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A Facile and Efficient Synthesis of Bisazine Derivatives

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ABSTRACT: *1,4-Phenylenediamine was condensed with acetylacetone to give 4,4′-[1,4-phenylenedi-(nitrilo)]dipenten-2-ol* **1**. *Compound* **1** *reacted with different organic reagent to give bisazine derivatives*. © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:293–299, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20017

INTRODUCTION

Much attention has been directed toward the synthesis of polyfunctionally substituted azines due to their biological and pharmaceutical activity. For example, pyridines show anti-HIV activity [1], anticonvulsant activity [2], act as antihistaminic agents [3], and help in cardiovascular disorder treatment [4,5]. Antihypertensive activity among the Hantzsch type dihydropyridines depends mainly on the nature of 4-substitution [6], while pyrimidines have attracted considerable interest in recent time because of their promising activities as calcium channel blockers, α-1a-antagonists [7,8], anticancer activity [9], antituberculosis agents [10], and KDR kinase inhibitors [11]. In last few years we were involved in a program aimed at designing simple and efficient approaches to polyfunctionally substituted heterocycles utilizing inexpensive, readily obtainable starting materials. During this phase of our research syntheses of azines were developed [12–18]. We reported here on the synthesis of pyridines and pyrimidines using phenylenediamine as starting material.

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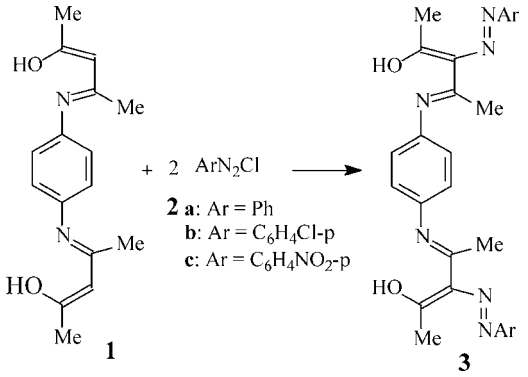
RESULTS AND DISCUSSION

1,4-Phenylenediamine reacted readily under reflux, without solvent or even in ethanol with acetylacetone to afford the enol form dipent-2-en-2-ol derivative **1**. The latter compound, **1**, readily coupled in ethanolic sodium acetate, with two moles of arene diazonium salts **2a–c** to give a product which was established as having structures **3a–c**. The three possible hydrazone forms were ruled out based on the IR spectrum which reveals the absence of carbonyl group. Coupling at benzene ring which may have occurred was also ruled out based on ^{1}H NMR which shows the absence of ethylenic proton and presence of four protons of 1,4-substituted benzene, in addition to other aromatic protons (cf. experimental part). The mass spectrum of **3a** showed *m/z* 480 [M^+], while that of **3b** shows *m/z* 548 (M^+), 550 (M + 2), 552 (M + 4). IR reveals the presence of OH at 3447–3448 cm^{-1}. Moreover, both ^{1}H and ^{13}C NMR were agreeable with the obtainable structure. Similarly, compounds **3b,c** were established.

The reactivity of compound **3** was investigated toward different active methylene reagents. Thus, azo derivatives **3a,b** when heated under reflux in ethanolic triethylamine with active methylene compounds **4a–c** afforded **6a–f**. These compounds, **6a–f** were assumed to proceed via tautomerization of compound **3** under reaction condition to give the keto form which was condensed with the active methylene group in compounds **4a–c** to afford the nonisolated intermediate **5**, which was cyclized through the addition of NH to cyano group or elimination of ethanol to give the final isolated products **6a–f**. The reaction products were established based on elemental analysis and spectral data. For example



SCHEME 1

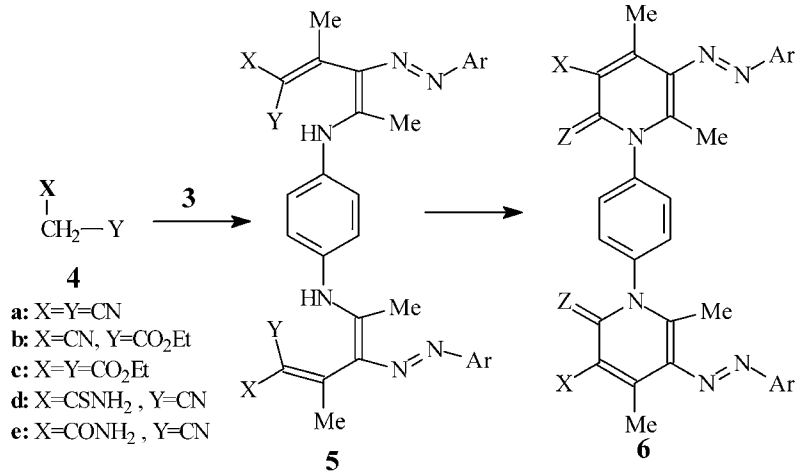
mass spectrum of **6a** shows *m/z* 576 (M^+). Moreover, IR spectrum reveals the presence of cyano group at 2212 cm^{-1}. In addition ^1H and ^{13}C NMR agree with the assumed structure. Similarly, compounds **6b–f** were established.

Active methylene nitriles **4a–e** reacted readily with compound **1** in acetic anhydride to give the bisazine derivatives **8a–c**. These products were believed to be formed through condensation of active methylene reagents **4a–e** with keto form of compound **1** to give the intermediate **7**, which cyclized to give the final isolated products **8a–c**. Both of **4a** and **4e** afforded the same reaction product **8a**. This may be through condensation followed by cyclization and transformation of imine to oxo derivative in acid medium in case of **4a** or elimination of ammonia in case of **4e**. Similarly, **4b** and **4c** furnished **8b**. Furthermore, compound **4a** reacted in ethanolic triethylamine with compound **1** to isolate the addition product **9**. This product was cyclized when heated in acetic anhydride to give the bisazine derivative **8a**.

Compound **1** reacted with a mixture of trichloroacetonitrile and malononitrile to give the bispyridine derivative **12**. At first, both of trichloroacetonitrile and compound **1** in dioxane were heated under reflux for 15 min, then malononitrile was added in situ. The reaction mixture was heated under reflux to give the final isolated product **12** through the nonisolated intermediate **10** and **11**.

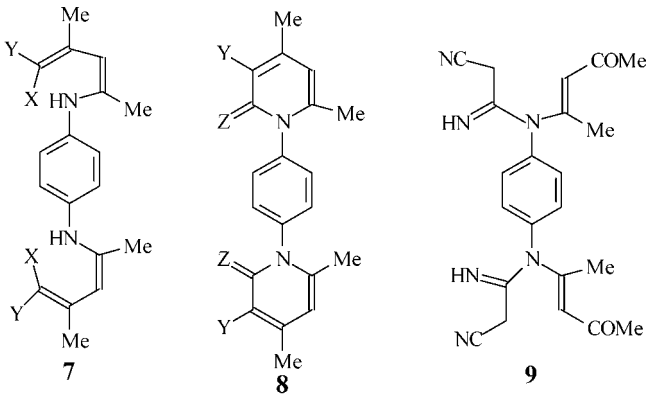
Similar pyridines could also be prepared via treating compound **1** with arylidenemalononitrile derivatives **13a–c** in pyridine to give the pyridine derivatives **16a–c**. The reaction products were believed to be formed through Michael addition product **14** followed by cyclization to give the non isolated pyran derivative **15**, which rearranged under reaction condition to give the final isolated product **16**. Isolation of pyran derivatives **15** can take place through treating **1** with ylidenemalononitrile derivatives **13a–c** in dioxane/triethylamine. Transformation of pyran **15** to the bispyridine derivatives **16** took place by heating in a mixture of glacial acetic acid/ammonium acetate mixture similar to that reported earlier [14,19–21]. These reaction products **16a–c** were established based on IR which reveals the presence of cyano group and amide carbonyl at expected regions.

Moreover, bispyrimidine derivatives **18a,b** could be obtained through treating compound **1** with urea or thiourea. This was believed to be formed through the addition of nucleophilic amino nitrogen to the electrophilic carbonyl carbon followed by water elimination to give the condensation product **17**,



5,6 **a**: Ar=Ph, Z=NH, X=CN, **b**: Ar=Ph, Z=NH, X=CO_2Et, **c**: Ar=Ph, Z=O, X=CO_2Et
d: Ar=C_6H_4Cl-p, Z=NH, X=CN, **e**: Ar=C_6H_4Cl-p, Z=NH, X=CO_2Et, **f**: Ar=C_6H_4Cl-p, Z=O, X=CO_2Et

SCHEME 2



7, 8 a: Y=CN, Z=O, **b:** Y=CO_2Et, Z=O, **c:** Y= CN, Z=S

SCHEME 3

which readily cyclized under reaction condition to give the final isolated product **18** through ammonia elimination.

EXPERIMENTAL

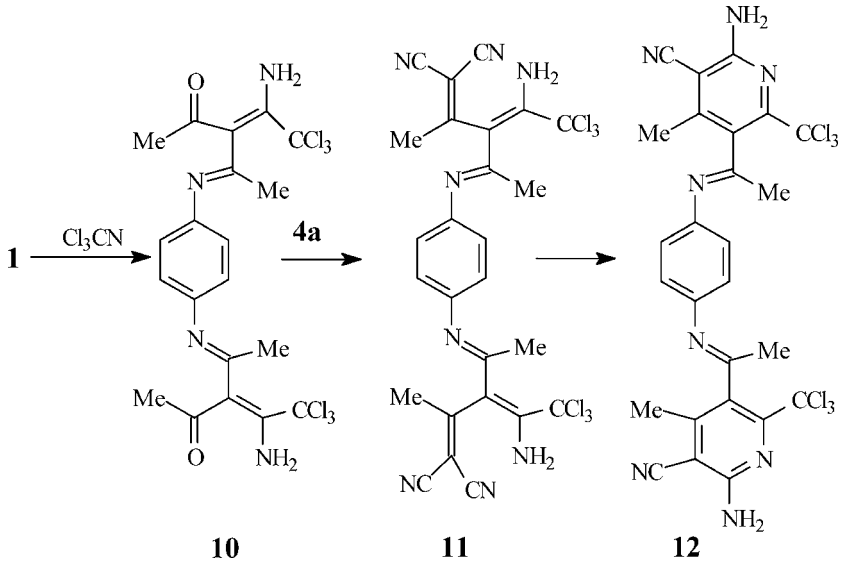
All melting points are uncorrected. IR spectra were recorded in KBr with an IR spectrophotometer Shimadzu 408. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian EM-390 MHz spectrometer using TMS as internal reference and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt.

General Method for the Preparation of **3a–c**

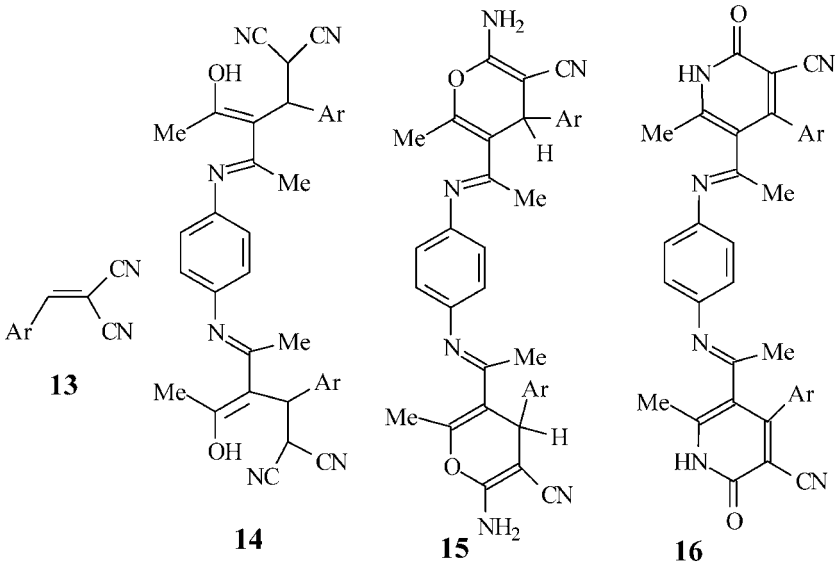
A solution of the diazonium salts (prepared from 0.01 mol of aromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was added to compound **1** (0.01 mol) in ethanol (50 ml) and sodium acetate (5.0 g). The reaction mixture was stirred at room temperature for 15 min. The solid product, so formed, was collected by filtration and recrystallized from ethanol.

*4,4′-[1,4-Phenylene(dinitrilo)-3,3′-(phenylazo)]-dipent-2-en-2-ol (***3a***).* Compound **3a** was obtained as orange crystals (81%) from ethanol; mp 176°C; IR: 3447 (OH), 1654 (C=N), 1499 (—N=N—); ^{1}H NMR: δ 12.46 (s, 2H, 2OH), 7.80 (d, 4H, 1,4-substituted benzene, $J = 7.53$), 7.78–6.46 (m, 10H, two phenyl groups), 2.20, 2.16, 2.15, 2.02 ppm (s, 12H, 4Me). ^{13}C NMR δ 160.76, 144.18, 130.53, 128.29, 127.60, 125.59, 122.90, 119.88, 116.82, 115.50, 98.71 (aromatic, imine, and enolic carbons), 29.23, 25.79, 21.00, 20.45 ppm (4Me). MS: *m/z* 480 (M^+); Anal. Requires for $C_{28}H_{28}N_6O_2$ (480.62): C, 69.96; H, 5.88; N, 17.48. Found: C, 69.90; H, 6.00; N, 17.68.

*4,4′-[1,4-Phenylene(dinitrilo)-3,3′-(4-chlorophenylazo)]-dipent-2-en-2-ol (***3b***).* Compound **3b** was obtained as orange crystals (78%) from ethanol; mp 166.6°C; IR: 3448 (OH), 1654 (C=N), 1498 (—N=N—); ^{1}H NMR: δ 12.46 (s, 2H, 2OH), 7.61 (d, 4H, 1,4-substituted benzene, $J = 7.67$) 7.59–7.19 (m, 8H, two aryl groups), 2.50, 2.43, 2.34, 2.02 ppm (s, 12H, 4Me). MS: *m/z* 548 (M^+), 550 (M + 2), 552 (M + 4); Anal.



SCHEME 4

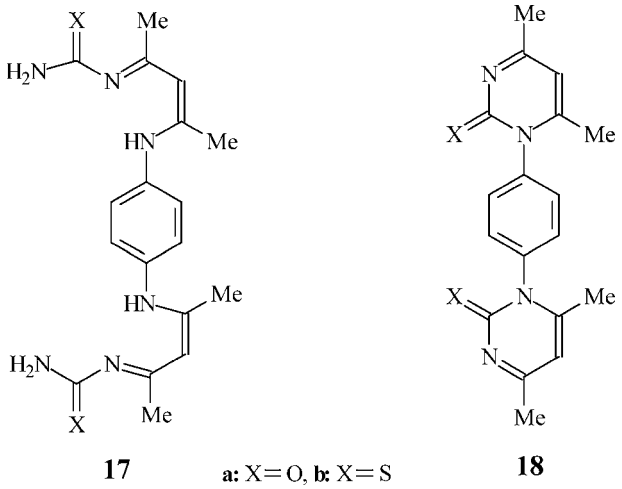


13-16 **a:** Ar=Ph, **b:** Ar=C_6H_4Cl-p, **c:** Ar=$C_6H_4NO_2$-p

SCHEME 5

Requires for $C_{28}H_{26}N_6Cl_2O_2$ (549.50): C, 61.19; H, 4.77; N, 15.29. Found: C, 61.28; H, 4.92; N, 15.63.

*4,4′-[1,4-Phenylene(dinitrilo)-3,3′-(4-nitrophenylazo)]-dipent-2-en-2-ol (***3c***).* Compound **3c** was obtained as orange crystals (85%) from ethanol; mp 154°C; IR: 3448 (OH), 1654 (C=N), 1569 (—NO_2), 1499 (—N=N—); ^{1}H NMR: δ 12.46 (s, 2H, 2OH), 7.89 (d, 4H, 1,4-substituted benzene, J = 7.65) 8.25–7.81, 7.77–6.53 (m, 8H, two aryl groups), 2.28, 2.19, 2.11, 2.02 ppm (s, 12H, 4Me). ^{13}C NMR δ 196.20, 160.775, 136.76, 136.343, 136.33, 130.90, 130.32, 125.82, 126.39, 125.67, 125.599, 125.16, 124.33, 120.19, 116.55, 115.08, 98.71 (aromatic, imine, and enolic carbons), 29.96, 29.71, 20.44, 20.10 (4Me). MS: *m/z* 570 (M^+); Anal. Requires for $C_{28}H_{26}N_8O_6$ (570.62): C, 58.93; H, 4.60; N, 19.64. Found: C, 59.01; H, 4.50; N, 19.42.



SCHEME 6

General Method for the Preparation of **6a–f**

To a solution of **3a** or **3b** (0.01 mol) in ethanol (25 ml), malononitrile **4a**, ethyl cyanoacetate **4b**, or diethyl malonate **4c** (0.01 mol), and few drops of triethylamine were added. The reaction mixture was heated under reflux for 3 h. The reaction product was treated with ice-cold water and the solid product so formed was filtered and crystallized from proper solvent.

*1,1′-(1,4-Phenylene)bis(2-imino-4,6-dimethyl-5-phenylazo-1,2-dihydropyridine-3-carbonitrile) (***6a***).* Compound **6a** was obtained as pale brown crystals (79%) from ethanol; mp 295.5°C; IR: 3369 (NH), 2212 (CN), 1670 (C=N); ^{1}H NMR: δ 7.80–7.03 (m, 14H, Ar), 6.95 (br, 2H, 2NH), 2.26, 2.20, 2.16, 2.04 ppm (s, 12H, 4Me). MS: *m/z* 576 (M^+); Anal. Requires for $C_{34}H_{28}N_{10}$ (576.72): C, 70.80; H, 4.90; N, 24.29. Found: C, 70.98; H, 4.83; N, 24.57.

*1,1′-(1,4-Phenylene)bis(ethyl 2-imino-4,6-dimethyl-5-phenylazo-1,2-dihydropyridine-3-oate) (***6b***).* Compound **6b** was obtained as pale orange crystals (78%) from ethanol; mp 78°C; IR: 3369 (NH), 1735

(CO), 1671 (C=N); ^{1}H NMR: δ 7.81–7.07 (m, 14H, Ar), 6.94 (br, 2H, 2NH), 4.20 (q, 4H, $2CH_2$), 2.26, 2.20, 2.16, 2.04 (s, 12H, 4Me), 1.94, 1.91 ppm (t, 6H, 2Me). ^{13}C NMR δ: 197.76, 161.98, 153.11, 148.01, 146.24, 142.76, 134.35, 130.36, 127.59, 123.12, 117.71, 117.31, 116.97, 115.08, 96.89 (carbonyl, aromatic, and imine carbons), 61.88, 29.72, 20.44, 14.88 ppm (aliphatic carbons). Anal. Requires for $C_{38}H_{38}N_8O_4$ (670.84): C, 68.03; H, 5.72; N, 16.70. Found: C, 68.42; H, 5.61; N, 16.71.

*1,1′-(1,4-Phenylene)bis(ethyl 2-oxo-4,6-dimethyl-5-phenylazo-1,2-dihydropyridine-3-oate) (***6c***).* Compound **6c** was obtained as deep yellow crystals (76%) from ethanol; mp 155°C; IR: 1735 (CO-ester), 1654 (CO-amide); ^{1}H NMR: δ 7.62–6.83 (m, 14H, Ar), 4.21 (q, 4H, $2CH_2$), 2.50, 2.48, 2.42, 2.34 (s, 12H, 4Me), 1.94, 1.98 ppm (t, 6H, $2CH_3$). ^{13}C NMR δ: 196.21, 161.97, 153.10, 146.23, 142.75, 136.42, 131.52, 130.37, 125.87, 123.11, 117.72, 115.09, 98.72 (carbonyl, aromatic, and imine carbons), 61.71, 29.71, 20.44, 14.94 (aliphatic carbons). Anal. Requires for $C_{38}H_{36}N_6O_6$ (672.80): C, 67.83; H, 5.40; N, 12.49. Found: C, 67.52; H, 5.39; N, 12.78.

*1,1′-(1,4-Phenylene)bis[2-imino-4,6-dimethyl-5-(p-chlorophenylazo)-1,2-dihydropyridine-3-carbonitrile] (***6d***).* Compound **6d** was obtained as brown crystals (69%) from ethanol; mp 142.7°C; IR: 3423 (NH), 2188 (CN); ^{1}H NMR: δ 7.98–7.13 (m, 12H, Ar), 6.85 (br, 2H, 2NH), 2.36, 2.29, 2.26, 2.14 ppm (s, 12H, 4Me). Anal. Requires for $C_{34}H_{26}Cl_2N_{10}$ (645.60): C, 63.24; H, 4.06; N, 21.70. Found: C, 63.35; H, 4.38; N, 21.37.

*1,1′-(1,4-Phenylene)bis[ethyl 2-imino-4,6-dimethyl-5-(p-chlorophenylazo)-1,2-dihydropyridine-3-oate) (***6e***).* Compound **6e** was obtained as light bright brown crystals (82%) from ethanol; mp 144°C; IR: 3367 (NH), 1735 (CO), 1671 (C=N); ^{1}H NMR: δ 7.82–7.17 (m, 12H, Ar), 6.92 (br, 2H, 2NH), 4.20 (q, 4H, $2CH_2$), 2.26, 2.20, 2.16, 2.04 (s, 12H, 4Me), 1.94, 1.91 ppm (t, 6H, $2CH_3$). Anal. Requires for $C_{38}H_{36}N_8Cl_2O_4$ (739.72): C, 61.69; H, 4.91; N, 15.15. Found: C, 61.49; H, 5.01; N, 15.20.

*1,1′-(1,4-Phenylene)bis[ethyl 2-oxo-4,6-dimethyl-5-(p-chlorophenylazo)-1,2-dihydropyridine-3-oate] (***6f***).* Compound **6f** was obtained as bright brown crystals (80%) from ethanol; mp 168°C; IR: 1734 (CO-ester), 1656 (CO-amide); ^{1}H NMR: δ 7.64–6.80 (m, 12H, Ar), 4.20 (q, 4H, $2CH_2$), 2.50, 2.48, 2.42, 2.34 (s, 12H, 4Me), 1.94, 1.98 ppm (t, 6H, $2CH_3$). Anal. Requires for $C_{38}H_{34}N_6Cl_2O_6$ (741.68): C, 61.53; H, 4.63; N, 11.33. Found: C, 61.52; H, 4.38; N, 11.77.

General Method for the Preparation of **8a,b**

To a solution of **1** (0.01 mol) in acetic anhydride (20 ml), **4a–e** (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h. The acetic anhydride was evaporated under vacuum and the solid product so formed was collected by filtration, washed with small amount of sodium bicarbonate solution, and crystallized from proper solvent.

*1,1′-(1,4-Phenylene)bis(2-oxo-4,6-dimethyl-1,2-dihydropyridine-3-carbonitrile) (***8a***).* Compound **8a** was obtained as yellow crystals (74%) from ethanol; mp 190°C; IR: 2210 (CN), 1660 (CO-amide); ^{1}H NMR: δ 8.23 (s, 2H, pyridime-H), 7.22 (s, 4H, Ar), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{22}H_{18}N_4O_2$ (370.44): C, 71.32; H, 4.90; N, 15.12. Found: C, 71.53; H, 4.56; N, 15.07.

*1,1′-(1,4-Phenylene)bis(ethyl 2-oxo-4,6-dimethyl-1,2-dihydropyridine-3-oate) (***8b***).* Compound **8b** was obtained as bright white crystals (79%) from ethanol; mp 172°C; IR: 1735 (CO-ester), 1658 (CO-amide); ^{1}H NMR: δ 8.23 (s, 2H, pyridime-H), 7.33 (s, 4H, Ar), 4.23 (q, 4H, $2CH_2$), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me), 1.93, 1.91 (t, 6H, 2Me). Anal. Requires for $C_{26}H_{28}N_2O_6$ (464.56): C, 67.21; H, 6.08; N, 6.03. Found: C, 67.31; H, 6.18; N, 6.32.

*1,1′-(1,4-Phenylene)bis(ethyl 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-oate) (***8c***).* Compound **8c** was obtained as yellow crystals (76%) from ethanol; mp 211°C; IR: 2214 (CN), 1737 (CO); ^{1}H NMR: δ 8.23 (s, 2H, pyridime-H), 7.23 (s, 4H, Ar), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me), 1.93. Anal. Requires for $C_{22}H_{18}N_4S_2$ (402.56): C, 65.63; H, 4.51; N, 13.92. Found: C, 65.53; H, 4.56; N, 13.70.

*N,N-1,4-(Phenylene)bis(2-cyano-N-1-methyl-3-oxobut-1-en-1-yl)ethanimidamide (***9***).* To the solution of **1** (0.01 mol) in ethanol (20 ml), **4a** (0.01 mol) and few drops of triethylamine were added. The reaction mixture was heated under reflux for 3 h. The solid product obtained after cooling was collected by filtration and crystallized from ethanol.

Compound **9** was obtained as pale brown crystals (77%) from ethanol; mp 168°C; IR: 2205 (CN), 1713 (CO), 1652 (C=N); ^{1}H NMR: δ 7.37 (s, 4H, Ar), 6.85 (s, 2H, 2NH), 5.58 (s, 2H, 2CH), 3.37 (s, 4H, $2CH_2$), 2.50, 2.06 (s, 12H, 4Me). Anal. Requires for $C_{22}H_{24}N_6O_2$ (404.52): C, 65.31; H, 5.99; N, 20.78. Found: C, 65.53; H, 5.65; N, 21.07.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidene]}-bis(2-amino-6-hydroxy-4-methylpyridine-3-carbonitrile) (***12***).* To the solution of **1** (0.01 mol) in dioxane

(20 ml), trichloroacetonitrile (0.01 mol) and few drops of piperidine were added. The reaction mixture was heated under reflux for 15 min, then malononitrile (0.01 mol) was added to the reaction mixture and further heated under reflux for further 3 h. Cool the reaction product after evaporation of solvent under vacuum. The solid product so formed was collected by filtration and crystallized from dioxane-ethanol mixture (1:1).

Compound **12** was obtained as pale brown crystals (82%); mp 134°C; IR: 3409, 3386 (NH_2), 2218 (CN); ^{1}H NMR: δ 8.23 (br, 4H, $2NH_2$), 7.32 (s, 4H, Ar), 2.51, 2.50, 2.33, 2.26 (s, 12H, 4Me). Anal. Requires for $C_{26}H_{20}N_8Cl_6$ (657.24): C, 47.51; H, 3.07; N, 17.05. Found: C, 47.48; H, 3.15; N, 17.31.

General Method for Preparation of **15a–c**

A mixture of **1** (0.01 mol), arylidenemalononitrile **13a–c** (0.01 mol), dioxane (20 ml), and triethyl amine (5 drops) was heated under reflux for 6 h. Dioxane was evaporated under vacuum and the solid product so formed was collected by filtration and crystallized from proper solvent.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidene]}-bis(2-amino-3-cyano-4H-6-methyl-4-phenylpyran) (***15a***).* Compound **15a** was obtained as yellow crystals (74%) from ethyl acetate; mp 182°C; IR: 3409, 3389 (NH_2), 2212, 2210 (2CN); ^{1}H NMR: δ 8.93 (br, 4H, $2NH_2$), 7.84–7.70 (m, 14H, Ar), 5.42 (s, 2H, Pyran-4H), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{32}N_6O_2$ (580.74): C, 74.44; H, 5.56; N, 14.47. Found: C, 74.53; H, 5.36; N, 14.41.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidene]}-bis(2-amino-3-cyano-4-(4-chlorophenyl)-4H-6-methyl-pyran) (***15b***).* Compound **15b** was obtained as yellow crystals (74%) from ethyl acetate; mp 250°C; IR: 3411, 3387 (NH_2), 2212, 2211 (2CN); ^{1}H NMR: δ 8.77 (br, 4H, $2NH_2$), 7.85–7.70 (m, 12H, Ar), 5.42 (s, 2H, Pyran-4H), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{30}N_6Cl_2O_2$ (649.62): C, 66.55; H, 4.66; N, 12.93. Found: C, 66.53; H, 4.86; N, 13.01.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidene]}-bis(2-amino-3-cyano-4H-6-methyl-4-(4-nitrophenyl)-pyran) (***15c***).* Compound **15c** was obtained as yellow crystals (74%) from ethyl acetate; mp 150°C; IR: 3409, 3389 (NH_2), 2212, 2210 (2CN); ^{1}H NMR: δ 8.93 (br, 4H, $2NH_2$), 7.84–7.40 (m, 12H, Ar), 5.42 (s, 2H, Pyran-4H), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{30}N_8O_6$ (670.74): C, 64.46; H, 4.51; N, 16.70. Found: C, 64.53; H, 4.62, N, 16.83.

General Method for the Preparation of **16a–c**

Method A. A mixture of **15** (0.01 mol), glacial acetic acid (15 ml), and ammonium acetate (5 g) was heated under reflux for 3 h. The reaction mixture was neutralized with concentrated sodium bicarbonate solution. The solid product so formed was collected by filtration and crystallized from proper solvent.

Method B. To a solution of **1** (0.01 mol) in pyridine, benzylidene-malononitrile (0.01) was added. The reaction mixture was heated under reflux for 3 h. Pyridine was evaporated under vacuum and the solid product so formed was collected by filtration, wash with cold water, and crystallized from proper solvent.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidenes]}-bis(2-cyano-1,2-dihydro-6-methyl-4-phenylpyridine-2-one) (***16a***).* Compound **16a** was obtained as deep yellow crystals (74%) from ethanol; mp 117°C; IR: 3411, 3407 (NH), 2220, 2218 (2CN), 1665, 1664 (CO); ^{1}H NMR: δ 8.88 (br, 2H, 2NH), 7.82–7.30 (m, 14H, Ar), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{28}N_6O_2$ (576.7): C, 74.97; H, 4.90; N, 14.57. Found: C, 74.83; H, 4.81; N, 14.41.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidenes]}-bis(2-cyano-4-(4-chlorophenyl)-1,2-dihydro-6-methyl-pyridine-2-one) (***16b***).* Compound **16b** was obtained as yellow crystals (74%) from ethanol; mp 242°C; IR: 3411, 3409 (NH), 2221, 2219 (2CN), 1665, 1664 (CO); ^{1}H NMR: δ 8.87 (br, 2H, 2NH), 7.74–7.80 (m, 12H, Ar), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{26}N_6Cl_2O_2$ (645.58): C, 66.97; H, 4.06; N, 13.02. Found: C, 67.01; H, 4.16; N, 13.31.

*5,5′-{1,4-Phenylenebis[nitriloeth-1-yl-1-ylidenes]}-bis(2-cyano-1,2-dihydro-6-methyl-4-(4-nitrophenyl)-pyridine-2-one) (***16c***).* Compound **16c** was obtained as yellow crystals (74%) from ethanol; mp 265°C; IR: 3411, 3407 (NH), 2222, 2220 (2CN), 1666, 1664 (CO); ^{1}H NMR: δ 8.86 (br, 2H, 2NH), 7.74–7.80 (m, 12H, Ar), 2.54, 2.43, 2.32, 2.24 (s, 12H, 4Me). Anal. Requires for $C_{36}H_{26}N_8O_6$ (666.70): C, 64.85; H, 3.93; N, 16.81. Found: C, 64.65; H, 4.06; N, 16.48.

General Method for the Preparation of **18a,b**

A mixture of compound **1** and urea (0.01 mol) or thiourea (0.01 mol) was mixed with few drops conc. HCl and then heated at 160°C for 1 h. The obtained solid product was treated with ice-cold water after cooling and then collected the formed solid product by filtration and crystallized from proper solvent.

Compound **18a** was obtained as yellow crystals (92%) from ethanol; mp 275°C; IR: 1664 (CO); ^{1}H NMR: δ 6.97 (s, 4H, Ar), 5.99–6.00 (m, 2H, pyrimidine-H), 2.43, 2.42, 2.41, 2.39 (s, 12H, 4Me). ^{13}C NMR δ 163.34, 157.16, 155.68, 137.80, 127.45, 106.34 (aromatic, amide carbonyl, and pyrimidine ring carbons), 22.00, 21.01, 15.36, 14.96 ppm (4Me). Anal. Requires for $C_{18}H_{18}N_4O_2$ (322.40): C, 67.05; H, 5.63; N, 17.38. Found: C, 67.15; H, 5.60; N, 17.48.

Compound **18b** was obtained as orange crystals (91%) from ethanol; mp 265°C; IR: 1564 (C=N); ^{1}H NMR: δ 7.32 (s, 4H, Ar), 6.31–6.29 (m, 2H, pyrimidine-H), 2.58, 2.59, 2.40, 2.39 (s, 12H, 4Me).^{13}C NMR δ 178.73, 158.69, 155.34, 141.52, 128.37, 109.33 (aromatic, thioxo, and pyrimidine ring carbons), 20.01, 20.00, 18.36, 18.23 ppm (4Me). Anal. Requires for $C_{18}H_{18}N_4S_2$ (354.52): C, 60.97; H, 5.12; N, 15.80; S, 18.08. Found: C, 61.03; H, 5.09; N, 18.38; S, 18.42.

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