Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

$Na_2S_2O_4$: A Versatile Reagent for the One-Pot Synthesis of 2-Aryl-1H-imidazo[4,5-c]pyridines from 4-Amino-3-nitropyridine and Aldehydes via Reductive Cyclization

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Version of record first published: 04 Feb 2010

To cite this article: P. K. Dubey, K. S. Chowdary, B. Ramesh & P. V. V. Prasada Reddy (2010): $Na_2S_2O_4$: A Versatile Reagent for the One-Pot Synthesis of 2-Aryl-1H-imidazo[4,5-c]pyridines from 4-Amino-3-nitropyridine and Aldehydes via Reductive Cyclization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:5, 697-708

To link to this article: http://dx.doi.org/10.1080/00397910903011345

Synthetic Communications®, 40: 697–708, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903011345

Taylor & Francis
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$Na_2S_2O_4$: A VERSATILE REAGENT FOR THE ONE-POT SYNTHESIS OF 2-ARYL-1*H*-IMIDAZO[4,5-c]PYRIDINES FROM 4-AMINO-3-NITROPYRIDINE AND ALDEHYDES VIA REDUCTIVE CYCLIZATION

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A highly efficient and versatile method for the synthesis of 2-aryl-1H-imidazo[4,5-c]pyridines* 3 *was achieved in one step via reductive cyclization of 4-amino-3-nitro-pyridines* 4 *with aromatic aldehydes in the presence of $Na_2S_2O_4$. Treatment of* 3 *with benzyl chloride in nonaqueous media under phase-transfer conditions to afford N-benzylated derivatives* 10. *Compounds* 3 *and* 10 *could also be prepared by other routes: dehydrogenative cyclization of monoanil 4-amino-3-arylideneaminopyridine* 11 *with different oxidizing reagents resulted in the formation of* 3, *and reduction of* 11 *with $NaBH_4$, followed by cyclization with aromatic acids using $POCl_3$, gave the N-benzyl-2-aryl-imidazo[4,5-c]pyridines* 10. *Compound* 11 *could be synthesized from 3,4-diamino pyridine* 1. *The structures of all the compounds obtained in the present work are supported by spectral and analytical data.

Keywords: 4-Amino-3-nitro-pyridine; aromatic aldehydes; benzyl chloride; $Na_2S_2O_4$; one-pot; reductive cyclization

INTRODUCTION

The benzimidazole[1–3] and imidazopyridine[4–6] moieties are important pharmacophores that have proven to be useful for a number of biologically relevant targets. 3,4-Diaminopyridine derivatives possess a wide range of biological activities[7] such as treatment of multiple sclerosis[8] and antiviral, rodenticidal,[9] antimicrobial, and cytotoxic[10] activities. 3,4-Diaminopyridine is a drug approved for clinical use in the treatment of Lambert Eaton myasthenic syndrome.[11] Recently, it was reported[12] that the 3,4-diamino pyridine derivative of 2-[(aryl)-methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine was a potent antiosteoporotic agent, which was useful in inhibiting bone resorption in a host animal, including humans. Medicinal chemists consider these heterocycles to be privileged structures. Indeed, the development of new synthetic methods, which could render accessible chemistry space currently not attainable by existing methods, would be of considerable importance to chemistry.

Received February 8, 2009.

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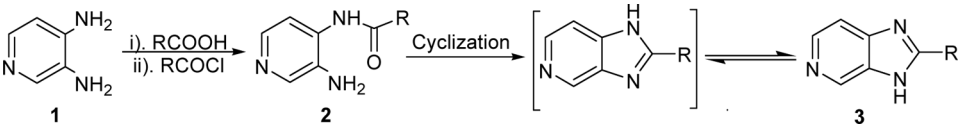


Scheme 1. General route for synthesis for 2-substituted-1*H*-imidazo[4,5-c]pyridines.

The preparations of these compounds are usually straightforward, and a number of synthetic methods are already available. The most popular synthetic approaches for the synthesis of benzimidazoles and imidazopyridines generally involve the condensation of diamines with carbonyl compounds[13–16] (Scheme 1). For example, the reaction of 3,4-pyridinediamine (**1**) with carboxylic acid or acid chloride results in intermediate amide (**2**). The latter, in turn, could undergo a cyclodehydration reaction under strong acidic or harsh dehydrating conditions, often at high temperatures, to afford imidazopyridines (**3**).

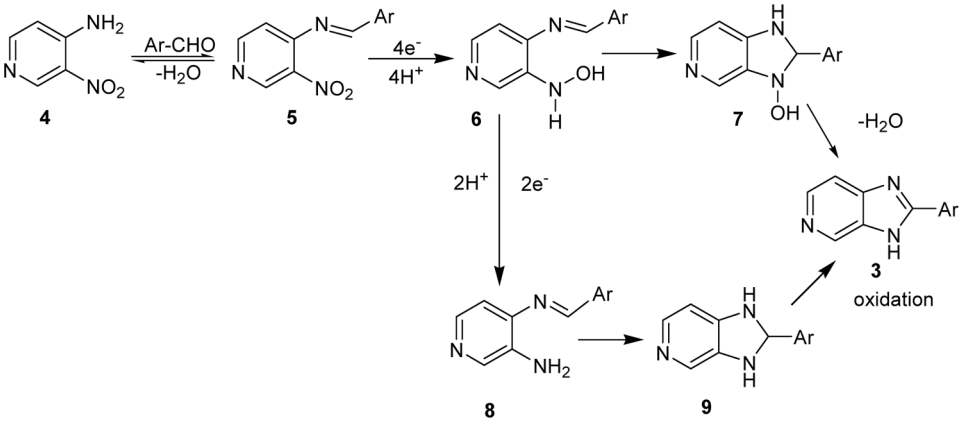
In continuation of our earlier work[17–20] on benzimidazoles and imidazo[4,5-c]pyridines, we now report our studies on the synthesis of 1*H*-imidazo[4,5-c]pyridines, in one pot via reductive cyclization using sodium dithionite without the need for preparation or isolation of any intermediates, followed by aralkylation studies on 1*H*-imidazo[4,5-c]pyridines in nonaqueous media using triethylbenzylammonium chloride (TEBAC) to get the selective products. We also report regioselective condensation of 3,4-diaminopyridines with aromatic aldehydes, followed by dehydrogenative cyclization with different oxidizing reagents, to get the title compounds. The results of our studies in this direction are presented in this communication.

RESULTS AND DISCUSSION

In an initial endeavor, a mixture of 4-amino-3-nitropyridine **4** with *p*-methoxy benzaldehyde in ethanol in the presence of sodium dithionate ($Na_2S_2O_4$) resulted in the formation of 2-*p*-methoxy phenyl-1*H*-imidazo[4,5-c]pyridine **3a** (i.e., **3**, Ar = -C_6H_4-4-OCH_3), via reductive cyclization. This was confirmed on the basis of spectral data and on an oxidation–reduction mechanism. An oxidation–reduction mechanism[21] (Scheme 2) is postulated here by condensation of an aldehyde with 4-amino-3-nitropyridine to form the corresponding imine **5**. The subsequent four-electron reduction of the nitro group, which results in hydroxylamine **6**, followed by cyclization to 2-aryl-1-N-hydroxy-imidazo[4,5-c]pyridine **7** and consequent dehydration, could account for the formation of 2-aryl-1*H*-imidazo[4,5-c]pyridine **3**. This method leads to the exclusive formation of 2-aryl-1*H*-imidazo[4,5-c]pyridine in good yield. It was proposed that entry to 2-aryl-1*H*-imidazo[4,5-c]pyridine might involve the intermediacy of primary amine, the six-electron reduction product of nitroimine, and subsequently the oxidation of imidazoline.

An authentic sample was also obtained by direct condensation of 3,4-diaminopyridine **1** with *p*-methoxy benzoic acid in refluxing $POCl_3$ conditions using the literature procedure.[22,23]

To extend the scope of the reaction and to generalize the procedure, a variety of electronically divergent aromatic aldehydes and 4-amino-3-nitropyridine **4** were



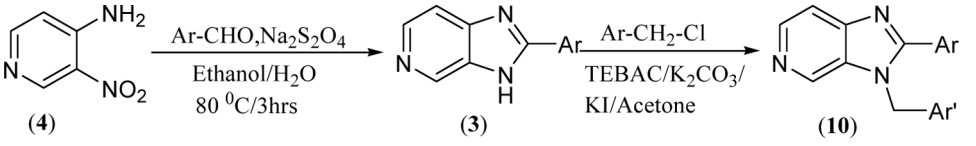
Scheme 2. The possible reaction mechanism.

examined, and the results are summarized in the experimental section. In all cases, aromatic aldehydes carrying either an electron-withdrawing group or electron-donating group reacted successfully and gave the products in good yields. The results proved that this method is superior to the previously reported method in terms of good yields, one-pot cyclization, few steps, and simple processing.

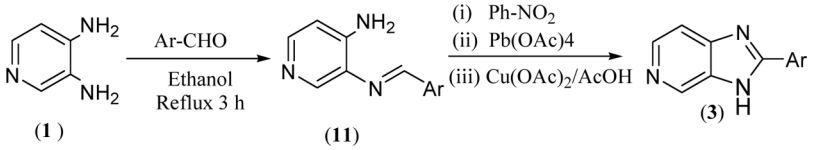
Puerstinger and coworkers reported[24] that the benzylations on 2-aryl-1*H*-imidazo[4,5-c]pyridine **3** with substituted benzyl halides in dimethylformanide (DMF) solvent using 50% NaOH solution as a base gave an N-benzylated derivative on pyridine in imidazopyridines, not on an imidazole ring. We carried out the benzylation reactions under phase-transfer catalytic (PTC) conditions, using K_2CO_3 as a mild base and a catalytic amount of KI, regardless of whether N-benzylation occurs on the imidazole ring or pyridine ring.

Reaction of **3a** (Ar = -C_6H_4-4-OCH_3) with benzyl chloride in CH_3CN using TEBAC as a PTC, anhyd. K_2CO_3 as base, and a catalytic amount of KI under anhydrous conditions at room temperature (2 h) afforded the 1-benyl-2-*p*-methoxyphenyl-1*H*-imidazo[4,5-c]pyridine **10a** (Ar = -C_6H_4-4-OCH_3, Ar′ = -C_6H_5) selectively. It was confirmed on the basis of spectral data (Scheme 3). When the same reaction was carried out in the absence of KI, the reaction completed in 10–12 h.

Perchance, conversion of **3a** to corresponding **10a** is favored in the presence of KI. This is probably because in presence of KI, chlorine of benzyl is initially replaced by iodine, and subsequent reaction of iodo derivative of benzyl with the nitrogen nucleophile such as 1*H*-imidazo[4,5-c]pyridine **3** is facile.



Scheme 3. Preparation of 2-aryl-1*H*-imidazo[4,5-c]pyridines followed by aralkylation.



Scheme 4. Preparation of 2-aryl-1*H*-imidazo[4,5-c]pyridines using oxidative dehydrogenating agents.

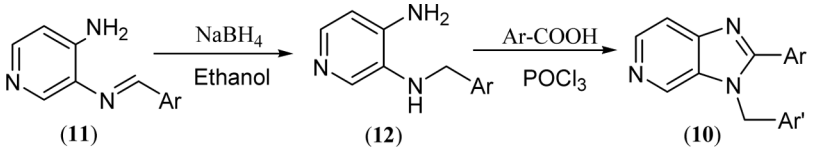
The reaction between **4** and 4-methoxy benzaldehyde, followed by benzylation studies, has been found to be general, and it has been extended to other aromatic aldehydes, followed by reactions with benzyl chloride in nonaqueous medium. The products thus obtained were assigned structures **3** and **10,** respectively, on the basis of spectral and analytical data (Scheme 3).

Alternatively, the compounds **3** and **10** can also be synthesized another two sequences of reactions as shown in Schemes 4 and 5.

Alternatively, compound **3** could also be synthesized by the following sequence of reactions. Reduction of **4** with H_2/Pd-C in ethanol gave previously reported[25–27] 3,4-diaminopyridine **1**. The condensation of **1** with *p*-methoxy benzaldehyde in ethanol under refluxing conditions,[20] followed by simple processing, yielded product **11a** (Ar = -C_6H_4-4-OCH_3), which was found to be homogeneous on thin-layer chromatography (TLC). Its infrared (IR), ^{1}H NMR, and mass spectral data indicated it to be a monoanil formed by a simple 1:1 condensation of **1** with *p*-methoxy benzaldehyde. The latter, on dehydrogenative cyclization using oxidizing agents such as lead tetraacetate [$Pb(OAc)_4$] in acetic acid, followed by simple aqueous workup, once again gave **3a** in good yield (Scheme 4). This was confirmed based on comparison of thin-layer chromatography (TLC) results mp, mmp, and super-impossible IR with those of the compounds obtained through the one-pot reductive cyclization approach (Scheme 3).

Further, we examined with other oxidative dehydrogenating agents, such as cupric acetate [$Cu(OAc)_2$] and nitrobenzene (Ph-NO_2), for the dehydrogenative cyclization of **11a** to get **3a.** The reaction of **11** with cupric acetate [$Cu(OAc)_2$] in acetic acid, followed by simple processing, resulted in the formation of respective 2-*p*-methoxyphenyl-1*H*-imidazo[4,5-c]pyridine **3a** (i.e., **3**, Ar = -C_6H_4-4-OCH_3), in good yields. Similarly, when nitrobenzene was used as an oxidizing reagent, it gave the same results. See experimental data for yields (Scheme 4).

Compound **10** could also be synthesized another sequence of reactions as shown [i.e., reduction of Schiff's base **11a** with $NaBH_4$ in ethanol at room temperature, resulting in the formation of 3-benzylamino-4-aminopyridine **12a**, which on cyclization with *p*-methoxy benzoic acid in refluxing $POCl_3$ gave **10a** (Ar = -C_6H_4-4-OCH_3, Ar′ = -C_6H_5)]. This product is identical with compound obtained from **3a**



Scheme 5. Preparation of N-aralkyl-1*H*-imidazo[4,5-c]pyridines.

using benzyl chloride under nonaqueous conditions in the presence of K_2CO_3 in all respects (mp, TLC, ^{1}H NMR, mass).

Based on these results, when benzylation reactions are carried out using K_2CO_3 as a base in nonaqueous medium in the presence of a PTC such as TEBAC, the benzylation occurs on the imidazole ring, not on the pyridine ring as in imidazopyridines.

CONCLUSION

In summary, we have found an efficient and versatile method for the preparation of a series of 2-aryl-1*H*-imidazo[4,5-c]pyridines in one pot via reductive cyclization from 4-amino-3-nitropyridines and various aromatic aldehydes using solid $Na_2S_2O_4$, followed by benzylation studies on imidazopyridines under PTC conditions using TEBAC. In this article, we also reprot alternate synthesis of 2-aryl-1*H*-imidazo[4,5-c]pyridines and 1-benyl-2-aryl-1*H*-imidazo[4,5-c] pyridines.

EXPERIMENTAL

General Conditions

Melting points were determined in open glass capillaries using a Buchi melting-point apparatus and are uncorrected. IR spectra were recorded on sample as diluted solutions (chloroform or carbon tetrachloride) in matched sodium chloride cells or as potassium bromide pellets with a Perkin IR spectrometer. All ^{1}H NMR spectra were recorded on a Varian 200-MHz instrument with an internal standard of tetramethylsilane. Mass spectra were recorded on an Agilent-LC-MS instrument giving only $M^{+\bullet}$ values using $(M^{\bullet+} + 1)$ mode. Analytical TLC was performed with silica gel GF_{254} from Merck (Germany) containing a fluorescent indicator. Spots were detected with ultraviolet (UV) light or iodine. Column chromatography was performed with Baker 60 to 120-mesh silica gel. The starting materials **1** and **4** were prepared from 4-amino pyridine using a known procedure.[28] The following experimental procedures are representive of the general procedures used to synthesize all compounds.

Preparation of 3 Using Na_2SO_4

A mixture of **4** (1.39 g, 10 mmol) and aromatic aldehyde (10 mmol) in EtOH (20 mL) was treated with solid $Na_2S_2O_4$ (1.75 g, 10 mmol), then heated at 80°C for 4 h. The progress of reaction was monitored on TLC for the disappearance of **4**. At the end of this period, the mixture was poured into 5 N aqueous NH_4OH solution; the precipitated solid was filtered, washed with water, dried, and recrystallized from suitable solvent to obtain pure **3** (Scheme 3).

Data

2-(4-Methoxy-phenyl)-imidazo[4,5-c]pyridine (3a). Ar = -C_6H_4-4-OCH_3, yield 88%, mp 268–70°C; IR (KBr): 3415 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS)

δ 3.8 (s, 3H, -OCH_3), 7.2–7.4 (m, 2H, Ar-H), 7.4–7.6 (m, 1H, Ar-H), 8.0–8.2 (m, 2H, Ar-H), 8.2–8.4 (m, 1H, Ar-H), 8.9 (s, 1H, Ar-H), 13.0 (s, 1H, -NH); $M^{\bullet+}+1$: 226. Anal. calcd. for ($C_{13}H_{11}N_3O$): C, 69.32; H, 4.92; N, 18.66. Found: C, 69.26; H, 4.86; N, 18.58%.

2-*p*-Tolyl-imidazo[4,5-c]pyridine (3b). Ar = -C_6H_4-4-CH_3, yield 90%, mp 268–270°C; IR (KBr): 3434 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS) δ 2.4 (s, 3H, -CH_3), 7.2–7.4 (m, 3H, Ar-H), 7.8–8.0 (m, 2H, Ar-H), 8.0–8.2 (m, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 13.1 (s, 1H, -NH); $M^{\bullet+}+1$: 210. Anal. calcd. for ($C_{13}H_{11}N_3$): C, 74.62; H, 5.30; N, 20.08, Found: C, 74.56; H, 5.24; N, 20.00%.

2-Phenyl-imidazo[4,5-c]pyridine (3c). Ar = -C_6H_5, yield 84%, mp 230–232°C; IR (KBr): 3441 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS) δ 7.3–7.6 (m, 4H, Ar-H), 8.1–8.3 (m, 3H, Ar-H), 8.90 (s, 1H, Ar-H), 12.95 (s, 1H, -NH); $M^{\bullet+}+1$: 196. Anal. calcd. for ($C_{12}H_9N_3$): C, 73.83; H, 4.65; N, 21.52, Found: C, 73.76; H, 4.61; N, 21.48%.

2(4-Chloro-phenyl)-imidazo[4,5-c]pyridine (3d). Ar = -C_6H_4-4-Cl, yield 84%, mp 246–248°C; IR (KBr): 3436 cm^{-1} (b, -NH_2); ^{1}H NMR ($CDCl_3$/TMS): δ 7.4–7.6 (m, 4H, Ar-H), 8.2–8.4 (m, 2H, Ar-H), 8.90 (s, 1H, Ar-H), 13.0 (s, 1H, -NH); $M^{\bullet+}+1$: 230. Anal. calcd. for ($C_{12}H_8ClN_3$): C, 62.76; H, 3.51; N, 18.30, Found: C, 62.70; H, 3.46; N, 18.26%.

2(2-Chloro-phenyl)-imidazo[4,5-c]pyridine (3e). Ar = -C_6H_4-2-Cl, yield 82%, mp 296–298°C; IR (KBr): 3432 cm^{-1} (b, -NH_2); ^{1}H NMR ($CDCl_3$/TMS) δ 7.2–7.4 (m, 4H, Ar-H), 8.0–8.2 (m, 2H, Ar-H), 8.90 (s, 1H, Ar-H), 12.9 (s, 1H, -NH); $M^{\bullet+}+1$: 230. Anal. calcd. for ($C_{12}H_8ClN_3$): C, 62.76; H, 3.51; N, 18.30, Found: C, 62.72; H, 3.42; N, 18.24%.

2(4-Nitro-phenyl)-3*H*-imidazo[4,5-c]pyridine (3f). Ar = -C_6H_4-4-NO_2, yield 82%, mp > 300°C; IR (KBr): 1514 (-NO_2), 3452–3449 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS) δ 7.2–7.4 (m, 3H, Ar-H), 7.8–8.0 (m, 2H, Ar-H), 8.0–8.2 (m, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 12.95 (s, 1H, -NH); $M^{\bullet+}+1$: 241. Anal. calcd. for ($C_{12}H_8N_4O_2$): C, 60.00; H, 3.36; N, 23.32. Found: C, 59.96; H, 3.30; N, 23.26%.

2-*o*-tolyl-3*H*-imidazo[4,5-c]pyridine (3g). Ar = -C_6H_4-2-CH_3, yield 84%, mp 260–262°C; IR (KBr): 3435 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS) δ 2.35 (s, 3H, -CH_3), 7.0–7.2 (m, 3H, Ar-H), 7.8–8.0 (m, 2H, Ar-H), 8.0–8.2 (m, 1H, Ar-H), 8.90 (s, 1H, Ar-H), 13.0 (s, 1H, -NH); $M^{\bullet+}+1$: 210. Anal. calcd. for ($C_{13}H_{11}N_3$): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.52; H, 5.25; N, 20.00%.

[4-(3*H*-Imidazo[4, 5-c]pyridine-2-yl]-dimethyl Amine (3h). Ar = -C_6H_4-4-NMe_2, yield 80%, mp 292–294°C; IR (KBr): 3440 cm^{-1} (b, -NH); ^{1}H NMR ($CDCl_3$/TMS) δ 2.85 (s, 6H, -NMe_2) 6.8–7.0 (m, 2H, Ar-H), 7.4–7.8 (m, 3H, Ar-H), 8.0–8.1 (m, 1H, Ar-H); 8.95 (s, 1H, Ar-H), 12.95 (s, 1H, -NH); $M^{\bullet+}+1$: 239. Anal. calcd. for ($C_{14}H_{14}N_4$): C, 70.57; H, 5.92; N, 23.51. Found: C, 70.51; H, 5.84; N, 23.43%.

Preparation of 10 (Benzylation of 3)

K_2CO_3 (1.52 g, 11 mmol) and KI (0.16 g, 1 mmol) were added to a solution of TEBAC (0.2 g) in CH_3CN (10 mL), and the mixture was stirred at RT for 10 min. To this mixture, under stirring, a solution of **3** (10 mmol) in CH_3CN (5 mL) was added, which was then stirred another 10 min. Benzyl chloride (11 mmol) was added. The whole reaction mass was stirred at rT. The progress of the reaction was monitored by TLC for the disappearance of **3**. On completion of the reaction (~2 h), the mixture was diluted with water. The solid product was thrown out from the reaction mass, filtered, washed with water, and dried to give crude **10**. The crude product was recrystallized from suitable solvent and gave **10** in moderate yields (Scheme 3).

Data

3-Benzyl-2-(4-methoxy-phenyl)-imidazo[4,5-c]pyridine (10a). Ar = -C_6H_4-4-OCH_3, yield 86%, mp 226–228°C; ^{1}H NMR ($CDCl_3$/TMS) δ 3.84 (s, 3H, -OCH_3), 5.40 (s, 2H, -CH_2-), 7.20–7.35(m, 7H, Ar-H), 7.3–7.7 (m, 2H, Ar-H), 8.25–8.35 (m, 2H, Ar-H), 8.52 (s, 1H, Ar-H); $M^{\bullet+}+1$: 316. Anal. calcd. for ($C_{20}H_{17}N_3O$): C, 76.17; H, 5.43; N, 13.32. Found: C, 76.12; H, 5.36; N, 13.26%.

3-Benzyl-2-p-tolyl-imidazo[4,5-c]pyridine (10b). Ar = -C_6H_4-4-CH_3, yield 88%, mp 230–232°C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.41 (s, 3H, -CH_3), 5.41 (s, 2H, -CH_2-), 7.21–7.31 (m, 7H, Ar-H), 7.4–7.7 (m, 2H, Ar-H), 8.2–8.3 (m, 2H, Ar-H), 8.4 (s, 1H, Ar-H); $M^{\bullet+}+1$: 300. Anal. calcd. for ($C_{20}H_{17}N_3$): C, 80.24; H, 5.72; N, 14.07. Found: C, 80.18; H, 5.66; N, 13.98%.

3-Benzyl-2-phenyl-imidazo[4,5-c]pyridine (10c). Ar = -C_6H_5, yield 78%, mp 216–218°C; ^{1}H NMR ($CDCl_3$/TMS) δ 5.38 (s, 2H, -CH_2-), 7.25–7.40 (m, 8H, Ar-H), 7.6–7.7(m, 2H, Ar-H), 8.1–8.2 (m, 2H, Ar-H), 8.45 (s, 1H, Ar-H); $M^{\bullet+}+1$: 286. Anal. calcd. for ($C_{19}H_{15}N_3$): C, 79.98; H, 5.30; N, 14.73. Found: C, 79.92; H, 5.26; N, 14.68%.

3-Benzyl-2-(4-chloro-phenyl)-imidazo[4,5-c]pyridine (10d). Ar = -C_6H_4-4-Cl, yield 72%, mp 246–248°C; ^{1}H NMR ($CDCl_3$/TMS): δ 5.40 (s, 2H, -CH_2-), 7.0–7.4 (m, 7H, Ar-H), 7.4–7.6 (m, 2H, Ar-H), 7.9–8.0 (s, 2H, Ar-H), 8.48 (s, 1H, Ar-H); $M^{\bullet+}+1$: 320. Anal. calcd. for ($C_{19}H_{14}ClN_3$): C, 71.36; H, 4.41; N, 13.14. Found: C, 71.32; H, 4.35; N, 13.06%.

Preparation of 11 (General Procedure)

A mixture of **1** (1.09 g, 10 mmol) and respective aldehydes (10 mmol) in ethanol (20 mL) was stirred at reflux until the condensation was complete as shown by TLC. At the end of this period, ethanol was removed under reduced pressure. The residual crude **11**, thus obtained, was purified by column chromatography using hexane and ethyl acetate (9:1) to give **11** as a pure product.

Data

(E)-N^3-(4-Methoxybenzylidene)pyridine-3,4-diamine (11a). Ar = -C_6H_4-4-OCH_3, yield = 95%, mp 48–50°C; IR (KBr) 3435–3433 cm^{-1} (b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 3.8 (s, 3H, -OCH_3), 4.6 (bs, 2H, -NH_2), 6.6–6.8 (d, J = 5.4 Hz, 1H, pyridine proton 5th), 7.4–8.3 (m, 6H, four phenyl and two pyridyl), 8.3 (s, 1H = CH, vinyl proton); $M^{\bullet+}+1$: 228. Anal. calcd. for ($C_{13}H_{13}N_3O$): C, 68.70; H, 5.77; N, 18.49. Found: C, 68.64; H, 5.72; N, 18.44%.

(E) N^3-(4-Methylbenzylidene)pyridine-3,4-diamine (11b). Ar = -C_6H_4-4-CH_3, yield 92%, mp 40–42°C; IR (KBr) 3427–3431 cm^{-1} (b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 2.4 (s, 3H, -CH_3), 4.65 (bs, 2H, -NH_2), 6.55–6.75 (d, J = 5.4 Hz, 1H, pyridine proton 5th), 7.4–8.2 (m, 6H, four phenyl and two pyridyl), 8.25 (s, 1H = CH, vinyl proton); $M^{\bullet+}+1$: 212. Anal. calcd. for ($C_{13}H_{13}N_3$): C, 73.91; H, 6.20; N, 19.89. Found: C, 73.86; H, 6.12; N, 19.85%.

(E)-N^3-Benzylidenepyridine-3,4-diamine (11c). Ar = -C_6H_5, yield 90%, mp 29–31°C; IR (KBr) 3452–3449 cm^{-1} (b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 5.0 (bs, 2H, -NH_2), 6.6–6.8 (d, J = 5.2 Hz, 1H, pyridine proton 5th), 7.4–8.2 (m, 7H, five phenyl and two pyridyl) & 8.4 (s, 1H = CH, vinyl proton); $M^{\bullet+}+1$: 198. Anal. calcd. for ($C_{12}H_{11}N_3$): C, 73.07; H, 5.62; N, 21.30. Found: C, 72.97; H, 5.58; N, 21.22%.

(E)-N^3-(4-Chlorobenzylidene)pyridine-3,4-diamine (11d). Ar = -C_6H_4-4-Cl, yield 95%, mp 38–40°C; IR (KBr) 3429–3428 cm^{-1}(b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 4.6 (bs, 2H, -NH_2), 6.55 (d, J = 5.0 Hz, 1H, pyridine 5th), 7.45–8.1 (m, 6H, four phenyl and two pyridyl), 8.2 (s, 1H = CH, vinyl proton); $M^{\bullet+}+1$: 232. Anal. calcd. for ($C_{12}H_{10}ClN_3$): 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 (11e). Ar = -C_6H_4-2-Cl, yield = 88%, mp 45–47°C; IR (KBr) 3454–3451 cm^{-1} (b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 4.68 (bs, 2H, -NH_2), 6.6 (d, J = 5.2 Hz, 1H, pyridine 5th), 7.4–8.3 (m, 6H, four phenyl and two pyridyl), 9.55 (s, IH = CH, vinyl proton); $M^{\bullet+}+1$: 232. Anal. calcd. for ($C_{12}H_{10}ClN_3$): C, 62.21; H, 4.35; N, 18.14. Found: C, 62.16; H, 4.28; N, 18.08%.

(E)-N^3-(4-Nitrobenzylidene)pyridine-3,4-diamine (11f). Ar = -C_6H_4-4-NO_2, yield 95%, mp 53–55°C; IR (KBr): 3409–3454 cm^{-1} (b, doublet, -NH_2); ^{1}H NMR (DMSO-d_6/TMS) showed signals at δ 5.5 (bs, 2H, -NH_2), 6.55 (d, J = 5.3 Hz, 1H, pyridine 5th), 7.45–8.1 (m, 6H, four phenyl and two pyridyl), 8.2 (s, 1H = CH, vinyl proton); $M^{\bullet+}+1$: 243. Anal. calcd. for ($C_{10}H_{10}N_4O_2$): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.44; H, 4.10; N, 23.06%.

Cyclization of 11 Under Different Conditions

With nitro benzene. A mixture of **11** (10 mmol) and nitro benzene (20 mL) was heated under reflux (210–215°C) for 2 h. The progress of the reaction was monitored on TLC for the disappearance of **11**. After completion of reaction, the solvent was removed under reduced pressure to get residue **2**. The residue was triturate with

hexane to get free-flowing solid. It was purified by column chromatography using hexane and ethyl acetate (8:2) to yield a pure **3** in good yields (Scheme 4).

Yields (%): **3a** = 84, **3b** = 82, **3c** = 80, **3d** = 82, **3e** = 78, and **3f** = 78.

With $Pb(OAc)_4$ (or) $Cu(OAc)_2$. The respective dehydrogenating agent [(i.e., $Pb(OAc)_4$ (or) $Cu(OAc)_2$(10 mmol)] to a solution of **11** (10 mmol) in acetic acid (20 mL) was added at room temperature, and the mixture was stirred for 1 h at 80°C. At the end of this period, the reaction mixture was cooled to room temperature and poured into ice-cold water (100 mL). The separated solid was filtered, washed with water (2 × 50 mL) and dried. The crude products were recrystallized from suitable solvent to get pure **3**.

Yield (%): ($Pb(OAc)_4$/$Cu(OAc)_2$): **3a** = 79/86, **3b** = 80/84, **3c** = 79/80, **3d** = 74/78, **3e** = 78/82, and **3f** = 78/76.

Typical Procedure for Reduction of 11 (Schiff's Base)

Sodium borohydride (0.38 g, 10 mmol) was added to a solution of **11** (10 mmol) in methanol (30 mL) portionwise at 20–25°C with stirring. After completion of the addition (10–15 min), the reaction mixture was heated on a water bath for 1 h until 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 × 40 mL), and dried to obtain a crude product, which on recrystallization from ethanol gave pure **12**.

Data

N^3-(4-Methoxybenzyl)pyridine-3,4-diamine (12a). 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 5th), 6.9–7.3 (m, 4H, phenyl), 7.8 (d, J = 6.2 Hz, 2H, pyridine); $M^{\bullet+}$ + 1: 230. Anal. calcd. for ($C_{13}H_{15}N_3O$): C, 68.10. H, 6.59; N, 18.33. Found: C, 68.02; H, 4.06; N, 23.00%.

N^3-(4-Methylbenzyl)-pyridine-3,4-diamine (12b). Ar = -C_6H_4-4-CH_3, yield 72%, mp 152–54°C; IR (KBr): 3428 cm^{-1} (-NH); ^{1}H NMR (DMSO-d_6/TMS) δ 2.4 (s, 3H, -CH_3), 3.35 (bs, 1H, -NH), 4.2 (bs, 2H, -NH_2), 4.4 (s, 2H, -CH_2-), 6.55 (d, J = 5.4 Hz, 1H, Pyridine 5th), 7.4–8.2 (m, 7H, phenyl and two pyridyl); $M^{\bullet+}$ + 1: 214. Anal. calcd. for ($C_{13}H_{15}N_3$): C, 73.21; H, 7.09; N, 19.70. Found: C, 73.15; H, 7.02; N, 19.62%.

N^3-Benzylpyridine-3,4-diamine (12c). 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 5th), 7.5–8.3 (m, 7H, phenyl and two pyridyl); $M^{\bullet+}$ + 1: 200. Anal. calcd. for ($C_{12}H_{13}N_3$): C, 72.33; H, 6.58; N, 21.09. Found: C, 72.26; H, 4.06; N, 21.01%.

N^3-(4-Chlorobenzyl)pyridine-3,4-diamine (12d). 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

5th), 7.3–7.4 (m, 4H, phenyl), 7.8 (d, $J = 6.2$ Hz, 2H, pyridine); $M^{\bullet+} + 1$: 234. Anal. calcd. for ($C_{12}H_{12}ClN_3$): 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 (12e). Ar = -C_6H_4-2-Cl, yield 71%, mp 136–138°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 5th), 7.5–7.8 (m, 4H, phenyl), 7.8 (d, $J = 6.2$ Hz, 2H, pyridine); $M^{\bullet+} + 1$: 234. Anal. calcd. for ($C_{12}H_{12}ClN_3$): C, 61.67; H, 5.18; N, 17.98. Found: C, 61.65; H, 5.15; N, 17.94%.

N^3-(4-Nitrobenzyl)pyridine-3,4-diamine (12f). Ar = -C_6H_4-4-NO_2, yield 81%, mp 191–193°C; IR (KBr): 1514 (-NO_2), 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, Hz, 1H, pyridine 5th), 7.5–8.6 (m, 4H, phenyl protons), 7.8 (d, $J = 7.2$ Hz, 2H, pyridine protons); $M^{\bullet+} + 1$: 245. Anal. calcd. for ($C_{12}H_{12}N_4O_2$): C, 59.01; H, 4.95; N, 22.94. Found: C, 58.95; H, 4.89; N, 22.90%.

Preparation of 10 from 12

A mixture of **12** (10 mmol) and aromatic acid (10 mmol) was added to $POCl_3$ (20 mL), and the resulting mixture was heated to reflux for 4 h. The progress of the reaction was monitored by TLC. On completion of reaction, excess of $POCl_3$ was removed under reduced pressure. The residue was treated with ice-cold water and neutralized with aqueous NaOH solution. The precipitated product was filtered, washed with water, and dried to give crude **10**. The crude products were recrystallized from a suitable solvent to get pure **10** in good yields.

Yields (%): **10a** = 73, **10b** = 69, **10c** = 68, and **10d** = 71.

ACKNOWLEDGMENTS

We thank Azakem Laboratories Pvt. Ltd. management for encouragement and the staff of the analytical laboratories of our research center for spectral analyses.

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