

Article

A Route to Dicyanomethylene Pyridines and Substituted Benzonitriles Utilizing Malononitrile Dimer as a Precursor

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Abstract: The conditions of the reaction of malononitrile dimer with enamines and arylidenemalononitrile could be adapted to yield either pyridines or benzene derivatives. A new synthesis of pyrido[1,2-*a*]pyrimidines from the reaction of malononitrile dimer **1** and 2-phenyl-3-piperidin-1-yl-acrylonitrile (**11**) is described. Compound **1** condensed with DMFDMA to yield an enamionitrile that reacted with hydrazine hydrate to yield *N*,4,6-triamino-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (**17**).

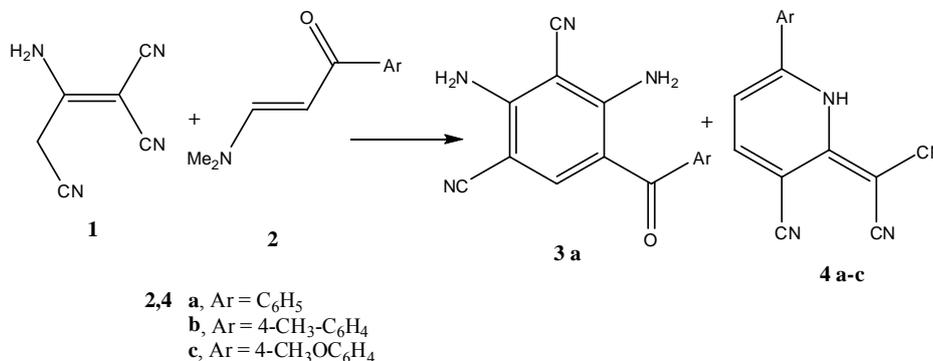
Keywords: malononitrile dimer; arylmethylenemalononitrile; benzyldenemalononitrile; pyrazolopyridine

1. Introduction

Polyfunctionally substituted nitriles are versatile reagents that have been extensively utilized in the past as precursors to polyfunctionally substituted heteroaromatics [1-4]. Interest in further developing the synthetic potential of these compounds has been revived [5-7]. 2-Aminoprop-1-ene-1,1,3-tricarbonitrile (**1**) has proved to be an excellent precursor to condensed pyridines, pyridazines, and pyrazoles [8-10]. However, to our knowledge the utility of **1** as a precursor to polyfunctional aromatics has received little attention. Elnagdi *et al.* have noted the formation of **3** as a side product from the reaction of **2** with **1**, while compound **4** was obtained as the main product [11] (Scheme 1). In

connection to results reported earlier [11] we were able to react **1** with **5a,b** to afford either pyridines or benzene derivatives after changing the reaction conditions.

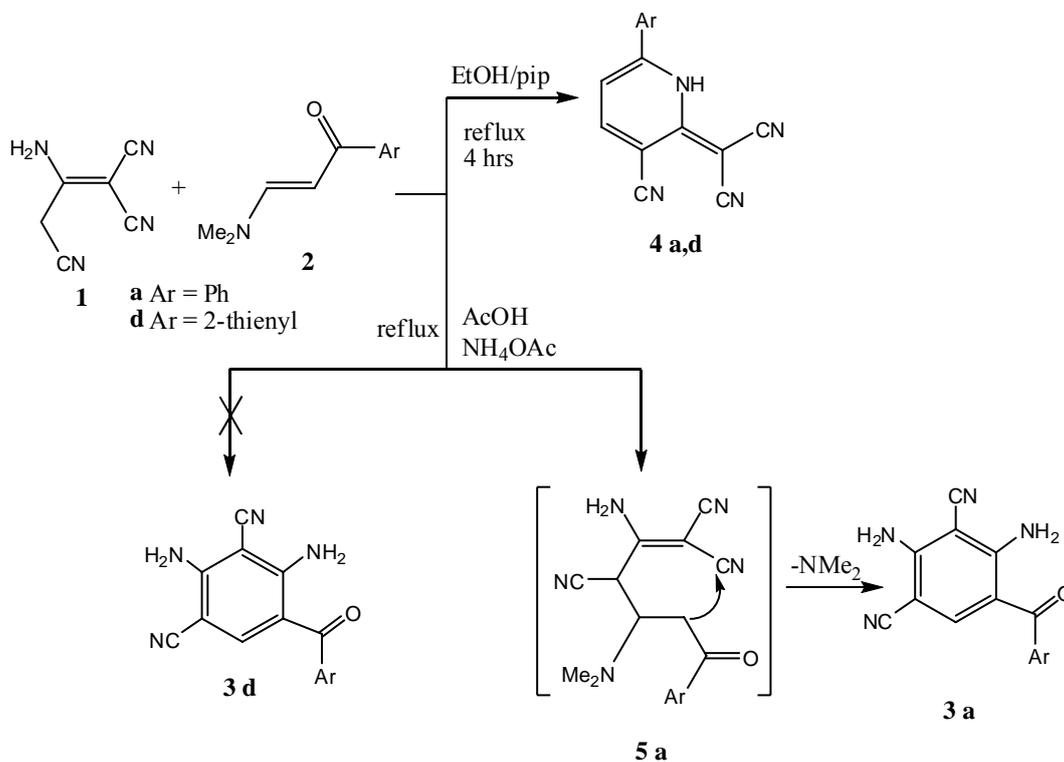
Scheme 1. Malononitrile dimer as precursor to heterocycles and substituted benzenes [11].



2. Results and Discussion

Thus reaction of **1** with **2a,b** in ethanolic piperidine has afforded **4a,d** as a sole product. On the other hand, when the reaction was conducted in acetic acid in the presence of ammonium acetate and refluxing for 4 hrs only **3a** was formed via intermediate **5** (Scheme 2) The ¹H-NMR of **4a**, in addition to phenyl proton signals, showed two doublets at $\delta = 7.16$ ppm and $\delta = 7.86$ ppm with $J = 8$ Hz, typical for pyridine H-5 and H-4, respectively. A D₂O exchangeable one proton signal for a NH group appeared at $\delta = 9.42$ ppm.

Scheme 2. Synthesis of pyridine **3a** and substituted benzenes **4a,d**.

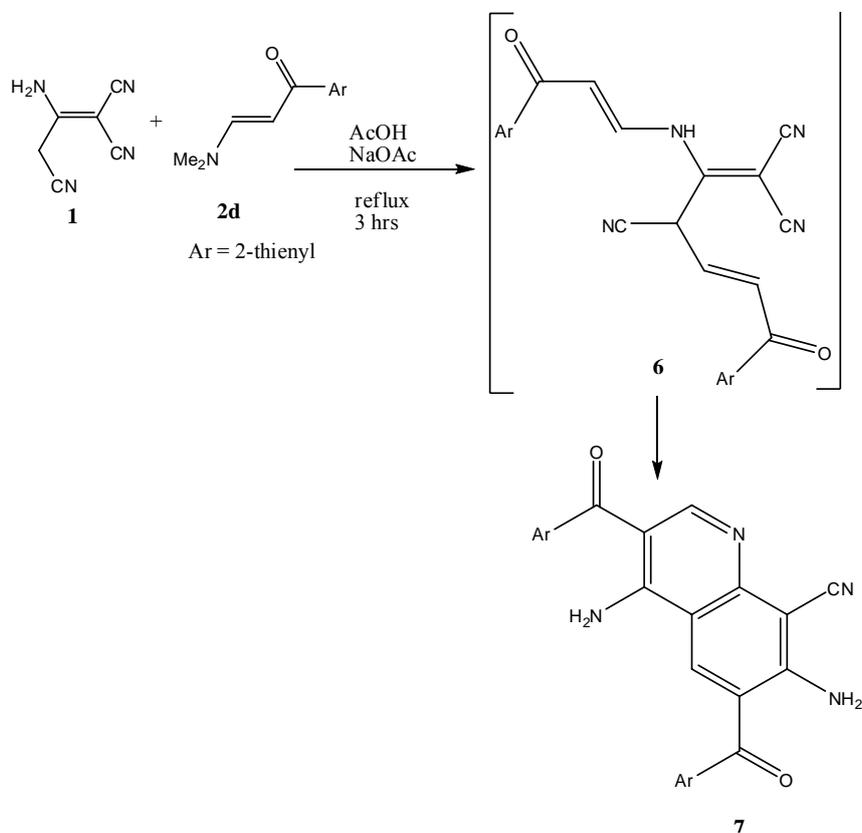


The $^1\text{H-NMR}$ spectrum of **3a** revealed a singlet at $\delta = 8.29$ ppm for H-6 and two D_2O exchangeable amino signals at $\delta = 7.08$ ppm and $\delta = 7.77$ ppm, in addition to the phenyl protons (see Experimental). The $^{13}\text{C-NMR}$ clearly indicated the carbonyl carbon at $\delta = 190.23$ ppm and two CN signals at $\delta = 114.13$ and 113.85 ppm.

In an attempt to generate further examples of the synthesis of substituted benzenes **3**, malononitrile dimer **1** was reacted with **2d** in acetic acid/ammonium acetate, and a product with molecular formula $\text{C}_{13}\text{H}_8\text{N}_4\text{OS}$ (M^+ at $m/z = 268$) which we think to be **3d** was isolated after reflux for 1/2 hrs; prolonged heating did not change the identity of the compound. The $^1\text{H-NMR}$ under D_2O exchange of the presumed structure **3d**; showed, along with three thienyl protons, two amino group singlets at $\delta = 7.1$ ppm and $\delta = 7.9$ ppm, and a doublet at $\delta = 8.2$ ppm with $J = 8$ Hz, that could not be explained or assigned to any proton in the suggested structure.

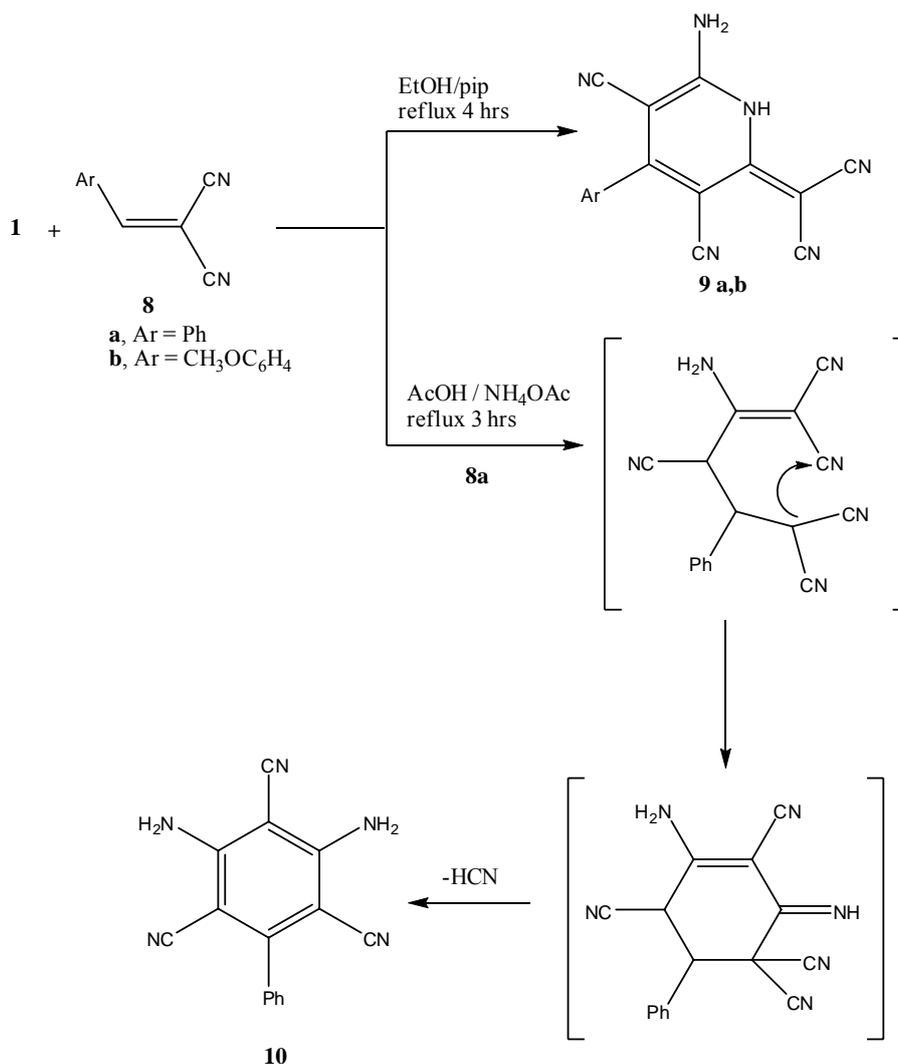
Repeating the same reaction using sodium acetate instead of ammonium acetate, and refluxing for 3 hrs, a whole new set of data were obtained. A compound with molecular formula $\text{C}_{20}\text{H}_{12}\text{N}_4\text{O}_2\text{S}_2$ (M^+ 404) was obtained. $^1\text{H-NMR}$ of this compound showed two singlets at $\delta = 7.47$ ppm and $\delta = 8.98$ ppm each for one proton of C-5 and C-2 of the pyridine ring, respectively, in addition to six thienyl protons and two amino signals. The $^{13}\text{C-NMR}$ spectrum showed the presence of 19 different carbon atoms with two carbonyl carbons at $\delta = 184.7$ ppm. These data can be interpreted as corresponding to structure **7** that is assumed to result from initial reaction of the active methylene moiety and the amino function in **1** with **2d** to yield the intermediate **6** that then cyclizes to **7** (Scheme 3).

Scheme 3. Synthesis of 4,7-diamino-3,6-di(thiophene-2-carbonyl)quinoline-8-carbonitrile (**7**).



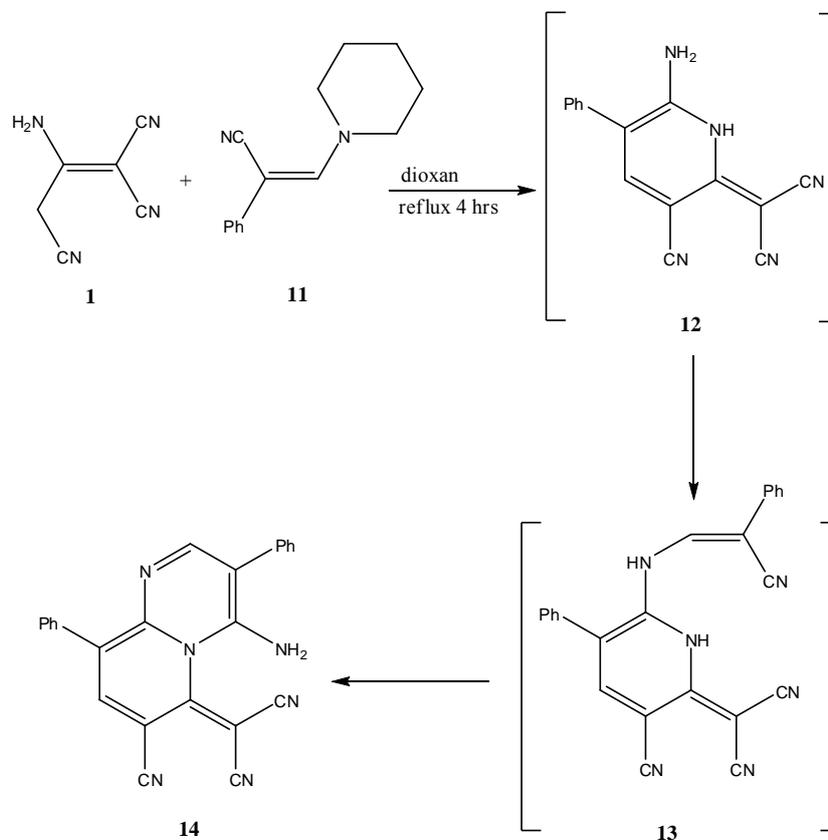
Like the recently reported formation of **9** from reaction of **1** and **8a,b** in ethanolic chitosan, compound **1** reacted with **8a,b** to yield dihydropyridine **9a,b**. However in refluxing acetic acid in the presence of ammonium acetate, the benzene derivative **10** was obtained as indicated by the spectral data (Scheme 4).

Scheme 4. Synthesis of 6-amino-2-dicyanomethylene-4-aryl-2,3-dihydropyridine-3,5-dicarbonitriles **9a,b** and 3,5-diaminobiphenyl-2,4,6-tricarbonitrile (**10**).

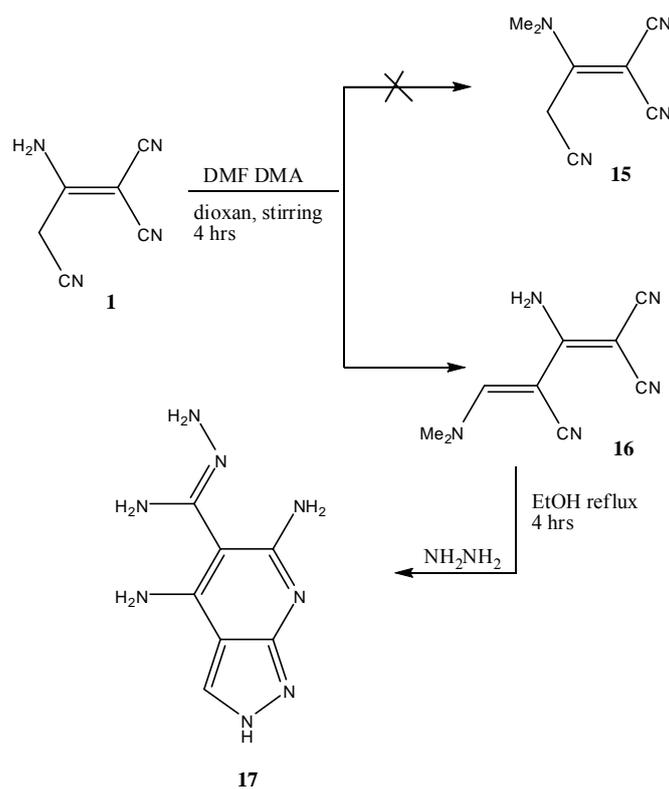


The reaction of **1** with **11**, which was recently obtained by reacting benzyl cyanide with triethyl orthoformate and piperidine [12], afforded **14** via intermediates **12** and **13**. Attempts to isolate **13** have failed (cf. Scheme 5). The reaction of **1** with DMFDMA afforded **16** which may exist in *E* or *Z* forms. Isomeric structure **15** was ruled out based on ^1H NMR that revealed the D_2O exchangeable amino signal at $\delta = 7.19$ ppm. In addition, the ^{13}C NMR did not reveal any signals for the sp^3 carbons other than those of the dimethylamino moiety. Reacting **16** with hydrazine hydrate afforded 4,6-diamino-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide hydrazone **17** (cf. scheme 6).

Scheme 5. Synthesis of 2-(4-amino-7-cyano-3,9-diphenyl-pyrido[1,2-*a*]pyrimidin-6-ylidene)-malononitrile (**14**).



Scheme 6. Synthesis of 4,6-diamino-2H-pyrazolo[3,4-*b*]pyridine-5-carboxamide hydrazone (**17**).



3. Experimental

3.1. General

All melting points are uncorrected and were determined on a Sanyo (Gallenkamp) instrument. Infrared spectra were recorded from KBr discs on a Perkin-Elmer 2000 FT-IR system. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were determined on a Bruker DPX spectrometer operating at 400 MHz for $^1\text{H-NMR}$ and 100 MHz for $^{13}\text{C-NMR}$ using DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI at 70 eV. Elemental analyses were measured by means of LEOCHNS-932 Elemental Analyzer. General purpose silica gel on polyester 20 x 20 cm TLC plates with UV indicator were used in TLC experiments to monitor completion of reactions, in which ethyl acetate-petroleum ether (1:1) was used as eluent.

3.2. 2,4-Diamino-5-benzoyl-isophthalonitrile (**3a**)

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and enaminone **2a** (0.01 mol) in AcOH (10 cm) and 0.2 gm of NH_4OAc , was kept at reflux temperature for 4 hrs. The mixture was cooled and then poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH to give yellow crystals; Yield 83%; m.p. 298–299 °C; Anal. Calcd. for $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}$ (262.27): C, 68.69; H, 3.84; N, 21.36%. Found: C, 68.53; H, 3.92; N, 21.34%; IR (KBr, cm^{-1}): 3,443, 3,352 (NH_2), 3,322, 3,209 (NH_2), 2,210, 2,206 (2CN); $^1\text{H-NMR}$: δ , ppm = 7.08 (br s, 2H, NH_2 , D_2O exchangeable) 7.50–7.57 (3H, m, H-3',4',5'), 7.77 (2H, br. s, NH_2 , D_2O exchangeable), 8.22 (2H, dd, $^3J = 8.0$, $^4J = 1.6$, H-2',6'), 8.29 (1H, s, H-6); $^{13}\text{C-NMR}$: δ , ppm = 190.23, 159.85, 159.62, 157.90, 154.44, 154.12, 143.65, 136.01, 130.21 (2C), 127.32 (2C), 115.89, 114.13, 113.85; MS: m/z (%) 262 (M^+ , 100), 234 (15), 217 (5), 192 (5), 164 (25), 131 (10).

3.3. General procedure for the synthesis of compounds **4a,d**

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and enaminone **2a,b** (0.01 mol) in EtOH (10 mL) was treated with piperidine (5 drops). The reaction mixture was refluxed for 4 h. The mixture was cooled and then poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH to give yellow crystals.

2-(3-Cyano-6-phenyl-1H-pyridin-2-ylidene)malononitrile (4a). Yield 80%; m.p. 257–259 °C; Anal. Calcd. for $\text{C}_{15}\text{H}_8\text{N}_4$ (244.26): C, 73.76; H, 3.30; N, 22.94%. Found: C, 73.94; H, 3.52; N, 23.04%; IR (KBr, cm^{-1}): 3,097 (NH), 2,210, 2,182 (3CN); $^1\text{H-NMR}$: δ , ppm = 7.16 (1H, d, $J = 8.0$ Hz, H-5), 7.48–7.51 (3H, m, H-3',4',5'), 7.86 (1H, d, $J = 8.0$ Hz, H-4), 8.01 (2H, m, H-2',6'), 9.42 (1H, br. s, NH, D_2O exchangeable); $^{13}\text{C-NMR}$: δ , ppm = 180.88, 160.54, 159.45, 155.50, 136.89, 132.09, 128.31 (2C), 127.32 (2C), 114.72, 113.88 (2C), 91.82, 63.25; MS: m/z (%) 243 (M^+ , 100), 217 (25), 152 (25), 128 (15), 105 (100), 77 (10).

2-(3-Cyano-6-thiophen-2-yl-1H-pyridin-2-ylidene)malononitrile (4d). Yield 75%; m.p. 200–202 °C; Anal. Calcd. for $\text{C}_{13}\text{H}_6\text{N}_4\text{S}$ (250.28): C, 62.93; H, 2.42; N, 22.39; S, 12.81%. Found: C, 63.06; H, 2.54;

N, 22.54; S, 12.98%; IR (KBr, cm^{-1}): 3,189 (NH), 2,230, 2,210 (3CN); $^1\text{H-NMR}$: δ , ppm = 7.04 (1H, d, $J = 8.0$, H-5), 7.14 (1H, t, $J = 4.0$, thienyl H-4'), 7.66–7.68 (2H, m, H-4, thienyl H-3'), 7.76 (1H, d, $J = 4.0$, thienyl H-5'), 8.06 (1H, br. s, NH, D_2O exchangeable); MS: m/z (%) 250 (M^+ , 100), 223 (20), 185 (30), 158 (15), 141 (20), 114 (25), 82 (10), 69 (15).

3.4. Synthesis of 4,7-diamino-3,6-di(thiophene-2-carbonyl)quinoline-8-carbonitrile (7).

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and enaminone **2d** (0.01 mol) in AcOH (10 cm) and 0.2 gm of NH_4OAc , was kept at reflux temperature for 3 hrs. The mixture was cooled and then poured onto ice-water. The solid so formed was collected by filtration and recrystallized from EtOH to give yellow crystals; Yield 88%; m.p. 330–332 °C; Anal. Calcd. for $\text{C}_{20}\text{H}_{12}\text{N}_4\text{O}_2\text{S}_2$ (404): C, 59.40; H, 2.97; N, 13.86; O, 7.92; S, 15.84%. Found: C, 59.50; H, 2.78; N, 13.96; O, 7.87; S, 15.89%.; $^1\text{H-NMR}$: δ , ppm = 7.05 (br. s, 2H, NH_2), 7.27 (t, $J = 4.0$, 1H, thienyl H-4'), 7.31 (t, $J = 4.0$, 1H, thienyl H-4''), 7.47 (s, 1H, H-5), 7.79 (d, 1H, $J = 3.2$, thienyl H-3'), 7.85 (d, 3H, $J = 3.2$, thienyl H-3'' & NH_2), 7.93 (d, 1H, $J = 5.2$, H-5'), 8.17 (d, 1H, $J = 5.2$, H-5''), 8.98 (s, 1H, H-2); $^{13}\text{C-NMR}$: δ , ppm = 128.9, 154.0 (2C), 184.7 (2 C=O), 77.1, 98.3, 103.9, 115.85, 118.0, 129.2, 131.6, 134.0, 135.7, 136.1, 140.6, 143.67, 156.1, 157.1, 160.4, 162.0; MS: m/z (%) 404 (M^+ , 100), 373 (10), 358 (5), 319 (20), 187 (5), 11 (20).

3.5. General procedure for the synthesis of compounds 9a,b

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and enaminone **8a,b** (0.01 mol) in EtOH (10 mL) as a solvent was treated with piperidine (5 drops). The reaction mixture was refluxed for 4 hr. The mixture was cooled and then poured onto ice-water. The solid so formed was collected by filtration and recrystallized from EtOH to give yellow crystals.

6-Amino-2-dicyanomethylene-4-phenyl-2,3-dihydro-pyridine-3,5-dicarbonitrile (9a). Yield 82%; m.p. 195–197 °C; Anal. Calcd. for $\text{C}_{16}\text{H}_8\text{N}_6$ (284.28): C, 67.60; H, 2.84; N, 29.56%. Found: C, 67.43; H, 2.61; N, 29.33%; IR (KBr, cm^{-1}): 3,467, 3,323 (NH_2), 3,222 (NH), 2,314, 2,219 (4CN); $^1\text{H-NMR}$: δ , ppm = 7.52–7.61 (7H, m, Ar-H, NH_2 , D_2O exchangeable), 8.19 (1H, br. s, NH, D_2O exchangeable); $^{13}\text{C-NMR}$: δ , ppm = 160.35, 158.81, 158.71, 133.82, 130.47, 128.76 (2C), 128.67, 128.36 (2C), 116.10, 114.60, 113.5, 95.29, 89.17; MS: m/z (%) 284 (M^+ , 100), 257 (25), 219 (10), 165 (25), 127 (10), 77 (5).

2-[6-Amino-3-aminoethynyl-5-cyano-4-(4-methoxy-phenyl)-1H-pyridin-2-ylidene]malononitrile (9b). Yield 82%; m.p. 248–250 °C; Anal. Calcd. for $\text{C}_{17}\text{H}_{10}\text{N}_6\text{O}$ (314.31): C, 64.96; H, 3.21; N, 26.74%. Found: C, 65.01; H, 3.22; N, 26.44%; IR (KBr, cm^{-1}): 3,423, 3,327 (NH_2), 3,212 (NH), 2,187, 2,150 (3CN); $^1\text{H-NMR}$: δ , ppm = 3.82 (s, 3H, OCH_3), 6.86 (br, 2H, NH_2 , D_2O exchangeable), 7.04 (2H, d, $J = 8.0$, H-3',5'), 7.35 (2H, d, $J = 8.0$, H-2',6'), 8.22 (1H, br. s, NH, D_2O exchangeable); $^{13}\text{C-NMR}$: δ , ppm = 162.95, 160.23, 159.47, 158.97, 133.45, 130.19 (2C), 127.80, 121.39, 117.24, 116.92, 113.82 (2C), 85.26, 80.48, 55.31; MS: m/z (%) 284 (M^+ , 100), 257 (25), 219 (10), 165 (25), 127 (10), 77 (5).

3.6. Synthesis of 3,5-Diaminobiphenyl-2,4,6-tricarbonitrile (10)

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and benzylidene-malononitrile (**8**, 0.01 mol) in AcOH (10 cm) and 0.2 gm of NH₄OAc, was kept under reflux temperature for 3 hr. The mixture was cooled and then poured onto ice-water. The solid so formed was collected by filtration and recrystallized from EtOH to give yellow crystals; yield 80%; m.p. 290–292 °C; Anal. Calcd. for C₁₅H₉N₅ (259.27): C, 69.49; H, 3.50; N, 27.01%. Found: C, 69.62; H, 3.34; N, 27.17%; IR (KBr, cm⁻¹): 3,371, 3,305 (NH₂), 3,265, 3,213 (NH₂), 2,218 (3CN); ¹H NMR: δ, ppm = 4.51 (br. s, 4H, 2NH₂, D₂O exchangeable), 7.41–7.44 (2H, m, H-3',5'), 7.50–7.53 (3H, m, H-2',4',6'); ¹³C NMR: δ, ppm = 160.92 (2C), 157.07, 135.08, 129.92, 128.49 (2C), 128.21 (2C), 115.61 (2C), 85.65, 81.06, 75.95, 66.31; MS: *m/z* (%) 259 (M⁺, 100), 234 (20), 205 (15), 165 (20), 127 (10), 77 (50).

3.7. Synthesis of 2-(4-Amino-7-cyano-3,9-diphenylpyrido[1,2-a]pyrimidin-6-ylidene)-malononitrile (14)

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and 2-phenyl-3-piperidin-1-yl-acrylonitrile (**11**, 0.01 mol) in dioxane (10 mL) was kept under reflux temperature for 3–4 hrs. The mixture was cooled and then poured onto ice-water. The solid so formed was collected by filtration and recrystallized from AcOH to give yellow crystals; yield 85%; m.p. 270–272 °C; Anal. Calcd. for C₂₄H₁₄N₆ (386.42): C, 64.60; H, 3.65; N, 21.75%. Found: C, 64.48; H, 3.55; N, 21.90%; IR (KBr, cm⁻¹): 3,383, 3,186 (NH₂), 2,237, 2,196 (3CN); ¹H-NMR: δ, ppm = 6.82 (2H, br. s, NH₂, D₂O exchangeable), 7.24–7.52 (m, 12H, Ar-H); MS: *m/z* (%) 386 (M⁺, 10), 379 (40), 337 (70), 319 (100), 278 (95), 259 (35), 251 (30), 210 (20), 179 (20), 155 (10), 140 (25), 115 (15), 140 (25), 115 (10), 77 (15), 59 (20).

3.8. Synthesis of 2-amino-4-(dimethylamino)buta-1,3-diene-1,1,3-tricarbonitrile (16)

A mixture of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**1**, 1.32 g, 0.01 mol) and DMFDMA (1.19 g, 0.01 mol) in dioxane (10 mL) was stirred for 3–4 hrs. The mixture then poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH to give yellow crystals; yield 90 % m.p. 189–190 °C. Anal. Calcd. for C₉H₉N₅ (187.2): C, 57.74; H, 4.85; N, 37.41%. Found: C, 57.61; H, 4.57; N, 37.19%; IR (KBr, cm⁻¹): 3,344, 3,221 (NH₂), 2,208, 2,193 (3CN); ¹H NMR (400 MHz, DMSO-d₆): δ, ppm = 2.50 (3H, s, CH₃), 2.57 (3H, s, CH₃), 7.19 (br. s, 2H, NH₂, D₂O exchangeable), 8.54 (1H, s, olefinic CH); MS: *m/z* (%) 187 (M⁺, 100), 172 (30), 159 (35), 144 (25), 122 (60), 117 (20), 97 (15), 95 (15), 81 (20), 67 (20), 57 (30).

3.9. Synthesis of 4,6-diamino-2H-pyrazolo[3,4-b]pyridine-5-carboxamide hydrazone (17)

A mixture of **13** (1.87 g, 0.01 mol) and hydrazine monohydrate (1.00 g, 0.02 mol) in EtOH (20 mL) was refluxed for 3–4. The mixture then poured onto ice-water. The solid so formed was collected by filtration and recrystallized from EtOH to give a faint yellow product; yield 87 %; m.p. 210–212 °C; Anal. Calcd. for C₇H₁₀N₈ (206.21): C, 40.77; H, 4.89; N, 54.34%. Found: C, 40.58; H, 4.65; N, 54.05%; IR (KBr, cm⁻¹): complicated signals from 3,402 to 3,156 for (NH) and (4NH₂); ¹H-NMR: δ, ppm = 5.34 (2H, br. s, NH₂, D₂O exchangeable), 5.97 (2H, br. s, NH₂, D₂O exchangeable), 7.10 (2H, br. s, NH₂, D₂O exchangeable), 7.29 (2H, br. s, NH₂, D₂O exchangeable), 8.00 (1H, s, H-3), 8.82 (1H,

br. s, NH, D₂O exchangeable); MS: *m/z* (%) 106 (M⁺, 100), 190 (95), 174 (100), 159 (75), 145 (40), 109 (35), 92 (40), 77 (60), 67 (100).

4. Conclusions

We could successfully utilize **1** as precursor to a variety of polyfunctionally substituted aminoaromatics that seem of value as potential precursors to dyes and pharmaceuticals.

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Sample Availability: Samples of the compounds **3a**, **4a-d**, **7**, **9a-b**, **10**, **14** and **17** are available from the authors.