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Utilization of 2-Ylidene-4-thiazolidinones in Synthesis of Heterocyclic Compounds Part (II): Transformation of (4-Oxo-3-phenyl-1,3-thiazolidin-2-ylidene)malononitrile to 3-Aminothiophene Derivatives

M.F. FARHAT[1], M.A. MAKHLOUF[1], A.B. ELMEZOUGHI[1], A.A.M. EL-MEHDI[2] and A.M.M. EL-SAGHIER[3,*]

[1]Chemistry Department, Faculty of Science, Tripoli University, P.O. Box 13494, Tripoli, Libya
[2]Chemistry Department, Faculty of Science and Arts, University of Al-Jabal Al-Gharbi, Gharian, Libya
[3]Chemistry Department, Faculty of Science, Sohag University, Sohag, Egypt

*Corresponding author: Fax: +20 93 4601159; E-mail: el_saghier@yahoo.com

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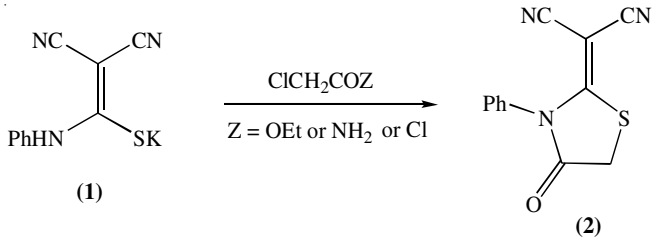
Alkyl 3-aminothiophene carboxylates derivatives (**3a-d**) were prepared *via* reaction of (4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)malononitrile (**2**) with alcohols. Compound **3a** was allowed to react with acetic anhydride, chloroacetyl chloride and nitrous acid to afford N,N,N-triacetylthiophene, 3-chloro-acetamidothiophene and 3-diazothiophene derivatives (**6**, **7** and **8**), respectively. Compound **8** was allowed to react with sodium azide to afford the 3-azidothiophene derivative (**9**). On the other hand, 3-amino-2-carboxamidothiophene derivatives (**10a-c**) were prepared via reaction of compound **2** with a variety of amines. Compound **10a** was allowed to react with acetic anhydride to afford thieno[3,2d]oxazinone (**12**).

Keywords: 3-Aminothiophene carboxylates, Thieno[3,2-d]oxazinone, 3-Azidothiophene.

INTRODUCTION

Ketene N,S-acetals are known to be useful reagents in heterocyclic synthesis [1]. Among these, particular attention has been given to oxoketene N,S-acetals as functionalized enaminones [2,3]. Previously we reported the synthesis of 4-thiazolidinones from ketene N,S-acetals [4].



(1) **(2)**

It is well known that aminothiophenes are used for the synthesis of a variety of biologically active compounds [5]. Their activities include antimicrobial [6,7], antifungal [8,9a], inhibition of cancer cell proliferation [9b], antagonism of α1-adrenoceptors [10] and prevention of cartilage destruction in articular diseases [11]. We have reported the facile transformation of 2-ylidene and 2,5-diylidene-4-thiazolidinones into pyrazoles [12]. Also, 4-thiazolidinones are used as a key intermediates for the synthesis of 2-arylamino derivatives which are used as starting materials for the synthesis of polyfunctionally substituted fused pyrimidine derivatives [13]. In continuation of our work in this field, we report herein the transformation of 2-ylidene-4-thiazolidinones into 3-aminothiophene derivatives and their conversions into other thiophene compounds.

3-Aminoothiophene are usually prepared from the corresponding nitriles with hydrogen sulfide [14,15]. They have antibacterial activity, particularly against *Tubercle bacillus* [16,17]. Thiophene-2-thioamides with further substitution have not yet been reported, although derivatives of 5-substituted 3-aminothiophene-2-carboxylic acids are known to be valuable synthons for the preparation of various medicinal substances [18,19]. They are available by condensation of chloroacrylonitriles with the corresponding mercaptoacetic acid analogues [20,21].

EXPERIMENTAL

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker Avance 300 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm), ^{13}C NMR spectra were recorded on a Brüker Avance 75 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm) and IR in KBr were obtained on a Brüker FT-IR ISS 25 spectrophotometer.

Synthesis of alkyl 3-amino-4-cyano-5-(phenylamino)-thiophene-2-carboxylates (3a-d)

General procedure: A mixture of compound **2** (0.0025 mol) and the appropriate alcohol in the presence of 3 drops of piperidine as catalyst was heated under reflux for 2 h. The precipitated product was then filtered off, dried and recrystallized from benzene.

Synthesis of *N*-(7-cyano-2-methyl-4-oxo-4*H*-thieno-[3,2-d][1,3]oxazin-6-yl)-*N*- phenylacetamide (5): A solution of compound **10b** (0.002 mol) in acetic anhydride (30 mL) was refluxed for 3 h. The reaction mixture was cooled and the precipitated solid was filtered off and recrystallized from benzene to give red crystals.

Synthesis of ethyl 3-(*N*,*N*-diacetylamino)-5-(*N*-acetyl-*N*-phenylamino)-4-cyano-2- carboxylate (6): A solution of compound **3b** (0.0017 mol) in acetic anhydride (30 mL) was heated under reflux for 2 h and then evaporated to half of its volume. The solid formed after dilution with ethanol was collected by filtration, dried and recrystallized from ethanol as white crystals.

Synthesis of ethyl 3-(2-chloroacetamido)-4-cyano-5-(phenylamino)-thiophene-2- carboxylate (7): To a solution of compound **3b** (0.005 mol) in dioxane (30 mL) was added chloroacetyl chloride (0.005 mol) dropwise with stirring at room temperature. The reaction mixture was refluxed for about 0.5 h and left overnight. The separated solid was collected by filtration and recrystallized from benzene as white crystals.

Synthesis of ethyl 4-cyano-3-diazo-5-(phenylamino)-thiophene-2-carboxylate (8): To an ice-cold solution of compound **3b** (0.001 mol) in 60 mL acetic acid, 5 mL sulfuric acid and 4 mL water placed in 250 mL beaker. A solution of sodium nitrite (0.004 mol) in 10 mL water was added slowly, the resulting diazonium salt solution was stirred for 20 min, at 0-5 °C and the diazonium salt solution was used without isolation in the next experiment.

Synthesis of ethyl 3-azido-4-cyano-5-phenylamino-thiophene-2-carboxylate (9): To the diazonium salt solution (**8**) (0.001 mol) was added sodium azide (0.001mol) and the mixture was stirred for 5 h, concentrated by evaporation and the solid produced was collected and recrystallized from benzene.

Synthesis of 3-amino-5-anilino-4-cyano-*N*-[2-(1*H*-indol-3-yl)ethyl]thiophene-2- carboxamide (10a): A mixture of compound **2** (0.01 mol) and tryptamine (0.01 mol) in dioxane (80 mL), was heated under reflux for about 3 h and the precipitate obtained was collected by filtration while hot and recrystallized from benzene as yellowish white crystals.

Synthesis of 4-amino-2-anilino-5-(piperidin-1-ylcarbonyl)thiophene-3-carbonitrile (10b): A mixture of compound **2** (0.002 mol) and piperidine (0.015 mol) in dioxane (15 mL) was stirred for 24 h at room temperature. The solution formed was poured into ice-cold water and the yellow solid that formed on cooling was collected by filtration and recrystallized from benzene.

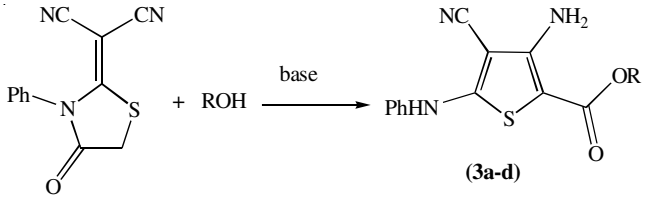
Synthesis of 3-amino-5-anilino-4-cyano-*N*-cyclohexyl-thiophene-2-carboxamide (10c): A mixture of compound **2** (0.004 mol) and cyclohexylamine (0.008 mol) in dioxane (20 mL) was refluxed for 3 h. The reaction mixture was then poured into ice-cold water and the precipitated was filtered off and recrystallized from petroleum ether-chloroform mixture as yellowish white crystals.

Synthesis of 2-[(1-anilino-2,2-dicyanovinyl)thio]-*N*-cyclohexylacetamide (11): A mixture of compound **2** (0.002 mol) and cyclohexylamine (0.004 mol) was stirred in dioxane (20 mL) at room temperature for 24 h. The reaction mixture was then poured into ice-cold water and the solid product was filtered off and recrystallized from benzene as white crystals.

Synthesis of ethyl [5-anilino-4-cyano-2-({[2-(1*H*-indol-3yl)ethyl]amino}carbonyl)-3- thienyl]imidoformate (13): A solution of compound **10d** (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 as pale yellow crystals.

RESULTS AND DISCUSSION

Reaction of compound **2** with different alcohols namely; methanol, ethanol, 2-propanol and 1-butanol, using sodium alkoxide, piperidine or triethylamine (TEA) as catalyst at refluxing temperature, gave the corresponding alkyl 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxylates (**3a-d**). The ester (**3a,b**) was obtained in poor yields by Sommen *et al.* [22], using a different procedure (**Scheme-I**).



(2) **(3a-d)**

a; R = CH_3, **b**; R = C_2H_5,
c; R = $CH(CH_3)_2$, **d**; R = $(CH_2)_3CH_3$

Scheme-I

The reaction can be explained by three postulated related mechanisms depending on the base used. They all involve nucleophilic attack at the ring amidic carbonyl by alkoxide or piperidine. In case where the reaction is carried out in refluxing alcohols in the presence of sodium alkoxide as a base, the alkoxide ion attacks at the ring carbonyl group, which results in ring opening and the formation of the alkoxy carbonyl derivative. This is followed by cyclization *via* the nucleophilic attack of the generated carbanion at the cyano group to give alkyl 3-amino-4-cyano-5-(phenylamino)thiophene-2- carboxylates (**3a-d**). On the other hand, on using triethylamine as a base, the same nucleophilic attack occurs after removal of a proton from alcohol by triethylamine to produce alkoxy ion, followed by cleavage of the amide bond and cyclization (Fig. 1).

However, when piperidine is used as a base, a nucleophilic attack at the amidic carbonyl takes place by the piperidine nitrogen with ring opening producing the non-isolated intermediate (**4**) followed by cyclization and substitution of piperidyl group by alkoxy group (Fig. 2).

The fact that the piperidyl amide (**10b**) prepared by reacting (**2**) with piperidine at room temperature, is transformed easily into the ester (**3b**) on refluxing in ethanol proves that the displacement of the amide group occurs after the formation of the thiophene ring. Refluxing of compound (**3b**) with acetic

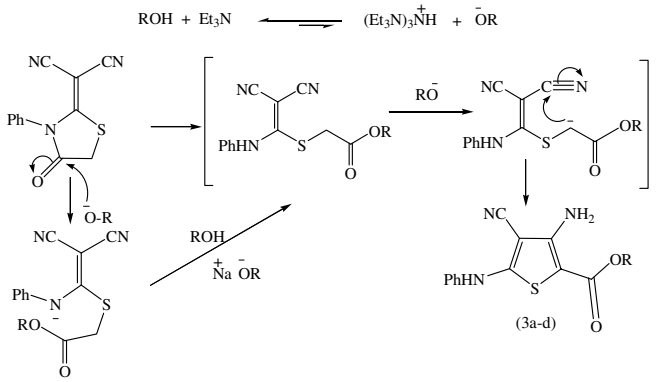


Fig. 1

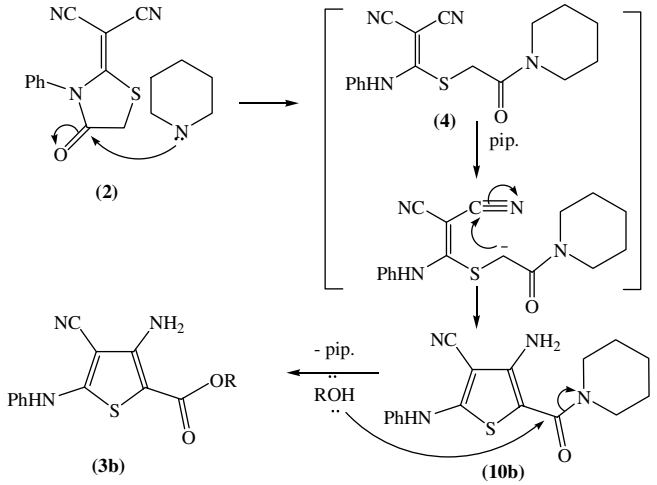
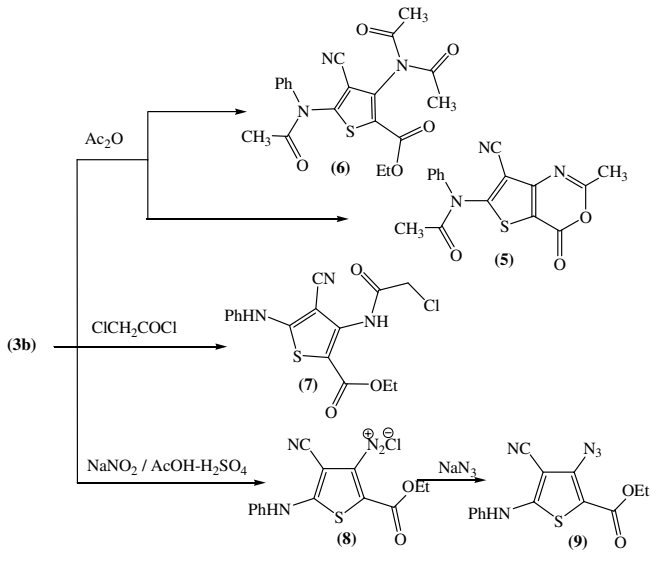


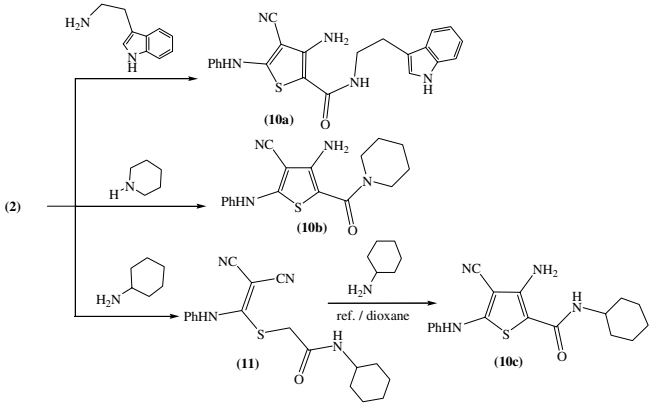
Fig. 2

anhydride did not give the expected thieno[3,2-d]oxazinone derivative (**5**), but yielded the triacetyl derivative (**6**) instead. When compound (**3b**) was treated with chloroacetyl chloride in refluxing 1,4-dioxane in the presence of triethylamine, it gave only the amide (**7**). The preparation of ethyl 3-diazo-4-cyano-5-phenyl-aminothiophene-2-carboxylate (**8**) was achieved by diazotization of compound (**3b**). This diazonium salt (**8**) when treated with sodium azide afforded the azido derivative (**9**) (**Scheme-II**).



Scheme-II

A series of carboxamides (**10a-c**) were obtained by the reaction of compound **2** with a variety of amines, namely; tryptamine, piperidine and cyclohexylamine (**Scheme-III**).



Scheme-III

The reaction mechanism is assumed to involve a nucleophilic attack of the amino group at the amidic carbonyl of the thiazolidinone, followed by ring opening and then cyclization to produce the thiophene amides (**10a-c**) (Fig. 3).

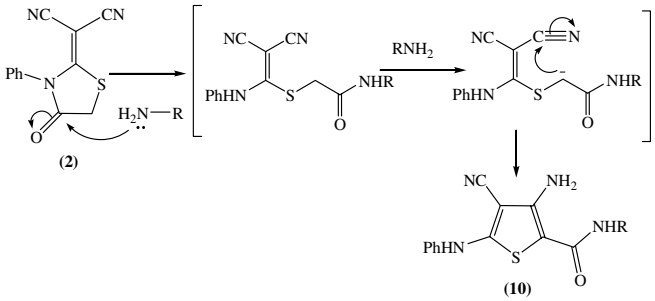


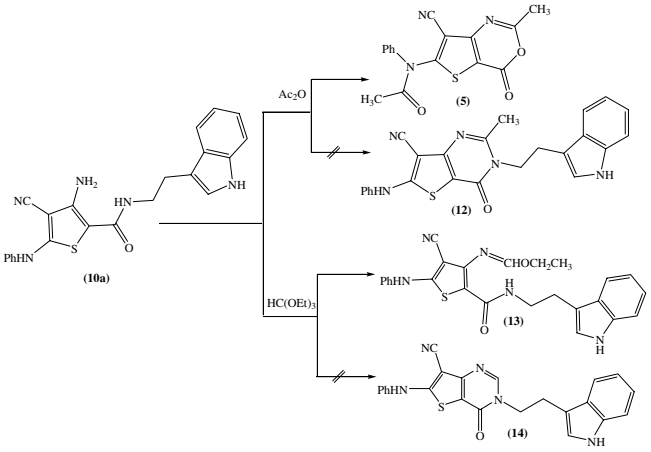
Fig. 3

Support for this sequence of reactions comes from the fact that compound **2** reacted with cyclohexylamine at room temperature, giving intermediate (**11**) which could be isolated and then converted into 2-cyclohexyl-amidothiophene derivative (**10c**) on heating in the same base. It is believed that the transformation of 2-ylidene-4-thiazolidenone (**2**) into amino thiophene esters and aminothiophene amides is a novel reaction.

Refluxing the carboxamide (**10a**) in acetic anhydride gave the unexpected thieno[3,2-d]oxazinone (**5**) instead of the expected thieno[3,2-d]-pyrimidinone derivative (**12**). This type of reaction was reported by Farhat *et al.* [23] and latter by Ahmed [24], where the carboxamide (**10**, R=H) was similarly transformed into the same oxazinone (**5**). The attempt to cyclize the amide (**10a**), by refluxing with triethylorthoformate gave only the open chain compound **13** instead of the desired thienopyrimidenone derivative (**14**) (**Scheme-IV**).

The formation of the oxazinone (**5**) involves acylation of NH_2 and NH-Ph groups, followed by enolization of carbonyl group and nucleophilic attack of the enol OH on the carbonyl amide and then loss of a tryptamine molecule (Fig. 4).

The structures of all synthesized compounds were elucidated from their spectral data shown in Table-1.



Scheme-IV

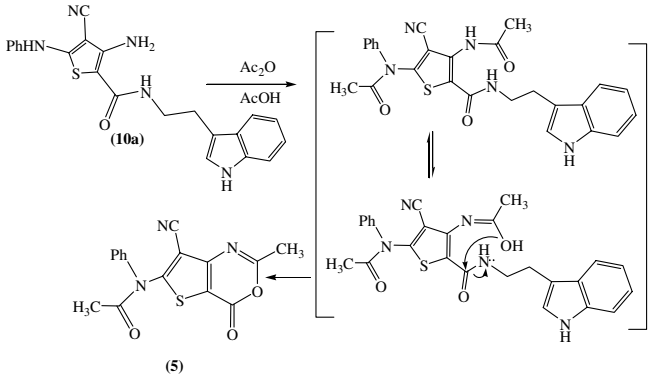


Fig. 4

TABLE-1
PHYSICAL AND SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

Compd. No.	m.p. (°C), yield (%)	IR (ν_{max}, cm^{-1})	^1H NMR (ppm)	^{13}C NMR (ppm)
3a	244-246, (80)	3441-3338 (NH_2, NH), 2206 (CN), 1661 (CO_{ester})	10.30 (s, 1H, NH), 7.50-7.15 (m, 5H, Ph), 6.80 (br, 2H, NH_2), 3.65 (s, 3H, CH_3)	163.10 (CO), 162.76, 154.14, 140.06, 129.42, 125.00, 121.22, 81.60, 80.71, (Ar-C), 113.67 (CN), 50.69 (CH_3)
3b	212-214, (82)	3420-3325 (NH_2), 3270 (NH), 2206 (CN), 1654 (CO_{ester})	10.30 (s, 1H, NH), 7.46-7.15 (m, 5H, Ph), 6.75 (br, 2H, NH_2), 4.13 (q, 2H, CH_2), 1.18 (t, 3H, CH_3)	162.81 (CO), 162.81, 154.16, 140.16, 129.45, 125.02, 120.20, 81.78, 80.70, (Ar-C), 113.73 (CN), 59.20 (CH_2), 14.42 (CH_3)
3c	202-204, (69)	3420, 3325 (NH_2), 3277 (NH), 2206 (CN), 1654 (CO_{ester})	10.00 (s, 1H, NH), 7.45-7.30 (m, 5H, Ph), 6.73 (br, 2H, NH_2), 4.98 (heptet, 1H, CH), 1.20 (d, 6H, $2CH_3$)	162.85 (CO), 162.45, 154.30, 140.12, 129.45, 125.07, 121.43, 81.70, 81.00 (Ar-C), 113.69 (CN), 66.50 (CH), 22.00 ($2CH_3$)
3d	124-126, (57)	3420-3325 (NH_2), 3277 (NH) 2200 (CN) 1654 (CO_{ester})	10.30 (s, 1H, NH), 7.507.15 (m, 5H, Ph), 6.75 (br, 2H, NH_2), 4.10 (t, 2H, CH_2), 1.50 (pentet, 2H, CH_2), 1.30 (six., 2H, CH_2), 0.85 (q, 3H, CH_3)	162.83 (CO), 162.80, 154.16, 140.10, 129.44, 125.04, 121.34, 81.72, 80.71, (Ar-C), 113.68 (CN), 59.18, (CH_2), 30.42 (CH_2), 18.58 (CH_2), 13.48 (CH_3)
5	294-296 Lit. [17], 296-298, (59)	2207 (CN), 1758 (CO), 1690 (CO)	7.73-7.58 (m, 5H, Ph), 4.40 (s, 3H, CH_3), 2.05 (s, 3H, CH_3)	171.30 (CO, oxazinone), 166.16 (CON), 157.06, 154.54, 154.39, 138.53, 131.26, 130.25, 128.22, 107.18, 91.40, , (Ar-C), 109.39 (CN), 23.319 (CH_3), 20.93 (CH_3)
6	153-155, (67)	3434 (NH), 3344 (NH), 3257 (NH), 2221 (CN), 1719 br., (3CON, 1684 (CO_{ester})	7.727.59 (m, 5H, Ph), 4.30 (q, 2H, OCH_2), 2.22 (s, 6H, $2COCH_3$), 2.09 (s, 3H, $COCH_3$), 1.30 (t, 3H, CH_3)	171.76 (CO), 171.66 (CO), 160.86 (CO), 153.39 (CO), 141.28, 139.93, 139.92, 132.07, 131.39, 130.76, 120.80, 98.27 (Ar-C), 110.50 (CN), 62.33 (OCH_2), 25.95, 25.57, 23.48, 14.41 (4 CH_3)
7	258-260, (72)	3250, br. (2NH), 2220 (CN), 1690br. ($2C=O_{ester}$)	10.39 (br, 2H, 2NH), 7.51-7.16 (m, 5H, Ph), 4.40 (s, 2H, CH_2Cl), 4.19 (q, $2HOCH_2$), 1.23 (t, 3H, CH_3)	164.74 (CO), 161.69 (CO), 160.18, 140.18, 129.65, 125.22, 121.11, 112.50, 102.64, 88.64 (Ar-C), 113.15 (CN), 60.69 (OCH_2), 42.38 (CH_2Cl), 14.03 (CH_3)
9	163-165, (98)	3255 (NH), 2220 (CN), 2132 (N_3), 1695 (CO)	7.70 (br, 1H, NH), 7.50-7.20 (m, 5H, Ph), 4.31 (q, 2H, OCH_2), 1.34 (t, 3H (CH_3)	161.74 (CO), 160.60, 141.89, 138.66, 130.03, 126.04, 120.87, 101.40, 86.40 (Ar-C), 112.87 (CN), 61.41 (OCH_2), 14.38 (CH_3)
10a	234-237, (43)	3467 (NH), 3342, 3266 (NH_2), 3204 (NH), 3209 (NH), 2213 (CN), 1606 (CO)	10.80 (s, 1H pyrroleNH), 10.05 (br, 1H, NH), 7.55 (1H, pyrrole H), 7.45-7.0 (m, 5H, Ph), 6.95 (s, 1H, CONH), 6.75 (br, 2H, NH_2), 3.40 (t, 2H, NCH_2), 2.85 (t, 2H, CH_2)	163.70 (CO), 114.04 (CN), 159.56-82.22 (Ar-C), 39.95 (NCH_2), 25.50 (CH_2)
10b	143-145, (68)	3414, 3300 (NH_2), 3210 (NH), 2200 (CN), 1658 (CO).	9.05 (br, 1H, NH), 7.50-7.10 (m, 5H, Ph), 6.23 (br, 2H, NH_2), 3.52 (t, 4H, $2CH_2$), 1.63 (pentet, 4H, ($2CH_2$), 1.55 (pentet, 2H, CH_2).	166.68 (CO), 160.56, 152.70, 141.52, 130.41, 125.42, 121.28, 88.02, 84.03 (Ar-C), 114.10 (CN), 47.29, 26.90, 25.35 (piperidyl-C).
10c	190-192, (91)	3446, 3394 (NH_2), 3341 (NH), 3280 (NH), 2206 (CN).	9.01 (br, 1H, NH), 7.50-7.15 (m, 5H, Ph), 6.50 (br, 2H, NH_2), 6.25 (1H, CONH), 3.80 (m, 1H, CH), 2.00-0.85 (m, 10H, ($5CH_{2,}$ cyclohexyl).	164.29 (CO), 114.05 (CN), 160.22, 152.52, 141.68, 130.42, 125.60, 121.50, 87.83, 84.18, (Ar-C), 49.11, 33.89, 26.40, 26.14 (cyclohexyl-C).

11	181-183, (58)	3294 (2NH), 2200 (CN), 1622 (C=O).	12.20 (s, 1H, CONH), 8.05 (br, 1H, NH), 7.47-7.22 (m, 5H, Ph), 3.95 (s, 2H, CH_2), 3.75 (pentet, 1H, CH), 1.95-1.11 ($5CH_2$- cyclohexyl).	170.82 (CO), 169.65 (C=) 139.35 (C=) 130.06, 127.37, 124.34 (Ar-C), 124.00 (CN), 50.25 (CH_2-S), 52.73 (C-N), 36.19 (C_3), 32.97, 26.11, 25.00 (cyclohexyl-C).
13	212-215, (54)	3434 (NH), 3344 (NH), 3257 (NH), 2221 (CN), 1614 ($C=O_{amide}$)	10.85 (br, 1H, CONH), 10.20 (br, 1H, NH-indole), 6.95 (s, 1H, CH indole), 8.26 (s, 1H, N=CH), 7.60-6.90 (m, 9H, ArH), 3.80 (t, 2H, CH_2), 3.60 (t, 2H, CH_2), 2.90 (t, CH_3)	160.60 (CO), 160.49 (N=CH), 143.29, 140.39, 136.30, 129.59, 128.28, 127.02, 126.94, 124.45, 122.76, 121.50, 120.35, 120.35, 119.95, 118.23, 111.36, 107.89, 85.39 (Ar-C), 114.53 (CN), 62.79 (OCH_2), 39.74 (N-CH_2), 25.34 (CH_2), 13.61 (CH_3)

Conclusion

In this article, the synthesis and characterization of some new 3-aminothiophene carboxylates and 3-aminothiophene carboxamides as well as postulated mechanisms of reactions are discussed.

REFERENCES

1. M. Yokoyama, H. Togo and S. Kondo, *Sulfur Reports*, **10**, 23 (1990).
2. R.K. Dieter, *Tetrahedron*, **42**, 3029 (1986).
3. H. Junjappa, H. Ila and C.V. Asokan, *Tetrahedron*, **46**, 5423 (1990).
4. M.F. Farhat, A.M.M. El-Saghier, M.A. Makhlouf, K.M. Kreddan and A.B. Elmezoughi, *J. Sulfur Chem.*, **28**, 563 (2007).
5. F.E.M. El-Baih, H.A.S. Al-Blowy and H.M. Al-Hazimi, *Molecules*, **11**, 498 (2006).
6. R.V. Chambhare, B.G. Khadse, A.S. Bobde and R.H. Bahekar, *Eur. J. Med. Chem.*, **38**, 89 (2003).
7. N. Hosseinzadeh, M. Hasani, A. Foroumadi, H. Nadri, S. Emami, N. Samadi, M.A. Faramarzi, P. Saniee, F. Siavoshi, N. Abadian, Y. Mahmoudjanlou, A. Sakhteman, A. Moradi and A. Shafiee, *Med. Chem. Res.*, **22**, 2293 (2013).
8. G.M.K.N. Jayaveera, L.K.R. Nath, B.S. Kumar and P.N. Raddy, *J. Chem. Pharm. Res.*, **4**, 2928 (2012).
9. (a) L.D. Jennings, S.L. Kincaid, Y.D. Wang, G. Krishnamurthy, C.F. Beyer, J.P. McGinnis, M. Miranda, C.M. Discafani and S.K. Rabindran, *Bioorg. Med. Chem. Lett.*, **15**, 4731 (2005); (b) A. Deep, P. Kumar, B. Narasimhan, K. Ramasamy, V. Mani, R. Mishra and A. Majeed, *Curr. Top. Med. Chem.*, **15**, 990 (2015).
10. M.D. Meyer, R.J. Altenbach, F.Z. Basha, W.A. Carroll, S. Condon, S.W. Elmore, J.F. Kerwin, K.B. Sippy, K. Tietje, M.D. Wendt, A.A. Hancock, M.E. Brune, S.A. Buckner and I. Drizin, *J. Med. Chem.*, **43**, 1586 (2000).
11. A. Panico, V. Cardile, A. Santagati and B. Gentile, *IL Farmaco*, **56**, 959 (2001).
12. M.F. Farhat, M.A. Makhlouf, A.M. El-Saghier, A.B.A. Mezoughi, S.M. Awhida and A.A.M. El-Mehdi, *Arabian J. Chem.*, **4**, 307 (2011).
13. H. Behbehani and H.M. Ibrahim, *Molecules*, **17**, 6362 (2012).
14. R.I. Meltzer, A.D. Lewis and J.A. King, *J. Am. Chem. Soc*., **77**, 4062 (1955).
15. M. Bercot-Vatteroni, *Ann. Chim*., **7**, 303 (1962).
16. S. Kakimoto, J. Seydel and E. Wempe, *Tuberk-Forschunginst. Borstel, Jahresber*, **5**, 240 (1961).
17. G. Pappalardo, B. Tornetta, P. Condorelli and A. Bernardini, *Farmaco Ed Sci*, **22**, 808 (1967).
18. R.V. Davies, Eur. Pat. Appl. EP 269,295 (1988).
19. F. Russo, A. Santagati, M. Santagati, A. Caruso, M.G. Leone, A. Felice and M. Amico-Roxas, *Eur. J. Med. Chem.*, **24**, 91 (1989).
20. C.J. Shishoo, U.S. Pathak, K.S. Jain, I.T. Devani and M.T. Chhabria, *Indian J. Chem.*, **33B**, 436 (1994).
21. K. Gewald, H. Schaefer and P. Bellmann, German (E) Patent 263,055 (1988).
22. G. Sommen, A. Comel and G. Kirsch, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), [A0019]; http://www.mdpi.org/ecsoc-5.htm, 1-30 September, 2001
23. M.F. Farhat, G.A. Ahmed, A.M.M. El-Saghier, M.A. Makhlouf, W.A. Ehwellat, K.M. Kreddan and A.B. Elmezoughi, In Proceedings of 10th IBN SINA International Conference on Pure and Applied Heterocyclic Chemistry, Luxor, Egypt, Feb. 17-20 (2007).
24. G.A. Ahmed, *Phosphorus Sulfur Silicon Rel. Elem.*, **183**, 74 (2007).