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Facile and Convenient Synthesis of Pyrazole, Pyridine, Pyridazine, Pyrazolo[3,4-*b*]pyridine, and Pyrazolo[5,1-*c*][1,2,4]triazine Derivatives

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Abstract: A convenient synthesis of a series of pyrazole, pyridine, pyridinethione, pyridazine, pyrazolo[3,4-*b*]pyridine, imidazo[1,2-*a*]pyrimidine, and pyrazolo[5,1-*c*][1,2,4]triazine derivatives incorporating a pyrimidine moiety, via the reactions of the versatile, readily accessible 3-oxo-*N*-(pyrimid-2-yl)butanamide with the appropriate reagents, is described.

Keywords: *N*-(pyrimid-2-yl)butanamide, imidazo[1,2-*a*]pyrimidine, pyrazole, pyrazolo[3,4-*b*]pyridine, pyrazolo[5,1-*c*][1,2,4]triazine], pyridazine, pyridinethione

In addition to being essential components of naturally occurring nucleic acids, pyrimidines are integral parts of biologically important compounds such as antiviral[1] antiherpes,[2] and cardiovascular agents.[3] On the other hand, acetamido derivatives, in general, have been found to possess fungicidal[4] and herbicidal[5] activities. Moreover, amides in which amidic hydrogen has been substituted with a heterocyclic moiety have been found to possess local anesthetic effects.[6] In view of these reports and in continuation of our interest in the synthesis of a variety of heterocyclic systems for biological evaluation,[7–19] we describe here a facile synthesis of pyrazole, pyridinethione, pyrazolo[3,4-*b*]pyridine, imidazo[1,2-*a*] pyrimidine, pyridazine, and pyrazolo[5,1-*c*][1,2,4]triazine, starting from the readily accesible 3-oxo-*N*-(pyrimid-2yl)butanamide.

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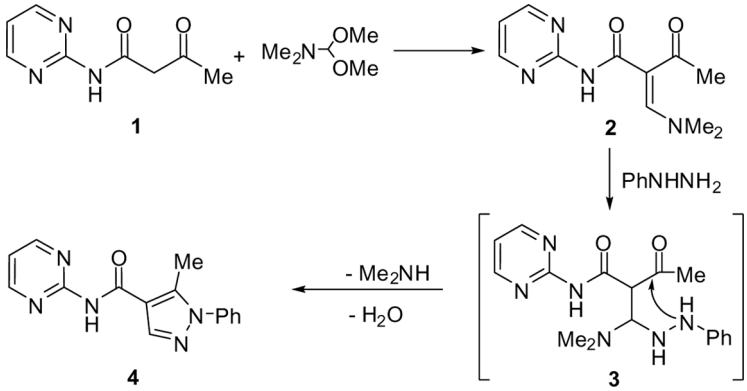


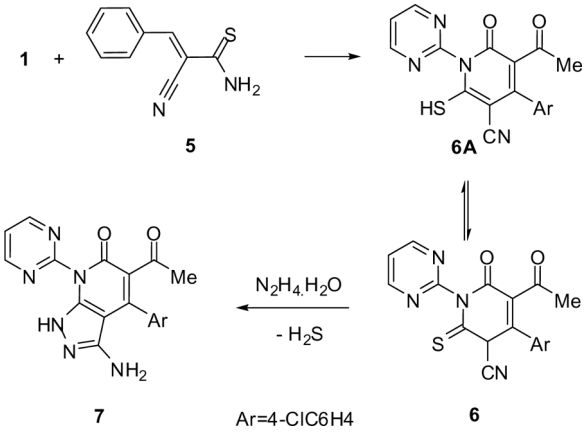
Scheme 1. Synthetic route of compound **4**.

Thus, when 3-oxo-*N*-(pyrimid-2-yl)butanamide (**1**) was treated with dimethylformamide–dimethylacetal (DMF-DMA), it afforded the corresponding 3-oxo-*N*-(pyrimid-2-yl)-2-(*N,N*-dimethylaminomethylene)butanamide (**2**) (Scheme 1). The IR spectrum of the latter product revealed absorption bands at 1650, 1681, and 3365 cm^{-1} due to two carbonyl and imino functions. Its ^1H NMR revealed signals at δ 2.41, 3.21, and 3.26 due to acetyl CH_3 protons and N,N-dimethyl protons, in addition to the D_2O-exchangeable signal at δ 11.4 due to the NH proton, and an aromatic multiplet and methine proton in the region δ 8.33–8.80.

Compound **2** was treated with phenylhydrazine, in refluxing ethanol, to afford the pyrazole derivative **4** (Scheme 1). IR spectrum of compound **4** revealed absorption bands at 1651 and 3150 cm^{-1} due to carbonyl groups and an imino function. Its ^1H NMR revealed signals at δ 2.14 due to CH_3 protons, D_2O-exchangeable signals at δ 8.9 due to a NH proton, and an aromatic multiplet in the region δ 6.67–7.82.

Reaction of equimolar amounts of the butanamide **1** and 2-cyano-2-(4-chlorophenylmethylene)thioacetamide (**5**) in the presence of piperdine afforded 5-acetyl-N-(pyrimid-2-yl)-3-cyano-4-(4-chlorophenyl)-6-oxo-2-thioxopyridine (**6**) (Scheme 2). The IR spectrum of compound **6** showed typical strong absorption bands at 1542, 1674, 1710, and 2222 cm^{-1} due to thiocarbonyl, two carbonyls, and a nitrile function, respectively.

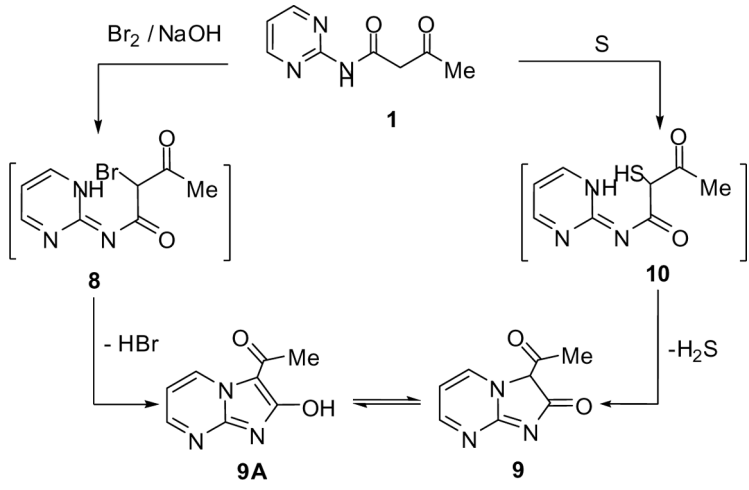
Treatment of the pyridinethione **6** with hydrazine hydrate afforded 1*H*-3-amino-4-(4-chlorophenyl)-5-acetyl-6-oxo-7-(*N*-pyrimid-2-yl)pyrazolo-[3,4-*b*]pyridine (**7**) (Scheme 2). The IR spectrum of the latter compound revealed absorption bands at 1674, 1720, 3063, 3132, and 3479 cm^{-1} due to two carbonyl groups: NH_2 and NH functions, respectively. Its ^1H NMR spectrum showed signal at δ 2.36 due to CH_3 protons, two



Scheme 2. Synthetic routes of compounds **6** and **7**.

D_2O-exchangeable signals at δ 7.29 and 10.82 due to NH_2 and NH protons, respectively, and an aromatic multiplet in the region δ 7.13–8.56. Also, its mass spectrum revealed a molecular ion peak at m/z 381.

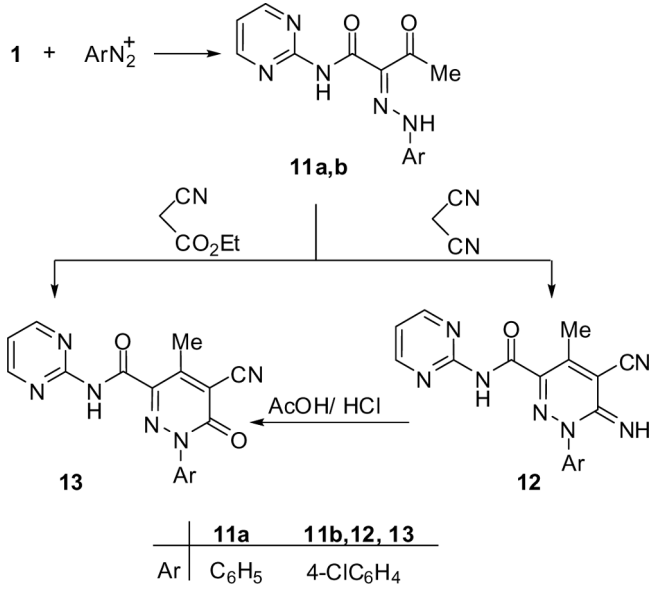
Treatment of the butanamide **1** with bromine in sodium hydroxide solution, at room temperature, furnished only one isolable product (as tested by thin-layer chromatography, TLC) that was identified as imidazo[1,2-*a*]pyrimidine **9** (Scheme 3). Compound **9** was thought to



Scheme 3. Synthetic routes of compound **9**.

be formed via initial bromination of the methylene group followed by elimination of hydrogen bromide under the reaction conditions. The IR spectrum of compound **9** showed absorption bands at 1620 and 1674 cm^{-1} due to two carbonyl groups. Its ^1H NMR revealed signals at δ 2.39 due to CH_3 protons, D_2O-exchangeable signal at δ 12.7 due to an OH proton, and an aromatic multiplet in the region δ 7.33–9.99. Its mass spectrum showed a molecular ion peak at m/z 177. Compound **9** was alternatively prepared via the reaction of the butanamide **1** with elemental sulfur in the presence of a catalytic amount of triethylamine (Scheme 3).

3-Oxo-(*N*-pyrimid-2-yl)butanamide (**1**) coupled smoothly with the diazonium salts of aniline and p-chloroaniline, in ethanol buffered with sodium acetate, to afford the corresponding hydrazone derivatives **11a, b** (Scheme 4). When compound **11b**, taken as typical example, was treated with malononitrile in ethanol, in the presence of a catalytic amount of piperdine, it afforded 1-(4-chlorophenyl)-3-(pyrimid-2-ylcarboxamido)-4-methyl-6-iminopyridazine-5-carbonitrile (**12**) (Scheme 4). The IR spectrum of the conjugated carbonyl of amide group should absorption bands at 2199, 3150, and 3333 cm^{-1} due to a nitrile function and two NH groups, respectively. Its ^1H NMR spectrum revealed signal at δ 2.49 due to CH_3 and two D_2O-exchangeable signals at δ 10.33 and

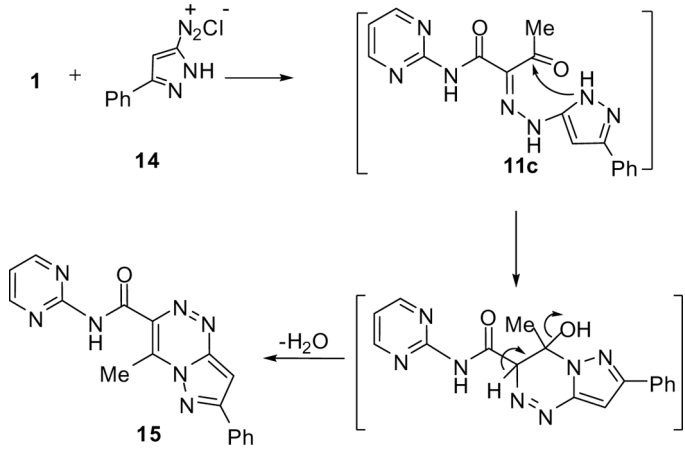


Scheme 4. Synthetic routes of compounds **12** and **13**.

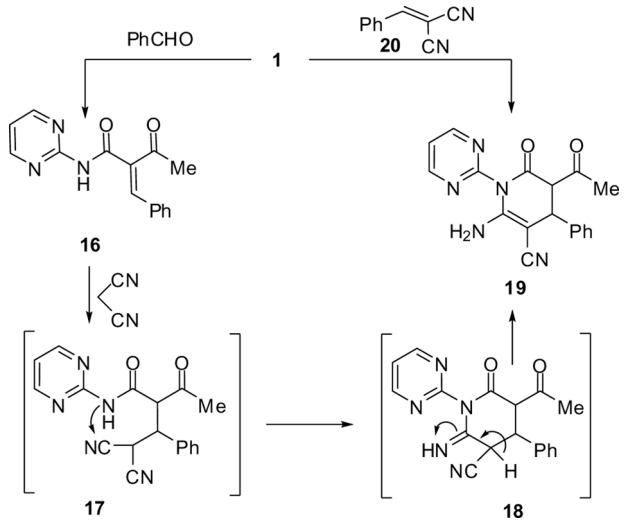
11.76 due to two NH protons, in addition to an aromatic multiplet in the region δ 8.23–8.90.

The hydrazone **11b** reacts also with ethyl cyanoacetate to afford the 1-(4-chlorophenyl)-6-oxo-3-(pyrimid-2-ylcarboxamido)-4-methyl-pyridazin-5-carbonitrile (**13**). Heating of the iminopyridazine derivative **12** in acetic acid/hydrochloric acid mixture afforded a product that was found to be identical in all respects with compound **13**. The IR spectrum of the latter product showed absorption bands at 1660, 1689, 2120, and 3225 cm^{-1} due to two carbonyl, nitrile function, and NH groups, respectively. Its ^1H NMR spectrum revealed signals at δ 2.49 due to CH_3 and a broad signal at δ 10.90 (D_2O-exchangeable) due to NH, in addition to an aromatic multiplet in the region δ 7.24–7.68. Treatment of the butanamide **1** with the diazonium salt of 3-phenyl-5-aminopyrazole (**14**) afforded the corresponding 4-methyl-7-phenyl-*N*-(pyrimidin-2-yl)pyrazolo[5,1-c]-[1,2,4]triazine-3-carboxamide **(15)** via the none-isolable hydrazone intermediate **11c** (Scheme 5). The IR spectrum of the product **15** revealed the presence of an amide carbonyl absorption band at 1684 cm^{-1} and one NH band at 3360 cm^{-1}. Its ^1H NMR spectrum revealed signals at δ 2.49 due to CH_3 and a broad signal at δ 11.12 (D_2O-exchangeable) due to an NH proton, in addition to an aromatic multiplet in the region δ 7.27–8.74.

When the butanamide **1** was trated with benzaldehyde, in the presence of a catalytic amount of piperdine, it afforded the corresponding 2-phenylmethylene-3-oxo-*N*-(pyrimid-2-ylcarboxamido)butanamide **(16)** (Scheme 6). The IR spectrum of compound **16** showed absorption bands at 1655, 1709, and 3234 cm^{-1} due to two carbonyl groups and the NH function,



Scheme 5. Synthetic route of compound **15**.



Scheme 6. Synthetic routes of compound **19**.

respectively. Its ^{1}H NMR spectrum revealed a singlet signal at δ 2.13 due to CH_3, a broad signal at δ 10.03 (D_2O-exchangeable) due to the NH proton, and an aromatic multiplet in the region δ 6.55–8.27.

Treatment of compound **16** with malononitrile in the presence of a catalytic amount of piperidine furnished the corresponding 2-amino-5-acetyl-4-phenyl-6-oxo-1,4,5,6-tetrahydro-N-(pyrimid-2-yl)pyridine (**19**) (Scheme 6). The IR spectrum of compound **19** revealed absorption bands at 1638, 1651, 2214, 3066, and 3233 cm^{-1} due to two carbonyl, nitrile, and amino functions, respectively. Its ^{1}H NMR spectrum exhibited a singlet signal at δ 2.4 due to CH_3, two doublets at δ 4.82 and 5.48 with $J = 11.22$ Hz due to two CH protons, and a broad signal at δ 8.17 due to NH_2, in addition to an aromatic multiplet in the region δ 7.00–8.37.

Compound **19** was assumed to be formed via an initial Michael-type adduct **17** followed by an intramolecular cyclization to the final product **19** (Scheme 6). Additionally, the elucidation of structures **19** was supported chemically through its alternative synthesis from the reaction of the butanamide **1** with phenylmethylenepropandinitrile **20** under the same reaction condition.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting-point apparatus. The infrared spectra were recorded in potassium bromide

disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt, and the results were in good agreement ($\pm$ 0.3%) with the calculated values. The starting materials 3-oxo-*N*-(pyrimid-2-yl)-butanamid(**1**),[20] 2-cyano-2-(4-chlorophenylmethylene)thioacetamide (**5**),[21] 3-phenyl-(1*H*)-pyrazole-5-diazonium chloride (**14**),[22] and phenylmethylenepropanedinitrile (**20**)[23] were prepared according to the reported literature.

3-Oxo-2-(*N,N*-dimethylaminomethylene)-*N*-(pyrimid-2-yl)butanamide (2)

A mixture of butanamide **1** (3.58 g, 20 mmol) and DMF-DMA (**2**) (2.66 cm^3, 20 mmol) in 30 cm^3 dry xylene was refluxed for 3 h and then left to cool. The yellow precipitated product was filtered off, washed with light petroleum, and dried. Recrystallization from EtOH/DMF afforded yellow crystals. Yield 50%; mp 250–251°C (DMF/EtOH). IR (KBr): v 3365 (NH), 1681 (C=O), 1650 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 8.33–8.80 (m, 4H, ArH's), 11.4 (s, br, 1H, D_2O-exchangeable NH). Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.42; H, 6.08; N, 23.91.

Reaction of 3-Oxo-2-(*N,N*-dimethylaminomethylene)-*N*-(pyrimid-2-yl)-butanamide (2) with Phenylhydrazine

Phenyl hydrazine (0.2 cm^3, 2 mmol) was added to a solution of **2** (0.468 g, 2 mmol) in 20 cm^3 EtOH, and the reaction mixture was refluxed for 4 h, then left to cool. The obtained solid product was filtered off, washed with EtOH, and dried. Recrystallization from EtOH afforded an orange product of 1-phenyl-3-methyl-4-(pyrimid-2-ylcarboxamido)-pyrazole (**4**). Yield 60%; mp 220–221°C (DMF/EtOH). IR (KBr): ν 3150 (NH), 1651 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, CH_3), 6.67–7.82 (m, 9H, ArH's), 8.9 (s, br, 1H, D_2O-exchangeable NH). Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.48; H, 4.66; N, 25.03.

Reaction of the Butanamide 1 with 2-Cyano-2-(4-chlorophenyl methylene)thioacetamide (5)

To a mixture of the butanamide **1** (0.358 g, 2 mmol) and 2-cyano-2-(4-chlorophenyl-methylene)thioacetamide (**5**) (0.445 g, 2 mmol) in 20 cm^3 EtOH, a few drops of piperdine were added. The reaction mixture was heated under reflux for 2 h. The solid product that precipitated from the hot solution was filtered off, washed with EtOH, and recrystallized from DMF to afford yellow crystals of 5-acetyl-*N*-(pyrimid-2-yl)-3-cyano-4-(4-chlorophenyl)-6-oxo-2-thioxopyridine (**6**) in 70% yield. Mp $> 300°C$ (DMF). IR (KBr): ν 2222 (C≡N), 1710 (C=O), 1674 (C=O), 1574 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.4 (s, 3H, CH_3), 7.15–8.57 (m, 7H, ArH's), 14.34 (s, 1H, D_2O-exchangeable SH). Calcd. for $C_{18}H_{11}N_4O_2SCl$: C, 56.47; H, 2.90; N, 14.64; S, 8.38; Cl, 9.26. Found: C, 56.49; H, 2.92; N, 14.64; S, 8.39; Cl, 9.25.

3-Amino-5-acetyl-6-oxo-4-(4-chlorophenyl)-1,4,5,6-tetrahydro-7-(pyrimid-2-yl)pyrazolo[3,4-*b*]pyridine (7)

Hydrazine hydrate (80%, 0.1 cm^3, 1 mmol) was added to a solution of the pyridinethione **6** (0.384 g, 1 mmol) in 20 cm^3 EtOH. The reaction mixture was heated under reflux for 4 h, then left to cool. The solid product was filtered off, washed with EtOH, and dried. Recrystallization from DMF afforded yellow crystals of **7**. Yield 70%; mp 285–286°C (DMF). IR (KBr): ν 3479 (NH), 3063–3132 (NH_2), 1720 (C=O), 1674 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 7.13–8.56 (m, 7H, ArH's), 7.29 (s, br, 2H, D_2O-exchangeable NH_2), 10.82 (s, br, 1H, D_2O-exchangeable NH). MS m/z (%) 383 (16.3), 382 (7.8), 381 (M^+, 33.6), 366 (100), 340 (6.1), 112 (4.5), 111 (5.5), 78 (2.6), 77 (4.4). Calcd. for $C_{18}H_{13}N_6O_2Cl$: C, 56.78; H, 3.443.44; N, 22.07; Cl, 9.31. Found: C, 56.75; H, 3.48; N, 22.10; Cl, 9.27.

Bromination of 3-Oxo-*N*-(pyrimid-2-yl)butanamide (1)

To a cold solution of the butanamide **1** (0.358 g, 2 mmol), sodium hydroxide (2 mmol), and 20 cm^3 absolute methanol, bromine (0.16 g, 0.05 cm^3, 2 mmol) was added portionwise to the resulting solution with continuous stirring. After complete addition, the reaction was left for 1 h. The solid product that formed was filtered off, washed with water, and crystallized from DMF to give white crystals of 3-acetylimidazo[1,2-*a*]pyrimidin-2(3*H*)-one **9**, in 80% yield. mp $> 300°C$ (DMF). IR (KBr): ν 1674 (C=O), 1620 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3),

7.33–9.99 (m, 3H, ArH's), 12.7 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 27.35, 103.76, 113.51, 135.82, 141.86, 152.50, 159.98, 184.44. MS, m/z (%) 179 (1.0), 178 ($M^+ + 1$, 8.5), 177 (M^+, 82.9), 176 (1.6), 122 (0.8), 94 (1.6), 79 (26.8), 78 (3.0). Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.22; H, 4.00; N, 23.68.

Reaction of 3-Oxo-*N*-(pyrimid-2-yl)butanamide (1) with Elemental Sulfur

Ethyl acetoacetate or ethyl cyanoacetate (2 mmol) and a catalytic amount of triethylamine were added to a solution of the butanamide **1** (0.358, 2 mmol) in 20 cm^3 EtOH and elemental sulfur (0.064 g, 2 mmol). The reaction mixture was heated at 60–65°C for 30 min and then allowed to cool. The precipitated solid was filtered off, washed with EtOH, and recrystallized from DMF to afford the same product identical in all respects (mp, mixed mp, and spectra) with that obtained from the reaction of butanamide **1** with bromine.

General Procedure for the Reaction of 3-oxo-*N*-(pyrimid-2-yl)-butanamide (1) with the Diazonium Salts of Aromatic Amines and 5-Amino-3-Phenylpyrazole

The appropriate diazonium salt of aromatic amines or 5-amino-3-phenylpyrazole (**14**) (2 mmol) was added to a cold solution of butanamide **1** (0.358 g, 2 mmol) in 50 cm^3 EtOH, buffered with sodium acetate trihydrate (3 g). The addition was carried out portionwise with stirring at 0–5°C over a period of 30 min. After complete addition, the reaction mixture was stirred for a further 4 h, then kept in an ice chest for 12 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized from the proper solvent to afford hydrazones **11a,b** and the pyrazolo[5,1-*c*]-1,2,4-triazine **15**, respectively.

3-Oxo-2-(phenylhydrazono)-*N*-(pyrimid-2-yl)butanamide (11a)

Yield 92%; mp 174–175°C (EtOH). IR (KBr): ν 3200 (NH), 3130 (NH), 1670 (C=O), 1636 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3), 7.24–8.71 (m, 7H, ArH's), 11.80 (s, br, 1H, D_2O-exchangeable, NH), 14.0 (s, br, 1H, D_2O-exchangeable, NH). Calcd. for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. Found: C, 59.39; H, 4.60; N, 24.69.

3-Oxo-2-(4-chlorophenylhydrazono)-*N*-(pyrimid-2-yl)butanamide (11b)

Yield 80%; mp 180–181°C (EtOH). IR (KBr): ν 3200 (NH), 3163 (NH), 1670 (C=O), 1638 (C=O) cm^{-1}. Calcd. for $C_{14}H_{12}N_5O_2Cl$: C, 52.92; H, 3.81; N, 22.04; Cl, 11.16. Found: C, 52.94; H, 3.85; N, 22.07; Cl, 11.20.

4-Methyl-7-phenyl-*N*-(pyrimidin-2-yl)pyrazolo[5,1-c][1,2,4]triazine-3-carboxamide (15)

Yield 85%; mp > 300°C (DMF). IR (KBr): ν 3360 (NH), 1684 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.27–8.74 (m, 9H, ArH's), 11.12 (s, br, 1H, D_2O-exchangeable, NH). MS, m/z (%) 331 (M^+, 0.6), 209 (1.9), 122 (20.0), 93 (0.4), 79 (14.4). Calcd. for $C_{17}H_{13}N_7O$: C, 61.62; H, 3.96; N, 29.59. Found: C, 61.68; H, 3.98; N, 29.55.

Reaction of 3-Oxo-2-(4-chlorophenylhydrazono)-*N*-(pyrimid-2-yl)butanamide (11b) with Malononitrile and Ethyl Cyanoacetate

A few drops of piperdine were added to an ethanolic solution of the hydrazone **11b** (0.64 g, 2 mmol) and malononitrile (0.165 g, 2.5 mmol) or ethyl cyanoacetate (0.226 g, 2 mmol), and the reaction mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue was triturated with EtOH. The solid product was filtered off, washed with ethanol, and finally purified by recrystallization from the proper solvent to afford brown crystals of **12** and yellow crystals of **13**, respectively.

1-(4-Chlorophenyl)-3-(pyrimid-2-ylcarboxamido)-4-methyl-6-iminopyridazine-5-carbonitrile (12)

Yield 80%; mp 265–266°C (DMF/EtOH). IR (KBr): ν 3333 (NH), 3150 (NH), 2199 (C≡N), 1655 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 8.23–8.90 (m, 7H, ArH's), 10.33 (s, 1H, D_2O-exchangeable, NH), 11.76 (s, br, 1H, D_2O-exchangeable, NH). Calcd. for $C_{17}H_{12}N_7OCl$: C, 55.82; H, 3.31; N, 26.81; Cl, 9.69. Found: C, 55.79; H, 3.33; N, 26.78; Cl, 9.72.

1-(4-Chlorophenyl)-6-oxo-3-(pyrimid-2-ylcarboxamido)-4-methyl-pyridazine-5-carbonitrile (13)

Yield 75%; mp > 300°C (DMF). IR (KBr): ν 3225 (NH), 2120 (C≡N), 1689 (C=O), 1660 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H,

CH_3), 7.24–7.68(m, 7H, ArH's), 10.9 (s, D_2O-exchangeable, NH). Calcd. for $C_{17}H_{11}N_6O_2Cl$: C, 55.67; H, 3.02; N, 22.91; Cl, 9.67. Found: C, 55.62; H, 3.06; N, 22.88; Cl, 9.62.

2-Phenylmethylene-3-oxo-*N*-(pyrimid-2-ylcarboxamido)butanamide (16)

A few drops of piperdine were added to an ethanolic solution of the butanamide **1** (0.358 g, 2 mmol) and benzaldehyde (0.212 g, 2 mmol), and the reaction mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue was triturated with EtOH. The solid product was filtered off, washed with ethanol, and purified by recrystallization from EtOH to afford pale yellow crystals of **16** in 70% yield. Mp 219–220°C (DMF/EtOH). IR (KBr): ν 3234 (NH), 1709 (C=O), 1655 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 6.55–8.27 (m, 9H, ArH's), 10.03 (s, 1H, D_2O-exchangeable, NH). Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.46; H, 4.88; N, 15.77.

Synthesis of 5-Acetyl-2-amino-6-oxo-4-phenyl-1,4,5,6-tetrahydro-1-(pyrimid-2-yl)pyridine-3-carbonitrile (19)

Method A

An equimolar amount of the malononitrile (0.132 g, 2 mmol), and a few drops of pipredine were added a solution of 2-phenylmethylene-3-oxo-*N*-(pyrimid-2-ylcarboxamido)butanamide (**16**) (0.267 g, 2 mmol) in 20 cm^3 EtOH. The reaction mixture was heated under reflux for 2 h, then allowed to cool to room temperature. The solid product was collected by filtration, washed with EtOH, and then recrystallized from the DMF/EtOH to give yellow crystals of **19**. Yield 80%; mp 265–266°C (DMF/EtOH). IR (KBr): ν 3233–3066 (NH_2), 2214 (C≡N), 1651 (C=O), 1638 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 4.82 (d, 1H, $J = 11.22$ Hz), 5.48 (d, 1H, CH, $J = 11.22$ Hz), 7.00–8.37 (m, 8H, ArH's), 8.17 (s, br, 2H, D_2O-exchangeable, NH_2). Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.83; H, 4.49; N, 21.03.

Method B

An equimolar amount of the butanamide **1** (0.358 g, 2 mmol) and a few drops of piperdine were added to a solution of phenylmethylenepropandinitrile (**20**) (0.308 g, 2 mmol) in 20 cm^3 EtOH, and the reaction mixture

was heated under reflux for 2 h. The solid product that formed was collected by filtration, washed with EtOH, and then recrystallized from DMF/EtOH to give a product identical in all respects (mp, mixed mp, and spectra) with **19** obtained from method A above.

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