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Heterocyclization of 2-thiophenamine: Design of novel thiophene with azole and azine moieties

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ABSTRACT **:** Thiophenamine of type **1** undergo several functionalization and heterocyclization, thus reaction of target **1** with diethyl succinate furnished benzothiophene derivative **4** through condensation followed by intramolecular cyclocondensation and subsequent evolution of 3 H_2. Keeping diethyl malonate and amino derivative **1** provide hydroxypyridine derivative **7**, may be via 3 °r amine **5** that added the active methylene to the ester group followed by hydrolysis and subsequent decarboxylation. Also, Target **1** undergo cyclocondensation with ethyl acetoacetate to produce acetyl pyridine of type **10**. Alkylation of **1** with *N*-phenyl chloroacetamide provided alkylation derivative **11**. Acylation of compound **1** with chloroacetyl chloride followed by cyclization leads to chloropyrrole derivative **14**. Compound **14** reacted with NH_4SCN to give non isolable pyrrole **15** followed by enolization and subsequent intramolecular cycloaddition providing fused pyrrole **16**. Compound **1** reacted with succinic anhydride and ethyl cyanoacetate to provide acylated derivative **17** and aminocyanopyridine **19**, respectively. Compound **19** undergo azidolysis and acetylation producing pyridine derivatives **20** and **21**, respectively. Compound **19** added its amino group to heteroallene electrophilic carbon of benzoyl isothiocyanate followed by intramolecular heterocyclization producing pyridopyrimidine derivative **23**.

KEYWORDS: Thiophene amine, Pyridine, Pyrrole, Pyridopyrimidines.

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I. INTRODUCTION

Heterocyclic compounds are necessary compounds within the chemistry attributable to their vital properties within the numerous areas like medicinal, food and agricultural industries[1,2]. Extremely substituted thiophene are necessary heterocycles found in varied biologically active and natural compounds[3]. Historically, polysubstituted 2-thiophenamines has an electron-attracting groups such as carbethoxy, cyano, or carboxamide in the 3-position and alkyl, aryl or hetaryl groups in the 4- and 5-positions have been produced by the Gewald reaction [4]. Moreover, 2-aminothiophene has incontestible a broad spectrum of uses together with production of prescription drugs [5] and dyes [6] and starting materials for the synthesis of amalgamated heterocyclic systems [7-9]. Thiophene will extraordinarily behave reactive like benzene in terms of getting a pie electron cloud structure. The substituted thiophene derivatives are all right known for healthful applications. Several substituted thiophene compounds have performed as therapy and malignant tumor agents. For these reasons, substituted thiophene compounds were additionally applied with success in alternative fields like pharmacological medicine, agriculture and industrial applications. These compounds were employed in the event of agricultural merchandise and in

drug analysis since they need various biological activities. Some known activities are antitubercular, analgesic, medicinal drug, anti-metabolite, anti-bacterial, antifungal, and antineoplastic. [10-17]

II. MATERIALS AND METHODS

All melting points were obtained uncorrected using an Electro thermal IA 9100. Drying solvents were used in all of the experiments. Recrystallization was used to purify the products. The infrared spectrum of the obtained compounds (KBr disc) were obtained using a Pye Unicom Sp-3-300 or a Shimadzu FTIR 8101 PC spectrophotometer. In addition, the ^{1}H/ (^{13}C) NMR spectrum were obtained using Varian Mercury VX-300 NMR spectrometer 400 (75.4) MHz using DMSO-d_6. All chemical shifts were recorded using tetramethylsilane as an internal standard reference as δ ppm. The coupling constant (J) values are shown in Hz. Mass spectrometer and elemental analysis were done at the Microanalysis Center at Cairo University, Giza, Egypt.

2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzo[*b*]thiophene-3-carbonitrile (4). A mixture of (**1**) (1.7 g, 9.5 mmol), diethyl succinate (1.4 ml) in dimethyl formamide (DMF) (30ml) and triethyl amine was refluxed for 12 hours then cooled, poured into crushed ice and the solid was seperated, dried and recrystallized from EtOH and DMF. Black crystals (yield 2.1g, 91%), m.p. 330-333 °C. IR spectrum, ν, cm^{-1}: 1535 (C=C), 1624 (C=O), 2196(CN); ^{1}H NMR, δ, ppm: 7.17- 8.36 (m, 6H, ArH's, pyrrole H). Calculated, %: C, 61.41; H, 2.38; N, 11.02; S, 12.61. $C_{13}H_6N_2O_2S$. Found: C, 61.00; H, 2.30; N, 11.00, S, 12.50.

2-(2,4,6-Trioxopiperidin-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (7). A mixture of compound (**1**) (1.7 g, 9.5 mmol), diethyl malonate (3.2 ml) and triethyl amine (5 drops) in xylene was refluxed for 12 hours. The product obtained upon adding into ice/H_2O mixture was separated, dried and recrystallized from ethyl alcohol and DMF. Black crystals (2g, 90%), mp >350 °C. FTIR, *ν*, cm^{-1}: 1678 (C=O), 2210 (CN), 3429 (OH); ^{1}H-NMR, δ, ppm: 1.76, 2.50, 3.34 (3s, 8H, cyclohexane H's), 3.34(s, 2H, Pyridine CH_2), 7.95 (s, 1H, CH=C), 11.80 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR , δ, ppm: (23.03, 23.77, 23.95, 31.25, 36.37) sp^3, (165.19, 146.59) 2C=O, Calculated, %: C, 59.15; H, 2.84; N, 9.85; S, 11.28. $C_{14}H_8N_2O_3S$. Found: C, 58.99; H, 2.75; N, 9.80, S, 11.20.

2-(5-Acetyl-4-methyl-2,6-diox-3,6-dihydropyridin-1(2*H*)-yl)benzo[*b*]thiophene-3-carbonitrile (10). A mixture of thiophene (**1**) (1.7 g, 9.5 mmol), ethyl acetoacetate (2.6 ml) and triethyl amine (5 drops) in xylene (30 ml) was refluxed for 12 hours, then concentrated, and cooled. The precipitate obtained up on addition to ice was separated, dried and recrystallized from ethyl alcohol. Black crystals (2.4 g, 80%), mp >300 °C. IR spectrum, ν, cm^{-1}: 1519 (C=C), 1624 (C=O), 2202 (CN); ^{1}H-NMR, δ, ppm: 2.24-2.26 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$), 6.95-7.30 (m, 5H, Ar H, pyridine H), 8.42 (s, 1H, OH), Calculated, %: C, 62.95; H, 3.73; N, 8.64; S, 9.89. $C_{17}H_{12}N_2O_3S$. Found: C, 62.85; H, 3.50; N, 8.61, S, 9.77.

2-((3-Cyano-4,5,6,7-tetrahydro-1*H*-inden-2-yl)amino)-*N*-phenyl acetamide (11). A mixture of compound (**1**) (1g, 5.6 mmol) and *N*-phenylchloroacetamide (1 g, 5.3 mmol) in AcOH (50 mL) and sodium acetate (5 g) was refluxed for 10 hours then cooled, and placed into H_2O. The produced product was separated, dried and recrystallized from ethayl alcohol and DMF. Black crystals (1.5 g, 90%), m.p 140-144 °C. FTIR, ν, cm^{-1}: 1554 (C=C), 1657 (C=O), 2210 (CN), 3271 (NH); ^{1}H NMR, δ, ppm: 1.75, 2.17, 2.51 (3s, 8H, cyclohexane H's), 2.89 (s, 2H, CH_2), 7.29-7.58 (m, 5H, ArH's), 11.51-7.95 (s, 2H, 2NH). Calculated, %: C, 65.57; H, 5.50; N, 13.49; S, 10.30. $C_{17}H_{17}N_3OS$. Found: C, 65.40; H, 5.45; N, 13.45; S, 9.90.

2-(4-Chloro-5-hydroxy-2-oxo-2,3-dihydro-1*H*-pyrrole-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (14). A mixture of (**1**) (1.5 g, 8.4 mmol) and chloroacetyl chloride (0.9 ml) was treated in refluxing dioxane (30 ml) for 10 hours. The obtained product was separated, dried and recrystallized from ethyl alcohol and DMF. Black crystals (2g, 87%), mp >300 °C. FTIR, ν, cm^{-1}: 1620 (C=O), 2194 (CN), 3417- 3433 (OH); ^{1}H NMR, δ, ppm: 1.72, 1.90, 2.87 (3s, 8H, cyclohexane H's), 3.91 (s, 2H, pyrrole CH_2), 7.95 (s, 1H, D_2O exchangeable, OH); Calculated, %: C, 52.97; H, 3.76; Cl, 12.02; N, 9.50; S, 10.88. $C_{13}H_{11}ClN_2O_2S$. Found: C, 52.90; H, 3.69; Cl, 11.95; N, 9.00; S, 10.80.

2-(2-Imino-5-oxo-5,6-dihydro-4*H*-[1,3]oxathiolo[5,4-*b*]pyrrol-4-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (16). Ammonium thiocyanate (0.13 g, 1.7 mmol) was added to a solution of compound (**14**) (0.5 g, 1.6 mmol) in sodium ethoxide (30 ml), and refluxed for 13 hours. The mixture was poured into water /ice. The product obtained was separated, dried and recrystallized from DMF. Black crystals (0.3 g, 85%), mp >300 °C. FTIR, ν, cm^{-1}: 1624 (C=O), 2206 (CN), 3332 (NH); ^{1}H NMR, δ, ppm: 2.50, 2.73, 2.89 (3s, 8H, cyclohexane H's), 3.34 (s, 2H, pyrrole CH_2), 7.95 (s, 1H, NH); ^{13}C NMR , δ, ppm: (31.23, 36.26, 39.34, 39.96, 40.17, 40.17) sp^3, 148.39 (CN), 162.69(CO); Calculated, %: C, 60.18; H, 4.38; N, 14.04; S, 10.71. $C_{15}H_{13}N_3O_2S$. Found: C, 60.00; H, 4.30; N, 13.90; S, 10.25.

4-((3-Cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-4-oxobutanoic acid (17). A mixture of thiophene **1** (1.5 g, 8.4 mmol), succinic anhydride (0.8 g, 8 mmol) in DMF (30 ml) and triethyl amine (5 drops) was heated for 3 hours. The resulted product was separated, dried and recrystallized from DMF. Brown solid (1.9 g, 83 %), mp 350-351 °C. IR spectrum, ν, cm-1: 1651 (C=O), 2206 (CN), 3174 (NH), 3317 (OH); ^{1}H NMR, δ, ppm: 1.74, 2.51, 2.61(3s, 8H, cyclohexane protons), 2.73-2.97 (m, 4H, CH_2CH_2), 11.87 (s, 1H, NH), 12.15-12.23 (broad, 1H, COOH); ^{13}C NMR , δ, ppm: (21.85, 22.15, 23.71, 24.80, 28.92, 31.27, 35.34, 36.29, 36.97) sp^3, (114.76, 108.40) sp^2, 130.97(C=N), (162.93, 175.87) 2C=O; Calculated, %: C, 56.10; H, 5.07; N, 10.06; S, 11.52. $C_{13}H_{14}N_2O_3S$. Found: C, 56.00; H, 4.90; N, 9.90; S, 11.45.

4-Amino-1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (19). A mixture of (**1**) (5 g, 28 mmol), ethyl cyanoacetate (6.5 ml) and dimethyl formamide (30 ml) was refluxed for 8 hours. The reaction mixture was poured into crushed ice, the formed product was filtered and recrystallized from DMF. Black crystals (7.4 g, 85%), mp 238-240 °C. IR spectrum, ν, cm^{-1}: 1619 (C=O), 2194 (CN), 3330 (NH_2); ^{1}H NMR, δ, ppm: 1.79, 2.52, 2.80 (3s, 8H, cyclohexane protons), 3.98 (s, 2H, pyridine CH_2), 8.30 (s, 2H, NH_2); Calculated, %: C, 57.68; H, 3.87; N, 17.94; S, 10.27. $C_{15}H_{12}N_4O_2S$. Found: C, 57.55; H, 3.80; N, 17.90, S, 10.18.

4-Azido-1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (20). A solution of (**19**) (0.5 g, 1.6 mmol) and sodium azide (0.13 g, 2 mmol) in DMF (30 ml) was refluxed for 7 hours. The obtained solid was separated, dried and recrystallized from DMF. Black crystals (0.48 g, 90%), mp 350-351 °C. FTIR, ν, cm^{-1}: 1662 (C=O), 2202 (CN), 2337-2360 (N_3), 3209 (NH), 3332 (OH); ^{1}H NMR, δ, ppm: 2.50, 2.73, 2.89 (3s, 8H, cyclohexane H), 7.95 (s, 1H, pyridine H), 8.15 (s, 1H, OH). Calculated, %: C, 53.25; H, 2.98; N, 24.84; S, 9.48. $C_{15}H_{10}N_6O_2S$. Found: C, 52.89; H, 2.80; N, 24.77; S, 9.38.

***N*-(5-Cyano-1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-yl)acetamide (21).**

A mixture of compound (**19**) (1.5 g, 4.8 mmol) and Ac_2O (0.5ml, 4.8 mmol) and in xylene (30ml) was refluxed for 6 hours then cooled. The produced precipitate was separated, dried and recrystallized from DMF. Black crystals (1.4 g, 85%), mp >300 °C. FTIR spectrum, ν, cm^{-1}: 1658 (C=O), 2232 (CN), 3325 (NH); ^{1}H NMR, δ, ppm: 2.50, 2.73, 2.89 (3s, 8H, cyclohexane protons), 3.34 (s, 5H, pyridine CH_2, $COCH_3$), 7.95 (s, 1H, NH); ^{13}C NMR , δ, ppm: (31.24, 36.26, 39.33, 39.54, 40.17, 40.58) sp^3-C, 162.80 (C=O). Calculated, %: C, 57.62; H, 3.98; N, 15.18; S, 9.05. $C_{17}H_{14}N_4O_3S$. Found: C, 57.60; H, 3.88; N, 15.00, S, 8.99.

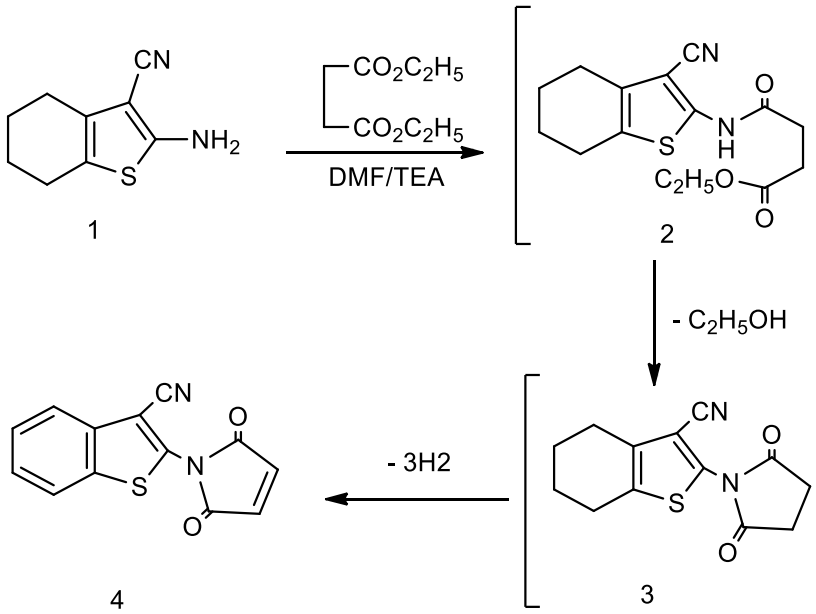
2-(3-Benzoyl-4-imino-5,7-dioxo-1,3,4,5,7,8-hexahydropyrido[4,3-*d*]pyrimidin-6(2*H*)-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (23). A solution of (**19**) (1 g, 3.2 mmol) and benzoyl isothiocyanate (0.5 g, 3.1 mmol) in dry dioxane (30 ml) was refluxed for 10 hours and cooled. The mixture was added into crushed ice and the product was separated, dried and recrystallized from DMF. Black crystals (yield 1.3 g, 90%), mp 130-131°C. FTIR, ν, cm^{-1}: 1138(C=C), 1384(C=O), 1573(C=S), 3155(NH), 3309(OH); ^{1}H NMR, δ, ppm: 2.50, 2.73, 2.89 (3s, 8H, cyclohexane protons), 3.34 (s, 2H, pyridine CH_2), 7.43-7.95 (m, 5H, Ar H's), 9.56 (s, 1H, D_2O exchangeable, NH), 9.86 (s, 1H, D_2O exchangeable, OH), 11.24 (s, 1H, D_2O exchangeable, SH); Calculated, %: C, 58.09; H, 3.60; N, 14.73; S, 13.49. $C_{23}H_{17}N_5O_3S_2$. Found: C, 57.99; H, 3.54; N, 14.60; S, 13.25.

III. RESULTS AND DISCUSSION

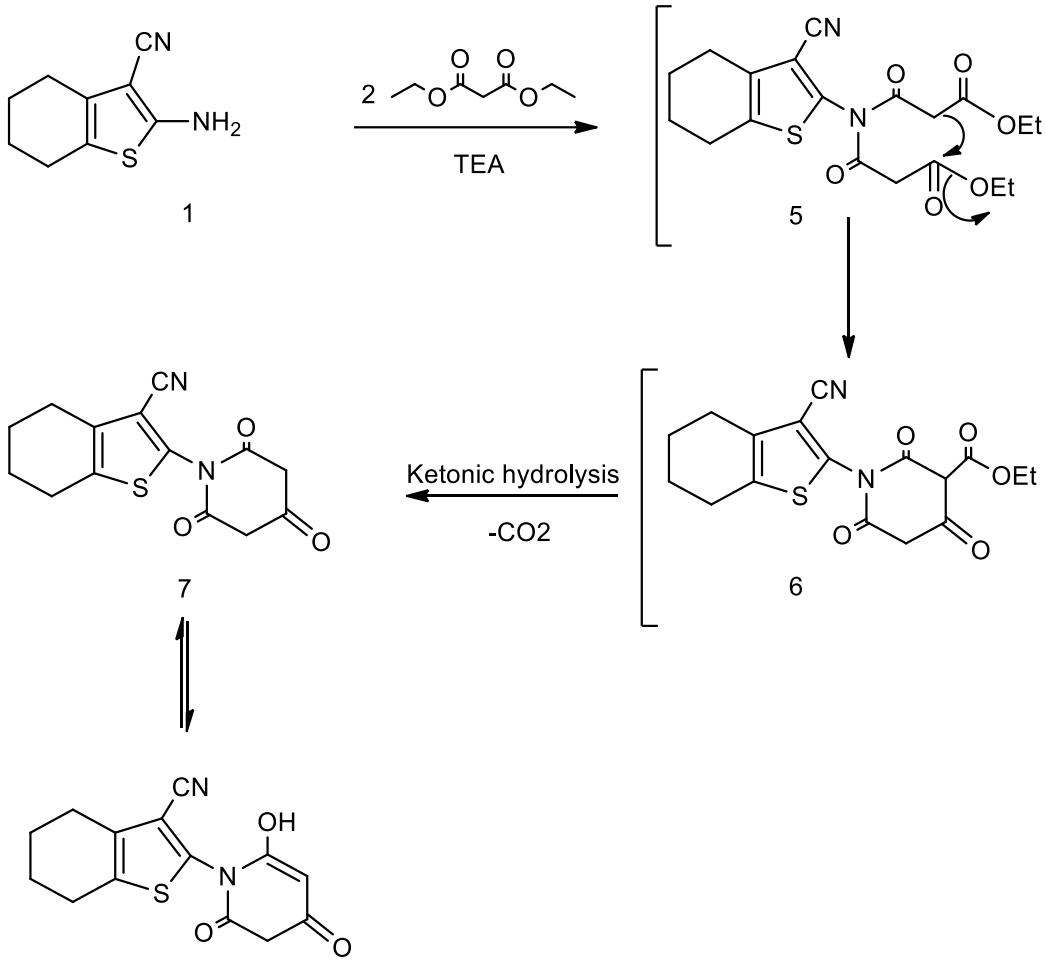
Upon reaction of aminocyanothiophene **1** with diethyl succinate resulted in benzothiophene with pyrrole moiety **4**. The reaction may be proceed via formation of amide **2**, pyrrole cyclization through the intramolecular nucleophilic attack of imino function to electrophilic carbon of ester with the departure of ethanol, followed by dehydrogenation and subsequent aromatization of cyclohexane ring (Scheme 1) . The target **4** provided CN, C=O, and C=C at 2196, 1624 and 1535 cm^{-1} respectively. The aromatic multiplet was observed at 7.17 - 8.36 ppm.

The starting material **1** condensed with two equivalent of diethyl malonate under basic condition to provide pyridine derivative **7**. Initially, the reaction may be started with the formation of **5**, pyridine cyclization, ketonic hydrolysis followed by evolution of CO_2 and subsequent enolization (Scheme2). Compound **7** contains stretching frequencies at 3429, 2210, and 1678 cm^{-1} for OH, CN, and C=O functions. The OH signal was observed at down field position 11.80 ppm, while CH_2 pyridine was located at δ 3.34, more over the cyclohexane protons were detected at 1.76, 2.17 and 2.50 ppm. Carbon signal for 7 leads to two values at 165.19 and 146.5 ppm. The acetyl pyridine of type **10** was generated as a result of condensation of two ethyl acetoacetate with compound **1** using TEA as a catalyst (Scheme 3). Compound **10** was proved by analytical and spectral data those, IR spectrum leads to CN, CO and C=C absorption peaks at 2202, 1624 and 1519 cm^{-1}. OH signal was detected at 8.42, while aromatic multiplet was observed at 6.95-7.30 ppm. Alkylation of amino function of **1** using N-phenyl

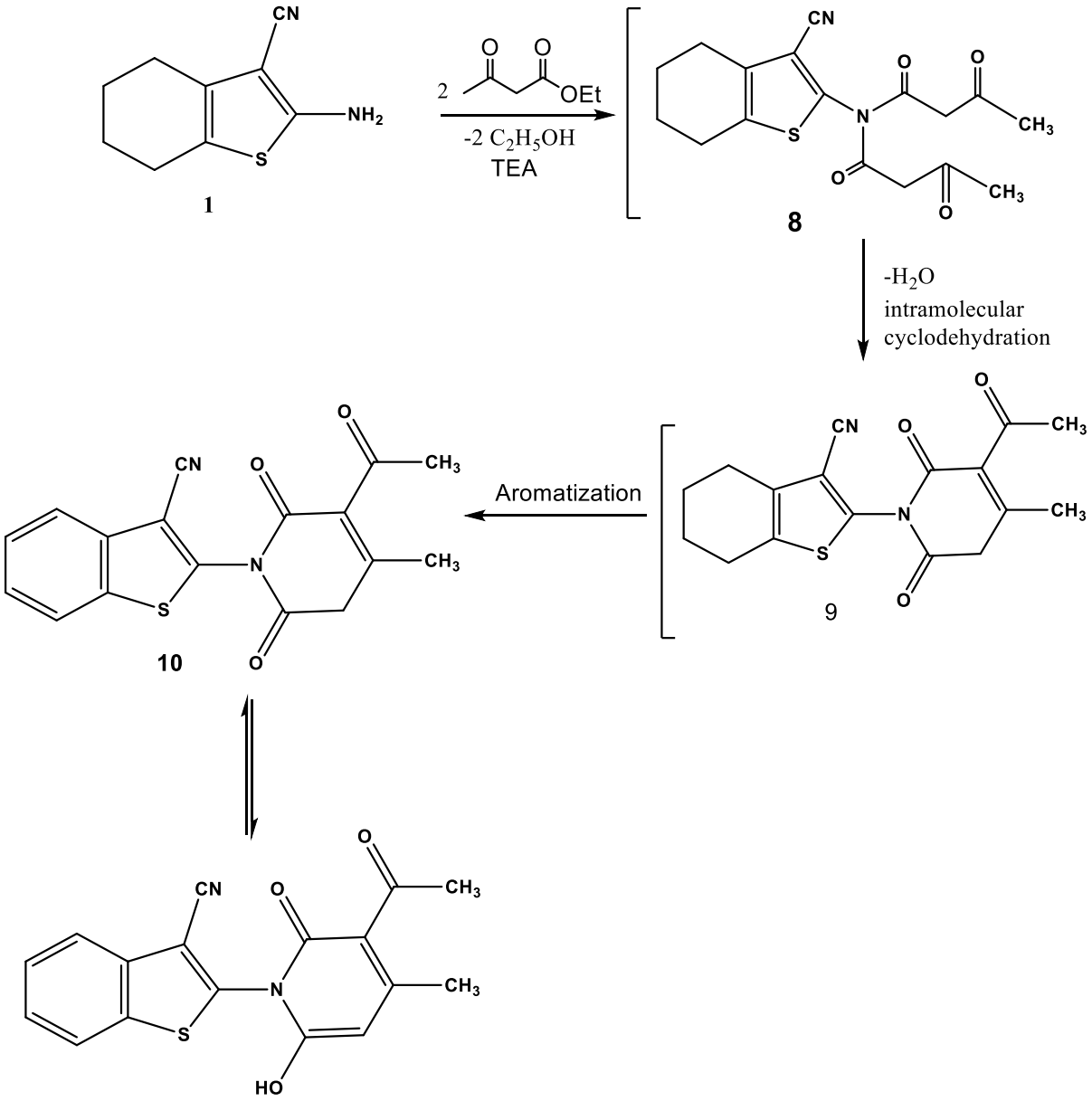
chloroacetamide afforded the alkylated derivative **11**. The NH, CN, CO and C=C absorption peaks were detected at 3271, 2210, 1657 and 1554 cm^{-1} respectively. The NH protons signals were located at 11.51 and 7.95 ppm. Acylation of starting material **1** with chloroacetyl chloride provide the non-isolable open structure **12**, That cyclized via the intramolecular alkylation to pyrrole derivative **14** , the OH, CN and C=C absorption peaks were located at 3417, 2194 and 1620 cm^{-1} respectively. The CH_2 signal of pyrrole ring was located at 3.91 ppm (Scheme 4). Pyrrole compound **14** undergo replacement reaction with NH_4SCN to form the non-isolable isothiocyanate **15**. The enolic OH was added to CN to furnish condensed system **16** (Scheme 4). The NH, CN and C=O peaks were located at 3332, 2206 and 1624 cm^{-1}. The NH signal was located at 7.95ppm. ^{13}C NMR lead to CO and CN carbon signals at 162.69 and 148.39 ppm.



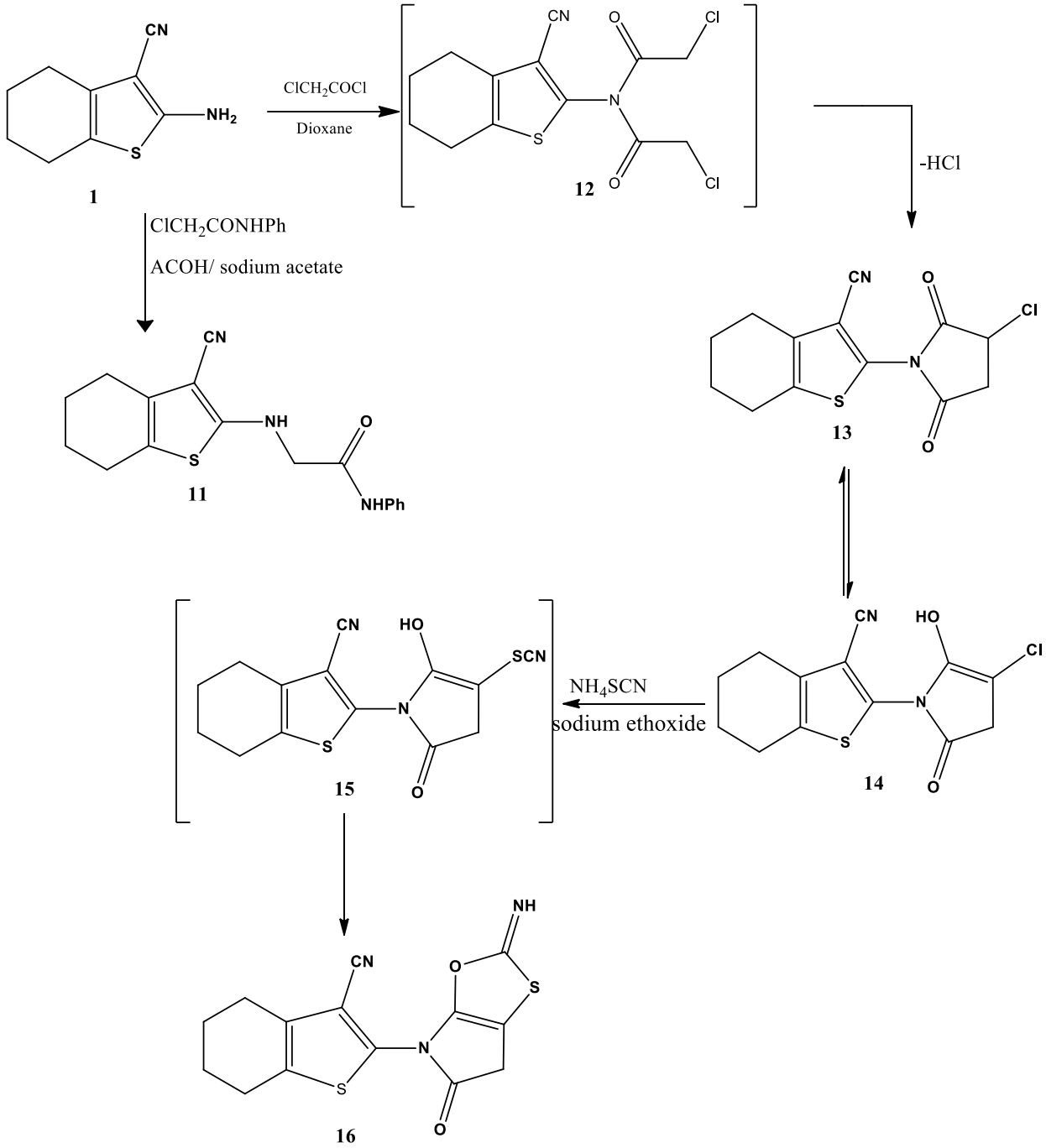
Scheme 1. Synthesis of pyrrole derivative **4**.



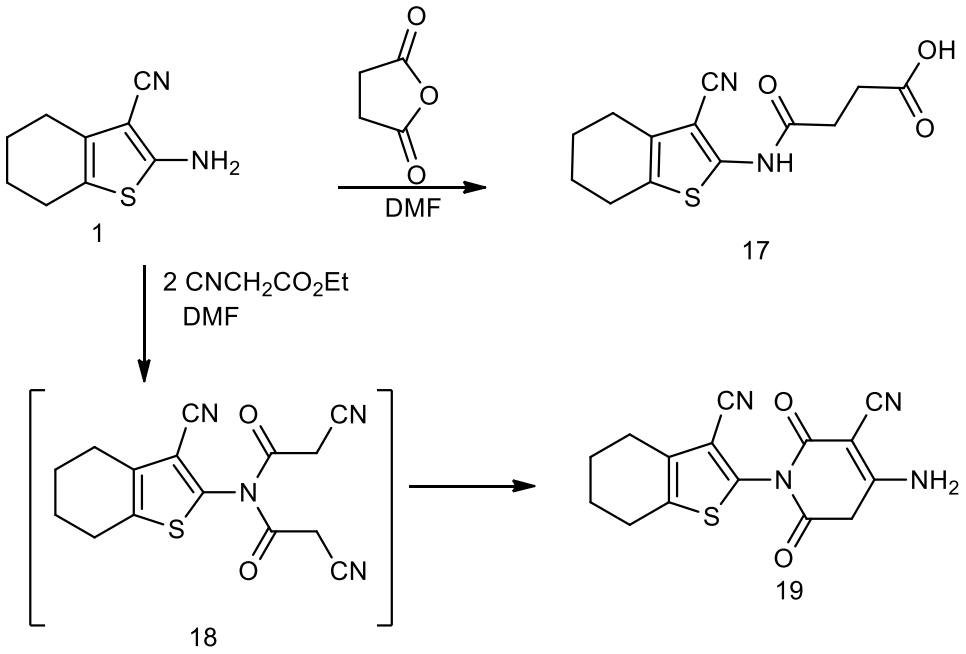
Scheme 2. Formation of pyridone derivative **7.**



Scheme 3. Producing of acetylpyridone **10** from compound **1**



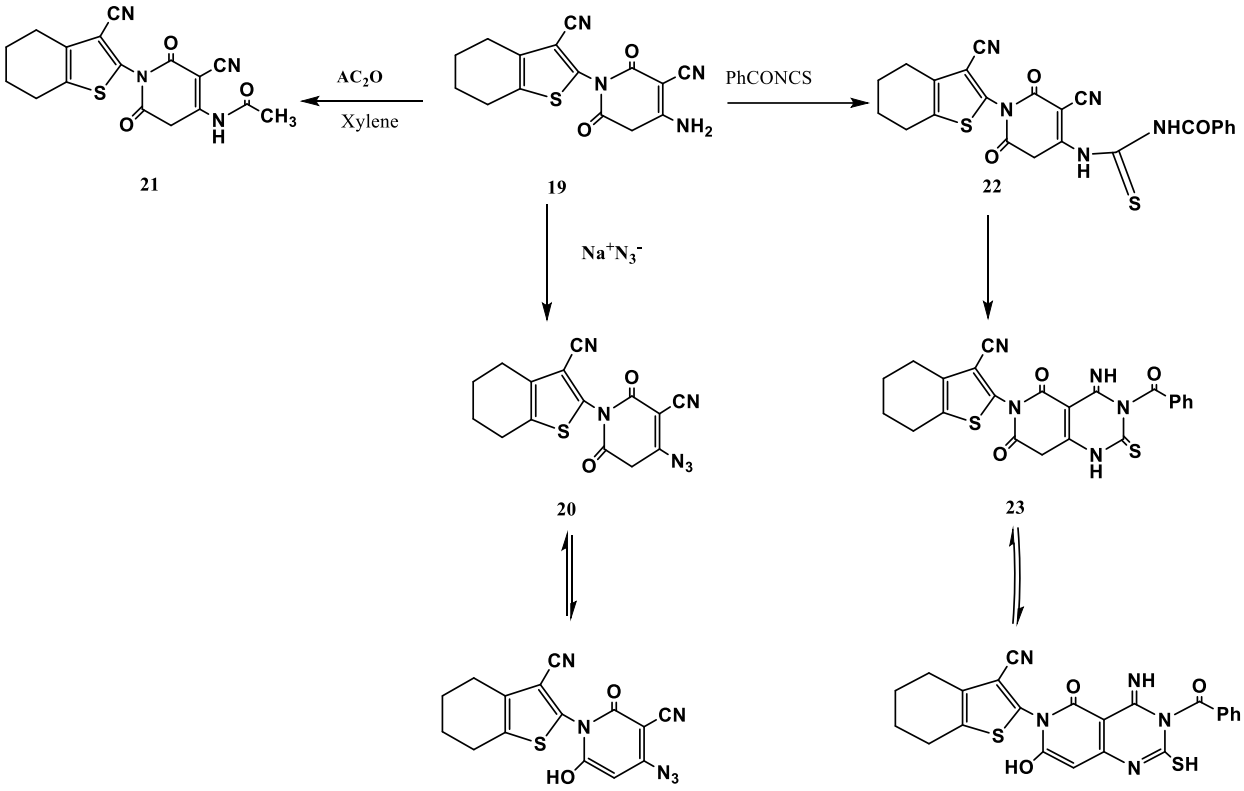
Scheme 4. Producing condensed pyrrole from pyrrole derivative **14**



Scheme 5. Synthesis of amide **17** and pyridine **19**

Succinic anhydride and target **1** were reacted to furnish acylated derivative **17** (Scheme 5). Compound **17** contained OH, NH, CN, and C=O groups at 3317, 3174, 2206 and 1651cm^{-1} respectively. The carboxylic proton signal was observed at 12.15-12.23 ppm, while amide NH was detected at 11.87 ppm. The carbonyl carbon signal was shown at 175.87, 162.93 ppm, while cyano carbon signal was located at 130.97ppm (Scheme 5). Upon reaction of two equivalent of ethyl cyanoacetate with aminothiophene **1** resulted in the imide derivative **18**, which undergoes intramolecular addition of active methylene group to cyano function providing aminocyanopyridine **19**.

Azide undergo substitution reaction with amino function of aminopyridine 19 with the evolution of NH3 to form azidopyridine 20 (Scheme 6). Compound 20 provided OH, NH, N3, CN and CO in IR spectrum at 3332, 3209, 2337, 2202 and 1662cm-1 respectively. 1HNMR showed down field signal at 8.15 for OH proton. Pyridine derivative 19 was reacted with acetic anhydride to provide amid derivative 21 (Scheme 6). The absorption peaks for 21 was detected at 3325, 2232 and 1658 for NH, CN and CO groups. The signal at 7.95 as the result of the resonance of NH proton (Scheme 6). [4+2] Cycloaddition of aminocyanopyridine derivative 19 and benzoyl isothiocyanate resulted in pyridopyrimidine 23 via the non-isolable product 22 that cyclized via nucleophilic addition of nitrogen to the electrophilic carbon of cyano group (Scheme 6). IR spectrum of 23 resulted in OH, NH, CO, C=S and C=C at 3309, 3155, 1573, 1384 and 1138 cm^{-1} respectively. The down field signals for SH, OH and NH protons were shown at 11.24, 9.86, 9.56 ppm.



Scheme 6. Formation and azidolysis of pyridine derivative **20**

V.Conclusion

In summary, we reported a simple synthetic strategy for efficient synthesis of some annulated heterocyclic compounds upon heterocyclization of 2-thiophenamine with different reagents. The present study opens the way for the preparation of other libraries of condensed nitrogen-containing heterocyclic compounds with potential biological activities.

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