Unambiguous structural assignment of monoanils of 3,4-pyridinediamine via regioselective synthesis

P. K. Dubey,* K. S. Chowdary, B. Ramesh, and P. V. V. Prasada Reddy

Dept. of Chemistry, College of Engg., J N T University, Kukatpally, Hyderabad, (A.P) -500 085, India
E-mail: pvvpr@rediffmail.com

Abstract

Condensation of 3,4-pyridinediamine **1** with aromatic aldehydes results in the selective formation of the regioisomer 4-amino-3-benzylideneamino pyridine **2**, which on reduction with $NaBH_4$ affords 3-benzylamino-4-aminopyridine **4**. The structure of the compound **4** was established by an unambiguous synthesis of another regioisomer 3-amino-4-benzylaminopyridine **5** via another sequence of reactions. Based on the Regiospecific chemical synthesis of **5**, the structures of **2** and **4** were established. The structures of all the new compounds have been confirmed by spectral studies (IR, ^{1}H NMR and Mass spectroscopy).

Keywords: 3,4-Diaminopyridine, aromatic aldehydes, reduction, PTC, Raney nickel, aralkyl chlorides

Introduction

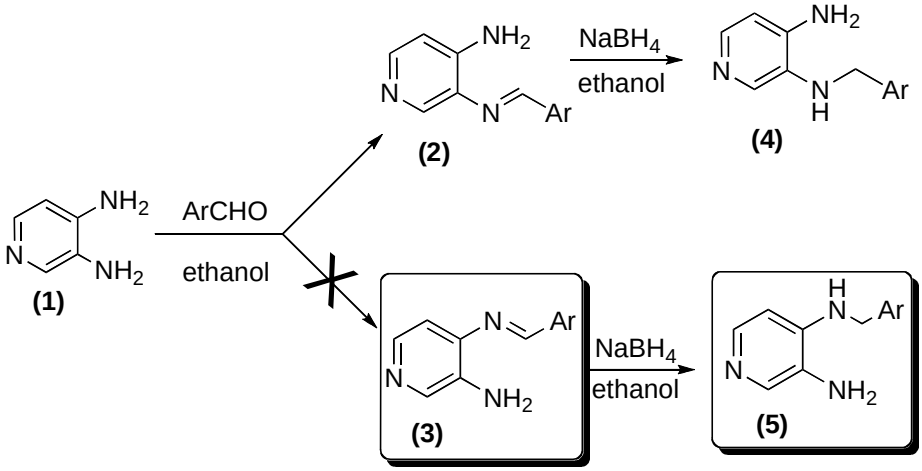
3,4-Diaminopyridine derivatives possess a wide range of biological activities[1-4] such as antiviral[5], rodenticidal[6], antimicrobial[7], cytotoxic[8], anti-osteoporosis and protein kinase C inhibitor[9] activities. The condensation of 2,3-pyridinediamine with carbonyl compounds[10,11] and their derivatives[12-14] has been studied previously. It was reported earlier from these laboratories[15] that the reaction between 2,3-pyridinediamine and aromatic aldehydes results in monoanils, which were assigned 2-amino-3-aryledeneaminopyridine structures. Further, this[16] assignment was confirmed by the single crystal X-ray analysis of the products obtained in these reactions.

In continuation of our earlier work,[17-21] we now wish to report our studies on the condensation of 3,4-pyridinediamines with aromatic aldehydes and the unambiguous structural assignment for the products based purely on chemical methods.

Results and Discussion

The reaction of 3,4-pyridinediamine[22,23] **(1)** with benzaldehyde in ethanol under refluxing conditions, followed by simple processing, yielded a product which was found to be homogeneous on TLC. Its IR, ^{1}H NMR and mass spectral data indicated it to be a monoanil formed by a simple 1:1 condensation of **1** with benzaldehyde. Accordingly this product could be one of the two regioisomers, namely, 4-amino-3-benzylideneaminopyridine **(2)** or 3-amino-4-benzylideneaminopyridine **(3)**. Treatment of this compound with sodium borohydride in methanol and subsequent processing gave another product which was found to be homogeneous on TLC. This product was found to be a dihydro derivative of the monoanil formed by a simple reduction of -C=N- group, based on its spectral data (IR, ^{1}H NMR and mass). Once again, this product could be one of the two isomers namely, 4-amino-3-benzylaminopyridine **(4)** or 3-amino-4-benzylaminopyridine **(5)** based on whether the starting compound is **2** or **3** respectively (Scheme 1).

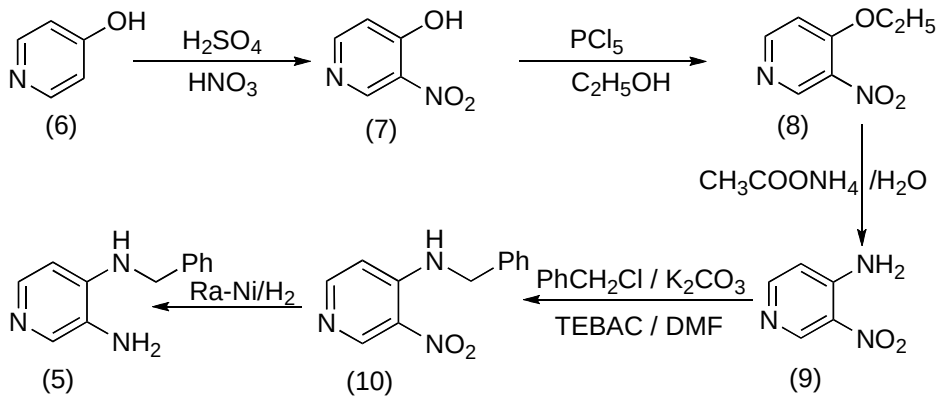
That the final product formed by sodium borohydride reduction of monoanil, is exclusively **4** and not **5** was shown by the unambiguous regiospecific chemical synthesis of **5** and its non-identity with the sample, i.e. **4,** obtained in the **1**→ monoanil → sodium borohydride reduction product route. The unambiguous chemical synthesis of **5** was carried out as given below.



Scheme 1

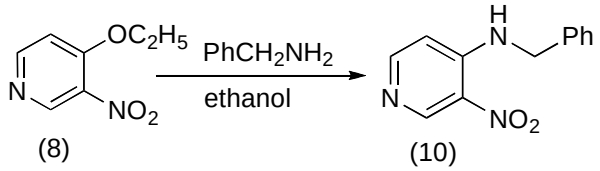
Nitration of commercially available 4-hydroxypyridine[24] **(6)** with a mixture of fuming HNO_3 and H_2SO_4, gave 4-hydroxy-3-nitropyridine **(7)**, which with PCl_5 and then ethanol in a one-pot reaction gave the previously reported[24] 4-ethoxy-3-nitropyridine **(8)**. Treatment of **8** with ammonium acetate gave the well-known[25] 4-amino-3-nitropyridine (**9**) which with benzyl chloride, under phase transfer catalytic (PTC) conditions, in the presence of K_2CO_3 as a base, resulted in the formation[25] of 4-benzylamino-3-nitropyridine (**10**). Reduction of compound **10**

with hydrogen in the presence of Raney-nickel in methanol yielded 3-amino-4-benzylaminopyridine **5**, which was fully characterized by spectral methods (Scheme 2).



Scheme 2

Alternatively, **10** could also be obtained by the reaction of **8** with benzylamine in ethanol under refluxing conditions (Scheme 3).



Scheme 3

The above results can be rationalized on the basis of the fact that the 3-amino group is more nucleophilic than that at C-4 in 3,4-pyridinediamines. Stephane *et al.* also reported[26] that when they treated **1** with acetyl chloride in the presence of dimethylacetamide, acetylation accured at the 3-amino group selectively. Furthermore, Burli *et al.* also reported[27] HBTU-mediated coupling of carboxylic acids with **1**.

The condensation of **1** with benzaldehyde has been found to be general one and it has been extended to other aldehydes containing a variety of substitutents such as electron-donating as well as electron-withdrawing groups. The product monoanils could be readily reduced with $NaBH_4$ in ethanol to obtain products which were assigned structures on the basis of spectral and analytical data and the compounds **7-9** are reported in the literature[25] (Scheme 1).

In conclusion, it can be said that condensation of **1** with aromatic aldehydes yields **2** whose structures have been assigned by unambiguously by chemical method.

Experimental Section

General Procedures. Melting points were determined in open glass capillaries using Buchi melting point apparatus and are uncorrected. IR spectra were recorded with Perkin Elmer 1000 instrument using KBr pellets. All ^{1}H NMR spectra were recorded on a VARIAN 200 MHz instrument with an internal standard of tetramethylsilane. Mass spectra were recorded Agilent-LC-MS instrument giving only $M^{+\cdot}$ Values using ($M^{\cdot +}$+1) mode. Analytical TLC was performed with silica gel GF-254 from Merck & Co., (Germany). Spots were detected with UV-light or in iodine. The starting material **1** was prepared from 4-aminopyridine using a known procedure.[28] The following experimental procedures are representive of the general procedures used to synthesize all compounds.

Condensation of 1 with aromatic aldehydes. General Procedure

A mixture of **1** (0.545 g, 5 mmol) and the aldehyde (5 mmol) in ethanol (20 mL), was stirred at reflux till the condensation was complete (as shown by TLC). At the end of this period, the ethanol was removed under reduced pressure giving a residue. The latter on purification by column chromatography using hexane and ethyl acetate (9:1), gave **2** as a pure product.

(*E*)-*N*^{3}-Benzylidenepyridine-3,4-diamine (2a). Ar = C_6H_5, Yield=90%, Mp 29-31 °C; IR (KBr) 3452-3449 cm^{-1} (b, NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 5.0 (bs, 2H, NH_2), 6.6-6.8 (d, *J*=5.2 Hz, 1H, pyridine C-5–H), 7.4-8.2 (m, 7H, phenyl and two pyridyl), 8.4 (s, 1H, =CH, CH=N); M ‡+1: 198. Anal. Calcd. for ($C_{12}H_{11}N_3$) requires: C, 73.07; H, 5.62; N, 21.30% Found: C, 72.97; H, 5.58; N, 21.22%.

(*E*)-*N*^{3}-(4-Methoxybenzylidene)pyridine-3,4-diamine(2b). Ar = C_6H_4-4-OCH_3, Yield= 95%, Mp 48-50 °C; IR (KBr) 3435-3433 cm^{-1} (b, NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 3.8 (s, 3H, OCH_3), 4.6 (bs, 2H, NH_2), 6.6-6.8 (d, *J*=5.4 Hz, 1H, pyridine), 7.4-8.3 (m, 6H, phenyl and two pyridyl), 8.3 (s, 1H, CH=N); M ‡+1: 228. Anal. Calcd. for ($C_{13}H_{13}N_3O$) requires: C, 68.70; H, 5.77; N, 18.49% Found: C, 68.64; H, 5.72; N, 18.44%.

(*E*)-*N*^{3}-(4-Chlorobenzylidene)pyridine-3,4-diamine(2c). Ar = C_6H_4-4-Cl, Yield=95%, Mp 38-40 °C; IR (KBr) 3429-3428 cm^{-1} (b, NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 4.6 (bs, 2H, NH_2), 6.55 (d, *J*=5.0 Hz, 1H, pyridine C-5–H), 7.45-8.1 (m, 6H, phenyl and two pyridyl), 8.2 (s, 1H, CH=N); M ‡+1: 232. Anal. Calcd. for ($C_{12}H_{10}ClN_3$) requires: C, 62.21; H, 4.35; N, 18.14% Found: C, 62.16; H, 4.31; N, 18.06%.

(*E*)-*N*^{3}-(2-Chlorobenzylidene)pyridine-3,4-diamine(2d). Ar = C_6H_4-2-Cl, Yield=88%, Mp 45-47 °C; IR (KBr) 3454-3451 cm^{-1} (b, NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 4.68 (bs, 2H, NH_2), 6.6 (d, *J*=5.2 Hz, 1H, pyridine C-5–H), 7.4-8.3 (m, 6H, phenyl and two pyridyl), 9.55 (s, IH, CH=N); M ‡+1: 232. Anal. Calcd. for ($C_{12}H_{10}ClN_3$) requires: C, 62.21; H, 4.35; N, 18.14% Found: C, 62.16; H, 4.28; N, 18.08%.

(*E*)-*N*^{3}-(4-Bromobenzylidene)pyridine-3,4-diamine(2e). Ar = C_6H_4-4-Br, Yield=90%, Mp 48-49 °C; IR (KBr) 3451-3440 cm^{-1} (b, NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 4.65 (bs, 2H, NH_2), 6.8 (d, *J*=5.3 Hz, pyridine C-5–H), 7.4-8.2 (m, 6H, phenyl and two pyridyl), 8.5 (s, 1H, CH=N);

M ⁺+1: 277. Anal. Calcd. for ($C_{12}H_{10}BrN_3$) requires: C, 52.20; H, 3.65; N, 15.22% Found: C, 52.16; H, 3.58; N, 15.16%.

(*E*)-*N*^{3}-(4-Nitrobenzylidene)pyridine-3,4-diamine(2f). Ar = C_6H_4-4-NO_2, Yield=95%, Mp 53-55 °C; IR (KBr): 3409-3454cm^{-1}(b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) δ 5.5 (bs, 2H, NH_2), 6.55 (d, *J*=5.3 Hz, 1H, pyridine C-5–H), 7.45-8.1 (m, 6H, phenyl and two pyridyl), 8.2 (s, 1H, CH=N); M ⁺+1: 243. Anal. Calcd. for ($C_{10}H_{10}N_4O_2$) requires: C, 59.50; H, 4.16; N, 23.13% Found: C, 59.44; H, 4.10; N, 23.06%.

Reduction of 2 with sodium borohydride. General Procedure

To a solution of **2** (0.985 g, 5 mmol) in methanol (30 mL) was added sodium borohydride (0.2 g 5 mmol) portion wise at 20-25 °C with stirring. After completion of the addition (10-15 min), the reaction mixture was heated on water bath for 1 h till the reaction went to completion as shown by TLC. Then the reaction mixture was cooled to room temperature and treated with water. The separated solid was filtered, washed with water (2 x 20 mL) and dried to obtain a crude product which on recrystallisation from ethanol gave pure **4.**

***N*^{3}-Benzylpyridine-3,4-diamine (4a).** Ar = C_6H_5, Yield=70%, Mp 169-71 °C; IR (KBr): 3437 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 3.4 (bs, 1H, NH), 4.0 (bs, 2H, NH_2), 4.6 (s, 2H, CH_2), 6.5 (d, *J*=5.2 Hz, 1H, pyridine C-5–H), 7.5-8.3 (m, 7H, phenyl and two pyridyl); M ⁺+1: 200. Anal. Calcd. for ($C_{12}H_{13}N_3$) requires: C, 72.33; H, 6.58; N, 21.09% Found: C, 72.26; H, 4.06; N, 21.01%.

***N*^{3}-(4-methoxybenzyl)pyridine-3,4-diamine(4b).** Ar = C_6H_4-4-OCH_3, Yield=69%, Mp 132-134 °C; IR (KBr): 3408 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 2.3 (bs, 2H, NH_2), 3.8 (s, 3H, OCH_3), 3.9 (bs, 1H, NH_2), 4.2 (s, 2H, CH_2), 6.6 (d, *J*=5.2 Hz, 1H, pyridine C-5–H), 6.9-7.3 (m, 4H, phenyl), 7.8 (d, *J*=6.2 Hz, 2H, pyridine); M ⁺+1: 230. Anal. Calcd. for ($C_{13}H_{15}N_3O$) requires: C, 68.10; H, 6.59; N, 18.33% Found: C, 68.02; H, 4.06; N, 23.00%.

***N*^{3}-(4-Chlorobenzyl)pyridine-3,4-diamine(4c).** Ar = C_6H_4-4-Cl, Yield=72%, Mp 146-148 °C; IR (KBr): 3416 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 3.3 (bs, 1H, NH) , 4.0 (bs, 2H, NH_2), 4.3 (s, 2H, CH_2), 6.5 (d, *J*=5.4 Hz, 1H, pyridine C-5–H), 7.3-7.4 (m, 4H, phenyl), 7.8 (d, *J*=6.2 Hz, 2H, pyridine); M ⁺+1: 234. Anal. Calcd. for ($C_{12}H_{12}ClN_3$) requires: C, 61.67; H, 5.18; N, 17.98% Found: C, 61.64; H, 5.14; N, 17.92%.

***N*^{3}-(2-Chlorobenzyl)pyridine-3,4-diamine(4d).** Ar = C_6H_4-2-Cl, Yield=71%, Mp 136-38 °C; IR (KBr): 3408 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 3.4 (bs, 1H, NH), 4.3 (bs, 2H, NH_2), 4.6 (s, 2H, CH_2), 6.7 (d, *J*=5.6 Hz, 1H, pyridine C-5–H), 7.5-7.8 (m, 4H, phenyl), 7.8 (d, *J*=6.2 Hz, 2H, pyridine); M ⁺+1: 234. Anal. Calcd. for ($C_{12}H_{12}ClN_3$) requires: C, 61.67; H, 5.18; N, 17.98% Found: C, 61.65; H, 5.15; N, 17.94%.

***N*^{3}-(4-Bromobenzyl)pyridine-3,4-diamine(4e).** A= C_6H_4-4-Br, Yield=68%, Mp 141-43 °C; IR (KBr): 3412 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 3.1 (bs, 1H, NH-), 4.2 (bs, 2H, NH_2), 4.4 (s, 2H, CH_2), 6.7 (d, *J*=5.4 Hz, 1H, pyridine C-5–H), 7.1-7.3 (m, 4H, phenyl), 7.8 (d, *J*=6.6 Hz, 2H, pyridine); M ⁺+1: 279. Anal. Calcd. for ($C_{12}H_{12}BrN_3$) requires: C, 51.82; H,4.35; N, 15.11% Found: C, 51.76; H, 4.29; N, 15.06%.

***N*^{3}-(4-Nitrobenzyl)pyridine-3,4-diamine(4f).** Ar = C_6H_4-4-NO_2, Yield=81%, Mp 191-193 °C; IR (KBr): 3410 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 3.4 (bs, 1H, NH), 4.0 (bs, 2H, NH_2), 4.7 (s, 2H, CH_2), 6.6 (d, *J*=5.2 Hz, 1H, pyridine C-5–H), 7.5-8.6 (m, 4H, phenyl), 7.8 (d, *J*=7.2 Hz, 2H, pyridine); M †+1: 245. Anal. Calcd. for ($C_{12}H_{12}N_4O_2$) requires: C, 59.01; H, 4.95; N, 22.94% Found: C, 58.95; H, 4.89; N, 22.90%.

Preparation of 10 from 9

***N*-Benzyl-3-nitropyridin-4-amine (10).** To a solution of TEBAC (0.2 g, 0.88 mmol) in DMF (20 mL), K_2CO_3 (1.4 g, 10 mmol) was added, and the mixture was stirred at rt. To this mixture, under stirring, a solution of **9** (2.0 g, 10 mmol) in DMF (10 mL) was added followed by the benzyl chloride (1.386 g, 11 mmol). The reaction mixture was stirred at 110 °C for 3-4 h. The progress of the reaction was monitored on TLC for the disappearance of **9**. On completion of reaction (~3-4 h), the mixture was poured into ice-cold water, and neutralized with AcOH. The separated product was filtered, washed with water and dried to obtain crude product which on recrystallisation from hot ethanol gave a pure compound **10**.

10: Ph= -C_6H_5, Yield=85%, Mp 102-103 °C; IR (KBr): 3393 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6/TMS) δ 4.55 (s, 2H, CH_2), 6.7 (d, *J*=6.2 Hz, 1H, pyridine C-5–H), 7.2-7.5 (m, 5H, phenyl), 8.3 (d, *J*=6.6 Hz, 1H, pyridine C-6–H), 8.5 (s, 1H, N-), 9.3 (s, 1H, pyridine C-2–H); M †+1: 230. Anal. Calcd. for ($C_{12}H_{11}N_3O_2$) requires: C, 62.87; H, 4.84; N, 18.33% Found: C, 62.82; H, 4.80; N, 18.26%.

Preparation of 10 from 8

A mixture of benzylamine (1.0 g, 10 mmol), **8** (1.7 g, 10 mmol) and ethanol (100 mL) was refluxed for 20 h. The progress of the reaction was monitored on TLC for the disappearance of starting material. On completion of the reaction, ethanol was removed from the reaction mixture to halve of its volume, then the mixture was cooled to 0 °C when a solid product was precipitated which was filtered, washed with chilled ethanol and filter press dried in vacuum. The crude product was recrystallised from ethanol to give pure product **10**.

Yield (%): 85 (Ph = C_6H_5)

Preparation of 5 from 10

A solution of 4-benzylamino-3-nitropyridine **10** (1.14 g, 5 mmol) in ethanol (100 mL) was hydrogenated at room temperature in the presence of Raney nickel (1 g) at a pressure of 60 psi. During the reduction, the temperature of the solution rose to 50 °C and was then allowed to decrease to room temperature. The theoretical uptake of hydrogen was achieved after 2 h. The catalyst was removed by filtration and the solvent was concentrated in vacuum to get a light grey solid as crude product, which was recrystallized from ethanol to give pure **5**.

***N*^{4}-Benzylpyridine-3,4-diamine(5).** Ph = C_6H_5, Yield=90%, Mp 102-103 °C; IR (KBr) 3386 cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS) δ 4.4 (s, 2H, CH_2) , 4.6 (bs, 2H, NH_2), 6.1 (s, 1H, phenyl), 6.25 (s, 1H, pyridine C-5–H) , 7.2 (s, 1H, phenyl), 7.3 (m, 3H, phenyl), 7.3 (s, 1H, pyridine C-6–H),

7.6 (s, 1H, pyridine C-2–H); M ‡+1: 200. Anal. Calcd. for ($C_{12}H_{13}N_3$) requires: C, 72.33; H, 6.58; N, 21.09% Found: C, 72.29; H, 6.52; N, 21.02%.

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