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Synthesis of Polysubstituted Imidazo[1,2-*a*]pyridines via Microwave-Assisted One-Pot Cyclization/Suzuki Coupling/ Palladium-Catalyzed Heteroarylation

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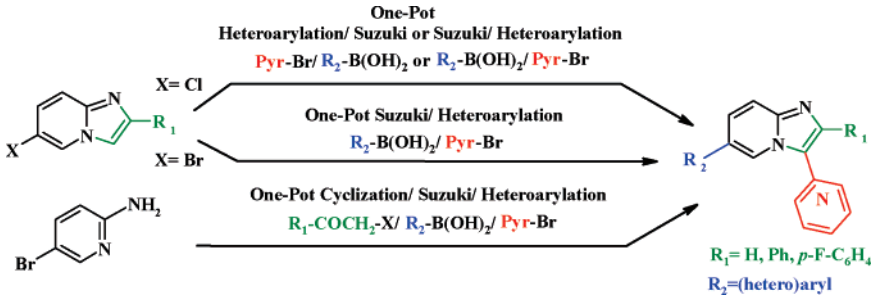
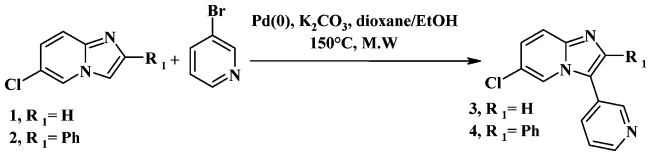


A new and efficient method for the synthesis of 2,3,6-trisubstituted imidazo[1,2-*a*]pyridine derivatives using a microwave-assisted one-pot, two-step Suzuki/heteroarylation or one-pot, three-step cyclization/ Suzuki/heteroarylation was developed. Polysubstituted compounds are obtained in good yield from 2-amino-5-halogenopyridines, 2-halogenocarbonyl derivatives, boronic acids, and heteroaryl bromides.

Introduction

Imidazo[1,2-*a*]pyridine derivatives have been shown to exhibit a diverse range of therapeutic properties such as melatonin receptor ligands,[1] antiviral,[2] antiulcer,[3] antibacterial,[4] antifungal,[5] agonist of benzodiazepine receptor,[6] calcium channel blocker,[7] β-amyloid formation inhibitor,[8] or ligand for detecting

SCHEME 1. Heteroarylation on 6-Chloroimidazo[1,2-*a*]pyridines 1 and 2



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[‡] Université Cadi-Ayyad.

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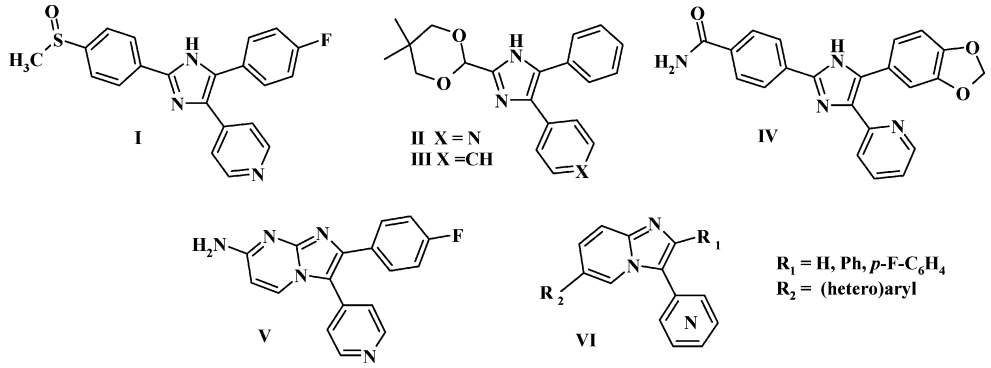
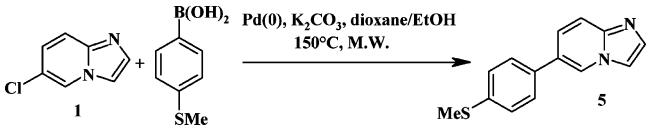


FIGURE 1. Trisubstituted imidazoles and imidazopyrimidines.

TABLE 1. Optimization of Heteroarylation on 6-Chloroimidazo[1,2-*a*]pyridines 1 and 2

entry	R_1	catalyst system	reaction time (h) /*T* (°C)	compd	conv (%)	yield (%)
1	H	$Pd(PPh_3)_4$	3/150	**3**	80	61
2	H	$Pd(OAc)_2/PPh_3$	2/150	**3**	100	80
3	Ph	$Pd(PPh_3)_4$	3/150	**4**	45	29
4	Ph	$Pd(OAc)_2/PPh_3$	2/150	**4**	100	91

SCHEME 2. Suzuki Cross-Coupling on 6-Chloroimidazo[1,2-*a*]pyridines 1



β-amyloid[9] and constitute a novel class of orally active nonpeptide bradykinin B_2 receptor antagonists.[10] Moreover, the imidazo[1,2-*a*]pyridine derivative zolpidem was commercialized as a hypnotic.[11]

Recently, new trisubstituted imidazoles and imidazopyrimidines have been described as kinase inhibitors (compounds **I**, **II**,[12] and **V**,[13] Scheme 1), acyl-COAs (cholesterol *O*-acyltransferase) (compound **III**,[14] Figure 1), and ALK5 inhibitors (compound **IV**,[15] Figure 1). Interestingly, all of these compounds show strong similarity to 3,6-di- or 2,3,6-tri(hetero)arylimidazo-[1,2-*a*]pyridines **VI** (Figure 1). For this reason, we focused our attention on an expeditious approach to compounds **VI**.

In continuation with our research on imidazo[1,2-*a*]pyridine derivatives,[1,16] we recently reported a versatile ring transformation providing access to 3-(hetero)arylimidazo[1,2-*a*]pyridines.[17] In this paper, we report a microwave-assisted one-pot Suzuki/heteroarylation preparation of 2,3,6-tri(hetero)arylimidazo[1,2-*a*]pyridines from 6-halogeno-2-substituted imidazo[1,2-*a*]-pyridines, boronic acids, and heteroaryl bromides. We have also developed a one-pot synthesis of these substrates by tandem cyclization, Suzuki coupling, and heteroarylation reactions using 2-amino-5-bromopyridine as starting material. As far as we know, the previous published methods toward making 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines required four separate steps: cyclization,[18] Suzuki[19] or Stille coupling[20] at the 6-position, preparation of 3-halogenoimidazo[1,2-*a*]pyridines,[2f,21] and then Suzuki[22] or Stille[23] coupling at the 3-position. Therefore, within the area of heteroaromatic systems, palladium is often used to catalyze only one single reaction; hence, a few examples of one-pot coupling are known.[24]

TABLE 2. Results of One-Pot Suzuki/Heteroarylation or Heteroarylation/Suzuki on 1

entry	catalyst system	method	reaction time (step 1)	reaction time (step 2)	% yield (**3**/**5**/**6**)
1	$Pd(PPh_3)_4$	A[a]	1 h 15 min	3 h	0/42/25
2		B[b]	3 h	1 h 15 min	0/40/23
3	$Pd(OAc)_2/PPh_3$	A′[a]	3 h	2 h	53/0/20
4		B′[b]	2 h	3 h	51/0/22

[a] One-pot Suzuki/heteroarylation. [b] One-pot heteroarylation/Suzuki.

Results and Discussion

One-Pot Suzuki/Heteroarylation or Heteroarylation/Suzuki on 6-Chloroimidazo[1,2-*a*]pyridines. The required imi-

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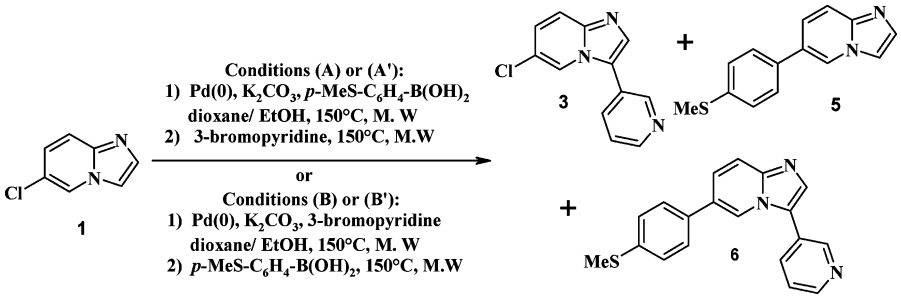
SCHEME 3. One-Pot Suzuki/Heteroarylation or Heteroarylation/Suzuki on Compound 1



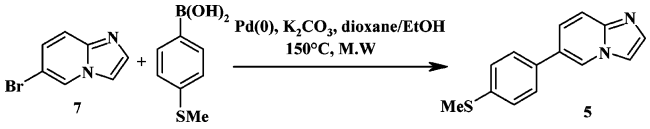
dazo[1,2-*a*]pyridine intermediates **1** and **2** were prepared by condensation of the suitable 2-amino-5-substituted pyridines with α-halogenocarbonyl derivatives in refluxing ethanol according to a literature procedure.[18]

Heteroarylation. In our previous work, we mentioned that the chloro substituent survived during the (hetero)arylation reaction conditions on 6-chloroimidazo[1,2-*a*]pyridines.[17] We anticipated that this chloro substituent would react in the same pot (one-pot polycoupling) with boronic acid in the presence of Pd(0) which could be generated in situ after the heteroarylation reaction. To explore the potential of this approach, first, we sought to investigate the best methods reported for Suzuki coupling[21] [$Pd(Ph_3)_4$] and heteroarylation reactions[17] [$Pd(OAc)_2$/PPh_3] on 6-chloroimidazo[1,2-*a*]pyridines in the heteroarylation reaction under microwave irradiation (Scheme 1). Thus, the reactions between starting material **1** or **2** and 3-bromopyridine in the presence of $Pd(PPh_3)_4$ at 150 °C for 3 h in a mixture of dioxane/EtOH gave the desired compounds **3** and **4** in 61% and 29% yields, respectively (Table 1, entries 1 and 3). Interestingly, the use of $Pd(OAc)_2$/PPh_3 under similar reaction conditions (150 °C, 2 h) also proceeded smoothly, and the expected compounds **3** and **4** were obtained in 80% and 91% yields (Table 1, entries 2 and 4).

Suzuki Cross-Coupling. The scope and limitation of the Suzuki cross-coupling under the optimized heteroarylation conditions was then investigated. The coupling between 6-chloroimidazo[1,2-*a*]pyridine **1** and *p*-thiomethylphenylboronic acid (Scheme 2) using $Pd(PPh_3)$ resulted in total conversion after 1 h 15 min and in 82% yield, while the $Pd(OAc)_2$/PPh_3 catalyst system only led to incomplete conversion (62% after 3 h) and compound **5** was obtained in only 45% yield.

One-Pot Reaction. We studied these palladium catalysts on the one-pot cross-coupling using **1** as starting substrate to identify the best routes to lead to disubstituted compound **6** (Scheme 3). We investigated different ways: methods A and A′ (one-pot Suzuki/heteroarylation) or B and B′ (one-pot heteroarylation/Suzuki). Thus, when **1** was treated under conditions A or A′ (Table 2, Scheme 3), two different compounds was generated in each case. The monocoupled side product **5** was formed as the major compound in 42% yield (method A),

SCHEME 4. Suzuki Cross-Coupling on 6-Bromoimidazo[1,2-*a*]pyridines 7



while 53% yield of monocoupled side product **3** was obtained using method A′. In contrast, the desired compound **6** was only isolated in 25% and 20% yield (Table 2, entries 1 and 3). Switching of the reaction sequence (conditions B and B′) gave similar results (Table 2, entries 2 and 4). It is noteworthy that the advantage of using 6-chloroimidazo[1,2-*a*]pyridine **1** as starting material was that the reaction could be carried out in two different directions: Suzuki/heteroarylation (A, A′) and heteroarylation/Suzuki (B, B′). Unfortunately, a major limitation with this substrate is the poor yield of the expected double coupled compound **6**.

One-Pot Suzuki/Heteroarylation on 6-Bromoimidazo[1,2-*a*]pyridines. Suzuki Cross-Coupling. To overcome these limitations, an alternative strategy was then investigated. This approach is based on the use of 6-bromoimidazo[1,2-*a*]pyridine derivatives as starting material (Scheme 4). In this case, it was essential to start with Suzuki cross-coupling[17] to achieve this catalytic process in the same pot. We found the coupling on 6-bromoimidazo[1,2-*a*]pyridine **7** afforded the desired compound **5** in excellent yields and quickly using both catalyst systems [$Pd(PPh_3)_4$ (method A), 20 min] in 87% yield or [$Pd(OAc)_2$/PPh_3 (method A′), 20 min] in 89% yield.

One-Pot Reaction. The one-pot cross-coupling (Scheme 5) between **7**, *p*-thiomethylphenylboronic acid, and 3-bromopyridine under reaction conditions A ($Pd(PPh_3)_4$) afforded a mixture of **5** and expected product **6** in moderate yield (30 and 35%, respectively) while the use of method A′ ($Pd(OAc)_2$/PPh_3) gave 3,6-disubstituted imidazo[1,2-*a*]pyridine **6** in 71% yield without traces of monosubstituted compound **5**.

With a suitable protocol in hand ($Pd(OAc)_2$/PPh_3 as catalyst in a mixture of dioxane/EtOH at 150 °C, MW), the scope of the one-pot tandem Suzuki and heteroarylation coupling was extended to the synthesis of various polysubstituted imidazo-[1,2-*a*]pyridine analogues. In all cases, the starting materials **7**,[18] **8**,[18] and **9**[18] (Scheme 6) were first treated with various boronic acids for 20 min, and then heteroaryl bromides were added and the reactions were irradiated for 2 h (150 °C). The expected products (Table 3, entries 1−9) were obtained in good yields.

One-Pot Cyclization/Suzuki Coupling/Palladium-Catalyzed Heteroarylatio. In the final phase of our studies, we generated the desired 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines in a one-pot, three-step reaction starting from the commercially

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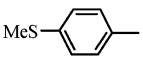
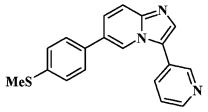
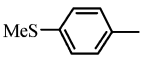
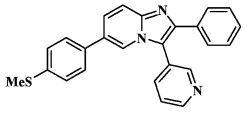
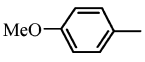
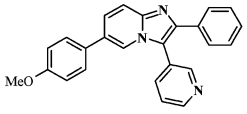
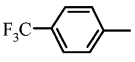
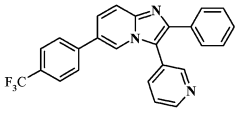
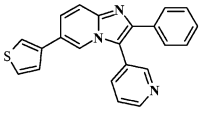
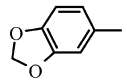
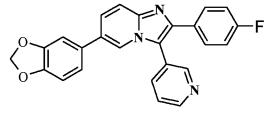
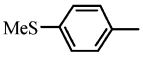
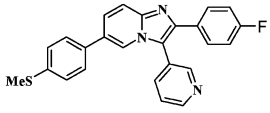
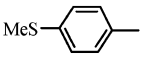
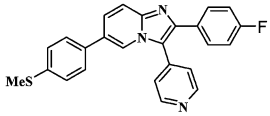
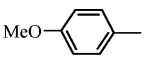
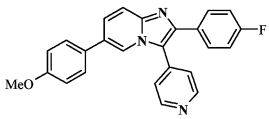
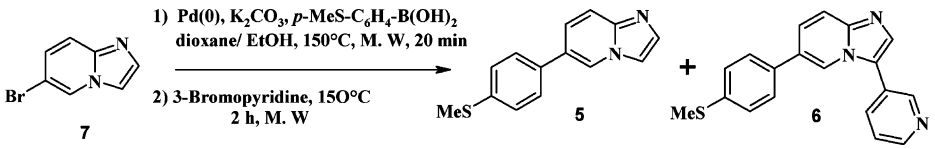
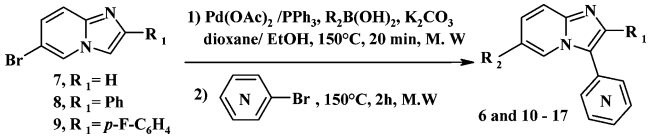
TABLE 3. Results of the One-Pot, Two-Step Suzuki/Heteroarylation

Entry	R_1	R_2	Pyridine derivatives	Product	Yield
1	H			 **6**	71 %
2	Ph			 **10**	75 %
3	Ph			 **11**	73 %
4	Ph			 **12**	72 %
5	Ph			 **13**	64 %
6	*p*-F-C_6H_4			 **14**	70 %
7	*p*-F-C_6H_4			 **15**	73 %
8	*p*-F-C_6H_4			 **16**	69 %
9	*p*-F-C_6H_4			 **17**	74 %

SCHEME 5. One-Pot Reaction on 6-Bromoimidazo[1,2-*a*]pyridines 7



SCHEME 6. One-Pot, Two-Step Suzuki/Heteroarylation



available 2-amino-5-bromopyridine by tandem cyclization/Suzuki cross-coupling/palladium-catalyzed heteroarylation. After careful screening of the reaction conditions, we found the optimized procedure. Thus, under microwave irradiation, 2-amino-5-bromopyridine was treated successively in the same pot without workup with α-halogenocarbonyl derivatives (cyclization for 20 min). After cooling to ambient temperature, palladium acetate, triphenylphosphine, and boronic acids were added, and the reaction mixture was irradiated for 20 min (Suzuki coupling), and finally, after another cooling to room temperature, pyridine bromide derivatives were added and the reaction mixture was irradiated again for 2 h (heteroarylation reaction). These sequences afforded desired 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines in nearly quantitative conversions. This whole sequence was carried out under microwave irradiation at 150 °C (Scheme 7). The compounds **6**, **10**, **16**, and **18**−**20** were isolated in good overall yields (Table 4, entries 1−6).

SCHEME 7. One-Pot, Three-Step Cyclization/Suzuki/Heteroarylation

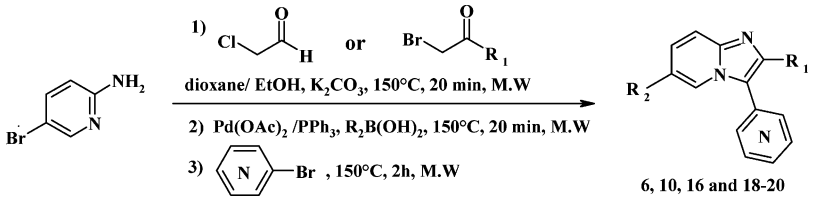
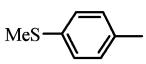
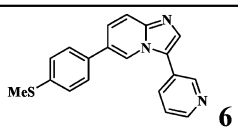
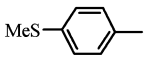
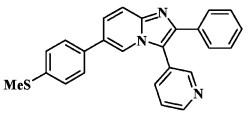
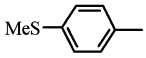
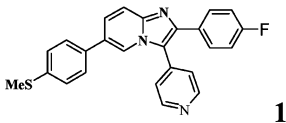
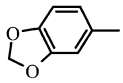
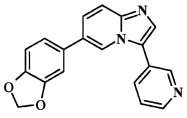
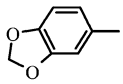
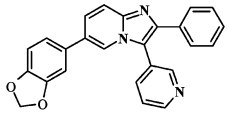
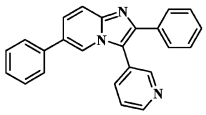


TABLE 4. Results of the One-Pot, Three-Steps Cyclization/Suzuki/Heteroarylation

Entry	R_1	R_2	pyridine derivatives	product	Yield
1	H			 **6**	51 %
2	Ph			 **10**	44 %
3	*p*-F-C_6H_4			 **16**	32 %
4	H			 **18**	46 %
5	Ph			 **19**	38 %
6	Ph			 **20**	40 %

In conclusion, we have developed a novel and rapid approach for the synthesis of 3,6-di- or 2,3,6-tri(hetero)arylimidazo[1,2-*a*]pyridines by a microwave-assisted one-pot, two-step Suzuki coupling/palladium-catalyzed heteroarylation or one-pot, three-step cyclization/Suzuki coupling/palladium-catalyzed heteroarylation reaction. We found optimal conditions using the Pd-$(OAc)_2$/PPh_3 system as catalyst in the mixture of dioxane/EtOH at 150 °C. This approach has the potential to be of great benefit in the rapid and convergent synthesis of substituted imidazo-[1,2-*a*]pyridines. The overall process represents the first example of the one-pot cyclization/Suzuki cross-coupling/regioselective heteroarylation under microwave irradiations. We are currently working on the extension of this method to include other heterocyclic systems and other palladium and/or copper cross-coupling reactions.

Experimental Section

Procedure for Heteroarylation of 6-Chloroimidazo[1,2-*a*]-pyridine or 6-Chloro-2-phenylimidazo[1,2-*a*]pyridine and 3-Bromopyridine under Microwave Irradiation (Scheme 1, Table 1). Method 1. To a solution of 6-chloroimidazo[1,2-*a*]pyridine or 6-chloro-2-phenylimidazo[1,2-*a*]pyridine (0.1 g) dissolved in 2 mL of a mixture of 1,4-dioxane/ EtOH (2/1, v/v) in a vial microwave tube with a stir bar were added 3-bromopyridine (1.5 equiv), potassium carbonate (2 equiv), triphenylphosphine (0.2 equiv), and palladium(II) acetate (0.1 equiv) under argon, and then the tube was sealed with a silicon septum and subjected to microwave irradiation at 150 °C with stirring. The reaction vessel was allowed to cool to room temperature, and the solution was diluted with dichloromethane (15 mL) and extracted (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/PE) to give the desired products **3** and **4**.

Method 2. The reaction was carried out as described in method 1 using the corresponding 3-bromopyridine (1.5 equiv); in this case, the catalyst ($Pd(OAc)_2$/PPh_3) was changed to $Pd(PPh_3)_4$.

Procedure for Suzuki Cross-Coupling Reaction of 6-Chloro- or 6-Bromoimidazo[1,2-*a*]pyridine and *p*-Methylsulfanylphenylboronic Acid under Microwave Irradiation (Scheme 2). Method 3. To a solution of 6-chloro- or 6-bromoimidazo[1,2-*a*]-pyridine (0.1 g) dissolved in 2 mL of a mixture of 1,4-dioxane/ EtOH (2/1, v/v) in a vial microwave tube with a stir bar were added *p*-methylsulfanylphenylboronic acid (1.2 equiv), potassium carbonate (2 equiv), triphenylphosphine (0.2 equiv), and palladium(II) acetate (0.1 equiv) under argon. The reaction vessel was sealed with a silicon septum and subjected to microwave irradiation at

150 °C with stirring. The reaction mixture was then allowed to cool to room temperature, diluted with dichloromethane (15 mL), and extracted (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (EtOAc/PE) to give 6-(4-methylsulfanylphenyl)imidazo[1,2-*a*]pyridine **5**.

Method 4. The reaction was carried out as described in method 3 using the corresponding *p*-methylsulfanylphenylboronic acid (1.2 equiv); in this case, the catalyst ($Pd(OAc)_2/PPh_3$) was changed to $Pd(PPh_3)_4$.

General Procedure for One-Pot Suzuki/Heteroarylation on 6-Bromoimidazo[1,2-*a*]pyridines (Scheme 3, Table 2). Method A′. To a solution of 6-bromoimidazo[1,2-*a*]pyridine (0.1 g) in 2 mL of a mixture of 1,4-dioxane/ EtOH (2/1, v/v) in a vial microwave tube were added arylboronic acid (1.2 equiv), potassium carbonate (2 equiv), triphenylphosphine (0.2 equiv), and palladium-(II) acetate (0.1 equiv) under argon. The reaction vessel was sealed with a silicon septum and subjected to microwave irradiation for 20 min at 150 °C with stirring. After the mixture was cooled to room temperature, heteroaryl bromide (1.5 equiv) was injected into the tube via a syringe, and the reaction mixture was subjected again to microwave irradiation at 150 °C for 2 h. The reaction vessel was cooled to room temperature, diluted with dichloromethane (15 mL), and extracted (3×). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude material thus obtained was purified by column chromatography on silica gel (EtOAc/PE) to give polysubstitued imidazo[1,2-*a*]pyridine derivatives **6** and **10**−**17**.

General Procedure for One-Pot Cyclization/Suzuki/Heteroarylation Reaction (Scheme 7, Table 4). To a solution of 2-amino-5-bromopyridine (0.1 g) in 2 mL of a mixture of 1,4-dioxane/EtOH (2/1, v/v) in a vial microwave tube with a stir bar were added potassium carbonate (2 equiv) and α-halgeno ketone (1.05 equiv) under argon. The reaction mixture was subjected to microwave irradiation for 20 min at 150 °C with stirring. After being cooled to room temperature, the reaction vessel was unsealed, and arylboronic acid (1.2 equiv), triphenylphosphine (0.2 equiv), and palladium(II) acetate (0.1 equiv) were added under argon. The reaction vessel was sealed again with a silicon septum and irradiated for 20 min at 150 °C with stirring. After another cooling to room temperature, heteroaryl bromide (1.5 equiv) was injected into the tube via syringe and the reaction mixture was irradiated at 150 °C for 2 h. Finally, the mixture was cooled to room temperature, diluted with dichloromethane (15 mL), and extracted (3×). The combined organic layers were dried over $MgSO_4$ and solvents removed under reduced pressure. The crude material obtained was purified by column chromatography on silica gel (EtOAc/PE) to give polysubstitued imidazo[1,2-*a*]pyridine derivatives **6**, **15**, **16**, **18** , and **20**. All yields mentioned in the tables are isolated yields.

6-(4-Methylsulfanylphenyl)-3-pyridin-3-ylimidazo[1,2-*a*]pyridine 6: yellow solid; one-pot, three-steps, 51% yield; mp 124−125 °C; ^{1}H NMR ($CDCl_3$, 250 Hz) δ 2.50 (s, 3H), 7.31 (d, 1H, J = 8.4 Hz), 7. 46 (m, 4H), 7.75 (d, 2H, J = 10.6 Hz), 7.91 (dt, 1H, J = 1.9, 7.8 Hz), 8.39 (s, 1H), 8.67 (dd, 1H, J = 1.5, 4.7 Hz), 8.89 (d, 1H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 Hz) δ 15.9, 118.5, 120.0, 122.9, 124.2, 125.6, 125.8, 127.2, 127.3, 127.5, 133.9, 134.2, 135.4, 139.1, 146.1, 149.1, 149.5; HRMS calcd for $C_{19}H_{15}N_3S$ (M^+) 317.09867, found 317. 0967.

Note Added after ASAP Publication: Reference 21b was incorrect in the version published September 5, 2007; the correct version was published September 7, 2007.

Supporting Information Available: Full characterization data for compounds **3**−**6** and **10**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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