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Imidazo[1,2-*a*]pyridines Susceptible to Excited State Intramolecular Proton Transfer: One-Pot Synthesis via an Ortoleva–King Reaction

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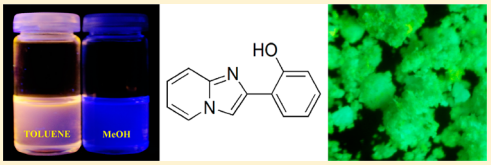
Supporting Information

ABSTRACT: A short and efficient route to a broad range of imidazo[1,2-*a*]pyridines from 2-aminopyridines and acetophenones is achieved by a tandem, one-pot process starting with an Ortoleva–King reaction. Optimal conditions for the first step were established after examining various reaction parameters (solvent, reagent ratios, and temperature). The conditions identified (1st step, neat, 2.3 equiv of 2-aminopyridine, 1.20 equiv of I_2, 4 h, 110 °C; 2nd step, $NaOH_{aq}$, 1 h, 100 °C) resulted in the formation of imidazo[1,2-*a*]pyridines in 40–60% yields. The synthesis is compatible with various functionalities (OH, NMe_2, Br, OMe). Products containing a 2-(2′-hydroxyphenyl) substituent undergo excited state intramolecular proton transfer (ESIPT) in nonpolar and polar-aprotic solvents. Although ESIPT-type emission in nonpolar solvents is weak, the Stokes shifts are very high (11000 cm^{-1}). The comparison of the properties of six ESIPT-capable imidazo[1,2-*a*]pyridines shows the influence of various substituents on emission characteristics. All of them also display strong, solid-state emission in blue–green–yellow region. 2-Aryl-imidazo[1,2-*a*]pyridines not capable of ESIPT emit in the blue region, displaying high fluorescence quantum yield.



INTRODUCTION

The chemistry of imidazo[1,2-*a*]pyridines has been intensively investigated since the beginning of the last century.[1] This area is still of great interest, mainly due to important biological activity of these molecules. Imidazo[1,2-*a*]pyridines have significant importance in the pharmaceutical industry owing to their interesting biological activity displayed over a broad range of therapeutic classes; these molecules exhibit antiviral (anti-cytomegalo-zoster and antivaricella-zoster virus),[2] anti-inflammatory,[3] analgesic, antipyretic,[4] antiulcer,[5] and antibacterial[6] properties. They are also *β*-amyloid formation inhibitors,[7] GABA and benzodiazepine receptor agonists,[8] and cardiotonic agents.[9] Drug formulations containing imidazo[1,2-*a*]pyridine that are currently available on the market include alpidem (anxiolytic),[10] zolpidem (hypnotic),[11] and olprinone (PDE-3 inhibitor).[12]

Acuña and co-workers were the first to report that imidazo[1,2-*a*]pyridines possessing a 2-hydroxyphenyl substituent at position 2 display excited-state intramolecular proton transfer (ESIPT).[13] More recently, the photophysics of these compounds was studied by Araki and co-workers, who discovered their strong solid-state emission.[14] The design and characterization of compounds that undergo ESIPT continues to engage the interest of scientists throughout the world[15] because of the wide applications of this phenomenon to such systems as laser dyes,[16] fluorescence sensors,[17] and molecular switches.[18]

A variety of synthetic methods have been reported for the preparation of substituted imidazo[1,2-*a*]pyridines. The most important approaches embrace: (i) condensation of 2-aminopyridine with *α*-halocarbonyl compounds,[19] (ii) one-pot condensations of aldehydes, isonitriles, and 2-aminopyridines,[20] and (iii) copper-catalyzed three-component reactions of 2-aminopyridines, aldehydes, and alkynes.[21] Other methods have also been developed within the last three decades.[22−26] Although new methods are continuously published,[27] the reaction of 2-aminopyridines with *α*-halogenoketones and *α*-halogenoaldehydes is still the most popular. There are however two intrinsic limitations to this methodology, namely, the small variety of commercially available *α*-halogenocarbonyl compounds and their lachrymatory properties.

Herein we describe a new approach to the synthesis of substituted imidazo[1,2-*a*]pyridines, based on the condensation of 2-aminopyridine with various aromatic ketones under Ortoleva–King reaction conditions, followed by cyclization under the influence of base.

RESULTS AND DISCUSSION

We have observed that the structure of the intermediate product in the synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridine and *α*-halocarbonyl compounds (i.e., the corresponding pyridinium salt with a halogen counterion) represents the same type of compound as is formed in the Ortoleva–King reaction. First Ortoleva,[28] and then King,[29] demonstrated that pyridinium salts can often be conveniently prepared in a direct synthesis by heating active methyl and methylene compounds with iodine in pyridine. The yields of

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this elegant method are usually very good,[30] and a variety of heterocyclic bases may be used instead of pyridine, including quinolines,[31] isoquinolines, picolines,[32] and nicotinamide.[33] The reaction has been extended to include a variety other compounds containing active methyl and methylene groups.

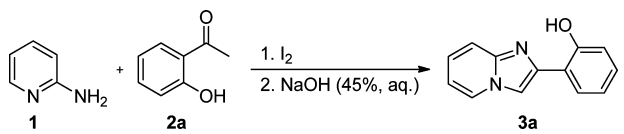
We envisioned that if 2-aminopyridine (**1**) could be used as a component in an Ortoleva–King reaction with methylketones, the initially formed pyridinium salts would bear suitable functional groups to form 2-substituted imidazo[1,2-*a*]-pyridines in the second step. Needless to say, one must take into consideration the numerous side reactions that may occur, including iodination of 2-aminopyridine.[34]

Careful analysis of published data showed that the yields in Ortoleva–King reaction are usually very good but that separation of the iodide byproducts is sometimes accompanied by considerable losses. These difficulties can be circumvented by precipitating the product from aqueous solution with sodium perchlorate.[35] However, this route appeared unproductive to us, because it required additional time and led to inevitable losses of the intermediate product.

It has been shown by Pearson[36] that the Ortoleva–King reaction can be represented as stepwise mechanism. In this representation, the first step is α-proton detachment from the ketone with pyridine serving as a base. This forms the corresponding conjugate base of the ketone, which is able to interact with iodine giving α-iodomethylketone. The latter can react relatively easily with another molecule of pyridine. Pearson has also shown that the rate of formation of β-ketoalkyl pyridinium iodides is much faster than both the rate of reaction between ketone and heterocyclic amine base and the rate of reaction of the conjugate base with iodine. The limiting step of the whole process is the interaction of ketone with amine. Therefore, we reasoned that when carrying out the reaction in excess of 2-aminopyridine, it might be possible to obtain reaction kinetics that were first order with respect to ketone and apparent-zero-order with respect to 2-aminopyridine. An another mechanistic possibility that has to be taken into consideration is initial formation enamine intermediates in reaction of 2-aminopyridine with acetophenone followed by iodination and subsequent cyclization to provide imidazo[1,2-*a*]pyridines.

Since our aim was to develop a methodology with the widest possible scope, as a model, we chose the reaction between 2-aminopyridine (**1**) and 2-hydroxyacetophenone (**2a**) (the presence of a phenolic hydroxyl group makes ketone **2a** prone to iodination under the reaction conditions) (Scheme 1).

Scheme 1



An additional reason for the choice of substrates was that the prospective product of this reaction (2-(imidazo[1,2-*a*]pyridin-2-yl)phenol (**3a**) had been shown to display ESIPT,[13,14] which was of interest to us. Initially, we performed the model reaction using acetonitrile as a solvent, which led to the formation of desired product **3a** but in only 10% yield. Since reactions in other solvents did not bring any appreciable change (Table 1), we attempted to perform the first step in the neat, which improved the yield of product **3a** considerably (Table 2, entry 1).

Table 1. Results of Reactions of 2-Aminopyridine (1) with 2-Hydroxyacetophenone (2a) in Various Solvents[a]

entry	solvent	yield (%)
1	MeCN	10
2	toluene	12
3	CH_2Cl_2	2
4	THF	6

[a]All reactions were performed under the following constant conditions: 1st step, 4 h at 110 °C followed by overnight stirring at 70 °C; 2nd step, excess aqueous NaOH (45%), 100 °C, 1 h.

Table 2. Optimization of Relative Quantities of Reagents in the Reaction of 2-Aminopyridine (1) with 2-Hydroxyacetophenone (2a)[a]

entry	ratio **1**:**2a**	iodine (equiv vs **2a**)	yield (%)
1	1	1	26
2	2	1	53
3	3	1	52
4	2	1.20	55
5	2.3	1.20	57
6	2	1.5	54
7	2	2	53

[a]All reactions were performed under the following constant conditions: 1st step, solvent free, 4 h at 110 °C followed by overnight stirring at 70 °C; 2nd step, excess aqueous NaOH (45%), 100 °C, 1 h.

Inspired by these preliminary results, we initiated a systematic study of solvent-free reaction conditions. The experiments were focused on the number of equivalents of 2-aminopyridine (**1**) used (Table 2). For these experiments, the second step (cyclization reaction) was carried out under conditions of excess aqueous alkali to create apparent-zero-order reaction conditions with respect to the aqueous base.

During this study, it was found that the reaction is sensitive to the molar ratio between reagents. It seems that a key requirement of the reaction is a minimum 2-fold excess of 2-aminopyridine and slight excess of iodine with respect to ketone (Table 2, entries 2–5). Further increases to the amounts of these components did not lead to any increase in the yield of the reaction but caused difficulties in the isolation and purification of the final product (Table 2, entries 6–7). Under the reaction conditions (110 °C), 2-aminopyridine becomes a liquid and dissolves all components of the reaction sufficiently. These data are in good agreement with the data obtained in kinetic[36] and other studies[28−34] of the Ortoleva–King reaction.

The optimized procedure (Table 2, entry 5: 1 equiv ketone, 1.20 equiv of iodine, excess (2.3 equiv) 2-aminopyridine) was subsequently used in the preparation of various 2-substituted imidazo[1,2-*a*]pyridines. Acetophenones **2b–2f** with diverse substituents (OMe, Br, OH, NEt_2) were reacted with 2-aminopyridine (**1**) (Table 3). All reactions gave rise to the corresponding 2-substituted imidazo[1,2-*a*]pyridines **3b–3f** in moderate-to-good yields (39–61%). Subsequently, we have shown that this methodology may be the extended to other acetophenones including heterocyclic substrates (**2g–2j**). Imidazo[1,2-*a*]pyridines **3g–3j**, bearing both electron-donating

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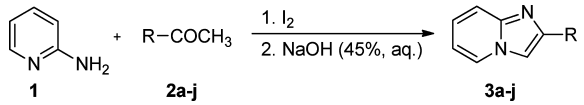
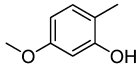
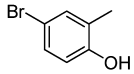
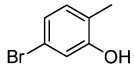
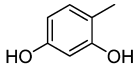
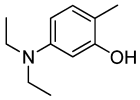
Table 3. Scope of the Synthesis of Imidazo[1,2-*a*]pyridines Directly from Acetophenones



1 2a-j 3a-j

Ketone	R	Imidazo[1,2-*a*]pyridine	Yield
2a		3a	57%
2b		3b	61%
2c		3c	53%
2d		3d	56%
2e		3e	39%
2f		3f	41%
2g		3g	55%
2h		3h	54%
2i		3i	43%
2j		3j	51%

and electron-withdrawing moieties, were obtained in good yields (Table 3).

To demonstrate the scalability of this process, a multigram preparation of imidazo[1,2-*a*]pyridine **3a** was attempted. The reaction of 2-aminopyridine (**1**) with 2-hydroxyacetophenone (**2a**) performed at a 37 mmol (5 g) scale (20 times larger than the experiments described in Table 3) furnished 3.94 g of imidazo[1,2-*a*]pyridine **3a** in a very similar yield (51%).

The spectral characteristics of imidazo[1,2-*a*]pyridines **3a−3f** were examined and compared to those of imidazo[1,2-*a*]pyridines **3g−3j** (Table 4). Optical measurements were performed in several solvents: toluene (nonpolar, aprotic), dichloromethane (moderately polar, aprotic), acetonitrile (polar, aprotic), methanol (polar, protic). The most notable feature of all of the imidazo[1,2-*a*]pyridines is an intense UV absorption band (λ_{abs} = 320−360 nm) regardless of the substituent at position 2. The absorption maxima shifted hypsochromically with increased solvent polarity (Table 4). The emission spectra of all of the studied compounds that possess a 2-hydroxyphenyl substituent strongly depend on the nature of the solvent. In all aprotic solvents, the emission is very weak (Φ_{fl} = 1−3% typically) and is situated around 560 nm. In polar but aprotic CH_3CN, compounds **3a−f** showed both blue and orange fluorescence (Table 4). While Stokes shifts in unpolar solvents reach 11000 cm^{-1}, in CH_3CN they are even higher (up to 13000 cm^{-1}), mainly because of the hypsochromically shifted absorption. By contrast, the emission spectrum in methanol shows a stronger non-ESIPT emission band in the blue region (λ_{max} = 370−390 nm, Φ_{fl} = 5−17%). Stokes shifts are moderate in MeOH (2500−4600 cm^{-1}). The only exception is compound **3f**, which possesses an additional strongly electron-donating Me_2N group at position 4 of the phenyl ring. Both absorption and emission of **3f** in MeOH are significantly bathochromically shifted when compared with imidazo[1,2-*a*]pyridines **3a−3e** (Table 4). The resulting Stokes shift reaches 6700 cm^{-1} in this case. The dramatic increase in

Table 4. Spectroscopic Properties of Compounds 3a−3j

compound	solvent	λ_{abs}/nm	ε	λ_{em}/nm	Φ_{fl}[a]	Stokes shift (cm^{-1})
3a	toluene	351	8800	573	0.011	11000
	CH_2Cl_2	345	7900	573	0.005	11500
	CH_3CN	328	12100	380	0.006	4200
				577	0.003	13100
	MeOH	328	12000	375	0.084	3800
3b	toluene	340	13900	560	0.036	11500
	CH_2Cl_2	334	14900	572	0.010	12500
	CH_3CN	330	15000	385	0.002	4300
				579	0.001	13000
	MeOH	331	15000	385	0.124	4200
3c	toluene	352	10000	561	0.036	10600
	CH_2Cl_2	347	10800	370	0.013	1800
	CH_3CN	344	10600	378	0.002	2600
				583	0.003	11900
	MeOH	330	14600	372	0.046	3100
				562	0.002	12200
3d	toluene	351	11800	541	0.087	10000
	CH_2Cl_2	347	12200	541	0.055	10300
	CH_3CN	344	11700	379	0.002	2700
				556	0.015	11100
	MeOH	342	11000	374	0.059	2500
				538	0.010	10600
3e	toluene	355	12100	559	0.048	10300
	CH_2Cl_2	351	13400	560	0.019	10600
	CH_3CN	331	13300	387	0.004	4400
				583	0.002	13100
	MeOH	332	11900	393	0.168	4700
3f	toluene	361	20300	572	0.034	10200
	CH_2Cl_2	354	22700	579	0.015	11000
	CH_3CN	350	23500	455	0.002	6600
				584	0.002	11500
	MeOH	350	22600	458	0.092	6700
3g	toluene	332	8100	381	0.607	3900
	CH_2Cl_2	328	8200	376	0.552	3900
	CH_3CN	325	8500	378	0.555	4300
	MeOH	321	8900	374	0.796	4400
3h	toluene	333	8600	382	0.571	3900
	CH_2Cl_2	330	8400	378	0.515	3900
	CH_3CN	328	8500	377	0.525	4000
	MeOH	323	9600	374	0.170	4200
3i	toluene	342	11500	393	0.590	3800
	CH_2Cl_2	355	11600	401	0.427	3200
	CH_3CN	333	11000	406	0.544	5400
	MeOH	333	11800	410	0.481	5600
3j	toluene	351	6900	383	0.585	2400
	CH_2Cl_2	333	10600	380	0.660	3700
	CH_3CN	331	10500	382	0.644	4000
	MeOH	327	11300	377	0.767	4100

[a]Determined in MeOH using quinine sulfate in 0.5 M H_2SO_4 as a standard

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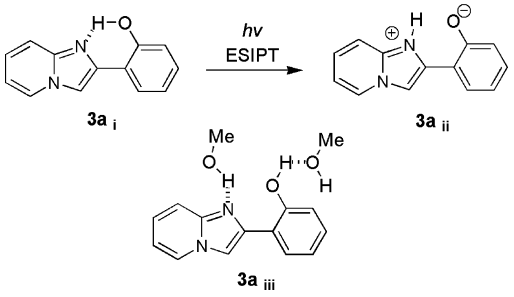
the fluorescence quantum yield of compounds **3a**−**3f** in MeOH can be attributed to the fact that, as reported by Douhal et al.,[13] in hydrogen-bonding media (such as MeOH), solvated structures such as $\mathbf{3a}_{iii}$, which emit in near-UV/blue-violet region, are favored, and consequently ESIPT is prevented (Scheme 2). These results indicate that blue fluorescence is due

Scheme 2



to direct emission from a localized excited state, and that orange fluorescence is the ESIPT fluorescence from zwitterionic $\mathbf{3a}_{ii}$. Interestingly, for dyes **3c** and **3d** containing bromine atom, ESIPT-type emission was also visible in MeOH (albeit very weak, Table 4). Emission of the remaining compounds **3g**−**3j**, which are not capable of ESIPT, is not so strongly solvent-dependent. Upon excitation at 330 nm, **3g**−**3j** show strong blue fluorescence at 370−380 nm. Again the exception is imidazo[1,2-*a*]pyridine **3i**, which possesses a strongly electron-donating pyrrole moiety. In this case the emission maximum is shifted into the violet region (390−410 nm). The nearly identical emission wavelengths for compounds **3a** and **3g** (λ_{max} = 372−376 nm) is evidence that their geometries in the excited state are very similar. For non-ESIPT imidazo[1,2-*a*]pyridines, the Stokes shift is moderate (∼4200 cm^{-1}), except for compound **3i** in polar solvents (∼5500 cm^{-1}). The notable difference is that Φ_{fl} of dyes **3g**−**3j** in MeOH is very high (40−80%). Of particular interest is the fact that the values of the Stokes shifts are essentially the same for groups of compounds regardless of whether they possess the proton donor necessary for ESPIT. Stokes shifts lower than 6000−8000 cm^{-1} can typically be explained on the basis of a "solute−solvent" polarizable continuum model of interaction. This solute−solvent model of interaction considers only a change in the dipole interaction energy of the fluorophore, which is induced by the electric field of the solvent by increasing the dipole moment of the fluorophore in the excited state. Thus, a red shift is associated with the macroscopic rate of solvent: dielectric constant and refraction index. The optical properties of compound **3g**−**3j** can be explained according to this model. The assumptions applied are in a good agreement with data published by Douhal et al.[13]

Araki and co-workers reported[14] that the ESIPT process, accompanied by a large Stokes shift (∼ 9700 cm^{-1}) and dependent on the structure of polymorphs, in imidazo[1,2-*a*]pyridines derivatives is strongly visible in the solid state. The idea developed by Acuña and co-workers and presented in Scheme 2 provides a satisfactory explanation of the observed large Stokes shift of the blue−green−yellow emission in the solid state. 2′-Hydroxy derivatives of 2-phenylimidazo[1,2-*a*]pyridine in solid state do not experience solvation effects, allowing them to stay in the zwitterionic ESIPT-active form $\mathbf{3a}_{iii}$.[13,14] We performed solid-state emission measurements for imidazo[1,2-*a*]pyridines **3a**−**j** (Table 5). Strong fluorescence was observed for ESIPT-capable imidazopyridines **3a**−**f** (λ_{em} = 490−520 nm). The emission maximum for compound **3a** (494 nm) perfectly correlates with properties of polymorph BG described by Araki and co-workers.[14b] Again, emission maximum is strongly bathochromically shifted for imidazopyridine **3f** (546 nm). Two out of non-ESIPT imidazopyridines also display luminescence in the solid state; however, emission is weak and hypsochromically shifted (Table 5).

Table 5. Solid State Emission Maxima of Compounds 3a−j

compound	$\lambda_{em\ max}$ [nm]
3a	494
3b	520
3c	483
3d	492
3e	503
3f	546
3g	
3h	
3i	395
3j	390

CONCLUSIONS

In summary, we have developed a new method for the direct preparation of imidazo[1,2-*a*]pyridines from acetophenones and 2-aminopyridine, via an Ortoleva−King reaction followed by ring closure. We have demonstrated that the initially formed pyridinium salts undergo efficient ring-closure in the presence of base. The reaction is functional group tolerant and allows for the preparation of an unprecedented library of derivatives including compounds bearing a strongly electron-donating group at position 2. Imidazo[1,2-*a*]pyridines possessing a 2-hydroxyphenyl substituent at position 2 exhibit ESIPT in the majority of solvents, resulting in weak but highly bathochromically shifted emission peaks. In MeOH, however, ESIPT is prevented by intermolecular hydrogen bonding; as a result, compounds emit in the violet−blue region. Solid state emission maxima follow the same trend as fluorescence in the solution, i.e., the presence of strongly electron-donating groups at phenyl ring shift emission from blue−green region to yellow one. Imidazo[1,2-*a*]pyridines possessing aryl substituents at position 2 display strong emission bands in the blue region (fluorescence quantum yields = 0.40−0.80). These results are not only of theoretical significance in that they provide new insight into factors influencing the optical properties of imidazo[1,2-*a*]pyridines, but they may also open the door to practical applications. The use of the described approach can open the way to the synthesis of a wide range of these heterocycles, which can serve as an ideal platform to obtaining more complex systems.

EXPERIMENTAL SECTION

General Methods. All chemicals were used as received unless noted otherwise. Reagent grade solvents (CH_2Cl_2, hexanes) were distilled prior to use. Spectrophotometric grade solvents were used without further purification. All reported ^1H NMR and ^{13}C NMR spectra were collected using 500 or 600 MHz spectrometers. Chemical shifts (δ ppm) were determined with TMS as an internal standard; *J* values are given in Hz. The UV/vis absorption spectra were recorded on a spectrophotometer in toluene, CH_2Cl_2, acetonitrile, or methanol. Emission spectra were recorded on a fluorescence spectrophotometer

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in methanol. Emission spectra are presented in photon units with the extinction coefficient in M^{-1} cm^{-1} in brackets and have been corrected for instrumental factors. Fluorescence quantum yields (Φ_{fl}) were measured with quinine sulfate in 0.5 M H_2SO_4 as a reference and were corrected for the refractive index of the solvent. Melting points were determined using a capillary-type apparatus. Chromatography was performed on silica (230−400 mesh). Dry column vacuum chromatography (DCVC) was performed on preparative thin-layer chromatography alumina. Mass spectra were obtained via electron impact mass spectrometry with double focusing sector mass analyzer (EI-MS).

Exemplary Procedure for the Preparation of Imidazo[1,2-*a*]pyridines Starting from 2-Aminopyridine (1). 2-(Imidazo[1,2-*a*]pyridin-2-yl)phenol (3a). A sealed tube was charged with 1-(2-hydroxyphenyl)ethanone (**2a**) (250 mg, 1.84 mmol), 2-aminopyridine (**1**) (398 mg, 4.23 mmol), and iodine (560 mg, 2.21 mmol). The reaction mixture was stirred at 110 °C. After 4 h, the mixture was cooled to 70 °C and stirred overnight. The residue was diluted with 5 mL of distilled water, and an excess of aqueous sodium hydroxide (45%) was added. The reaction mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with 25 mL of CH_2Cl_2. 10% aqueous HCl was added to the water−organic mixture until a neutral pH was obtained. The mixture was then extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The solid was isolated by column chromatography (silica, CH_2Cl_2/hexanes 1:2 → CH_2Cl_2/hexanes 3:1). The pure product was obtained as a solid after crystallization from ethanol−water (219 mg, 57%). Data for **3a**: mp 142−143 °C (lit.[13a] mp 141−142 °C); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 6.79 (t, 1H, J = 6.6 Hz), 6.84 (t, 1H, J = 7.4 Hz), 7.02 (d, 1H, J = 8.2 Hz), 7.17−7.25 (m, 2H), 7.52 (t, 2H, J = 8.6 Hz), 7.78 (s, 1H), 8.08 (d, 1H J = 6.6 Hz), 12.81 (broad s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 106.9, 113.3, 115.5, 116.4, 116.8, 117.8, 119.1, 125.3, 125.6, 125.7, 125.9, 129.8, 157.5; EI-HR obsd 210.0797, calcd exact mass 210.0793 ($C_{13}H_{10}N_2O$).

2-(Imidazo[1,2-*a*]pyridin-2-yl)-5-methoxyphenol (3b). Prepared following exemplary procedure from 1-(2-hydroxy-4-methoxyphenyl)ethanone (**2b**) (250 mg, 1.50 mmol), 2-aminopyridine (**1**) (325 mg, 3.46 mmol), and iodine (426 mg, 1.81 mmol). The solid was isolated by column chromatography (silica, CH_2Cl_2/hexanes 1:2 → CH_2Cl_2/hexanes 3:1). The pure product was obtained as a solid after crystallization from ethanol (220 mg, 61%). Data for **3b**: mp 153−155 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 3.82 (s, 3H), 6.46 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.6 Hz), 6.58 (d, 1H, J = 2.5 Hz), 6.81 (t, 1H J = 6.7 Hz), 7.18 (t, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 8.6 Hz), 7.54 (d, 1H, J = 9.0 Hz), 7.74 (s, 1H), 8.11 (d, 1H, J = 6.7), 12.86 (broad s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 55.4, 101.9, 105.7, 106.7, 109.5, 113.1, 116.6, 125.0, 125.4, 126.8, 143.5, 145.6, 159.0, 161.2; EI-HR obsd 240.0892, calcd exact mass 240.0899 ($C_{14}H_{12}N_2O_2$).

4-Bromo-2-(imidazo[1,2-*a*]pyridin-2-yl)phenol (3c). Prepared following exemplary procedure from 1-(5-bromo-2-hydroxyphenyl)-ethanone (**2c**) (250 mg, 1.16 mmol), 2-aminopyridine (**1**) (252 mg, 2.67 mmol), and iodine (353 mg, 1.39 mmol). The solid was isolated by column chromatography (silica, CH_2Cl_2/hexanes 1:2 → CH_2Cl_2/hexanes 3:2). The pure product was obtained as a solid (178 mg, 53%). Data for **3c**: mp 208−209 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 6.87−6.92 (m, 2H), 7.24−7.27 (m, 1H), 7.28 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.58 (d, 1H, J = 9.0 Hz), 7.68 (d, 1H, J = 2.4 Hz), 7.84 (s, 1H), 8.15 (d, 1H, J = 6.7), 12.75 (broad s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 107.2, 110.8, 113.6, 117.0, 118.2, 119.7, 125.6, 125.7, 132.3, 143.6, 144.1, 156.6; EI-HR obsd 287.9904, calcd exact mass 287.9898 ($C_{13}H_9BrN_2O$).

5-Bromo-2-(imidazo[1,2-*a*]pyridin-2-yl)phenol (3d). Prepared following exemplary procedure from 1-(4-bromo-2-hydroxyphenyl)-ethanone (**2d**) (210 mg, 0.98 mmol), 2-aminopyridine (**1**) (211 mg, 2.25 mmol), and iodine (297 mg, 1.17 mmol). The solid was isolated by column chromatography (silica, CH_2Cl_2/hexanes 1:1 → CH_2Cl_2). The pure product was obtained as a solid (158 mg, 56%). Data for **3d**: mp 154−155 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 6.85 (t, 1H, J = 5.9 Hz), 6.97−6.99 (m, 1H), 7.19 (s, 1H), 7.22 (d, 1H, J = 7.8 Hz), 7.38 (t, 1H, J = 7.0 Hz), 7.55 (dd, 1 h, J_1 = 2.7 Hz, J_2 = 8.7 Hz), 7.8 (d, 1H, J = 6.3 Hz), 8.12 (t, 1H, J = 5.0 Hz), 12.94 (broad s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 106.9, 113.5, 115.4, 116.9, 120.9, 122.3, 122.7, 125.6, 126.8, 126.9, 143.5, 144.6, 158.3; EI-HR obsd 287.9890, calcd exact mass 287.9898 ($C_{13}H_9BrN_2O$).

4-(Imidazo[1,2-*a*]pyridin-2-yl)benzene-1,3-diol (3e). Prepared following exemplary procedure from 1-(2,4-dihydroxyphenyl)-ethanone (**2e**) (150 mg, 0.99 mmol), 2-aminopyridine (**1**) (213 mg, 2.27 mmol), and iodine (300 mg, 1.18 mmol). The solid was isolated by column chromatography (silica, CH_2Cl_2/ethyl acetate 1:1). The pure product was obtained as a solid (87 mg, 39%). Data for **3e**: mp 114−115 °C (lit.[37] mp 115 °C); ^{1}H NMR (500 MHz, DMSO-d_6, δ) 6.33 (d, 2H, J = 11.6 Hz), 6.94 (t, 1H, J = 6.4 Hz), 7.28 (t, 1H, J = 7.6 Hz), 7.60−7.64 (m, 1H), 8.28 (s, 1H), 8.56 (d, 1H, J = 6.4 Hz), 9.52 (s, 1H), 12.09 (broad s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, δ) 103.4, 107.7, 107.9, 109.1, 113.2, 115.9, 125.8, 127.1, 127.9, 143.2, 144.2, 158.1, 159.1; EI-HR obsd 226.0739, calcd exact mass 226.0742 ($C_{13}H_{10}N_2O_2$).

5-(Diethylamino)-2-(imidazo[1,2-*a*]pyridin-2-yl)phenol (3f). Prepared following exemplary procedure from 1-(4-(diethylamino)-2-hydroxyphenyl)ethanone (**2f**) (250 mg, 1.21 mmol), 2-aminopyridine (**1**) (261 mg, 2.77 mmol), and iodine (367 mg, 1.45 mmol). The solid was isolated by column chromatography (silica, ethyl acetate/CH_2Cl_2 3:2). The pure product was obtained as a solid (139 mg, 41%). Data for **3f**: mp 167−169 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ) 1.09 (t, 6H, 6.8 Hz), 3.34 (d, 4H, J = 6.5 Hz), 6.14 (s, 1H), 6.25 (d, 1H, J = 8.5 Hz), 6.92 (t, 1H, J = 6.6 Hz), 7.26 (t, 1H, J = 7.8 Hz), 7.54 (dd, 2H J_1 = 8.8 Hz, J_2 = 15.5 Hz), 8.22 (s, 1H), 8.53 (d, 1H, J = 6.6 Hz), 12.04 (broad s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ) 12.6, 43.7, 98.5, 103.6, 104.6, 106.4, 125.1, 126.4, 127.3, 142.8, 144.6, 148.6, 157.8; EI-HR obsd 281.1536, calcd exact mass 281.1528 ($C_{17}H_{19}N_3O$).

2-Phenyl-imidazo[1,2-*a*]pyridine (3g). Prepared following exemplary procedure from acetophenone (**2g**) (500 mg, 4.16 mmol), 2-aminopyridine (**1**) (901 mg, 9.57 mmol), and iodine (1268 mg, 5.00 mmol). The solid was chromatographed by DCVC (alumina, CH_2Cl_2/hexanes 1:2 → CH_2Cl_2). The pure product was obtained as a solid (445 mg, 55%). Data for **3g**: mp 133−134 °C (lit.[18] mp 134 °C); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 6.75 (t, 1H, J = 6.6 Hz), 7.15 (t, 1H, J = 7.8 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.42 (t, 2H, J = 7.6 Hz), 7.62 (d, 1H, J = 9.0), 7.86 (s, 1H), 7.95 (d, 2H, J = 7.3 Hz), 8.10 (d, 1H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 108.1, 112.4, 117.6, 124.57, 124.64, 125.6, 126.1, 128.0, 128.7, 133.8, 145.7, 145.9; EI-HR obsd 194.0836, calcd exact mass 194.0844 ($C_{13}H_{10}N_2$).

2-(Pyridin-2-yl)-imidazo[1,2-*a*]pyridine (3h). Prepared following exemplary procedure from 1-(pyridin-2-yl)ethanone (**2h**) (250 mg, 2.06 mmol), 2-aminopyridine (**1**) (447 mg, 4.75 mmol), and iodine (629 mg, 2.48 mmol). The solid was chromatographed by DCVC (alumina, CH_2Cl_2/hexanes 1:1 → CH_2Cl_2). The pure product was obtained as a solid (217 mg, 54%). Data for **3h**: mp 139−140 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ) 6.90 (t, 1H, J = 6.7 Hz), 7.25 (t, 1H, J = 7.8 Hz), 7.30 (t, 1H, J = 5.9 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.86 (t, 1H, J = 7.5 Hz), 8.11 (d, 1H, J = 7.8 Hz), 8.49 (s, 1H), 8.57−8.60 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, δ) 111.3, 113.5, 117.0, 119.8, 122.7, 125.3, 127.2, 137.0, 144.7, 144.8, 149.4, 152.8; EI-HR obsd 195.0789, calcd exact mass 195.0797 ($C_{12}H_9N_3$).

2-(Pyrrol-2-yl)-imidazo[1,2-*a*]pyridine (3i). Prepared following exemplary procedure from 1-(pyrrol-2-yl)ethanone (**2i**) (150 mg, 1.37 mmol), 2-aminopyridine (**1**) (298 mg, 3.16 mmol), and iodine (419 mg, 1.65 mmol). The solid was isolated by column chromatography (silica, CH_2Cl_2/ethyl acetate 5:1 → CH_2Cl_2/ethyl acetate 1:1). The pure product was obtained as a solid (108 mg, 43%). Data for **3i**: mp 198−199 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ) 6.10 (d, 1H, J = 2.6 Hz), 6.48 (s, 1H), 6.79 (s, 1H), 6.82 (t, 1H J = 6.7 Hz), 7.17 (t, 1H, J = 7.48 Hz), 7.47 (d, 1H, J = 9.00 Hz), 8.04 (s, 1H), 8.50 (d, 1H, J = 6.65 Hz), 11.32 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ) 105.9, 106.5, 108.6, 111.8, 115.8, 118.6, 124.3, 126.3, 126.6, 139.6, 144.4; EI-HR obsd 183.0796, calcd exact mass 183.0797 ($C_{11}H_9N_3$).

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2-(Thiophen-2-yl)-imidazo[1,2-*a*]pyridine (3j). Prepared following exemplary procedure from 1-(thiophen-2-yl)ethanone (**2j**) (250 mg, 1.98 mmol), 2-aminopyridine (**1**) (429 mg, 4.56 mmol), and iodine (603 mg, 2.38 mmol).The solid was chromatographed by DCVC (alumina, CH_2Cl_2/hexane 1:1 → CH_2Cl_2). The pure product was obtained as a solid (202 mg, 51%). Data for **3j**: mp 151−153 °C (lit.[38] mp 137−138 °C); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 6.75 (t, 1H, J = 6.7 Hz), 7.08 (dd, 1H, J_1 = 3.7 Hz, J_2 = 4.9 Hz), 7.14 (t, 1H, J = 7.9 Hz), 7.30 (d, 1H, 5.0 Hz), 7.47 (d, 1H, J = 3.5 Hz), 7.60 (d, 1H, J = 9.0 Hz), 7.76 (s, 1H), 8.06 (d, 1H, 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, δ)107.6, 112.7, 117.5, 123.8, 124.9, 125.2, 125.6, 127.9, 137.7, 141.0, 145.6; EI-HR obsd 200.0403, calcd exact mass 200.0408 ($C_{11}H_8N_2S$).

Multigram Scale Preparation of 2-(Imidazo[1,2-*a*]pyridin-2-yl)phenol (3a). A sealed tube was charged with 1-(2-hydroxyphenyl)-ethanone (**2a**) (5.000 g, 36.72 mmol), 2-aminopyridine (**1**) (7.948 g, 84.47 mmol), and iodine (11.183 g, 44.06 mmol). After cooling to room temperature, the reaction mixture was diluted with 25 mL CH_2Cl_2. 10% aqueous HCl was added to the water−organic mixture until a neutral pH was obtained. The mixture was then extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The solid was isolated by column chromatography (silica, CH_2Cl_2/hexanes 1:2 → CH_2Cl_2/hexanes 3:1). The pure product was obtained as a solid (3.937 g, 51%).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of compounds **3a**−**3j**. 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.

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