Cyanoacetanilides Intermediates in Heterocyclic Synthesis. Part 2: Preparation of Some Hitherto Unknown Ketene Dithioacetal, Benzoazole and Pyridone Derivatives

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Ketene dithioacetal **3**, aminopyrazole **5**, tetrazine **7**, benzoazole **9** and pyridone **11**, **12**, **13** and **16** derivatives were prepared from cyanoacetanilide **1** as a starting material.

Keywords: Ketene dithioacetal; Benzoazole; Aminopyrazole and pyridone derivatives.

INTRODUCTION

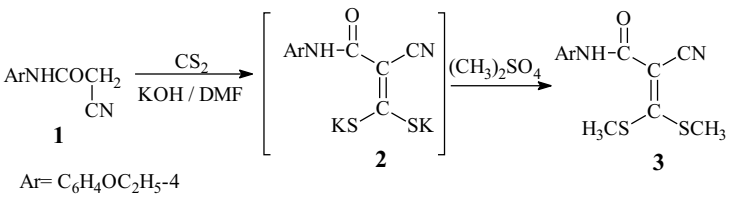
Cyanoacetanilides are important and versatile reagents which have been especially used for the synthesis of polyfunctionalized heterocycles.[1-3] Aminopyrazole,[4] benzoazole[5] and 3-cyanopyridine-2-one[6] derivatives have been reported to exhibit biological activities. In view of the above and in continuation of our studies on the synthesis of heterocyclic compounds exhibiting biological activity,[7-9] we report here the synthesis of novel ketene dithioacetal, benzoazole and pyridone derivatives from cyanoacetanilide derivative **1** as readily available starting material.

RESULTS AND DISCUSSION

Reaction of compound **1** with carbon disulfide in dimethylformamide and in the presence of potassium hydroxide gave the non-isolable intermediate **2**. The latter was converted into 2-cyano-*N*-(4-ethoxyphenyl)-3,3-bis(methylsulfanyl)acrylamide **3** by treatment with dimethyl sulfate at room temperature in good yield, Scheme I. The structure of **3** was confirmed by analytical and spectroscopic data. The ^{1}H NMR spectrum of **3** in DMSO-d_6 revealed the presence of a singlet at δ = 2.37, 2.48 ppm characteristic for two methylthio groups in addition to the expected signals attributed to NH, ethoxy and aromtic protons. Also, the structure **3** is supported by its mass spectrum which showed a molecular ion peak at *m/z* = 308 (12.4%) corresponding to the formula $C_{14}H_{16}N_2O_2S_2$. Also, the base peak was found in the spectrum at *m/z* = 75.

The reactivity of compound **3** towards some nitrogen and carbon nucleophiles was studied. Thus, treatment of compound **3** with aromatic amine in refluxing ethanol gave acrylamide derivatives **4a,b**, through Michael addition followed by elimination of methyl mercaptan.[10] The mass spectrum of compound **4a** showed a molecular ion peak at *m/z* = 367 (48.7%) with base peak at *m/z* = 137 ($H_2NC_6H_4OC_2H_5$-4). Cyclocondensation of compound **3** with phenyl hydrazine furnished the novel aminopyrazole derivative **5**. The isolated product was established by analytical and spectral data. In the mass spectrum of compound **5** a molecular ion peak was found at *m/z* = 368 (39%) with base peak at *m/z* = 232 (M-$HNC_6H_4OC_2H_5$). The formation of **5** is assumed to proceed through Michael addition of the amino group to the ethylenic bond in **3** with elimination of methyl mercaptan followed by intramolecular cyclization at the cyano group to form **5**. On

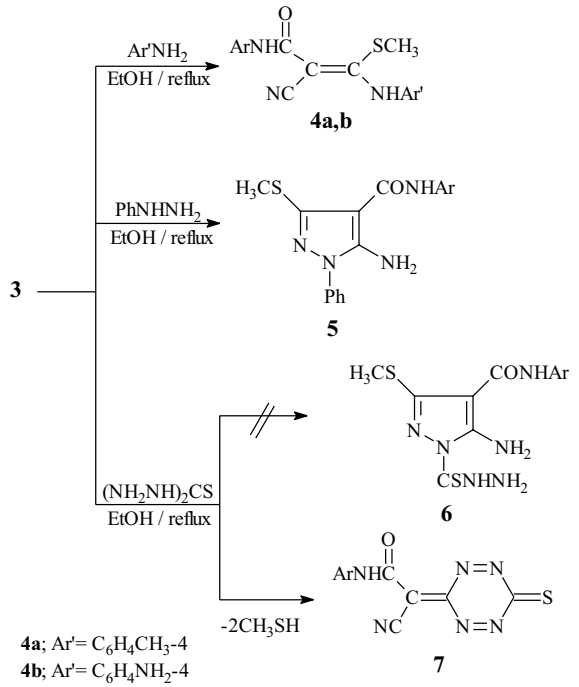
Scheme I



Ar= $C_6H_4OC_2H_5$-4

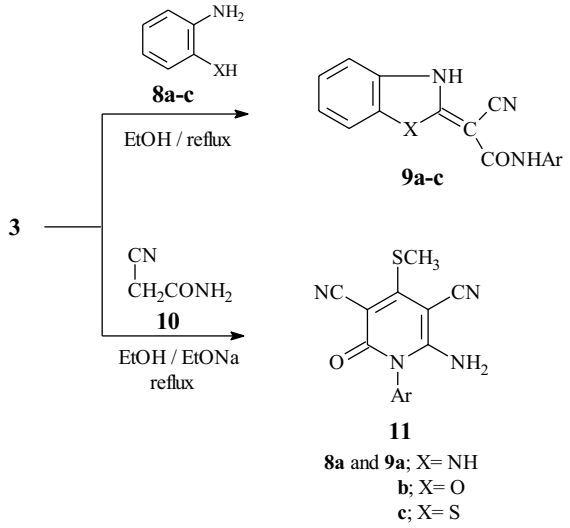
the other hand, reaction of compound **3** with thiocarbohydrazide in ethanol under reflux gave the tetrazine derivative **7** and discarded the other possible structure **6** on the basis of analytical and spectral data. The infrared spectrum of compound **7** was characterized by the appearance of absorption bands corresponding to NH, C≡N and C=O at 3174, 2191 and 1660 cm^{-1}, respectively. Also, the mass spectrum of **7** showed a molecular ion peak at *m/z* = 312 (M-2; 5.1%) with base peak at *m/z* = 146.

Scheme II



Our investigation was extended to include the behavior of **3** towards bifunctional nucleophilic reagents. When compound **3** was treated with 1,2-phenylenediamine **8a** in refluxing ethanol containing triethylamine, the benzimidazole derivative **9a** was obtained. The reaction is assumed to proceed via a nucleophilic attack of the NH_2 to the ethylenic bond in **3** with elimination of two moles of methyl mercaptan.[10] In a similar manner, the reactions of 2-aminophenol **8b** and 2-aminothiophenol **8c** with compound **3** led to the formation of benzoazole derivatives **9b** and **9c**, respectively. Compound **3** reacted with cyanoacetamide **10** as carbon nucleophile in refluxing in the presence of sodium ethoxide to yield the pyridine derivative **11**. The formation of **11** was suggested to proceed via the addition of the active methylene group of **10** to the ethylenic bond with elimination of methyl mercaptan followed by loss of water[11] to form **11**, Scheme III.

Scheme III

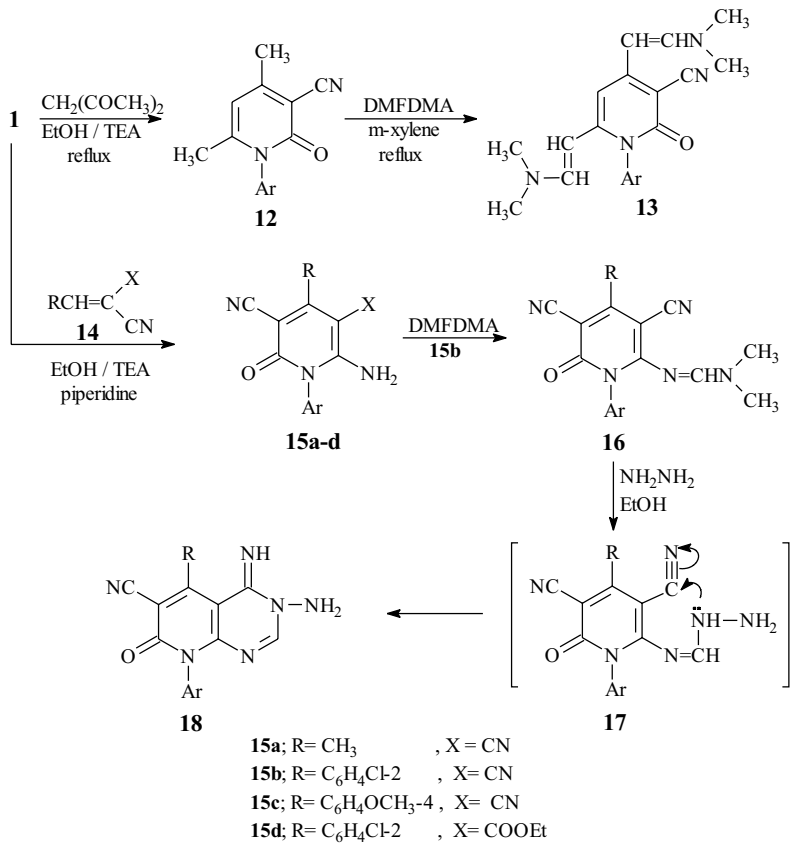


The reactivity of compound **1** towards certain nucleophilic and electrophilic reagents was studied. Thus, cyclocondensation of compound **1** with acetylacetone as nucleophile in ethanol in the presence of triethylamine[12] yielded pyridone derivative **12** in excellent yield. Condensation of compound **12** with excess dimethylformamide-dimethylacetal in refluxing *m*-xylene furnished 4,6-bis-(2-dimethylamino-vinyl)-1-(4-ethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **13**. Also, compound **1** was cyclized with activated nitriles **14** to furnish pyridone derivatives **15a-d**. The novel azomethine **16** was achieved by treatment of compound **15b** with dimethylformamide-dimethylacetal in refluxing dioxane. On refluxing compound **16** with hydrazine hydrate in ethanol, *N*-amino derivative **18** was obtained. The formation of compound **18** is assumed to proceed via loss of a dimethylamine to form non-isolated intermediate **17** which undergoes intramolecular cyclization into **18**, Scheme IV.

EXPERIMENTAL

Melting points are recorded on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Varian Gemini Spectrometer 200 (200 MHz) using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C micro-analyzer. The physical and spectral data are collected in Tables 1 and 2, respectively.

Scheme IV



Formation of 2-cyano-*N*-(4-ethoxyphenyl)-3,3-bis(methylsulfanyl)-acrylamide (3)

To a stirred suspension of finely powdered potassium hydroxide (0.01 mole) in dry dimethyformamide (10 mL) cooled to 0 °C the active methylene **1** (0.01 mole) and next carbon disulfide were added gradually. The reaction mixture was stirred at room temperature for 3 h, then cooled again to 0 °C, treated with dimethyl sulfate and stirred at room temperature for an additional 6 h. Then it was poured into ice/water; the resulting precipitate was filtered off, dried and recrystallized to give **3**.

MS (**3**): 308 (M^+; 12.4%), 309 (M+1; 2.3%), 310 (M+2; 1.5%), 261 (M-SCH_3; 1.2%), 172 (M-$NHC_6H_4OC_2H_5$; 54%), 137 ($H_2NC_6H_4OC_2H_5$; 8.9%), 76 (3.6%), 75 (100%).

3-(4-Ethoxyphenylamino)-2-methylsulfanyl-2-(4-tolylamino-methylene)-but-3-enenitrile (4a) and 3-(4-aminophenylamino)-2-cyano-*N*-(4-ethoxyphenyl)-3-(methylsulfanyl)-acrylamide (4b): General procedure

A mixture of **3** (0.01 mole) and the aromatic amine (0.01 mole) in ethanol (30 mL) was heated under reflux for 1 h. The reaction mixture was concentrated and the obtained product was recrystallized to give **4**.

MS (**4a**): 367 (M^+; 48%), 368 (M+1; 11.7%), 369 (M+2; 8.5%); 320 (M-SCH_3; 19.3%), 231 (29.3%), 137 ($H_2NC_6H_4OC_2H_5$; 100%), 108 (56%), 91 (27%), 107 (37.7%), 76 (5.9%).

MS (**4b**): 354 [M-14(N); 9.5%], 218 (10%), 190 (10%), 137 ($H_2NC_6H_4OC_2H_5$; 100%), 108 (38%), 76 (1.9%), 75 (1.6%).

Synthesis of 5-amino-3-methylsulfanyl-1-phenyl-1H-pyrazole-4-carboxylic acid (4-ethoxyphenyl)amide (5) and 2-cyano-*N*-(4-ethoxyphenyl)-2-(6-thioxo-6H-[1,2,4,5]-tetrazine-3-ylidene)acetamide (7): General procedure

A mixture of **3** (0.01 mole) and phenyl hydrazine or thiocarbohydrazide was heated at 100 °C for 0.5 h. The obtained product was collected and recrystallized to give **5** or **7**, respectively.

MS (**5**): 368 (M^+; 39%), 369 (M+1; 8.5%), 323 (M-$HNC_6H_4OC_2H_5$; 100%), 137 ($H_2NC_6H_4OC_2H_5$; 32%), 108 (6.8%), 119 (24%), 91 (5.3%), 76 (1.3%), 75 (1.5%).

MS (**7**): 312 (M-2; 5.1%), 292 (47%), 246 (16%), 218 (10%), 163 (12%), 146 (100%), 137 (76%), 108 (65%), 76

Table 1. Physical and analytical data of the synthesized compounds

Compd. No.	M.p. (°C)	Yield (%)	Solvent	Molecular formula (Mol. Wt.)	Elemental analyses		
					C%	H%	N%
3	80-2	87	EtOH	$C_{14}H_{16}N_2O_2S_2$	54.52	5.23	9.08
				(308.42)	54.60	5.10	9.00
4a	150-1	82	EtOH	$C_{20}H_{21}N_3O_2S$	65.37	5.76	11.43
				(367.47)	65.30	5.70	11.40
4b	170-2	76	EtOH	$C_{19}H_{20}N_4O_2S$	61.94	5.47	15.21
				(368.46)	61.80	5.40	15.10
5	120-3	68	EtOH	$C_{19}H_{20}N_4O_2S$	61.94	5.47	15.21
				(368.46)	61.80	5.50	15.20
7	> 300	70	EtOH	$C_{13}H_{10}N_6O_2S$	49.68	3.21	26.74
				(314.33)	49.60	3.10	26.60
9a	275-6	74	EtOH	$C_{18}H_{16}N_4O_2$	67.49	5.03	17.49
				(320.35)	67.10	5.00	17.40
9b	210-2	87	EtOH	$C_{18}H_{15}N_3O_3$	67.28	4.71	13.08
				(321.34)	67.20	4.70	13.00
9c	240-1	80	EtOH	$C_{18}H_{15}N_3O_2S$	64.08	4.48	12.45
				(337.40)	64.20	4.50	12.40
11	190-2	74	EtOH	$C_{16}H_{14}N_4O_2S$	58.88	4.32	17.17
				(326.38)	58.70	4.40	17.10
12	230-1	84	EtOH	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44
				(268.32)	71.60	6.00	10.40
13	115-6	88	Dioxane	$C_{22}H_{26}N_4O_2$	69.82	6.92	14.80
				(378.48)	69.70	6.80	14.90
15a	268-9	72	Benzene	$C_{16}H_{14}N_4O_2$	65.30	4.79	19.04
				(294.32)	65.30	4.70	19.10
15b	> 300	76	Benzene	$C_{21}H_{15}ClN_4O_2$	64.54	3.87	14.34
				(390.83)	64.60	3.70	14.30
15c	> 300	75	Benzene	$C_{22}H_{18}N_4O_2$	71.34	4.90	15.13
				(370.41)	71.30	4.80	15.10
15d	230-2	73	Benzene	$C_{23}H_{20}ClN_3O_4$	63.09	4.60	9.60
				(437.89)	63.10	4.60	9.60
16	247-8	76	EtOH	$C_{24}H_{20}ClN_5O_2$	64.65	4.52	15.71
				(445.91)	64.60	4.50	15.70
18	260-1	65	EtOH	$C_{22}H_{17}N_6O_2$	66.49	4.31	21.15
				(397.43)	66.30	4.60	21.40

(11%), 60 (54%).

2-Cyano-2-(1,3-dihydro-benzimidazol-2-ylidene)-*N*-(4-ethoxyphenyl)acetamide (9a), 2-(3H-benzoxazol-2-ylidene)-2-cyano-*N*-(4-ethoxyphenyl)acetamide (9b) and 2-(3H-benzothiazol-2-ylidene)-2-cyano-*N*-(4-ethoxyphenyl)-acetamide (9c): General procedure

A mixture of compound **3** (0.01 mole) and binucleophile (0.01 mole) in ethanol (30 mL) was heated under reflux for 48 h. The reaction mixture was concentrated and the obtained product was collected and recrystallized to give **9a-c**.

6-Amino-1-(4-ethoxyphenyl)-4-methylsulfanyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (11)

A mixture of compound **3** (0.01 mole), cyanoacetamide (0.01 mole) and sodium ethoxide (0.01 mole) in ethanol (30 mL) was heated under reflux for 3 h, then allowed to cool and poured into cold water (50 mL) and acidified with HCl to give **11**.

1-(4-Ethoxyphenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (12)

A mixture of compound **1** (0.01 mole), acetylacetone

Table 2. Spectral data of the synthesized compounds

Compd No.	IR/ν_{max} (cm^{-1})	^{1}H NMR (DMSO-d_6; δ/ppm)
3	3373 (NH), 2980 (CH-aliph), 2202 (C≡N), 1660 (C=O).	1.34 (t, 3H, CH_3), 2.37, 2.48 (2s, 6H, $2SCH_3$), 4.12 (q, 2H, CH_2), 6.91-7.15 (m, 4H, Ar-H), 9.34 (s, 1H, NH).
4a	3224 (NH), 2977, 2923 (CH-aliph), 2191 (C≡N), 1620 (C=O).	
4b	3399, 3178 (NH_2), 2174 (C≡N), 1640 (C=O).	1.41 (t, 3H, CH_3), 2.53 (s, 3H, SCH_3), 4.12 (q, 2H, CH_2), 6.91-7.39 (m, 8H, Ar-H), 8.29, 8.33 (2s, 2H, 2NH), 12.56 (hump, 2H, NH_2).
5	3425, 3363, 3317 (NH/NH_2), 3047 (CH-arom), 2923 (CH-aliph), 1643 (C=O).	1.45 (t, 3H, CH_3), 2.58 (s, 3H, SCH_3), 4.18 (q, 2H, CH_2), 6.72 (s, 2H, NH_2), 6.94-7.59 (m, 9H, Ar-H), 9.41 (s, 1H, NH).
7	3174 (NH), 2977, 2923 (CH-aliph), 2191 (C≡N), 1660 (C=O).	1.18 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 6.81, 7.49 (2d, 4H, Ar-H), 8.79 (s, 1H, NH).
9a	3250, 3420 (2NH), 2169 (C≡N), 1643 (C=O).	1.40 (t, 3H, CH_3), 4.11 (q, 2H, CH_2), 6.90-7.45 (m, 8H, Ar-H), 8.15, 8.32, 12.40 (3s, 3H, 3NH).
9b	3301, 3201 (2NH), 2985, 2923 (CH-aliph), 2214 (C≡N), 1674 (C=O).	
9c	3402, 3201 (2NH), 2183 (C≡N), 1651 (C=O).	1.41 (t, 3H, CH_3), 4.12 (q, 2H, CH_2), 7.01-7.85 (m, 8H, Ar-H), 8.28, 8.39 (2s, 2H, 2NH).
11	3306, 3204 (NH_2), 2984, 2928 (CH-aliph), 2214 (C≡N), 1670 (C=O).	1.19 (t, 3H, CH_3), 2.81 (s, 3H, SCH_3), 4.07 (q, 2H, CH_2), 6.81-7.55 (m, 4H, Ar-H), 7.89 (hump, 2H, NH_2).
12	3064 (CH-arom), 2984, 2910 (CH-aliph), 2218 (C≡N), 1600 (C=O).	1.37 (t, 3H, CH_3), 1.99, 2.39 (2s, 6H, $2CH_3$), 4.08 (q, 2H, CH_2), 6.45 (s, 1H, pyridine-H), 7.04, 7.24 (2d, 4H, Ar-H).
13	2916 (CH-aliph), 2191 (C≡N), 1630 (C=O).	1.36 (t, 3H, CH_3), 2.71, 3.00 (2s, 12H, $2N(CH_3)_2$), 4.10 (q, 2H, CH_2), 6.54 (s, 1H, pyridine-H), 6.99 (s, 4H, Ar-H), 7.43, 7.71 (2d, 4H, ethylene-H).
15a	3309, 3193 (NH_2), 2977 (CH-aliph), 2214 (C≡N), 1660 (C=O).	1.28 (t, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.81 (s, 2H, NH_2), 4.02 (q, 2H, CH_2), 6.87, 7.42 (2d, 4H, Ar-H).
15c	3320, 3186 (NH_2), 2206 (C≡N), 1640 (C=O).	1.37 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.12 (q, 2H, CH_2), 7.08-7.51 (m, 8H, Ar-H), 7.67 (hump, 2H, NH_2).
15d	3420, 3224 (NH_2), 2229 (C≡N), 1700 (C=O; ester), 1658 (C=O; pyridone).	0.61, 1.38 (2t, 6H, $2CH_3$), 3.80, 4.14 (q, 4H, $2CH_2$), 7.12-7.58 (m, 10H, Ar-H and NH_2).
16	2977, 2931 (CH-aliph), 3214 (C≡N), 1651 (C=O).	1.37 (t, 3H, CH_2), 2.71, 3.06 (2s, 6H, $2CH_3$), 4.10 (q, 2H, CH_2), 7.01-7.73 (m, 8H, Ar-H), 8.22 (s, 1H, CH=N).
18	3448, 3178 (NH_2), 2977 (CH-aliph), 2221 (C≡N), 1658 (C=O).	1.35 (t, 3H, CH_3), 4.13 (q, 2H, CH_2), 7.10-7.71 (m, 11H, Ar-H+NH_2+NH), 7.98 (s, 1H, pyrimidine-H).

(0.01 mole) and triethylamine (0.01 mole) in ethanol (40 mL) was heated under reflux for 4 h; the solid product which was produced on heating was collected and recrystallized to give **12**.

4,6-Bis(2-dimethylamino-vinyl)-1-(4-ethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (13)

A mixture of compound **12** (0.01 mole) and dimethylformamide-dimethylacetal (0.02 mole) in dry *m*-xylene (30 mL) was heated under reflux for 3 h; the solid product which was produced on heating was collected and recrystallized to give **13**.

6-Amino-1-(4-ethoxyphenyl)-2-oxo-4-R-1,2-dihydropyridine-3,5-dicarbonitriles (15a-c) and ethyl 6-amino-3-cyano-1-(4-ethoxyphenyl)-2-oxo-4-(2-chlorophenyl)-1,2-dihydropyridine-5-carboxylate (15d): General procedure

A mixture of compound **1** (0.01 mole), activated nitrile

14 (0.01 mole) and piperidine (0.01 mole) in ethanol (40 mL) was heated under reflux for 1 h; the solid product which was produced on heating was collected and recrystallized to give **15a-c**.

MS (**15d**): 437 (M^+; 100%), 438 (24.8%), 439 (33.1%), 392 (9%), 362 (10.8%), 364 (16.6%), 336 (11.1%), 137 (2.9%), 108 (25.8%), 76 (2.1%).

N′-[3,5-Dicyano-1-(4-ethoxyphenyl)-6-oxo-4-(2-chlorophenyl)-1,6-dihydro-pyridine-2-yl]-*N,N*-dimethylformamidine (16)

A mixture of compound **15b** (0.01 mole) and dimethylformamide-dimethylacetal (0.01 mole) in dry dioxane (30 mL) was heated under reflux for 1 h, then allowed to cool and poured into cold water (40 mL). The solid product was collected and recrystallized to give **16**.

MS (**16**): 445 (M^+; 84.4%), 446 (27.8%), 447 (30.8%), 416 (17.6%), 410 (15%), 273 (10%), 199 (13%), 137 (7.3%), 108 (4.9%), 99 (100%), 76 (6%).

3-Amino-8-(4-ethoxyphenyl)-4-imino-7-oxo-5-(2-chlorophenyl)-3,4,7,8-tetra-hydropyrido[2,3-d]pyrimidine-6-carbonitrile (18)

A mixture of compound **16** (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (30 mL) was refluxed for 3 h, and then allowed to cool. The solid product was collected and recrystallized to give **18**.

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