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Eco-friendly and facile synthesis of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine in aqueous medium by air oxidation

Rajesh P. Kale [a], Mohammad U. Shaikh [a], Ganesh R. Jadhav [a,b], Charansingh H. Gill [a,*]

[a] Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra 431 004, India
[b] Wockhardt Research Centre, D-4 Chikalthana M.I.D.C. Area, Aurangabad, Maharashtra 431 210, India

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ABSTRACT

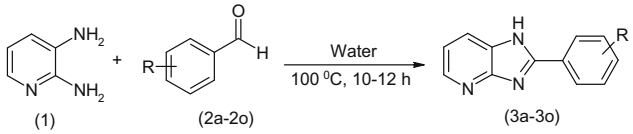
We report a new environmentally-benign, convenient, and facile methodology for the synthesis of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine. The reaction of 2,3-diaminopyridine with substituted aryl aldehydes in water under thermal conditions without the use of any oxidative reagent has been studied. The reaction has yielded 1*H*-imidazo[4,5-*b*]pyridine derivatives by an air oxidative cyclocondensation reaction in one step in an excellent yield. Furthermore, a series of compounds were synthesized and characterized by melting point, EI-MS, NMR, and IR tools. For comparison, the reference samples were prepared by the reported method. Utilization of aqueous medium, easy reaction conditions, isolation, and purification make this manipulation very interesting from an economic and environmental perspective.

2,3-Diaminopyridine and imidazo[4,5-*b*]pyridines have been proved to be useful precursors for the synthesis of a variety of medicinal agents. The heterocycles derived from these intermediates have recently been evaluated as antagonists of various biological receptors, including angiotensin-II,[1] platelet activating factor (PAF)[2] metabotropic glutamate subtype V.[3] Substituted imidazo[4,5-*b*]pyridines have also been tested for their potential as anticancer,[4] inotropic,[5] and selective antihistamine (H_1) agents.[6] Imidazo[4,5-*b*]pyridine derivatives were also reported as Aurora kinases,[7] cyclic PDE inhibitors.[8] Hence, the synthesis of imidazo[4,5-*b*]pyridine derivatives is currently of great interest. Despite the importance of these intermediates, the methodologies[1–7] available for the synthesis were generally target-specific and restrictive in their scope. Various methods[9–16] reported for the synthesis of imidazo[4,5-*b*]pyridines were based on cyclocondensation of 2,3-pyridinediamine with carboxylic acid derivatives or on condensation with aldehydes. However, it is noticed that all these methods are not straightforward and involve various disadvantages such as low yields, prolonged reaction times, and the use of toxic organic reagents such as $POCl_3$, TMS-Cl, and PPA (Polyphosphoric acid). In addition to this, harsh reaction conditions such as high reaction temperatures (>170 °C), use of catalyst/oxidizing agents such as $Pb(OAc)_4$, $Py(Cr_2O_7)_2$, and $Cu(OAc)_2$, and continuous O_2 bubbling in the reaction are also present. The one major drawback of many of these reported methods is that the synthesis involves a two-step process, namely isolation of the Schiff base by condensation of diamine with aldehyde in step one and dehydrogenative cyclization in a subsequent step to yield 1*H*-imdazo[4,5-*b*]pyridine. Hence, it is imperative to develop a convenient, efficient, and user friendly method for the synthesis of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine.

Nowadays, the organic reactions in aqueous media have attracted much attention in synthetic organic chemistry as water is the most abundant, cheapest, and environmental-friendly solvent. It also exhibits a unique reactivity and selectivity different from conventional organic solvents.

Recently, it has been reported[17] that some organic molecules can react on the surface of water. Often a very strong enhancement of reaction rates was noticed in this case, particularly when at least one component involved in this reaction bore a polar group, enabling some degree of solubility.

As a continuation of our research work devoted to the development of biologically active substituted benzimidazole derivatives,[18,19] we herein report an eco-friendly, facile, and efficient methodology for the synthesis of 1*H*-imidazo[4,5-*b*]pyridine. This method involves a one-pot reaction of 2,3-diaminopyridine and substituted aryl aldehydes in water without the use of any



Scheme 1. Preparation of title compounds (**3a–o**).

* Corresponding author.
E-mail address: chgill50@gmail.com (C.H. Gill).

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Table 1
Solvent effects on reaction[#] of 2,3-diaminopyridine and benzaldehyde

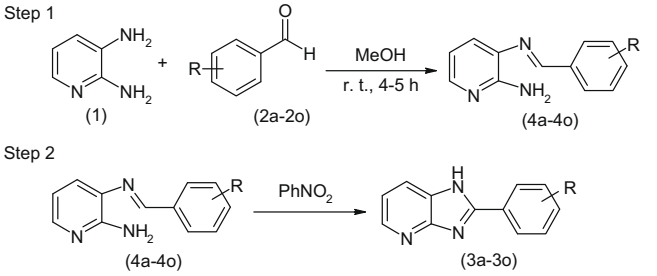
Entry	Solvent	Condition		Yield[a] (%)
		Temp (°C)	Time (h)	
1	Methanol[b]	67	12	<40
2	Methanol[b]	67	24	<40
3	Ethanol[c]	80	12	—
4	Ethanol[c]	80	24	—
5	10% aq Ethanol[c]	80	12	—
6	10% aq Ethanol[c]	80	24	—
7	50% aq Ethanol[c]	80	12	—
8	50% aq Ethanol[c]	80	24	—
9	Water	100	10–12	87

[#] Reaction carried out with 2,3-diaminopyridine (0.1 mol) and benzaldehyde (0.11 mol).
[a] Isolated yields.
[b] Reaction incomplete, unreacted 2,3-diaminopyridine recovered.
[c] Reaction stopped at imine intermediate stage, no product formation.

oxidizing agent or catalyst (Scheme 1). The isolation of the product was done by simple filtration, and purification was carried out by recrystallization. No column chromatography was required for the isolation of the pure product. The use of water as a solvent, simple reaction conditions, ease in isolation, and purification make this methodology environmentally benign, efficient, and user friendly.

A series of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine (**3a**–**o**) were prepared (Scheme 1) and characterized. The reaction was carried out between 2,3-diaminopyridine[20] (**1**) and substituted aryl aldehydes (**2a**–**o**) in water at 100 °C for 10–12 h. The progress of the reaction was monitored by TLC (dichloromethane/methanol; 9:1). Upon completion of the reaction, it was allowed to cool to room temperature; the solid was filtered and washed with water. The crude material was purified by recrystallization in ethanol to give title compounds in excellent yields (83–87%). The structures for these products (**3a**–**o**) were characterized on the basis of the following observations:

(i) Melting point matching with examples demonstrated in the literature.
(ii) The product showed a molecular ion peak in mass spectra corresponding to the desired cyclized product.
(iii) The ^{1}H NMR spectra (DMSO) showed a singlet at δ 13.06–13.10 characteristic of –N*H* of imidazopyridine which tallied with the structures assigned.



Scheme 2. Preparation of reference compounds.

(iv) IR peak at 3060–3100 cm^{-1} assignable to –NH of imidazopyridine.

The reaction of 2,3-diaminopyridine with various substituted aryl aldehydes was carried out in water at 100 °C, the product was isolated by simple filtration, and purification was carried out by recrystallization. Melting point, ^{1}H NMR, EI-MS, and IR analysis confirmed the structures of pure isolated products.

To study the reaction in water, we tested the reaction of 2,3-diaminopyridine and benzaldehydes as a simple model substrate in different solvents, namely methanol, ethanol, and 10% and 50% aqueous ethanol. The results are shown in Table 1. It was found that water (entry 9) was a solvent of choice for the reaction, and the desired product was obtained in excellent yields (87%). Not only water but methanol (entries 1 and 2) also displayed the same result. In methanol, the desired product was formed but the reaction was incomplete even after 24 h. The formation of the product was low (<40%), and unreacted 2,3-diaminopyridine was recovered. It was observed that ethanol and aqueous ethanol (10% and 50%) behaved poorly in the reaction. In these cases, the reaction stopped at the imine stage **4** (Scheme 2). Even longer reaction times failed to produce the desired product. The formation of imines was confirmed on the basis of the MS, NMR, and IR data generated. The molecular ion peak in mass spectrum (M+H = 196) corresponds with the open-chain imine compound. The ^{1}H NMR (DMSO) spectrum displayed a singlet at δ 5.0 and δ 8.5 that were assignable to –NH_2 of pyridine and exocyclic N=CH of Schiff base, respectively, while the IR spectrum in KBr phase showed a doublet at 3350 and 3300 cm^{-1} that were assignable to the –NH_2 group of pyridine.

Table 2
Physical characteristic data for compounds **3a**–**o**

Entry[a]	R	M.F/M.Wt.	Mp (°C)		Yield[b] (%)
			Observed	Lit.	
3a	C_6H_5	$C_{12}H_9N_3$/195.23	288–290	291–293[9]	87
3b	3-CH_3–C_6H_4	$C_{13}H_{11}N_3$/209.25	240–242	240–241[9]	84
3c	4-CH_3–C_6H_4	$C_{13}H_{11}N_3$/209.25	260–263	261–262[9]	86
3d	4-OMe–C_6H_4	$C_{13}H_{11}N_3O$/225.25	228–230	230–232[21]	83
3e	4-*N*,*N*-$(CH_3)_2$–C_6H_4	$C_{14}H_{14}N_4$/238.29	>300	>300[11]	83
3f	2-Cl–C_6H_4	$C_{12}H_8ClN_3$/229.67	190–192	188–189[22]	83
3g	3-Cl–C_6H_4	$C_{12}H_8ClN_3$/229.67	298–190	287–288[22]	86
3h	4-Cl–C_6H_4	$C_{12}H_8ClN_3$/229.67	>300	>300[9]	87
3i	3-F–C_6H_4[c]	$C_{12}H_8FN_3$/213.22	>300	—	87
3j	4-F–C_6H_4	$C_{12}H_8FN_3$/213.22	221	219[9]	85
3k	3-Br–C_6H_4	$C_{12}H_8BrN_3$/274.12	>300	>300[22]	83
3l	4-Br–C_6H_4	$C_{12}H_8BrN_3$/274.12	>300	>300[22]	83
3m	3-NO_2–C_6H_4	$C_{12}H_8N_4O_2$/240.22	>300	>300[22]	85
3n	4-NO_2–C_6H_4	$C_{12}H_8N4O_2$/240.22	>300	>300[22]	84
3o	2-Pyridyl	$C_{11}H_8N_4$/196.21	240–242	242–243[23]	83

[a] All compounds showed satisfactory ^{1}H NMR, mass, and IR spectral data.
[b] Yields after purification.
[c] Novel derivative.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl aldehydes with 2,3-diaminopyridine. The results are shown in Table 2. The newly synthesized compounds were compared (mp, MS, NMR, and IR) with compounds that were prepared by using the literature method[11] (Scheme 2). This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds.

In conclusion, we have developed a new, facile, and efficient methodology for the eco-compatible preparation of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine from 2,3-diaminopyridine and aldehydes in an aqueous medium. The use of water as a solvent and easy reaction conditions to deliver the target products in good yields, often in analytically pure form, suggest a good applicability of this process. We have also shown the versatility of this methodology by applying it to a wide variety of aldehyde substrates. To the best of our knowledge, this is the first report on the synthesis of 1*H*-imidazo[4,5-*b*]pyridine derivatives in aqueous medium.

General procedure for synthesis of title compounds **3a–o**: A mixture of 2,3-diaminopyridine (**1**) (10 mmol) and substituted aryl aldehyde (**2a–o**) (11 mmol) in water was heated at 100 °C for 10–12 h. The progress of the reaction was followed by TLC (dichloromethane/methanol; 9:1). The reaction mixture was cooled to room temperature, and the product was collected by filtration, washed with water, and suck dried. The product was recrystallised from ethanol to give title compounds (**3a–o**) in 83–87% yields.

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