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Utilization of 2-Ylidene-4-Thiazolidinones in the Synthesis ofHeterocyclic 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-phenyl-thiazolidin-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-carbo- hydrazide, ethyl 2-substituted-5-(pheny laminothio phene)- 3-ylformimidates.

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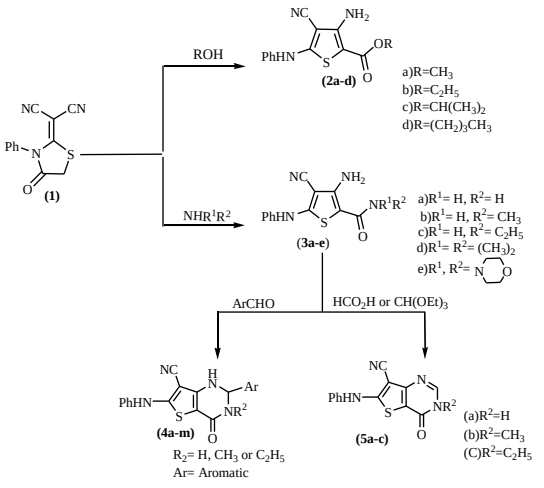
I. INTRODUCTION:

Derivatives of thiophenehave attracted tremendous interest mostly due to theirchemical 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 asanti-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 derivativeswere 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].1n addition, these carboxamides were transformed into a number of tetrahy drothienopyrimidinones (4a-m) and dihydrothienopyrimidinones (5a-c) as shown in (cf. scheme 1) [25].



Scheme 1

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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. scheme1)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 ^{1}HNMR and 100 MHz for ^{13}CNMR using DMSOor $CDCl_3$ as solvent and tetramethylsilane(TMS) as the internal standardand given in δ scale ppm. The chemical shift (δ) values are expressed in parts per million (ppm). Legend: s = singlet, d = doublet, t = triplet andm = multiplet. The structures and names of all the compounds were generated using Chemdraw ultra 12.0.

Synthesis:

4-Amino4cyano5(phenylamino)thiophene-2-carboxamides(3ae)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 ormorpholine respectively. Ethyl 4-cyano-3-amino-5(phenylamino)thiophene2carboxy late (2b) was synthesized by treatment of 2(4oxo3phenylthiazolidin2ylidene)malononitrile(1) with ethanol in the presence of triethylamine (TEA) [24].

3Arylideneamino4cyano5phenylaminothiophene-2-carboxamides (6a-d):

General procedure:

A solution of 3-amino-4-cyano-5-(pheny lamino)thiophene2carboxamides**(3c,d)**(0.0017mol), aromatic aldehyde (0.0017mol) 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 thencooled. The precipitated solid that formed was filtered off andrecrystallized from ethanol

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

Refluxing for 2 h.; Yield: 55%,red solid, mp.204206°C;ν_{max}(neat)3281(NH),3173(NH),2203(CN),1617(C=O),1595(C=N); δ_HDMSO10.28 (br, 1H, PhNH), 9.04 (s,1H,N=CH), 8.43-7.41 (m, 9H, arom. andbr,1H, NH), 3.38-3.24(q, 2H, NCH_2), 1.09-1.04(t,3H,CH_3);δ_CDMSO164.95(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)thio-phene-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_HDMSO10.21(br.1H,NH),8.85(s,1H,N=CH),7.917.14(m,9H,arom.andbr.1H,NH),3.273.21(q,2H,CH_2),2.27(s,3H,(CH_3Ph),1.091.05(t,3H,CH_3);δ_C DMSO166.29(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_3Ph),15.25(CH_3).

3-(4-Nitrobenzylideneamino)-4-cyano-N,N-dimethyl5(phenylamino)thiophene2carboxamide (6c)::

Refluxing for 2 h.; Yield: 70%, Orang crystalline solid,mp.218220°C;ν_{max}(neat)3310(NH),2203(CN), 1617(C=O),1578 (C=N);δ_HDMSO10.13(br,1H, NH), 8.73(s,1H,N=CH), 8.41-7.12 (m, 9H, arom.), 2.85(s,6H,2CH_3);δ_CDMSO164.18(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[$N(CH_3)_2$].

3-(4-Chlorobenzylideneamino)-4-cyano-N,N-dimethyl-5-(phenylamino)thio- phene-2-carboxamide (6d)::RT for 5days.Yield: 54%, yellowcrystalline solid. Mp 226-228°C; νmax(neat)3227(NH), 2206(CN), 1600 (C=O), 1556(C=N);δHDMSO9.98(br,1H,NH), 8.56(s,1H, N=CH), 7.98-7.12 (m, 9H, arom.), 2.86 (s,6H,2CH3);δCDMSO164.56(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, (Carom.),37.20 [N(CH3)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 triethylortho formate (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; νmax(neat) 3270 (NH), 2206(CN), 1645(C=O), 1594(C=N); δHDMSO

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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); δcDMSO162.86 (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-(phenyl-amino)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; νmax (cm-1) 3330 (NH), 3223(NH), 2210 (CN),1665 (br.) two (C=O), 1627 (CH3-HNCO); δH DMSO10.50 (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); δC 1 DMSO65.93 (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 (CH_3CH_2-HNCO); δ_HDMSO 10.54 (thienyl-NHCO), 10.07 (br,1H, CONH), 7.74-7.14 (m, 5H, arom.), 4.37 (s, 2H,(OCH_2Cl), 3.57 (s, 2H, (OCH_2Cl), 3.21-3.15 (q, 2H, CH_2),1.08-1.04 (t, 3H, CH_3); δ_CDMSO165.85 (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 (CH_2Cl), 43.21(CH_2Cl), 34.52 (CH_2),15.16 (CH_3).

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-carbox- amide**(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)**(0.001mol) and triethylorthoformate (25ml) 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 $CDCl_3$,7.75 (s, 1H,PhNH), 7.37-7.06 (m, 5Harom.and N=CH), 4.38-4.33(q,2H,OCH_2), 4.18-4.13 (q, 2H, (OCH_2)1.46-1.33 (t, 3H, CH_3), 1.24-1.20 (t, 3H, CH_3); δc $CDCl_3$,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 (OCH_2), 65.27 (OCH_2), 14.25 (CH_3), 14.30 (CH_3).

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, 0.0029mol), hydrazine hydrate (98%) (6mL) and acetic acid (2.5mL) in ethanol (25mL) was heated under refluxfor 1h. 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(NH_2), 3204(NH),1669 (CO),1635 (CO); δ_HDMSO11.19 (NH), 8.40 (s, 1H, CONH), 8.25 (s, 1H, CH=N), 7.36-6.99 (m, 5H, arom),5.73 (br, 2H, NH_2), 4.85 (br, 2H, NH_2);δ_CDMSO163.90(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.).

EthylN2(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 (2.4mL) and acetic acid (1mL) in ethanol (15mL) was heated under reflux for 5h. 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_HDMSO10.87 (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, OCH_2), 1.32-1.29 (t,3H, CH_3); δ_CDMSO162.31(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}),

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60.49 (OCH_2),14.95 CH_3.

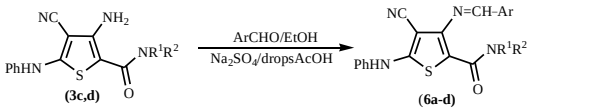
EthylN-2-(hydroxycarbamoyl)-5-(phenylamino) thiophene-3-ylformimi- date (15):

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_HDMSO11.07 (s,1H, NH), 10.40, (br,1H, OH)), 9.77 (s,1H, NHPh, 7.55-7.12 (m, 6H, arom. and 1H, N=CH), 4.26-4.16 (q, 2H, OCH_2), 1.29-1.20 (t,3H, CH_3); δ_CDMSO161.39 (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 (OCH_2),14.96 (CH_3).

II. RESULTS AND DISCUSSION:

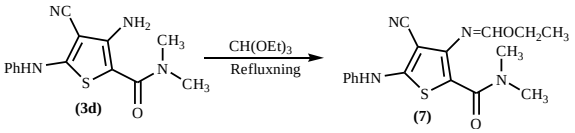
The presence of active amino groups in the synthesized multifunctional alkyl 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxaamides **(3b-d)**would make them very versatile synthons. Hence, some new Schiff bases **(6a-d)** were synthesized by reacting these 3-aminothiophene-2-carboxamides **(3c,d)** 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-carbox- amides (**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.



3c)R^1=H, R^2=C_2H_5
3d)R^1=R^2=CH_3

(**6a**)R^1= H, R^2=C_2H_5, Ar=p-$NO_2C_6H_4$
(**6b**)R^1=H, R^2=C_2H_5, Ar=p-$CH_3C_6H_4$
(**6c**)R^1=R^2=CH_3, Ar=p-$NO_2C_6H_4$
(**6d**)R^1=R^2=CH_3, Ar=p-ClC_6H_4

IR spectra of the Schiff bases **(6a-d)** did not show any $NH_2$and NH absorption bands. Bands at 2211-2203 and 1644-1600 are assigned for CN groups, and the amidic carbonyls respectively. The **^{1}HNMR** of all Schiff bases **(6a-d)** spectra showed new signals at δ 9.04-7.42 ppm for azomethine protons and D_2O-exchangable singlet signals at δ 10.30-9.89 ppm for NHPh protons. The signals at δ 7.91-6.72 ppm represent the aromatic protons together with the D_2O-exchangable amidic NHproton. **^{13}CNMR** 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 **^{13}CNMR** spectra for all 3-arylideneamines **(6a-d)**revealed signals at δ166.83-160.58 ppm which were assigned to amidic C=O and azomethineN=CH- carbons respectively.When 3-amino-4-cyano-5-(phenylamino)thiophene-2-N,N-dimethylcarboxamide **(3d)** was reacted with triethylorthoformatethe expected ethyl N-4-cyano-2-(dimethylcarbamoyl)-5-(phenylamino)thiophene-3-ylform- imidate**(7)** was produced. This compound could betransformed into other useful compounds by some cycloaddition and nucleophilic reactionsat the formimidate group.



The **IR** spectrum of this compound did not show any NH_2 group absorption. **^{1}HNMR**spectrum showed new signalsa singlet at δ 7.96 ppm (N=CH) and a quartet at δ 4.30-4.27 ppm (OCH_2) and a triplet at δ 1.34-1.29 ppm (CH_3)indicating the presence of azomethine and ethoxy groupsrespectively. The **^{13}CNMR** 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 CH_2 and CH_3 of the ethoxy group. When 3-aminothiophenes-2-carboxamides **(3b,c)**, in which the amides are secondary, where 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 inscheme 2. The spectral data of the products **(8a,b)** are in accordance with their proposed structures.

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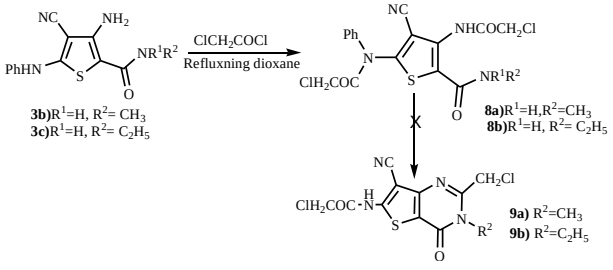
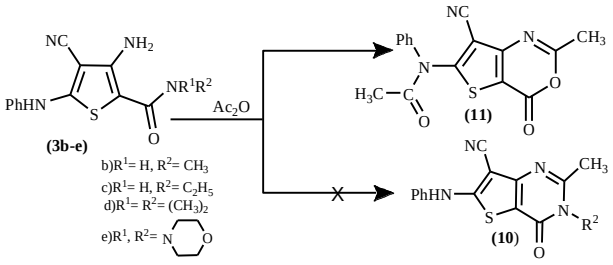


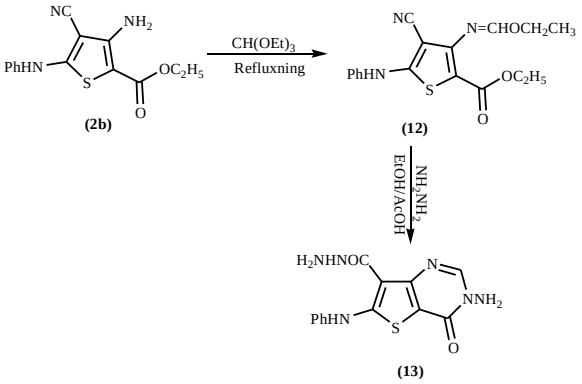
Scheme 2

Their **IR** spectra revealed new bands at ν 3330-3223 cm^{-1} for NH groups instead of the NH_2 groups. It also gave two new bands at ν1670 and 1665 cm^{-1} representing the chloroacetamido carbonyl groups.The **^{1}HNMR** spectrum lacked the NH_2 signal and showed new signals at δ 10.54 and 10.07 ppm indicating the presence of two NH protons. The**^{13}CNMR**spectra also showed new carbonyl groups at δ165.94-165.93 ($COCH_2Cl$), 161.19 and 160.66 ppm (CONH), and new CH_2 groups for (14b) at δ 66.79, 43.31 and 43.21 ppm which were clearly confirmed by DEPT technique. The presence of considered thegood 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]pyrimidin4(3H)ones**(10)**, 3-aminothiophene-2-carboxamides **(3a-e)** were refluxed in acetic anhydride but the product of each reaction was theunexpected thienooxazinone**(11)** (cf. scheme3). 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

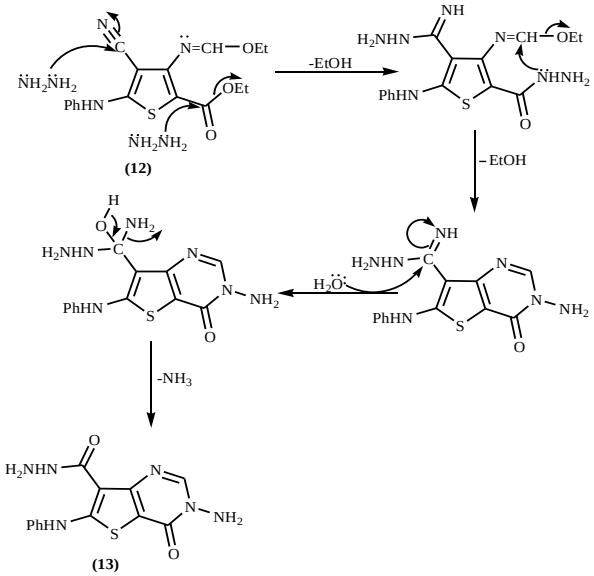
Amino-2-thiophenecarboxamides **(3a-c)** were not the only versatile synthons employed in the synthesis of thiophene compounds, but also ethyl 4-cyano-3-amino-5-(phenylamino)-2-carboxylate **(2b).** This amino esterwhich was synthesized by reacting 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (**1**) with ethanol, as previously reported(24),gave ethyl 4-cyano3[(ethoxymethylene)amino]5(phenylamino)t hiophene-2-carboxylate **(12)**when reacted with triethylorthoformate. The **IR** spectrum of this compound **(12)**did not show any NH_2 group absorption but showed new band at 1599 cm^{-1} which was attributed to N=CH group. The ^{1}H-NMR spectra showed a CH proton as a singlet at 7.75 ppm and two ethoxy groups astwo quartets 4.13-4.18 ppm and 4.33-4.38 ppm representingtwoOCH_2protons and two tripletsat 1.20-1.24 ppm and 1.33-1.46 ppm for two CH_3 groups.The aromatic protons together with NH protonsappeared asmultiplets at 7.06-7.37 ppm. **^{13}CNMR** spectrum revealed the presence of the amidic CO at 161.86ppm 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

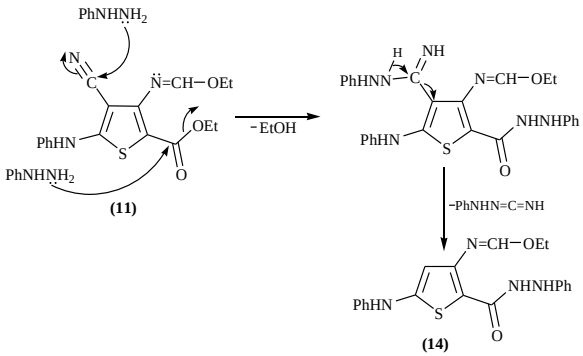
The **IR** spectrum of this compound **(13)** revealed the disappearance of the cyano absorption and the presence of the absorption band at 3389 $cm^{-1}$for NH group and at33316-3204cm^{-1}representing NH_2 group. The absorption at 1668cm^{-1} indicated the carbonyl group of the pyrimidinone ring. In addition, the absorption at ν 1635 cm^{-1}indicated the presence of a carbohydrazide carbonyl group. The**^{1}HNMR** 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 twoNH_2 groups. The presence of these NH and NH_2 groups were confirmed by the disappearance of their signals on deuteration. The **^{13}CNMR** spectrum did not have any signal of the ethoxygroup 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 carbo- hydrazide 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

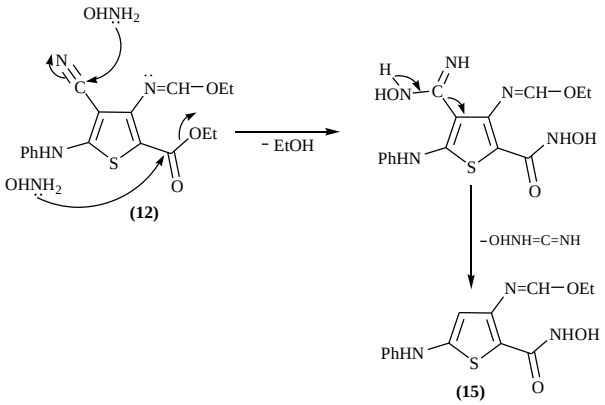
However, the reaction of ethyl 4-cyano-3-[(ethoxymethylene)amino]5(phenylamino)thiophene-2-carboxylate **(12)**with the lesser reactive phenyl-hydrazine and hydroxylamine did not proceed,as expected, to cyclization and gave ethyl 2-substituted-5-(phenylaminothiophene)-3-ylformimidates **(14)**and **(15)**. So, phenylhydrazine (12) yielded ethyl N-5-(phenylamino)-2-(phenylcarbohy drazide) thiophene-3-ylformimidate **(14)**with unexpected loss of a cyano group. This is revealed by the its spectral data. **IR** spectrum did not show cyano andester carbonyl group absorptions but revealed NH and carbohy drazide carbonyl bands at 3376-3329 cm^{-1} and 1643cm^{-}. In addition, **^{1}HNMR** 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 6.71ppm. The ethoxy group appeared as a quartet for OCH_2 at 4.31-4.25 ppm and a triplet for CH_3 at 1.32-1.29 ppm. The**^{13}CNMR** 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 OCH_2 of ethoxy group.This CH_2signal 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 (scheme6).



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 productconfirmed 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 1701cm^{-1}. In addition, **^{1}HNMR** showed HNCO signal at 11.07 ppm and the signals at 10.40 and 9.77 ppm represent (HO-N) and NHPh protons respectively. The **^{13}CNMR** spectrum also showed the appearance of new carbonyl group at 165.94 ppm. This reaction is a standard methods 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.

 DOI: 10.9790/9622-1001034148



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 thienooxazinonederivative(11).

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

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