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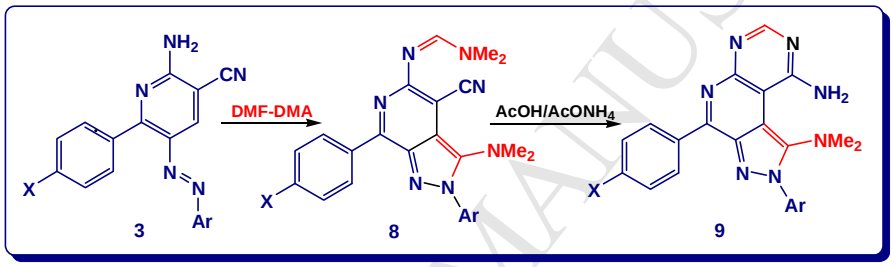

Non-concerted nucleophilic [4+1] cycloaddition of (dimethylamino)methoxycarbene to arylazonicotinates in the synthesis of a pyrazolo[3,4-*c*]pyridines and pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidines

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Abstract

A novel reaction between 2-amino-5-arylazonicotinonitriles **3c-g** and dimethylformamide dimethylacetal (DMF-DMA), leading to the formation of a new class of pyrazolo[3,4-*c*]-pyridine derivatives **8**, has been developed. The process is believed to take place *via a* non-concerted [4+1] cycloaddition pathway involving nucleophilic addition of (dimethylamino)-methoxycarbene, generated from DMF-DMA, to the arylazonicotinates **3c-g**. The pyridine derivatives **8** were observed to react with ammonia in refluxing acetic acid to yield novel pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine derivatives **9**. Other members of the pyrido[2,3-*d*]pyrimidine family **13** were synthesized by reactions between 2-amino-5-arylazonicotinate ethyl esters **3a-b** and DMF-DMA, which produce amidine derivatives **10a-b**, that undergo cyclization to generate the corresponding pyrido[2,3-*d*]pyrimidines**13a-b** when treated with ammonia in refluxing acetic acid. Finally, the results of this effort revealed that pyrido[2,3-

d]pyrimidines **13a-b** also react with DMF-DMA to produce pentaazacyclopenta [*a*]naphthalene derivatives **14**. The structures of all new substances prepared in this investigation were determined by using X-ray crystallographic analysis and spectroscopic methods.

Keywords

nucleophilic [4+1] cycloaddition; nicotinonitrile; pyrazolo[3,4-*c*]pyridine; pyrido[2,3-*d*]pyrimidine; pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine

Introduction

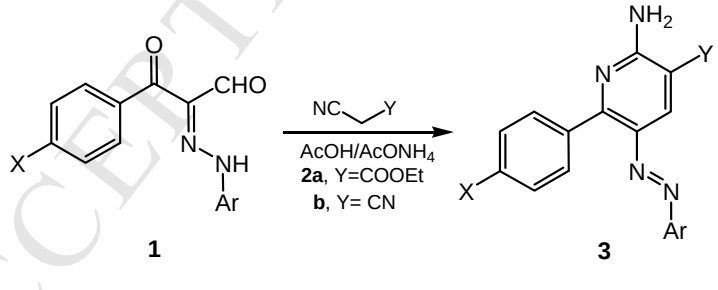
Among the nitrogen-containing heterocyclic compounds, those possessing pyridine and fused polycyclic pyridine structures are perhaps the most common. The biologically activities of these substances have been used widely as antimicrobial,[1] anti-inflammatory,[2] anti-HIV,[3] antiplasmodial,[4] antitubercular,[5] antibacterial,[6] anticonvulsant,[7] antimitotic,[8] anticancer agents,[9,10] antinociceptive,[11] as well as substances possessing insecticidal and fungicidal,[12] and agrochemical importance.[13] Also, pyridine ring containing compounds play an exceptionally important role in biological redox chemistry, and a number of these substances serve as substructures of therapeutically important natural products.[14-21] In addition to their biological importance, pyridines play important roles as starting materials, key intermediates or reagents in preparative organic chemistry. One example is 4-dimethylaminopyridine (DMAP), which is a widely used catalyst in acylation reactions, and also as an activator of α-chiral carboxylic acids without accompanying racemisation.[22] Moreover, their ability to form complexes with metal ions makes pyridine derivatives highly sensitive reagents in analytical sensor systems, luminescent agents and as building block in supramolecular chemistry.[23,24]

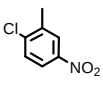
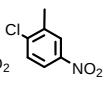
As a consequence of these fascinating properties and uses, pyridines and polycyclic fused pyridines represent privileged structures and, thus, they have attracted the general and

continuing interest of synthetic organic chemists. The study described below was aimed at the development of novel methods to prepare representative members of a class of pyrazolo[3,4-*c*]pyridines and pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidines, based on the use of the unique chemistry of N,N-dimethylformamide dimethylacetal (DMF-DMA). To this effect, we have developed a new process that utilizes this acetal to transform pyridyl-hydrazones to pyrazolo[3,4-*c*]pyridine and pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine derivatives in moderate to high yields.

Results and Discussion

In recent studies, we have developed general methods for the efficient synthesis of arylazonicotinates,[25] and 2-amino-5-arylazo-6-aryl substituted nicotinates.[26] We have employed this process to prepare pyridyl-hydrazone substrates required to explore the unique chemistry of DMF-DMA. Specifically, independent reactions of 3-oxo-2-arylhydrazono-propanals **1** (Scheme 1) with ethyl cyanoacetate (**2a**) and malononitrile (**2b**) produced 2-amino-5-arylazo nicotinic acid ethyl esters **3a-b** and 2-amino-5-arylazonicotinonitriles **3c-g** respectively (Scheme **1** and Figure **1**).



3	a	b	c	d	e	f	g
Ar							
X	Cl	Br	Cl	Br	Cl	Cl	Cl
Y	COOEt	COOEt	CN	CN	CN	CN	CN

Scheme 1: Synthesis of 2-amino-5-arylazonicotinic acid derivatives **3a-g**.

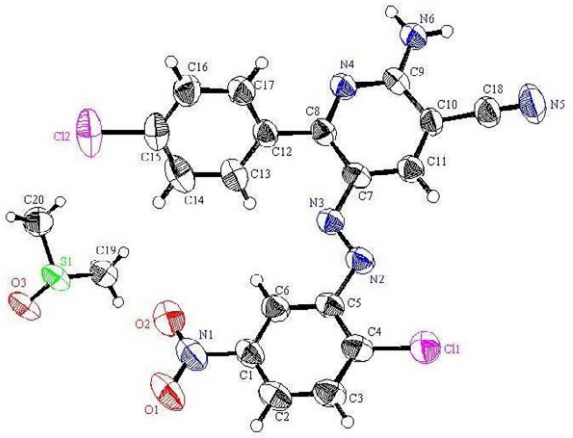
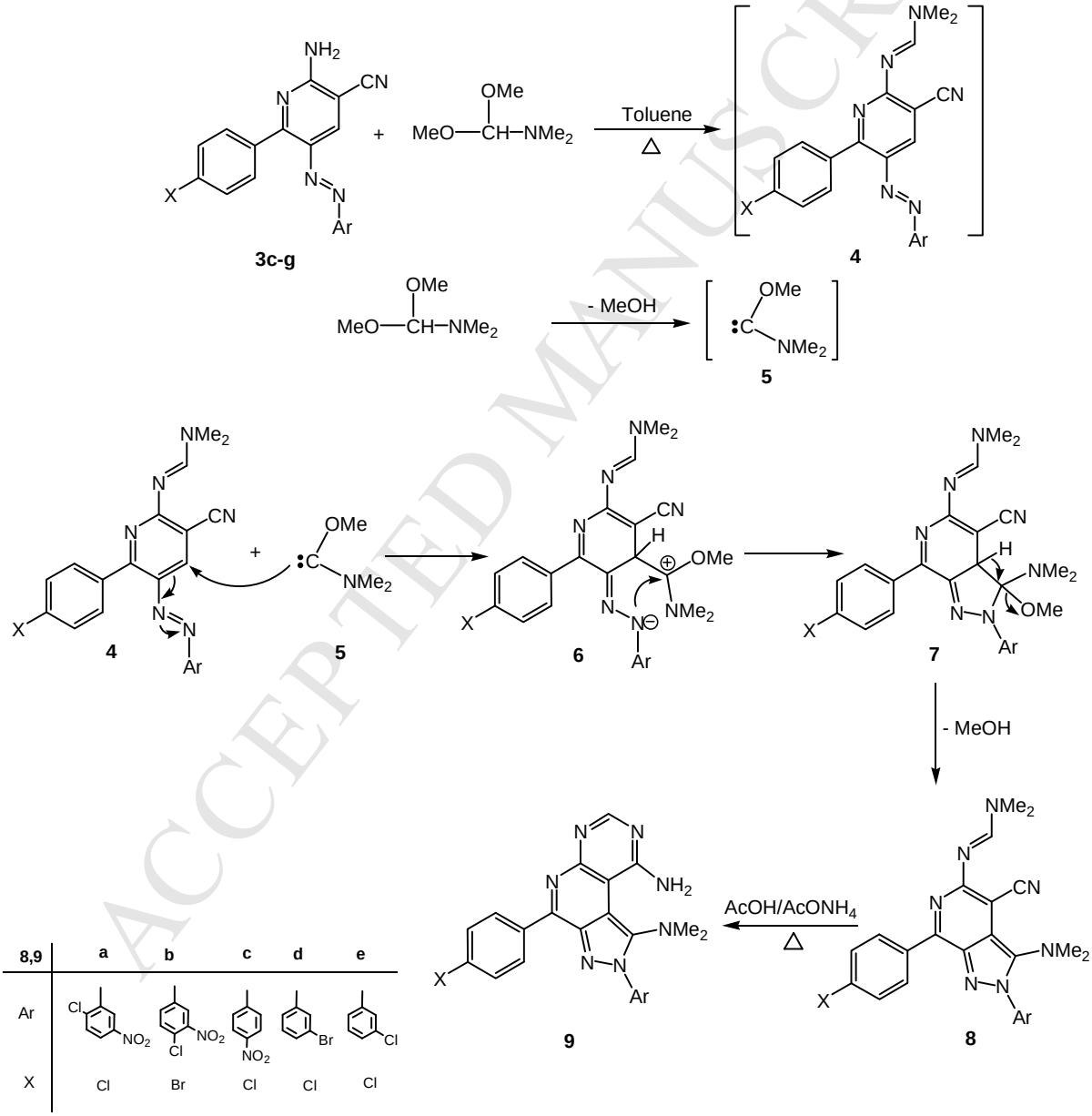


Figure 1: ORTEP plot of the X-ray crystallographic data determined for **3c**.[27]

Prior to initiating this effort, we envisaged that reaction of the nucleophilic carbene, produced by methanol elimination from DMF-DMA, would undergo [4+1] cycloaddition reactions with pyridyl-hydrazone derivatives like the 2-amino-5-arylazonicotinic acids **3**, and that this process would serve as a new approach for the preparation of pyrazolo[3,4-*c*]pyridines. To test this proposal, reactions of the 2-amino-5-arylazo-nicotinonitriles **3c-g** with excess DMF-DMA in refluxing toluene were explored. Detailed spectroscopic and X-ray crystallographic analyses (Figures 2 and 3, and Table 1) showed that the products **8c-g** formed in these reactions possess pyrazolo[3,4-*c*]pyridine amidine structures (Scheme 2). In addition, the pyrazolo[3,4-*c*]pyridines **8** were found to react with ammonia in refluxing acetic acid to yield the corresponding fused tricyclic pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine derivatives **9** (Scheme **2**). A plausible mechanism for the formation of the pyrazolo[3,4-*c*]pyridine amidines **8** begins with reaction of DMF-DMA with the amine moiety in **3** to afford the corresponding amidine **4**. Under the reaction conditions, DMF-DMA is expected to undergo methanol elimination to produce (dimethylamino)methoxycarbene **5,** in analogy to the reported formation of (dimethylamino)ethoxycarbene upon heating dimethylformamide diethylacetal (DMF-DEA).[28] As a nucleophilic carbene, **5** then adds to the electron deficient C-4 center in the pyridine ring of **4** to form adduct **6**. Subsequent bond formation between the positively

charged carbenium ion carbon and the negatively charged nitrogen in **6** then gives bicyclic intermediate **7**, which upon loss of methanol finally forms the pyrazolo[3,4-c]pyridine derivative **8**. The overall process transforming **4** to **8** can be visualized as a non-concerted nucleophilic [4+1] cycloaddition reaction. Although similar cycloaddition reactions were observed earlier by Seitz *et. al.*,[28] as far as we are aware these are the first examples of such reactions occurring between (dimethylamino)methoxycarbene and arylazonicotinates.



Scheme 2: Synthesis of pyrazolo[3,4-*c*]pyridines **8** and pyrazolo[4',3':4,5]pyrido[2,3-*d*]-pyrimidines **9**.

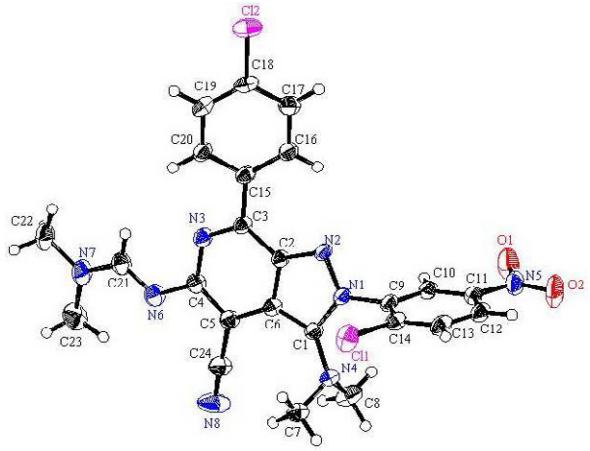


Figure 2. ORTEP plot of the X-ray crystallographic data determined for **8a**. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 913248.[29]

Table 1: Selected bond lengths and bond angles in the crystal structure of **8a**.

Bond	Bond length(Å)	Bond	Bond angle(°)
N3-C3	1.316	C3-N3-C4	121.38
N3-C4	1.373	N3-C3-C2	120.44(
C3-C2	1.436	N3-C4-C5	122.35
C4-C5	1.399	C2-C6-C5	118.99
C2-C6	1.419	N2-C2-C6	112.47
N2-C2	1.352	C1-C6-C5	136.13
N1-N2	1.356	N1-N2-C2	102.51
N1-C1	1.363	N1-C1-C6	104.72
N4-C1	1.400	N2-N1-C1	115.40

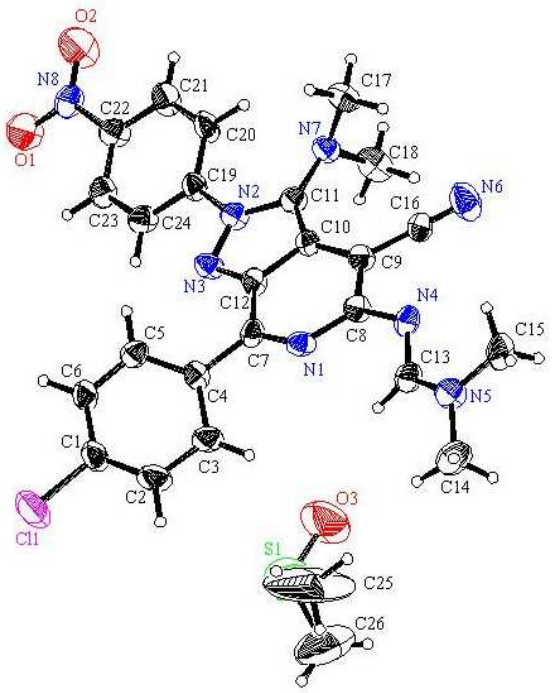
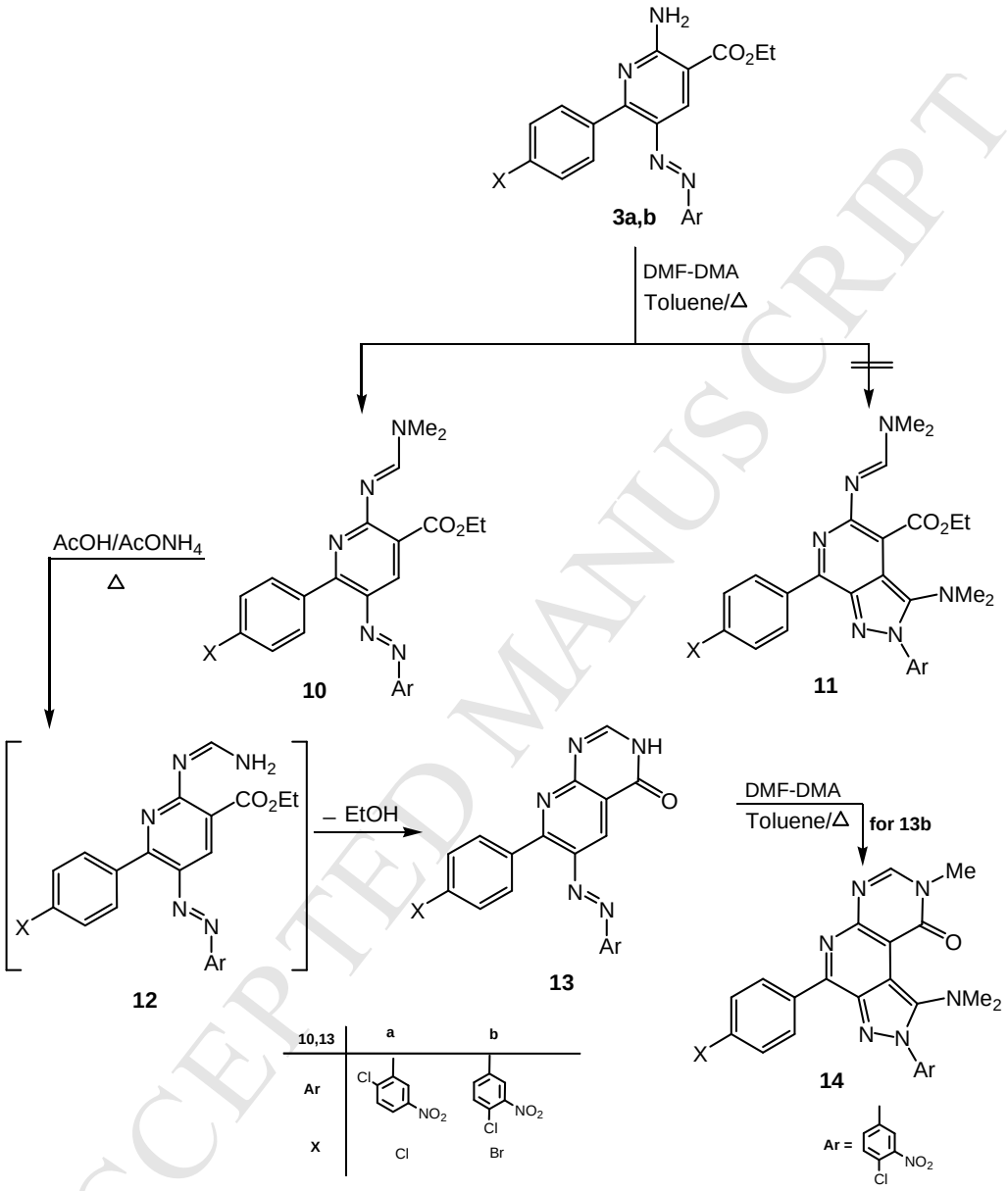


Figure 3. ORTEP plot of the X-ray crystallographic data determined for **8c**. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 925395.[30]

In order to develop an alternative route for the synthesis of the pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine derivatives **9,** we explored reactions between 2-amino-5-arylazo nicotinic acid ethyl esters **3a-b** and dimethylformamide dimethylacetal (DMF-DMA). These processes afford products which were shown to be the respective amidine derivatives **10a-b** and not the corresponding pyrazolo[3,4-*c*]pyridines **11a-b**. The amidine derivatives **10a-b** were reacted with ammonia in refluxing acetic acid to yield the corresponding pyrido[2,3-*d*]pyrimidine derivatives **13a-b**. The pyrido[2,3-*d*]pyrimidines **13a-b** were found to undergo nonconcerted nucleophilic [4+1] cycloaddition reactions with DMF-DMA to produce the novel pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine derivative **14**. The structures of these substances were assigned based on their spectroscopic and mass spectrometric properties (Scheme **3**). From the previous findings we can conclude that the existence of the CN group at position 3 in the pyridine ring make the nucleophilic [4+1] cycloaddition between the

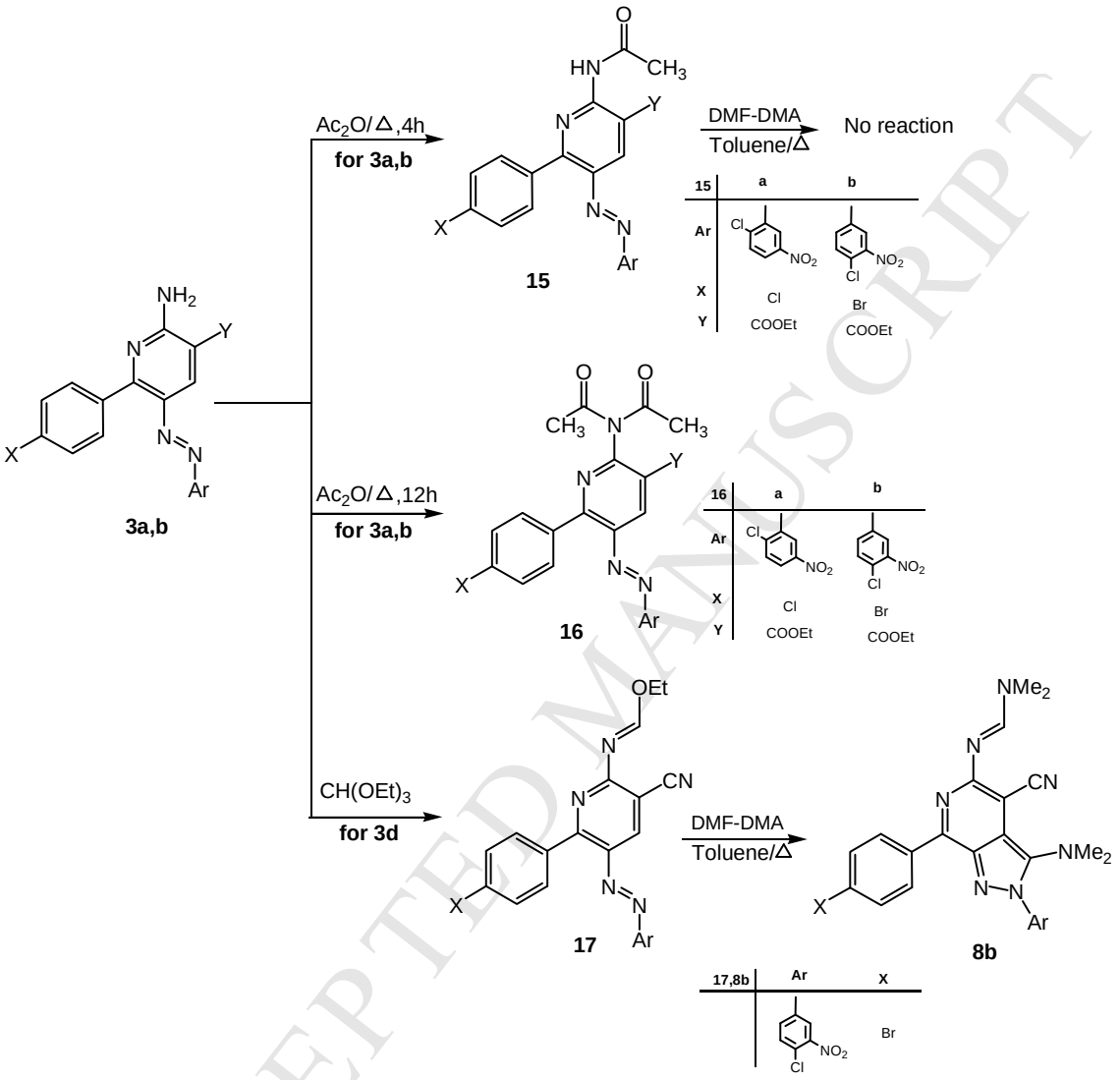
(dimethylamino)methoxycarbene and arylazonicotinates easier since it make the C-4 center in the pyridine ring more electron deficient in comparison with the COOEt group.



Scheme 3: Synthesis of compounds **13a-b** and pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidine **14**.

In further studies, we observed that the 2-amino-5-arylazo nicotinates **3a-b** readily react with acetic anhydride to yield either the monoacylated derivatives **15a-b** or the bis-acylated derivatives **16a-b**, depending upon the reaction time. Attempts to react **16a-b** with DMF-DMA were unsuccessful. Finally, the nicotinate **3d** undergoes reaction with

triethylorthoformate to yield the ethyl formimidate derivative **17**, which does participate in reaction with DMF-DMA to yield the pyrazolo[3,4-*c*]pyridine **8b** (Scheme **4** and Figure **4)**.



Scheme 4: Reaction of 2-aminonicotinates **3** with acetic anhydride and triethylorthoformate.

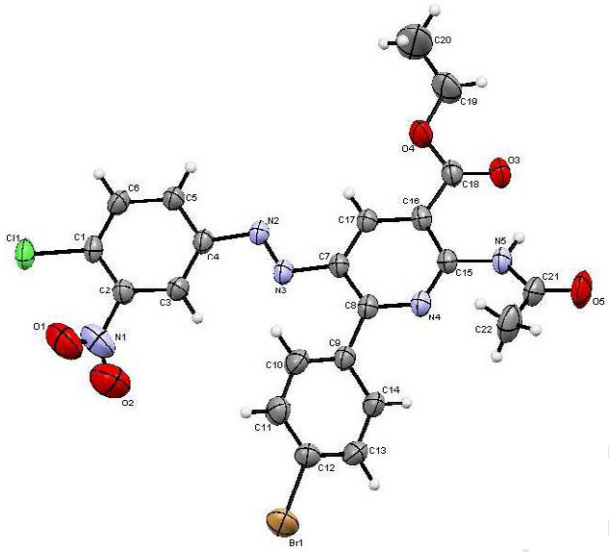


Figure 4. ORTEP plot of the X-ray crystallographic data obtained for **15b**. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 917642.[31]

Conclusion

In this study, a novel route for the synthesis of pyrazolo[3,4-c]pyridines and pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidines was developed. The methodology utilizes a simple and efficient non-concerted nucleophilic [4+1] cycloaddition of (dimethylamino)-methoxycarbene, generated from the DMF-DMA, to the arylazonicotinates.

Experimental

General:

Melting points were recorded on a Griffin melting point apparatus and are reported uncorrected. IR spectra were recorded as KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H-NMR (400 MHz) or (600 MHz) and ^{13}C-NMR (100 MHz) or (150 MHz) spectra were recorded at 25 °C using $CDCl_3$ or DMSO-d_6 solutions with TMS as an internal standard on a Bruker DPX 400 or 600 super-conducting NMR spectrometer.

Chemical shifts are reported in ppm. Mass spectra and HRMS were measured using high resolution GC-MS (DFS) thermo spectrometers with EI (70 EV). Reaction monitoring and determination of the homogeneity of the prepared compounds were performed by using thin layer chromatography (TLC). Crystal structures were determined by uaing a Rigaku R-AXIS RAPID diffractometer and Bruker X8 Prospector. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer.

General procedure for the preparation 2-amino-5-arylazo-6-aryl nicotinates 3a-g.

Independent mixtures of **1** (10 mmol), active methylenenitrile derivatives **2a-b** (10 mmol), and ammonium acetate (2 g) in acetic acid (20 mL) were stirred at reflux for 1-2 h. with progress of the reactions monitored using TLC with 1:1 ethyl acetate-petroleum ether as eluent. The mixtures were cooled and then poured into ice-water. The formed solids were collected by filtration and crystallized from the indicated solvents to give **3** as pure products.

2-Amino-5-(2-chloro-5-nitrophenylazo)-6-(4-chlorophenyl)nicotinic acid ethyl ester (3a). Recrystallized from DMF as deep orange crystals, yield: (89%), m.p. 266–268 °C; IR (KBr): ν/cm^{-1} 3378, 3281 (NH_2), 1709 (CO ester); ^{1}H-NMR (DMSO-d_6): δ = 1.35 (t, 3H, J = 7.2 Hz, CH_3CH_2), 4.38 (q, 2H, J = 7.2 Hz, CH_3CH_2), 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.85 (d, J = 8.4 Hz, 2H, Ar-H), 7.96-8.41 (m, 5H, 3Ar-H and NH_2) and 8.63 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6, at 100°C): δ = 13.95 (CH_3CH_2), 61.24 (CH_3CH_2), 106.27 (pyridine C3), 112.67, 124.64, 127.54, 128.12, 131.94, 132.63, 134.75, 135.81, 137.06, 139.12, 147.22, 148.64, 160.30, 161.67 and 165.88 ppm (Ar-C and CO); MS (EI): m/z (%) 460 (M^++1, 71.22), 459 (M^+, 100); HRMS (EI): m/z calcd. for $C_{20}H_{15}{}^{35}Cl_2N_5O_4$ (M^+) 459.0495, found

459.0493. Anal. calcd. for $C_{20}H_{15}Cl_2N_5O_4$ (460.28): C, 52.19; H, 3.28; N, 15.22. Found: C, 52.23; H, 3.35; N, 15.19.

2-Amino-5-(4-chloro-3-nitrophenylazo)-6-(4-bromophenyl)nicotinic acid ethyl ester (3b). Recrystallized from DMF as orange crystals, yield: (83%), m.p. 245–246 °C; IR (KBr): ν/cm^{-1} 3388, 3278 (NH_2), 1702 (CO ester); ^{1}H-NMR (DMSO-d_6): δ = 1.36 (t, 3H, J = 7.2 Hz, CH_3CH_2), 4.37 (q, 2H, J = 7.2 Hz, CH_3CH_2), 7.72 (d, J = 8.4 Hz, 2H, Ar-H), 7.76 (d, J = 8.4 Hz, 2H, Ar-H), 7.94-7.96 (m, 3H, Ar-H), 8.33 (br, 2H, NH_2, D_2O exchangeable), and 8.60 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6, at 100°C): δ = 14.01 (CH_3CH_2), 61.21 (CH_3CH_2), 106.05 (pyridine C3), 119.04, 123.36, 126.57, 127.78, 130.53, 131.95, 132.75, 132.84, 136.22, 136.66, 148.22, 151.37, 160.11, 161.16 and 165.97 ppm (Ar-C and CO); MS (EI): m/z (%) 505 (M^+ +2, 58.32), 504 (M^+ +1, 100), 503 (M^+, 43.30), 502 (66.67); HRMS (EI): m/z calcd. for $C_{20}H_{15}{}^{79}Br^{35}ClN_5O_4$ (M^+) 502.9990, found 502.9960. Anal. calcd. for $C_{20}H_{15}BrClN_5O_4$ (504.73): C, 47.59; H, 3.00; N, 13.88. Found: C, 47.70; H, 2.94; N, 13.79.

2-Amino-5-(2-chloro-5-nitrophenylazo)-6-(4-chlorophenyl)nicotinonitrile (3c). Recrystallized from DMSO as reddish brown crystals, yield: (77%), m.p. above 300 °C; IR (KBr): ν/cm^{-1} 3489, 3379 (NH_2), 2220 (CN), 1628(C=N); ^{1}H-NMR (DMSO-d_6): δ = 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.81 (d, J = 8.4 Hz, 2H, Ar-H), 7.96 (d, J = 8.8 Hz, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 8.17 (br, 2H, NH_2, D_2O exchangeable), 8.27 (d, J = 8.8 Hz, 1H, Ar-H) and 8.36 ppm

(s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 90.85 (pyridine C3), 112.58, 115.83, 125.24, 127.69, 131.14, 132.13, 132.81, 134.92, 135.42, 136.15, 139.71, 146.97, 148.04, 160.51 and 161.67 ppm (CN and Ar-C); MS (EI): m/z (%) 414 (M^+ +2, 73.05), 413 (M^+ +1, 61.45), 412 (M^+, 100); HRMS (EI): m/z calcd. for $C_{18}H_{10}{}^{35}Cl_2N_6O_2$ (M^+) 412.0236, found 412.0237. Anal. calcd. for $C_{18}H_{10}Cl_2N_6O_2$ (413.23): C, 52.32; H, 2.44; N, 20.34. Found: C, 52.25; H, 2.53; N, 20.40. **Crystallographic Analysis for 3c**. The crystals were mounted on a glass fiber. All measurements were performed on a Rigaku R-AXIS RAPID diffractometer using filtered Mo-kα radiation. The data were collected at a temperature of 20 ± 1 °C to a maximum 2θ value of 55.0° using the ω scanning technique. The structure was solved by the charge flipping method and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. **Crystal Data,** $C_{18}H_{10}Cl_2N_6O_2$, M = 413.23, triclinic, a = 8.918(1) Å, b = 10.696(1) Å, c = 13.217(2) Å, V =1132.2(2) Å^3, α = 73.044(6)°, β = 81.609(6)°, γ = 70.078(5)°, space group: P-1, Z = 2, D_{calc} = 1.441 g cm^{-3} , No. of reflection measured 4609, 2 θ_{max} = 52.7°, R1 = 0.047. **Figure 1** illustrates the structure as determined. Full data can be obtained on request from the CCDC.[27]

2-Amino-5-(4-chloro-3-nitrophenylazo)-6-(4-bromophenyl)nicotinonitrile (3d). Recrystallized from DMF as reddish brown crystals, yield: (73%), m.p. above 300 °C; IR (KBr): ν/cm^{-1} 3459, 3352 (NH_2), 2225 (CN), 1639 (C=N); ^{1}H-NMR (DMSO-d_6): δ = 7.68-7.71 (m, 4H, Ar-H), 7.91-7.94 (m, 2H, Ar-H), 8.03 (br, 2H, NH_2, D_2O exchangeable), 8.29 (s, 1H, Ar-H) and 8.37 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6, at 100°C): δ = 91.08 (pyridine C3), 116.32, 120.01, 124.15, 126.85, 127.13, 131.14, 131.77, 133.42, 133.47, 136.28, 136.48, 148.56, 151.32, 160.76 and 161.40 ppm (CN and Ar-C); MS (EI): m/z (%) 458 (M^+ +2,

48.15), 457 (M^+ +1, 100), 456 (M^+, 65.79), 455(35.26); HRMS (EI): m/z calcd. for $C_{18}H_{10}{}^{79}Br{}^{35}ClN_6O_2$ (M^+) 455.9731, found 455.9732. Anal. calcd. for $C_{18}H_{10}BrClN_6O_2$ (457.68): C, 47.24; H, 2.20; N, 18.36. Found: C, 47.17; H, 2.28; N, 18.29.

2-Amino-6-(4-chlorophenyl)-5-(4-nitrophenylazo)nicotinonitrile (3e). Recrystallized from EtOH/dioxane mixture (1:1) as pale brown crystals, yield: (71%), m.p. 219-220 °C; IR (KBr): ν/cm^{-1} 3331, 3214 (NH_2), 2225 (CN), 1654 (C=N); ^{1}H-NMR (DMSO-d_6): δ = 7.58 (d, J = 8.0 Hz, 2H, Ar-H), 7.79 (d, J = 8.0 Hz, 2H, Ar-H), 7.85 (d, J = 8.0 Hz, 2H, Ar-H), 8.06 (s, 2H, NH_2, D_2O exchangeable), 8.36 (d, J = 8.0 Hz, 2H, Ar-H) and 8.42 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 90.71 (pyridine C3), 115.96, 123.43, 125.21, 127.90, 131.26, 132.87, 134.92, 135.54, 136.54, 147.87, 155.46, 160.40 and 161.17 ppm (CN and Ar-C) MS (EI): m/z (%) 379 (M^+ +1, 41.22), 378 (M^+, 100); HRMS (EI): m/z calcd. for $C_{18}H_{11}{}^{35}ClN_6O_2$ (M^+) 378.0626, found 378.0625. Anal. calcd. for $C_{18}H_{11}ClN_6O_2$ (378.78): C, 57.08; H, 2.93; N, 22.19. Found: C, 57.17; H, 2.99; N, 22.26.

2-Amino-5-(3-bromophenylazo)-6-(4-chlorophenyl)nicotinonitrile (3f). Recrystallized from dioxane as brown crystals, yield: (72%), m.p. above 300 °C; IR (KBr): ν/cm^{-1} 3424, 3317 (NH_2), 2208(CN), 1639(C=N); ^{1}H-NMR (DMSO-d_6): δ = 7.56-7.63 (m, 5H, Ar-H), 7.77-7.91 (m, 3H, 1 Ar-H and NH_2), 7.97 (d, J = 8.4 Hz, 2H, Ar-H) and 8.22 ppm (s, 1H, pyridine H4); MS (EI): m/z (%) 413 (M^++2, 100), 412 (M^++1, 25.22), 411 (M^+, 71.85);

HRMS (EI): m/z calcd. for $C_{18}H_{11}{}^{79}Br^{35}ClN_5$ (M^+) 410.9880, found 410.9879. Anal. calcd. for $C_{18}H_{11}BrClN_5$ (412.68): C, 52.39; H, 2.69; N, 16.97. Found: C, 52.47; H, 2.75; N, 17.06.

2-Amino-5-(3-chlorophenylazo)-6-(4-chlorophenyl)nicotinonitrile (3g). Recrystallized from dioxane as brown crystals, yield: (68%), m.p. 248-250 °C; IR (KBr): ν/cm^{-1} 3337, 3201 (NH_2), 2217 (CN), 1656 (C=N); ^{1}H-NMR (DMSO-d_6): δ = 7.56-7.60 (m, 4H, Ar-H), 7.67-7.71 (m, 2H, Ar-H), 7.80 (d, J = 7.6 Hz, 2H, Ar-H), 7.92 (brs, 2H, NH_2, D_2O exchangeable) and 8.37 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 90.36 (pyridine C3), 115.99, 121.65, 121.72, 127.70, 128.31, 130.32, 131.10, 131.28, 132.72, 134.05, 134.66, 135.63, 153.11, 160.08 and 160.37 ppm (CN and Ar-C); MS (EI): m/z (%) 369 (M^++2, 72.50), 368 (M^++1, 53.24), 367 (M^+, 100); HRMS (EI): m/z calcd. for $C_{18}H_{11}{}^{35}Cl_2N_5$ (M^+) 367.0386, found 367.0384. Anal. calcd. for $C_{18}H_{11}Cl_2N_5$ (368.23): C, 58.71; H, 3.01; N, 19.02. Found: C, 58.59; H, 2.96; N, 19.10.

General procedure for the preparation of 8, 10 and 14.

Independent mixtures of the 5-arylazonicotinonitriles **3c-g,** 2-amino-5-arylazonicotinates ethyl ester **3a-b**, pyrido[2,3-*d*]pyrimidine **13b** (5 mmol) in dry toluene (20 mL), all containing N,N-dimethylformamide dimethylacetal (DMF-DMA) (1.2 mL, 10 mmol), were stirred at reflux under nitrogen for 6 h. The separated solid products obtained on standing at room temperature were collected by filtration, washed with petroleum ether and crystallized from the proper solvent.

(*E*)-*N′*-[2-(2-Chloro-5-nitrophenyl)-7-(4-chlorophenyl)-4-cyano-3-dimethylamino-2*H*-pyrazolo[3,4-*c*]pyridin-5-yl]-*N*,*N*-dimethylformamidine (8a). Recrystallized from EtOH/

dioxane (1:1) mixture as orange crystals, yield: (77%), m.p. 230-231 °C; IR (KBr): ν/cm^{-1} 2211 (CN); ^{1}H-NMR (DMSO-d_6): δ = 2.85 (s, 6H, 2CH$_3$), 3.15 (s, 3H, CH$_3$), 3.24 (s, 3H, CH$_3$), 7.64 (d, J = 8.4 Hz, 2H, Ar-H), 8.11 (d, J = 8.8 Hz, 1H, Ar-H), 8.50 (d, J = 8.8 Hz, 1H, Ar-H), 8.71 (d, J = 8.4 Hz, 2H, Ar-H), 8.80 (s, 1H, Ar-H) and 8.95 ppm (s, 1H, amidine H); ^{13}C-NMR (DMSO-d_6): δ = 34.85 (CH$_3$), 40.93 (CH$_3$), 43.98 (2CH$_3$), 83.21, 120.12, 120.66, 125.25, 127.03, 129.06, 131.91, 135.03, 136.51, 137.91, 138.40, 140.90, 144.49, 147.07, 151.51, 156.75, 158.37 and 163.19 ppm (Ar-C and CN); MS (EI): m/z (%) 524 (M^++2, 63.14), 523 (M^++1, 26.10), 522 (M^+, 100); HRMS (EI): m/z calcd. for $C_{24}H_{20}{}^{35}Cl_2N_8O_2$ (M^+) 522.1080, found 522.1080. Anal. calcd. for $C_{24}H_{20}Cl_2N_8O_2$ (523.39): C, 55.08; H, 3.85; N, 21.41. Found: C, 55.15; H, 3.89; N, 21.44. **Crystallographic Analysis for 8a**. The crystals were mounted on a glass fiber. All measurements were performed on a Rigaku R-AXIS RAPID diffractometer using filtered Mo-kα radiation. The data were collected at a temperature of 20 ± 1 °C to a maximum 2θ value of 55.0° using the ω scanning technique. The structure was solved by the charge flipping method and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. **Crystal Data,** $C_{24}H_{20}Cl_2N_8O_2$, M = 523.38, triclinic, a = 10.688(2) Å, b = 11.032(2) (1) Å, c = 12.728(2) Å, V =1300.8(4) Å^3, α = 82.587(6)°, β = 81.792(6)°, γ = 61.393(5)°, space group: P-1 (#2), Z = 2, D_{calc} = 1.336 g cm^{-3} , No. of reflection measured 5903, 2 θ $_{max}$ = 54.9 °, R1 = 0.0463. **Figure 2** illustrates the structure as determined. Full data can be obtained on request from the CCDC.[29]

(*E*)-*N′*-[2-(4-Chloro-3-nitrophenyl)-7-(4-bromophenyl)-4-cyano-3-dimethylamino-2*H*-pyrazolo[3,4-*c*]pyridin-5-yl]-*N*,*N*-dimethylformamidine (8b). Recrystallized from EtOH as

orange crystals, yield: (69%), m.p. 131-132 °C; IR (KBr): ν/cm^{-1} 2207 (CN); ^{1}H-NMR (DMSO-d_6): δ = 2.96 (s, 6H, 2CH$_3$), 3.16 (s, 3H, CH$_3$), 3.26 (s, 3H, CH$_3$), 7.79 (d, J = 8.8 Hz, 2H, Ar-H), 8.07 (d, J = 8.8 Hz, 1H, Ar-H), 8.15 (d, J = 8.8 Hz, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 8.69 (d, J = 8.8 Hz, 2H, Ar-H) and 8.94 ppm (s, 1H, amidine H); ^{13}C-NMR (DMSO-d_6): δ = 34.90 (CH$_3$), 40.94 (CH$_3$), 43.99 (2CH$_3$), 83.38, 120.12, 122.20, 123.00, 125.55, 126.14, 130.91, 132.05, 132.23, 132.91, 135.52, 138.49, 140.37, 143.00, 147.93, 151.42, 156.70 and 158.31 ppm (Ar-C and CN); MS (EI): m/z (%) 568 (M$^+$+2, 100), 567 (M$^+$+1, 21.80), 566 (M$^+$, 71.88), 538(44.96); HRMS (EI): m/z calcd. for $C_{24}H_{20}{}^{79}Br^{35}ClN_8O_2$ (M$^+$) 566.0575, found 522.0574. Anal. calcd. for $C_{24}H_{20}BrClN_8O_2$ (567.84): C, 50.77; H, 3.55; N, 19.73. Found: C, 50.85; H, 3.48; N, 19.62.

(*E*)-*N′*-[7-(4-Chlorophenyl)-4-cyano-3-dimethylamino-2-(4-nitrophenyl)-2*H*-pyrazolo[3,4-*c*]pyridin-5-yl]-*N*,*N*-dimethylformamidine (8c). Recrystallized from EtOH/dioxane (2:1) mixture as deep orange powder and recrystallized from DMSO as orange crystals which were used for the X-ray single crystal measurement, yield: (72%), m.p. 147–148 °C; IR (KBr): ν/cm^{-1} 2208 (CN); ^{1}H-NMR (DMSO-d_6): δ = 2.88 (s, 6H, 2CH$_3$), 3.12 (s, 3H, CH$_3$), 3.20 (s, 3H, CH$_3$), 7.59 (d, J = 8.4 Hz, 2H, Ar-H), 8.04 (d, J = 8.8 Hz, 2H, Ar-H), 8.45 (d, J = 8.8 Hz, 2H, Ar-H), 8.72 (d, J = 8.4 Hz, 2H, Ar-H) and 8.87 ppm (s, 1H, amidine H); ^{13}C-NMR (DMSO-d_6): δ = 34.64(CH$_3$), 40.72(CH$_3$), 43.72(2CH$_3$), 82.91, 119.85, 121.97, 124.82,

126.59, 128.80, 131.74, 134.86, 136.21, 140.29, 142.72, 143.81, 147.35, 151.01, 156.41 and 157.99 ppm (Ar-C and CN); MS (EI): m/z (%) 490 (M^++2, 35.77), 489 (M^++1, 29.94) 488 (M^+, 100); HRMS (EI): m/z calcd. for $C_{24}H_{21}{}^{35}ClN_8O_2$ (M^+) 488.1470, found 488.1470. Anal. calcd. for $C_{24}H_{21}ClN_8O_2$ (488.94): C, 58.96; H, 4.33; N, 22.92. Found: C, 58.88; H, 4.36; N, 22.84. **Crystallographic Analysis for 8c**. The crystals were mounted on a glass fiber. All measurements were performed on a Rigaku R-AXIS RAPID diffractometer using filtered Mo-kα radiation. The data were collected at a temperature of 20 ± 1 °C to a maximum 2θ value of 55.0° using the ω scanning technique. The structure was solved by the charge flipping method and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. **Crystal Data,** $C_{24}H_{21}{}^{35}ClN_8O_2$, M = 488.94, triclinic, a = 9.627(6) Å, b = 11.130(7) (1) Å, c = 13.467(8) Å, V =1410(2) $Å^3$, α = 89.789(7)°, β = 83.98(1)°, γ = 79.452(9)°, space group: P-1 (#2), Z = 2, D_{calc} = 1.335g cm^{-3}, No. of reflection measured 5903, 2 θ_{max} = 48.6°, R1 = 4461. **Figure 3** illustrates the structure as determined. Full data can be obtained on request from the CCDC.[30]

(*E*)-*N′*-[2-(3-Bromophenyl)-7-(4-chlorophenyl)-4-cyano-3-dimethylamino-2*H*-pyrazolo-[3,4-*c*]pyridin-5-yl]-*N*,*N*-dimethylformamidine (8d). Recrystallized from EtOH as pale orange crystals, yield: (71%), m.p. 170–171 °C; IR (KBr): ν/cm^{-1} 2207 (CN); ^{1}H-NMR (DMSO-d_6): δ = 2.90 (s, 6H, $2CH_3$), 3.02 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 7.57-7.65 (m, 4H, Ar-H), 7.78 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.85 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 8.40 (d, *J* = 8.4 Hz, 1H, Ar-H) and 8.85 ppm (s, 1H, amidine H); MS (EI): m/z (%) 523 (M^++2, 100), 522 (M^++1, 26.91), 521 (M^+, 73.31); HRMS (EI): m/z calcd. for $C_{24}H_{21}{}^{79}Br$

$^{35}ClN_7$ (M^+) 521.0724, found 521.0724. Anal. calcd. for $C_{24}H_{21}BrClN_7$ (522.84): C, 55.14; H, 4.05; N, 18.75. Found: C, 55.22; H, 3.94; N, 18.79.

(*E*)-*N′*-[2-(3-Chlorophenyl)-7-(4-chlorophenyl)-4-cyano-3-dimethylamino-2H-pyrazolo-[3,4-c]pyridin-5-yl]-*N*,*N*-dimethylformamidine (8e). Recrystallized from EtOH as orange crystals, yield: (68%), m.p. 191–192 °C; IR (KBr): ν/cm^{-1} 2205 (CN); ^{1}H-NMR (DMSO-d_6): δ = 2.89 (s, 6H, 2CH$_3$), 3.01 (s, 3H, CH$_3$), 3.10 (s, 3H, CH3), 7.57-7.64 (m, 4H, Ar-H), 7.77 (d, J = 8.0 Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), and 8.89 ppm (s, 1H, amidine H); MS (EI): m/z (%) 478 (M^++1, 56.95), 477 (M^+, 100); HRMS (EI): m/z calcd. for $C_{24}H_{21}{}^{35}Cl_2N_7$ (M^+) 477.1230, found 477.1230. Anal. calcd. for $C_{24}H_{21}Cl_2N_7$ (478.39): C, 60.26; H, 4.42; N, 20.50. Found: C, 60.34; H, 4.51; N, 20.42.

(*E*)-5-(2-Chloro-5-nitrophenylazo)-6-(4-chlorophenyl)-2-(dimethylaminomethyleneamino)-nicotinic acid ethyl ester (10a). Recrystallized from dioxane as red crystals, yield: (79%), m.p. 196–197 °C; IR (KBr): ν/cm^{-1} 1745 (CO ester); ^{1}H-NMR (DMSO-d_6): δ = 1.33 (t, 3H, J = 7.2 Hz, CH_3CH$_2$), 3.12 (s, 3H, CH$_3$), 3.23 (s, 3H, CH$_3$), 4.33 (q, 2H, J = 7.2 Hz, CH$_3$$CH_2$), 7.57 (d, J = 8.8 Hz, 2H, Ar-H), 7.91 (d, J = 8.8 Hz, 2H, Ar-H), 7.99 (d, J = 8.4 Hz, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 8.23 (s, 1H, amidine H), 8.30 (d, J = 8.4 Hz, 1H, Ar-H) and 8.82 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 14.52 (CH_3CH$_2$), 35.29 (CH$_3$), 40.84 (CH$_3$), 61.23 (CH$_3$$CH_2$), 113.22, 122.14, 125.54, 125.92, 128.08, 132.50, 133.30, 134.95, 136.80, 139.98,

140.08, 147.72, 149.14, 157.25, 158.55, 162.17 and 166.99 ppm (Ar-C and CO); MS (EI): m/z (%) 516 (M^++2, 69.24), 515 (M^++1, 24.71), 514 (M^+, 100); HRMS (EI): m/z calcd. for $C_{23}H_{20}{}^{35}Cl_2N_6O_4$ (M^+) 514.0917, found 514.0917. Anal. calcd. for $C_{23}H_{20}Cl_2N_6O_4$ (515.36): C, 53.60; H, 3.91; N, 16.31. Found: C, 53.57; H, 3.87; N, 16.24.

(*E*)-5-(4-Chloro-3-nitrophenylazo)-6-(4-bromophenyl)-2-(dimethylaminomethyleneamino)-nicotinic acid ethyl ester (10b). Recrystallized from dioxane as orange crystals, yield: (77%), m.p. 218–220 °C; IR (KBr): ν/cm^{-1} 1729 (CO ester); ^{1}H-NMR (DMSO-d_6): δ = 1.33 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 3.10 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.32 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 7.70 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.79(d, *J* = 8.4 Hz, 2H, Ar-H), 7.96-7.97 (m, 2H, Ar-H), 8.22 (s, 1H, amidine H), 8.34 (s, 1H, Ar-H) and 8.76 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 14.15 (CH_3CH_2), 34.61 (CH_3), 42.08 (CH_3), 60.83 (CH_3CH_2), 112.45, 121.26, 123.16, 125.29, 125.37, 125.92, 126.70, 128.18, 128.87, 130.52, 130.64, 133.08, 133.23, 137.32, 146.90, 156.70 and 166.48 ppm (Ar-C and CO); MS (EI): m/z (%) 560 (M^++2, 100), 559 (M^++1, 65.19), 558 (M^+, 72.46), 529(89.23); HRMS (EI): m/z calcd. for $C_{23}H_{20}{}^{79}Br^{35}ClN_6O4$ (M^+) 558.0412, found 558.0412. Anal. calcd. for $C_{23}H_{20}BrClN_6O_4$ (559.81): C, 49.35; H, 3.60; N, 15.01. Found: C, 49.44; H, 3.66; N, 14.94.

4-(4-Bromophenyl)-2-(4-chloro-3-nitrophenyl)-1-dimethylamino-8-methyl-2,8-di-hydro-pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidin-9-one (14). Recrystallized from EtOH/dioxane (1:1) mixture as pale orange crystals, yield: (70%), m.p. 215–216 °C; IR (KBr): ν/cm^{-1} 1672

(CO); ^{1}H-NMR (DMSO-d_6): δ = 2.91 (s, 6H, $2CH_3$), 3.62 (s, 3H, CH_3), 7.83 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.07 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.16 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.56 (s, 1H, Ar-H), 8.63 (d, *J* = 8.4 Hz, 2H, Ar-H) and 8.65 ppm (s, 1H, pyrimidine H7); ^{13}C-NMR (DMSO-d_6): δ = 34.58 (CH_3), 44.65 ($2CH_3$), 108.50, 115.16, 123.24, 125.65, 126.17, 131.22, 132.00, 132.14, 132.38, 132.56, 132.83, 135.21, 142.24, 146.85, 149.89, 154.90, 155.66 and 160.06 ppm (Ar-C and CO); MS (EI): m/z (%) 555 (M^++2, 100), 554 (M^++1, 26.96), 553(M^+, 76.39); HRMS (EI): m/z calcd. for $C_{23}H_{17}{}^{79}Br^{35}ClN_7O_3$ (M^+) 553.0259, found 553.0253. Anal. calcd. for $C_{23}H_{17}BrClN_7O_3$ (554.79): C, 49.79; H, 3.09; N, 17.67. Found: C, 49.87; H, 3.16; N, 17.64.

General Procedure for the Preparation of 9a-c and 13a-b.

Independent solutions of the pyrazolo[3,4-*c*]pyridine **8a-c**, and amidines **10a-b** (2.5 mmol) in AcOH (10 mL) containing ammonium acetate (1.0 g) were stirred at reflux for 3 h. The mixtures were cooled to room temperature and poured into ice cold water. The formed solids were collected by filtration, washed with water and crystallized from the indicated solvents to afford **9a-c** and **13a-b** as pure products.

2-(2-Chloro-5-nitrophenyl)-4-(4-chlorophenyl)-1-dimethylamino-2*H*-pyrazolo[4',3':4,5]-pyrido[2,3-*d*]pyrimidine-9-amine (9a). Recrystallized from acetic acid as pale yellow crystals, yield: (67%), m.p. 287-288 °C; IR (KBr): ν /cm^{-1} 3433, 3267 (NH_2); ^{1}H-NMR (DMSO-d_6): δ = 2.80 (s, 6H, $2CH_3$), 7.69 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.19 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.58-8.65 (m, 4H, 3Ar-H and pyrimidine H7), 9.04 (s, 1H, Ar-H) and 7.99, 9.21 (2 br, 2H, NH_2, D_2O exchangeable); MS (EI): m/z (%) 496 (M^+ +2, 60.67), 495 (M^+ +1, 22.00), 494 (M^+, 100); HRMS (EI): m/z calcd. for $C_{22}H_{16}{}^{35}Cl_2N_8O_2$ (M^+) 494.0767, found 494.0767.

Anal. calcd. for $C_{22}H_{16}Cl_2N_8O_2$ (495.33): C, 53.35; H, 3.26; N, 22.62. Found: C, 53.23; H, 3.33; N, 22.55.

4-(4-Bromophenyl)-2-(4-chloro-3-nitrophenyl)-1-dimethylamino-2*H*-pyrazolo[4',3':4,5]-pyrido[2,3-*d*]pyrimidine-9-amine (9b). Recrystallized from acetic acid as yellow crystals, yield: (71%), m.p. 259-260 °C; IR (KBr): ν /cm^{-1} 3445, 3272 (NH_2); ^{1}H-NMR (DMSO-d_6): δ = 2.76 (s, 6H, $2CH_3$), 7.82 (d, J = 8.4 Hz, 2H, Ar-H), 8.15 (d, J = 8.8 Hz, 1H, Ar-H), 8.23 (d, J = 8.8 Hz, 1H, Ar-H), 8.57(s, 1H, pyrimidine H7), 8.59 (d, J = 8.4 Hz, 2H, Ar-H), 8.70 (s, 1H, Ar-H) and 7.97, 9.13 (2 br, 2H, NH_2, D_2O exchangeable); MS (EI): m/z (%) 540 (M^+ +2, 100), 539 (M^+ +1, 21.66), 538 (M^+, 77.59); HRMS (EI): m/z calcd. for $C_{22}H_{16}{}^{79}BrClN_8O_2$ (M^+) 538.0262, found 538.0266. Anal. calcd. for $C_{22}H_{16}BrClN_8O_2$ (539.78): C, 48.95; H, 2.99; N, 20.76. Found: C, 48.88; H, 2.97; N, 20.69.

4-(4-Chlorophenyl)-2-(4-nitrophenyl)-1-dimethylamino-2*H*-pyrazolo[4',3':4,5]pyrido-[2,3-*d*]pyrimidine-9-amine (9c). Recrystallized from acetic acid as pale orange crystals, yield: (73 %), m.p. 265-266 °C; IR (KBr): ν /cm^{-1} 3437, 3263 (NH_2); ^{1}H-NMR (DMSO-d_6): δ = 2.75 (s, 6H, $2CH_3$), 7.68 (d, J = 8.8 Hz, 2H, Ar-H), 8.13 (d, J = 8.8 Hz, 2H, Ar-H), 8.54 (d, J = 8.8 Hz, 2H, Ar-H), 8.57 (s, 1H, pyrimidine H7), 8.67 (d, J = 8.8 Hz, 2H, Ar-H) and 7.99, 9.11 (2 br, 2H, NH_2, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6): δ = 44.01 ($2CH_3$), 100.24, 114.27, 125.04, 125.35, 129.09, 129.35, 132.01, 135.22, 136.47, 141.71, 144.08, 145.57,

148.95, 155.42, 157.04 and 162.14 ppm (Ar-C); MS (EI): m/z (%) 462 (M^+ +2, 33.85), 461 (M^+ +1, 27.05), 460 (M^+, 100); HRMS (EI): m/z calcd. for $C_{22}H_{17}{}^{35}ClN_8O_2$ (M^+) 460.1157, found 460.1156. Anal. calcd. for $C_{22}H_{17}ClN_8O_2$ (460.88): C, 57.33; H, 3.72; N, 24.31. Found: C, 57.45; H, 3.58; N, 24.22.

6-(2-Chloro-5-nitrophenylazo)-7-(4-chlorophenyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (13a). Recrystallized from DMF/dioxane mixture (1:1) as reddish brown crystals, yield: (74%), m.p. above 300 °C; IR (KBr): ν/cm^{-1} 3212 (NH), 1702 (CO); ^{1}H-NMR (DMSO-d_6): δ = 7.62 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.04 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 8.37 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.46 (s, 1H, pyrimidine H2), 8.66 (s, 1H, pyridine H5) and 12.74 ppm (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 112.84, 117.23, 123.10, 126.31, 127.88, 132.31, 133.12, 134.84, 135.78, 135.93, 140.48, 142.44, 146.98, 148.06, 154.98, 158.82 and 160.94 ppm (Ar-C and CO); MS (EI): m/z (%) 442 (M^++2, 55.15), 441 (M^++1, 21.67), 440 (M^+, 100); HRMS (EI): m/z calcd. for $C_{19}H_{10}{}^{35}Cl_2N_6O_3$ (M^+) 440.0185, found 440.0183. Anal. calcd. for $C_{19}H_{10}Cl_2N_6O_3$ (441.24): C, 51.72; H, 2.28; N, 19.05. Found: C, 51.68; H, 2.34; N, 19.13.

7-(4-Bromophenyl)-6-(4-chloro-3-nitrophenylazo)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (13b). Recrystallized from DMF/dioxane mixture (2:1) as pale orange crystals, yield: (75%), m.p. above 300 °C; IR (KBr): ν/cm^{-1} 3218 (NH), 1713 (CO); ^{1}H-NMR (DMSO-d_6): δ = 7.72-7.78

(m, 4H, Ar-H), 8.00 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.06 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.46 (s, 1H, pyrimidine H2), 8.48 (s, 1H, Ar-H), 8.64 (s, 1H, pyridine H5) and 12.79 ppm (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 117.41, 117.47, 120.45, 123.24, 124.04, 127.02, 128.05, 130.99, 133.10, 133.31, 135.71, 142.90, 148.12, 150.55, 150.77, 160.00 and 160.72 ppm (Ar-C and CO); MS (EI): m/z (%) 486 (M^++2, 100), 485 (M^++1, 83.28), 484 (M^+, 75.53), 483(52.26); HRMS (EI): m/z calcd. for $C_{19}H_{10}{}^{79}Br^{35}ClN_6O_3$ (M^+) 483.9680, found 483.9680. Anal. calcd. for $C_{19}H_{10}BrClN_6O_3$ (485.69): C, 46.99; H, 2.08; N, 17.30. Found: C, 46.87; H, 2.17; N, 17.23.

General procedure for the preparation 15a-b and 16a-b.

Independent solutions of the azonicotinates **3a-b** (5 mmol) in acetic anhydride (10 mL) were stirred at reflux for 4 h in the cases for **15a-b** formation and in the case of **16a-b** formation for 12 h. The mixtures were cooled to room temperature and the formed solids were collected by filtration, washed with ethanol and rcrystallized from the indicated solvent.

2-Acetylamino-5-(2-chloro-5-nitrophenylazo)-6-(4-chlorophenyl)nicotinic acid ethyl ester (15a). Recrystallized from EtOH/dioxane (2:1) mixture as reddish orange crystals, yield: (83%), m.p. 257-258 °C; IR (KBr): ν/cm^{-1} 3231 (NH), 1719, 1673 (2 CO); ^{1}H-NMR (DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 2.23 (s, 3H, COCH_3), 4.29 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.06 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 8.39 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.43 (s, 1H, pyridine H4) and 11.22 ppm (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 14.49 (CH_3), 24.38 (CH_3), 61.78 (CH_2), 113.36, 119.16, 126.98, 128.44, 129.16, 131.98, 132.11, 132.78, 133.57, 135.32, 135.57, 141.21, 147.48, 148.45, 158.16, 165.63 and 170.34 ppm (Ar-C and CO); MS (EI): m/z (%)

502 (M^++1, 72.45), 501 (M^+, 100),. HRMS (EI): m/z calcd. for $C_{22}H_{17}{}^{35}Cl_2N_5O_5$ (M^+) 501.0601, found 501.0602. Anal. calcd. for $C_{22}H_{17}Cl_2N_5O_5$ (502.32): C, 52.61; H, 3.41; N, 13.94. Found: C, 52.64; H, 3.37; N, 13.88.

2-Acetylamino-5-(4-chloro-3-nitrophenylazo)-6-(4-bromophenyl)nicotinic acid ethyl ester (15b). Recrystallized from EtOH/dioxane (2:1) mixture as reddish orange crystals, yield: (85%), m.p. 207-208 °C; IR (KBr): ν/cm^{-1} 3265 (NH), 1713, 1668 (2 CO); ^{1}H-NMR (DMSO-d_6): δ = 1.30 (t, 3H, J = 7.2 Hz, CH_3CH_2), 2.22 (s, 3H, COCH_3), 4.28 (q, 2H, J = 7.2 Hz, CH_3CH_2), 7.74-7.81 (m, 4H, Ar-H), 8.00 (d, J = 8.8 Hz, 1H, Ar-H), 8.07 (d, J = 8.8 Hz, 1H, Ar-H), 8.41 (s, 1H, pyridine H4), 8.47 (s, 1H, Ar-H) and 11.17 ppm (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 14.06 (CH_3), 23.93(CH_3), 61.31(CH_2), 118.55, 120.40, 123.91, 126.86, 127.06, 127.64, 130.98, 133.06, 133.26, 135.21, 140.51, 148.18, 150.62, 150.73, 157.14, 165.19 and 169.81 ppm (Ar-C and CO); MS (EI): m/z (%) 547 (M^++2, 100), 546 (M^++1, 80.16), 545 (M^+, 75.53), 544(47.46); HRMS (EI): m/z calcd. for $C_{22}H_{17}{}^{79}Br^{35}ClN_5O_5$ (M^+) 545.0096, found 545.0096. Anal. calcd. for $C_{22}H_{17}BrClN_5O_5$ (546.77): C, 48.33; H, 3.13; N, 12.81. Found: C, 48.39; H, 3.21; N, 12.77. **Crystallographic Analysis for 15b**. The crystals were mounted on a glass fiber. All measurements were performed on Bruker X8 Prospector. The data were collected at a temperature of 20 ± 1 °C to a maximum θ value of 66.61° using the ω scanning technique. The structure was solved by the direct method using SHELXS-97 (Sheldrick, 2008) and refined by Full-matrix least-squares on F^2. The non-hydrogen atoms were refined anisotropically. Data were corrected for absorption effects using the multi-scan method (SADABS). **Crystal Data,** $C_{22}H_{17}BrClN_5O_5$, M = 546.76, monoclinic, a = 9.6837(2) Å, b = 22.9877(4) Å, c = 20.6329(4) Å, V = 4574.66(15) Å^3, α = γ = 90.00°, β =

95.1230(10)°, space group: P 1 21/c 1, Z = 4, D_{calc} = 1.588 g cm^{-3}, No. of reflection measured 8056, 2 θ_{max} = 66.68°, R1 = 0.064. **Figure 4** illustrates the structure as determined. Full data can be obtained on request from the CCDC.[31]

5-(2-Chloro-5-nitrophenylazo)-6-(4-chlorophenyl)-2-diacetylaminonicotinic acid ethyl ester (16a). Recrystallized from EtOH as red crystals, yield: (89%), m.p. 229-230 °C; IR (KBr): ν/cm^{-1} 3231 (NH), 1720, 1705, 1681 (3 CO); ^{1}H-NMR (DMSO-d_6): δ = 1.31 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 2.31 (s, 6H, 2COCH_3), 4.36 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.10 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 8.45 (d, *J* = 8.4 Hz, 1H, Ar-H) and 8.64 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-d_6): δ = 14.34 (CH_3), 26.75 (CH_3), 62.67 (CH_2), 113.56, 124.98, 127.68, 128.44, 128.73, 129.79, 132.93, 133.57, 133.76, 134.51, 136.14, 141.32, 144.73, 147.51, 148.43, 152.96, 158.34, 163.37 and 172.37 ppm (Ar-C and CO); MS (EI): m/z (%) 544 (M^++1, 2.95), 543 (M^+, 8.55); HRMS (EI): m/z calcd. for $C_{24}H_{19}{}^{35}Cl_2N_5O_6$ (M^+) 543.0706, found 543.0709. Anal. calcd. for $C_{24}H_{19}Cl_2N_5O_6$ (544.35): C, 52.96; H, 3.52; N, 12.87. Found: C, 53.02; H, 3.45; N, 12.94.

6-(4-Bromophenyl)-5-(4-chloro-3-nitrophenylazo)-2-diacetylaminonicotinic acid ethyl ester (16b). Recrystallized from EtOH as orange crystals, yield: (89%), m.p. 180-181 °C; IR (KBr): ν/cm^{-1} 1720, 1696, 1672 (3 CO); ^{1}H-NMR (DMSO-d_6): δ = 1.31 (t, 3H, *J* = 7.2 Hz,

CH$_3$CH$_2$), 2.30 (s, 6H, 2CO*CH*$_3$), 4.35 (q, 2H, *J* = 7.2 Hz, CH$_3$*CH*$_2$), 7.76-7.82 (m, 4H, Ar-H), 8.07 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.14 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.60 (s, 1H, Ar-H) and 8.65 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-*d*$_6$): δ = 13.93 (CH$_3$), 26.31(2CH$_3$), 62.18(CH$_2$), 121.00, 124.39, 124.53, 126.96, 128.52, 129.22, 131.27, 133.18, 133.44, 134.42, 144.17, 148.30, 150.55, 152.26, 157.49, 162.97 (Ar-C) and 171.92 ppm (2 CO); MS (EI): m/z (%) 589 (M^++2, 100), 588 (M^++1, 24.27), 587 (M^+, 75.54), 586(4.03); HRMS (EI): m/z calcd. for $C_{24}H_{19}{}^{79}Br^{35}ClN_5O_6$ (M^+) 587.0201, found 587.0201. Anal. calcd. for $C_{24}H_{19}BrClN_5O_6$ (588.81): C, 48.96; H, 3.25; N, 11.89. Found: C, 48.88; H, 3.28; N, 11.97.

(*E*)-*N*-[6-(4-Bromophenyl)-5-(4-chloro-3-nitrophenylazo)-3-cyanopyridin-2-yl]form-imidic acid ethyl ester (17). A mixture of 5-arylazonicotinonitrile **3d** (1.14 g, 5 mmol) and triethylorthoformate (1.2 mL, 10 mmol) in dry toluene (20 mL) was stirred at reflux under nitrogen for 12 h. The separated solid product obtained upon standing at room temperature was collected by filtration, washed with petroleum ether and crystallized from EtOH/dioxane (1:1) mixture as orange crystals. yield: (74 %), m.p. 208-209 °C; IR (KBr): ν/cm^{-1} 2232 (CN), 1621 (C=N); ^{1}H-NMR (DMSO-*d*$_6$): δ = 1.40 (t, 3H, *J* = 7.2 Hz, *CH*$_3$CH$_2$), 4.47 (q, 2H, *J* = 7.2 Hz, CH$_3$*CH*$_2$), 7.74 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.82 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.02-8.08 (m, 2H, Ar-H), 8.46 (s, 1H, Ar-H), 8.58 (s, 1H, amidine H) and 8.82 ppm (s, 1H, pyridine H4); ^{13}C-NMR (DMSO-*d*$_6$): δ = 14.40 (CH$_3$), 64.85 (CH$_2$), 103.34, 116.10, 120.86, 124.82, 127.53, 128.49, 131.51, 131.82, 133.66, 133.92, 135.67, 141.96, 148.61, 150.92, 158.51, 161.87 and 163.50 ppm (Ar-C and CN), MS (EI): m/z (%) 514 (M^+ +2, 85.15), 513 (M^+ +1, 100), 512 (M^+, 65.77), 511 (70.10); HRMS (EI): m/z calcd. for $C_{21}H_{14}{}^{79}Br^{35}ClN_6O_3$

(M^+) 511.9993, found 511.9993. Anal. calcd. for $C_{21}H_{14}BrClN_6O_3$ (513.74): C, 49.10; H, 2.75; N, 16.36. Found: C, 49.14; H, 2.69; N, 16.29.

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