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Utility of Cyanoacetohydrazide in Synthesis of Some New Sulphur Containing Heterocyclic Compounds

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Abstract

The reaction of 2-cyano-N'-(pyridin-4-ylmethylene) acetohydrazide (1) with phenyl isothiocyanate gave thiocarbamoyl derivative 3 which reacted with α-halocarbonyl compounds in N,N-dimethylformamide in the presence of triethylamine to afford thiazoles 6, 9, 11, 13, 15 and thiophene 8 derivatives, while when the same reaction was stirred in N,N-dimethylformamide, it only afforded the acyclic compounds 4, 7, 10, 12 and 14 which when refluxed in N,N-dimethylformamide in the presence of triethylamine, they gave the corresponding above thiazole and thiophene derivatives. The newly synthesized compounds were characterized by analytical and spectral data.

Introduction

Aryl isothiocyanates are versatile reagents that have been used as synthetic intermediates to prepare biologically active heterocyclic compounds (Mukerjee & Ashare, 1991). The diversity of biological and physiological activities of several organic sulfur heterocycles may be attributed to the presence of the N=C=S fragment which is a characteristic of thiazoles, thiazolines and thiazolidines (Ead, et al.; 1997). These are known to exhibit pesticidal (Misra & singh, 1971), anticonvulsant (Rao & Singh, 1973), nematocidal (Parmer & Chaudhari, 1972), herbicidal (Pavlenko & Moshchitiskii, 1967), antiviral (Tisler, et al.; 1971), fungicidal (Singh, 1975), bactericidal (Chaudhari & Pujari, 1972 and Dhal, et al.; 1975), antiprotozal (Mallick, 1971) and hypoglycemic activity (Burton, 1970). They also act as chemotherapeutic agents. This encouraged us to design a specific program aiming at the synthesis of several new derivatives of these ring systems. The present work outlines the chemistry of thiocarbamoyl derivatives, not all, but the most important in the synthesis of heterocyclic compounds. The vast majority of thiocarbamoyl derivatives has been the subject of many studies for the preparation of potentially biologically active compounds and for some industrial uses (Fadda, et al. 1999, Fadda, et al.; 2002 and Fadda, et al.; 2003). In this work, the utility of the title compounds in heterocyclic synthesis has been studied. We have been particularly interested to study if reactions of such thiocarbamoyl might be extended to include a more general synthesis of other classes of organic compounds and its utility as a synthetic intermediate for the synthesis of new

heterocyclic compounds. The present work reports on the synthesis of several new thiazole and thiophene derivatives by the reaction of thiocarbamoyl of type **3** with compounds containing an active methylene group in the presence of a base. Reactions of this type have not been reported previously, but were found to give products in excellent yields under very mild conditions. Moreover, in continuation of the previously reported work (Bondock & Fadda, 2011 and Bondock, et al.; 2010), the resulting thiazole and thiophene derivatives have latent functional substituents which have potential for further chemical transformations and new routes for the preparation of substituted thiazole and thiophene derivatives. Now, we have extended our synthetic program to the synthesis of otherwise inaccessible heterocyclic ring system utilizing phenyl isothiocyanate as a key starting material. It is known that a great variety of reactants bearing the N=C=S fragment undergoes cyclization on reaction with α-halocarbonyl compounds to afford thiophenes (Fadda, et al.; 2010, El-Shafei, et al. 2009, Fadda, et al.; 2008, Fadda, et al.; 2012 and Fadda, et al.; 2009), thiazoles and 2,3- dihydrothiazoles (Rao & Singh, 1973) which have been shown to exhibit antiprotozoal (Mallick, 1971) and fungicidal properties (Singh, 1975).

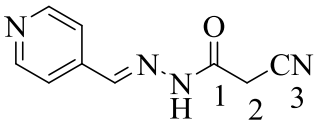
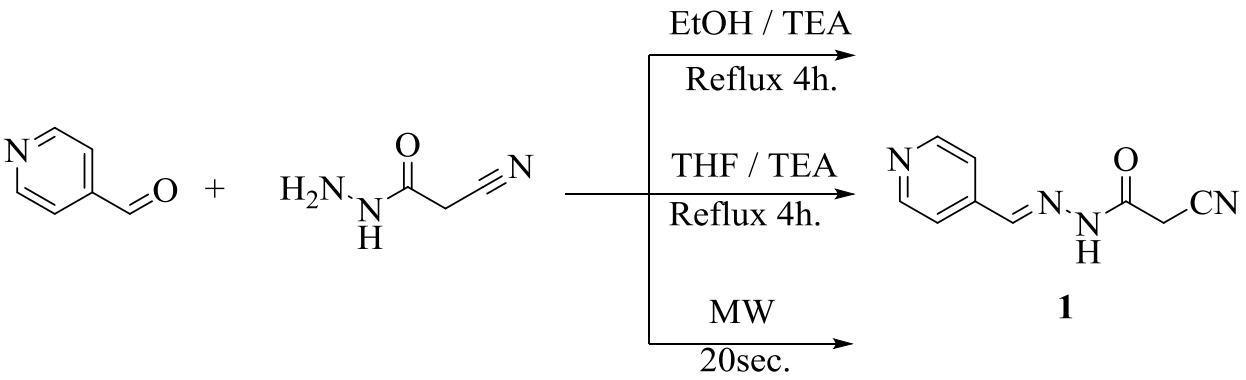


Figure 1

Results and Discussion

Synthesis of the new starting compound, 2-cyano-N'-(pyridin-4-ylmethylene) acetohydrazide (**1**) was carried out in several ways. It was prepared via treatment of 4-formyl pyridine with 2-cyanoacetyl hydrazide in tetrahydrofuran and / or by refluxing in absolute ethanol containing a catalytic amount of triethylamine or via microwave irradiation under free a solvent and catalyst conditions. The reaction which occurred in the presence of ethanol, afforded the product in lower yield than THF. Using microwave irradiation afforded the product in higher yield and shorter reaction time as shown in (**scheme 1**).



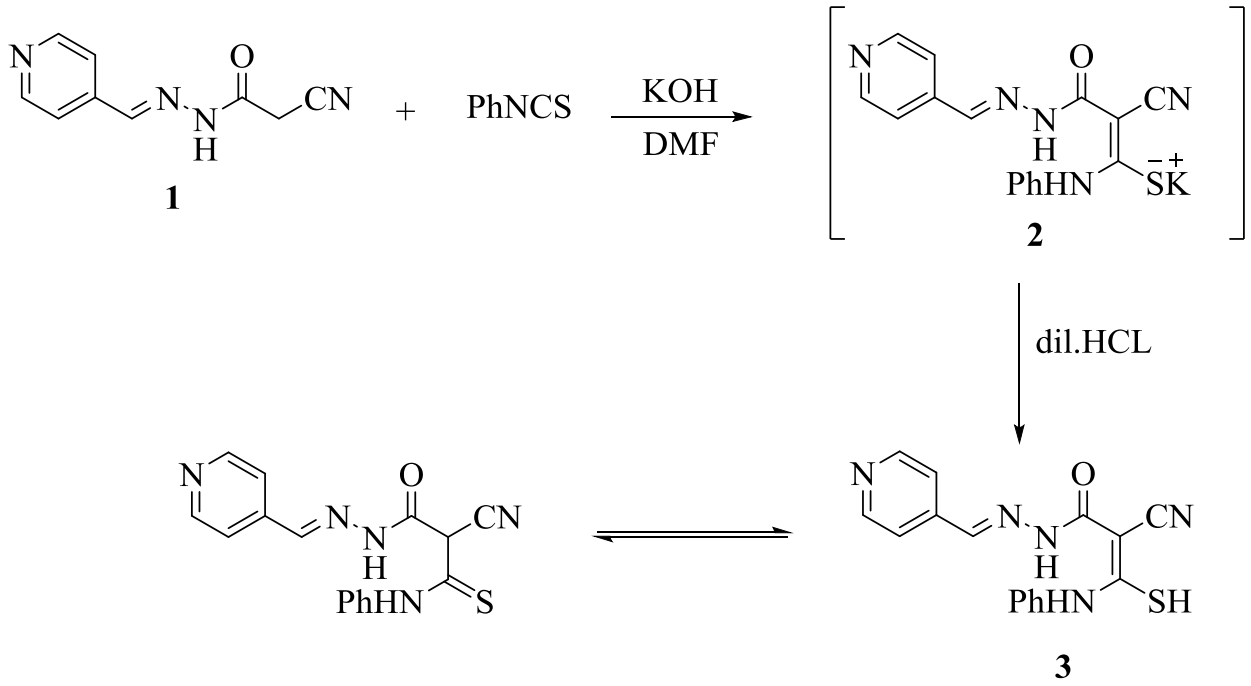
Scheme 1

The structure **1** was established on the basis of spectral data and an elemental analysis. The IR spectrum revealed absorption bands at υ 3235 cm^{-1} for an NH group, a sharp band at 2259 cm^{-1} for a cyano function and a strong band at 1704 cm^{1} for a carbonyl group. Its ^{1}H NMR spectrum (DMSO-d_6) revealed the presence of three singlet signals at δ 4.26, 8.31 11.86 ppm assignable to the methylene protons, CH=N proton, and NH proton , respectively, and two doublet signals at δ 7.96 due to C_3-H and C_5-H pyridine and at δ 8.64 ppm due to C_2-H and C_6-H pyridine. Moreover, mass spectrum showed a molecular ion peak at *m/z* =188 (M+, 76 %) corresponding to a molecular formula ($C_9H_8N_4O$).

In this work, we describe generally applicable extension of this synthetic approach, which was first reported by Hantzsch and Weber (Hantzsch & Weber, 1887). Thus, the base catalyzed reaction of the

acidic methylene compound 1 with phenyl isothiocyanate in dry *N,N*-dimethylformamide at room temperature in a basic medium led to the formation of the non-isolable intermediate **2** which gave thiocarbamoyl derivative **3** upon treatment with dilute HCl (**Scheme 2**).

The structure **3** was established from its corrected spectral data and elemental analysis. Thus, the IR spectrum showed absorption bands at υ 3266, 3199, 2207 and 1655 cm^{-1} corresponding to two NH, CN, C=O respectively. Also, ^{1}H-NMR spectrum (DMSO-d_6) revealed singlet signal at δ 1.9 ppm due to SH proton besides a multiplet at δ 6.90-8.10 ppm for aromatic protons, doublet signal at δ 7.69 ppm for C_2-H, C_6-H pyridine protons and two singlet signals at δ 10.77 and 12.11 ppm for two NH. The mass spectrum of compound **3** showed the molecular ion peak at *m/z*= 322 (M^+-1, 76 %) which is in agreement with the molecular formula $C_{16}H_{13}N_5OS$.



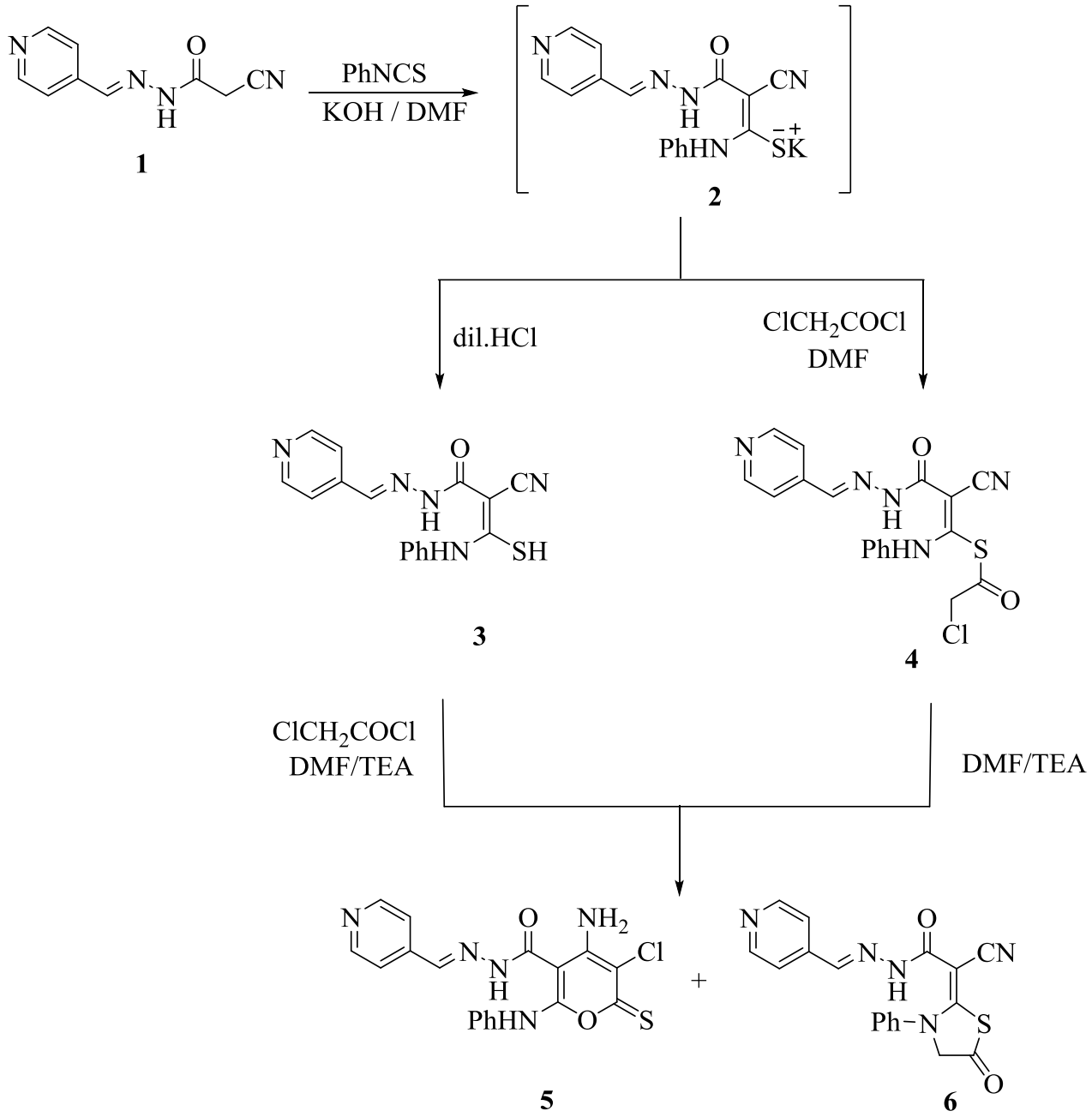
1 **2** **3**

Scheme 2

Compound **3** also undergoes cyclization upon the reaction with chloroacetyl chloride in *N,N* dimethylformamide in the presence of a catalytic amount of triethylamine to yield a mixture of thiopyran **5** and thiazole **6** derivatives which could be separated by fractional crystallization. On the other hand, it was found that stirring of compound **2** with chloroacetyl chloride in *N,N*dimethylformamide at room temperature produced acyclic intermediate **4** by HCl elimination (**Scheme 3**).

Compound **4** when subjected to reflux in DMF containing a catalytic amount of triethylamine, it afforded a mixture of compounds that separated by fractional crystallization to give products identical in all respects (mp, IR, mass) to **5** and **6** (**Scheme 3**).

The structure of compound **4** was ascertained by spectroscopic data and an elemental analysis. The IR spectrum showed absorption bands at υ 3298, 3205 cm^{-1} for two NH, at 2206 cm^{-1} for a CN group, at 1711, 1654 cm^{-1} for two carbonyl groups. Its ^{1}H NMR spectrum (DMSO-d_6) showed four singlet signals at δ 4.32, 8.46, 10.68 and 11.95 ppm due to CH_2 CH=N and 2 NH protons, respectively, multiplet signals at δ 6.9-8.0 ppm for aromatic protons and doublet signal which were observed at δ 8.67 ppm for C_2, C_6 –H pyridine protons. Its mass spectrum showed a molecular ion peak at *m/z* = 400 (M^++1, 10 %) corresponding to a molecular formula ($C_{18}H_{14}ClN_5O_2S$).



Scheme 3

The IR spectrum of compound **5** showed absorption bands at υ 3402, 3384, 3217, 3186, 1730 and 1655 cm^{-1}corresponding to NH_2, 2 NH, and 2 CO. Its ^1H NMR spectrum (DMSO-d_6) showed four singlet signals at δ 4.18, 8.39, 10.79 and 11.99 ppm for NH_2 , CH=N, two NH protons, in addition to a multiplet signals at δ 7.0-8.0 ppm for aromatic protons, and doublet which were observed at δ 8.67 ppm for C_2 and C_6 pyridine protons. The mass spectrum showed a molecular ion peak at *m/z* = 400 (M^++1, 9%) corresponding to a molecular formula ($C_{18}H_{14}ClN_5O_2S$).

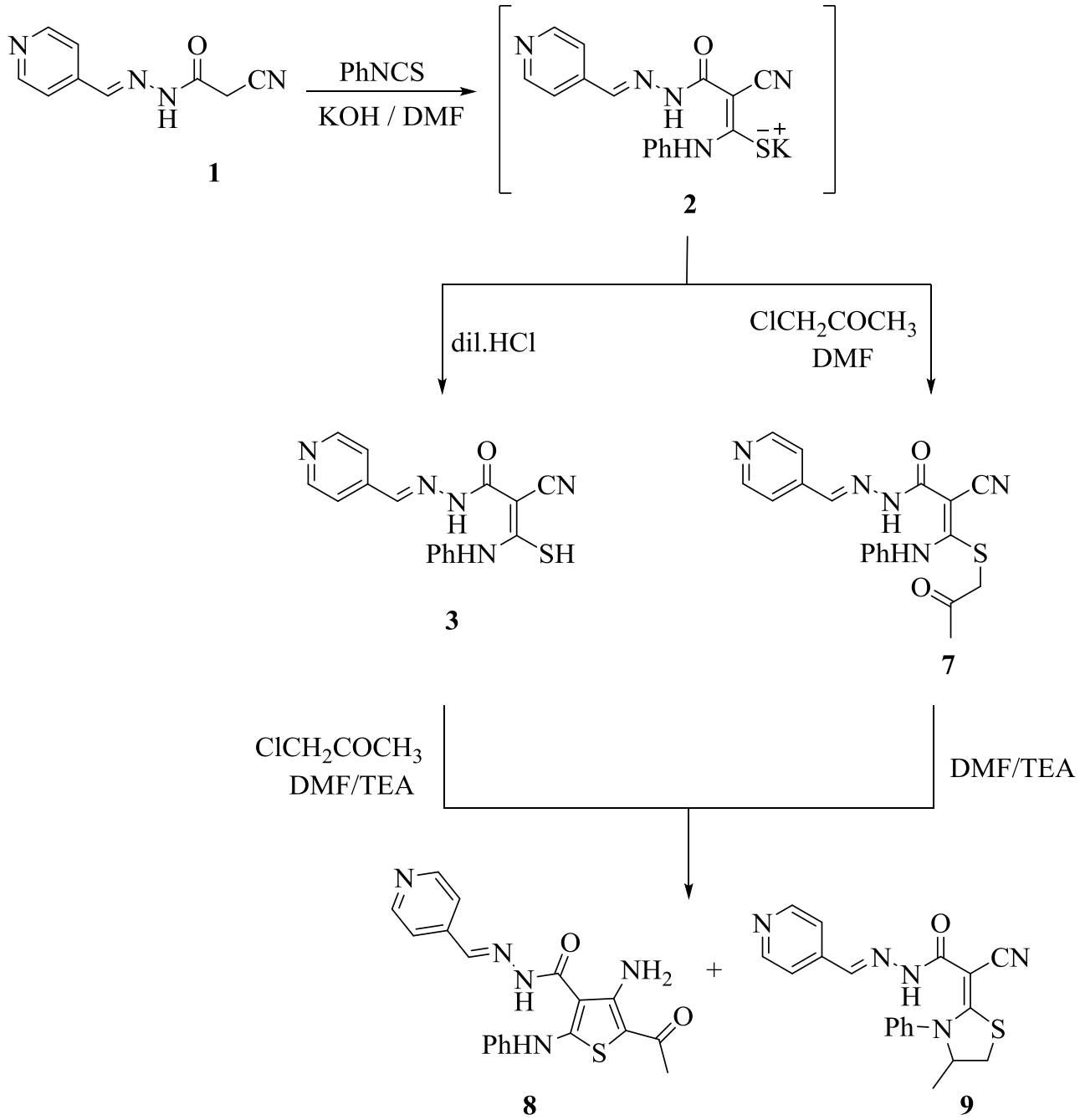
The IR spectrum of **6** displayed absorption bands at υ at 3216 cm^{-1} for NH, 2207 cm^{-1} for CN and 1741, 1641 cm^{-1} for 2 CO. Its ^1H NMR spectrum (DMSO-d_6) showed three singlet signals at δ 4.66, 8.49 and 12.11 ppm corresponding to CH_2, CH=N and NH protons, respectively, multiplet signals at δ 6.90-8.00 ppm for aromatic protons, doublet

signal which were observed at δ 8.62 ppm for C_2 and C_6 pyridine protons. The mass spectrum showed a molecular ion peak at *m/z* = 365 (M^++2, 3 %) corresponding to a molecular formula ($C_{18}H_{13}N_5O_2S$).

Stirring of compound **2** with chloroacetone in a mixture of ethanol and N,N-dimethylformamide at room temperature afforded the acyclic intermediate **7** by NaCl elimination. The acyclic intermediate **7** was inferred from its spectral data and elemental analysis. Thus, the IR spectrum showed absorption bands at υ 3238, 3216, 2200, 1773, 1649 and 1597 cm^{-1} corresponding to 2NH, CN, 2C=O and C=C. The mass spectrum of **7** showed the molecular ion peak at *m/z* =378 (M^+-1, 25%) which is in agreement with the molecular formula $C_{19}H_{17}N_5O_2S$. ^{1}H-NMR spectrum (DMSO-d_6) showed three singlet signals at δ 2.33, 4.11 and 8.39 ppm corresponding to CH_3, CH_2-S and CH=N protons, respectively, multiplet signals at δ 6.90-8.00 ppm for aromatic protons, doublet signal at δ 8.56 ppm for pyridine protons, and two singlet signals at δ 10.78, 12.09 ppm for 2 NH protons.

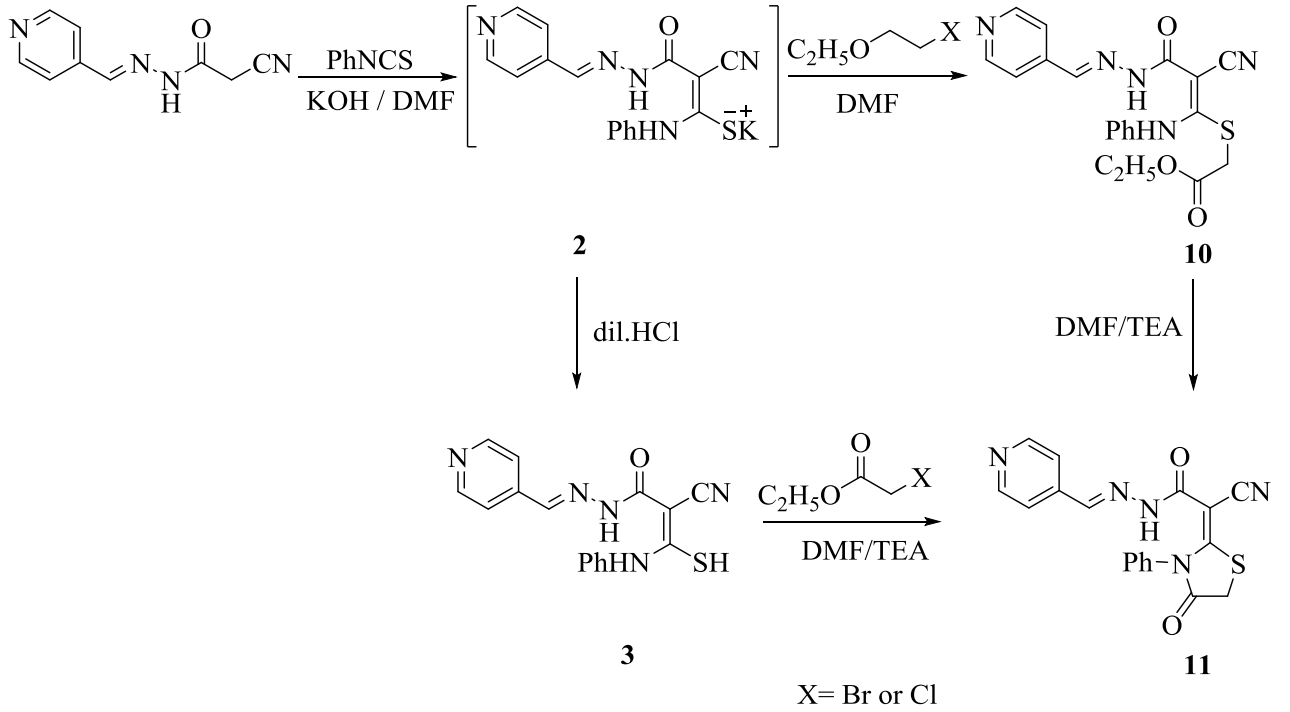
Refluxing of compound 7 in N,N-dimethylformamide in the presence of a catalytic amount of triethylamine gave a mixture of the thiophene **8** and thiazole **9** derivatives (**Scheme 4).** These structures were confirmed by their alternative synthesis. Thus, refluxing of compound **3** with chloroacetone in N,N-dimethylformamide (2:1) in the presence of a catalytic amount of triethylamine afforded the thiophene **8** and thiazole **9** derivatives in a reasonably good yield. The structures **8** and **9** were established based on their IR spectrum and spectral data.

The structure **8** was inferred from its spectral data and elemental analysis. Thus, the IR spectrum showed absorption bands at υ 3447, 3422 cm^{-1} corresponding to NH_2, at υ 3264, 3232 cm^{-1} corresponding to 2NH and at υ 1699, 1653 cm^{-1} corresponding to 2CO. The mass spectrum of **8** showed the molecular ion peak at *m/z* = 379 (M^+, 19 %) which is in agreement with the molecular formula $C_{19}H_{17}N_5O_2S$. ^{1}H-NMR spectrum (DMSO-d_6) showed five singlet signals at δ 2.99, 5.45, 8,34, 9.19 and 10.41 ppm corresponding to CH_3, NH_2, CH=N, NH-Ph and NH protons, respectively, multiplet signals at δ 7.00-8.00 ppm for aromatic protons, doublet doublet signals at δ 8.71 ppm for C_2 and C_6 –H pyridine protons.



Scheme 4

The structure **9** was inferred from its spectral data and elemental analysis. Thus, the IR spectrum showed absorption bands at υ 3241, 2206, 1673 and 1595 cm^{-1} corresponding to NH, CN, CO and C=C respectively. The mass spectrum of **9** showed the molecular ion peak at *m/z* = 363 (M^++2, 19 %) which is in agreement with the molecular formula $C_{19}H_{17}N_5OS$. ^{1}H-NMR spectrum (DMSO-d_6) showed five singlet signals at δ 2.17, 5.33, 8.11, and 10.83 ppm corresponding to CH_3, C_5-H thiazolidine, CH=N, and NH protons, respectively, multiplet signals at δ 7.00-8.00 ppm for aromatic protons and doublet doublet signals at δ 8.73 ppm for C_2-H and C_6-H pyridine protons.

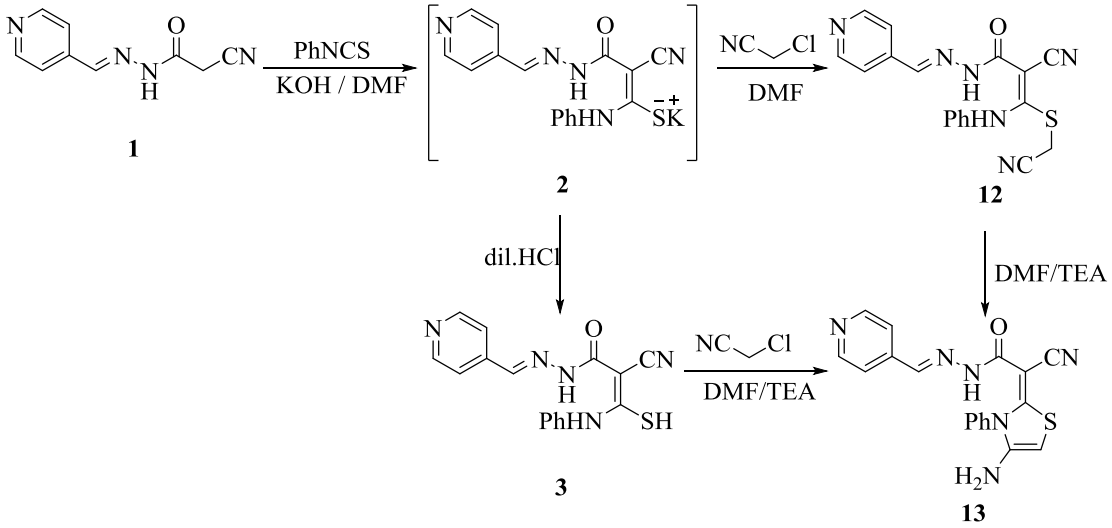


Scheme 5

When compound **3** was treated with ethyl chloroacetate or with ethyl bromoacetate in N, N-dimethylformamide
with few drops of triethylamine, it afforded a product **11** that was analyzed for $C_{20}H_{19}N_5O_3S$. While the reaction of intermediate **2** with ethyl chloroacetate or with ethyl bromoacetate in *N*, N-dimethylformamide led to the formation of compound **10 (Scheme 5)**. The acyclic structure **10** was confirmed by its spectral data and an elemental analysis. The IR spectrum showed bands at υ 3331, 3224, 2202, 1710, 1669 and 1596 cm^{-1} related to 2NH, CN, 2CO and C=C function groups, respectively. Moreover, its mass spectrum showed a molecular ion peak at *m/z* = 408 (M^+-1, 6 %) corresponding to a molecular formula ($C_{20}H_{19}N_5O_3S$). ^{1}H-NMR spectrum (DMSO-d_6) of compound **10** revealed triplet signal at δ 1.11 ppm corresponding to CH_3 protons, a singlet signal at δ 4.03 ppm corresponding to CH_2CO protons, a quartet signal at δ 4.25 ppm due to CH_2O, a multiplet at δ 6.90-8.00 ppm due to aromatic protons, doublet signal at δ 8.59 ppm due to C_2-H and C_6-H pyridine protons, a singlet signal at δ 8.51 ppm corresponding to CH=N protons and two singlet signals at δ 10.59 and 12.10 ppm for 2 NH protons.

Refluxing of **10** in N,N- dimethylformamide and a catalytic amount of triethylamine afforded the corresponding thiazole derivative **11 (Scheme 5)**. Structure **11** has been confirmed on the basis of elemental and spectral data, e.g. the IR spectrum exhibits bands at υ 3338 cm^{-1} (NH), 2201 cm^{-1} (CN), 1700, 1656 (2C=O) and 1596 cm^{-1} (C=C). The mass spectrum showed a molecular ion peak at *m/z* =360 (M^+-3, 6 %) corresponding to a molecular formula ($C_{18}H_{13}N_5O_2S$). The ^{1}H-NMR spectrum (DMSO-d_6) of **11** showed three singlet signals at δ 4.23, 8.49 and 12.12 ppm corresponding to CH_2, CH=N and NH protons, respectively, multiplet signals at δ 6.90-8.00 ppm due to aromatic protons and doublet signal at δ 8.69 ppm due to pyridine protons.

Similarly, when intermediate sodium salt **2** is stirred with chloroacetonitrile in *N*,*N*dimethyl- formamide at room temperature, the corresponding acyclic intermediate **12** is exclusively isolated in good yield.



Scheme 6

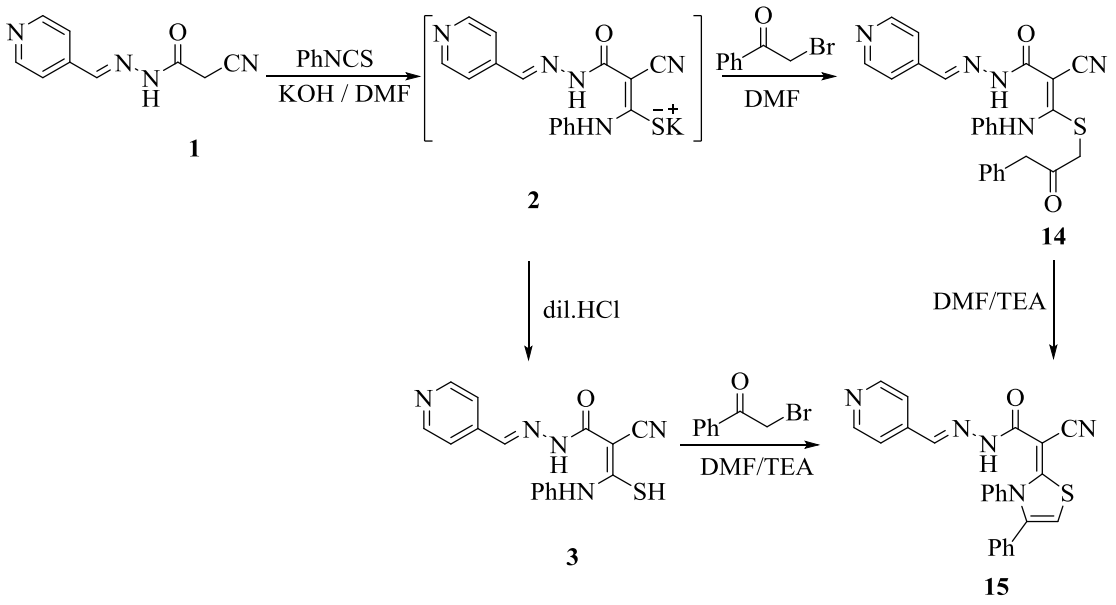
The structure of **12** has been confirmed on the basis of elemental and spectral data. The IR spectrum that showed bands at υ 3243, 3194 cm^{-1} (two NH groups), 2195, 2200 cm^{-1} (two CN), 1674 (C=O). Its mass spectrum showed a molecular ion peak at *m/z*= 363 (M^++1, 97%) corresponding to a molecular formula ($C_{18}H_{14}N_6OS$). Moreover, ^{1}H-NMR spectrum (DMSO-d_6) of compound **12** showed four singlet signals at δ 4.23 ,8.47, 10.88 and 12.12 ppm corresponding to CH_2, CH=N and 2NH protons, respectively, besides a multiplet at δ 6.90-8.00 ppm for aromatic protons and doublet signal at δ 8.79 for C_2-H and C_6-H pyridine protons (**Scheme 6**).

Furthermore, refluxing of the acyclic intermediate 12 in N,N-dimethylformamide containing a catalytic amount of triethylamine afforded the thiazole derivative **13**. The thiazole derivative **13** was established based on its IR spectrum which showed bands at υ 3431, 3347, 3190, 2202 and 1659 cm^{-1} related to NH_2, NH, CN and CO functions. Its mass spectrum showed a molecular ion peak at m/z = 363 (M^++1, 23 %) corresponding to a molecular formula ($C_{18}H_{14}N_6OS$). Moreover, ^{1}H-NMR spectrum (DMSO-d_6) revealed four singlet signals at δ 5.29, 5.87, 8.28 and 11.92 ppm due to NH_2, CH, CH=N and NH protons, respectively, besides a multiplet at δ 6.90-8.00 ppm for aromatic protons and doublet signal at δ 8.56 ppm for C_2-H and C_6-H pyridine protons (**Scheme 6**). On the other hand, it has been found that compound **13** was directly formed by refluxing compound **3** with chloroacetonitrile in *N,N-dimethylformamide* and in the presence of catalytic amount of triethylamine (**Scheme 6**).

Compound **3** also underwent cyclization upon the reaction with phenacyl bromide in *N,N*dimethylformamide in the presence of a catalytic amount of triethylamine and yielded product **15**, which was analyzed correctly for $C_{24}H_{19}N_5O_2S$. The structure of compound **15** was confirmed by its spectral data and elemental analysis. IR spectrum showed absorption frequencies at υ 3428, 2212, 1651 and 1502 cm^{-1} corresponding to NH, CN, CO and C=C groups, respectively. Moreover, its mass spectrum showed a molecular ion peak at m/z = 424 (M^++1, 10 %) corresponding to a molecular formula ($C_{24}H_{17}N_5OS$) (**Scheme 7**). The^{1}H-NMR spectrum (DMSO-d_6) revealed three singlet signals at δ 6.87, 8.26 and 12.22 ppm attributable to CH, CH=N and NH protons besides a multiplet at δ 7.25-8.01 ppm for aromatic protons and doublet signals at δ 8.59 ppm for C_2-H and C_6-H pyridine protons (**Scheme 7**).

The structure **15** was further confirmed by an alternative synthesis. Thus, it was found that stirring of **2** with phenacyl bromide in *N,N*dimethylformamide at room temperature afforded the acyclic intermediate **14** by HBr elimination. Structure **14** was suggested for the

reaction product on the basis of both elemental and spectral analyses. IR spectrum showed absorption frequencies at υ 3230, 3195, 2211, 1693, 1659 and 1502 cm^{-1} corresponding to 2NH, CN, 2CO and C=C groups, respectively.



Scheme 7

The ^{1}H-NMR spectrum (DMSO-d_6) revealed four singlet signals at δ 4.87, 8.39, 10.56 and 12.22 ppm attributable to CH_2, CH=N, NH-Ph and NH protons besides a multiplet at δ 6.90-8.00 ppm for aromatic protons and doublet signal at δ 8.66 ppm for C_2-H and C_6-H pyridine protons (**Scheme 7**). The structure of compound **14** was also confirmed also by its mass spectrum which showed a peak at *m/z* = 442 (M^++1, 25 %) corresponding to a molecular formula ($C_{24}H_{19}N_5O_2S$) (Scheme 7). (M+ -2, 30%). Refluxing of compound 14 in N,N-dimethylformamide with few drops of triethylamine led to the formation of a product identical in all respects (M.p., mixed m.p., IR and 1H NMR) to **15** (Scheme 2).

Experimental

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are incorrected. Infrared spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer (Thermoelectron Co. Egelsbach, Germany) using a KBr wafer technique. The P1PH NMR spectra were determined on Varian Gemini 300 MHz (Varian Co, Fort Collins, USA). DMSO-dR6R was used as a solvent. TMS was used as an internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 at the Microanalytical Center at Cairo University, Cairo, Egypt.

Synthesis of 2-cyano-N'-(pyridin-4-ylmethylene)acetohydrazide (1).

Method A: A mixture of 4-formylpyridine (1.07 g, 0.01 mol) and 2-cyanoacetohydrazide (9.9 g, 0.01 mol) in tetrahydrofuran (15 ml) containing triethylamine (2 drops) was refluxed for 4 h. The solid precipitate was collected by filtration, washed with ethyl acetate and petroleum ether and recrystallized from absolute ethanol to give compound **1** yield (39%).

Pale yellow crystal; yield (100%). m.p.165-170°C. IR (KBr) υ cm^{-1}: 3235 (NH), 2259 (CN), 1704 (C=O); 1H NMR (DMSO-*d6*): δ ppm= 4.26 (s, 2H, CH_2), 7.96 (d, 2H, C_3-H, C_5-H pyridine), 8.31 (s, 1H, CH=N), 8.64(d, 2H, C_3-H, C_5-H pyridine), 11.86 (s, 1H, NH D_2O exchangeable). MS (*m/z, %*): 188 (M^+, 10 %), 143 (48%), 116 (68%), 115 (23%), 88 (91%), 87 (59%), 73 (33%), 70 (37%), 59 (46%), 41 (28%), 29 (100%), 27 (30%). Anal. Calcd. For $C_9H_8N_4O$ (188.2): C, 57.44; H,

4.29; N, 29.77; found: C, 57.39; H, 4.33; N, 29.81.

Synthesis of 2-cyano-3-mercapto-3-(phenylamino)-N'-(pyridin-4-ylmethylene) acrylohydrazide (3).

To a stirred solution of powdered KOH (0.56 g, 0.015 mol) in DMF (20 ml) the titled compound **1** was added (1.88 g, 0.01 mol) and followed by Phenyl isothiocyanate (1.35 ml, 0.01 mol). The reaction mixture was stirred at room temperature overnight, poured into ice-cold water, and then neutralized with dilute HCl (0.1N). The resultant solid product was collected by filtration, washed with water, dried and recrystallized from absolute ethanol to afford compound **3**.

Brown crystal; yield (57%); m.p 220°C. IR (KBr) υ cm^{-1}: 3266, 3199 (2NH), 2207 (CN), 1655 (C=O), 1300 (C=S); 1H NMR (DMSO-*d6*): δ ppm= 1.9 (s, 1H, SH), 6.90-8.10 (m, 7H, Ar-H), 7.69 (d, 2H, C_2-H, C_6-H pyridine), 8.44 (s, 1H, CH=N), 10.77 (s, 1H, NH), 12.11(s, 1H, NH). MS (*m/z %*): 322 (M^+-1, 76 %), 290 (81%), 274 (49%), 256 (20%), 248 (33%), 232 (33%), 214 (30%), 207 (20%), 105 (100%), 119 (48%), 91 (20%), 84 (32%), 43 (25%). Anal. Calcd. For $C_{16}H_{13}N_5OS$ (323.4): C, 59.43; H, 4.05; N, 21.66; found: C, 59.45; H, 4.02; N, 21.67.

Synthesis of 4-amino-3-chloro-6-(phenylamino)-N'-(pyridin-4-ylmethylene)-2-thioxo-2H-pyran-5-carbohydrazide (5) and 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-N'-(pyridin-4-ylmethylene) acetohydrazide (6).

Method A: A mixture of compound **3** (3.23 g, 0.01 mol), in DMF (30 mL), and chloroacetyl chloride (1.13 g, 0.01 mol), in the presence of triethylamine (4 drops) was refluxed for 6 h. The reaction mixture was allowed to cool at room temperature. The separated solid material was identified as compound **5.** The filtrate was then poured onto ice-cold water to give solid material identified as compound **6.**

Method B: A solution of compound **4** (3.99 g, 0.01 mol), in DMF (30 mL), in the presence of triethylamine (4 drops), was refluxed for 4 h. The reaction mixture was allowed to cool. The precipitate formed was collected by filtration to give compound **5.** The filtrate was poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compound **6**.

4-amino-3-chloro-6-(phenylamino)-N'-(pyridin-4-ylmethylene)-2-thioxo-2H-pyran-5-carbohydrazide (5).

Buff crystal; yield (41%); m.p 90-95°C. IR (KBr) υ cm^{-1}: 3402, 3384 (NH_2), 3217, 3186 (two NH), 1730 and 1655 (two C=O); ^{1}H NMR (DMSO-d_6): δ ppm= 4.18 (s, 2H, NH_2), 7.0-8.0 (m, 7H, Ar-H), 8.39(s, 1H, CH=N), 8.67 (d, 2H, C_2-H, C_6-H pyridine),10.79 (s, 1H, NH-Ph), 11.99 (s, 1H, NH). MS (*m/z%*): 400 (M^++1, 9%), 351 (10%), 261 (18%), 212 (10%), 180 (22%), 160 (9%), 149 (100%), 119 (18%), 91 (25%), 68 (9%). Anal. Calcd. For $C_{18}H_{14}ClN_5O_2S$ (399.9): C, 54.07; H, 3.53; Cl, 8.87; N, 17.52; S, 8.02; found: C, 54.13; H, 3.47; Cl, 8.91; N, 17.45; S, 7.99.

2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-N'-(pyridin-4-ylmethylene) acetohydrazide (6).

Brown crystal; yield (39%); m.p 220°C. IR (KBr) υ cm^{-1}: 3216 (NH), 2207 (CN), 1741, 1641 (2C=O), 1507 (Ph); ^{1}H NMR (DMSO-d_6): δ ppm= 4.66 (s, 1H, CH_2), 6.90-8.00 (m, 7H, Ar-H), 8.62 (d, 2H, C_2-H, C_6-H pyridine), 8.49 (s, 1H, CH=N), 12.11 (s, 1H, NH). MS (*m/z%*): 365 (M^++2, 3 %), 264 (15%), 263 (13%), 237 (5%), 223 (11%), 142 (25%), 128 (5%), 114 (100%), 44 (20%). Anal. Calcd. For $C_{18}H_{13}N_5O_2S$ (363.4): C, 59.49; H, 3.61; N, 19.27; S, 8.82; found: C, 59.45; H, 3.66; N, 19.31; S, 8.77.

Synthesis of the 2-cyano-3-(alkylthio)-3-(phenylamino)-N'--pyridin-4-ylmethylene)acrylohydrazide derivatives 4, 7, 10, 12 and 14.

General procedure

To a stirred solution of KOH (0.56 g, 0.015 mol) in DMF (20 ml) was added compound **1** (1.88 g, 0.01 mol). After the mixture was stirred for 0.5 h. Phenyl isothiocyanate (1.35 ml, 0.01 mol) was adde, the stirring continued at room temperature for 24 h.chloroacetyl chloride (1.13g, 0.01mol) and/or chloroacetone (0.925 g, 0.01 mol), and/or ethyl

chloroacetate (1.225 g, 0.01 mol) and/or ethyl bromoacetate (1.67 g, 0.01 mol) and/or chloroacetonitrile (0.755 g, 0.01 mol) and/or phenacyl bromide (1.99 g, 0.01 mol) were added to the reaction mixture, stirred for 4- 6 h.at room temperature the reaction mixture was poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compounds **4, 7, 10, 12** and **14**, respectively.

2-cyano-3-oxo-1-(phenylamino)-3-(2-(pyridin-4-ylmethylene) hydrazinyl) prop-1-en-1-yl) 2-chloroethanethioate (4).

Brown crystal; yield (40%); m.p.>300 °C. IR (KBr) υ cm^{-1}: 3298, 3205 (two NH), 2206 (CN), 1711, 1654 (two C=O), 1600 (C=C),; ^{1}H NMR (DMSO-*d6*): δ ppm= 4.32 (s, 2H, CH_2Cl), 6.90-8.00 (m, 7H, Ar-H), 8.46 (s, 1H, CH=N), 8.67 (d, 2H, C_2-H, C_6-H pyridine), 10.68 (s, 1H, NH), 11.95 (s, 1H, NH). MS (*m/z %*): 400 (M^++1, 10%), 399 (20%), 309 (10%), 254 (25%), 243 (11%), 202 (14%),142 (22%), 126 (30%), 112 (21%), 99 (15%),86 (100%),58 (20%),36 (13%). Anal. Calcd. For $C_{18}H_{14}ClN_5O_2S$ (399.9): C, 54.07; H, 3.53; Cl, 8.87; N, 17.52; S, 8.02. Found: C, 54.12; H, 3.49; Cl, 8.93; N, 17.47; S, 7.89.

2-cyano-3-((2-oxopropyl)thio)-3-(phenylamino)-N'-(pyridin-4-ylmethylene)acrylohydrazide (7).

Reddish brown crystal; yield (37%); m.p125°C. IR (KBr) υ cm^{-1}: 3238, 3216 (2NH), 2200 (CN), 1773, 1649 (2 C=O), 1597 (C=C); 1H NMR (DMSO-*d6*): δ ppm= 2.33 (s, 3H, CH_3), 4.11(s, 2H, CH_2-S), 6.90-8.00 (m, 7H, Ar-H), 8.39 (s, 1H, CH=N), 8.56 (d, 2H, C_2-H, C_6-H pyridine), 10.78 (s, 1H, NH-Ph), 12.09 (s, 1H, NH). MS (*m/z%*): 378 (M^+-1, 25%), 352 (12%), 280 (64%), 252 (27%), 208 (27%), 196 (25%),179 (75%), 166 (70%), 152 (75%), 140 (39%), 126 (80%), 63 (13%), 29 (100%). Anal. Calcd. For $C_{19}H_{17}N_5O_2S$ (379.44): C, 60.14; H, 4.52; N, 18.46; S, 8.45 found: C, 60.18; H, 4.49; N, 18.41; S, 8.51.

Ethyl 2-((2-cyano-3-oxo-1-(phenylamino)-3-(2-(pyridin-4-ylmethylene) hydrazinyl) prop-1-en-1-yl) thio) acetate (10).

Brown crystal; yield (51%); m.p >300°C. IR (KBr) υ cm^{-1}: 3331, 3224, (2NH), 2202 (CN), , 1710, 1669 (two C=O) and 1596 (C=C); ^{1}H NMR (DMSO-d_6): δ ppm= 1.11 (t, 3H, CH_3), 4.03 (s, 2H, CH_2CO), 4.25 (q, 2H, CH_2O), 6.90-8.00 (m, 7H, Ar-H), 8.51 (s, 1H, CH=N), 8.59 (d, 2H, C_2-H, C_6-H pyridine), 10.59 (s, 1H, NH-Ph), 12.10 (s, 1H, NH). MS (*m/z%*): 408 (M^+-1, 6 %), 342 (10%), 311 (18%), 266 (17%), 208 (46%), 160 (15%),151 (94%), 137 (20%), 28 (9%). Anal. Calcd. For $C_{20}H_{19}N_5O_3S$ (409.46): C, 58.67; H, 4.68; N, 17.10; S, 7.83; found: C, 58.61; H, 4.73; N, 17.13; S, 7.78.

2-cyano-3-((cyanomethyl)thio)-3-(phenylamino)-N'-(pyridin-4-ylmethylene)acrylohydrazide (12).

Brown crystal; yield (76%); m.p212°C. IR (KBr) υ cm^{-1}: 3343, 3194 (2NH), 2195, 2009 (2CN), 1674 (C=O), 1597 (C=C); ^{1}H NMR (DMSO-d_6): δ ppm= 4.23 (s, 2H, CH_2), 6.90-8.00 (m, 7H, Ar-H), 8.47 (s, 1H, CH=N), 8.79 (d, 2H, C_2-H, C_6-H pyridine), 10.88 (s, 1H, NH-Ph), 12.12 (s, 1H, NH). MS (*m/z*%):363 (M^++1, 97%), 286 (15%), 258 (72%), 184 (10%), 168 (9%),105 (10%), 77 (48%).Anal. Calcd. For $C_{18}H_{14}N_6OS$ (362.41): C, 59.66; H, 3.89; N, 23.19; S, 8.85; found: C, 59.69; H, 3.95; N, 23.11; S, 8.81.

2-cyano-3-((2-oxo-2-phenylethyl)thio)-3-(phenylamino)-N'-(pyridin-4-ylmethylene)acrylohydrazide (14).

Dark brown crystal; yield (69%); m.p 110°C.IR (KBr) υ cm^{-1}: 3230, 3195 (2NH), 2211 (CN), 1693, 1659 (2C=O), 1502 (C=C); ^{1}H NMR (DMSO-d_6): δ ppm= 4.87 (s, 2H CH_2), 6.90-8.00 (m, 12H, Ar-H), 8.39 (s, 1H, CH=N), 8.66 (d, 2H, C_2-H, C_6-H pyridine), 10.56 (s, 1H, NH-Ph), 12.22 (s, 1H, NH). MS (*m/z*%): 442 (M^++1, 25 %), 410 (45%), 395 (33%), 379 (50%), 333 (13%), 317 (70%), 302 (47%), 289 (55%), 221 (100%), 189 (61%), 175 (45%), 151 (29%), 105 (25%). Anal. Calcd. For $C_{24}H_{19}N_5O_2S$ (441.51): C, 65.29; H, 4.34; N, 15.86; S, 7.26; found: C, 65.33; H, 4.39; N, 15.81; S, 7.19.

Synthesis of 5-acetyl-4-amino-2-(phenylamino)-N'-(pyridin-4-ylmethylene) thiophene-3-carbohydrazide (8) and 2-

cyano-2-(4-methyl-3-phenylthiazolidin-2-ylidene)-N'-(pyridin-4-ylmethylene) acetohydrazide (9).

Method A: A solution of compound **3** (3.23 g, 0.01 mol), in DMF (30 mL), and chloroacetone (0.925 g, 0.01 mol), in the presence of triethylamine (4 drops), was refluxed for 6 h. The reaction mixture was allowed to cool, the formed precipitate was collected by filtration to give compound **8.** The filtrate was poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compound **9.**

Method B: A solution of compound **7** (3.53 g, 0.01 mol), in DMF (30 mL), in presence of triethylamine (4 drops), was refluxed for 4 h. The reaction mixture was allowed to cool. The formed precipitate formed collected by filtration to give compound **8.** The filtrate was poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compound **9**.

5-acetyl-4-amino-2-(phenylamino)-N'-(pyridin-4-ylmethylene) thiophene-3-carbohydrazide (8).

Pale brown crystal; yield (44%); m.p >300°C. IR (KBr) υ cm^{-1}: 3447, 3422 (NH_2), 3264, 3232 (2NH), 1699, 1653 (2C=O); ^{1}H NMR (DMSO-d_6): δ ppm= 2.99 (s, 3H, CH_3), 5.45 (s, 2H, NH_2), 7.00-8.00 (m, 7H, Ar-H), 8.34 (s, 1H, CH=N), 8.71 (d, 2H, C_2-H, C_6-H pyridine), 9.19 (s, 1H, NH-Ph), 10.41 (s, 1H, NH). MS (*m/z%*): 379 (M^+, 19 %), 363 (10%), 249 (18%), 236 (100%), 151 (69%), 127 (9%),57 (23%), 43 (7%). Anal. Calcd. For $C_{19}H_{17}N_5O_2S$ (379.44): C, 60.14; H, 4.52; N, 18.46; S, 8.45; found: C, 60.20; H, 4.48; N, 18.42; S, 8.37.

2-cyano-2-(4-methyl-3-phenylthiazolidin-2-ylidene)-N'-(pyridin-4-ylmethylene) acetohydrazide (9).

Redish brown crystal; yield (53%); m.p130°C. IR (KBr) υ cm^{-1}: 3241 (NH), 2206 (CN), 1673 (C=O), 1595 (C=C); ^{1}H NMR (DMSO-*d6*): δ ppm= 2.5 (s, 1H, CH_3), 5.33 (s, 1H, CH), 6.90-8.00 (m, 7H, Ar-H), 8.11 (s, 1H, CH=N), 8.73 (d, 2H, C_2-H, C_6-H pyridine), (s, 1H, NH). MS (*m/z %*): 363 (M^+, 29 %), 362 (33%), 361 (100%), 332 (31%), 288 (10%), 258 (19%), 215 (20%), 186 (10%), 119 (9%),81 (23%). Anal. Calcd. For $C_{19}H_{17}N_5OS$ (363.4): C, 62.79; H, 4.71; N, 19.27; S, 8.82; found: C, 62.84; H, 4.75; N, 19.14; S, 8.77.

Synthesis of thiazolylidene derivatives 11, 13 and 15.

General procedure:

Method A: A solution of compound **3** (3.23 g, 0.01 mol), in a DMF (30 mL) and ethyl chloroacetate (1.225 g, 0.01 mol) and/or ethyl bromoacetate (1.67 g, 0.01 mol) and/or chloroacetonitrile (0.755 g, 0.01 mol) and/or phenacyl bromide (1.99 g, 0.01 mol) in the presence of triethylamine (4 drops), was refluxed for 4 h. The reaction mixture was allowed to cool, then poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compounds **11, 13** and **15**, respectively.

Method B: A solution of compound **10** (3.67 g, 0.01 mol) and/or **12** (3.62 g, 0.01 mol) and/or **14** (4.41 g, 0.01 mol), in DMF (30 mL), in the presence of triethylamine (4 drops), was refluxed for 4 h. The reaction mixture was allowed to cool, then poured onto crushed ice. The obtained solid product was collected by filtration, washed, dried and crystallized from ethanol to give compounds **11, 13** and **15**, respectively.

2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-N'-(pyridin-4-ylmethylene)acetohydrazide (11)

Brown crystal; yield (58%); m.p 200°C. IR (KBr) υ cm^{-1}:3338 (NH), 2201 (CN), 1700, 1656 (2C=O), 1596 (C=C); ^{1}H NMR (DMSO-*d6*): δ ppm= 4.23 (s, 2H, CH_2), 6.90-8.00 (m, 7H, Ar-H), 8.69 (d, 2H, C_2-H, C_6-H pyridine), 8.49 (s, 1H, CH=N), 12.12 (s, 1H, NH). MS (m/z%): 360 (M^+-3, 6 %), 349 (11%), 321 (14%), 275 (23%), 248(80%), 216 (92%),156 (42%), 131 (14%), 106 (18%).Anal. Calcd. For $C_{18}H_{13}N_5O_2S$ (363.39): C, 59.49; H, 3.61; N, 19.27; S, 8.82; found: C, 58.52; H, 3.58; N, 19.23; S, 8.88.

2-(4-amino-3-phenylthiazol-2(3H)-ylidene)-2-cyano-N'-(pyridin-4-ylmethylene)acetohydrazide (13).

Dark brown crystal; yield (95%); m.p >300°C.IR (KBr) υ cm^{-1}: 3431, 3347 (NH_2), 3190 (NH), 2202 (CN), 1659 (C=O); ^{1}H NMR (DMSO-*d6*): δ ppm= 5.29 (s, 2H, NH_2), 5.87 (s, 1H CH), 6.90-8.00 (m, 7H, Ar-H), 8.56 (d, 2H, C_2-H, C_6-H pyridine), 8.28 (s, 1H, CH=N), 11.92 (s, 1H, NH). MS (*m/z*%): 363 (M^++1, 23 %), 362 (100%), 347 (55%), 331 (36%), 319 (37%), 291 (59%),276 (11%), 263 (23%), 235 (22%), 205 (9%),107 (7%), 83 (48%). Anal. Calcd. For $C_{18}H_{14}N_6OS$ (362.41): C, 59.66; H, 3.89; N, 23.19; S, 8.85; found: C, 59.61; H, 3.92; N, 23 22; S, 8.81.

2-cyano-2-(3,4-diphenylthiazol-2(3H)-ylidene)-N'-(pyridin-4-ylmethylene)acetohydrazide (15).

Buff crystal; yield (71%); m.p >300°C.IR (KBr) υ cm^{-1}: 3428 (NH), 2212 (CN), 1651 (C=O), 1502 (C=C); ^{1}H NMR (DMSO-*d6*): δ ppm= 6.87 (s, 1H CH), 6.90-8.00 (m, 12H, Ar-H), 8.59 (d, 2H, C_2-H, C_6-H pyridine), 8.26 (s, 1H, CH=N), 12.22 (s, 1H, NH). MS (*m/z*%): 424 (M^++1, 10 %), 380 (18%), 232 (29%), 191 (23%), 189 (100%), 174 (9%),162 (16%), 134 (25%), 76 (7%), 43 (19%). Anal. Calcd. For Chemical Formula: $C_{24}H_{17}N_5OS$ (423.49): C, 68.07; H, 4.05; N, 16.54; S, 7.57; found: C, 68.11; H, 3.98; N, 16.49; S, 7.63.

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تشييد بعض المشتقات الجديدة للمركبات الحلقية غير المتجانسة المحتوية على حلقة البيردين مع تقييم تأثيرها البيولوجي

ان تفاعل ٢- سيانو-ن-(البيريدينايل-٤-الميثلين)اسيتوهايدرازيد (١) مع ايزوثيوسيانات الفنيل يؤدي الى تخليق مشتقات الثايوكاربوميل (٣)، ان تفاعل المركب(٣) مع مركبات الفا هالو كاربونايل في ثنائي ميثيل الفورماميد بوجود العامل الحفاز ثلاثي الايثيل امين لتخليق كل من مشتقات الثيازول **15 ,13 ,11 ,9 ,6** و مشتق الثيوفين ٨ بينما وجد نفس التفاعل في ثنائي ميثيل الفورماميد عند درجة حرارة الغرفة يؤدي الى تخليق مشتقات **12 ,10 ,7 ,4** و **14 بينما فى حالة تكثيف التفاعل** في ثنائي ميثيل الفورماميد بوجود العامل الحفاز ثلاثي الايثيل امين **يعطى كل من مشتقات** الثيازول و الثيوفين وتم التعرف على المركبات من خلال التحاليل الطيفية وبيانات التحاليل .

رؤوس الموضوعات: 4-فورميليبيريدين، 2-سيانواسيتوهيدرازيد، فينيليسوثيوسيانات.