A Convenient and Facile Synthesis of Pyridine, Pyridazine, Pyrimido-[4,5-*c*]pyridazine, Pyrido[3,4-*c*]pyridazine, 1,6-Naphthyridine and Phthalazine Derivatives

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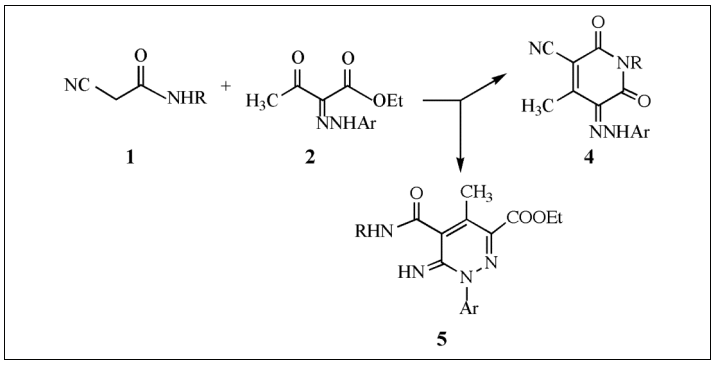

Ethyl 2-arylhydrazono-3-butyrates **2** reacted with 2-cyano-*N*-(4-methylphenyl) acetamide **1a** and 2-cyano-*N*-(thiazol-2-yl)acetamide **1b** to give the pyridinedione, **4** and pyridazine **5** derivatives in 3:1 ratio. The products **4** and **5** have been transformed into different phthalazine, pyrimido[4,5-*c*]-pyridazine, pyrido[3,4-*c*]pyridazine and 1,6-naphthyridine derivatives. The chemical structures have been confirmed by analytical and spectral analysis.

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Introduction.

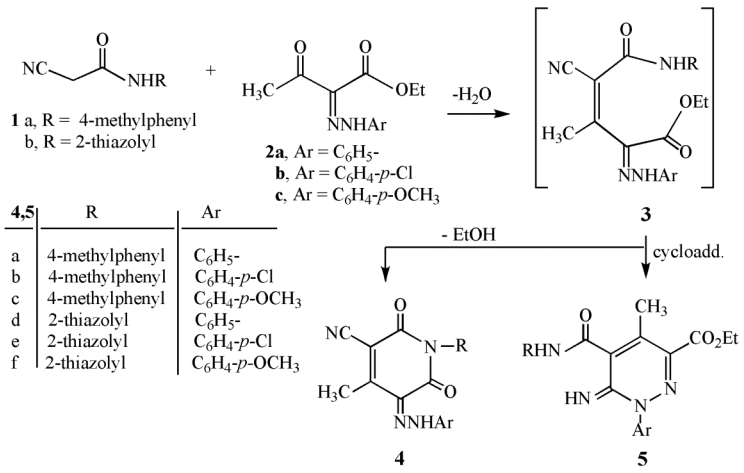
A considerable number of pyridazine derivatives were found to have analgesic [1], antibacterial [2], anticonvulsant [3], antiinflammatory [4], acetylcholin-esterase inhibition [5], aldose reductase inhibition and oxidant properties [6]. Also, pyridine derivatives have been found to possess biological and physiological activities [7,8]. Many pyridine compounds exhibit high antimicrobial activity comparable to ampicillin and chloramphenicol [9]. However, some similar ring core of pyridine, pyridazine and phthalazine derivatives have been reported based on nitrogen transfer from diazocarbonyl compounds to enaminone derivatives [10-12]. In continuation with our previous interest in preparing nitrogen six-membered ring systems [13-18] we herein report a simple and one-pot approach to the synthesis of pyridine, pyridazine, pyrido-pyridazine, 1,6-naphthyridine, pyrimidopyridazine and phthalazine derivatives *via* reaction of diazocarbonyls and active nitrile compounds.

Result and Discussion.

The reaction of ethyl 2-arylhydrazono-3-butyrates **2a** (Ar = Ph) with cyano acetamide derivatives **1a** (R = C_6H_4-*p*-CH_3) in a mixture of benzene/acetic acid solution afforded each of pyridinedione **4** and pyridazine **5** derivatives, respectively, as is shown in Scheme 1. The key precursor for the products is the expected Knoevenagel condensation intermediate **3**. Elimination of ethanol yields the isolable pyridinedione **4a**, while an intramolecular cycloaddition of hydrazo hydrogen to the cyano function affords the insoluble pyridazine compound **5a**. The structure of pyridinediones **4** and pyridazines **5** were based on analytical and spectral data. The IR spectra of **4a-f** revealed an intense absorption bands at ν 2220-2222 cm^{-1} due to the cyano function, whereas it disappeared in the IR spectra of pyridazines **5a-f** indicating the intramolecular addition step. The MS of **4a** showed *m/z* at 344 (M^+, 50), 328 (30), 300 (20), 207 (39 %). The ^{1}H NMR of **4a** revealed two singlet signals at δ 2.2 and 2.3 ppm assigned for two methyl protons and a multiplets at δ 7.1- 7.9 due to aryl and NH protons, respectively. The ^{13}C NMR of **4a** showed a characteristic signal at 115.3 ppm assigned for one cyano carbon. However, the MS of **5a** showed *m/z* at 390 (M^+, 10 %). A typical absorption pattern due to the protons of ester group at δ 1.2 and 4.1 ppm were recorded, whereas ^{13}C NMR showed no absorption signal due to the cyano carbon, however, two characteristic signals were recorded at δ 10.2 and 62.5 ppm were assigned for the ethyl carbon atoms of the ester group.

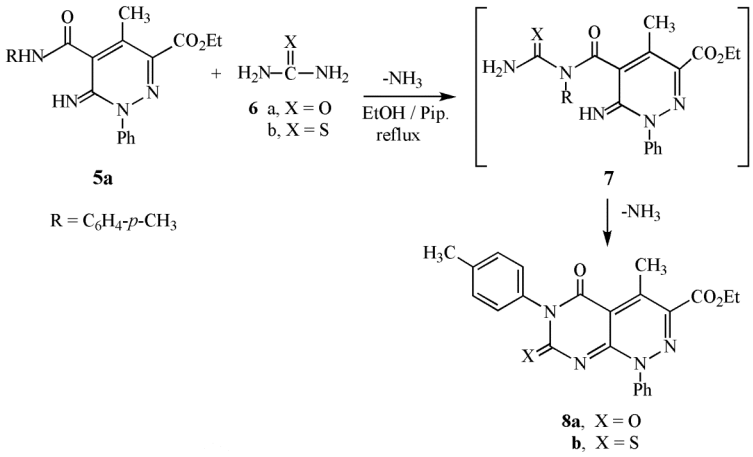
The pyridinedione **4** and pyridazine **5** represent a good synthon for further synthesis of new heterocyclic

Scheme 1

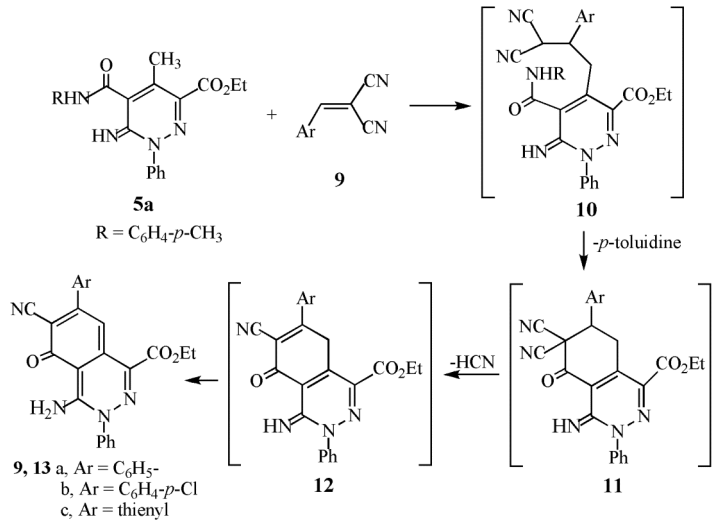


4,5	R	Ar
a	4-methylphenyl	C_6H_5-
b	4-methylphenyl	C_6H_4-*p*-Cl
c	4-methylphenyl	C_6H_4-*p*-OCH_3
d	2-thiazolyl	C_6H_5-
e	2-thiazolyl	C_6H_4-*p*-Cl
f	2-thiazolyl	C_6H_4-*p*-OCH_3

Scheme 2



Scheme 3

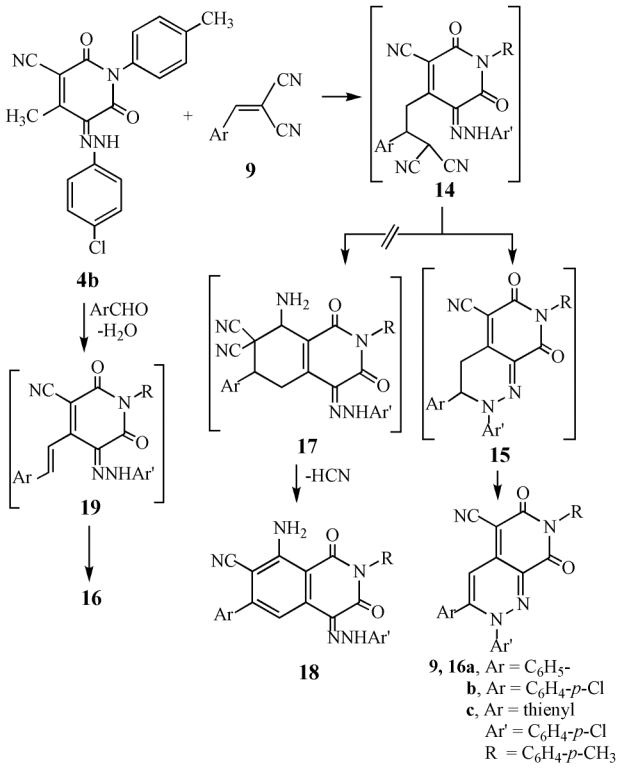


compounds, therefor **4b** and **5a** are selected for their solubility in polar organic solvents. The reactivity of the pyridazine **5a** toward uera and thiourea as binucleophile reagents afforded the pyrimido[4,5-*c*]pyridazine derivative **8** which may formed *via* successive elimination of two moles of ammonia as is shown in Scheme 2. The structure of **8** was based on spectral and elemental analysis. The MS of **8a** showed *m/z* at 416 (M^+, 30). The ^{1}H NMR of **8a** showed signals due to the protons of the ester group at δ 1.3 and 4.3 ppm, as well as two singlet signals at δ 2.3 and 2.5 assigned for two methyl protons and multiplets at δ 7.2- 7.9 ppm due to the aryl protons, respectively. The IR spectra of **8a** showed intense absorption bands at ν 1689, 1710 cm^{-1} due to C=O groups.

However, compound **5a** reacted with arylidenemalononitrile derivatives **9a-c** in ethanol in the presence of piperidine at reflux to gave the phthalazine derivatives **13a-c**, as is shown in Scheme 3. Formation of **13** seemed to proceed *via* Michael addition of the activated methyl group of **5** to the activated double bond in **9** affording the intermediate **10**, which then cyclizes to **11** *via* releasing *p*-toluidine. The intermediate **11** loses HCN to yield finally the phthalazine derivatives **13a-c**. The IR spectra of **13** showed intense absorption bands at ν 1695-1705 and 3320-3330 cm^{-1} due to C=O and NH_2 groups, respectively. The MS of **13c** (Ar = thienyl) showed *m/z* at 416 (M^+, 100), 343 (4), 387 (20), 315 (7), 252 (13), 196 (17 %). The ^{1}H NMR of **13c** showed absorption signals due to protons of ester groups at δ 1.1 and 4.4 ppm, a singlet at δ 2.3 ppm assigned for NH_2 proton and multiplets at δ 7.2- 8.0 due to the aryl protons, respectively.

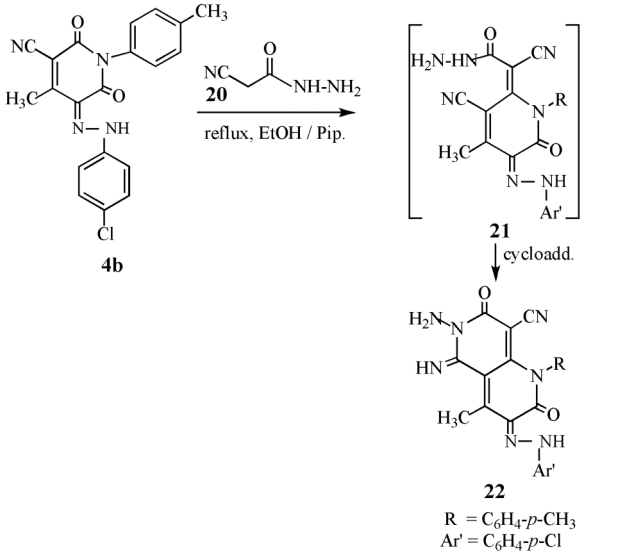
Compound **4b** reacted with arylidenemalononitrile derivatives **9a-c** in ethanol in the presence of piperidine at reflux temperature affording the pyrido[3,4-*c*]pyridazine derivatives **16a-c**, as is shown in Scheme 4. Formation of **16** seemed to proceed through the intermediate of the Michael adduct **14**, which then cyclizing *via* losing malononitrile [19,20] to the dihydropyridopyridazine **15**. The intermediate **15** may undergoes air oxidation to yield finally the pyrido[3,4-*c*]pyridazine derivatives **16a-c**. However, formation of isoquinoline **18** was ruled out based on spectral and elemental analysis. The IR spectra of **16** showed intense absorption bands at ν 2220-2225 and 1690-1696 cm^{-1} due to the cyano and carbonyl groups, respectively. The MS of **16a** showed *m/z* at 464 (M^+, 30 %). The ^{1}H NMR of **16a** showed signals at δ 6.3 and 7.1-7.9 ppm assigned for pyridazine and aryl protons, respectively. On the other hand, refluxing of the pyridinedione **4b** with benzaldehyde afforded the final product **16** *via* formation of intermediate **19**, which then cyclised *via* intramolecular cycloaddition of hydrazo hydrogen into the arylidene double bond. The product gave the same spectral and analytical data.

Scheme 4



Furthermore, compound **4b** reacted with cyanoaceto acid hydrazide **20** in ethanol in the presence of piperidine at reflux to give the 1,6-naphthyridine **22**, as is shown in Scheme 5.

Scheme 5



A condensation step afforded the intermediate **21**, which then cyclized *via* addition of the hydrazo hydrogen to the cyano function to yield the polysubstituted 1,6-

naphthyridine **22**. The IR spectrum of **22** showed intense absorption bands at ν 3350, 3190, 3120, 2220 and 1695 cm^{-1} due to NH_2, NH, CN and C=O groups, respectively. The MS of **22** showed *m/z* at 459 (M^+, 30). The ^1H NMR of **22** showed absorption signals at δ 2.1, 2.7, 7.1-7.9 and 9.1 ppm assigned for two methyl, aryl and amino protons, respectively.

Conclusion.

New derivatives of pyridine, pyridazine, pyrido-pyridazine, 1,6-naphthyridine, pyrimidopyridazine and phthalazine have been synthesized from reaction of diazocarbonyls and active nitrile compounds in a one-pot reaction.

EXPERIMENTAL

Melting points were determined on a Gallen Kamp melting point apparatus. The ir spectra (potassium bromide, ν in cm^{-1}) were recorded on a Pye-Unicam SP-1100 Spectrophotometer. ^1H NMR spectra (deuterodimethylsulfoxide, δ in ppm) were run on a Varian EM-390 Spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a Varian MAT 311 A spectrometer, and the elemental analysis were determined at the Micro-analytical Center, Cairo University, Egypt

Reaction of Arylhydrazones (**2a,b**) with Cyanoacetamide Derivatives (**1a,b**).

General Procedure.

A mixture of equimolar amounts of **2a** (2 g, 0.01 mol), cyanoacetamide derivatives **1a** (1.8 g, 0.01 mol) in acetic acid/benzene mixture (50:10 v/v) and anhydrous ammonium acetate (2 g, 2 mol) was heated for 5 hours under reflux using a device of continuous separation of water. The solid product that separated while hot was collected by filtration and identified as compound **5a**. The filtrate was evaporated under vacuum to give compound **4a**. Analogously, **1a** reacted with **2b,c** to give **4b,c** and **5b,c**. Also, **1b** reacted with **2a-c** to give **4d-f** and **5d-f** derivatives, respectively.

4-Methyl-1-(4-methylphenyl)-2,6-dioxo-5-(phenylhydrazono)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4a**).

This compound has mp: 240 °C, Yield: 75 %. IR: ν 3170, 3095 (NH), 2220 (CN), 1684 (CO) cm^{-1}; ^1H nmr: δ 2.2 (*s*, 3H, CH_3), 2.3 (*s*, 3H, CH_3), 7.1-7.9 (*m*, 10H, Ar-*H* + *NH*); ^{13}C nmr: 13.5 (CH_3), 14.2 (CH_3), 115.3 (CN), 126.5-131.4 (aryl-C), 133.1 (C-4), 134.3 (C-5), 172.4 (C-3), 183.2-183.4 (CO); MS (70 eV) *m/z* (%): 344 (M^+, 50).

Anal. Calcd. For $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27. Found: C, 70.14; H, 4.27; N, 16.66.

4-Methyl-1-(4-methylphenyl)-2,6-dioxo-5-(4-chlorophenylhydrazono)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4b**).

This compound has mp: 280 °C, Yield: 70 %. IR: ν 3190, 3100 (NH), 2222 (CN), 1689 (CO) cm^{-1}; ^1H nmr: δ 2.3 (*s*, 3H, CH_3), 2.5 (*s*, 3H, CH_3), 7.1-7.9 (*m*, 9H, Ar-*H* + *NH*); MS (70 eV) *m/z* (%): 378 (M^+, 95), 380 (M+2, 28).

Anal. Calcd. For $C_{20}H_{15}ClN_4O_2$ (378.82): C, 63.41; H, 3.99; N, 14.79. Found: C, 63.81; H, 4.39; N, 14.99.

4-Methyl-1-(4-methylphenyl)-2,6-dioxo-5-(4-methoxyphenylhydrazono)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4c**).

This compound has mp: 235 °C, Yield: 65 %. IR: ν 3180, 3109 (NH), 2221 (CN), 1687 (CO) cm^{-1}; ^1H nmr: δ 2.1 (*s*, 3H, CH_3), 2.6 (*s*, 3H, CH_3), 3.3 (s. 3H, OCH_3), 7.0-7.9 (*m*, 9H, Ar-*H* + *NH*); MS (70 eV) *m/z* (%): 374 (M^+, 65).

Anal. Calcd. For $C_{21}H_{18}N_4O_3$ (374.40): C, 67.37; H, 4.85; N, 14.96. Found: C, 67.94; H, 5.22; N, 15.33.

4-Methyl-2,6-dioxo-5-(phenylhydrazono)-1-(2-thiazoyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4d**).

mp: 240 °C, Yield: 60 %. IR: ν 3166, 3010 (NH), 2219 (CN), 1686 (CO) cm^{-1}; ^1H nmr: δ 2.3 (*s*, 3H, CH_3), 7.1-7.9 (*m*, 8H, Ar-*H* + *NH*); MS (70 eV) *m/z* (%): 377 (M^+, 65).

Anal. Calcd. For $C_{16}H_{11}N_5O_2S$ (377.36): C, 50.93; H, 2.94; N, 18.56. Found: C, 51.49; H, 3.29; N, 18.95.

4-Methyl-2,6-dioxo-5-(4-chlorophenylhydrazono)-1-(2-thiazoyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4e**).

This compound has mp: 140 °C, Yield: 64 %. IR: ν 3170, 3011 (NH), 2221 (CN), 1685 (CO) cm^{-1}; ^1H nmr: δ 2.2 (*s*, 3H, CH_3), 7.0-7.8 (*m*, 7H, Ar-*H* + *NH*); MS (70 eV) *m/z* (%): 371 (M^+, 55), 373 (M+, 16).

Anal. Calcd. For $C_{16}H_{10}ClN_5O_2S$ (371.80): C, 51.69; H, 2.71; N, 18.84; S, 8.62. Found: C, 52.06; H, 3.08; N, 18.19; S, 8.99.

4-Methyl-2,6-dioxo-5-(4-methoxyphenylhydrazono)-1-(2-thiazoyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4f**).

This compound has mp: 180 °C, Yield: 60 %. IR: ν 3136, 3019 (NH), 2223(CN), 1685 (CO) cm^{-1}; ^1H nmr: δ 2.3 (*s*, 3H, CH_3), 3.8 (*s*, 3H, OCH_3), 7.1-7.9 (*m*, 7H, Ar-*H* + *NH*); MS (70 eV) *m/z* (%): 367 (M^+, 60).

Anal. Calcd. For $C_{17}H_{13}N_5O_3S$ (367.38): C, 55.58; H, 3.57; N, 19.06. Found: C, 55.59; H, 3.99; N, 19.43.

Ethyl 6-imino-4-methyl-5-{[(4-methylphenyl)amino]carbonyl}-1-phenyl-1,6-dihydropyridazine-3-carboxalate (**5a**).

This compound has mp: 305 °C, Yield: 25 %. IR: ν 3200, 3120 (NH), 1720, 1680 (CO) cm^{-1}; ^1H nmr: δ 1.2 (*t*, 3H, CH_3), 2.4 (*s*, 3H, CH_3), 2.7 (*s*, 3H, CH_3), 4.1 (*q*, 2H, CH_2), 7.1-7.9 (*m*, 9H, Ar-*H*), 9.2 (*s*, 1H, NH), 9.7 (*s*, 1H, NH); ^{13}C nmr: 10.2 (CH_3-ester), 15.5, (CH_3), 16.3 (CH_3), 62.5 (CH_2-ester), 128-130 (aryl-C), 134.4 (C-3), 135.3 (C-4), 148.6 (C-2), 170.3 (C-6), 185.5 (CO-amide), 190.6 (CO-ester); MS (70 eV) *m/z* (%): 390 (M^+, 10).

Anal. Calcd. For $C_{22}H_{22}N_4O_3$ (390.44): C, 67.68; H, 5.68; N, 14.35. Found: C, 67.99; H, 6.06; N, 14.72.

Ethyl 6-imino-4-methyl-5-{[(4-methylphenyl)amino]carbonyl}-1-(4-chlorophenyl)-1,6-dihydropyridazine-3-carboxalate (**5b**).

This compound has mp: 280 °C, Yield: 23 %. IR: ν 3205, 3128 (NH), 1729, 1684 (CO) cm^{-1}; ^1H nmr: δ 1.2 (*t*, 3H, CH_3), 2.6 (*s*, 3H, CH_3), 2.7 (*s*, 3H, CH_3), 4.4 (*q*, 2H, CH_2), 7.2-7.9 (*m*, 8H, Ar-*H*), 9.2 (*s*, 1H, NH), 9.7 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 424 (M^+, 35), 426 (M+2, 10).

Anal. Calcd. For $C_{22}H_{21}ClN_4O_3$ (424.89): C, 62.19; H, 4.98; N, 13.19. Found: C, 62.59; H, 5.35; N, 13.57.

Ethyl 6-Imino-4-methyl-5-{[(4-methylphenyl)amino]carbonyl}-1-(4-methoxyphenyl)-1,6-dihydropyridazine-3-carboxalate (**5c**).

This compound has mp: 235 °C, Yield: 21 %. IR: ν 3209, 3125 (NH), 1725, 1683 (CO) cm^{-1}; ^1H nmr: δ 1.1 (*t*, 3H, CH_3), 2.4 (*s*, 3H, CH_3), 2.7 (*s*, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.1 (*q*, 2H, CH_2), 7.1-7.9 (*m*, 8H, Ar-*H*), 9.1(*s*, 1H, NH), 9.9 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 420 (M^+, 45).

Anal. Calcd. For $C_{23}H_{24}N_4O_4$ (420.47): C, 65.70; H, 5.75; N, 13.33. Found: C, 66.10; H, 5.18; N, 13.71.

Ethyl 6-Imino-4-methyl-5-{[(2-thiazoyl)amino]carbonyl}-1-phenyl-1,6-dihydropyridazine-3-carboxalate (**5d**).

This compound has mp: 270 °C, Yield: 18 %. IR: ν 3190, 3129 (NH), 1721, 1680 (CO) cm^{-1}; ^1H nmr: δ 1.4 (*t*, 3H, CH_3), 2.4 (*s*, 3H, CH_3), 4.2 (*q*, 2H, CH_2), 7.1-7.9 (*m*, 7H, Ar-*H*), 9.2 (*s*, 1H, NH), 9.7 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 383 (M^+, 45).

Anal. Calcd. For $C_{18}H_{17}N_5O_3S$ (383.43): C, 56.39; H, 4.47; N, 18.27; S, 8.36. Found: C, 56.78; H, 4.84; N, 18.65; S, 8.76.

Ethyl 6-Imino-4-methyl-5-{[(2-thiazoyl)amino]carbonyl}-1-(4-chlorophenyl)-1,6-dihydropyridazine-3-carboxalate (**5e**).

This compound has mp: 240 °C, Yield: 18 %. IR: ν 3190, 3129 (NH), 1721, 1680 (CO) cm^{-1}; ^1H nmr: δ 1.3 (*t*, 3H, CH_3), 2.7 (*s*, 3H, CH_3), 4.1 (*q*, 2H, CH_2), 7.1-7.9 (*m*, 6H, Ar-*H*), 9.2 (*s*, 1H, NH), 9.9 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 417 (M^+, 45), 419, (M+2, 13).

Anal. Calcd. For $C_{18}H_{16}ClN_5O_3S$ (417.87): C, 51.74; H, 3.86; N, 16.76; S, 7.67. Found: C, 52.09; H, 4.25; N, 17.13; S, 8.05.

Ethyl 6-Imino-4-methyl-5-{[(2-thiazoyl)amino]carbonyl}-1-(4-methoxyphenyl)-1,6-dihydropyridazine-3-carboxalate (**5f**).

This compound has mp: 320 °C, Yield: 20 %. IR: ν 3194, 3128 (NH), 1723, 1680 (CO) cm^{-1}; ^1H nmr: δ 1.2 (*t*, 3H, CH_3), 2.3 (s, 3H,CH_3), 3.5 (*s*, 3H, OCH_3), 4.2 (*q*, 2H, CH_2), 7.1-7.8 (*m*, 6H, Ar-*H*), 9.3 (*s*, 1H, NH), 9.8 (*s*, 1H, NH); MS (70 eV) *m/z* (%): 413 (M^+, 35).

Anal. Calcd. For $C_{19}H_{19}N_5O_4S$ (413.45): C, 55.20; H, 4.63; N, 16.94; S, 7.75. Found: C, 55.59; H, 5.97; N, 17.28; S, 8.11.

Reaction of Pyridazine Derivatives (**5a**) with Urea (**6a**) and Thiourea (**6b**).

A solution of **5a** (0.8 g, 2 mmole), urea **6a** (0.12 g, 2 mmole), and 0.5 ml of piperidine in 30 ml of dry ethanol was warmed to reflux for five hours and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by by filtration, washed well with 100 ml of cold water and crystallized from methanol to give **8a**. Analogously, **5a** (0.8 g, 2 mmole) was reacted with **6b** to give **8b**.

Ethyl 4-Methyl-6-(4-methylphenyl)-5,7-dioxo-1-phenyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]pyridazine-3-carboxylate (**8a**).

This compound has mp: 160 °C, Yield: 56 %. IR: ν 1689, 1710 (CO) cm^{-1}; ^1H nmr: δ 1.3 (*t*, 3H, CH_3), 2.3 (*s*, 3H, CH_3), 2.5 (*s*, 3H, CH_3), 4.3 (*q*, 2H, CH_2), 7.2-7.9 (*m*, 9H, Ar-*H*); MS (70 eV) *m/z* (%): 416 (M^+, 30).

Anal. Calcd. For $C_{23}H_{20}N_4O_4$ (416.44): C, 66.34; H, 4.84; N, 13.45. Found: C, 66.73; H, 5.20; N, 13.81.

Ethyl 4-Methyl-6-(4-methylphenyl)-5-oxo-7-thio-1-phenyl-1,5,6,7-tetrahydropyrimido[4,5-c]pyridazine-3-carboxylate (**8b**).

This compound has mp: 170 °C, Yield: 52 %. IR: ν 1698 (CO) cm^{-1}; ^1H nmr: δ 1.2 (*t*, 3H, CH_3), 2.2 (*s*, 3H, CH_3), 2.7(*s*, 3H, CH_3), 4.3 (*q*, 2H, CH_2), 7.0-7.8 (*m*, 9H, Ar-*H*); MS (70 eV) *m/z* (%): 432 (M^+, 20).

Anal. Calcd. For $C_{23}H_{20}N_4O_3S$ (432.50): C, 63.87; H, 4.66; N, 12.95. Found: C, 64.22; H, 4.99; N, 13.18.

Reaction of Pyridazine Derivatives (**5a**) with Arylidenemalononitrile (**9a-c**).

A solution of **5a** (0.8 g, 2 mmole), arylidenemalononitrile **9a** (0.3 g, 2 mmole) and 0.5 ml of piperidine in 30 ml of dry ethanol was warmed to reflux for five hours. The solid product so formed during reflux was collected by filtration, washed well with 5 ml of methanol and crystallized from ethanol to give **13a**. Analogously, **5a** (0.8 g, 2 mmole) was reacted with **9b** to give **13b**.

Ethyl 4-Amino-6-cyano-5-oxo-3,7-diphenyl-3,5-dihydrophthalazine-1-carboxlate (**13a**).

This compound has mp: 275 °C, Yield: 52 %. IR: ν 3320 (NH_2), 2225 (CN), 1695, 1705 (CO) cm^{-1}; ^1H nmr: δ 1.2 (*t*, 3H, CH_3), 2.1 (*s*, 2H, NH_2), 4.3 (*q*, 2H, CH_2), 7.0-7.8 (*m*, 11H, Ar-*H*); MS (70 eV) *m/z* (%): 410 (M^+, 20).

Anal. Calcd. For $C_{24}H_{18}N_4O_3$ (410.43): C, 70.23; H, 4.42; N, 13.65. Found: C, 70.58; H, 4.78; N, 13.95.

Ethyl 4-Amino-6-cyano-5-oxo-3-phenyl-7-(4-chlorophenyl)-3,5-dihydrophthalazine-1-carboxlate (**13b**).

This compound has mp: 270 °C, Yield: 56 %. IR: ν 3328 (NH_2), 2220 (CN), 1696, 1703 (CO) cm^{-1}; ^1H nmr: δ 1.1 (*t*, 3H, CH_3), 2.3 (s, 2H, NH_2), 4.3 (*q*, 2H, CH_2), 7.0-7.9 (*m*, 10H, Ar); MS (70 eV) *m/z* (%): 444 (M^+, 29), 446 (M+2, 8).

Anal. Calcd. For $C_{24}H_{17}ClN_4O_3$ (444.88): C, 64.80; H, 3.85; N, 12. 60. Found: C, 65.13; H, 4.20; N, 12.92.

Ethyl 4-Amino-6-cyano-5-oxo-3-phenyl-7-(thienyl)-3,5-dihydrophthalazine-1-carboxlate (**13c**).

This compound has mp: 260 °C, Yield: 50 %. IR: ν 3330 (NH_2), 2224 (CN), 1699, 1701 (CO) cm^{-1}; ^1H nmr: δ 1.1 (*t*, 3H, CH_3), 2.3 (s, 2H, NH_2), 4.4 (*q*, 2H, CH_2), 7.2-8.0 (*m*, 9H, Ar-*H*); MS (70 eV) *m/z* (%): 416 (M^+, 100).

Anal. Calcd. For $C_{22}H_{16}N_4O_3S$ (416.46): C, 63.45; H, 3.87; N, 13.45. Found: C, 63.55; H, 3.98; N, 13.57.

Reaction of Pyridazine Derivatives (**4b**) with Arylidenemalononitrile (**9a-c**).

A solution of **4b** (0.7 g, 2 mmole), arylidenemalononitrile **9a** (0.3 g, 2 mmole), and 0.5 ml of piperidine in 30 ml of dry ethanol was warmed to reflux for five hours and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from methanol to give **16a**. Analogously, **4b** (0.7 g, 2 mmole) was reacted with **9b,c** to give **16b,c**.

2-(4-Chlorophenyl)-7-(4-methylphenyl)-6,8-dioxo-3-phenyl-2,6,7,8-tetrahydropyrido[3,4-*c*]pyridazine-5-carbonitrile (**16a**).

This compound has mp: 190 °C, Yield: 50 %. IR: ν 2220 (CN), 1690 (CO) cm^{-1}; ^1H nmr: δ 2.6 (*s*, 3H, CH_3), 6.3 (*s*, 1H, pyridazine-*H*), 7.1-7.9 (*m*, 13H, Ar-*H*); MS (70 eV) *m/z* (%): 464 (M^+, 30), 466 (M+2, 10).

Anal. Calcd. For $C_{27}H_{17}ClN_4O_2$ (464.91): C, 69.75; H, 3.69; N, 12.05. Found: C, 69.99; H, 4.03; N, 12.42.

2,3-Di-(4-chlorophenyl)-7-(4-methylphenyl)-6,8-dioxo-2,6,7,8-tetrahydropyrido[3,4-*c*]pyridazine-5-carbonitrile (**16b**).

This compound has mp: 182 °C, Yield: 52 %. IR: ν 2222 (CN), 1693 (CO) cm^{-1}; ^1H nmr: δ 2.5 (*s*, 3H, CH_3), 6.1 (*s*, 1H, pyridazine-*H*), 7.0-7.9 (*m*, 12H, Ar-*H*); MS (70 eV) *m/z* (%): 499 (M^+, 29), 501 (M+2, 10).

Anal. Calcd. For $C_{27}H_{16}Cl_2N_4O_2$ (499.36): C, 64. 94; H, 3.23; N, 11.22. Found: C, 65.29; H, 3.59; N, 11.58.

2-(4-Chlorophenyl)-7-(4-methylphenyl)-6,8-dioxo-3-thienyl-2,6,7,8-tetrahydropyrido[3,4-*c*]pyridazine-5-carbonitrile (**16c**).

This compound has mp: 150 °C, Yield: 53 %. IR: ν 2225 (CN), 1696 (CO) cm^{-1}; ^1H nmr: δ 2.1 (*s*, 3H, CH_3), 6.3 (*s*, 1H, pyridazine-*H*), 7.0-7.8 (*m*, 11H, Ar-*H*); MS (70 eV) *m/z* (%): 470 (M^+, 27) 472 (M+2, 8).

Anal. Calcd. For $C_{25}H_{15}ClN_4O_2S$ (470.93): C, 63.76; H, 3.21; N, 11.90. Found: 64.13; H, 3.55; N, 12.12.

6-Amino-5-imino-4-methyl-1-(4-methylphenyl)-3-[(4-chlorophenyl)hydrazono]-2,7-dioxo-1,2,3,5,6,7-hexahydro-1,6-naphthyridine-8-carbonitrile (**22**).

A solution of **4b** (0.7 g, 2 mmole), cyanoacetoacid hydrazide **20** (0.2 g, 2 mmole), and 0.5 ml of piperidine in 30 ml of dry ethanol was warmed to reflux for five hours and then concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from methanol to give **22**; mp: 140 °C, Yield: 55 %; IR: ν 3350 (NH_2), 3190, 3120 (NH), 2220 (CN), 1695 (CO) cm^{-1}; ^1H nmr: δ 2.1 (*s*, 3H, CH_3), 2.7 (*s*, 3H, CH_3), 7.1-7.9 (*m*, 10H, Ar-*H* + *2 NH*), 9.1 (*s*, 2H, NH_2); MS (70 eV) *m/z* (%): 459 (M^+, 30), 461 (M+2, 10).

Anal. Calcd. For $C_{23}H_{18}ClN_7O_2$ (459.90): C, 60.07; H, 3.95; N, 21.32. Found: C, 60.41; H, 4.28; N, 21.64.

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