Facile route to novel 2-pyridone, pyrazolo[3,4-*d*]-1,2,3-triazine, and pyrazolo[3,4-*d*]- and [1,5-*a*]-pyrimidine derivatives

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Abstract

Treatment of 2-cyano-*N*-(2-pyridyl)acetamide (**1**) with hydrazonoyl chlorides **2a-e** afforded aminopyrazoles **4a-e** which on treatment with sodium nitrite in acetic acid furnished the pyrazolo[3,4-*d*]-1,2,3-triazin-4-one derivatives **8a-e**. Reaction of aminopyrazoles **4c-e** with triethylorthoformate in glacial acetic acid afforded pyrazolo[3,4-*d*]pyrimidin-4-one derivatives **10a-c**. Compound **1** reacted with DMF-DMA in refluxing xylene affording a mixture of 3-(*N,N*-dimethylamino)propenenitrile **11** and *N*,1-di(pyridin-2-yl)pyridine-3-carboxamide **15** derivatives. When compound **11** was treated with hydrazine, phenylhydrazine or with 5-amino-3-phenyl-1*H*-pyrazole **16** in refluxing ethanol, the novel aminopyrazoles **13a,b** and pyrazolo[1,5-*a*]pyrimidine **18** derivatives were obtained.

Keywords: Cyanoacetamides, hydrazonoyl chlorides, pyrazolo[3,4-*d*]pyrimidinones, pyrazolo[3,4-*d*]-1,2,3-triazinones, pyrazolo[1,5-*a*]pyrimidines

Introduction

The pyrazolo[3,4-*d*]pyrimidine derivatives attracted much attention because of their applications as anti-mycobacterial[1] and antidiabetic[2] agents, kinase[3] and phophodiestrase[4] inhibitors, and also for their valuable antiangiogenic,[5] fungicidal,[6] cytotoxic[7] antitubercular,[8] antimicrobial and anthelmintic[9] activities. In contrast to the wide publications about pyrazolo[3,4-*d*]pyrimidine derivatives, the pyrazolo[3,4-*d*]-1,2,3-triazine derivatives are rare in the literature and some of the reported examples were found to possess anticonvulsant[10] and cytotoxic[11] activities. Pyrazole derivatives have also important applications in the field of medicinal chemistry and pharmacueticals.[12-14] Recently, our research work has been directed to the synthesis of several azolo-azine derivatives.[15-24] In the course of our investigations, we found that 2-cyano-*N*-(2-pyridyl)acetamide is a highly versatile and useful building block for the synthesis of a wide variety of pyridyl pyrazolo[3,4-*d*]pyrimidine and pyrazolo[3,4-*d*]-1,2,3-triazine derivatives.

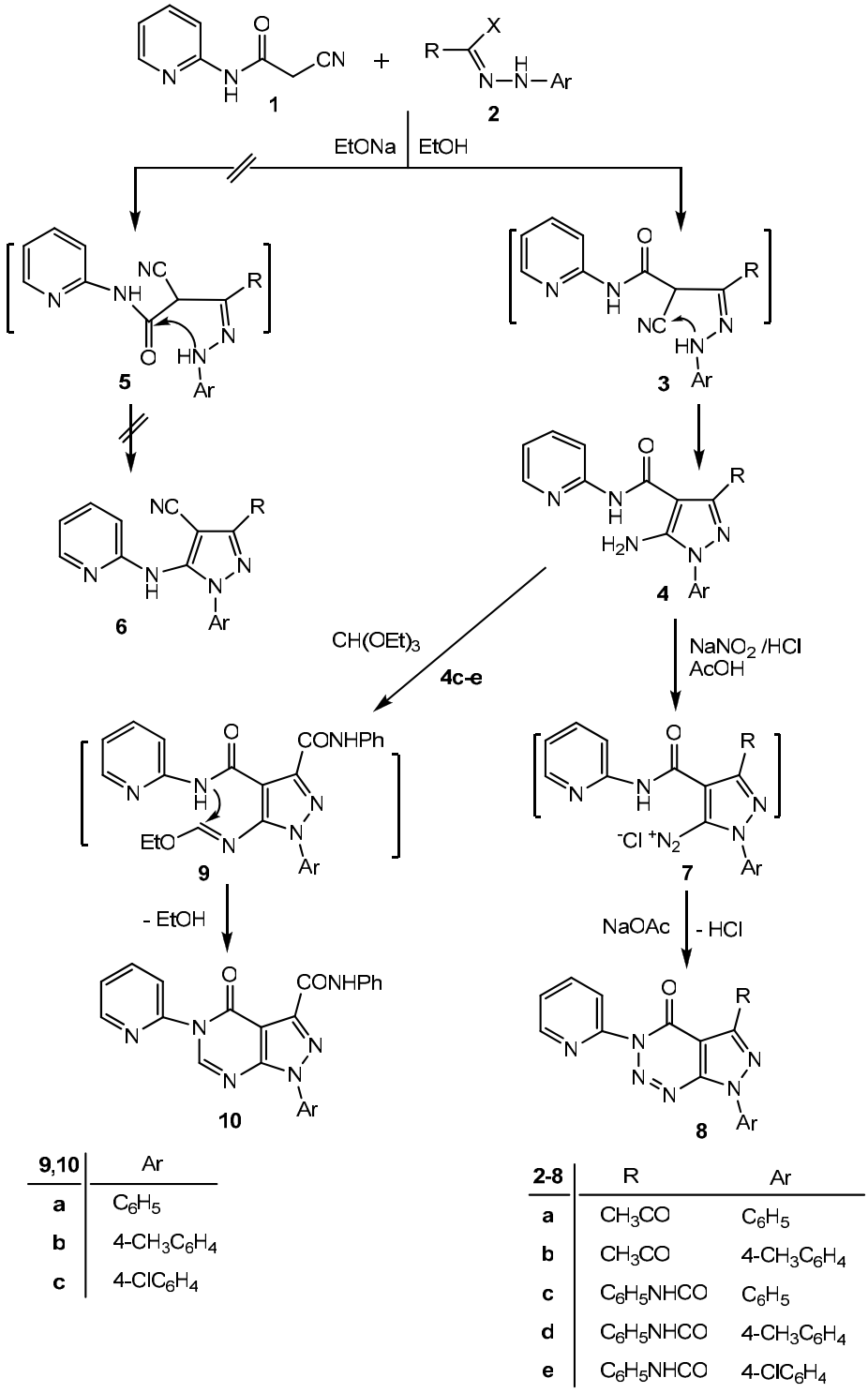
Results and Discussion

Treatment of 2-cyano-*N*-(2-pyridyl)acetamide (**1**) with hydrazonoyl chloride **2a** in ethanolic sodium ethoxide solution at room temperature furnished a single product for which the two possible structures **4a** and **6a** can be envisaged (Scheme 1). However, elemental analyses and spectral data were in complete accordance with the aminopyrazole structure **4a**. The IR spectrum of the reaction product showed absorption bands at 3443, 3331, 3142, 1670 and 1638 cm^{-1} due to amino, amide-NH and two carbonyl groups, respectively. Moreover, the mass spectrum of the isolated product revealed a molecular ion peak at *m/z* 321. When the aminopyrazole **4a** was treated with sodium nitrite in acetic acid it furnished one isolable product which was analysed correctly for $C_{17}H_{12}N_6O_2$. The structure of the isolated product was assigned as 5-acetyl-7-phenyl-3-(pyridin-2-yl)-3*H*-pyrazolo[3,4-*d*]-1,2,3-triazin-4(7*H*)-one (**8a**) as shown in Scheme 1, based on its elemental analyses and spectral data. Its IR spectrum was free of amino and amide-NH absorption bands in the region 3450–3000 cm^{-1} and showed two strong carbonyl bands at 1729 and 1702 cm^{-1}. Prompted by the foregoing results and to generalize this finding we also studied the reaction of the acetamide **1** with other hydrazonoyl chlorides **2b-e** under the same experimental conditions and obtained the respective aminopyrazole derivatives **4b-e**. The latter pyrazoles reacted similary with nitrous acid and afforded the corresponding pyrazolo[3,4-*d*]-1,2,3-triazine derivative **8b-e** as depicted in Scheme 1. The structure of the isolated products **4b-e** and **8b-e** were established from their elemental analyses and spectral data (see experimental part).

Next, the reaction of aminopyrazoles **4c–e** with triethyl orthoformate was carried out in glacial acetic acid to afford, in each case, a single product as examined by TLC. The structures of the isolated products were assigned as 1,3-disubstituted-5-(pyridin-2-yl)pyrazolo[3,4-*d*]pyrimidin-4-one derivatives **10a–c** (Scheme 1), on the basis of their elemental analyses and spectral data. The IR spectra of **10a-c** were free of amino absorption bands and showed two carbonyl absorptions around 1690 and 1670 cm^{-1}, in addition, their mass spectra revealed the corresponding molecular ion peaks. ^{1}H NMR spectra of compounds **10a-c** were in complete agreement with the assigned structures.

Treatment of 2-cyano(pyridin-2-yl)acetamide (**1**) with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) in refluxing xylene afforded two products based on TLC. One product was isolated in 75% yield and was idenfied as 2-cyano-3-(dimethylamino)-*N*-(pyridin-2-yl)acrylamide (**11**) on the basis of its spectal analyses. The ^{1}H NMR spectrum of compound **11** revealed signals at δ 3.12, 3.26, 7.76 and 8.16 due to *N,N*–dimethylamino, C=*CH*-N and amide-*NH* protons, respectively, in addition to an aromatic multiplet in the region δ 6.85–8.05 ppm. The second product was isolated in 17% yield and its elemental analyses and mass spectrum confirmed its molecular formula as $C_{17}H_{12}N_6O_2$. Its IR spectrum showed NH_2 and amide-NH absorption peaks in the region 4000-3170 in addition to a nitrile and two carbonyl bands at 2212, 1678 and 1649 cm^{-1}, respectively. The ^{1}H NMR spectrum of the second compound was free of *N,N*–dimethylamino protons and showed aromatic multiplet in the region δ 7.13-8.83 and two

singlets at δ 7.61 and 8.88 due to NH_2 and NH protons, respectively. All the foregoing data are in agreement with 2-amino-5-cyano-1,6-dihydro-6-oxo-*N*,1-di(pyridin-2-yl)pyridine-3-carboxamide (**15**), (Scheme 2). Compound **15** was alternatively prepared from the reaction of acetamide **1** and propenenitrile **11** as outlined in Scheme 2.



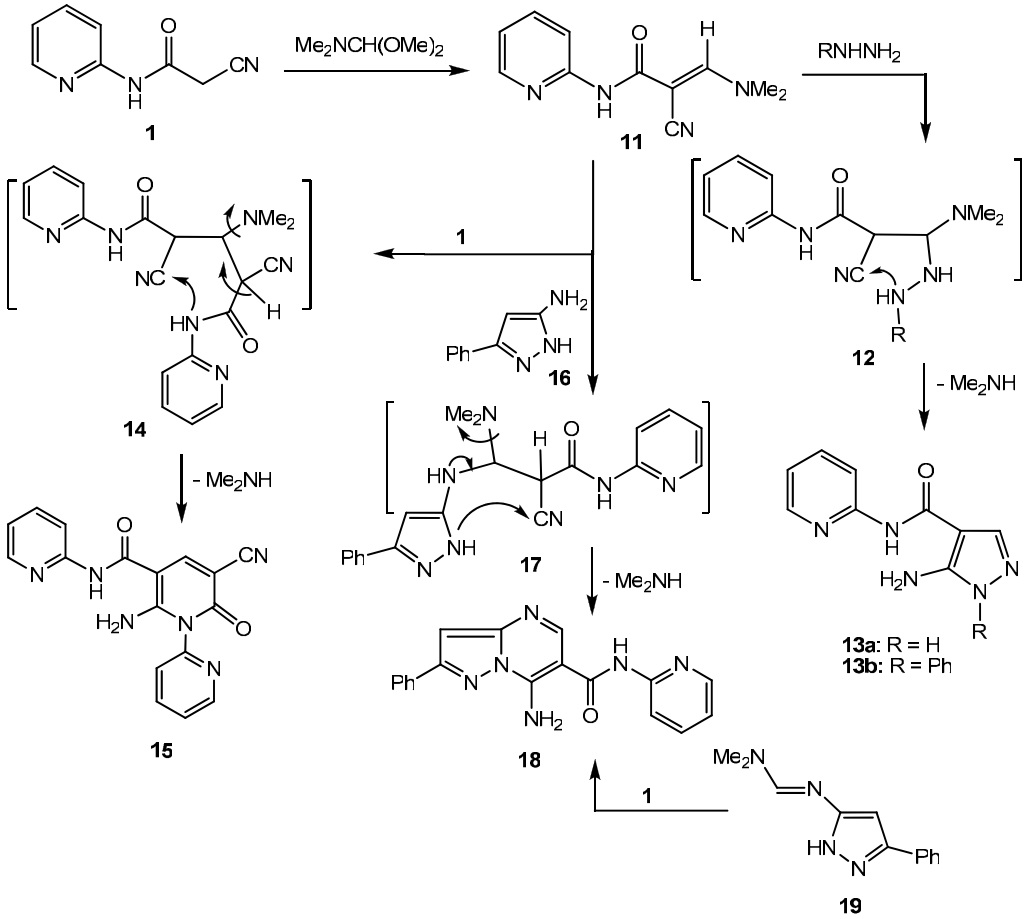
9,10	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4

2-8	R	Ar
a	CH_3CO	C_6H_5
b	CH_3CO	4-$CH_3C_6H_4$
c	C_6H_5NHCO	C_6H_5
d	C_6H_5NHCO	4-$CH_3C_6H_4$
e	C_6H_5NHCO	4-ClC_6H_4

Scheme 1

The reactivity of the propenenitrile **11** towards some nitrogen nucleophiles was also investigated. Thus, when compound **11** was treated with hydrazine hydrate and with phenylhydrazine in refluxing ethanol, the novel aminopyrazoles **13a** and **13b** were produced respectively (Scheme 2). The structures of the latter products were deduced from their elemental analyses and spectral data.

Prompted by the aforementioned results, we also investigated the reactivity of the propenenitrile **11** towards 5-amino-3-phenyl-1*H*-pyrazole **16** in refluxing ethanol, in the presence of piperidine, to afford a single product as examined by TLC. The structure of the obtained product was assigned as 7-amino-2-phenyl-*N*-(pyridin-2-yl)pyrazolo[1,5-*a*] pyrimidine-6-carboxamide (**18**) (Scheme 2) based on its elemental analysis and spectral data. Compound **18** was alternatively obtained by an independent synthesis *via* treatment of 5-*N*-(*N,N*-dimethylaminomethylene)imino-3-phenyl-1*H*-pyrazole (**19**) with the acetamide derivative **1** in ethanol, in the presence of a catalytic amount of piperidine. Although the endocyclic-NH in compound **16** is the most nucleophilic center it is also the most sterically hindered site.[25,26] Therefore, addition takes place at the exocyclic-NH_2 to afford the pyrazolopyrimidine derivative **18**.



Scheme 2

In conclusion, we have been able to describe convenient protocols for the preparation of a number of heterocyclic structures *e.g.* pyrazolo[3,4-*d*]-1,2,3-triazin-4-one, pyrazolo[3,4-*d*]pyrimidin-4-one, and pyrazolo[1,5-*a*]pyrimidine derivatives.

Experimental Section

General Procedures. All melting points were measured on a Gallenkamp electrothermal melting point apparatus. The infrared spectra were recorded for potassium bromide pellets on a Pye Unicam SP 3-300 and FT IR 8101 PC Schimadzu infrared spectrophotometers. The ^{1}H NMR spectra were recorded in deuterated chloroform or dimethyl sulfoxide at 300 MHz on a Varian Mercury VX-300 NMR spectrometers using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS–QP 1000 EX Shimadzu mass spectrometer at 70eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 2-Cyano-*N*-(2-pyridyl)acetamide (**1**),[27] hydrazonoyl chlorides **2a**,[28] **2b**,[29] and **2c-e**,[30] were prepared following literatured procedures.

Reaction of 2-cyano-*N*-(2-pyridyl)acetamide (1) with hydrazonoyl halides. General procedure

2-Cyano-*N*-(2-pyridyl)acetamide (**1**) (0.322 g, 2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute ethanol (20 mL)] with stirring. After stirring the resulting solution for 15 min, the appropriate hydrazonoyl halide **2a-e** (2 mmol) was added portionwise and the reaction mixture was stirred further for 12 h at room temperature. The solid that formed was filtered off, washed with water and dried. Recrystallization from the proper solvent afforded the corresponding pyrazole derivatives **4a-e** in 53-88% yields.

3-Acetyl-5-amino-1-phenyl-*N*-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (4a). Yield (53%), mp.183-4 ^{o}C; IR (KBr) ν 3443, 3331, 3142 (NH_2, NH), 1670, 1638 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H, $COCH_3$), 7.02 (s, 2H, D_2O-exchangeable, NH_2), 7.11 (dd, 1H, *J* = 7.2, 4.8 Hz), 7.62-7.80 (m, 6H), 8.23 (dd, 1H, *J* = 8.4, 1.0 Hz), 8.35 (m, 1H), 12.13 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 321 (M^+, 22.3), 278 (100), 121 (4.4), 78 (2.1). Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.55; H, 4.75; N, 21.78%.

3-Acetyl-5-amino-*N*-(pyridin-2-yl)-1-p-tolyl-1*H*-pyrazole-4-carboxamide (4b). Yield (59%); mp.186-7 ^{o}C; IR (KBr) ν3418, 3310, 3132 (NH_2, NH), 1674, 1655 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 2.71 (s, 3H, $COCH_3$), 5.99 (s, 2H, NH_2), 6.96 (m, 1H), 7.34-7.49 (m, 5H), 8.27 (d, 1H, *J* = 8.4 Hz), 8.4 (d, 1H, *J* = 5.8 Hz), 12.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.7, 26.8, 95.8, 113.5, 119.1, 124.5, 130.1, 134.3, 138, 138.5, 145.9, 148.1, 152, 153.1, 162.3, 198.2; MS *m/z* (%) 335 (M^+, 28.6), 292 (100), 242 (88.9), 91 (21.6). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.51; H, 5.15; N, 20.79%.

5-Amino-*N*^{3},1-diphenyl-*N*^{4}-(pyridin-2-yl)-1*H*-pyrazole-3,4-dicarboxamide (4c). Yield (88%); mp. 210-1 ^{o}C; IR (KBr) ν 3449, 3387, 3373, 3342 (NH_2, 2 NH), 1647, 1625 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.09 (s, 2H, D_2O-exchangeable, NH_2), 6.97-6.76 (m, 12H, ArH), 8.29 (d, 1H, *J* = 8.4 Hz), 8.41 (d, 1H, *J* = 5.0 Hz), 9.15 (s, 1H, NH), 12.96 (s, 1H, NH); MS *m/z* (%) 398 (M^+, 66.4), 312 (67.5), 278 (71.4), 186 (23.6), 95 (37.5). Anal. Calcd. for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.03; H, 4.60; N, 21.00%.

5-Amino-*N*^{3}-phenyl-*N*^{4}-(pyridin-2-yl)-1-*p*-tolyl-1*H*-pyrazole-3,4-dicarboxamide (4d). Yield (77%); mp. 195-6 ^{o}C; IR (KBr) ν 3379, 3250, 3200 (NH_2, NH), 1649, 1638 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H, CH_3), 6.95 (s, 2H, D_2O-exchangeable, NH_2), 7.17-7.25 (m, 2H), 7.37-7.45 (m, 4H), 7.58-7.66 (m, 3H), 7.79 (d, 2H, *J* = 7.8 Hz), 8.26 (d, 1H, *J* = 8.7 Hz), 8.40 (m, 1H), 10.41 (s, 1H, NH), 12.6 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.6, 95.9, 113.6, 115.8, 118.9, 120.2, 121.4, 124.5, 128.9, 129.9, 134.3, 137.5, 138.2, 141.2, 148.1, 152.2, 152.7, 162.1, 162.3. Anal. Calcd. for $C_{23}H_{20}N_6O_2$: C, 66.98; H, 4.89; N, 20.38. Found: C, 66.87; H, 4.98; N, 20.40%.

5-Amino-1-(4-chlorophenyl)-*N*^{3}-phenyl-*N*^{4}-(pyridin-2-yl)-1*H*-pyrazole-3,4-dicarboxamide (4e). Yield (78%); mp. 243-4 ^{o}C; IR (KBr) ν 3391, 3366, 3177, 3113 (NH_2, 2NH), 1647, 1630 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 2H, D_2O-exchangeable, NH_2), 7.18-8.27 (m, 13H, ArH), 10.41 (s, 1H, NH), 12.60 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 95.9, 113.6, 118.4, 121.4, 124.6, 126.4, 128.6, 129.5, 132.2, 135.8, 137.4, 137.9, 142.1, 148.1, 152.1, 152.9, 162, 162.2; MS *m/z* (%) 433 (M^++1, 21.8), 432 (M^+, 79.9), 312 (100), 220 (3.8), 121 (43.2), 95 (44.1). For $C_{22}H_{17}N_6O_2Cl$ Calcd.: C, 61.04; H, 3.96; N, 19.41. Found: C, 61.12; H, 3.98; N, 19.37 %.

Reaction of 5-aminopyrazole derivatives 4a-e with nitrous acid. General procedure To a solution of the appropriate 5-aminopyrazole **4a-e** (1 mmol) in acetic acid (5 mL) was added conc HCl (5 ml). The mixture was then cooled to 0-5 ^{o}C and sodium nitrite (69 mg) was added portionwise while stirring. The reaction mixture was left to stand in an ice bath for 1 h and was then diluted with water, filtered off, washed with water and finally recrystallized from ethanol or ethanol/DMF to afford the corresponding pyrazolo[3,4-*d*]-1,2,3-triazine derivatives **8a-e** in 40-72% yields.

5-Acetyl-7-phenyl-3-(pyridin-2-yl)-3*H*-pyrazolo[3,4-*d*]-1,2,3-triazin-4(7*H*)-one (8a). Yield (40%); mp. 231-2 ^{o}C (ethanol); IR (KBr) ν 1729, 1702 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.51 (s, 3H, CH_3CO), 7.20 (m, 1H), 7.47-7.65 (m, 5H), 7.92 (d, 1H, *J* = 3.6 Hz), 8.18 (m, 1H), 8.66 (d, 1H, *J* = 4.2 Hz); MS *m/z* (%) 332 (M^+, 5.7), 289 (5.3), 121 (31), 78 (75). Anal. Calcd. for $C_{17}H_{12}N_6O_2$: C, 61.44; H, 3.64; N, 25.29. Found: C, 61.51; H, 3.66; N, 25.22%.

5-Acetyl-3-(pyridin-2-yl)-7-*p*-tolyl-3*H*-pyrazolo[3,4-*d*]-1,2,3-triazin-4(7*H*)-one (8b). Yield (45%); mp. 257-8 ^{o}C (ethanol/DMF); IR (KBr) ν1732, 1695 (2C=O) cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 2.44 (s, 3H, CH_3), 2.49 (s, 3H, CH_3CO), 7.5 (d, 2H, *J* = 8.1 Hz), 7.67 (m, 1H), 7.75 (d, 2H, *J* = 7.8 Hz), 7.95 (d, 1H, *J* = 3.6 Hz), 8.14 (m, 1H), 8.71 (d, 1H, *J* = 3.9 Hz). Anal. Calcd. for $C_{18}H_{14}N_6O_2$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.44; H, 4.08; N, 24.32%.

4,7-Dihydro-4-oxo-*N*,7-diphenyl-3-(pyridin-2-yl)-3*H*-pyrazolo[3,4-*d*]-1,2,3-triazine-5-carboxamide (8c). Yield (66%); mp. 282-3 ^{o}C (ethanol / DMF); IR (KBr) ν 3138 (NH), 1693,

1682 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.20 (m, 1H), 7.37-7.46 (m, 2H), 7.64-7.87 (m, 7H), 8.12-8.25 (m, 3H), 8.77 (d, 1H, *J* = 3.8 Hz), 11.45 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 409 (M^+, 20.2), 289 (7.4), 121 (50), 78 (47), 77 (22.8). Anal. Calcd. for $C_{22}H_{15}N_7O_2$: C, 64.54; H, 3.69; N, 23.95. Found: C, 64.76; H, 3.64; N, 23.89%.

4,7-Dihydro-4-oxo-*N*-phenyl-3-(pyridin-2-yl)-7-*p*-tolyl-3*H*-pyrazolo[3,4-*d*]-1,2,3-triazine-5-carboxamide (8d). Yield (67%); mp. 283-4 °C (ethanol/DMF); IR (KBr) ν 3268 (NH), 1681, 1638 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.47 (s, 3H, CH_3), 7.18 (m, 1H), 7.42 (m, 2H), 7.56 (d, 2H, *J* = 8.2 Hz), 7.71-7.86 (m, 4H), 7.80 (d, 2H, *J* = 8.0 Hz), 8.20 (dd, 1H, *J* = 7.8, 5.8 Hz)), 8.77 (d, 1H, *J* = 3.6 Hz)), 11.42 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 423 (M^+, 23.0), 303 (12), 250 (100), 121 (47.8), 78 (76.1). For $C_{23}H_{17}N_7O_2$ Calcd.: C, 65.24; H, 4.05; N, 23.16. Found: C, 65.31; H, 4.02; N, 23.22%.

7-(4-Chlorophenyl)-4,7-dihydro-4-oxo-*N*-phenyl-3-(pyridin-2-yl)-3*H*-pyrazolo[3,4-*d*] -1,2,3-triazine-5-carboxamide (8e). Yield (72%); mp. 298-300 °C (ethanol/DMF); IR (KBr) ν 3267 (NH), 1678, 1628 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.16 (m, 1H), 7.40 (m, 2H), 7.72-7.83 (m, 7H), 8.19 (d, 2H, *J* = 8.7 Hz), 8.76 (m, 1H), 11.38 (s, 1H, NH); MS *m/z* 444 (M^++1, 4.8), 443 (M^+, 18.2), 323 (9.7), 121 (70), 78 (63). Anal. Calcd. for $C_{22}H_{14}ClN_7O_2$: C, 59.53; H, 3.18; N, 22.09. Found: C, 59.55; H, 3.19; N, 22.15%.

Reaction of 5-aminopyrazole derivatives 4a-c with triethyl orthoformate

A mixture of the appropriate 5-aminopyrazole **4a-c** (10 mmol), triethyl orthoformate (3 mL) and glacial acetic acid (3 mL), was refluxed for 3 h. After cooling to room temperature, the solid precipitate that formed was filtered off, washed with ethanol, dried and finally recystallized from DMF to afford **10a-c** in 82-92% yields.

4,5-Dihydro-4-oxo-*N*,1-diphenyl-5-(pyridin-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-3-carboxamide (10a). Yield (82%); mp. 298-300 °C; IR (KBr) ν3180 (NH), 1695, 1674 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13 (m, 1H), 7.38 (m, 2H), 7.41-7.74 (m, 6H), 7.87-8.12 (m, 4H), 8.71 (d, 1H, *J* = 5.7 Hz), 8.81 (s, 1H), 11.92 (s, 1H, NH); MS *m/z* (%) 409 (M^++1, 57.2), 408 (M^+, 65), 316 (100), 288 (1.6), 120 (1.9), 78 (99), 77 (41.5). Anal. Calcd. for $C_{23}H_{16}N_6O_2$: C, 67.64; H, 3.95; N, 20.58. Found: C, 67.65; H, 3.94; N, 20.63%.

4,5-Dihydro-4-oxo-*N*-phenyl-5-(pyridin-2-yl)-1-p-tolyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine-3-carboxamide (10b). Yield (90%); mp. > 300 °C; IR (KBr) ν 3100 (NH), 1693, 1670 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 7.13 (m, 1H), 7.35-7.45 (m, 4H), 7.65-7.74 (m, 3H), 7.86-7.95 (m, 3H), 8.15 (m, 1H), 8.72 (d, 1H, *J* = 4.8 Hz), 8.79 (s, 1H), 11.91 (s, 1H, NH); MS *m/z* (%) 422 (M^+, 53.6), 330 (75), 120 (1.6), 92 (30), 78 (66.1), 77 (67). Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.25; H, 4.28; N, 19.83%.

1-(4-Chlorophenyl)-4,5-dihydro-4-oxo-*N*-phenyl-5-(pyridin-2-yl)-1*H*-pyrazolo[3,4-*d*] -pyrimidine-3-carboxamide (10c). Yield (92%); mp. > 300 °C; IR (KBr) ν 3199 (NH), 1692, 1660 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.14 (m, 1H), 7.38 (m, 2H), 7.66-7.86 (m, 7H), 8.13 (d, 2H, *J* = 7.8 Hz), 8.72 (m, 1H), 8.84 (s, 1H), 11.89 (s, 1H, NH); MS *m/z* (%) 442 (M^+, 45.1),

350 (100), 255 (17.5), 121 (12.7), 78 (91.4). Anal. Calcd. for $C_{23}H_{15}ClN_6O_2$: C, 62.38; H, 3.41; N, 18.98. Found: C, 62.44; H, 3.42; N, 18.87%.

Reaction of 2-cyano-*N*-(pyrid-2-yl)acetamide (1) with DMF-DMA

A mixture of the acetamide derivative **1** (3.22 g, 20 mmol) and *N,N*-dimethylformamide dimethylacetal (DMF-DMA) (2.66 ml, 20 mmol) in dry xylene (30 mL) was refluxed for 3 h, then left to cool to room temperature. The yellow precipitated product was filtered off, washed with petroleum ether and dried. Fractional crystallization from ethanol gave compounds **11** and **15**, in 75 and 17% yields, respectively.

2-Cyano-3-(dimethylamino)-*N*-(pyridin-2-yl)acrylamide (11). Yield (75%); mp. 181-2 ^oC; IR (KBr) ν 3400, 3304 (NH_2), 2181 (C≡N), 1689 (C=O), 1623 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.88 (dd, 1H, *J* = 7.2, 6.4 Hz), 7.55 (m, 1H), 7.76 (s, 1H), 8.02 (d, 1H, *J* = 8.4 Hz), 8.16 (m, 1H), 8.22 (s, 1H, NH); MS *m/z* (%) 216 (M^+, 28.1), 121 (25), 78 (31.3). Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.32; H, 5.70; N, 25.88%.

2-Amino-5-cyano-1,6-dihydro-6-oxo-*N*,1-di(pyridin-2-yl)pyridine-3-carboxamide (15). Yield (17%); mp. > 300 ^oC; IR (KBr) ν 4000, 3360, 3177 (NH_2, NH), 2212 (C≡N), 1678, 1649 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.58 (m, 3H), 7.61 (s, 2H, NH_2), 7.76-8.10 (m, 3H), 8.65 (m, 2H), 8.72 (s, 1H), 8.88 (s, 1H, NH); MS *m/z* (%) 332 (M^+, 21.9), 239 (34.4), 121 (25), 94 (61.5), 78 (75). Anal. Calcd. for $C_{17}H_{12}N_6O_2$: C, 61.44; H, 3.64; N, 25.29. Found: C, 61.50; H, 3.44; N, 25.30%.

Reaction of propenenitrile 11 with 2-cyano-*N*-(pyrid-2-yl)acetamide (1)

A mixture of the propenenitrile **11** (0.432 g, 2 mmol) and acetamide **1** (0.322 g, 2 mmol) in ethanol (30 mL) was heated to reflux temperature. To the resulting hot solution, a catalytic amount of piperidine (0.1 mL) was added and the reflux was continued for 4 h, then allowed to cool to room temperature. The precipitated product was filtered off, washed with ethanol, dried and finally recrystallized from DMF to give 0.4 g (60% yield) of a product identical in all respects (mp., mixed mp. and spectral data) with compound **15** obtained above.

Reaction of propenenitrile 11 with hydrazine derivatives

To a solution of the propenenitrile **11** (0.432 g, 2 mmol) in ethanol (20 mL), hydrazine hydrate (80%, 0.2 ml, 2 mmol) or phenylhydrazine (0.2 ml, 2 mmol) was added and the reaction mixture was refluxed for 4 h, then left to cool. The solid product so formed was filtered off, washed with ethanol and dried. Recrystallized from ethanol/DMF afforded yellowish-orange 5-aminopyrazole derivatives **13a,b**, respectively.

5-Amino-*N*-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (13a). Yield (88%); mp. 245-6 ^oC; IR (KBr) ν 3406, 3350, 3250, 3152 (NH_2, 2NH), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.97 (s, 2H, D_2O-exchangeable NH_2), 7.04 (dd, 1H, *J* = 6.3, 5.7 Hz), 7.74 (dd, 1H, *J* = 7.8, 6.3 Hz), 8.13 (d, 1H, *J* = 8.4 Hz), 8.2 (s, 1H), 8.32 (d, 1H, *J* = 6.9 Hz), 10.03 (s, 1H, NH), 11.84 (s, 1H, NH);

MS *m/z* (%) 203 (M^+, 35), 187 (13.3), 121 (2.0), 110 (95.6), 93 (24.8), 78 (15.6), 66 (4.3). Anal. Calcd. for $C_9H_9N_5O$: C, 53.20; H, 4.46; N, 34.47. Found: C, 53.22; H, 4.44; N, 34.50%.

5-Amino-1-phenyl-*N*-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (13b). Yield (83%); mp. 296-8 °C; IR (KBr) ν 3400, 3356, 3260 (NH_2, NH), 1661 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.06 (m, 2H), 7.7.62-8.29 (m, 8H), 8.85 (s, 2H, D_2O-exchangeable NH_2), 10.60 (s, 1H, NH); MS *m/z* (%) 279 (M^+, 98.9), 262 (27.5), 187 (42.3), 158 (2.8), 121 (14.4), 93 (19.5), 78 (80.4). Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.62; H, 4.88; N, 25.19%.

Reaction of propenenitrile 11 with 5-amino-3-phenylpyrazole

Method A. A mixture of the propenenitrile **11** (0.432 g, 2 mmol) and 5-amino-3-phenylpyrazole (**16**) (0.35 g, 2.2 mmol) in ethanol (30 mL) in the presence of few drops of piperidine was refluxed for 8 h, then left to cool to room temperature. The precipitated product was filtered off, washed with ethanol, dried and finally recrystallized from DMF to afford the pyrazolo[1,5-*a*]pyrimidine derivative **18** in 0.52 g (79% yield).

Method B. A mixture of of 5-*N*-(dimethylaminomethylene)imino-3-phenyl-1H-pyrazole (**19**) and acetamide **1** in ethanol in the presence of a catalytic amount of piperidine was refluxed for 6 h till all the starting materials were completely consumed (as examined with TLC).The solid product so formed was collected by filtration and recrystallized from DMF to afford 0.46 g (70% yield) of a product identical in all respects (mp., mixed mp. and spectral data) with that obtained above from the reaction of 5-amino-3-phenyl-1H-pyrozole (**16**) with propenenitrile **11**.

7-Amino-2-phenyl-*N*-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-6-carboxamide (18). Yield (79%); mp. 273-4 °C; IR (KBr) ν 3380, 3317, 3130 (NH_2, NH), 1649 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.15 (s, 2H, NH_2), 7.03 (s, 1H), 7.14 (m, 1H), 7.44-7.53 (m, 5H), 8.09 (m, 2H), 8.35 (m, 1H), 8.91 (s, 1H), 10.35 (s, 1H, NH), ^{13}C NMR (DMSO-d_6) δ 93.2, 93.4, 115.1, 119.6, 126.3, 128.7, 129.2, 132.2, 137.9, 147.8, 148.8, 149.4, 149.6, 152, 155.6, 165.9; MS *m/z* (%) 330 (M^+, 100), 237 (83.6), 209 (2.3), 170 (63.4), 116 (21.4), 77 (25). For $C_{18}H_{14}N_6O$ Calcd.: C, 65.44; H, 4.27; N, 25.44. Found: C, 65.25; H, 4.36; N, 25.16%.

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