# Cyanoacetanilides Intermediates in Heterocyclic Synthesis. Part 1: A Facile Synthesis of Polysubstituted and Condensed Pyridones

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Polysubstituted pyridone derivatives were obtained through interaction of cyanoacetanilides with different reagents such as chalcones, 1,1,3-tricyano-2-aminopropene, and arylidenemalononitrile and acetylacetone.

**Keywords:** Acetanilide; Pyridine and pyrido[2,3-d]pyrimidine derivatives.

## INTRODUCTION

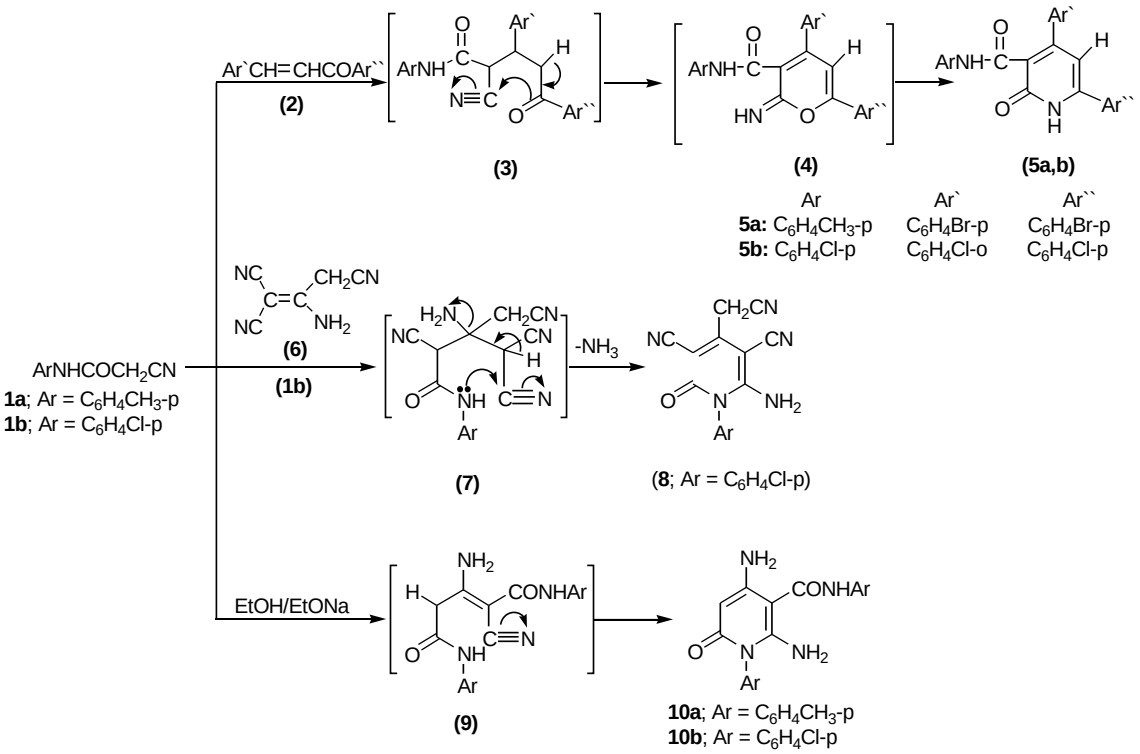
Pyridone and their fused derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance.[1-3] Particularly the pyridine ring can be found in a broad variety of drugs such as milirinone,[4] which is useful for the treatment of the heart; acetylcholine[5] enhancement is useful in the treatment of Alzheimer's disease and 4-aminopyridine derivatives were reported to have antiamnesic activity.[6] As a part of our program directed for the development of a new, simple and efficient procedure for the synthesis of biologically active heterocyclic nitrogenous compounds utilizing readily obtainable intermediates,[7-14] we have investigated the reaction of cyanoacetanilides **1a,b** with different reagents for the synthesis of polysubstituted and condensed pyridones. These compounds seem promising for further chemical transformation and biological evaluation studies.

## RESULTS AND DISCUSSION

When equimolecular amounts of cyanoacetanilides **1a,b**[15] and chalcones **2** were reacted in the presence of a catalytic amount of piperidine, pyridones of type **5a,b** were obtained. The structure **5** was confirmed for the reaction product on the basis of their elemental and spectral data. The infrared spectrum of **5a** showed the disappearance of C≡N band. $^1$H NMR of **5a** revealed two singlets at δ = 8.1, 10.2 ppm assignable to two NH groups and a multiplet at δ = 7.3-7.8 ppm assigned for aromatic protons. The formation of **5** assumed to proceed via Michael addition of the active methylene to the α,β-unsaturated ketone to yield the Michael adduct **3** followed by intramolecular cyclization to form **4** and subsequent Dimrouth rearrangement[16] to yield **5** (Scheme I). Also, interaction of **1b** with 1,1,3-tricyano-2-aminopropene **6** in the presence of piperidine yielded a single product that analysed as $C_{15}H_8ClN_5O$. This product was formulated as 1-(4-chlorophenyl)-6-amino-4-cyano-methyl-2-pyridon-3,5-dicarbonitrile **8**. Structure **8** was readily demonstrated on the basis of spectral data. Its infrared spectrum afforded bands at 3271, 3201 ($NH_2$), 2198 cm$^{-1}$ (C≡N) and $^1$H NMR showed a singlet at δ = 3.87 ppm ($CH_2$) and at δ = 7.2-7.5 ppm (AB system, 4H, Ar-H). The reaction proceeds through the formation of **7** as intermediate followed by cyclization, and the ammonia molecule was eliminated. Dimerization of **1a,b** in ethanol in the presence of sodium ethoxide under reflux produced the pyridone derivatives **10a,b** via the intermediate **9**. The structure of **10** could be established for the reaction product based on the absence of C≡N absorption band in the infrared spectrum, and $^1$H NMR of **10a** revealed a singlet at δ = 2.26 ppm ($2CH_3$), 3.2, 3.7, 9.9 ($2NH_2$, NH; cancelled with $D_2O$). Also, the mass spectrum of **10b** exhibited a molecular ion peak at *m/z* 388 (1.3%) and a base peak at *m/z* 127.

Condensation of **1b** with *p*-anisaldehyde in the presence of piperidine produced α-cyano-4-methoxy-*N*-(4-chlorophenyl)cinnamide **11**. This compound was utilized in synthesis of several new pyridone derivatives of potential and synthetic intermediates. Thus, interaction of compound **11** with cyanoacetamide **12a** and cyanoacetic acid hydrazide **12b** in the presence of piperidine affected cyclization to afford products with analytical and spectral data in complete

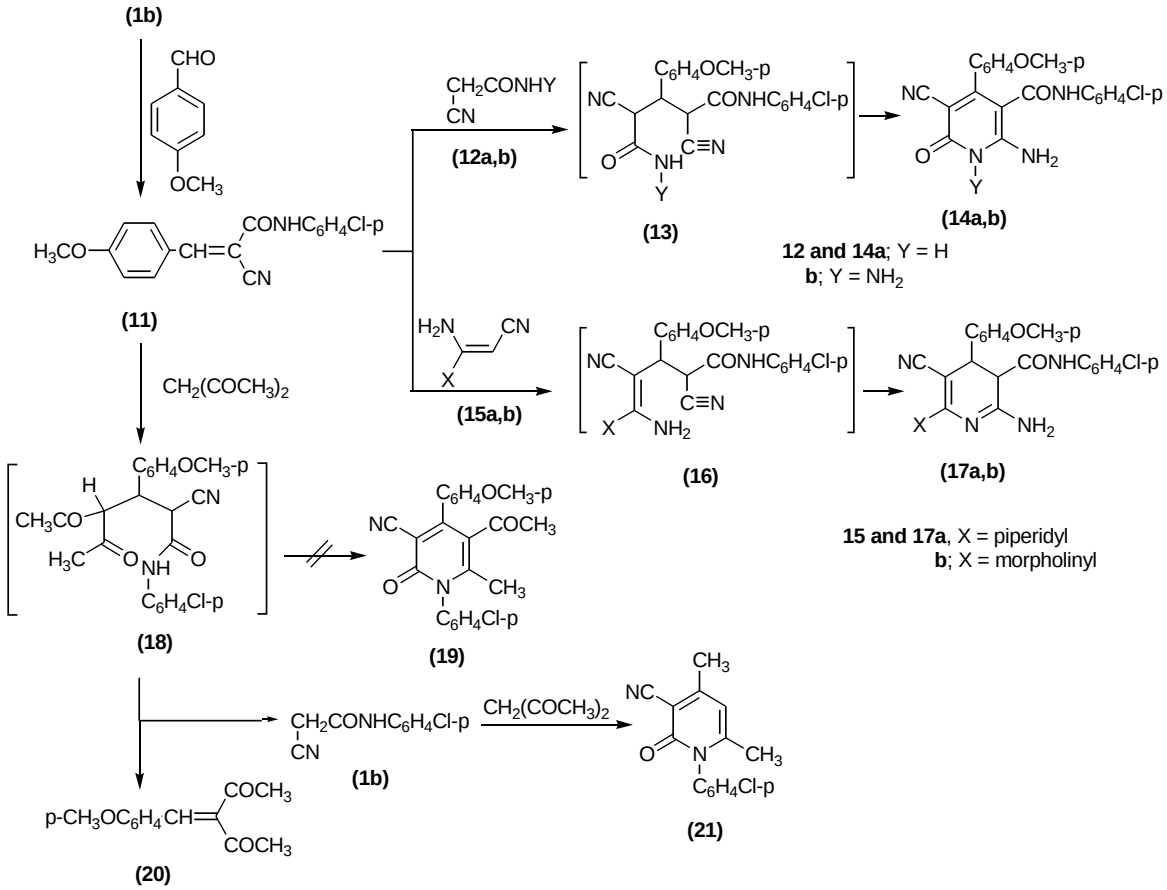
**Scheme I**




agreement with structures **14a** and **14b**, respectively. The $^1$H NMR spectrum of **14a** revealed a singlet at δ = 3.8 ppm for $OCH_3$ and a broad signal at δ = 7.99 for $NH_2$. It seems that **14** was formed via Michael type addition of the methylene function in **12** to the active double bond in **11** to yield acyclic Michael adduct **13** which cyclizes followed by oxidation to form **14**. When enaminonitriles **15a,b**[17] were reacted with an equimolecular quantity of **11** in ethanol, excellent yield from the corresponding dihydropyridine derivatives **17a,b** were formed. The structure of **17** was supported on the basis of elemental analysis and spectral data. The infrared spectrum of **17a** showed bands at 3349, 3197, 3119 ($NH_2$, NH), 2192 cm$^{-1}$ (C≡N). Also, $^1$H NMR spectrum of **17a** exhibited signals at δ = 1.5, 3.1 ppm (m, 8H, piperidyl), 3.79 (s, 3H, $OCH_3$), 5.27, 5.89 ppm (2d, 2H, Pyridine H-3, H-4). It can be postulated that the reaction initially proceeds via a nucleophilic addition to the double bond to form Michael type adduct **16** that subsequently cyclize intramolecularly. In addition, compound **11** was reacted with acetylacetone in boiling ethanol containing piperidine as catalyst and the pyridone derivative **21** was obtained, and the other possible structure **19** was excluded on the basis of analytical and spectral data. The structure of **21** was identified on the basis of satisfactory elemental analysis and spectral data. The infrared spectrum exhibited bands at 2217 (C≡N) and 1660 cm$^{-1}$ (C=O), while its $^1$H NMR spectrum showed signals at δ = 1.9, 2.41 (2s, 6H, $2CH_3$), 6.4 ppm (s, 1H, CH-pyridone). The reaction was assumed to proceed via the formation of the Michael adduct **18** as intermediate which split into *p*-methoxybenzylideneacetylacetone **20** and cyanoacetanilide **1b**, the latter underwent cyclocondensation with acetylacetone to form **21**. Compound **21** could also be obtained in good yield via the reaction of **1b** with acetylacetone in the presence of piperidine (Scheme II).

As a part of this research, the reaction of cyanoacetanilide with unsaturated nitriles was investigated. Thus, it has been found that compound **1b** was reacted with α-cinnamonitriles to yield 1:1 Michael adduct **22** as intermediate which underwent cyclization and oxidation, affording the pyridone derivatives **23a-c** as the final products. IR and $^1$H NMR spectra were utilized to establish structure **23**. IR spectrum of **23a** exhibited bands at 3397, 3295 ($NH_2$) and 2214 cm$^{-1}$ (C≡N). $^1$H NMR spectrum of **23a** showed a singlet at δ = 7.9 ppm assignable for $NH_2$ and multiplet at δ = 7.4-7.8 ppm assigned to aromatic protons. The proposed structure of **23c** was also confirmed through their synthesis from the reaction of **11** with malononitrile. The behavior of **23a** towards some re-

**Scheme II**




agents was discussed. Thus treatment of **23a** with acetic anhydride affected cyclization to afford pyrido[2,3-d]pyrimidine derivative **24**. Both elemental analysis and spectroscopic data are compatible with the assigned structure. Its infrared spectrum exhibited bands at 3340 (NH), 2221 $cm^{-1}$ (C≡N). Also, pyridopyrimidine derivative **25** was obtained upon treatment of **23a** with formamide. The structure of **25** was confirmed via inspection of elemental analysis and spectral data. Its $^1H$ NMR spectrum revealed a multiplet at δ = 7.3-7.8 ppm assigned for 8H, a singlet at δ = 8.6 ppm (CH-pyrimidine) and a singlet at δ = 9.1 ppm ($NH_2$). In addition, interaction of **23a** with phenyl isocyanate consumed two moles of the reagent to furnish pyrido[2,3-d]pyrimidine derivative **26** (Scheme III). Finally, condensation of **23a** with hydrazine hydrate caused cyclization to yield pyrazolo[3,4-b]pyridine derivative **27**. Its infrared spectrum exhibited bands at 3425, 3325 ($NH_2$), 2206 $cm^{-1}$ (C≡N). The formation of **27** is assumed to proceed via the addition of amino function of hydrazine to the cyano group followed by an intramolecular cyclization through $NH_3$ elimination.

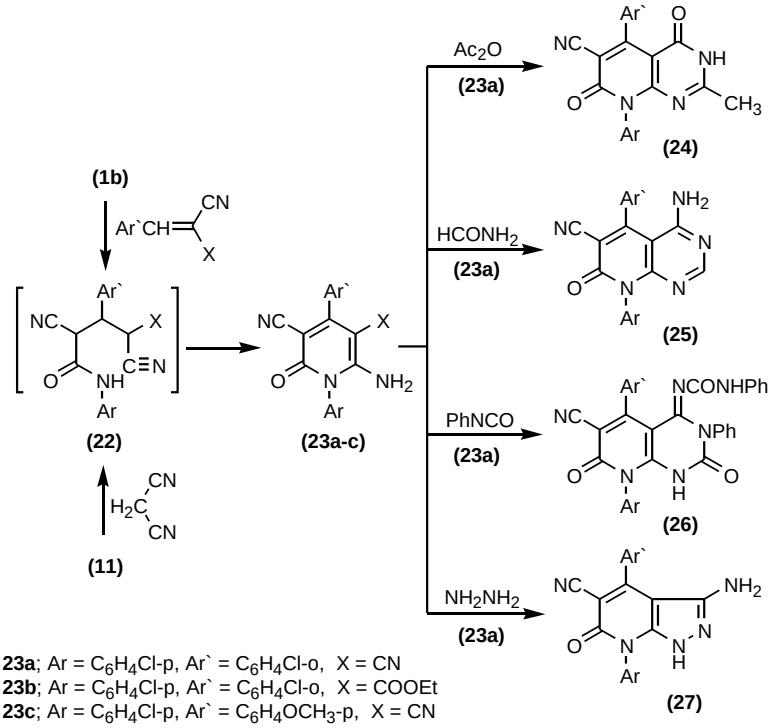
## CONCLUSION

These results indicate that cyanoacetanilides can be utilized as excellent intermediates for the synthesis of several polysubstituted pyridin-2-ones and their condensed derivatives. The synthesized compounds appear promising for further chemical transformations and for biological testing.

## EXPERIMENTAL

Melting points were determined on a stuart apparatus and are uncorrected. The infrared spectra were recorded on a FT/IR 5300 spectrometer. The $^1H$ NMR spectra were measured with a Varian Gemini 200 (200 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra were obtained on a GC-MS-QP 100 EX mass spectrometer at 70 ev. Elemental analyses were carried out at the Microanalytical Center, Cairo University. Physical data for the synthesized compounds are given in Ta-

**Scheme III**




ble 1, and the spectral data are collected in Table 2.

**4,6-Diaryl-2-oxo-1,2-dihydropyridin-3-(N-substituted-phenyl)carboxamides (5a,b): General procedure**

A mixture of **1** (0.01 mol), the chalcone derivatives **2** (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was refluxed for 3 h. The reaction was cooled and poured into crushed ice acidified with HCl. The solid product was filtered off and recrystallized from the proper solvent to give (**5a,b**).

**6-Amino-1-(4-chlorophenyl)-4-cyanomethyl-2-oxo-1,2-dihydropyridin-3,5-dicarbonitrile (8)**

To a solution of **1b** (0.01 mol) in ethanol (30 mL), 1,1,3-tricyano-2-aminopropene **6** (0.01 mol) and piperidine (0.5 mL) were added. The mixture was refluxed for 3 h, cooled and poured into crushed ice acidified with drops of HCl where the solid was filtered off and recrystallized from suitable solvent to give (**8**).

**1-Aryl-2,4-diamino-6-oxo-1,6-dihydropyridin-3-(N-substitutedphenyl)carboxamides (10a,b): General procedure**

To a solution of sodium ethoxide prepared from sodium (2.5 g) and ethanol (20 mL), a solution of **1** (0.01 mol) in ethanol (20 mL) was added. The reaction mixture was refluxed for 3 hr, cooled, poured into ice acidified with HCl and the precipitate filtered off to give (**10a,b**). Mass spectrum of **10b** exhibited a molecular ion peak at *m/z* 388 (M, 1.3%) and a base peak at *m/z* 127 (100%).

**α-Cyano-4-methoxy-N-(4-chlorophenyl)cinnamide (11)**

Equimolar amounts of **1b** (0.01 mol) and the appropriate *p*-anisaldehyde (0.01 mol) in ethanol (30 mL) were treated with a few drops of piperidine and refluxed for 1 h. The solid product formed was filtered off and recrystallized from the appropriate solvent to give (**11**).

**2-Amino-5-cyano-6-oxo-4-(4-methoxyphenyl)-1,6-dihydropyridine-3-(N-4-chlorophenyl)carboxamides (14a,b): General procedure**

A mixture of **11** (0.01 mol), cyanoacetamide or cyanoacetohydrazide (0.01 mol) and piperidine (0.5 mL) was refluxed for 3 h. cooled, poured into crushed ice and the resulting solid was filtered off and then recrystallized from the proper solvent to give (**14a,b**).

**2-Amino-5-cyano-4-(4-methoxyphenyl)-6-(piperidin-1-yl or morpholin-4-yl)pyridin-3-(N-4-chlorophenyl)carboxamides (17a,b): General procedure**

A solution of **11** (0.01 mol) in ethanol (30 mL) was treated with enaminonitriles **15a,b** (0.01 mol) and piperidine

Table 1. Physical data of synthesized compounds

| Compd. No. | Yield (%) | Solvent Cryst. | M.P. [°C] | Mol. Formula (Mol. Wt.) | Elemental analyses Calcd./Found [%] | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **5a** | 60 | Benzene | 140 | $C_{25}H_{18}Br_2N_2O_2$ | 55.76 | 3.34 | 5.20 |
| | | | | (538) | 55.67 | 3.29 | 5.16 |
| **5b** | 67 | Benzene | 90 | $C_{24}H_{15}Cl_3N_2O_2$ | 61.34 | 3.19 | 5.96 |
| | | | | (469.5) | 61.20 | 3.15 | 5.80 |
| **8** | 70 | MeOH | 170 | $C_{15}H_8ClN_5O$ | 58.15 | 2.58 | 2.61 |
| | | | | (309.5) | 58.40 | 2.70 | 2.70 |
| **10a** | 75 | Benzene | 160 | $C_{20}H_{20}N_4O_2$ | 68.96 | 5.74 | 16.09 |
| | | | | (348) | 68.70 | 5.90 | 16.30 |
| **10b** | 73 | Benzene | 140 | $C_{18}H_{14}Cl_2N_4O_2$ | 55.52 | 3.59 | 14.40 |
| | | | | (389) | 55.65 | 3.70 | 14.50 |
| **11** | 80 | Dioxane | 220 | $C_{17}H_{13}ClN_2O_2$ | 65.28 | 4.16 | 8.96 |
| | | | | (312.5) | 65.35 | 4.10 | 8.90 |
| **14a** | 50 | Benzene | 110 | $C_{20}H_{15}ClN_4O_3$ | 60.83 | 3.80 | 14.19 |
| | | | | (394.5) | 60.70 | 3.85 | 14.30 |
| **14b** | 52 | Benzene | 200 | $C_{20}H_{16}ClN_5O_3$ | 58.60 | 3.91 | 17.09 |
| | | | | (409.5) | 58. 70 | 3.80 | 17.17 |
| **17a** | 60 | MeOH | 130 | $C_{25}H_{26}ClN_5O_2$ | 64.72 | 5.60 | 15.10 |
| | | | | (463.5) | 64.90 | 5.60 | 15.20 |
| **17b** | 65 | MeOH | 250 | $C_{24}H_{24}ClN_5O_3$ | 61.86 | 5.15 | 15.03 |
| | | | | (465.5) | 61.90 | 5.26 | 15.13 |
| **21** | 80 | AcOH | 275 | $C_{14}H_{11}ClN_2O$ | 64.99 | 4.25 | 10.83 |
| | | | | (258.5) | 65.05 | 4.30 | 10.90 |
| **23a** | 70 | DMF | > 300 | $C_{19}H_{10}Cl_2N_4O$ | 59.84 | 2.62 | 14.69 |
| | | | | (381) | 59.70 | 2.70 | 14.70 |
| **23b** | 70 | AcOH | 300 | $C_{21}H_{15}Cl_2N_3O_3$ | 58.87 | 3.50 | 9.81 |
| | | | | (428) | 58.90 | 3.50 | 9.90 |
| **23c** | 80 | DMF | > 300 | $C_{20}H_{13}ClN_4O_2$ | 63.74 | 3.45 | 14.87 |
| | | | | (376.5) | 63.80 | 3.30 | 14.70 |
| **24** | 50 | DMF | > 300 | $C_{21}H_{12}Cl_2N_4O_2$ | 59.57 | 2.83 | 13.23 |
| | | | | (423) | 59.70 | 2.70 | 13.40 |
| **25** | 80 | DMF | > 300 | $C_{20}H_{11}Cl_2N_5O$ | 58.82 | 2.69 | 17.15 |
| | | | | (408) | 58.90 | 2.70 | 17.30 |
| **26** | 60 | Benzene | 120 | $C_{33}H_{20}Cl_2N_6O_3$ | 63.97 | 3.23 | 13.57 |
| | | | | (619) | 63.70 | 3.20 | 13.80 |
| **27** | 65 | Benzene | 200 | $C_{19}H_{11}Cl_2N_5O$ | 57.57 | 2.77 | 17.67 |
| | | | | (396) | 57.70 | 2.70 | 17.60 |

(0.5 mL). The mixture was refluxed for 3 h, cooled and the resulting solid was filtered off and recrystallized from the proper solvent to give (**17a,b**).

**4,6-Dimethyl-2-oxo-1-(4-chlorophenyl)-1,2-dihydropyridin-3-carbonitrile (21)**

**Method A**

To a solution of **11** (0.01 mol) in ethanol (30 mL), acetylacetone (0.01 mol) and piperidine (0.5 mL) were added and the mixture was refluxed for 3 h, cooled and the solid was filtered off and crystallized from the proper solvent to give (**21**).

**Method B**

A mixture of **1b** (0.01 mol), acetylacetone (0.01 mol) and piperidine (0.5 mL) was fused in an oil bath at 150 °C for 1/2 hr to give (**21**; m.p. and mixed m.p.).

**6-Amino-2-oxo-1,4-diaryl-5-cyano or ethoxycarbonyl-1,2-dihydropyridin-3-carbonitriles (23a-c): General procedure**

**Method A**

Equimolar amounts of **1b** (0.01 mol) and the appropri-

Table 2. Spectroscopic data of the synthesized compounds

| Compd. No. | IR (ν, $cm^{-1}$) | $^1H$ NMR (δ, ppm) (DMSO-$d_6$) |
|---|---|---|
| **5a** | 3267, 3187 (2NH), 2935 (CH-aliph), 1682 (C=O). | 6.4 (s, 1H, CH), 7.3-7.8 (m, 12H, Ar-H), 8.1, 10.2 (2s, 2H, 2NH). |
| **5b** | 3293 (NH), 2931 (CH-aliph), 1685, 1659 (C=O). | |
| **8** | 3271, 3201 ($NH_2$), 2954 (CH-aliph), 2198 (C≡N), 1666 (C=O). | 3.87 (s, 2H, $CH_2$), 7.2-7.5 (AB-system), 10.3 (s, 2H, $NH_2$). |
| **10a** | 3290, 3199 ($NH_2$), 3132 (NH), 1666 (C=O). | 2.26 (s, 6H, $2CH_3$), 3.2, 3.7 (s, 4H, $2NH_2$), 7.0-7.4 (m, 9H, Ar-H+CH pyridine), 9.9 (s, 1H, NH). |
| **10b** | 3275, 3205 ($NH_2$), 3137 (NH), 1663 (C=O). | |
| **11** | 3317 (NH), 2923 (CH-aliph), 2221 (C≡N), 1674 (C=O). | |
| **14a** | 3323 broad ($NH_2$, NH), 2945 (CH-aliph), 2199 (C≡N). | 3.8 (s, 3H, $OCH_3$), 6.9-7.2 (m, 8H, Ar-H) 7.99 (broad, 2H, $NH_2$), 9.3 (s, 2H, 2NH). |
| **14b** | 3347, 3171 ($NH_2$ + NH), 2979 (CH-aliph), 2260 (C≡N), 1688 (C=O). | |
| **17a** | 3349, 3197 ($NH_2$), 3119 (NH), 2192 (C≡N), 1640 (CO). | 1.5, 3.1 (m, 10H, piperidyl), 3.79 (s, 3H, $OCH_3$), 3.8 (s, 2H, $NH_2$), 5.27, 5.8 (2d, 2H, H-3, H-4-pyridyl), 6.8-7.9 (m, 8H, Ar-H), 10.2 (s, NH). |
| **17b** | 3422, 3229 ($NH_2$ + NH), 2965 (CH-aliph), 2209 (C≡N), 1638 (C=O). | |
| **21** | 2217 (C≡N), 1660 (C=O). | 1.9, 2.4 (2s, 6H, $2CH_3$), 6.4 (s, 1H, CH), 7.3-7.6 (m, 4H, Ar-H). |
| **23a** | 3397, 3295 ($NH_2$), 2214 (C≡N), 1660 (C=O). | 7.4-7.6 (m, 8H, Ar-H), 7.98 (s , 2H, $NH_2$). |
| **23b** | 3349, 3281 ($NH_2$), 2220 (C≡N), 1699, 1667 (C=O). | 0.6 (t, 3H, $CH_3$-ester), 3.8 (q, 2H, $CH_2$-ester), 7.2-7.6 (m, 8H, Ar-H), 7.7 (s, 2H, $NH_2$). |
| **23c** | 3319, 3102 ($NH_2$), 2212 (C≡N), 1661 (C=O). | 2.8 (s, 2H, $NH_2$), 3.8 (s, 3H, $OCH_3$), 7.0-7.3-7.8 (m, 8H, Ar-H), 8.5 (s, 1H, CH), 9.1 (s, 2H, $NH_2$). |
| **24** | 3340, (NH), 2221 (C≡N), 1666 (C=O). | |
| **25** | 3448, 3255 ($NH_2$), 2198 (C≡N), 1650 (C=O). | 7.3-7.8 (m, 8H, Ar-H), 8.6 (s, 1H, CH), 9.1 (s, 2H, $NH_2$). |
| **26** | 3379, 3247 (NH), 2221 (C≡N), 1735, 1689 (C=O). | |
| **27** | 3425, 3325 ($NH_2$ + NH), 2206 (C≡N), 1651 (C=O). | |

ate cinnamonitrile (0.01 mol) in ethanol (30 mL) was treated with piperidine (0.5 mL) and the reaction mixture was refluxed for 3 hr. The resulting solid was filtered off and recrystallized from the suitable solvent. The mass spectrum of **23a** showed a molecular ion peak at 380 (100%) and other peaks such as 354 (12.5%), 354 (44.2%), 282 (16.9%), 180 (8.0%) and 75 (35.9%) were observed.

**Method B**

A mixture of **11** (0.01 mol) and malononitrile (0.01 mol) in ethanol (30 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The obtained product was filtered and recrystallized to give (**23c**; m.p. and mixed m.p.).

**2-Methyl-4,7-dioxo-5-(2-chlorophenyl)-8-(4-chlorophenyl)-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-carbonitrile (24)**

A suspension of **23a** (0.01 mol) in acetic anhydride (15 mL) was refluxed for 6 h, cooled and the resulting precipitate was filtered off and recrystallized from the proper solvent to give **24**.

**4-Amino-7-oxo-5,8-diaryl-7,8-dihydropyrido[2,3-d]pyrimidin-6-carbonitrile (25)**

A solution of **23a** in formamide (10 mL) was refluxed for 2 h and the obtained product after cooling and filtration

was recrystallized.

**1-(6-Cyano-2,7-dioxo-3-phenyl-5-(2-chlorophenyl)-8-(4-chlorophenyl)-2,3,7,8-tetrahydropyrido[2,3-d]pyrimidin-4-ylidene)-3-phenyl urea (26)**

To a solution of **23a** (0.01 mol) in ethanol (20 mL), phenyl isocyanate (0.01 mol) and triethylamine (0.5 mL) were added. The reaction mixture was refluxed for 3 h, cooled and the resulting solid was filtered off and recrystallized to give (**26**).

**3-Amino-6-oxo-4-(2-chlorophenyl)-7-(4-chlorophenyl)-6,7-dihydro-1H-pyrazolo[3,4-b]pyridin-5-carbonitrile (27)**

A mixture of **23a** (0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (20 mL) was refluxed for 3 h. The mixture was cooled and the obtained product was recrystallized to furnish **27** (Table 1). Mass spectrum of **27** showed a molecular ion peak at *m/z* 395 (40%) with other peaks at 375 (100%), 359 (43%), 111 (30.2%).

Received October 17, 2003.

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