Microwave-Assisted Metal-Free Synthesis of 2,8-Diaryl-6-aminoimidazo-[1,2-*a*]pyridine via Amine-Triggered Benzannulation

Muthupandi Nagaraj,[a] Muthusamy Boominathan,[a] Shanmugam Muthusubramanian,*[a] Nattamai Bhuvanesh[b]

[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India
Fax +91(452)2459845; E-mail: muthumanian2001@yahoo.com

[b] X-ray Diffraction Lab, Department of Chemistry, Texas, A&M University, College Station, TX 77842, USA

Received: 16.02.2012; Accepted after revision: 22.03.2012

Abstract: An efficient microwave-assisted metal-free amino benzannulation of aryl(4-aryl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl)methanone with dialkylamines afforded a variety of 2,8-diaryl-6-aminoimidazo[1,2-*a*]pyridine in moderate to excellent yield.

Key words: alkynes, amination, annulation, fused ring systems, heterocycles, green chemistry

Imidazo[1,2-*a*]pyridine moieties represent important building blocks in both natural and synthetic bioactive compounds, which have been shown to possess diverse therapeutic activities including antibacterial,[1] antifungal,[2] antiviral,[3] and anti-inflammatory behaviors.[4] They have also been characterized as selective cyclin-dependent kinase inhibitors,[5] calcium channel blockers,[6] β-amyloid formation inhibitors.[7] Several imidazo[1,2-*a*]pyridines already on the market include zolimidine (antiulcer drug),[8] zolpidem (hypnotic drug), and alpidem (nonsedative anxiolytic).[9] Necopidem and saripidem (Figure 1) are drugs belonging to the imidazo[1,2-*a*]pyridine family. DS-1 is the first drug developed that acts as a $GABA_A$ receptor agonist selective for the α4β3δ subtype.[10]

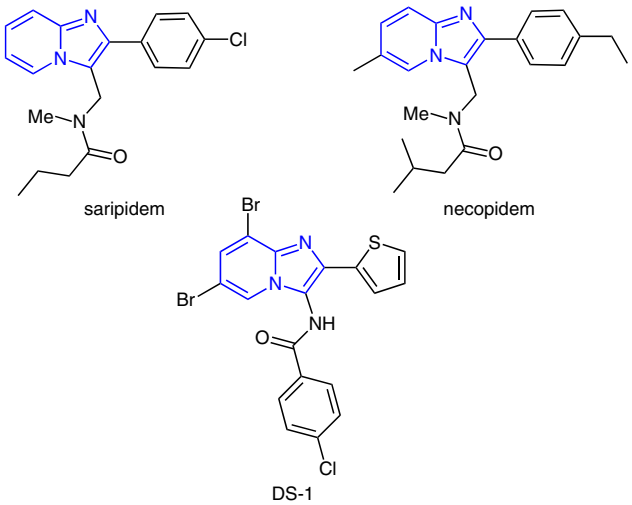


Figure 1 Imidazo[1,2-*a*]pyridine-based drugs

Besides the biological activities, the optical properties of imidazo[1,2-*a*]pyridines are interesting, finding applications in organic white luminescent materials[11] and fluorescent responses to mercury ion.[12] In the past few years, usage of microwave energy to drive chemical reactions has become increasingly popular in the medicinal chemistry community. The short reaction times and expanded reaction range offered by microwave-assisted organic synthesis are suited to the increased demands in industry.

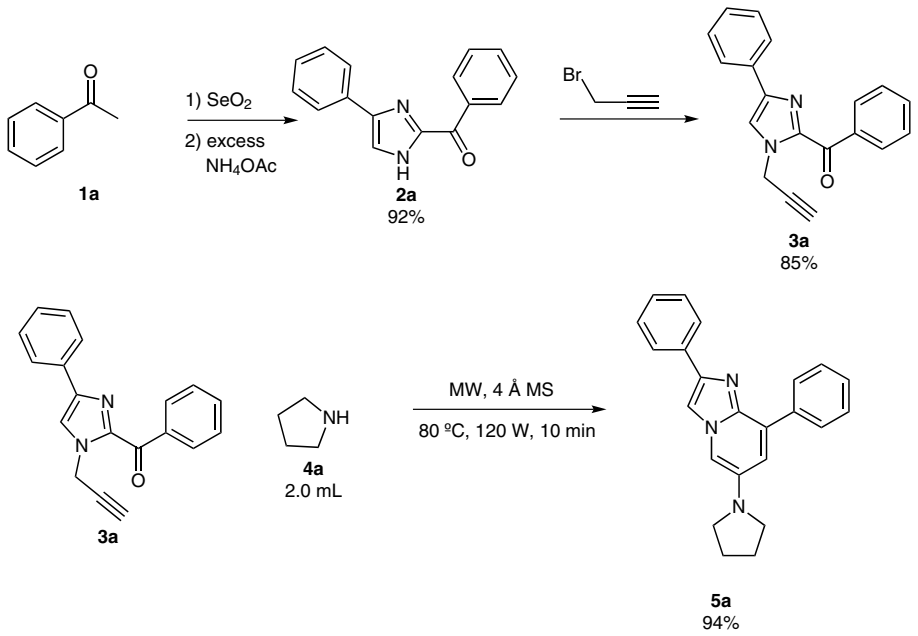
A number of synthetic methods have been designed for the preparation of imidazo[1,2-*a*]pyridine skeleton, a majority of them involving the formation of the imidazole ring.[13] However, a few methods are available based on the formation of the pyridine ring.[14] The coupling reaction of 2-aminopyridines with α-halocarbonyl compounds provides a practical method, which has found wide applications in medicinal chemistry and drug synthesis.[15] Very recently, Yu et al. has reported the oxidative coupling of 2-aminopyridines with β-keto esters or 1,3-diones leading to imidazo[1,2-*a*]pyridines formation.[16]

A variety of benzannulation strategies involving Lewis acid and transition-metal-catalyzed transformations, iodocyclization, and thermal cyclization have been reported.[17] Recently, the amine-triggered aminobenzannulation has been considered as an attractive route for the construction of useful amino-substituted aromatic rings and heterocycles.[18]

In an attempt to synthesize imidazo[1,2-*a*]pyridines with 2,8-diaryl and 6-amino functionalities by an atom-economical and environmentally friendly novel route, we describe a microwave-assisted, metal-free benzannulation of the aryl(4-aryl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl)-methanone **3** with dialkylamines providing a variety of 2,8-diaryl-6-aminoimidazo[1,2-*a*]pyridine **5** in moderate to excellent yield. To the best of our knowledge, aminobenzannulation for the construction of the 2,8-diaryl-6-aminoimidazo[1,2-*a*]pyridine has not been explored so far.

Imidazole derivatives **2** were easily obtained by two simple and high-yielding steps from commercially available acetophenones **1**.[19] These imidazoles could be converted to a set of new *N*-propargyl derivatives **3** using propargyl bromide.[20] After optimization, it was found that when phenyl(4-phenyl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl)-methanone (**3a**, 0.4 mmol) and pyrrolidine (**4a**, 2 mL)

SYNLETT 2012, 23, 1353–1357
Advanced online publication: 14.05.2012
DOI: 10.1055/s-0031-1290979; Art ID: ST-2012-B0143-L



Scheme 1 Benzannulation of phenyl[4-phenyl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl]methanone (**3a**) with pyrrolidine

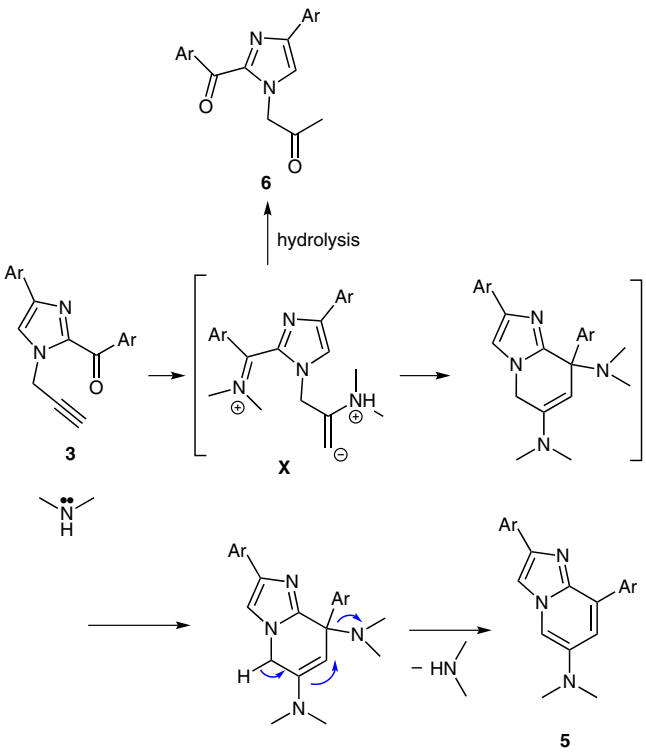
were irradiated in the presence of MS 4 Å (200 mg) at 80 °C and 120 W for 10 minutes, 2,8-diphenyl-6-aminoimidazo[1,2-*a*]pyridine (**5a**) was obtained in excellent yield after recovering the excess pyrrolidine by distillation and subsequent purification by a short silica gel column (Scheme 1).[21] This protocol, which is similar to the reported one,[18b] was then carried out with different acyclic and cyclic dialkylamines **4** to get a library of **5**. The conventional heating reaction requires more than an hour for completion. The structure of **5** has been unambiguously assigned based on spectroscopic and analytical data. The structures of **5b**,**c** and **3a** have been confirmed by single-crystal X-ray analyses also (Figure 2; see also Supporting Information).[22]

The reaction of **3a** with pyrrolidine, when carried out in the absence of molecular sieves, led to **5a** in relatively poor yield, less than 50%. Similarly when the reaction was carried out in other solvents like CH_2Cl_2, MeCN, toluene, THF, and MeOH with 1.5 equivalents of pyrrolidine with MS 4 Å resulted in poor yield of **5a** (40–50%).

The benzannulation reactions of various 2 aryl(4-aryl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl)methanones **3** are summarized in Table 1. Pyrrolidine has been found to be the best secondary amine to trigger the cyclization, though other secondary amines also resulted in an appreciable yield of **5**. However *N*-methylaniline and dicyclohexylamine fail to participate in the reaction. Details of the targeted **5** are provided in Table 1.

A trace amount of another compound **6** was also formed during the reaction of **3** with pyrrolidine in all the cases as shown by TLC of the crude reaction mixture. In one case (**6g**), it was successfully separated and shown to be 1-(2-aroyl-4-aryl-1*H*-imidazol-1-yl)propan-2-one. The formation of **6** helps to understand the mechanism of the main reaction, confirming the formation of the intermediate **X** in the reaction (Scheme 2). Initially, nucleophilic attacks of the secondary amine on the terminal alkyne and carbonyl carbon lead to the formation of intermediate **X**, which undergoes subsequent cyclization.[18b] This is followed by the elimination of amine leading to the formation of 6-aminoimidazo[1,2-*a*]pyridine **5**.

It was found that not only the substituted imidazoles, but also the pyrrole derivatives can be subjected to benzannu-

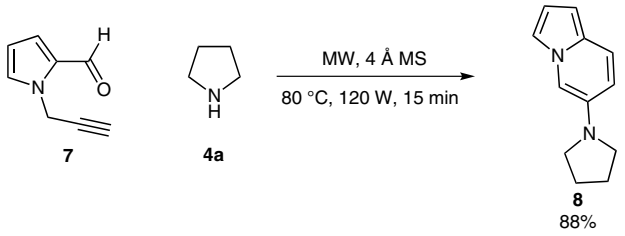


Scheme 2 Proposed mechanism for the formation of **5**

lation, and the reaction of **7**[23] with pyrrolidine proceeded smoothly at 80 °C in 15 minutes giving the corresponding 6-(pyrrolidin-1-yl)indolizine (**8**) in high yield (Scheme 3).

The scope of this methodology has also been tested in the acyclic 1,5-alkyne-carbonyl system. Accordingly, **9** was allowed to react with pyrrolidine in the expectation of getting 1,2-dihydropyridine derivative **10**. The reaction did not take place as anticipated even after 48 hours, and the starting materials were recovered (Scheme 4).

In summary, a microwave-assisted efficient synthesis of 2,8-diaryl-6-aminoimidazo[1,2-*a*]pyridine and 6-aminoindolizine through aminobenzannulation reaction has been achieved, and the reaction proceeds under mild reaction conditions without metal catalyst and additives.

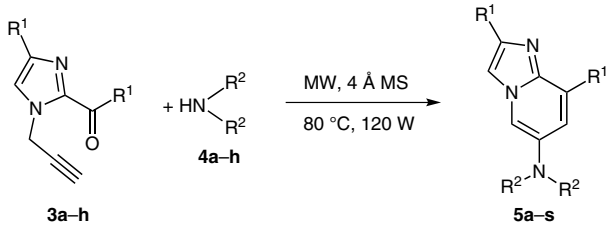


Scheme 3 Synthesis of 6-(pyrrolidin-1-yl)indolizine

Acknowledgment

The authors thank DST, New Delhi for assistance under the IRHPA program for the NMR facility. Financial support from CSIR-JRF, New Delhi is gratefully acknowledged.

Table 1 Benzannulation of Aryl[4-aryl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl]methanones **3** with Dialkylamines



Entry	**3**	R^1	Secondary amine **4**		**5**	Time (min)	Yield (%)[a]
1	**3a**	Ph	**4a**	pyrrolidine	**5a**	10	94
2	**3b**	4-ClC_6H_4	**4a**	pyrrolidine	**5b**	10	92
3	**3c**	4-BrC_6H_4	**4a**	pyrrolidine	**5c**	10	94
4	**3d**	4-MeC_6H_4	**4a**	pyrrolidine	**5d**	10	90
5	**3e**	4-$MeOC_6H_4$	**4a**	pyrrolidine	**5e**	15	92
6	**3f**	2-thienyl	**4a**	pyrrolidine	**5f**	15	89
7	**3g**	2-naphthyl	**4a**	pyrrolidine	**5g**	12	89
8	**3h**	4-PhC_6H_4	**4a**	pyrrolidine	**5h**	10	90
9	**3a**	Ph	**4b**	piperidine	**5i**	20	72
10	**3f**	2-thienyl	**4b**	piperidine	**5j**	20	68
11	**3b**	4-ClC_6H_4	**4c**	diethylamine	**5k**	20	66
12	**3c**	4-BrC_6H_4	**4c**	diethylamine	**5l**	20	61
13	**3f**	2-thienyl	**4c**	diethylamine	**5m**	25	58
14	**3a**	Ph	**4d**	dimethylamine	**5n**	40	15[b]
15	**3a**	Ph	**4e**	morpholine	**5o**	30	58[c]
16	**3e**	4-$MeOC_6H_4$	**4e**	morpholine	**5p**	30	56[c]
17	**3a**	Ph	**4f**	diisopropylamine	**5q**	20	62[d]
18	**3a**	Ph	**4g**	*N*-methylpiperazine	**5r**	20	56[d]
19	**3a**	Ph	**4h**	*N*-benzyl-*N*-methylamine	**5s**	20	58[d]

[a] Isolated yield.
[b] The yield was evaluated by the ^1H NMR spectrum of the crude product and not isolated.
[c] The reaction was carried out at 120 °C.
[d] The reaction was carried out at 100 °C.

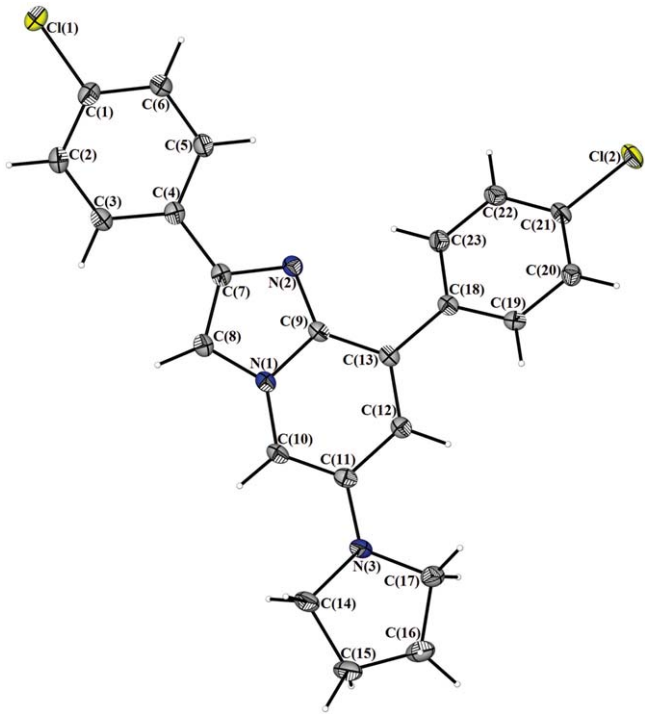
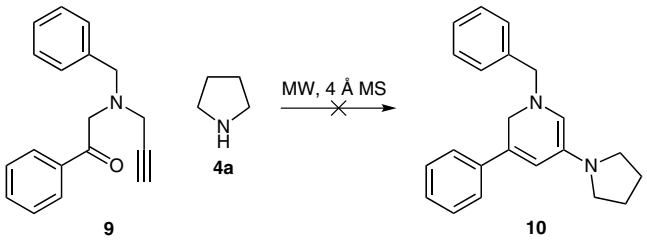


Figure 2 ORTEP diagram of **5b**



Scheme 4 Attempted synthesis of 1,2-dihydropyridine

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170.

(2) (a) Fisher, M. H.; Lusi, A. *J. Med. Chem.* **1972**, *15*, 982. (b) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, 13.

(3) (a) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50. (b) Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, 271.

(4) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347.

(5) Hamdouchi, C.; Zhong, B.; Mendoza, J.; Collins, E.; Jaramillo, C.; De Diego, J. E.; Robertson, D.; Spencer, C. D.; Anderson, B. D.; Watkins, S. A.; Zhanga, F.; Brooks, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1943.

(6) Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B. *J. Med. Chem.* **1991**, *34*, 2060.

(7) Goodacre, S. C.; Street, L. J.; Hallett, D. J.; Crawforth, J. M.; Kelly, S.; Owens, A. P.; Blackaby, W. P.; Lewis, R. T.; Stanley, J.; Smith, A. J.; Ferris, P.; Sohal, B.; Cook, S. M.; Pike, A.; Brown, N.; Wafford, K. A.; Marshall, G.; Castro, J. L.; Atack, J. R. *J. Med. Chem.* **2006**, *49*, 35.

(8) (a) Kaminsky, J. J.; Doweyko, A. M. *J. Med. Chem.* **1999**, *40*, 427. (b) Kaminsky, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliot, A. J.; Lovey, R. G.; Guzik, H.; Chui, P. J. S.; Long, J. F.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1686.

(9) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61.

(10) Wafford, K. A.; Niel, M. B.; Ma, Q. P.; Horridge, E.; Herd, M. B.; Peden, D. R.; Belelli, D.; Lamber, J. *J. Neuropharmacology* **2009**, *56*, 182.

(11) (a) Mutai, T.; Tomoda, H.; Ohkawa, T.; Yabe, Y.; Araki, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9522. (b) Shono, H.; Ohkawa, T.; Tomoda, H.; Mutai, T.; Araki, K. *ACS Appl. Mater. Interfaces* **2011**, *3*, 654.

(12) Shao, N.; Pang, G. X.; Yan, C. X.; Shi, G. F.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 7458.

(13) (a) Guchhait, S. K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631. (b) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079. (c) Dimauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013. (d) Aginagalde, M.; Vara, Y.; Arrieta, A.; Zangi, R.; Cebolla, V. L.; Delgado-Camon, A.; Cossio, F. P. *J. Org. Chem.* **2010**, *75*, 2776. (e) Adib, M.; Mohamadi, A.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. *Synlett* **2010**, 1606. (f) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941. (g) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4487. (h) Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647.

(14) (a) Galons, H.; Bergerat, I.; Combet Farnoux, C.; Miocque, M. *Synthesis* **1982**, 1103. (b) Davey, D.; Erhardt, P. W.; Lumma, W. C.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337. (c) Basso, D.; Broggini, G.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *Tetrahedron* **2002**, *58*, 4445. (d) Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647. (e) Nadipuram, A. K.; Kerwin, S. M. *Tetrahedron* **2006**, *62*, 3798. (f) Beebe, X.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 3225. (g) Barluenga, J.; Rodriguez, J. G.; Martinez, S.; Sobrino, A. S.; Tomas, M. *Chem.–Eur. J.* **2006**, *12*, 3201.

(15) (a) Ikemoto, T.; Wakimasu, M. *Heterocycles* **2001**, *55*, 99. (b) Rydzkowski, R.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett.* **1985**, *26*, 2571. (c) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97. (d) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1978**, *43*, 2900.

(16) (a) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (b) Wang, X.; Ma, L.; Yu, W. *Synthesis* **2011**, 2445.

(17) (a) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Dotz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (e) Trost, B. M. *Science* **1991**, *254*, 1471.

(18) (a) Belmont, P.; Belhadj, T. *Org. Lett.* **2005**, *7*, 1793. (b) Jin, T.; Yang, F.; Yamamoto, Y. *Org. Lett.* **2010**, *12*, 388.

(19) Khalili, B.; Tondro, T.; Hashemi, M. M. *Tetrahedron* **2009**, *65*, 6882.

(20) Abbiati, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839.

(21) **General Procedure for the Preparation of 2,8-Diaryl-6-aminoimidazo[1,2-*a*]pyridine (5)**
A mixture of 4-aryl-2-aryloyl-1-(prop-2-ynyl)-imidazole **3** (0.4 mmol), secondary amine **4** (2.0 mL), and 4 Å MS (200 mg) taken in a 10 mL closed microwave vial was subjected to microwave irradiation power of 120 W 80 °C for 10 min. Completion of the reaction was confirmed by TLC. After removing the excess base, the residue was purified by column chromatography using PE and EtOAc mixture (90:10) to yield **5**.
Spectroscopic Data for Compound 5a
Compound **5a** was isolated as pale green color solid; mp 140–142 °C. IR (KBr): 1626, 1477, 1392, 1240, 711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (t, *J* = 6.3 Hz, 4 H), 3.27 (t, *J* = 6.3 Hz, 4 H), 6.98 (d, *J* = 1.8 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.36–7.52 (m, 5 H), 7.77 (s, 1 H), 7.95 (dd, *J* = 7.8, 1.2 Hz, 2 H), 8.15 (dd, *J* = 7.8, 1.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 48.3, 104.3, 108.5, 115.9, 125.8, 127.2, 127.9, 128.2, 128.4, 129.1, 129.5, 134.6, 136.9, 137.3, 140.7, 144.7. LC–MS [M + 1]: *m/z* = 340.42. Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.18; H, 6.16; N, 12.24.

(22) CCDC No. 860197 (**3a**), 860199 (**5b**) and 860198 (**5c**).

(23) Loaiza, P. R.; Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem.* **2007**, *15*, 7248.

