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Studies with Polyfunctionally Substituted Heteroaromatics: A Facile Route for the Synthesis of Polyfunctionally Substituted N-Aminopyridines, 1,2,4-Triazolo[1,5-a]Pyridines and Isoquinolines

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ABSTRACT

The reactions of formaldehyde and acetaldehyde with active methylene compounds, followed by reaction with cyanoacetic acid hydrazide **2**, *afforded N-aminopyridine-2-one derivatives* **5a–f**. *In contrast, the reactions of cyanoacetic acid hydrazide* **2** *with aliphatic aldehydes and cyanothioacetamide afforded pyridinethione derivatives* **11a–b**. *Also, the reactions of active methylene compounds with formaldehyde and cyanoacetamide afforded pyridin(1H)-2-one derivatives* **12a–c**. *The reactions of* **5b** *with aldehydes and ketones afforded compounds* **13a, b**, **14**, *and* **15**, *respectively. The reactions of* **5b** *with arylidinemalononitriles* **16a,b** *afforded isoquinoline derivatives* **19a,b**. *Compound* **19b** *by hydrolysis gave the final product* **20**. *Compound* **20** *could also be formed by hydrolysis of* **5b** *to give* **21**, *followed by the reaction with* **16b**.

DISCUSSION

Polyfunctionally substituted heteroaromatics are interesting compounds for potential utility as dye intermediates [1,2], agrochemicals [3–5], and as pharmaceuticals [6–10]. In the past few years, we have been involved in a program aimed at developing new efficient synthetic approaches for these heteroaromatic compounds utilizing inexpensive starting materials. During this phase of our research, we have shown that mixtures of aliphatic aldehydes and malononitrile can be used in basic medium as synthetic equivalents of ylidine malononitrile [11]. In conjunction with this work, we report here results of our investigations that enabled syntheses of 1,6-diaminopyridones and their conversion into 1,2,4-triazolo[1,5-a]pyridines. Thus, it has been found that a mixture of formaldehyde and malononitrile reacted with cyanoacetic acid hydrazide in ethanolic triethylamine to yield a product of molecular formula $C_7H_5N_5O$ ($M^+ = 175$) that could conceivably be formulated as **5a** or the isomeric **10** (Scheme 1). Compound **5a** could be assumed to be formed by condensation of malononitrile with formaldehyde producing the ylidinemalononitrile **Ia**, which then adds cyanoacetic acid hydrazide **2** to yield the Michael adduct **3**. The adduct **3** is cyclized to **4** and dehydrogenated to **5a**. Compound **5a** can also be formed via initial formation of **6** that then reacts with malononitrile to yield the same Michael adduct **3**, which was cyclized to **4** and dehydrogenated to **5a**. Alternatively, initial condensation of formaldehyde with cyanoacetic acid hydrazide could conceivably lead to condensation at the hydrazide NH_2. This latter compound might then add malononitrile with

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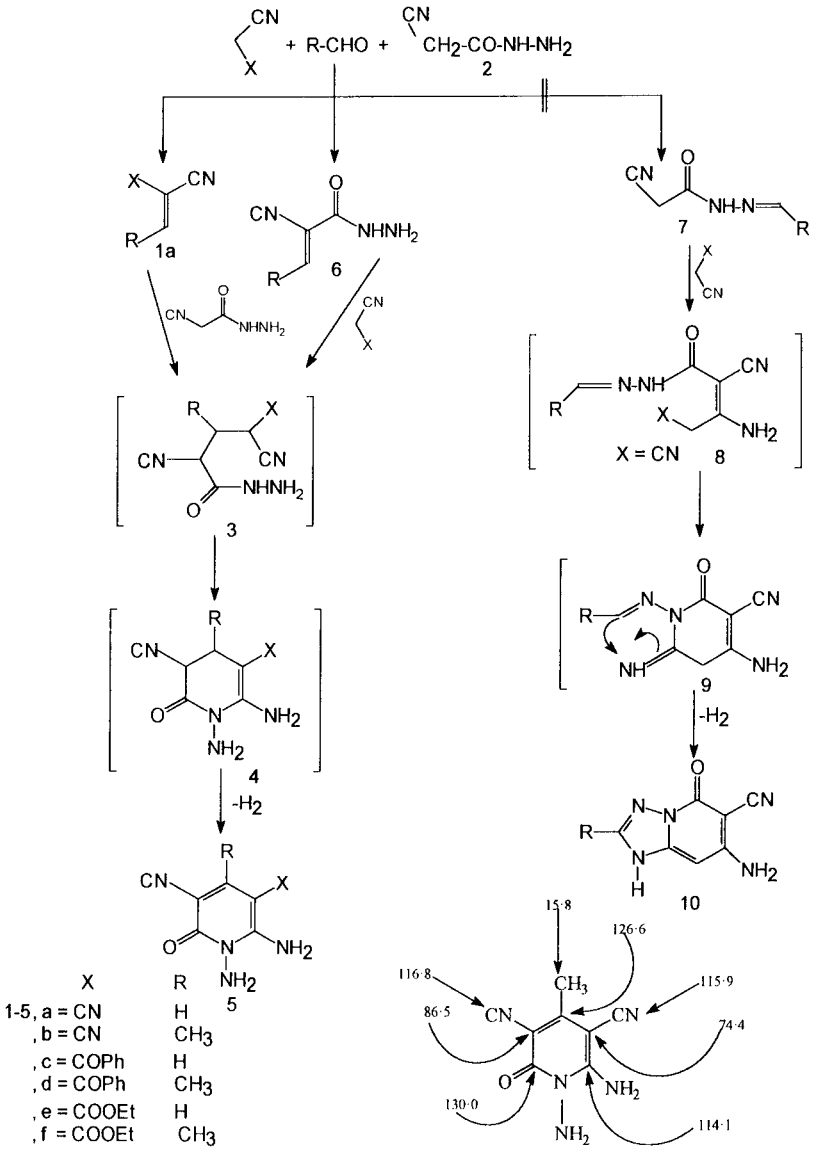
SCHEME 1



subsequent cyclization and dehydrogenation to give the 5-amino-7-oxo-6,7-dihydro-1,2,4-triazolo[1,5-a] pyridine **10**. Structure **5a** was actually established as the correct one based on spectral data, IR and ^{1}H NMR, which revealed a pattern that can be interpreted only for structure **5a**. Thus, the IR spectrum of the reaction product revealed two CN signals at 2200 cm^{-1}. Also, the ^{1}H NMR spectrum revealed only a single low-field CH signal at δ 7.4; if the product were 10, two low-field CH signals for H-2 and H-7 would be expected.

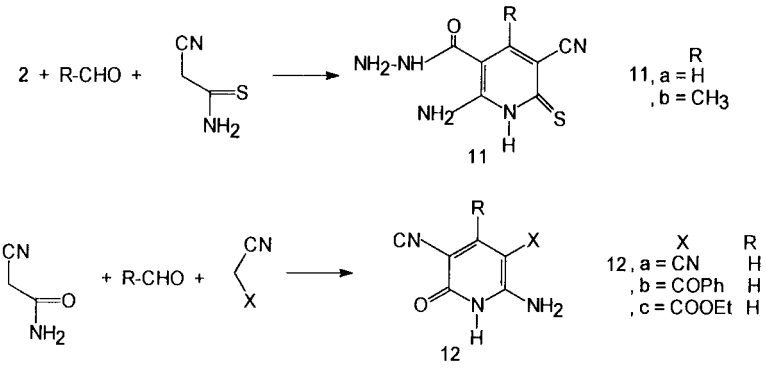
Similar to this, a mixture of acetaldehyde, cyanoacetic acid hydrazide **2**, and malononitrile reacted in ethanolic piperidine to yield **5b**. Also, mixtures of cyanoacetic acid hydrazide **2**, formaldehyde, or acetaldehyde and other active methylene reagents, namely, benzoylacetonitrile and ethyl cyanoacetate, were reacted similarly yielding the N-aminopyridines **5c–f**.

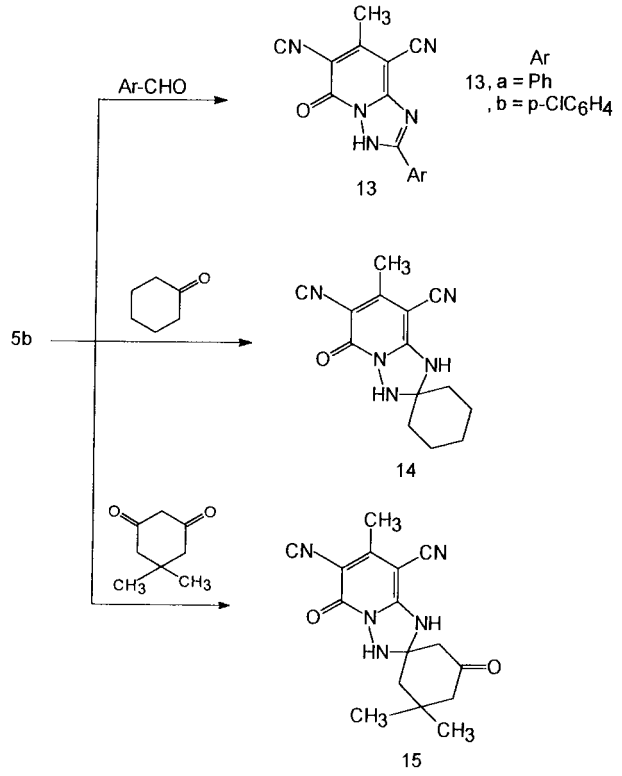
In contrast to this, the reaction of **2**, formaldehyde, or acetaldehyde and cyanothioacetamide in ethanolic piperidine led to the formation of the pyridinethiones **11a, b** (Scheme 2). Also, the reactions of cyanoacetamide with a mixture of formaldehyde and the appropriate active methylene compounds in ethanolic piperidine yielded the corresponding pyridones **12a–c**.

The condensations of N-aminopyridine **5b** with aromatic aldehydes afforded the triazolopyridines **13a, b** (Scheme 3). Condensation of **5b** with cyclohexanone and with 1,1-dimethyl cyclohexanedione afforded **14** and **15**, respectively.

Similar to the reported reactivity of methylazinylcarbonitriles toward α,β-unsaturated nitriles [11],

SCHEME 2



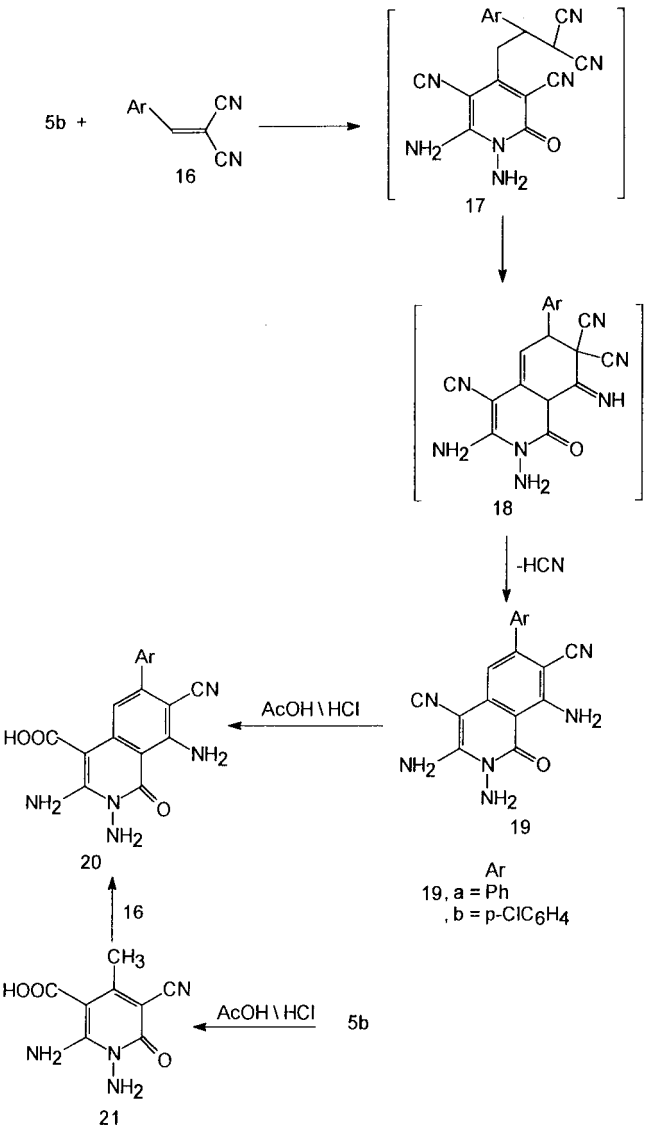


SCHEME 3

compound **5b** reacted with barylidinemalononitrile **16a,b** under basic conditions or in refluxing pyridine to yield the isoquinolines **19a,b**, most likely via the Michael adduct **17**, which then cyclized into **18** with subsequent loss of HCN (Scheme 4). Structure **19a** was established by hydrolysis with a mixture of AcOH/HCl to afford the carboxylic acid derivative **20b**, which could also be formed by hydrolysis of **5b** with a mixture of AcOH/HCl to give 21 that was then treated with the appropriate arylidinemalononitrile.

EXPERIMENTAL

All melting points are uncorrected; IR spectra were recorded on a Shemadzu 1470 spectrophotometer.



SCHEME 4

^{1}H NMR spectra were measured on a Varian EM-390 spectrometer. Microanalytical data were obtained by the microanalytical data unit at Cairo University. Mass spectra were recorded with an MS 30 and MS 9 (AEI), 70 ev.

Preparation of Compounds **5a–f**. *General Procedure*

A suspension of equimolar amounts of cyanoacetic acid hydrazide **2** (1 g, 0.01 mol) formaldehyde (1.0 mL, 30% formalin solution, 0.01 mol) or acetaldehyde (0.5 mL, 0.01 mol) and the appropriate active methylene compound (0.01 mol) in ethanol (50 mL) was treated with a few drops of piperidine. The reaction mixture was refluxed for 3 hours. The solid product so formed was collected by filtration and recrystallized from the proper solvent.

1,6-Diamino-2-oxo-1H-pyridine-3,5-dicarbonitrile (**5a**)

Orange crystals from ethanol; yield 1.3 g (78%); mp 270°C; IR (KBr) 3400–3200 cm^{-1} (2NH$_2$); 2200 cm^{-1} (2CN); 1660 cm^{-1} (CO). ^{1}H NMR (DMSO-d$_6$): δ = 6.0 (s, 2H, NH$_2$); 7.4 (s, 1H, ring CH); 8.4 (s, 2H, NH$_2$); MS: *m*/*z* = 175 (found: C, 48.2; H, 3.0; N, 40.1; calcd for $C_7H_5N_5O$: C, 48.00; H, 2.88; N, 39.98%).

1,6-Diamino-4-methyl-2-oxo-1H-pyridine-3,5-dicarbonitrile (**5b**)

Colorless crystals from dioxane; yield 1.6 g (82%); mp 285°C; IR (KBr) 3400–3300 cm^{-1} (2NH$_2$); 2220 cm^{-1} (2CN); 1680 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 3.4 (s, 3H, CH$_3$); 5.6 (s, 2H, NH$_2$); 8.4 (s, 2H, NH$_2$). ^{13}C NMR (cf. Scheme 1); MS: *m*/*z* = 189 (found: C, 50.9; H, 3.9; N, 37.2; calcd for $C_8H_7N_5O$: C, 50.79; H, 3.72; N, 37.02%).

1,6-Diamino-5-benzoyl-2-oxo-1H-pyridine-3-carbonitrile (**5c**)

Orange crystals from dioxane; yield 2 g (77%); mp 300°C; IR (KBr) 3400–3300 cm^{-1} (2NH$_2$); 2200 cm^{-1} (CN); 1680 cm^{-1} (CO); 1650 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 5.8 (s, 2H, NH$_2$); 7.2–7.8 (m, 6H, ring CH and aromatic CH); 8.5 (s, 2H, NH$_2$) (found: C, 61.6; H, 4.2; N, 23.0; calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.84%)

1,6-Diamino-5-benzoyl-3-methyl-2-oxo-1H-pyridine-3-carbonitrile (**5d**)

Yellow crystals from ethanol; yield 2.4 g (83%); mp 170°C; IR (KBr) 3350–3250 cm^{-1} (2NH$_2$); 2200 cm^{-1} (CN); 1680 cm^{-1} (CO); 1655 cm^{-1} (CO). ^{1}H NMR (CDCl$_3$): δ = 3.1 (s, 3H, CH$_3$); 5.7 (s, 2H, NH$_2$); 7.2–7.7 (m, 6H, ring CH and aromatic CH); 8.2 (s, 2H, NH$_2$); MS: *m*/*z* = 268 (found: C, 62.7; H, 4.7; N, 21.0; calcd for $C_{14}H_{12}N_4O_2$: C, 62.67; H, 4.51; N, 20.88%).

Ethyl-1,6-diamino-3-cyano-2-oxo-1H-pyridine-5-carboxylate (**5e**)

Orange crystals from DMF/ethanol; yield 1.6 g (75%); mp 290°C; IR (KBr) 3450–3300 cm^{-1} (2NH$_2$); 2210 cm^{-1} (CN); 1710 cm^{-1} (ester CO); 1650 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 1.2 (t, 3H, CH$_3$); 4.3 (q, 2H, CH$_2$); 5.0 (s, 2H, NH$_2$); 7.1 (m, 2H, NH$_2$, and ring CH); MS: *m*/*z* = 222; (found: C, 48.8; H, 4.6; N, 25.5; calcd for $C_9H_{10}N_4O_2$: C, 48.65; H, 4.54; N, 25.21%).

Ethyl-1,6-diamino-3-cyano-4-methyl-2-oxo-1H-pyridine-5-carboxylate (**5f**)

Colorless crystals from ethanol; yield 2 g (80%); mp 140°C; IR (KBr) 3420–3300 cm^{-1} (2NH$_2$); 2950 cm^{-1} (CH aliphatic); 2210 cm^{-1} (CN); 1720 cm^{-1} (CO ester); 1650 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 1.3 (m, 6H, 2CH$_3$); 4.2 (m, 4H, CH$_2$, NH$_2$); 7.3 (s, 2H, NH$_2$); MS: *m*/*z* = 236 (found: C, 51.0; H, 5.3; N, 23.8; calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72%).

Preparation of Compounds **11a,b**. *General Procedure*

To a solution of cyanoacetic acid hydrazide (1 g, 0.01 mol) in ethanol (50 mL), a mixture of acetaldehyde or formaldehyde (0.01 mol, 30% formaline solution) and cyanothioacetamide (1 g, 0.01 mol) was added. The reaction mixture was treated with a few drops of piperidine and then refluxed for 3 hours. The solid product so formed was collected by filtration and recrystallized from the proper solvent to give **11a, b**.

6-Amino-3-cyano-2-thioxo-1H-pyridine-5-carboxylic acid hydrazide (**11a**)

Orange crystals from DMF; yield 1.5 g (75%); mp 340°C; IR (KBr) 3380–3280 cm^{-1} (NH$_2$); 3280–3200 cm^{-1} (NH); 2180 cm^{-1} (CN); 1580 cm^{-1} (CS): ^{1}H NMR (DMSO-d$_6$): δ = 5.8 (m, 4H, 2NH$_2$); 7.6 (s, 1H, ring CH); 8.2 (m, 2H, 2NH); MS: *m*/*z* = 209 (found: C, 40.3; H, 3.9; N, 33.6; calcd for $C_7H_7N_5OS$: C, 40.18; H, 3.37; N, 33.47%).

6-Amino-3-cyano-4-methyl-2-thioxo-1H-pyridine-5-carboxylic acid hydrazide (**11b**)

Brown crystals from dioxane; yield 1.9 g (73%); mp 290°C; IR (KBr) 3420–3280 cm^{-1} (NH$_2$); 3280–3180

cm^{-1} (NH); 2200 cm^{-1} (CN); 1650 cm^{-1} (CO); 1590 cm^{-1} (CS): ^1H NMR (DMSO-d_6): δ = 2.2 (s, 3H, CH_3); 5.6 (m, 4H, $2NH_2$); 7.9 (m, 2H, 2NH); MS: *m/z* = 223 (found: C, 43.2; H, 4.3; N, 31.9; calcd for $C_8H_9N_5OS$: C, 43.04; H, 4.06; N, 31.37%).

Preparation of Compounds **12a–c**. *General Procedure*

To a solution of cyanoacetamide (0.84 g; 0.01 mol) in ethanol (50 mL) a mixture of formaldehyde (1.0 mL, 30% formalin solution, 0.01 mol) and the appropriate active methylene compound was added. The reaction mixture was treated with a few drops of piperidine, then refluxed for 3 hours. The solid product formed was collected by filtration and recrystallized from the proper solvent.

6-Amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**12a**)

Orange crystals from ethanol; yield 1.2 g (66%); mp 300°C; IR (KBr) 3420–3200 cm^{-1} (NH_2); 3100 cm^{-1} (NH); 2200 cm^{-1} (2CN); 1705 cm^{-1} (amide CO); MS: *m/z* = 160 (found: C, 52.7; H, 2.7; N, 35.1; calcd for $C_7H_4N_4O$: C, 52.50; H, 2.51; N, 34.98%).

6-Amino-5-benzoyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**12b**)

Yellow crystals from ethanol; yield 1.7 g (70%); mp 310°C; IR (KBr) 3400–3300 cm^{-1} (NH_2); 3150 cm^{-1} (NH); 2200 cm^{-1} (CN); 1700 cm^{-1} (amide CO); ^1H NMR (DMSO-d_6): δ = 5.3 (s, 2H, NH_2); 7.3 (s, 1H, ring CH); 12.5 (s, 1H, NH); MS: *m/z* = 239 (found: C, 65.4; H, 3.9; N, 17.6; calcd for $C_3H_9N_3O_2$: C, 65.26; H, 3.78; N, 17.56%).

Ethyl-6-amino-3-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate (**12c**)

Orange crystals from ethanol; yield 1.5 g (73%); mp 300°C; IR (KBr) 3420–3350 cm^{-1} (NH_2); 3100 cm^{-1} (NH); 2200 cm^{-1} (CN); 1710 cm^{-1} (ester CO); 1700 cm^{-1} (amide CO); ^1H NMR (DMSO-d_6): δ = 1.2 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 6.8 (s, 2H, NH_2); 7.4 (s, 1H, ring CH); 12.0 (s, 1H, NH); MS: *m/z* = 207 (found: C, 52.3; H, 4.5; N, 20.4; calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.37; N, 20.28%).

Reaction of **5b** *with Aromatic Aldehydes. General Procedure*

To a solution of **5b** (1.89 g, 0.01 mol) in pyridine (20 mL), aromatic aldehydes were added. The reaction mixture was refluxed for 5 hours, then poured into ice water and neutralized by dilute HCl. The solid product so formed was collected by filtration and recrystallized from the proper solvent.

5-Methyl-2-phenyl-7-oxo-1,7-dihydro-1,2,4-triazolo[1,5-a]pyridine-4,6-dicarbonitrile (**13a**)

Colorless crystals from ethanol; yield 2.1 g (78%); mp 250°C; IR (KBr) 3350–3170 cm^{-1} (NH);2220 cm^{-1} (2CN); 1650 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 3.0 (s, 3H, CH_3); 7.0–7.4 (m, 5H, aromatic CH); 12.5 (s, 1H, NH); MS: *m/z* = 275 (found: C, 65.5; H, 3.5; N, 25.7; calcd for $C_{15}H_9N_5O$: C, 65.45; H, 3.30; N, 25.44%).

5-Methyl-2(p-chlorophenyl)-7-oxo-1,7-dihydro-1,2,4-triazolo[1,5-a]pyridine-4,6-dicarbonitrile (**13b**)

Colorless crystals from ethanol; yield 2.5 g (80%); mp 260°C; IR (KBr) 3355 and 3280 cm^{-1} (2NH); 2222 cm^{-1} (2CN); 1656 cm^{-1} (CO); MS: *m/z* = 309 (found: C, 58.3; H, 2.8; N, 22.8; calcd for H_8 C_{15} N_5OCl:C, 58.17; H, 2.60; N, 22.61%).

Reaction of **5b** *with Ketones*

To a solution of **5b** (1.89 g, 0.01 mol) in pyridine (20 mL), cyclohexanone was added. The reaction mixture was refluxed for 5 hours, then poured into ice water and neutralized by dilute HCl. The solid product so formed was collected by filtration and recrystallized from the proper solvent.

5-Methyl-7-oxo-1H-2,3-dihydro-2-spiro[cyclohexane]-1,2,4-triazolo [1,5-a]pyridine-4,6-dicarbonitrile (**14**)

Orange crystals from ethanol; yield 1 g (75%); mp >300°C; IR (KBr) 3200–3190 cm^{-1} (2NH); 2930 cm^{-1} (CH_2 aliphatic); 2215 cm^1 (2CN); 1659 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 3.5 (m, 10H, $5CH_2$); 3.8 (s, 3H, CH_3); 12.1 (s, 1H, NH); 12.5 (s, 1H, NH); MS: *m/z* = 269 (found: C, 62.6; H, 5.7; N, 26.3; calcd for $C_{14}H_{15}N_5O$: C, 62.43; H, 5.6; N, 26.00%).

5-Methyl-7-oxo-1H-2,3-dihydro-2-spiro[5,5-dimethylcyclohexan]-3-one]-1,2,4-triazolo[1,5-a]pyridine-4,6-dicarbonitrile (**15**)

Brown crystals from dioxane; yield 1.7 g (65%); mp >300°C; IR (KBr) 3300–3200 cm^{-1} (2NH); 2920 cm^{-1} (aliphatic CH_2, CH3); 2200 cm^{-1} (2CN); 1680 cm^{-1} (CO); 1660 cm^{-1} (CO); MS: *m/z* = 311 (found:

C, 61.9; H, 5.6; N, 22.6; calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.49; N, 22.50%).

Preparation of Compounds (**19a,b**). *General Procedure*

Equimolecular amounts of **5b** (1.89 g, 0.01 mol) and arylidinemalononitrile **16** (0.01 mol) in pyridine (30 mL) were refluxed for 5 hours. The reaction mixture was poured into ice water and neutralized with dilute HCl. The solid product so formed was collected by filtration and recrystallized from the proper solvent.

2,3,8-Triamino-6-phenyl-1-oxo-1,2-dihydroisoquinoline-4,7-dicarbonitrile (**19a**)

Yellow crystals from ethanol; yield 2.4 g (75%); mp 270°C; IR (KBr) 3400–3200 cm^{-1} (br NH_2); 3050 cm^{-1} (CH aromatic); 2210 cm^{-1} (CN); 1660 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 5.5 (s, 2H, NH_2); 6.4 (m, 4H, $2NH_2$); 7.2–7.8 (m, 7H, aromatic CH, and ring CH); MS: m/z = 316 (found: C, 64.7; H, 4.0; N, 26.7; calcd for $C_{17}H_{12}N_6O$: C, 64.55; H, 3.81; N, 26.56%).

2,3,8-Triamino-6-(p-chlorophenyl)-1-oxo-1,2-dihydroisoquinoline-4,7-dicarbonitrile (**19b**)

Yellow crystals from ethanol; yield 2.5 g (70%); mp 140°C; IR (KBr) 3420–3200 cm^{-1} (br NH_2); 3045 cm^{-1} (CH aromatic); 2220 cm^{-1} (CN); 1650 cm^{-1} (CO); MS: m/z = 350 (found: C, 58.4; H, 3.2; N, 24.1; Cl, 10.1; calcd for $C_{17}H_{11}N_6OCl$: C, 58.21; H, 3.15; N, 23.95; Cl, 10.10%).

Reaction of **19a** *with Acetic Acid and Hydrochloric Acid* (**20b**)

Compound **19a** (2 g) was refluxed for 3 hours in acetic acid/hydrochloric acid mixture (30.10 mL). The reaction mixture then being poured into water. The solid product so formed was collected by filtration and recrystallized from ethanol as green recrystals; yield 1.8 g (85%); mp 170°C; IR (KBr) 3550 cm^{-1} (OH); 3400–3200 cm^{-1} (NH_2); 3050 cm^{-1} (CH aromatic); 2200 cm^{-1} (CN); 1730 cm^{-1} (CO acid); 1660 cm^{-1} (CO) (found: C, 55.4; H, 3.4; N, 19.1; Cl, 9.6; calcd for $C_{17}H_{12}N_5O_3Cl$: C, 55.21; H, 3.26; N, 18.93; Cl, 9.58%).

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