups and a signal for the amino group NHPH appeared at 11.19 ppm. The singlets at 8.40 ppm and 8.25 ppm were assigned for CONH and pyrimidinone CH=N respectively. The multiplet at 7.36-6.99 represent aromatic protons (Ph group). The singlets at 5.73 and 4.85 ppm are assigned for the two NH₂ groups. The presence of these NH and NH₂ groups were confirmed by the disappearance of their signals on deuteration. The ¹³C-NMR spectrum did not have any signal of the ethoxy group protons. It also showed a new signal at 163.90 ppm for the carbonyl group of the pyrimidinone ring. The signal at 159.49 ppm for carbonyl of hydrazide group and the signal at 154.72 ppm is for pyrimidinone (CH=N) carbon. This proves that

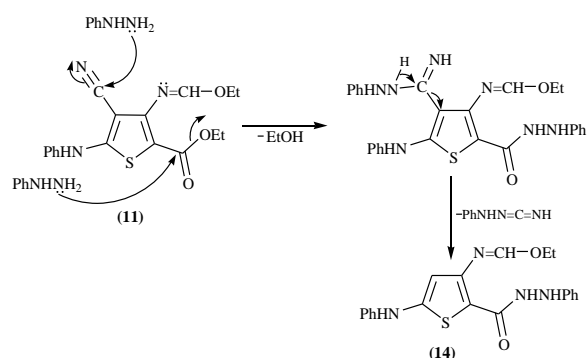
cyclization occurred. The transformation of (12) to (13) is assumed to involve nucleophilic attack of nitrogen atoms of hydrazine at the carbonyl ester resulting in loss of ethanol first followed by cyclization and loss of a second ethanol molecule. This process is accompanied by attack of hydrazine at the cyano group followed by hydrolysis of the carbohydrazide and elimination of ammonia to give the 3-amino-4-oxo-6-(phenylamino)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbohydrazide (13) (cf. scheme 5).



Scheme 5

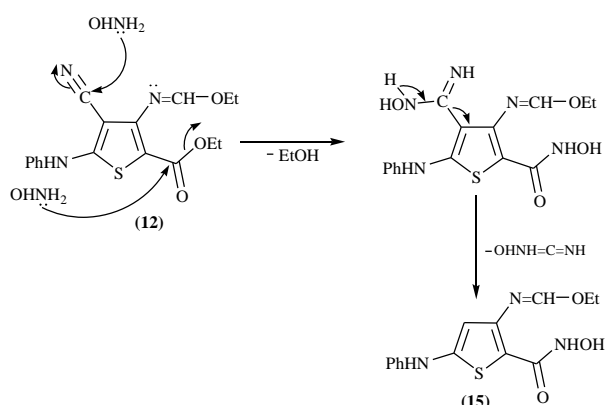
However, the reaction of ethyl 4-cyano-3-[(ethoxymethylene)amino]-5-(phenylamino)thiophene-2-carboxylate (12) with the lesser reactive phenylhydrazine and hydroxylamine did not proceed, as expected, to cyclization and gave ethyl 2-substituted-5-(phenylaminothiophene)-3-ylformimidates (14) and (15). So, phenylhydrazine (12) yielded ethyl N-5-(phenylamino)-2-(phenylcarbohydrazide)thiophene-3-ylformimidate (14) with unexpected loss of a cyano group. This is revealed by its spectral data. IR spectrum did not show cyano and ester carbonyl group absorptions but revealed NH and carbohydrazide carbonyl bands at 3376-3329 cm⁻¹ and 1643 cm⁻¹. In addition, ¹H NMR showed the two NH signals of the carbohydrazide group at 10.87 ppm and 10.63 ppm and the signal of NHPH group at 9.36 ppm. The presence of these NH groups was confirmed by the disappearance of their signals on deuteration. It also showed a singlet at 7.63 ppm representing (N=CH) proton. The multiplet at 7.54-6.09 ppm was attributed to 10H protons of the two phenyl groups. The thienyl-H signal at ppm 6.71 ppm. The ethoxy group appeared as a quartet for OCH₂ at 4.31-4.25 ppm and a triplet for CH₃ at

1.32-1.29 ppm. The ¹³C NMR spectrum showed a signal at 163.36 ppm for the carbonyl group and N=CH signal at 146.37 ppm. This group was clearly confirmed when DEPT 90 technique was applied. The peak at 60.49 ppm was assigned to OCH₂ of ethoxy group. This CH₂ signal did not disappear but is reversed to the opposite direction when applying DEPT 135 technique. The signal at 14.95 ppm was assigned to the methyl group. The proposed mechanism of this reaction involves two nucleophilic attacks by phenylhydrazine, as illustrated in (scheme 6).



Scheme 6

The reaction of ethyl 4-cyano-3-[(ethoxymethylene)amino]-5-(phenylamino)thiophene-2-carboxylate (12) with hydroxylamine hydrochloride did not also proceed to cyclization as expected and stopped at the hydroxamic acid derivative (15) with loss of a cyano group as well. IR spectrum of this product confirmed the disappearance of the cyano group absorption, and revealed the presence of amidic carbonyl at 1642 cm⁻¹ instead of the ester carbonyl of the starting 2-carboxylate derivative (12) which appears at 1701 cm⁻¹. In addition, ¹H NMR showed HNC=O signal at 11.07 ppm and the signals at 10.40 and 9.77 ppm represent (HO-N) and NHPH protons respectively. The ¹³C NMR spectrum also showed the appearance of new carbonyl group at 165.94 ppm. This reaction is a standard method used for identification of esters. However, the loss of the cyano group was unexpected, and we believe it is attributed to nucleophilic addition of the hydroxylamine on the cyano carbon as illustrated in scheme 7.



Scheme 7

III. CONCLUSIONS:

1,3-Aminothiophene-2-carboxamides (3a-e) synthesized from 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (1) were successfully used in the synthesis of 3-arylideneaminothiophene derivatives(6a-d), and 2-(chloroacetamido)-4-cyano-N-alkylthiophene-2-carboxamides (8a,b) and thienooxazinone derivative(11).

2. Ethyl 4-cyano-3-[(ethoxy-methylene)amino]-5-phenylaminothiophene-2-carboxylate (12) was utilized to synthesize the carbonylhydrazide derivatives (13) and (14) and the hydroxamic acid derivative (15) by treatment with hydrazine, phenylhydrazine and hydroxylamine respectively

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