JOC The Journal of Organic Chemistry

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Room-Temperature Transition-Metal-Free One-Pot Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines via Iodo-hemiaminal Intermediate

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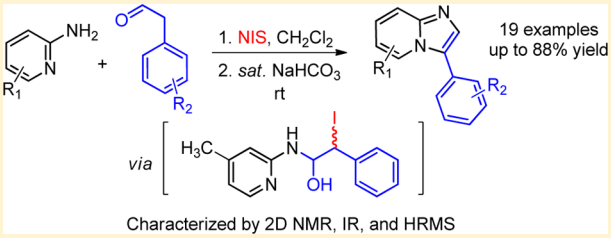
Supporting Information

ABSTRACT: A mild and efficient one-pot synthesis of 3-aryl imidazo[1,2-*a*]pyridines in up to 88% yield was developed. An adduct was formed after the simple mixing of 2-amino-4-methylpyridine, 2-phenylacetaldehyde, and *N*-iodosuccinimide in CH_2Cl_2, and the structure of the adduct was characterized by 2D NMR, IR, and high-resolution mass analysis. The adduct was readily cyclized by treatment with a saturated aqueous solution of $NaHCO_3$. The reactions proceeded to completion after several hours at room temperature.



Many natural products, biomolecules, and biologically active compounds are composed of fused heterocycles; therefore, they have frequently been found as a key structural unit in synthetic pharmaceutical and agrochemical agents.[1,2] Furthermore, the important photophysical and electron-withdrawing properties of fused heterocycles have been utilized for the development of organic conductors,[3,4] photovoltaic cells,[5] and organic light-emitting diodes.[6] Recent studies show that changing the substituents on 3-aryl imidazo[1,2-*a*]pyridine results in diverse biological activities.[7] The core structure of imidazo[1,2-*a*]pyridine is often present in organic light-emitting diodes. In addition, imidazo[1,2-*a*]pyridines exhibit a higher σ-donation tendency relative to normal *N*-heterocyclic carbenes (NHCs) in transition-metal chemistry[8] (Figure 1).

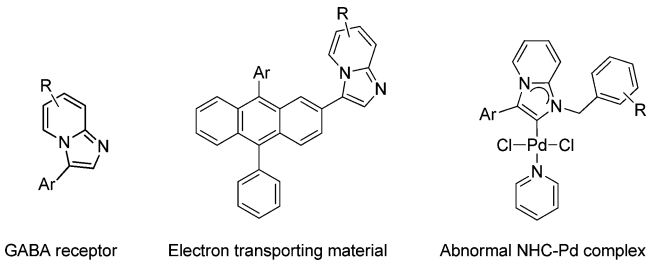


Figure 1. Representative important 3-aryl imidazo[1,2-*a*]pyridines.

To date, many transition-metal-catalyzed synthetic methods for the preparation of 3-aryl imidazo[1,2-*a*]pyridines have been reported.[9−13] Although diverse molecules were generated successfully, a transition-metal-free reaction strategy is sometimes preferred because of the milder reaction conditions, less-expensive reagents, and lack of residual metallic impurities.[14] Recently, several transition-metal-free synthetic methods have been developed for 3-aryl imidazo[1,2-*a*]pyridines (Scheme 1).[15−20] These transition-metal-free methods enabled the desired products to be obtained in satisfactory yields; however, they often required expensive, activated starting materials, such as bromoalkynes (eq 1),[15] bromoketones (eq 2),[16−18] bromoaldehydes (eq 3),[19] and iodonium salts (eq 4),[20] in addition to harsh conditions (e.g., high temperatures, polar solvents, and long reaction times). With these limitations in mind, we developed a mild synthetic method that utilized simple aldehydes, 2-aminopyridines, and a halogenating reagent in nonpolar solvent (Scheme 2). Herein, we describe a mild and efficient transition-metal-free condensation reaction to give 3-aryl imidazo[1,2-*a*]pyridines at room temperature in several hours.

N-Halosuccinimide (NXS) mediated α-halogenations of aldehydes catalyzed by proline or binaphthyl amine have been reported previously;[21] thus, we surmised that an α-halo imine would be selectively generated by halogenation of an enamine intermediate, followed by cyclization to afford the desired product. Halogenation of 2-aminopyridine[22] and an aldol reaction[23] were also considered as potential side reactions; however, neither were observed under the optimized reaction conditions.

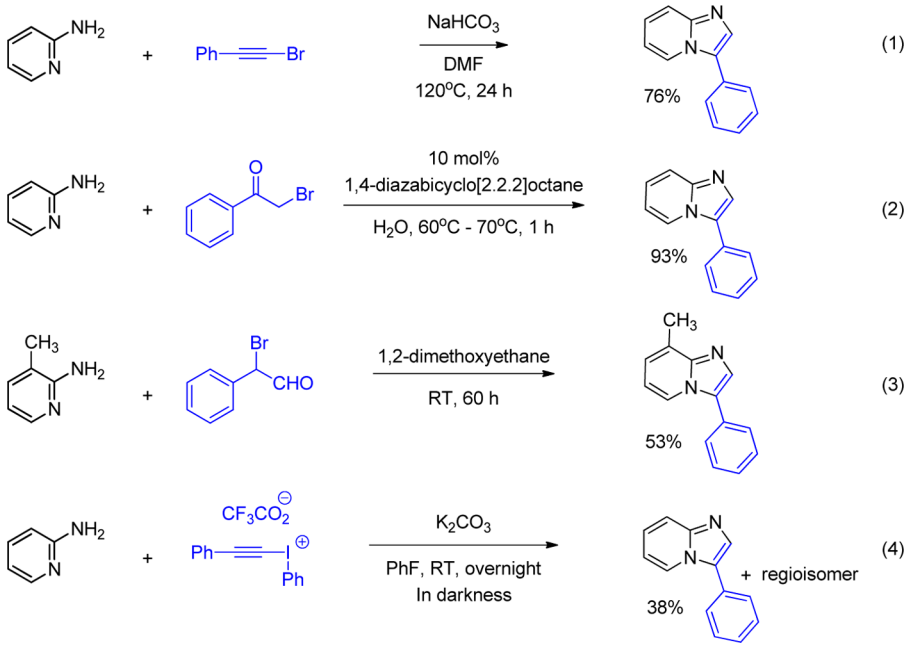
Initially, we performed the halogenation reaction with NCS, NBS, and NIS in dimethylacetamide (DMA). NCS and NIS gave the HX salt of the desired product in 15% and 38% yield, respectively (Table 1, entries 1 and 3). In other solvents such as methanol, acetonitrile, and 1,2-dichloroethane, the crude ^{1}H NMR spectrum was too messy to identify the product (Table 1, entries 4−6). Unexpectedly, we observed a simple spectrum for the crude reaction mixture in CH_2Cl_2, which is believed to be adduct **3** (Table 1, entry 7, *vide infra*). The condensation reaction to form a hemiaminal did not occur in the absence of NIS. With NBS and NCS, the spectra were messy again (Table 1, entries 8 and 9).

Knowing that adduct **3** was present in CH_2Cl_2, we attempted to make the subsequent cyclization step faster by the addition

Received: February 9, 2015
Published: March 5, 2015

DOI: 10.1021/acs.joc.5b00298
J. Org. Chem. 2015, 80, 3723−3729

Scheme 1. Previous Transition-Metal-Free Methods with Activated Halide Substrates



Scheme 2. Desired Reaction Scheme and Potential Side Reactions

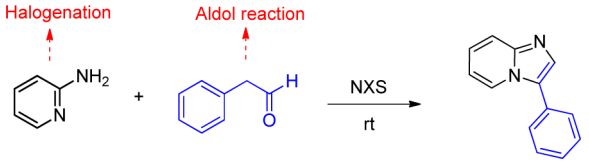
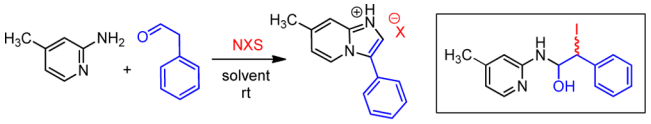


Table 1. Screening of Halogenating Reagents and Solvents[a]



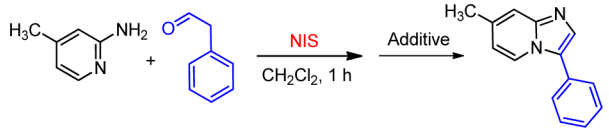
1a **2a** HX·**4a** adduct **3**

entry	NXS	solvent	time (h)	yield (%)[b]
1	NCS	DMA	12	15[c]
2	NBS	DMA	12	[d]
3	NIS	DMA	12	38[g]
4	NIS	CH_3OH	12	[d]
5	NIS	CH_3CN	12	[d]
6	NIS	$ClCH_2CH_2Cl$	12	[d]
7	**NIS**	**CH_2Cl_2**	**1**	**90[e](45)[f]**
8	NBS	CH_2Cl_2	1	[d]
9	NCS	CH_2Cl_2	1	[d]

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (1.3 equiv), and NXS (1.1 equiv) in solvent (1 mL). [b]Yield determined by ^{1}H NMR spectroscopy based on an internal standard (mesitylene). [c]HCl·**4a**. [d]Messy. [e]Adduct form **3**. [f]HI·**4a** in 24 h. [g]HI·**4a**.

of other additives. In the case of pyridine, 76% conversion to the HI salt of **4a** was observed within 24 h. We think the HI salt survived because the imidazopyridine is more basic than pyridine (Table 2, entry 1). Adduct **3** was stable in H_2O, even after 5 h (Table 2, entry 2). Gratifyingly, **3** was readily cyclized presumably via iodo-imine intermediate by treatment with a

Table 2. Sequential Reaction[a]



1a **2a** **4a**

entry	additive	time (h)	yield (%)[b]
1	pyridine	24	76[c]
2	H_2O	5	91[d]
3	**sat. $NaHCO_3$**	**0.5**	**93(88)[e]**

[a]Reaction conditions: (i) **1a** (1.0 equiv), **2a** (1.3 equiv), and NIS (1.1 equiv) in CH_2Cl_2 (1 mL); (ii) additive (1 mL). [b]Yield determined by ^{1}H NMR spectroscopy based upon internal standard (mesitylene). [c]HI salt form. [d]Adduct form **3**. [e]Isolated yield in parentheses.

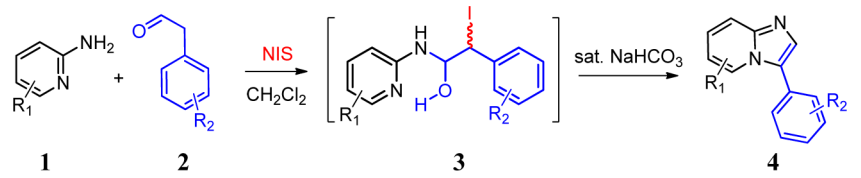
saturated aqueous solution of $NaHCO_3$ to give **4a** in 88% isolated yield (Table 2, entry 3, *vide infra*).

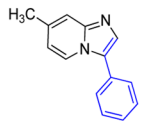
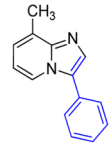
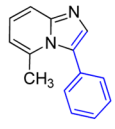
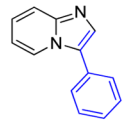
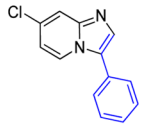
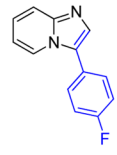
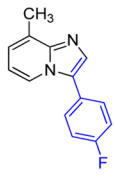
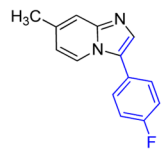
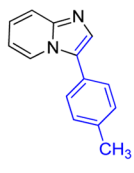
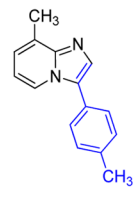
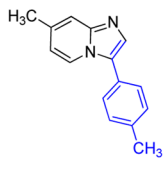
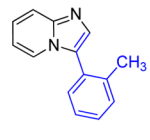
Crude adduct **3** was first characterized by ^{1}H NMR, COSY, and HSQC spectroscopic analysis.[24] We detected two broad doublet peaks at δ = 5.71 and 5.85 ppm, and their chemical shifts varied at measurements. Two peaks coupled to each other (COSY) and correlated with the ^{13}C NMR peaks at δ = 86.9 and 73.6 ppm, respectively (HSQC). These peak patterns led us to deduce the structure of adduct **3**. Some closely separated peaks in ^{13}C NMR indicate the presence of stereoisomers, and broad hydrogen-bonded O-H stretch observed in the IR spectrum also supports the hydrate structure of **3**.[24] When the first step was carried out in the presence of molecular sieves, the resulting NMR could not be obtained. We assumed that intramolecular hydrogen bonding could increase the stability of **3**. As another strong evidence for the structure, we found the base peak corresponding to [**3**-I]$^+$ of *m*/*z* 227.1173 (calculated 227.1179) in the ESI-MS spectrum.[24] The loss of iodide from **3** during electrospray ionization could possibly have accounted for the value.

Under the optimized conditions, we tried to expand the scope of the reaction with 2-arylacetaldehydes and 2-aminopyridines.

DOI: 10.1021/acs.joc.5b00298
J. Org. Chem. 2015, 80, 3723−3729

Table 3. Substrate Scope[a]



Entry	Time[b]	Product[c]	Entry	Time[b]	Product[c]
1	1 h/0.5 h	 **4a**, 88%	2	1 h/1.5 h	 **4b**, 60%
3	1 h/1 h	 **4c**, 80%	4	1 h/0.5 h	 **4d**, 56%
5	2 h/4 h	 **4e**, 67%	6	2 h/3 h	 **4f**, 48%
7	1 h/1 h	 **4g**, 56%	8	1 h/2 h	 **4h**, 77%
9	1 h/3 h	 **4i**, 58%	10	1 h/1 h	 **4j**, 36%
11	1 h/4 h	 **4k**, 65%	12	1 h/3 h	 **4l**, 40%

DOI: 10.1021/acs.joc.5b00298
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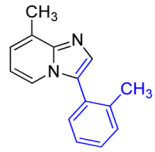
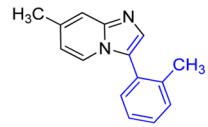
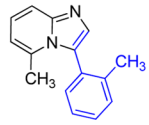
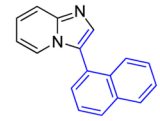
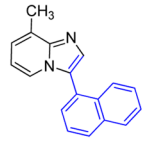
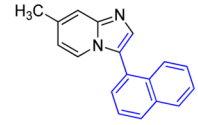
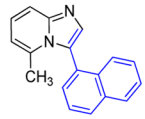
Table 3. continued

Entry	Time[b]	Product[c]	Entry	Time[b]	Product[c]
13	1 h/2 h	 **4m**, 78%	14	1 h/1 h	 **4n**, 73%
15	1 h/2 h	 **4o**, 64%	16	3 h/2 h	 **4p**, 71%
17	1 h/1 h	 **4q**, 84%	18	1 h/2 h	 **4r**, 74%
19	1 h/1 h	 **4s**, 46%	-		-

[a]Reaction conditions: (i) **1a** (1.0 equiv), **2a** (1.3 equiv), and NIS (1.1 equiv) in CH_2Cl_2 (1 mL); (ii) sat. $NaHCO_3$ (1 mL). [b]Reaction time of first step/reaction time of second step. [c]Isolated yield.

The results are summarized in Table 3. In general, substituted 2-phenylacetaldehydes that contained either electron-donating or electron-withdrawing groups reacted with 2-aminopyridines in 36−88% yield. The yield behavior was dependent on the structure of the substrate. For the reaction of 2-phenylacetaldehyde and various methyl-substituted 2-aminopyridines, the desired product was obtained in good yields (Table 3, entries 1−3). 2-Amino-4-chloropyridine was also successfully cyclized with 2-phenylacetaldehyde in 67% yield (Table 3, entry 5). *Para*-methyl and *para*-fluoro substituents on the 2-phenylacetaldehyde unit were tolerated and 36−77% of the desired product was obtained (Table 3, entries 6−11). The yield of the reaction of 2-amino-4-methylpyridine with 2-(4-fluorophenyl)acetaldehyde was the highest of the series (Table 3, entry 8). The sterically hindered substrate 2-(*o*-tolyl)acetaldehyde readily reacted to give the desired products in good yields (Table 3, entries 12−15). In the reactions of 2-(naphthalen-1-yl)acetaldehyde with various 2-aminopyridines, the desired products were obtained with good yields, except for the reaction with 2-amino-6-methylpyridine, presumably due to steric hindrance (Table 3, entries 16−19).

We hypothesized that enamine is derived by the condensation of 2-aminopyridine with 2-arylacetaldehyde, followed by the reaction with NIS to afford iodinated imine. The subsequent nucleophilic attack by water on the iodo-imine pushes the equilibrium in favor of the adduct **3**. Then, according to Le Chatelier's principle, the consumption of less favored iodo-imine by cyclization and deprotonation in the presence of $NaHCO_3$ shifts the equilibrium forward to favor the desired reaction (Scheme 3).

In summary, we have developed a mild and efficient one-pot method for the synthesis of 3-aryl imidazo[1,2-*a*]pyridines, in up to 88% yield. An adduct was formed after the simple mixing of 2-aminopyridine, 2-phenylacetaldehyde, and NIS in CH_2Cl_2; the structure of the adduct was characterized by 2D NMR, IR, and ESI-MS spectra analysis. The adduct was readily cyclized by treatment with a saturated aqueous solution of $NaHCO_3$. The methodology developed in this study has many advantages, including low reaction temperature and the use of readily available starting materials. We expect this rapid, transition-metal-free reaction to be quite promising for the preparation of a variety of useful 3-aryl imidazo[1,2-*a*]pyridines that are used in bioactive compounds, electronic materials, and potent NHCs.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (Cambridge isotope) with a 300 MHz Fourier transform spectrometer. COSY and HSQC NMR spectra were recorded in $CDCl_3$ with a 500 MHz Fourier transform spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hz. Infrared (IR) spectra were reported in frequency of the absorption (cm^{-1}).

DOI: 10.1021/acs.joc.5b00298
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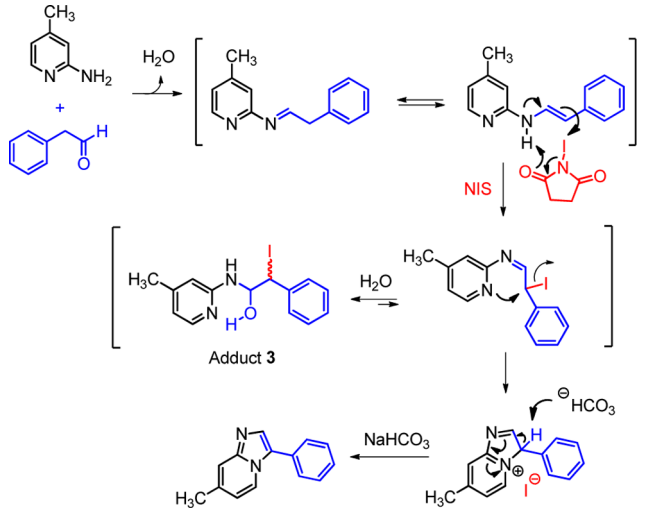
Scheme 3. Plausible Reaction Mechanism



High-resolution mass spectra (HRMS) were acquired on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Flash column chromatography was performed with Merck silica gel 60 (230−400 mesh) and elution with hexanes/ethyl acetate (containing 1−2 drops of ammonia−water in 100 mL of eluent) to afford the desired pure product.

General Procedure for the Synthesis of 3-Aryl Imidazo[1,2-*a*]-pyridines. A mixture of 2-aminopyridines (0.347 mmol), 2-arylacetaldehydes (0.451 mmol), and NIS (0.382 mmol) was stirred in CH_2Cl_2 (1 mL) at room temperature until 2-aminopyridines were consumed (confirmed by ^1H NMR analysis). Sat. $NaHCO_3$ (1 mL) was added to the reaction mixture with stirring. When the reaction was complete, sat. $NaHCO_3$ was added to the mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water (2 times), and then dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by column chromatography to give the desired product.

*Adduct (**3**).* After a mixture of 2-amino-4-methylpyridine, 2-phenylacetaldehyde, and NIS was stirred in CH_2Cl_2 at room temperature for 1 h, the reaction mixture was concentrated under vacuum. ^1H NMR, ^{13}C NMR, IR, and HRMS data of a sample taken from the crude mixture are shown as follows; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 6.5, 1H), 7.31−7.15 (m, 6H), 6.65 (d, J = 6.5, 1H), 5.83 (s, 1H), 5.60 (s, 1H), 2.32 (s, 3H), (NH and OH peaks were not detected in $CDCl_3$, while a broad singlet was observed in DMSO-d6 at δ 11.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 153.5, 134.6, 134.5, 134.3, 129.6−126.5(multiple peaks), 117.2, 109.4, 109.2, 85.67, 73.1, 73.0, 22.3 (some peaks are closely separated presumably due to diastereomer formation);[24] IR (KBr, cm^{-1}): ν_{max} 3207, 3084, 3064, 2954, 2934, 1772, 1706, 1655, 1539, 1178; HRMS (ESI) = m/z calcd. for $C_{14}H_{15}N_2O$ ($[M - I]^+$): 227.1179, found: 227.1173.

*7-Methyl-3-phenylimidazo[1,2-a]pyridine (**4a**).* Following the general procedure (1 and 0.5 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4a** was isolated as an oil. Yield (63.6 mg, 88%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.2, 1H), 7.62 (s, 1H), 7.57−7.48 (m, 4H), 7.43−7.38 (m, 2 H), 6.65 (d, J = 7.2, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 135.2, 132.1, 129.5, 129.2, 128.0, 127.9, 125.2, 122.6, 116.5, 115.2, 21.2. The NMR spectra were in agreement with those reported in the literature.[6,9d]

*8-Methyl-3-phenylimidazo[1,2-a]pyridine (**4b**).* Following the general procedure (1 and 1.5 h for each step, respectively) with column purification (hexanes/ethyl acetate = 90/10), **4b** was isolated as an oil. Yield (43.4 mg, 60%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 6.6, 1H), 7.69 (s, 1H), 7.56−7.49 (m, 4H), 7.44−7.39 (m, 1H), 7.01 (d, J = 6.6, 1H), 6.73 (t, J = 6.7, 1H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 131.7, 129.4, 129.2, 128.1, 128.0, 127.8, 126.1, 123.2, 121.2, 112.6, 17.1. The NMR spectra were in agreement with those reported in the literature.[9d]

*5-Methyl-3-phenylimidazo[1,2-a]pyridine (**4c**).* Following the general procedure (1 and 1 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4c** was isolated as an oil. Yield (57.7 mg, 80%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 2H), 7.45−7.40 (m, 5H), 7.11 (t, J = 7.9, 1H), 6.49 (d, J = 6.3, 1H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 136.4, 134.5, 132.0, 131.6, 128.4, 127.4, 126.2, 124.2, 116.2, 113.3, 21.8. The NMR spectra were in agreement with those reported in the literature.[9d,e]

*3-Phenylimidazo[1,2-a]pyridine (**4d**).* Following the general procedure (1 and 0.5 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4d** was isolated as an oil. Yield (37.7 mg, 56%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 6.9, 1H), 7.69−7.65 (m, 2H), 7.57−7.48 (m, 4H), 7.43−7.39 (m, 1H), 7.19 (t, J = 7.8, 1H), 6.80 (t, J = 6.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 132.5, 129.3. 129.2, 128.2, 128.0, 125.7, 124.2, 123.3, 118.3, 112.5. The NMR spectra were in agreement with those reported in the literature.[9a,d,i,12b]

*7-Chloro-3-phenylimidazo[1,2-a]pyridine (**4e**).* Following the general procedure (2 and 4 h for each step, respectively) with column purification (hexanes/ethyl acetate = 90/10), **4e** was isolated as an oil. Yield (53.2 mg, 67%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 7.5 Hz, 1H), 7.68 (s, 2H), 7.54−7.52 (m, J = 7.5, 4H), 7.46−7.43 (m, 1H), 6.80 (d, J = 6.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.2, 130.7, 129.4, 128.7, 128.5, 128.1, 126.1, 123.7, 117.0, 114.2. The NMR spectra were in agreement with those reported in the literature.[25]

*3-(4-Fluorophenyl)imidazo[1,2-a]pyridine (**4f**).* Following the general procedure (2 and 3 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4f** was isolated as an oil. Yield (35.2 mg, 48%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 6.9, 1H), 7.68−7.66 (m, 2H), 7.55−7.50 (m, 2H), 7.24−718 (m, 3H), 6.82 (t, J = 6.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}F}$ = 246), 146.0, 132.5, 130.0 (d, $J_{C\text{-}F}$ = 8.0), 125.3 (d, $J_{C\text{-}F}$ = 3.5) 124.7, 124.3, 123.1, 118.3, 116.4 (d, $J_{C\text{-}F}$ = 21), 112.7. The NMR spectra were in agreement with those reported in the literature.[7e,9d,j]

*3-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridine (**4g**).* Following the general procedure (1 and 1 h for each step, respectively) with column purification (hexanes/ethyl acetate = 90/10), **4g** was isolated as an oil. Yield (44.0 mg, 56%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 6.6 Hz, 1H), 7.62 (s, 1H), 7.52−7.47 (m, 2H), 7.22−7.16 (m, 2H), 6.98 (d, J = 6.6, 1H), 6.70 (t, J = 6.7, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 160.8, 146.4, 131.6, 130.1, 130.0, 127.9, 125.6, 125.5, 125.1, 123.2, 121.0, 116.4, 116.1, 112.8, 17.1; HRMS (ESI) = m/z calcd. for $C_{14}H_{12}FN_2$ ($[M + H]^+$): 227.0979, found: 227.0980.

*3-(4-Fluorophenyl)-7-methylimidazo[1,2-a]pyridine (**4h**).* Following the general procedure (1 and 2 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4h** was isolated as an oil. Yield (60.0 mg, 77%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 6.6 Hz, 1H), 7.62 (s, 1H), 7.52−7.48 (m, 2H), 7.22−7.16 (m, 2H), 7.00 (d, J = 6.6, 1H), 6.73 (t, J = 6.7, 1H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J = 246), 146.6, 135.2, 132.2, 129.8 (d, $J_{C\text{-}F}$ = 8.0), 125.6 (d, J = 3.5), 124.2, 122.3, 116.5 (d, $J_{C\text{-}F}$ = 12), 116.1, 115.3, 21.3; HRMS (ESI) = m/z calcd. for $C_{14}H_{12}FN_2$ ($[M + H]^+$): 227.0979, found: 227.0973.

*3-(p-Tolyl)imidazo[1,2-a]pyridine (**4i**).* Following the general procedure (1 and 3 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4i** was isolated as an oil. Yield (41.9 mg, 58%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 6.6, 1H), 7.67−7.65 (m, 2H), 7.45 (d, J = 8.1, 2H), 7.32 (d, J = 8.1, 2H), 7.17 (t, J = 7.6, 1H), 6.79 (t, J = 6.7, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 138.2, 132.3, 129.9, 128.0, 126.3, 125.8, 124.0, 123.4, 118.2, 112.4, 21.3. The NMR spectra were in agreement with those reported in the literature.[9d,i]

*8-Methyl-3-(p-tolyl)imidazo[1,2-a]pyridine (**4j**).* Following the general procedure (1 h for each step) with column purification (hexanes/ethyl acetate = 90/10), **4j** was isolated as an oil. Yield (27.8 mg, 36%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 6.6, 1H), 7.65 (s, 1H), 7.44 (d, J = 7.8, 1H), 7.31 (d, J = 7.8, 1H), 6.98 (d, J = 6.3, 1H), 6.71 (t, J = 6.7, 1H), 2.64 (s, 3H), 2.42 (s, 3H); ^{13}C NMR

DOI: 10.1021/acs.joc.5b00298
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(75 MHz, $CDCl_3$) δ 146.3, 138.1, 131.4, 129.9, 128.1, 127.8, 126.5, 126.2, 123.0, 121.3, 112.5, 21.3, 17.1; HRMS (ESI) = m/z calcd for $C_{15}H_{15}N_2$ ($[M + H]^+$): 223.1230, found: 223.1225.

*7-Methyl-3-(p-tolyl)imidazo[1,2-a]pyridine (**4k**).* Following the general procedure (1 and 4 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4k** was isolated as an oil. Yield (50.1 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.2, 1H), 7.59 (s, 1H), 7.45−7.42 (m, 3H), 7.31 (d, J = 8.4, 2H), 6.62 (d, J = 6.9, 1H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 137.9, 135.1, 131.8, 129.9, 127.9, 126.5, 125.2, 122.6, 116.5, 115.1, 21.3, 21.2; HRMS (ESI) = m/z calcd. for $C_{15}H_{15}N_2$ ($[M + H]^+$): 223.1230, found: 223.1225.

*3-(o-Tolyl)imidazo[1,2-a]pyridine (**4l**).* Following the general procedure (1 and 3 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4l** was isolated as an oil. Yield (29.0 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 6.9, 1H), 7.67 (d, J = 8.7, 1H), 7.60 (s, 1H), 7.36−7.29 (m, 4H), 7.18 (t, J = 7.8, 1H), 6.74 (t, J = 6.7, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 138.3, 132.7, 131.1, 130.7, 129.2, 128.2, 126.2, 124.6, 124.1, 123.7, 118.0, 112.3, 19.8; HRMS (ESI) = m/z calcd for $C_{14}H_{13}N_2$ ($[M + H]^+$): 209.1073; found: 209.1074.

*8-Methyl-3-(o-tolyl)imidazo[1,2-a]pyridine (**4m**).* Following the general procedure (1 and 2 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4m** was isolated as an oil. Yield (60.2 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.36−7.30 (m, 4H), 7.00 (d, J = 6.9, 1H), 6.68 (t, J = 6.9, 1H), 2.67 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 138.3, 132.0, 131.2, 130.7, 129.1, 128.5, 127.7, 126.2, 125.0, 122.9, 121.6, 112.3, 19.8, 17.1; HRMS (ESI) = m/z calcd for $C_{15}H_{15}N_2$ ($[M + H]^+$): 223.1230; found: 223.1232.

*7-Methyl-3-(o-tolyl)imidazo[1,2-a]pyridine (**4n**).* Following the general procedure (1 and 1 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4n** was isolated as an oil. Yield (56.3 mg, 73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 6.9, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 7.36−7.31 (m, 4H), 6.60 (d, J = 7.2, 1H), 2.41 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 138.3, 135.1, 132.2, 131.1, 130.7, 129.1, 128.3, 126.2, 124.1, 122.9, 116.3, 115.0, 21.3, 19.8; HRMS (ESI) = m/z calcd for $C_{15}H_{15}N_2$ ($[M + H]^+$): 223.1230; found: 223.1231.

*5-Methyl-3-(o-tolyl)imidazo[1,2-a]pyridine (**4o**).* Following the general procedure (1 and 2 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4o** was isolated as an oil. Yield (49.4 mg, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 9.0, 1H), 7.47 (s, 1H), 7.37−7.34 (m, 2H), 7.24−7.21 (m, 2H), 7.09 (t, J = 7.9, 1H) 6.46 (d, J = 6.6, 1H), 2.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 139.7, 136.2, 133.6, 132.4, 131.7, 129.3, 129.2, 125.04, 124.9, 124.3, 116.1, 113.1, 20.3; HRMS (ESI) = m/z calcd for $C_{15}H_{15}N_2$ ($[M + H]^+$): 223.1230; found: 223.1224.

*3-(Naphthalen-1-yl)imidazo[1,2-a]pyridine (**4p**).* Following the general procedure (3 and 2 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4p** was isolated as an oil. Yield (60.2 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.95 (m, 2H), 7.79 (s, 1H), 7.76−7.70 (m, 2H), 7.61−7.50 (m, 4H), 7.45−7.40 (m, 1H), 7.22 (t, J = 7.8, 1H), 6.70 (t, J = 6.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.9, 133.8, 132.0, 129.6, 129.2, 128.7, 127.0, 126.4, 126.3, 125.6, 125.2, 124.4, 124.1, 123.7, 118.0, 112.3. The NMR spectra were in agreement with those reported in the literature.[8a,9d,e,j]

*8-Methyl-3-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**4q**).* Following the general procedure (1 and 1 h for each step, respectively) with column purification (hexanes/ethyl acetate = 90/10), **4q** was isolated as an oil. Yield (75.3 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.95 (m, 2H), 7.79 (s, 1H), 7.61−7.59 (m, 3H), 7.57−7.52 (m, 2H), 7.46−7.41 (m, 1H), 7.03 (d, J = 7.2, 1H), 6.64 (d, J = 6.7, 1H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 133.9, 133.1, 132.1, 129.6, 129.1, 128.7, 127.7, 126.9, 126.6, 126.3, 125.6, 125.3, 124.1, 123.2, 122.0, 112.4, 17.1; HRMS (ESI) = m/z calcd for $C_{18}H_{15}N_2$ ($[M + H]^+$): 259.1229; found: 259.1236.

*7-Methyl-3-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**4r**).* Following the general procedure (1 and 2 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4r** was isolated as an oil. Yield (66.3 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.94 (m, 2H), 7.71 (s, 1H), 7.61−7.58 (m, 3H), 7.53−7.50 (m, 3H), 7.45−7.40 (m, 1H), 6.54 (d, J = 6.9, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 135.4, 133.9, 133.4, 132.0, 129.5, 129.0, 128.7, 126.9, 126.5, 126.3, 125.6, 125.3, 123.3, 123.1, 116.3, 115.0, 21.3; HRMS (ESI) = m/z calcd for $C_{18}H_{15}N_2$ ($[M + H]^+$): 259.1230; found: 259.1227.

*5-Methyl-3-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**4s**).* Following the general procedure (1 and 1 h for each step, respectively) with column purification (hexanes/ethyl acetate = 80/20), **4s** was isolated as an oil. Yield (41.2 mg, 46%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.91 (m, 2H), 7.66−7.58 (m, 3H), 7.54−7.47 (m, 2H), 7.43−7.32 (m, 4H), 7.14 (t, J = 7.9, 1H), 6.45 (d, J = 6.3, 1H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 136.6, 135.2, 135.1, 132.9, 130.5, 129.5, 129.5, 128.3, 126.9, 126.22, 126.15, 124.6, 124.5, 123.7, 116.2, 113.2, 20.1; HRMS (ESI) = m/z calcd for $C_{18}H_{15}N_2$ ($[M + H]^+$): 259.1230; found: 259.1225.

■ ASSOCIATED CONTENT

Supporting Information

COSY, HSQC, IR, and HRMS spectra of adduct **3** and ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) funded by the Korean Government (2013R1A1A1011793).

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DOI: 10.1021/acs.joc.5b00298
J. Org. Chem. 2015, 80, 3723−3729