Some New Methods for Preparing 2,3- and 3,4-Diaminopyridines

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New methods of preparing 2,3-diaminopyridine (**13**) from 2-chloro-3-nitropyridine (**11**) and 3,4-diaminopyridine (**8**) from 4-ethoxy-3-nitropyridine hydrochloride (**5**) have been explored and evaluated.

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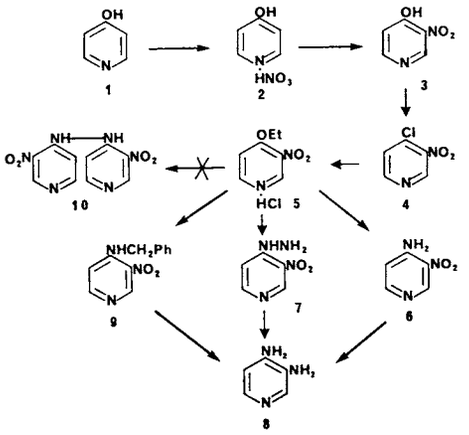
2,3-Diaminopyridine (**13**) and 3,4-diaminopyridine (**8**) are important intermediates that have been used to prepare heterocycles with demonstrated antiviral [1,2], cardiovascular [3], antimicrobial [4], rodenticidal [5] and cytotoxic [6,7] activity. In spite of their widespread use they remain expensive chemicals, costing on the average several dollars per gram. A recent project that required large quantities of **8** and **13** motivated us to explore some new strategies of synthesis that we believe may offer some economic and handling advantages over existing methods [8].

In 1962 Clark-Lewis and Singh [9] developed a method for preparing **8** utilizing nucleophilic displacement by ammonia of the ethoxy group in 4-ethoxy-3-nitropyridine (**5**) (scheme I) providing 4-amino-3-nitropyridine (**6**) which was then reduced to yield **8**. Since **5** can conveniently be prepared in large quantities from 4-hydroxypyridine (**1**) we examined this method in detail. Several improvements have been made in the overall process. The usual procedure [10] involves the conversion of **1** into its nitrate salt **2**

SCHEME I



in dilute nitric acid. The salt is isolated and then nitrated in a mixture of fuming nitric acid (90%) and 20% oleum. We observed that commercially available **1** can be nitrated directly by increasing the concentration of the oleum from 20% to 30% and increasing the amount of nitric acid.

4-Hydroxy-3-nitropyridine (**3**) is converted to **5** by melting **3** with phosphorus pentachloride [11] or in a mixture of phosphorus oxychloride and phosphorus pentachloride [12]. In the latter case the phosphorus oxychloride is distilled and the residue treated with ethanol. We observed that the reaction could be carried out safely and easily in 1,2-dichloroethane. When **3** is mixed in 1,2-dichloroethane with a slight excess of phosphorus pentachloride, the mixture refluxed for 4-8 hours and ethanol added, the hydrochloride salt **5** crystallizes from solution. The yield of **6** from **5** using ammonia was too capricious, especially on scale up, to be useful. In our hands the yields varied between 50% and 90%. On a large scale the reaction proved particularly difficult. The reaction had to be run at 120° for 8 hours in a pressure vessel. The need for a pressure vessel immediately limited the size of the reaction. Many times the crude product had to be chipped from the vessel. Although the recrystallized material thus produced gave acceptable analytical data, it gave a highly colored product when converted to **8**. We therefore investigated four other schemes for preparing **8** and **13**.

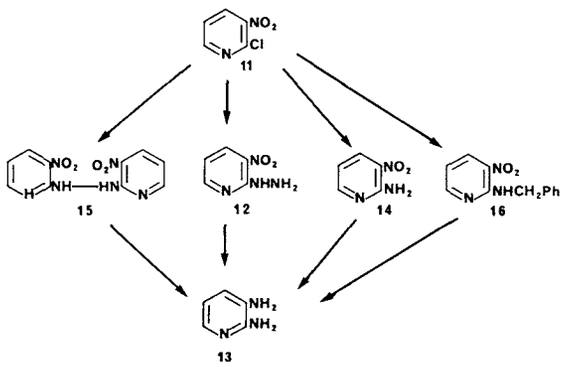
The reaction of hydrazine with **5** smoothly produces 4-hydrazino-3-nitropyridine (**7**) in 90% yield. This reaction can be carried out on a large scale and has the advantage that high pressure autoclaves are not needed as with the reaction with ammonia. It is well known [13] that the N-N bond in hydrazines is cleaved with hydrogen and Raney nickel. When this procedure is applied to **7** the nitro group is reduced at the same time generating a 94% yield of **8**.

The same strategy was applied to the commercially available 2-chloro-3-nitropyridine (**11**) (scheme II). It was converted to 2-hydrazino-3-nitropyridine (**12**) and in turn the hydrazino group was cleaved and the nitro group reduced with hydrogen and Raney nickel to produce **13** in 70% yield.

We have been able to effect with remarkable ease the

nucleophilic displacement of the ethoxy group in **5** to give **6** using aqueous ammonium acetate. The reaction is carried out by refluxing **5** in water with four equivalents of ammonium acetate. The material obtained is pure enough to take on to **8** without further treatment. Lower yields of **6** were generated when carrying out the reaction in alcoholic solvents (methanol, ethanol or 1-butanol), in acetic acid or as a melt of **5** with ammonium acetate. The reaction of ammonium acetate with **11** generates 2-amino-3-nitropyridine (**14**). Since **14** can be readily reduced either catalytically [14] or chemically [15], this provides another facile route to **13**.

SCHEME II



Benzylamine also reacts readily with **5** and **11** providing 4-benzylamino-3-nitropyridine (**9**) and 2-benzylamino-3-nitropyridine (**16**) in excellent yields. The strategy envisioned with these compounds was to effect an *N*-debenzylation and at the same time reduce the nitro group to afford **8** and **13**. Most *N*-debenzylations occur readily at room temperature and with a 10% catalyst load of 5% palladium on carbon [16]. With **9** and **16**, however, the nitro group was reduced readily, but the *N*-debenzylation required high catalyst loads, elevated temperatures and long reaction times. The economics of this transformation make it less desirable as a method of preparing **8** and **13** than the two above mentioned methods.

Another tactic that we explored was the possible reaction of one equivalent of hydrazine with two equivalents of **5** or **11** which could lead to the bis compounds **10** and **15**. Treatment with hydrogen and Raney nickel would then provide **8** and **13**. These reactions were not successful, and we were also unsuccessful in obtaining **10** from the reaction of **5** with **7**. Although we were able to obtain 2,2'-hydrazobis(3-nitropyridine) (**15**) from the reaction of **11** with **12**, the reaction was very sluggish, four days reflux in ethanol being required to achieve a low yield (31%) of **15**. As predicted, **15** when treated with Raney nickel generated **13** in 92% yield.

EXPERIMENTAL

All melting points were taken in glass capillary tubes on a Mel-Temp melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on JEOL FX-90 Q and GE QE 300 spectrometers. Chemical shifts are reported relative to tetramethylsilane. Electron impact mass spectra were determined on a CEC-21-10 mass spectrometer at an ionizing voltage of 70eV. Field desorption mass spectra were determined on a Varian Mat 731 mass spectrometer.

4-Hydroxy-3-nitropyridine (**3**) from **1**.

To 50 ml of fuming sulfuric acid (27-33%) cooled to −5° in an ice/acetone bath and under an atmosphere of nitrogen was added dropwise over 30 minutes 46 ml of fuming nitric acid (90%). The temperature of the reaction was maintained below 10° during the addition. In four portions, 20.0 g (0.189 mole) of 90% pure **1** was then added over 20 minutes. The temperature of the reaction mixture gradually increased to between 20° and 24°. The ice bath was removed and the solution was stirred for 15 minutes or until the solid material had dissolved. Then 15 ml of 1,2-dichoroethane was poured into the flask and the reaction heated to 70°. The solution exothermed to 80° at which point the dichloroethane began to reflux. The temperature held for five minutes and then began to drop. The reaction was then heated to reflux at 80-82° for seven hours. Heating was removed, and when the internal temperature had dropped to 70° the contents of the flask were poured over 350 ml (200 g) of ice. The resultant slurry was stirred for two hours in an ice/water bath. The material was then collected and washed with cold water. The crude product (approximately 30 g) was added to 350 ml of water and slurry heated to boiling. At the boiling point the solution was fast filtered, if necessary, to remove a slight amount of insoluble material. The filtrate was reheated to boiling and **3** was allowed to crystallize slowly. The flask was cooled for three hours. The crystals were collected, washed with cold water and dried *in vacuo* at 50° for 18 hours to yield 70% of off-white to light yellow **3**, mp 275-277°, lit [12] mp 278-279°; nmr (DMSO-d_6): 8.78 (d, J = 1.7, H2, 1H), 7.77 (d, d, J = 7.4, 1.6, H6, 1H), 6.48 (d, J = 7.5, H5, 1H), 3.60 (s [broad], NH).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.58; H, 2.93; N, 19.73.

4-Ethoxy-3-nitropyridine hydrochloride (**5**) from **3**.

To 63.1 g (0.45 mole) of **3** and 112.5 g (0.54 mole) of phosphorus pentachloride was added 400 ml of 1,2-dichloroethane and the resultant slurry heated to reflux (85-87°). Reflux was maintained until a clear solution resulted (approximately 4-8 hours). The temperature was then lowered to 35° with an ice bath. With the ice bath in place, 250 ml of absolute ethanol was added slowly. With the first 20 ml, a thick, stirrable slurry formed and an exotherm increased the temperature to 65°. As more ethanol was added the temperature dropped and the slurry became thinner. The ice bath was removed and the slurry was stirred for twenty minutes at room temperature or until the exotherm subsided. With a heating mantle attached to the flask the slurry was then refluxed for one hour at 62°. The completeness of the reaction was checked by tlc (silica, ethyl acetate:methanol:ammonium hydroxide 7:3:1, uv).

Heating was removed and the slurry was cooled for 2-3 hours in an ice bath. The crystals were collected, washed with cold ethanol and dried *in vacuo* at 50° to yield 87% of white to off-white crystalline **5**, mp 270-271°, lit [9] mp 270-271°; nmr (DMSO-d_6): 9.57 (s [broad], HCl, 1H), 9.15 (s, H2, 1H), 8.79 (d, J = 6.3, H6, 1H), 7.62 (d, J = 6.3, H5, 1H), 4.43 (q, J = 6.0, CH_2, 2H), 1.39 (t, J = 7.0, CH_3, 3H).

Anal. Calcd. for $C_7H_9ClN_2O_3$: C, 41.09; H, 4.43; N, 13.96; Cl, 17.33. Found: C, 40.83; H, 4.36; N, 13.84; Cl, 17.50.

4-Amino-3-nitropyridine (**6**) from **5**.

A mixture of 78.4 g (0.383 mole) of 4-ethoxy-3-nitropyridine hydrochloride (**5**), 118.1 g (1.53 moles) of ammonium acetate and 183 ml of water were combined and the slurry heated to reflux (104°) for seven hours.

Over the course of the reaction the reflux temperature dropped from 104° to 98°. Tlc was used to monitor the reaction progress (silica, ethyl acetate/triethyl amine 10:1). The heating mantle was replaced with an ice bath and as the internal temperature approached 25° the *p*H was adjusted from 5 to 8 using approximately 60 ml of concentrated ammonium hydroxide solution. The slurry was stirred for one hour at 4°, collected, washed with cold water and dried *in vacuo* at 50° to yield 87% (46.4 g) of yellow powdery **6**, mp 197-201°, lit [9] mp 204°; nmr (DMSO-d_6): 8.97 (s, H2, 1H), 8.13 (d, J = 6.0, H6, 1H), 7.93 (s [broad], NH_2, 2H), 6.89 (d, J = 6.0, H5, 1H).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 42.87; H, 3.36; N, 30.12.

Reduction of **6** to **8**.

In a Parr bottle was placed 350 mg of 5% palladium on carbon and 0.5 ml of water. Then 2.0 g (0.0143 mole) of **6** and 25 ml of methanol were added and the reaction was shaken under 50 psi of hydrogen for 1.5 hours at room temperature. The reaction exothermed to 30° over approximately 45 minutes. The catalyst was removed by filtration using a Hyflo pad. The filtrate was concentrated under vacuum to a slurry weighing 5 g. Water (10 ml) was added to the slurry and it was concentrated again to 10 g. The slurry was chilled to 4° for one hour, collected, rinsed with cold water and dried *in vacuo* at 50° to yield 1.32 g (85%) of white to beige colored crystalline **8**. Tlc (silica, ethyl acetate:methanol: ammonium hydroxide 7:3:1, uv) was one spot corresponding to the Rf of commercial material, mp 218-219°, lit [9] mp 220°; nmr (DMSO-d_6): 7.63 (s, H2, 1H), 7.48 (d, J = 5.0, H6, 1H), 6.39 (d, J = 5.0, H5, 1H), 5.29 (s, [broad], NH_2, 2H), 4.46 (s, [broad], NH_2, 2H).

Anal. Calcd. for $C_5H_7N_3$: C, 55.03: H, 6.47; N, 38.50. Found: C, 54.99; H, 6.30; N, 38.48.

4-Hydrazino-3-nitropyridine (**7**).

To a stirred solution of 310.0 g (1.84 moles) of **5** dissolved in approximately 6 liters of acetonitrile was added 77 g (2.4 moles) of anhydrous hydrazine over a five minute period. There was an immediate color change in the solution from yellow to red during the addition. The reaction mixture was then heated to reflux and the reaction followed by tlc (silica, ethyl acetate:triethylamine 10:1, iodine). A red precipitate started to appear in the reaction mixture in about 0.5 hour and at 2.5 hours the reaction was complete. After an additional 2.5 hours of refluxing the reaction mixture was allowed to cool slowly to room temperature and was then chilled in an ice-alcohol bath. The red crystals were collected and washed with cold acetonitrile and dried *in vacuo* to yield 254.5 g (90%) of **7**, mp 205°/dec, lit [17] mp 207°); nmr (deuteriochloroform): 4.8 (broad, NH_2, 2H), 7.5 and 8.4 (2 doublets, Ar, 2H), 9.1 (s, Ar, 1H), 9.6 (broad, NH, 1H); ms: m/e 154 (M+).

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 39.00; H, 3.80; N, 36.13.

3,4-Diaminopyridine (**8**) from **7**.

Compound **7** (100 g, 0.65 mole) was hydrogenated at room temperature in 3.9 liters of ethanol in the presence of 12 g of Raney nickel at an initial hydrogen pressure of 60 psi. During the reduction the temperature of the solution rose to 50° and then fell to room temperature. The theoretical uptake of hydrogen was achieved after two hours. The catalyst was removed by filtration and the solvent concentrated *in vacuo* to a light grey solid that was recrystallized from methyl alcohol to yield 66.9 g (94%) of **8**.

4-Benzylamino-3-nitropyridine (**9**).

A reaction mixture of 153 g (0.91 mole) of **5** and 158 g (1.47 moles) of benzylamine was refluxed in 900 ml of ethanol for 18 hours. Tlc (silica, ethyl acetate:triethylamine 10:1, uv) at this point indicated that no starting material was present. The reaction mixture was chilled and the flask scratched to induce crystallization. The crystals were collected and dried *in vacuo* to yield 196 g (94%) of **9** that was essentially one spot on tlc. Recrystallization from one liter of ethanol yielded 163 g of **9** as yellow crystals, mp 100-102°, lit [18] mp 103°; nmr (DMSO-d_6): 9.06 (H2, 1H), 9.02 (NH, 1H), 8.20 (H6, 1H), 7.2-7.4 (Ar, 5H), 6.86 (H5, 1H), 4.68 (CH_2, 2H); ms: m/e 229 (M+).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.80; H, 4.93; N, 18.03.

3,4-Diaminopyridine (**8**) from **9**.

A mixture of 5.7 g (0.025 mole) of **9** and 5.7 g of 5% palladium on carbon in 90 ml of ethanol was hydrogenated in a Parr apparatus at an initial hydrogen pressure of 60 psi. To achieve theoretical hydrogen uptake for the debenzylation and reduction of the nitro group required a temperature of 80° and 30 hours. The catalyst was removed by filtration and the filtrate concentrated to a solid. Recrystallization from ethyl acetate -methanol provided 2.0 g of **8** (76%).

2-Hydrazino-3-nitropyridine (**12**).

To 31.6 g (0.2 mole) of 2-chloro-3-nitropyridine dissolved in 500 ml of acetonitrile was added 10 g of anhydrous hydrazine. The solution immediately turned a red color and after five minutes exothermed slightly and a precipitate began to appear. After refluxing for one hour the reaction mixture was allowed to cool to room temperature and stand overnight. The orange crystals that separated were collected and recrystallized from acetonitrile. White crystals that were not soluble in acetonitrile during the recrystallization were shown to be hydrazine hydrochloride. The yield of **12** after drying was 24.1 g (78%), mp 165-167°, lit [17] mp 164°; ms: m/e 154 (M+).

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 39.15; H, 4.13; N, 36.34.

2,3-Diaminopyridine (**13**) from **12**.

In a Parr bottle 7 g (0.05 mole) of **12** was dissolved in a mixture of 50 ml of ethanol and 90 ml of tetrahydrofuran and hydrogenated at an initial hydrogen pressure of 60 psi at 65° for 16 hours with 5 g of Raney nickel. The theoretical hydrogen uptake was 100%. The mixture was cooled, the catalyst was removed by filtration and the filtrate was concentrated to a grey-white solid. This solid was one spot on tlc (silica, ethyl acetate:methanol:ammonium hydroxide 70:30:10, uv) corresponding to authentic **13**. The solid was recrystallized from 50 ml of ethyl acetate providing 3.8 g (70%) of **3** as white needles, mp 112-113°, lit [19] mp 115-116°; nmr (DMSO-d_6): 7.26 (H6, 1H), 6.66 (H4, 1H), 6.36 (H5, 1H), 5.32 (2H, NH_2), 4.63 (2H, NH_2); ms: m/e 109 (M+).

2-Benzylamino-3-nitropyridine (**16**).

A mixture of 25 g (0.158 mole) of 2-chloro-3-nitropyridine (**11**) and 34.2 g (0.32 mole) of benzylamine was refluxed in 150 ml of ethanol for 3 hours. The solvent was removed *in vacuo* and the residue dissolved in chloroform and washed three times with 100 ml portions of water to remove benzylamine hydrochloride. The chloroform solution was then dried over magnesium sulfate and concentrated to a yellow solid. Recrystallization from 500 ml of ethanol provided 31.0 g (86%) of **16**, mp 73-74°, lit [20] mp 80°. Tlc (silica, toluene:ethyl acetate 80:20, uv) was one spot, nmr (DMSO-d_6): 8.97 (NH, 1H), 8.46 (H4, 6, 2H), 7.2-7.4 (Ar, 5H), 6.77 (H5, 1H), 4.80 (CH_2, 2H); ms: m/e 229 (M+).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.60; H, 4.69; N, 18.13.

2,3-Diaminopyridine (**13**) from **16**.

Compound **16** (4.6 g, 0.02 mole) and 4.6 g of 5% palladium on carbon in 90 ml of ethanol was hydrogenated in a Parr apparatus at an initial hydrogen pressure of 60 psi. Theoretical hydrogen uptake was achieved after 18 hours at a temperature of 80°. The catalyst was removed by filtration and the filtrate concentrated to a solid. Recrystallization from ethyl acetate provided a 41% yield (890 mg) of **13** as white crystals, mp 111-113°.

2-Amino-3-nitropyridine (**14**) from **11**.

A mixture of 25 g (0.158 mole) of 2-chloro-3-nitropyridine and 48.7 g

(0.632 mole) of ammonium acetate was stirred and heated to reflux in 100 ml of diglyme. After four hours a tlc probe (silica, ethyl acetate, uv) indicated that the reaction had not gone to completion, so another 24 g of ammonium acetate was added and the mixture refluxed for an additional four hours. One final treatment with 24 g of ammonium acetate and a four hour reflux was necessary to eliminate any detectable amount (by tlc) of starting material. The reaction mixture was poured into an ice/water mixture and when the ice had melted the crystalline material was collected, washed with water and air dried to provide 17.5 g (80%) of crude **14** that was essentially one spot and at the same Rf as commercial material. Recrystallization from ethanol provided 14.2 g (65%) of yellow **14**, mp 162-164°, lit [21] mp 163-164°; nmr (DMSO-d_6): 8.40 (H4, 6, 2H), 7.90 (NH_2, 2H), 6.77 (H5, 1H); FD ms: m/e 139 (M+).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.07; H, 3.59; N, 29.97.

2,3-Diaminopyridine (**13**) from **14**.

A solution of 46 g (0.33 mole) of **14** in 2.95 ℓ of ethyl acetate was hydrogenated at an initial pressure of 60 psi of hydrogen at room temperature in the presence of 7.5 g of 5% Pd/C. The temperature exothermed to 35° during this process and after 2.5 hours had cooled to room temperature and the theoretical hydrogen uptake had been achieved. The catalyst was removed by filtration and the filtrate concentrated to a grey solid. Recrystallization from ethanol and then from toluene-ethyl acetate yielded 28.8 g (80%) of **13** as white needles, mp 111-112°.

In another experiment 3.5 g (0.025 mole) of **14** was dissolved in 45 ml of tetrahydrofuran and hydrogenated under the same conditions as above in the presence of 1 g of 5% Pd/C. The reaction exothermed to 55° and was complete in 0.5 hour. This yielded 2.0 g (73%) of **13**.

2,2'-Hydrazobis(3-nitropyridine) (**15**).

A mixture of 3.2 g (0.02 mole) of **11** and 3.1 g (0.02 mole) of **12** was refluxed in 250 ml of ethanol with 2.2 g of triethylamine for four days. During this time burgundy colored crystals gradually separated from the reaction mixture. The mixture was cooled and the crystals were collected to give 4.1 g of crude **15**. Recrystallization from 400 ml of diethyleneglycol dimethyl ether provided, after drying, 1.7 g (31%) of **15**, mp 257°/dec. Tlc (silica, toluene:ethyl acetate 80:20, uv) was one spot. With this system the hydrazine starting material **12** does not move from the point of application; ms: m/e 276 (M+).

Anal. Calcd. for $C_{10}H_8N_6O_4$: C, 43.48; H, 2.92; N, 30.43. Found: C, 43.59; H, 3.11; N, 30.17.

2,3-Diaminopyridine (**13**) from **15**.

A Parr bottle was charged with 1.7 g (0.006 mole) of **15** 0.7 g of Raney Nickel and 397 ml of ethanol. The bottle was pressurized to 60 psi with hydrogen and hydrogenated at room temperature for three hours. The catalyst was removed by filtration and the filtrate concentrated to 1.2 g (92%) of a light blue grey solid. This was identical to authentic material by tlc and field desorption ms.

REFERENCES AND NOTES

[1] O. P. Babbar and B. L. Chowdhury, *J. Sci. Ind. Res.*, **21c**, 312 (1962).

[2] L. B. Allen, *et al.*, 15th Interscience Conference Antimicrobial Agents and Chemotherapy, Abstract No. 245, Washington D.C., Sept. 1975.

[3] U. S. Patent 3,985,891; *Chem. Abstr.*, **82**, 4251y (1975).

[4] K. B. de Roos and C. A. Salemink, *Rec. Trav. Chim.*, **90**, 1166 (1971).

[5] G. O. P. O'Doherty, U. S. Patent 3,941,882 (Mar. 2, 1976); *Chem. Abstr.*, **84**, 160628y (1976).

[6] J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **9**, 105 (1966).

[7] J. A. Montgomery and K. Hewson, *ibid.*, **9**, 354, (1966).

[8] For comprehensive reviews of methods for preparing diaminopyridines see A. S. Tomcufcik and L. N. Starker in "The Chemistry of Heterocyclic Compounds", "Pyridine and Its Derivatives", part three, E. Klingsberg, ed, John Wiley and Sons, New York, NY, 1962, page 59; *ibid.*, C. S. Giam, Vol 14 supplement, Part three, R. A. Abramovitch, ed, 1974, p 93.

[9] J. W. Clark-Lewis and R. P. Singh, *J. Chem. Soc.*, 2379 (1962).

[10] D. C. Leis and B. C. Curran, *J. Am. Chem. Soc.*, **67**, 79 (1945).

[11] E. Koenigs and K. Freter, *Chem. Ber.*, **57**, 1187, (1924).

[12] S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755, (1955).

[13] J. S. Pizey, "Synthetic Reagents", Vol II;, John Wiley and Sons, New York, NY, 1974, p 275.

[14] J. B. Ziegler, *J. Am. Chem. Soc.*, **71**, 1891 (1949).

[15] V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

[16] P. N. Rylander, "Catalytic Hydrogenation in Organic Synthesis", Academic Press, New York, NY, 1979, p 280.

[17] T. Talik and Z. Talik, *Rocz. Chem.*, **41**, 483 (1967): *Chem. Abstr.*, **67**, 64192e (1967).

[18] O. Bremer, *Ann.* **518**, 274 (1935).

[19] B. A. Fox and T. L. Threlfall, *Org. Synth.*, Coll Vol V, p 346.

[20] Japanese Patent 15,194 (1965); *Chem. Abstr.*, **63**, 14826e (1965).

[21] L. N. Pino and W. S. Zehrung, *J. Am. Chem. Soc.*, **77**, 3154 (1955).