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A convenient synthesis and characterization of 1,2-dihydrpyridine-2-one, pyrido[2,3-*d*]pyrimidine and thieno [3,4-*c*]pyridine derivatives

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Abstract

Cyanoacetanilide (**1**) was reacted with aminocrotonitrile to give the corresponding 1,2-dihydropyridine (**3**). Also, 4,6-dimethyl-2-oxo-6-*l*,2-dihydro-pyridine-3-carbonitriles (**7**) was synthesized and subjected to some electrophilic reagents to produce compounds **8**, **9** and **11**. Ternary condensation of (**1**), aldehyde, and malononitrile (1:1:1 molar ratio) produced aminopyridines (**14a-c**). Compound (**14b**) was used in the synthesis of pyrido[2,3-*d*]pyrimidines **20** and **23** upon treatment with formamide and acetic anhydride respectively. Structures of the titled compounds cited in this article were elucidated by spectrometric data (IR, ¹H NMR, and EMS).

Keywords: Cyanoacetanilides, 1,2-Dihydrpyridine-2-one, pyrido[2,3-*d*]pyri-midine and thieno [3,4-*c*]pyridine derivatives

INTRODUCTION

Many publications report the biological properties of pyridinedicarbonitriles as being antihypertensive [1-3], antihistaminic [4], anticancer activity [5]. Some of them were reported to inhibit PrPSc accumulation in scrapie-infected mouse neuroblastoma cells (ScN_{2a}) [6,7]. .In addition 3-cyano-4,6-diaryl pyridin-2-ones exhibited marked anti-inflammatory and/or analgesic activities [8,9]. Furthermore, many fused pyridine derivatives such as pyrazolo[3,4-*b*]pyridines induced reduction of pro-inflammatory cytokines and were found to possess anti-inflammatory and analgesic activities [10,11]. Several reports revealed that pyrido[2,3-*d*]pyrimidine exerted promising anti-inflammatory and analgesic activities [12,13]. In the light of all the previous reports and in continuation of our program [14-17] on the synthesis and biological activity of heterocycles, it is intended in the present work to investigate the synthesis of novel pyridine and

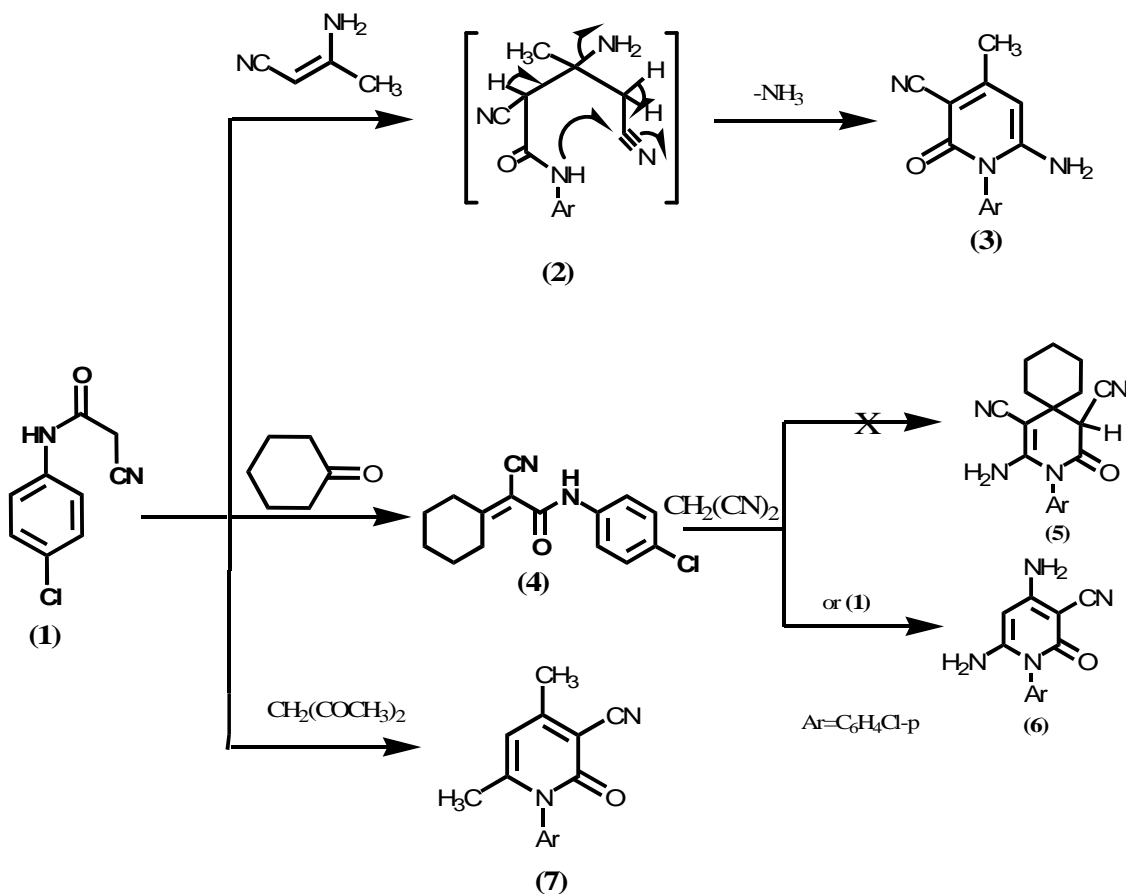
condensed derivatives *via* a facile synthetic approach utilizing easily prepared accessible chemical materials.

RESULTS AND DISCUSSION

Treatment of cyanoacetanilide derivative (**1**) with β -aminocrotonitrile in refluxing ethanol in presence of a catalytic amount of piperidine afforded the corresponding 3-aminopyridine derivative (**3**), (Scheme1). The structure of **3** was established through spectroscopic data (IR, ^1H NMR) and elemental analyses Table (1). The appearance of a singlet signal in ^1H NMR spectra at δ 2.1, 5.58 ppm attributed for a methyl proton and for pyridine-H respectively. The formation of **3** is assumed to proceed via Michael addition of active methylene in **1** to the double bond in crotonitrile to form the non-isolable intermediate (**2**) followed by intermolecular cyclization and loss of ammonia¹⁸, (Scheme1). Condensation of compound (**1**) with cyclohexanone at in refluxing ethanol in the presence piperidine furnished arylidene derivative (**4**). The reaction of compound **4** with malononitrile in ethanol containing piperidine yielded a product, the structure of which was established to be 4,6-diaminopyridine derivative (**6**) and the other possible structure (**5**) was eliminated on the basis of analytical and spectroscopic data (Scheme 1). The IR spectra of compound (**6**) revealed (2NH_2) and CN stretching vibration bands at ν 3409-3247, 2214 cm^{-1} respectively. Also, mass spectrum revealed a molecular ion peak at m/z 260 (5%) with the base peak at m/z 198. The formation of (**6**) is assumed to proceed via Michael adduct as intermediate which split into cyclohexaylidene malono- nitrile and cyanoacetanilide (**1**), the latter was cyclized with malononitrile to form (**6**). The structure of (**6**) was also confirmed on its independent synthesis through the reaction of anilide **1** with malononitrile in the presence of piperidine.

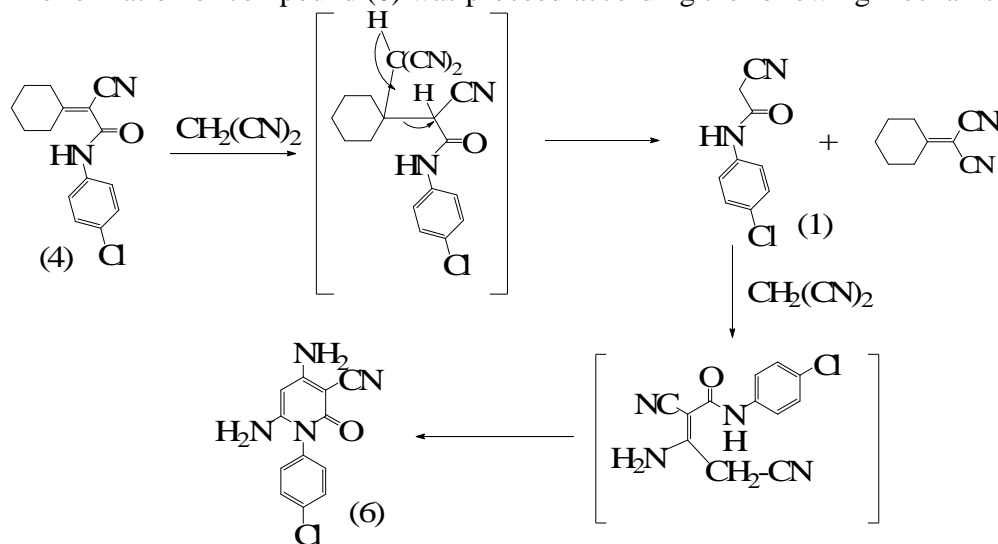
Cyclocondensation of **1** with acetylacetone in ethanol using catalytic amount of piperidine¹⁷ furnished 1-(*p*-chlorophenyl)-4,6-dimethyl-2-oxo-6-1,2-dihydropyridine-3-carbonitriles (**7**). Its ^1H NMR spectrum reveal the absence of the active methylene group and exhibit the dimethyl protons at δ 1.94, 2.41.

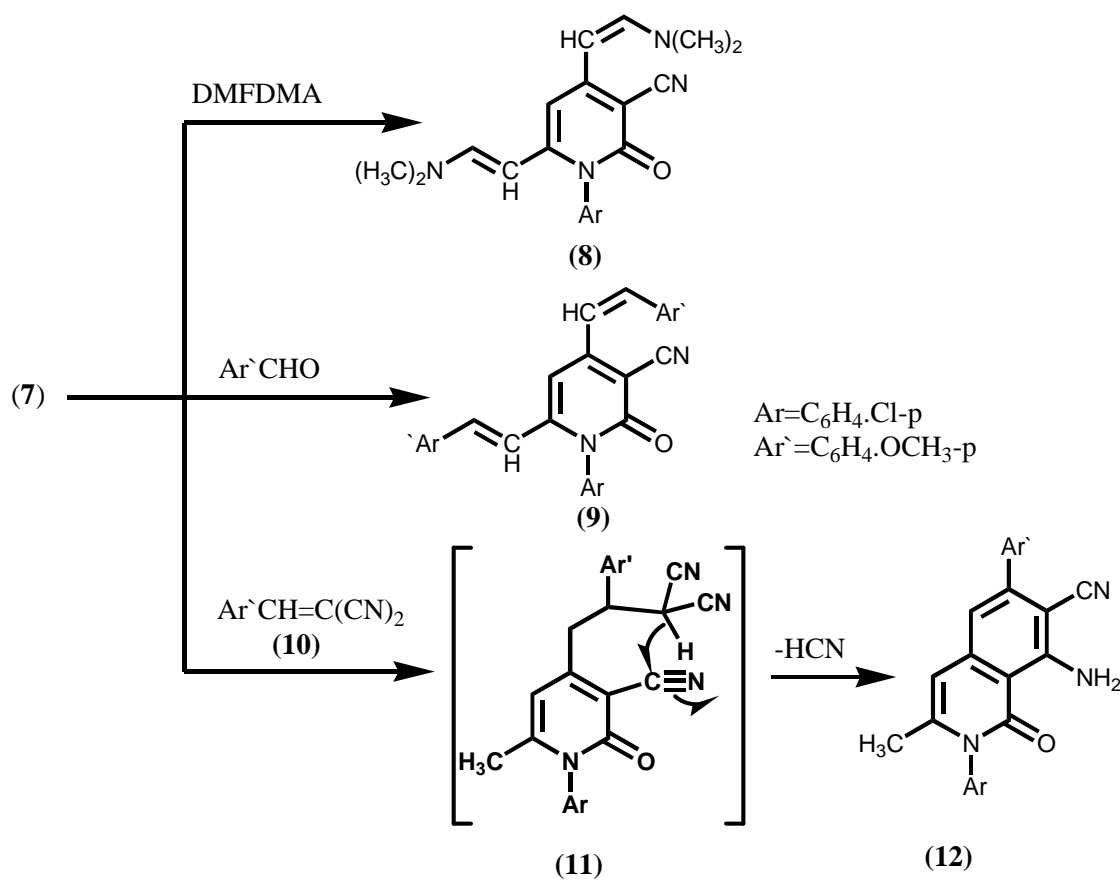
Compound (**7**) was used to synthesize some novel pyridine derivatives through its reaction with some electrophiles. It is important to emphasize that the presence of the nitrile group at the position-3 of the pyridine ring activates the methyl group at position 4. Thus, Condensation of compound (**7**) with dimethylformamide-dimethylacetal (DMF-DMA) in xylene^{19,20} produced the bis (enamine) derivative (**8**) Scheme 2. The ^1H NMR spectrum of compound (**8**) revealed the absence of the two methyl groups and exhibited the presence of a singlet at δ 3.01 attributed to $2\text{N}(\text{CH}_3)_2$ group. Also, the bis-styryl derivative (**9**) was obtained on treatment of (**7**) with *p*-anisaldehyde in the presence of sodium ethoxide, (Scheme 2). The ^1H NMR spectrum of (**9**) supports the proposed structure which reveals the presence of two methoxy groups which each appears as a singlet signal at δ 3.76, 3.89. Cyclization of compound (**7**) with 4-methoxy- α -cyano-cinnamionitrile (**10**) in the presence of sodium ethoxide furnished a product which was formulated as benzo[*c*]pyridine (**12**). Its infrared showed the presence of amino, cyano and carbonyl functional groups. In addition, the ^1H NMR spectrum revealed the presence of methyl, methoxy, amino and aromatic protons. The formation of benzopyridine **12** is assumed to proceed via the Michael adduct **11** followed by intramolecular cyclization and loss of hydrogen cyanide to yield the final product, (Scheme 2).



Scheme 1

The formation of compound (6) was proceed according the following mechanism:

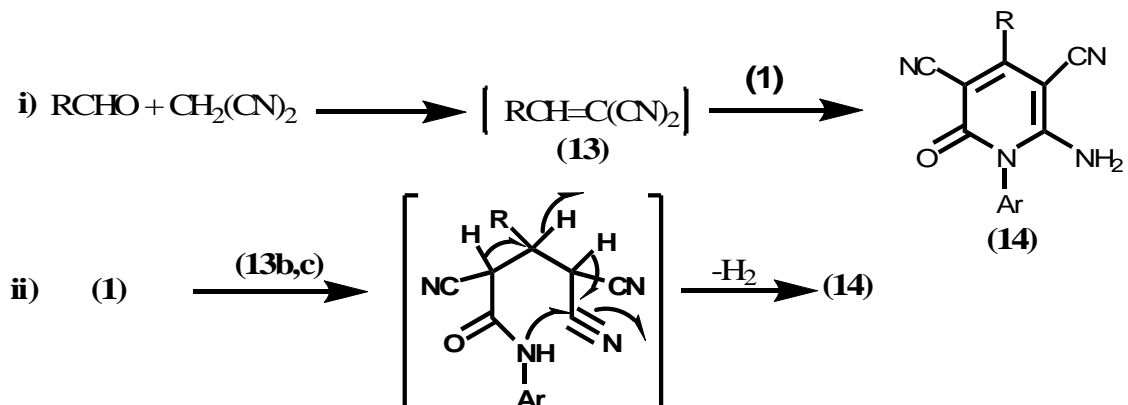




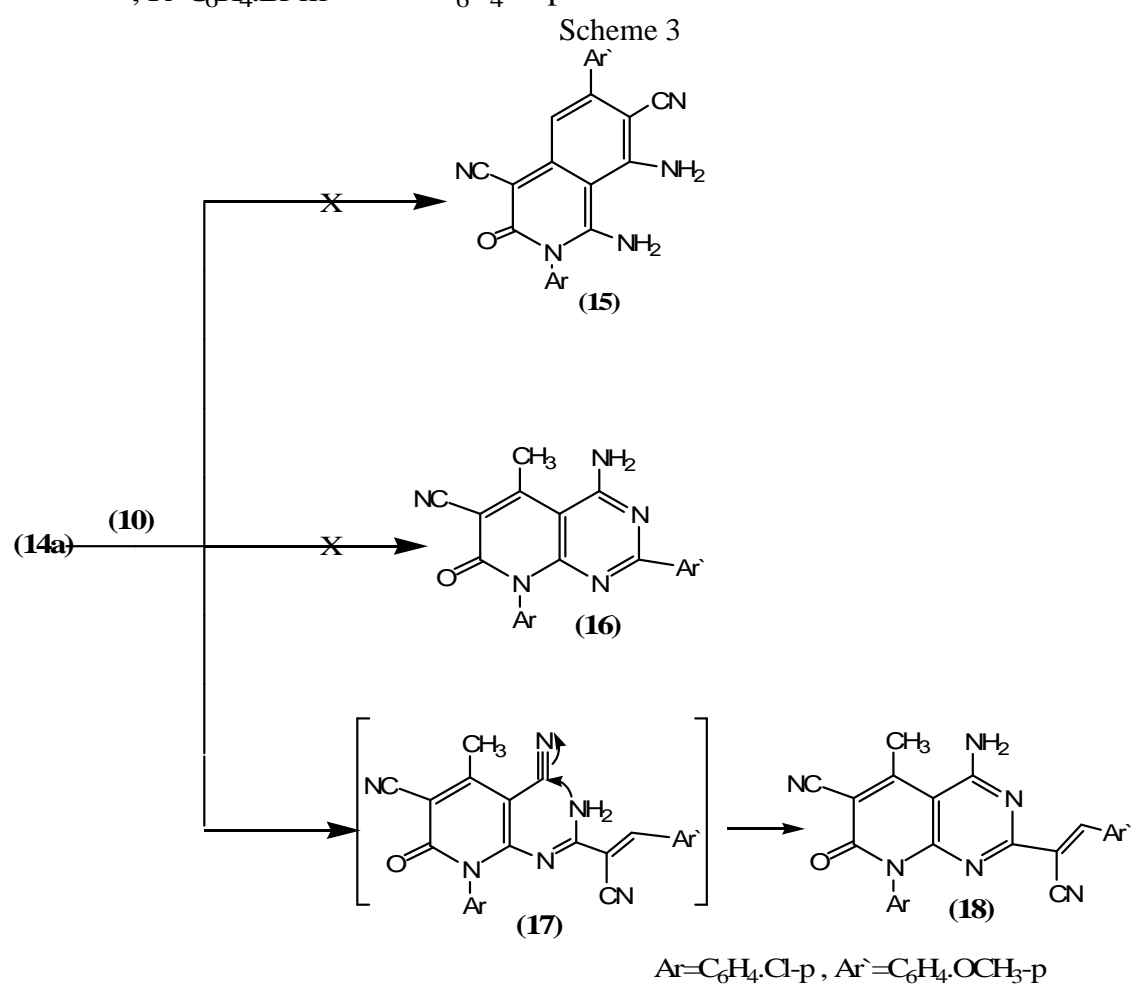
Scheme 2

Aminopyridines (**14a-c**) were synthesized via ternary condensation of compound (1), aldehyde and malononitrile (1:1:1 molar ratio) under reflux in ethanol in the presence of piperidine, (Scheme 3). The isolated products were confirmed based on the elementary analysis and spectral data. Mass spectrum of **14b** exhibited a molecular ion peak at m/z 380 which is the base peak in the spectrum. A reaction mechanism is proposed for the formation of pyridine (**14**) and illustrated in (Scheme 3).

Compound (**14a**) was found to be used as a starting material for the synthesis of some novel fused pyridine derivatives. Cyclization of compound (**14a**) with 4-methoxy- α -cyanocinnamitrile (**10**) at reflux temperature in the presence of piperidine furnished pyrido[2,3-d]pyrimidine derivative (**18**). The structures (**15**) and (**16**) were eliminated on the basis of analytical and spectral data. Its ^1H NMR spectrum showed the presence of a methyl group which is present in the parent compound in addition to methoxy, amino and aromatic protons. In addition, mass spectrum revealed a molecular ion peak at m/z 468 (10%) with base peak at m/z 380. The formation of (**18**) is assumed to proceed via nucleophilic addition of amino functional group (**14a**) to the cyano functional group at position 5 followed by intermolecular cyclization of the intermediate (**17**) and tautomerization to yield the final isolable product (**18**), (Scheme 4).



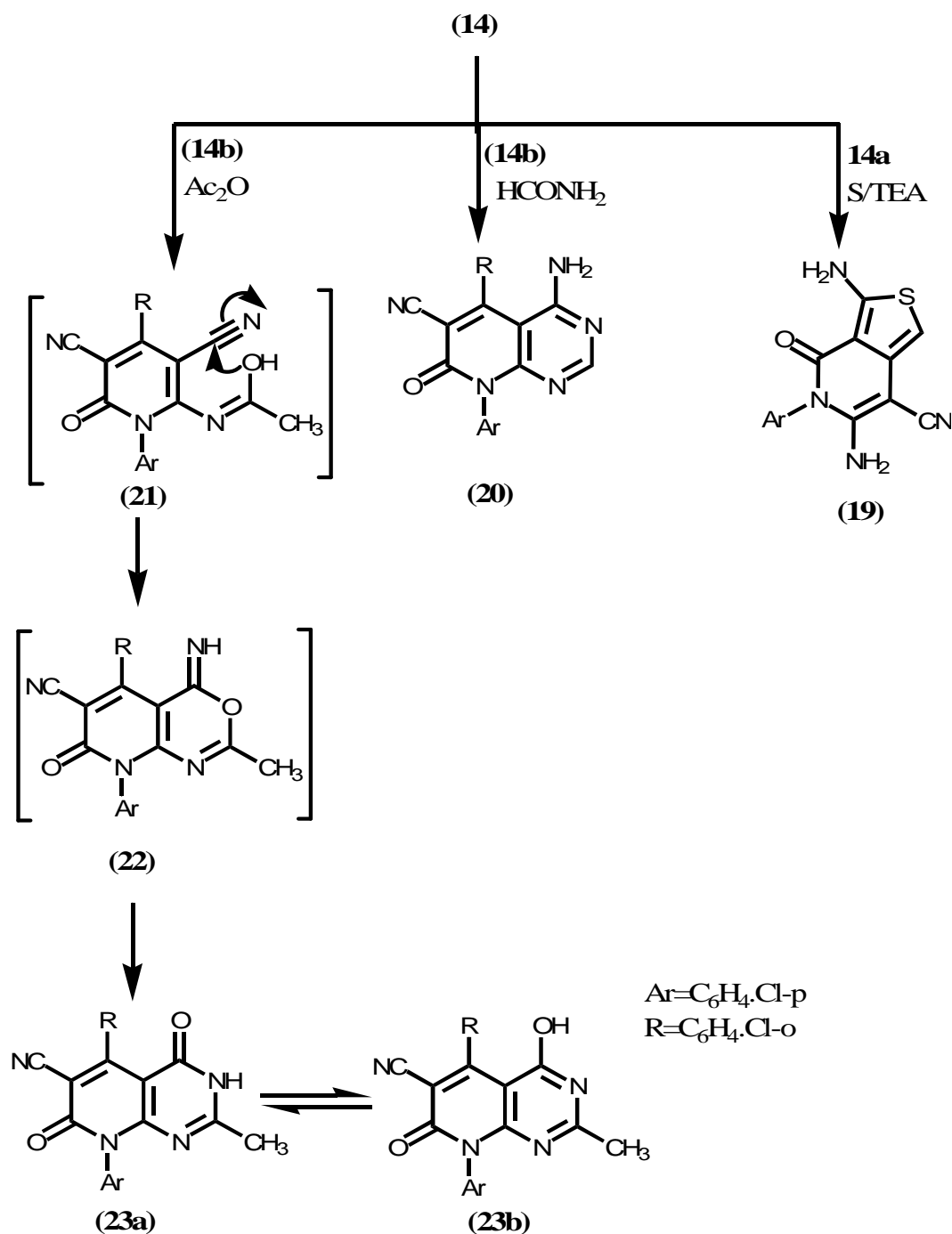
- 14a; R=CH₃ Ar=C₆H₄.Cl-p
 b; R=C₆H₄.Cl-o Ar=C₆H₄.Cl-p
 c; R=C₆H₄.Br-m Ar=C₆H₄.Cl-p



Scheme 4

Thieno[3,4-c]pyridine derivative (19) was achieved by refluxing of compound (14a) with sulfur in ethanol in the presence of triethylamine, (Scheme 5), the molecular structure of (19) was

proved on the basis of analytical and spectral data. Its ^1H NMR spectrum revealed the absence of methyl group. Refluxing of compound (14a) in formamide²¹ afforded pyrido[2,3-d]pyrimidine derivative (20). Finally, pyrido[2,3-d]pyrimidine derivative (23) was obtained by refluxing of compound (14b) in acetic anhydride. This compound was formed via intramolecular cyclization of the intermediate (21) to give (22) which rearrangement into (23), (Scheme 5).



Scheme 5

MATERIALS AND METHODS

All melting points are uncorrected and were determined on a digital Gallen-Kamp MFB-595 instrument. Infrared spectra were recorded on a Shimadzu 440 spectrometer. ^1H NMR spectra were recorded on Varian Gemini EM-300. DMSO- d_6 was used as solvent, TMS was used as internal standard, and chemical shifts were measured in δ ppm. Mass spectra were recorded on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses (C, H, N) were performed on an Perkin-Elmer 2400 analyzer at the Microanalytical Unit of Cairo University.

6-Amino-1-(4-chlorophenyl)-4-methyl-2(1H)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3):

A mixture of equimolar amounts of **1** (0.01 mol), β -aminocrotonitrile (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was allowed to cool and poured into ice/water and the separated solid was filtered and recrystallized from a suitable solvent to give **3** (Table 1). IR cm^{-1} (KBr) 3421, 3316 (NH_2), 2203 ($\text{C}\equiv\text{N}$), 1656 ($\text{C}=\text{O}$). ^1H NMR in DMSO- d_6 δ 2.1 (s, 3H, CH_3), 5.58 (s, 1H, pyridine-H), 7.01 (s, 2H, NH_2 ; exchangeable), 7.2-7.6 (m, 4H, Ar-H).

N-(4-chlorophenyl)-2-cyano-2-cyclohexylideneacetamide (4):

A mixture of equimolar amounts **1** (0.01 mole), cyclohexanone (0.01 mole) in ethanol (30 mL) containing few drops of piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was allowed to cool, and the solid so obtained was filtered and recrystallized from the appropriate solvent to give **4** (Table 1). IR cm^{-1} (KBr) 3280(NH), 2937, 2859 (CH-aliph), 2218 ($\text{C}\equiv\text{N}$), 1645 ($\text{C}=\text{O}$; amide). ^1H NMR in DMSO- d_6 δ 1.6-1.7(m, 10H, cyclohexyl), 7.2-7.7 (m, 4H, Ar-H), 10.6 (s, 1H, NH; exchangeable).

1-(4-Chlorophenyl)-4,6-diamino-2-oxo-1,2-dihydropyridine-3-carbonitrile (6):

A solution of **1** or **4** (0.01mol) and malononitrile (0.01mol) in ethanol (30 mL) was treated with piperidine (0.5 mL). The reaction mixture was refluxed for one hour, then cooled and the solid product was collected and recrystallized from the appropriate solvent to afford **6** (Table 1). IR cm^{-1} (KBr) 3409, 3332, 3247 (2NH_2), 2214 ($\text{C}\equiv\text{N}$), 1651 ($\text{C}=\text{O}$).

1-(4-Chlorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (7):

To a solution of compound **1** (0.01 mol) in ethanol (30 mL), acetylacetone (0.01mol) and piperidine (0.5 mL) were added and the reaction mixture was heated under reflux for one hour, then allowed to cool. The solid product was collected and recrystallized from the suitable solvent to give **7** (Table 1). IR cm^{-1} (KBr) 2217 ($\text{C}\equiv\text{N}$), 1660 ($\text{C}=\text{O}$). ^1H NMR in DMSO- d_6 δ 1.94, 2.41(2s, 6H, 2CH_3), 6.4 (s, 1H, pyridine-H), 7.16-7.81 (m, 4H, Ar-H).

1-(4-Chlorophenyl)-4,6-bis(dimethylaminovinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8):

A mixture of equimolar amounts **7** (0.01 mol) and DMF-DMA (0.02 mol) in xylene (20 mL) was refluxed for 4 h. The reaction mixture was cooled, washed with diethylether, and the separated solid was recrystallized from the required solvent to give **8** (Table 1). IR cm^{-1} (KBr) 2908 (CH-aliph), 2198 ($\text{C}\equiv\text{N}$) 1648 ($\text{C}=\text{O}$). ^1H NMR in DMSO- d_6 δ 3.01 (s, 12H, $2\text{N}(\text{CH}_3)_2$), 5.07, 5.19 (2d, 2H), 6.5 (s, 1H, pyridine-H), 7.1-7.9 (m, 6H, Ar-H + $2\text{CH}=\text{C}$).

1-(4-Chlorophenyl)-4,6-bis[2-(4-methoxyphenyl)vinyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile (9):

A mixture of compound **7** (0.01 mol), p-anisaldehyde (0.02 mol) and sodium ethoxide (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and the solid so obtained was filtered and recrystallized from the suitable solvent to produce **9** (Table 1). IR cm^{-1} (KBr) 2214 ($\text{C}\equiv\text{N}$), 1651 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 3.76, 3.89 (2s, 6H, 2OCH_3), 6.16 (s, 1H, pyridine-H), 6.99-8.01 (m, 20H, Ar-H + $4\text{CH}=\text{}$).

3-Amino-1-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydro-benzo[c]pyridine-4-carbonitrile (12):

A mixture of compound **7** (0.01 mol), 4-methoxy- α -cyanocinnamionitrile **10** (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and poured into ice acidified with HCl, the solid so obtained was filtered and recrystallized from the appropriate solvent to give **12** (Table 1). IR cm^{-1} (KBr) 3332, 3224 (NH_2), 2926 (CH -aliph.), 2221 ($\text{C}\equiv\text{N}$), 1658 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 2.36 (s, 3H, CH_3), 3.80 (s, 2H, NH_2 ; exchangeable), 3.9 (s, 3H, OCH_3), 6.44 (s, 1H, pyridine-H), 6.85-7.69 (m, 9H, Ar-H).

6-Amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (14a-c):

To a solution of compound **1** (0.01 mol) in ethanol (30 mL), aldehyde (0.01 mol), malononitrile (0.01 mol) and piperidine (0.01 mL) were added. The solution was refluxed for 3 h and cooled. The solid product was collected and recrystallized from the suitable solvent to produce **14a-c** (Table 1).

6-Amino-1-(4-chlorophenyl)-4-methyl-2-oxo-1,2-dihydro-pyridene-3,5-dicarbonitrile (14a):
IR cm^{-1} (KBr) 3389, 3316 (NH_2), 2209 ($\text{C}\equiv\text{N}$), 1670 ($\text{C}=\text{O}$).

6-Amino-1-(4-chlorophenyl)-4-(2-chlorophenyl)-2-oxo-1,2-dihydro-pyridene-3,5-dicarbonitrile (14b):
IR cm^{-1} (KBr) 3397, 3294 (NH_2), 2214 ($\text{C}\equiv\text{N}$), 1660 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 7.4-7.68 (m, 8H, Ar-H), 7.9 (s, 2H, NH_2 ; exchangeable).

6-Amino-1-(4-chlorophenyl)-4-(3-bromophenyl)-2-oxo-1,2-dihydro-pyridene-3,5-dicarbonitrile (14c):
IR cm^{-1} (KBr) 3441, 3370 (NH_2), 2211 ($\text{C}\equiv\text{N}$), 1689 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 7.3-7.79 (m, 8H, Ar-H), 7.81 (s, 2H, NH_2 ; exchangeable).

4-Amino-2-[1-cyano-2-(4-methoxyphenyl)vinyl]-1-(4-Chlorophenyl)-5-methyl-7-oxo-1,7-dihydro pyrido[2,3-d]pyrimidine-6-carbonitrile (18):

A mixture of compound **14a** (0.01 mol), 4-methoxy- α -cyanocinnamionitrile **10** (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was refluxed for 3h. The reaction mixture was cooled and poured into ice acidified with HCl, and the solid product was collected and recrystallized from the appropriate solvent to give **18** (Table 1). IR cm^{-1} (KBr) 3335, 3191 (NH_2), 2213, 2189 ($2\text{C}\equiv\text{N}$), 1654 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 2.4 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.95-7.85 (m, 9H, Ar-H + $\text{CH}=\text{}$), 8.4 (s, 2H, NH_2 ; exchangeable),

Table 1: Physical data of the synthesized compounds

Compd. No.	M.p. (°C)	Solvent Cryst.	Yield (%)	Molec. formula (Mol. Wt.)	Elemental analyses Calc./found		
					C%	H%	N%
3	250-1	DMF	50	C ₁₃ H ₁₀ ClN ₃ O (259.5)	60.12	3.85	16.18
					60.30	3.80	16.10
4	150-2	E/DMF	54	C ₁₅ H ₁₅ ClN ₂ O (274.5)	65.57	5.46	10.20
					65.80	5.60	10.10
6	>300	E/DMF	56	C ₁₂ H ₉ ClN ₄ O (260.5)	55.28	3.45	21.50
					55.10	3.30	21.60
7	275-6	Ac	60	C ₁₄ H ₁₁ ClN ₂ O (258.5)	64.99	4.25	10.83
					64.80	4.30	10.90
8	220-2	E	62	C ₂₀ H ₂₁ ClN ₄ O (368.5)	65.13	5.70	15.20
					65.30	5.80	15.10
9	190-1	E/DMF	65	C ₃₀ H ₂₃ ClN ₂ O ₃ (494.5)	72.80	4.65	5.66
					72.60	4.60	5.70
12	190-2	M	52	C ₂₄ H ₁₈ ClN ₃ O ₂ (415.5)	69.31	4.33	10.11
					69.20	4.50	10.30
14a	290-1	DMF	70	C ₁₄ H ₉ ClN ₄ O (284.5)	59.05	3.16	19.68
					59.20	3.20	19.80
14b	>300	DMF	72	C ₁₉ H ₁₀ Cl ₂ N ₄ O (381)	59.84	2.62	14.70
					59.70	2.40	14.90
14c	280-2	Ac	55	C ₁₉ H ₁₀ BrClN ₄ O (425.5)	53.58	2.35	13.16
					53.70	2.50	13.20
18	>300	M	56	C ₂₅ H ₁₇ ClN ₆ O ₂ (468.5)	64.03	3.62	17.93
					64.20	3.70	17.80
19	>300	E	62	C ₁₄ H ₉ ClN ₄ OS (316.5)	53.08	2.84	17.69
					53.10	2.90	17.60
20	>300	E/DMF	60	C ₂₀ H ₁₁ Cl ₂ N ₅ O (408)	58.82	2.70	17.16
					58.60	2.50	17.30
23	>300	E/DMF	50	C ₂₁ H ₁₂ Cl ₂ N ₄ O ₂ (423)	59.57	2.84	13.24
					59.30	2.60	13.40

Ac= Acetic acid, D= Dioxane, DMF= Dimethylformamide, E=Ethanol, and M=Methanol

3,6-Diamino-5-(4-Chlorophenyl)-4-oxo-4,5-dihydrothieno[3,4-c]pyridine-7-carbonitrile (19):

A mixture of compound **14a** (0.01mol), elemental sulfur (0.01mol) and triethylamine (0.5 mL) in ethanol (30 mL) was refluxed for 4h. The reaction mixture was cooled and poured into ice acidified with HCl, and the solid product was collected and recrystallized from the suitable solvent to produce **19** (Table1). IR cm⁻¹ (KBr) 3272, 3200 (NH₂), 2210 (C≡N), 1658 (C=O). ¹H NMR in DMSO-d₆ δ 3.52 (s, 2H, NH₂; exchangeable), 6.4 (s, 1H, thiophene-H), 7.36-7.77 (m, 4H, Ar-H), 9.0 (br, 2H, NH₂; exchangeable).

4-Amino-5-(2-Chlorophenyl)-8-(4-chlorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (20):

A suspension of compound **14b** (0.01mol) in formamide (10 mL) was refluxed for 5h., then cooled . The solid product that obtained and recrystallized from the required solvent to give **20**

(Table1). IR cm^{-1} (KBr) 3448, 3255 (NH_2), 2198 ($\text{C}\equiv\text{N}$), 1650 ($\text{C}=\text{O}$). ^1H NMR in DMSO-d_6 δ 7.3-7.78 (m, 8H, Ar-H), 8.5 (s, 1H pyrimidine-H), 9.1 (s, 2H, NH_2 ; exchangeable).

5-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4, 7-dioxo-3, 4, 7, 8-tetrahydropyrido [2, 3-d] pyrimidine-6-carbonitrile (**23**):

A suspension of compound 14b (0.01mol) in acetic anhydride (10 mL) was refluxed for 5h., then cooled . The solid product that obtained and recrystallized from appropriate solvent to give 23 (Table1). IR cm^{-1} (KBr) 3340 (NH), 2923(CH-aliph), 2221 ($\text{C}\equiv\text{N}$), 1666 ($\text{C}=\text{O}$).

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