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# An efficient and catalyst-free synthesis of N-arylidene-2-arylimidazo[1,2-a]pyridine-3-ylamine derivatives *via* Strecker reaction under controlled microwave heating

DOI 10.1515/gps-2017-0019

Received January 31, 2017; accepted April 11, 2017; previously published online June 13, 2017

**Abstract:** An efficient one-pot multicomponent reaction of 2-aminopyridine with aromatic aldehydes and either benzoyl cyanide or cyanamide in pyridine under controlled microwave heating afforded N-arylidene-2-arylimidazo[1,2-a]-pyridine-3-ylamine derivatives. The reaction is catalyst free and is of high atom economy.

**Keywords:** catalyst free; microwave heating; multicomponent reaction; N-arylidene-2-arylimidazo[1,2-a]-pyridine-3-ylamine; Strecker reaction.

## 1 Introduction

Imidazo[1,2-a]pyridine derivatives are highly potent heterocyclic scaffolds because of their biological activity and are found in numerous drugs, such as Zolpidem, Alpidem, Zolimidine, Alprinone, Saripidem, and Necopidem [1–9]. Imidazo[1,2-a]pyridines possess a variety of biological activities such as anticancer [10], antiviral [11], antimicrobial [12], antiparkinson [13], antimutagenics [14], antihypoxia [15], and antiinflammatory effects [16]. The synthesis of such scaffold has been extensively studied. Among these, the multicomponent reaction of 2-aminopyridine, aldehydes, and alkynes is one of the most common methods for their synthesis utilizing transition metal catalyst such as palladium [17], copper [18], silver [19], and gold [20]. Transition metal salts such as Ag (I),

Au (III), and Cu (II) in combination with either *p*-toluene-sulfonic acid (PTSA) or copper (I) complex have been utilized to catalyze such three-component reactions [21, 22]. Indium (III) bromide has also been used for the synthesis of imidazo[1,2-a]pyridines [23]. Multicomponent synthesis strategies to prepare a series of imidazo[1,2-a]pyridines have also been reported, however, the most utilized methodology to prepare such scaffold is the Grobke-Blackburn-Bienayme reaction [24–26], and its recent modifications [27–30] that mainly afforded 3-amino-imidazo[1,2-a]pyridines. It is worth to mention that other few protocols for the synthesis of 3-amino substituted products are reported such as nitration of C-3 and subsequent reduction [31]; multicomponent reaction of 2-aminopyridines aromatic aldehydes and imidazoline-2,4,5-trione [32]; as well as Strecker reaction using trimethylsilyl cyanide (TMSCN) or cyanohydrins as the source of cyanide ion utilizing either silica sulfuric acid or (bromo dimethylsulfonium) bromides catalysts [33] with reaction time ranging from 2–3 days to 10–20 h, the use of MCM-41 supported boron trifluoride (BF<sub>3</sub>MCM-41) as a nanosaturated solid acid catalyst with reaction time ranging from 40 to 240 min [34] or Ugi-type multicomponent reaction in water utilizing KF for activation of TMSCN [35]. Although these methods afford good to excellent yields, TMSCN or cyanohydrin is known to be highly toxic and thus an environmental pollutant. Only one recent protocol utilizing polymer-bound scandium triflate as a catalyst under microwave heating has been reported [36]. Though, these protocols are useful, many of these have some demerits such as the use of expensive and excess amount of catalyst, longer reaction times, difficult work-up procedures, and harsh reaction conditions. Extensive efforts have been invested in utilizing green technologies in synthetic organic chemistry. One such technology involves microwave heating with its advantageous features such as operational simplicity, enhanced reaction rates with short reaction times, high yields, and purity of production [37, 38]. In continuation of our interest and others [39–45] in performing

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reactions utilizing microwave heating we have developed an efficient catalyst-free multicomponent reaction for the synthesis of N-arylidene-2-arylimidazo[1,2-a]pyridine derivatives under controlled microwave heating.

## 2 Materials and methods

### 2.1 General information

All the reactions were carried out in a Milestone START microwave Labstation (temperature controlled by IR sensor). Melting points are reported uncorrected and were determined with a Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded using KBr pellets and a Jasco FT-IR 6300 instrument and absorption bands are reported in  $\text{cm}^{-1}$ .  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were determined by using a Bruker DPX instrument (Billerica, USA) at 400 and 600 MHz for  $^1\text{H}$ -NMR and 100 MHz for  $^{13}\text{C}$ -NMR and either  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  solutions with TMS as internal standards. Chemical shifts are reported in ppm. Mass spectra and accurate mass measurements were made using a GCMS DFS Thermo spectrometer with the EI (70 EV) mode. Starting materials were obtained from Aldrich (Mumbai, India) and used directly.

### 2.2 General procedure for the synthesis of 3-N-arylidene-2-arylimidazo[1,2-a]pyridines 4a–j

**Method A:** A solution of 2-aminopyridine **1** (1 mmol), aromatic aldehydes **2a–j** (2 mmol), and either benzoyl cyanide or cyanamide **3a,b** (1 mmol) in pyridine (10 ml) was heated under reflux in a Milestone

Microwave Lab station at  $120^\circ\text{C}$  for 30 min. On completion of the reaction monitored by thin layer chromatography (TLC), the reaction mixture was concentrated under reduced pressure and cooled at room temperature. The resulting precipitate was filtered, washed with ethyl alcohol, and recrystallized from absolute EtOH to give **4** (Table 1).

**Method B:** A solution of 2-aminopyridine **1** (1 mmol) and aromatic aldehydes **2a–j** (1 mmol) in pyridine (10 ml) was heated under reflux in a Milestone Microwave Lab station at  $120^\circ\text{C}$  for 10 min. The formation of corresponding Schiff's base could be detected by using TLC with 1:1 ethyl acetate-petroleum ether as eluant. To the reaction mixture either benzoyl cyanide or cyanamide **3a,b** (1 mmol) and aromatic aldehyde **2a–j** (1 mmol) were added and microwave irradiation was continued for additional 20 min. After evaporation of the solvent, the reaction mixture was left to cool to room temperature. The solid product so formed was collected by filtration, washed with ethanol, and purified by crystallization from EtOH to give **4**.

### Representative spectral and analytical data:

**N-(4-chlorobenzylidene)-[2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3yl]amine (4a)** Yellow solid, yield 88%; mp  $170^\circ\text{C}$ – $172^\circ\text{C}$  (Lit. mp  $170^\circ\text{C}$ – $172^\circ\text{C}$ ) [35];  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 7.04 (t, 1H,  $J$  = 6.2 Hz, Ar–H), 7.35–7.39 (m, 1H, Ar–H), 7.45–7.55 (m, 2H, Ar–H), 7.60–7.64 (m, 3H, Ar–H), 7.98–8.01 (m, 4H, Ar–H) 8.70 (t, 1H,  $J$  = 6.0 Hz, Ar–H) 8.94 (s, 1H, N = CH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 114.1, 114.6, 122.2, 126.2, 128.8, 129.2, 130.6, 131.1, 134.2, 134.5, 136.6, 138.8, 145.2, 158.7. MS:  $m/z$  (%) 365 ( $\text{M}^+$ , 100).

**N-(2-nitrobenzylidene)-[2-(2-nitrophenyl)imidazo[1,2-a]pyridine-3yl]amine (4b)** Buff solid, yield 83%; mp  $218^\circ\text{C}$ – $219^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 7.09 (t, 1H,  $J$  = 7.2 Hz, Ar–H), 7.43 (t, 1H,  $J$  = 7.6 Hz, Ar–H), 7.68 (d, 1H,  $J$  = 8.8 Hz, Ar–H), 7.77 (t, 1H,

**Table 1:** List of [1,2-a]pyridine-3-ylamine derivatives synthesized via microwave irradiation.

Entry	Aldehyde	X–CN	Time (min)	Yield %	Yield %	m.p. ( $^\circ\text{C}$ )
				Method (A)	Method (B)	
<b>4a</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	65	60	170–172
		PhCOCN	30	88	75	
<b>4b</b>	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	60	52	218–219
		PhCOCN	30	83	70	
<b>4c</b>	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	55	50	312–313
		PhCOCN	30	76	65	
<b>4d</b>	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	58	50	154–156
		PhCOCN	30	79	64	
<b>4e</b>	3,4-OMeC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	57	51	140–142
		PhCOCN	30	81	72	
<b>4f</b>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	59	52	290–291
		PhCOCN	30	85	76	
<b>4g</b>	<i>m</i> -OHC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	55	50	132–133
		PhCOCN	30	78	67	
<b>4h</b>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	64	60	184–186
<b>4i</b>	2-thienyl	PhCOCN	30	77	68	126–128
<b>4j</b>	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CN	30	57	50	94–96
		PhCOCN	30	79	66	
		NH <sub>2</sub> CN	30	53	50	
		PhCOCN	30	65	61	

$J=7.6$  Hz, Ar-H), 7.83 (t, 1H,  $J=8.0$  Hz, Ar-H), 8.20 (d, 1H,  $J=8.0$  Hz, Ar-H), 8.35 (d, 1H,  $J=8.0$  Hz, Ar-H), 8.45 (d, 1H,  $J=7.6$  Hz, Ar-H), 8.53 (d, 1H,  $J=7.6$  Hz, Ar-H), 8.79–9.01 (m, 3H, Ar-H), 9.2 (s, 1H, N=CH). MS:  $m/z$  (%) 387 ( $M^+$ , 100).

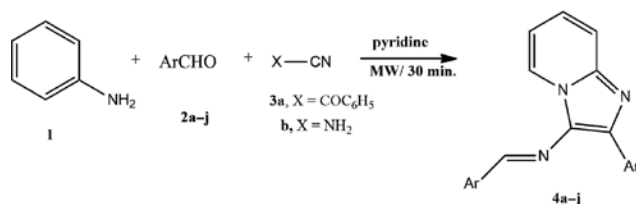
**N-(3-nitrobenzylidene)-[2-(3-nitrophenyl)imidazo[1,2-a]pyridine-3yl]amine (4c)** Orange crystals, yield 76%, m.p. 312–313°C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 7.12 (t, 1H,  $J=6.6$  Hz, Ar-H), 7.45 (t, 1H,  $J=7.2$  Hz, Ar-H), 7.70 (d, 1H,  $J=7.8$  Hz, Ar-H), 7.79 (t, 1H,  $J=8.0$  Hz, Ar-H), 7.85 (t, 1H,  $J=8.4$  Hz, Ar-H), 8.22 (d, 1H,  $J=7.8$  Hz, Ar-H), 8.37 (d, 1H,  $J=7.2$  Hz, Ar-H), 8.48 (d, 1H,  $J=7.8$  Hz, Ar-H), 8.54 (d, 1H,  $J=7.8$  Hz, Ar-H), 8.82 (s, 1H, Ar-H), 8.85 (d, 1H,  $J=6.6$  Hz, Ar-H), 9.01 (s, 1H, Ar-H), 9.24 (s, 1H, N=CH).

**N-(4-Bromobenzylidene)-[2-(4-Bromophenyl)imidazo[1,2-a]pyridine-3yl]amine (4h)** Yellow solid, yield 77%; mp 184°C–186°C (Lit. mp 184–186°C) [35];  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 6.91 (t, 1H,  $J=7.2$  Hz, Ar-H), 7.32 (t, 1H,  $J=7.2$  Hz, Ar-H), 7.52 (d, 2H,  $J=8.3$  Hz, Ar-H), 7.57 (d, 2H,  $J=8.3$  Hz, Ar-H), 7.64 (d, 2H,  $J=8.3$  Hz, Ar-H), 7.76 (t, 4H,  $J=7.2$  Hz, Ar-H), 8.75 (s, 1H, N=CH). MS:  $m/z$  (%) 455 ( $M^+$ , 80).

### 3 Results and discussion

With the initial aim of optimizing the experimental reaction conditions we explored the reaction of 2-aminopyridine (**1**), aromatic aldehyde (**2a**), and either benzoyl cyanide (**3a**) or cyanamide (**3b**) under both acidic and basic conditions. The reaction was promoted by microwave heating over 30 min (Scheme 1). When ethanol in the presence of 10 mol% PTSA was used, the process led to a low yield (36%) of the target imidazo[1,2-a]pyridine derivatives **4a**. Pyridine was also examined and found to be very convenient for such a reaction with a higher yield (88%). To determine the role of the reaction medium, other solvents were examined such as water, methanol, or ethanol without any catalyst. In this case **4a** was not formed even after prolonged microwave irradiation. Finally irrespective of the aryl substituent reactions took place in reasonable yields (Table 1).

The structure of products could be established based on the analytical and spectral data. Mass spectra of **4a** showed  $M^+$  peak at 365 (100%).  $^1\text{H}$  NMR showed peaks



**Scheme 1:** Synthesis of imidazo[1,2-a]pyridine derivatives **4a–j**.

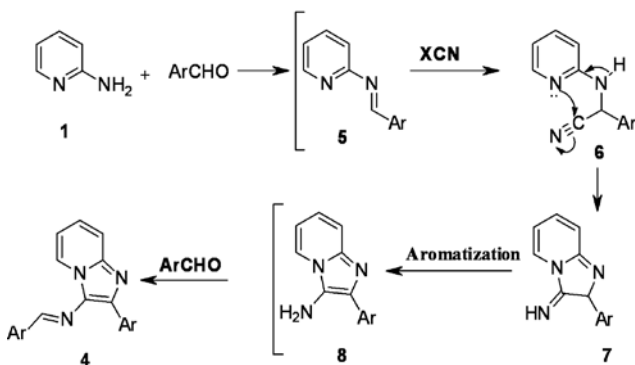
assigned for aromatic protons and a singlet at  $\delta=8.94$  ppm for CH=N function.  $^{13}\text{C}$  NMR was in agreement with the proposed structure.

In order to determine the effect of the reactants molar ratio on the overall yield we started our protocol by mixing the reactants 2-aminopyridine, aromatic aldehydes, and cyanating agent in the ratio 1:1:1 all dissolved in 10 ml pyridine and heated under reflux in a microwave lab station for 30 min. The products were obtained in almost 40% yield as a maximum. However, with a ratio of 1:2:1 of the reactants under the same reaction conditions, the yields increased as shown in Table 1.

To evaluate the advantages of performing the reaction under microwave heating, a control experiment was conducted under conventional heating. It was observed that lower amounts of the products were obtained after 3–4 h. The use of microwave irradiation provided a more efficient and clear reaction.

A suggested mechanism for the formation of compound **4** displayed in Scheme 2 involves the formation of Schiff's base **5** from the reaction of 2-aminopyridine with aldehydes which undergoes Strecker reaction by the cyanide ion to form the corresponding aminonitrile adduct **6**. Attack of the pyridine nitrogen ion pair to the CN function would result in the formation of the bicyclic imine product **7**. 1,3-Proton shift followed by aromatization led to the formation of the corresponding 3-aminoimidazo[1,2-a]pyridine **8** which react with another molecule of aromatic aldehyde to afford final isolable product.

In support of this mechanism, when 2-aminopyridine and aromatic aldehydes in pyridine were allowed to react first for 10 min followed by addition of cyanide ion source and another molecule of aldehyde and microwave heating continued for additional 20 min, compounds **4a–d** were obtained in lower yields (cf. Table 1)



**Scheme 2:** Proposed mechanism for the synthesis of imidazo[1,2-a]pyridine derivatives **4a–j**.

than method A. Although, method B is a one-pot synthesis it includes two steps. Accordingly, method A is much desired because it saves time while increasing chemical yields. This is contrary to the previously reported formation of the corresponding cyanohydrin [33] from the reaction of aldehydes with TMSCN followed by the reaction with 2-aminopyridine.

## 4 Conclusion

In conclusion, we have reported a catalyst-free, one-pot three component, general high yielding method for the synthesis of N-arylidene-2-arylimidazo[1,2-a]pyridine-3-ylamine derivatives under microwave heating. Only one article, which describes using microwave heating with polymer-bound scandium triflate as a catalyst and trimethylsilyl cyanide as a cyanide ion source, has been reported. Our protocol was developed to avoid the use of both the hazardous reagents and expensive catalysts, with the advantages of the short microwave-assisted reaction time.

**Acknowledgments:** The authors are grateful to the Kuwait University Research Administration for the financial support of project SC12/13. Analytical facilities provided by GFS projects nos. GS 01/01, GS 01/03, GS 01/05, GS 02/10, and GS 03/08 are greatly appreciated.

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## Bionotes



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