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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-ami- nopyridine-2-one derivatives* **5a-f***. In contrast, the re­actions of cyanoacetic acid hydrazide* **2** *with aliphatic aldehydes and cyanothioacetamide afforded pyridine- thione 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***. q 1997 John Wiley & Sons, Inc.*

*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

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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 ma- lononitrile 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-di- aminopyridones and their conversion into 1,2,4-tri- azolo[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 C7H5N5O (M**'** 4 175) 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 NH2. This latter compound might then add malononitrile with

1042-7163/97/010001-06 **1**

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 1H 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**1. Also, the 1H NMR spectrum revealed only a single low-field CH signal at *d* 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 pyr- idinethiones **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 pyr- idones **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 methylazin- ylcarbonitriles toward *a,b*-unsaturated nitriles [11],

SCHEME 2

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.

1H 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-Diι∣ιminn.∣-2-∣∣x∣∣-1H-p∖ridine-3,5- dicarbonitrile* (**5a**)

Orange crystals from ethanol; yield 1.3 g (78%); mp 270**8**C; IR(KBr) 3400-3200 cm**1**1 (2NH2); 2200 cm**1**1 (2CN); 1660 cm**1**1 (CO). 1H NMR (DMSO-d6): *d 4* 6.0 (s, 2H, NH2); 7.4 (s, 1H, ring CH); 8.4 (s, 2H, NH2); MS: *m*/*z 4* 175 (found: C, 48.2; H, 3.0; N, 40.1; calcd for C7H5N5O: 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**8**C; IR (KBr) 3400-3300 cm**1**1 (2NH2); 2220 cm**1**1 (2CN); 1680 cm**1**1 (CO); 1H NMR (DMSO-d6): *d 4* 3.4 (s, 3H, CH3); 5.6 (s, 2H, NH2); 8.4 (s, 2H, NH2). 13C NMR (cf. Scheme 1); MS: *m*/*z 4* 189 (found: C, 50.9; H, 3.9; N, 37.2; calcd for C8H7N5O: 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**8**C; IR (KBr) 3400-3300 cm**1**1 (2NH2); 2200 cm**1**1 (CN); 1680 cm**1**1 (CO); 1650 cm**1**1 (CO); 1H NMR (DMSO-d6): *d 4* 5.8 (s, 2H, NH2); 7.2-7.8 (m, 6H, ring CH and aromatic CH); 8.5 (s, 2H, NH2) (found: C, 61.6; H, 4.2; N, 23.0; calcd for C13H10N4O2: 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**8**C; IR (KBr) 3350-3250 cm**1**1 (2NH2); 2200 cm**1**1 (CN); 1680 cm**1**1 (CO); 1655 cm**1**1 (CO). 1H NMR (CDCl3): *d 4* 3.1 (s, 3H, CH3); 5.7 (s, 2H, NH2); 7.2­7.7 (m, 6H, ring CH and aromatic CH); 8.2 (s, 2H, NH2); MS: *m*/*z 4* 268 (found: C, 62.7; H, 4.7; N, 21.0; calcd for C14H12N4O2: 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**8**C; IR (KBr) 3450-3300 cm**1**1 (2NH2); 2210 cm**1**1 (CN); 1710 cm**1**1 (ester CO); 1650 cm**1**1 (CO); 1H NMR (DMSO-d6): *d 4* 1.2 (t, 3H, CH3); 4.3 (q, 2H, CH2); 5.0 (s, 2H, NH2); 7.1 (m, 2H, NH2, and ring CH); MS: *m*/*z 4* 222; (found: C, 48.8; H, 4.6; N, 25.5; calcd for C9H10N4O2: 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**8**C; IR (KBr) 3420-3300 cm**1**1 (2NH2); 2950 cm**1**1 (CH aliphatic); 2210 cm**1**1 (CN); 1720 cm**1**1 (CO es­ter); 1650 cm**1**1 (CO); 1H NMR (CDCl3): *d 4* 1.3 (m, 6H, 2CH3); 4.2 (m, 4H, CH2, NH2); 7.3 (s, 2H, NH2); MS: *m*/*z 4* 236 (found: C, 51.0; H, 5.3; N, 23.8; calcd for C10H12N4O3: 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**8**C; IR (KBr) 3380-3280 cm**1**1 (NH2); 3280-3200 cm**1**1 (NH); 2180 cm**1**1 (CN); 1580 cm**1**1 (CS): 1H NMR (DMSO-d6): *d 4* 5.8 (m, 4H, 2NH2); 7.6 (s, 1H, ring CH); 8.2 (m, 2H, 2NH); MS: *m*/*z 4* 209 (found: C, 40.3; H, 3.9; N, 33.6; calcd for C7H7N5OS: 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**8**C; IR (KBr) 3420-3280 cm**1**1 (NH2); 3280-3180 cm11 (NH); 2200 cm**1**1 (CN); 1650 cm**1**1 (CO); 1590 cmi1(CS): 1HNMR(DMSO-d6): *d 4* 2.2 (s, 3H, CH3); 5.6 (m, 4H, 2NH2); 7.9 (m, 2H, 2NH); MS: *m*/*z 4* 223 (found: C, 43.2; H, 4.3; N, 31.9; calcd for C8H9N5OS: 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-dihydrop∙yridine-3,5- dicarbonitrile* (**12a**)

Orange crystals from ethanol; yield 1.2 g (66%); mp 300**8**C; IR (KBr) 3420-3200 cm**1**1 (NH2); 3100 cm**1**1 (NH); 2200 cm**1**1 (2CN); 1705 cm**1**1 (amide CO); MS: *m*/*z 4* 160 (found: C, 52.7; H, 2.7; N, 35.1; calcd for C7H4N4O: C, 52.50; H, 2.51; N, 34.98%).

*6-Amino-5-benzσyl-2-oxo-1,2-dihydropy-ridine-3- carbonitrile* (**12b**)

Yellow crystals from ethanol; yield 1.7 g (70%); mp 310**8**C; IR (KBr) 3400-3300 cm**1**1 (NH2); 3150 cm**1**1 (NH); 2200 cm**1**1 (CN); 1700 cm**1**1 (amide CO); 1H NMR (DMSO-d6): *d 4* 5.3 (s, 2H, NH2); 7.3 (s, 1H, ring CH); 12.5 (s, 1H, NH); MS: *m*/*z 4* 239 (found: C, 65.4; H, 3.9; N, 17.6; calcd for C3H9N3O2: 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**8**C; IR (KBr) 3420-3350 cm**1**1 (NH2); 3100 cm**1**1 (NH); 2200 cm**1**1 (CN); 1710 cm11 (ester CO); 1700 cm11 (amide CO); 1H NMR (DMSO-d6): *d 4* 1.2 (t, 3H, CH3); 4.2 (q, 2H, CH2); 6.8 (s, 2H, NH2); 7.4 (s, 1H, ring CH); 12.0 (s, 1H, NH); MS: *m*/*z 4* 207 (found: C, 52.3; H, 4.5; N, 20.4; calcd for C9H9N3O3: 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 2.1g (78%); mp 250**8**C; IR (KBr) 3350-3170 cm11 (NH);2220 cm11 (2CN); 1650 cm11 (CO); 1H NMR (DMSO-d6): *d 4* 3.0 (s, 3H, CH3); 7.0-7.4 (m, 5H, aromatic CH); 12.5 (s, 1H, NH); MS: *m*/*z 4* 275 (found: C, 65.5; H, 3.5; N, 25.7; calcd for C15H9N5O: 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**8**C; IR (KBr) 3355 and 3280 cm11 (2NH); 2222 cm11 (2CN); 1656 cm11 (CO); MS: *m*/*z 4* 309 (found: C, 58.3; H, 2.8; N, 22.8; calcd for H8 C15 N5OCl: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**8**C; IR (KBr) 3200-3190 cm11 (2NH); 2930 cm11 (CH2 aliphatic); 2215 cm1 (2CN); 1659 cm11 (CO); 1H NMR (DMSO-d6): *d 4* 3.5 (m, 10H, 5CH2); 3.8 (s, 3H, CH3); 12.1 (s, 1H, NH); 12.5 (s, 1H, NH); MS: *m*/*z 4* 269 (found: C, 62.6; H, 5.7; N, 26.3; calcd for C14H15N5O: 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**8**C; IR (KBr) 3300-3200 cm11 (2NH); 2920 cm11 (aliphatic CH2, CH3); 2200 cm11 (2CN); 1680 cm11 (CO); 1660 cm11 (CO); MS: *m*/*z 4* 311 (found: C, 61.9; H, 5.6; N, 22.6; calcd for C16H17N5O2: 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**8**C; IR (KBr) 3400-3200 cm**1**1 (br NH2); 3050 cm**1**1 (CH aromatic); 2210 cm**1**1 (CN); 1660 cm**1**1 (CO); 1H NMR (DMSO-d6): *d 4* 5.5 (s, 2H, NH2); 6.4 (m, 4H, 2NH2); 7.2-7.8 (m, 7H, aromatic CH, and ring CH); MS: *m*/*z 4* 316 (found: C, 64.7; H, 4.0; N, 26.7; calcd for C17H12N6O: C, 64.55; H, 3.81; N, 26.56%).

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

Yellow crystals from ethanol; yield 2.5 g (70%); mp 140**8**C; IR (KBr) 3420-3200 cm**1**1 (br NH2); 3045 cm**1**1 (CH aromatic); 2220 cm**1**1 (CN); 1650 cm**1**1 (CO); MS: *m*/*z 4* 350 (found: C, 58.4; H, 3.2; N, 24.1; Cl, 10.1; calcd for C17H11N6OCL 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**8**C; IR (KBr) 3550 cm**1**1 (OH); 3400-3200 cmι1 (NH2); 3050 cm**1**1 (CH aro­matic); 2200 cm**1**1 (CN); 1730 cm**1**1 (CO acid); 1660 cm**1**1 (CO) (found: C, 55.4; H, 3.4; N, 19.1; Cl, 9.6; calcd for C17H12N5O3CL C, 55.21; H, 3.26; N, 18.93; Cl, 9.58%).

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