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Article

Iodine-Catalyzed Multicomponent Synthesis of Highly Fluorescent Pyrimidine-Linked Imidazopyridines

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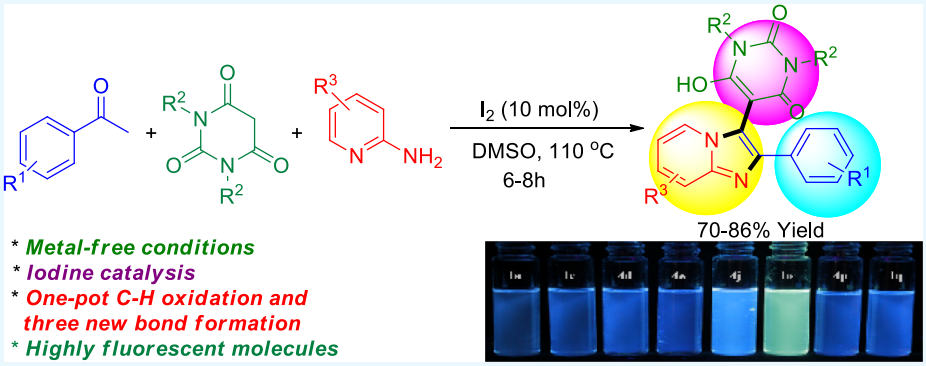

ABSTRACT: Herein, we report a metal-free one-pot three-component reaction of aryl methyl ketones, 2-aminopyridines, and barbituric acids for the synthesis of pyrimidine-linked imidazopyridines using a catalytic amount of molecular iodine in DMSO medium. This process involves a one-pot C−H oxidation, followed by the formation of one C−C and two C−N bonds. A wide variety of aryl methyl ketones and 2-aminopyridines were found to be suitable for this methodology. The UV and fluorescence properties of the synthesized products were studied in water and DMSO media. Most of the synthesized products exhibited very good to excellent fluorescence quantum yield. Among all the products, compounds **4p** and **4q** showed the maximum fluorescence quantum yield (0.36) in water medium under basic conditions and compound **4c** showed the maximum fluorescence quantum yield (0.75) in DMSO medium.

INTRODUCTION

Imidazopyridine is a privileged scaffold found in many natural products as well as in synthetic pharmaceuticals.[1] Imidazopyridine-containing molecules exhibit a wide range of bioactivities such as anticancer,[2] antiparasitic,[3] antiviral, antibacterial, and anti-inflammatory activities, and they are PD-L1 antagonists[4] as well as a suppressor of tumors.[5] Prescription medicines such as zolpidem, zolimidine, nicopidem, saripidem, and olprinone have an imidazopyridine core.[1a] Recently, many functionalized imidazopyridine derivatives have been reported in the literature using metal and photocatalyzed C−H activation processes.[6] In addition to its pharmaceutical importance, the imidazopyridine moiety has gained considerable attention due to its fluorescence and chemosensing properties.[7a−e] Considering the enormous applications of imidazopyridines over the years, several synthetic methods have been reported using metal-catalyzed,[8] metal-free,[9] electrochemical,[10] and light-induced[11] reaction conditions employing either two or multicomponent reactions (MCRs).

Similar to imidazopyridines, the pyrimidine moiety, especially barbituric acid and its derivatives, is an important pharmacophore and exhibits diverse medicinal properties.[12] The design and synthesis of hybrid molecules bearing more than one pharmacophore has gained considerable interest in recent times.[13] Considering the importance of hybrid molecules, imidazopyridines and the pyrimidine moiety, and in continuation of our work on the development of new methodologies,[14] we turned our attention to developing a new metal-free methodology for the synthesis of pyrimidine-linked imidazopyridines from the readily available starting materials. From the literature, we realized that the reaction of aryl methyl ketone and aminopyridine has been utilized for the preparation of diverse substituted imidazopyridine derivatives under different reaction conditions (Scheme 1). Wu et al. reported the reaction of aryl methyl ketone and 2-aminopyridines in the presence of a stoichiometric amount (1.5 equiv) of iodine in DMSO medium for the preparation of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridines (Scheme 1, eq a).[15] Zeng et

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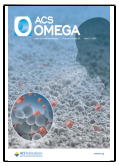
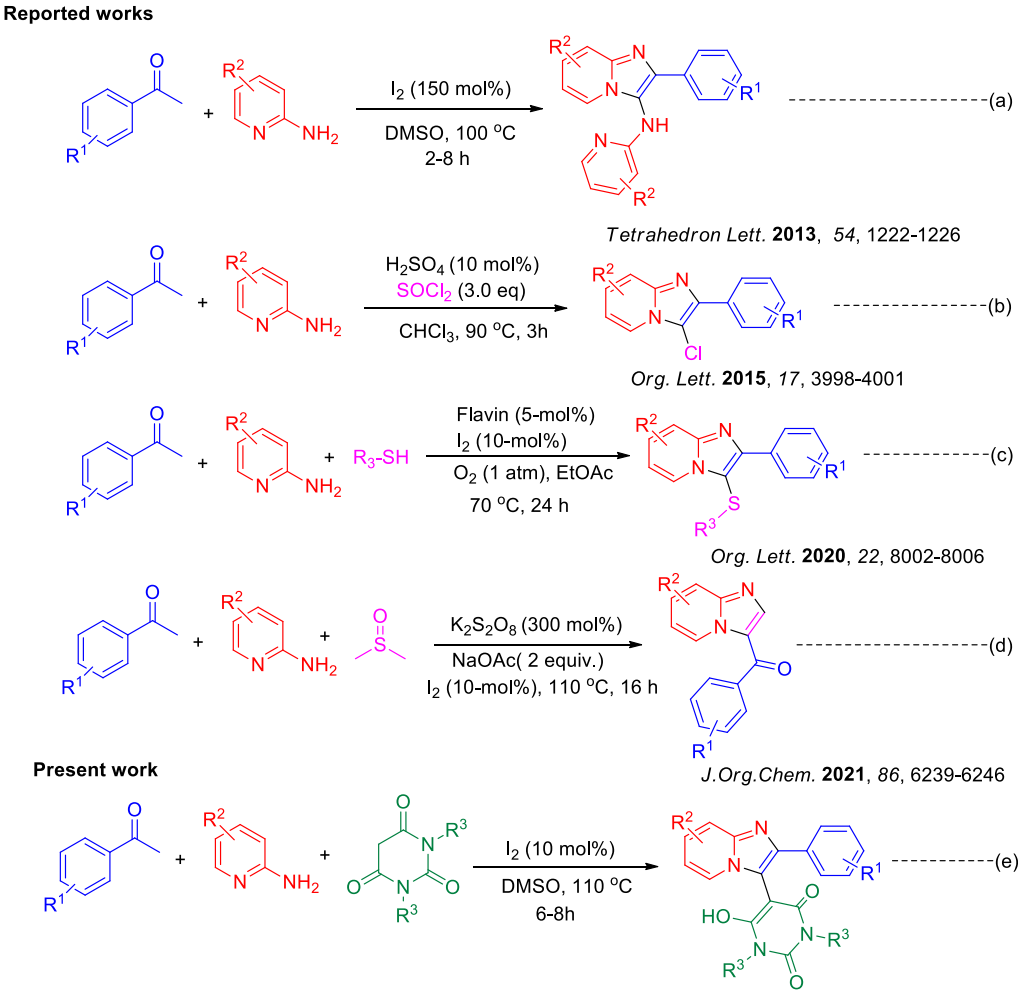


Scheme 1. Comparison of the Present Work with Some Reported Methods



al. demonstrated the synthesis of chloroimidazo[1,2-*a*]-pyridines from the reactions of aryl methyl ketones, 2-aminopyridine, and $SOCl_2$ in the presence of H_2SO_4 in $CHCl_3$ medium (Scheme 1, eq b).[16] Iida et al. developed a three-component reaction for the synthesis of thioether-linked imidazopyridines using the dual catalysis of flavin and iodine as shown in Scheme 1, eq c.[17] Very recently, Ma et al. have reported a one-pot three-component reaction for the synthesis of 3-arylimidazopyridines employing iodine catalysis and DMSO as the one-carbon source (Scheme 1, eq d).[18] In this paper, we report an iodine-catalyzed three-component reaction in DMSO medium for the synthesis of pyrimidine-linked imidazopyridine hybrids and study their photophysical properties (Scheme 1, eq e). Previously, we reported iodine−DMSO-mediated synthesis of 2-arylbenzo[*d*]imidazo[2,1-*b*]thiazole derivatives[14d] using a stoichiometric amount of iodine. Interestingly, we found that this reaction provides better results in the presence of a catalytic amount of iodine in DMSO medium. DMSO plays dual role as a solvent as well as an oxidant in this reaction.

RESULTS AND DISCUSSION

We initiated the present study by taking 4′-methoxyacetophenone (**1d**), 1,3-dimethylbarbituric acid (**2a**), and 2-aminopyridine (**3a**) as the model substrates. The initial reaction was tried on a 0.5 mmol scale using a 1:1:1 ratio of **1d**, **2a**, and **3a** in the presence of 1.5 equivalent of molecular iodine in 3.0 mL DMSO, and the mixture was kept at 110 °C for 6 h. Interestingly, in this attempt, the corresponding three-component product **4d** was obtained in 50% yield only. The product **4d** was fully characterized by recording the ^1H, ^{13}C NMR, as well as HRMS spectra. With this encouraging result in hand, we turned our attention to optimize the reaction conditions. For optimization, we performed the reaction at different temperatures keeping 150 mol % of molecular iodine in DMSO medium (Table 1, entries 2−4). From these reactions, we realized performing this reaction below 100 °C provided lower yields, and increasing the temperature above 110 °C provided no benefit in terms of the reaction time or yield. As a result, we decided to try all the other reactions at 110 °C. Replacing DMSO by other solvents such as DMF, acetonitrile, ethanol, water, and toluene did not provide the desired product **4d** (Table 1, entries 5−9). Thus, DMSO was considered as an essential solvent cum oxidizing agent for this three-component reaction.

After this, we turned our attention to optimize the amount of iodine. Interestingly, the model reaction in the presence of 200 mol% of iodine in DMSO medium provided only 25% yield (Table 1, entry 10). Thus, we started the screening of the model reactions using 100, 50, 30, 20, and 10 mol % of iodine in DMSO medium, and the results are summarized in Table 1, entries 11−15. It is noteworthy to mention that we observed

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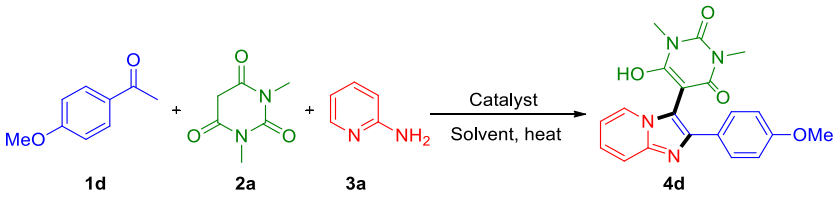
Table 1. Optimization of the Reaction Conditions[a]



1d 2a 3a 4d

entry	solvent	iodine source (mol %)	reaction temperature (°C)	**4d**, yield (%)[b]
1	DMSO	I_2 (150 mol %)	110	50
2	DMSO	I_2 (150 mol %)	130	50
3	DMSO	I_2 (150 mol %)	150	50
4	DMSO	I_2 (150 mol %)	90	45
5	DMF	I_2 (150 mol %)	110	0
6	acetonitrile	I_2 (150 mol %)	110	0
7	EtOH	I_2 (150 mol %)	110	0
8	H_2O	I_2 (150 mol %)	110	0
9	toluene	I_2 (150 mol %)	110	0
10	DMSO	I_2 (200 mol %)	110	25
11	DMSO	I_2 (100 mol %)	110	60
12	DMSO	I_2 (50 mol %)	110	66
13	DMSO	I_2 (30 mol %)	110	72
14	DMSO	I_2 (20 mol %)	110	78
15	**DMSO**	**I_2 (10 mol %)**	**110**	**85**
16	DMSO	I_2 (5 mol %)	110	40[c]
17	DMSO	NaI (100 mol %)	110	trace
18	DMSO	KI (100 mol %)	110	trace
19	DMSO	TBAI (100 mol %)	110	trace

[a]Reaction conditions: **1d** (0.5 mmol), **2a** (0.5 mmol), and **3a** (0.5 mmol) in 3.0 mL solvent, and the reaction was performed for 6−8 h. [b]Isolated Yield. [c]Reaction was performed for 24 h.

better yields on lowering the iodine stoichiometry. Further decreasing the amount of iodine took a very long time (24 h), and very less yield was observed (Table 1, entry 16). We have also tried other iodine sources such as NaI, KI, and TBAI; however, in all these cases, only trace amounts of the desired product were found (Table 1, entries 17−19). Thus, 10 mol % of molecular iodine in DMSO medium and 110 °C were considered as the optimized reaction conditions for this transformation.

With these optimized conditions, we next explored the generality and scope of this three-component reaction by taking several electron-donating and -withdrawing substituents on the aromatic ring of acetophenone and 2-aminopyridine derivatives. This MCR was found to be compatible with a wide range of acetophenone derivatives, and the results are summarized in Table 2. For this MCR, acetophenone derivatives with electron-donating substituents such as −Me, −Et, −OMe, and −methylenedioxy and electron-withdrawing groups such as −Cl, 3,4-diCl, −Br, $-CF_3$, and $-NO_2$ were found to be suitable. The reaction proceeded well, even with the bulky aryl methyl ketones such as naphthyl, fluorene, and biphenyl. Aryl methyl ketones having electron-withdrawing substituents provided relatively lesser yields than the ketones having electron-donating groups. We also varied 2-amino-pyridine, and, in all the cases, we observed good to very good yields. Similar to 1,3-dimethylbarbituric acid, barbituric acid was also found to be suitable for this three-component reaction and the corresponding three-component product **4u** was obtained in 69% yield under the standard reaction conditions. To further check whether the ortho-substituted acetophenone will give the similar result, we have reacted 2-chloro acetophenone and obtained the corresponding product **4v** in 57% yield.

From the literature, we found that imidazopyridine derivatives exhibit interesting fluorescence properties.[7a−e] We also found that most of our synthesized compounds are highly fluorescent under UV light, whereas some other compounds did not show any fluorescence. Thus, to study the electronic effect of substituents on the fluorescence property of our hybrid molecules having imidazopyridine and pyrimidine moieties, we then turned our focus toward their photophysical study. For the photophysical studies, first we prepared the sodium salt of our products by dissolving the product in 0.25 M NaOH aqueous solution. Under this basic condition, all the products were found to be highly soluble in water medium. Next, we studied photophysical properties of all the synthesized compounds in water medium. Initially, the UV−visible and steady-state fluorescence spectra of **4a** having an unsubstituted phenyl ring and a 1,3-dimethylbarbituric acid moiety in 0.25 M NaOH solution in water medium were recorded.

The quantum yield of **4a** was calculated using quinine sulfate dihydrate in 0.1 M H_2SO_4 (Φstd = 0.54) as the fluorescence standard. The calculated quantum yield (Φ) of **4a** was found to be 0.33. Then, quantum yield of compound **4d** having the 4-OMe substituent was recorded, in this case the quantum yield increased to 0.336, whereas for compound **4k** having the 4-NO_2 substituent, the fluorescent property vanished (Φ = 0). A comparative plot of the UV and fluorescence spectra of **4a**, **4d**, and **4k** is shown in Figure 1a,b. Interestingly, the compound having both $-NO_2$ and −OMe groups on the phenyl ring (**4l**) also did not show any fluorescence property (Φ = 0). Next,

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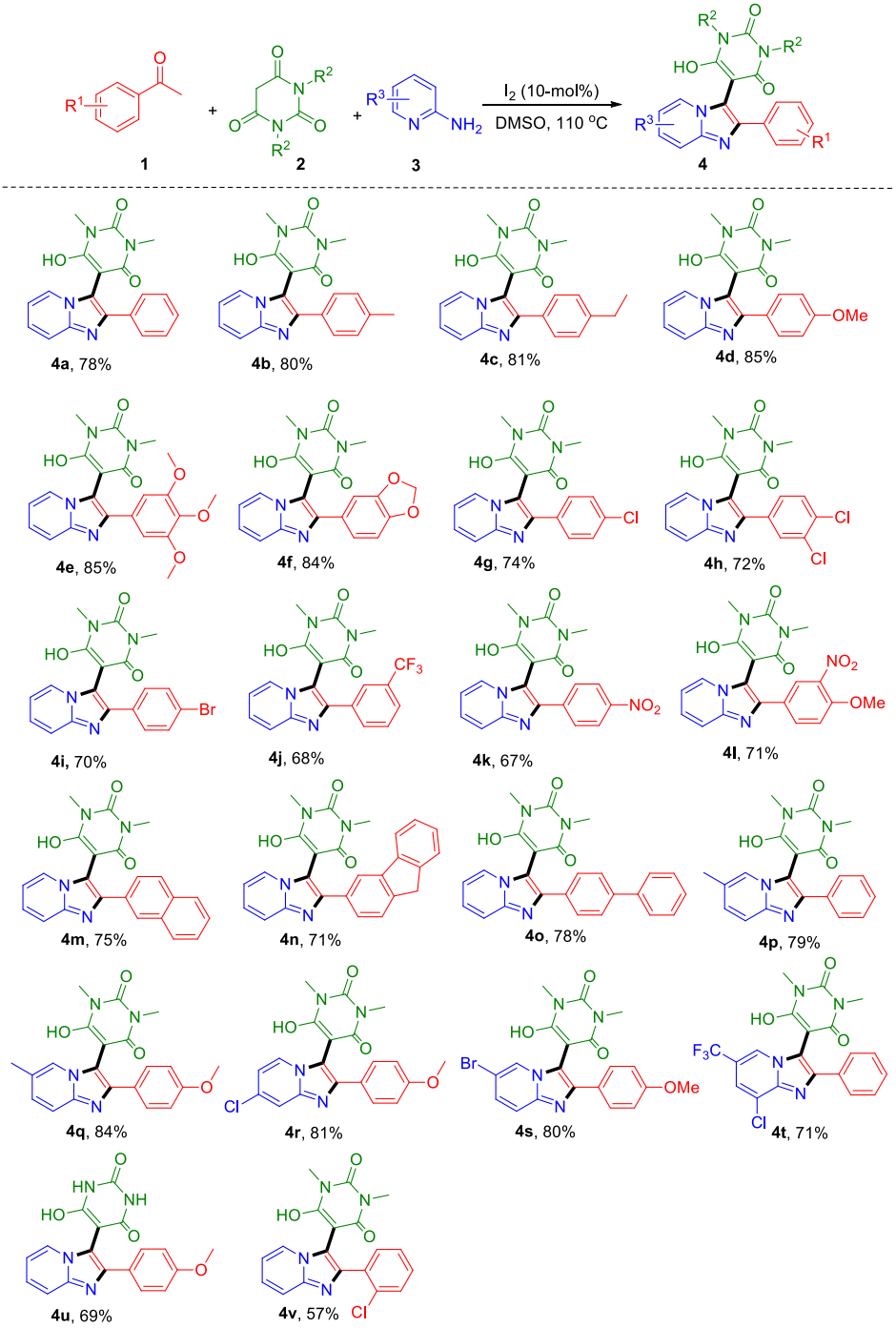
Table 2. Substrate Scope for the One-Pot Synthesis of Pyrimidine-Linked Imidazo[1,2-*a*]pyridines[a]



[a]Reaction conditions: compound **1** (0.5 mmol), molecular I_2 (10 mol %), and DMSO (2.0 mL) were taken in a 10 mL round-bottom flask. The mixture was stirred until the disappearance of **1** (by TLC monitoring) keeping the reaction temperature at 110 °C. To this mixture, **2** (0.5 mmol) and **3** (0.5 mmol) were added and continued stirring until the completion of the reaction.

using similar methods, photophysical data of all the synthesized products was recorded, and the results are summarized in Table 3. Among all the screened compounds, compounds **4p** and **4q** showed the maximum fluorescence quantum yield.

Next, we tried to check the photophysical properties of these pyrimidine-linked imidazo[1,2-a] pyridines in organic solvents. For that, the UV and steady-state fluorescence spectra of compound **4q** were recorded in various organic solvents such as DMSO, DMF, acetonitrile, chloroform, and ethanol (Figure 2a,b). Interestingly, in organic solvents, a drastic increase of quantum yield for **4q** was observed. In DMSO medium, **4q** showed the maximum quantum yield (Φ = 0.69), followed by in DMF (Φ = 0.51), in EtOH (Φ = 0.43), and in acetonitrile (Φ = 0.41), but in $CHCl_3$ the value decreased drastically (Φ = 0.18).

As we observed the highest fluorescence quantum yield of **4q** in DMSO medium, we turned our attention to study the

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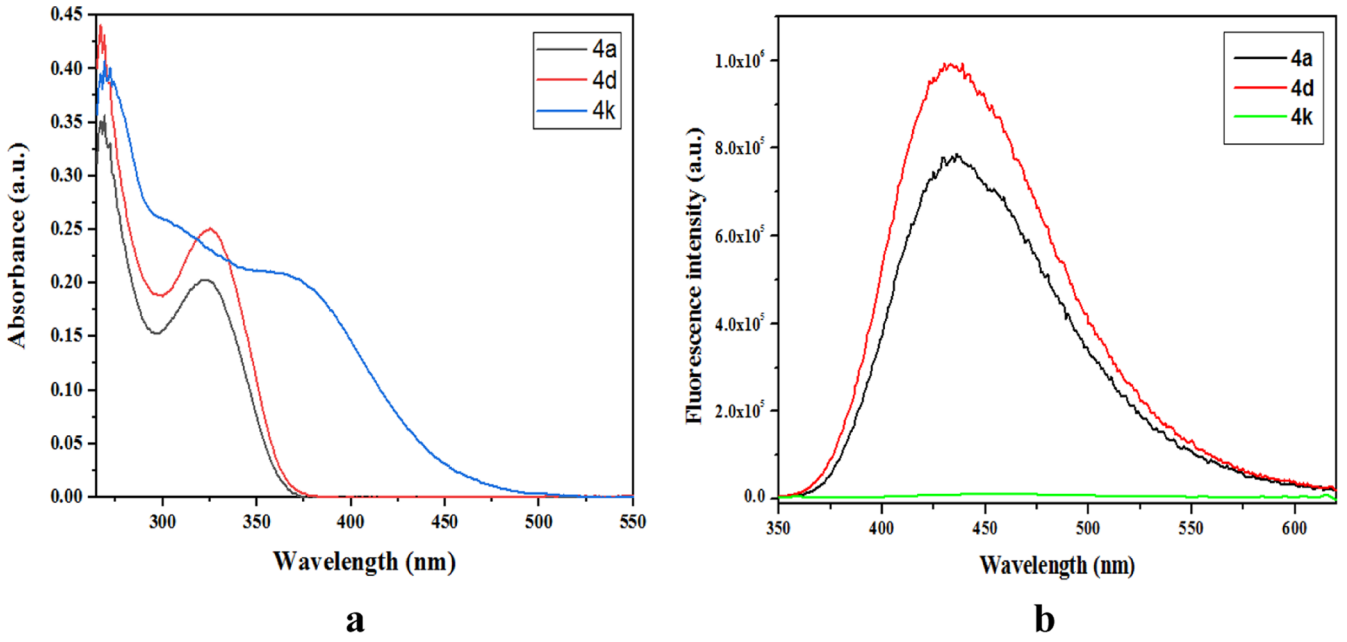

Figure 1. (a) UV spectra of **4a**, **4d**, and **4k**. (b) Fluorescence spectra of **4a**, **4d**, and **4k**.

Table 3. Photophysical Data of Compounds 4a−4u in Water Medium under Basic Conditions[a]

S. no.	compound	$\lambda_{abs(max)}$ (nm)	abs.	λ_{ex} (nm)	$\lambda_{em(max)}$ (nm)	Stokes shift (nm)	quantum yield (Φ)
1	**4a**	323	0.203	323	436	113	0.330
2	**4b**	323	0.133	323	438	115	0.309
3	**4c**	324	0.261	324	434	110	0.308
4	**4d**	325	0.250	325	435	110	0.336
5	**4e**	325	0.153	325	430	105	0.290
6	**4f**	323	0.149	323	435	112	0.311
7	**4g**	325	0.129	325	434	109	0.172
8	**4h**	325	0.268	325	438	113	0.005
9	**4i**	325	0.266	325	432	107	0.007
10	**4j**	324	0.13	324	434	110	0.138
11	**4k**	306	0.355	306	439	133	0.005
12	**4l**	323	0.254	323			
13	**4m**	325	0.275	325	476	151	0.057
14	**4n**	331	0.482	331	441	110	0.231
15	**4o**	328	0.421	328	474	146	0.150
16	**4p**	322	0.156	322	440	118	0.360
17	**4q**	324	0.246	324	434	110	0.360
18	**4r**	336	0.100	336	460	124	0.170
19	**4s**	335	0.181	335			
20	**4t**	334	0.112	334			
21	**4u**	327	0.21	327	467	140	0.125
22	**4v**	316	0.065	316	438	122	0.05

[a]All spectra were recorded in 0.25 M NaOH solution with the compound concentration $c = 3 \times 10^{-5}$ M at room temperature.

UV and fluorescence properties of remaining all the products in the same organic medium, and the results are summarized in Table 4.

Compound **4a** initially showed Φ = 0.33 in water under basic conditions, whereas in DMSO medium it increased to Φ = 0.61. Likewise, **4b**, **4c**, **4d**, **4e**, and **4f** having electron-donating substituents on the phenyl ring showed a significant increase in quantum yields with Φ = 0.57, 0.75, 0.614, 0.60, and 0.69, respectively, in DMSO medium. Compound **4g** having the 4-Cl substituent on the phenyl ring showed quantum yield Φ = 0.46 in DMSO medium. Similar to water medium, in DMSO also **4h** and **4i** did not exhibit fluorescence properties. Interestingly, **4j** having the $-CF_3$ substituent on the phenyl ring showed Φ = 0.651 in DMSO medium.

Like in water medium, in DMSO also, compounds **4k** and **4l**, which contain a $-NO_2$ group on the phenyl ring, did not show fluorescence. Our observation is also in agreement with the literature reports, which state that the introduction of a $-NO_2$ group to the fluorophore quenches the overall fluorescence intensity due to three factors: (i) it favors intersystem crossing leading to efficient triplet formation,[19] (ii) helps in the formation of dark charge transfer states for non-radiative decay to the ground state,[20] and (iii) provides non-radiative pathways for efficient internal conversion.[21] Com-

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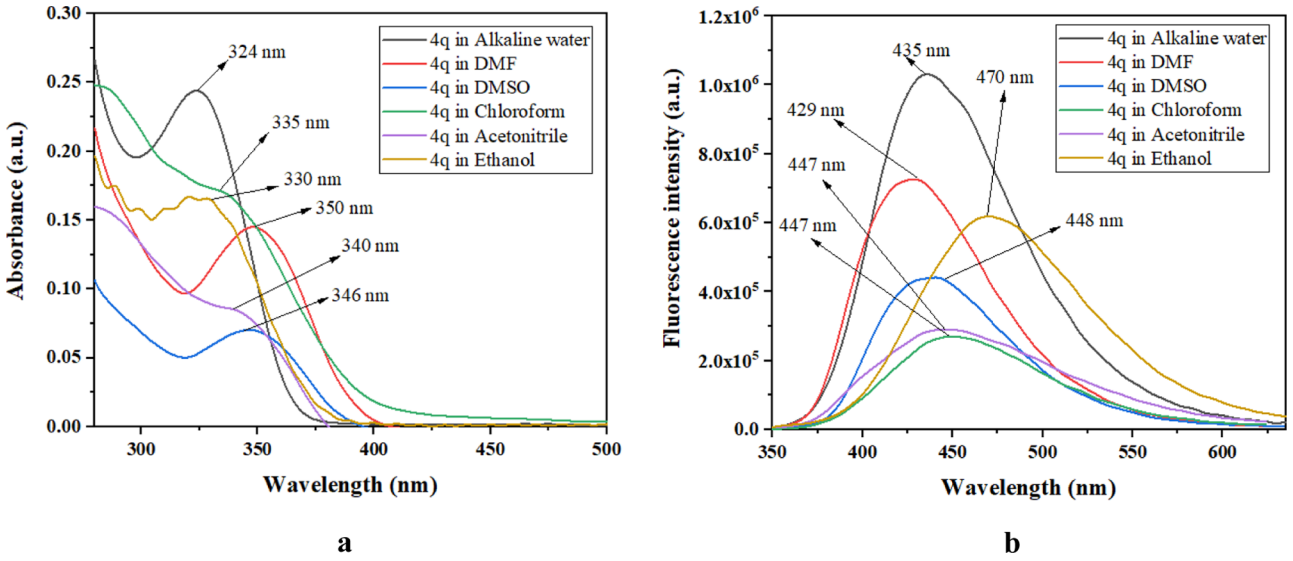

Figure 2. (a) UV spectra of compound **4q** in different solvents. (b) Fluorescence spectra of compound **4q** in different solvents.

Table 4. Photophysical Data of 4a−4u and 5 in DMSO Medium[a]

sample code	λ_{max} (nm)	abs.	λ_{ex} (nm)	λ_{em} (nm)	Stokes shift (nm)	quantum yield (Φ)
QS	346	0.098	346	449	103	0.546
4a	345	0.06	345	456	111	0.610
4b	346	0.052	346	455	109	0.571
4c	**346**	**0.036**	**346**	**456**	**110**	**0.750**
4d	346	0.088	346	453	107	0.614
4e	346	0.037	346	449	103	0.605
4f	346	0.03	346	455	109	0.591
4g	347	0.042	347	457	110	0.460
4h	355	0.143	355			
4i	346	0.012	346			
4j	350	0.036	350	457	107	0.651
4k	410	0.031	410			
4l	346	0.028	346			
4m	355	0.166	355	483	128	0.567
4n	356	0.157	356	466	110	0.448
4o	353	0.112	353	486	133	0.631
4p	346	0.042	346	455	109	0.663
4q	346	0.071	346	450	104	0.692
4r	360	0.041	360	481	121	0.200
4s	365	0.01	365			
4t	355	0.015	355			
4u	346	0.063	346	458	112	0.567
4v	340	0.024	340	457	117	0.16
5	317	0.08	317	379	62	0.48

[a]All spectra were recorded in DMSO with concentration $c = 3 \times 10^{-5}$ M at room temperature.

pound **4m** that has a naphthyl ring showed around 11 times higher quantum yield Φ = 0.56 in DMSO than in water medium. Likewise, imidazopyridines **4n** and **4o** having fluorenyl and biphenyl rings showed very good quantum yields Φ = 0.44 and 0.63, respectively, in DMSO medium. Compound **4u** that contains the unsubstituted barbituric acid moiety also showed a significant quantum yield (Φ = 0.56). Compound **4v** showed quantum yield Φ = 0.05 in basic solution of water and Φ = 0.16 in DMSO medium. In Figure 3, we have shown a picture of some highly fluorescent products in DMSO medium under UV light. Considering the high fluorescence intensity of most of the synthesized products, both in organic and aqueous media, it is expected that these molecules may find applications in chemosensing.

To further compare and check the effect of the barbituric acid moiety on fluorescence property, we have prepared the 2-phenylimidazo[1,2-*a*]pyridine **5** from the reaction of 2-aminopyridine **2a** and 2-bromoacetophenone and recorded the UV and fluorescence spectra in DMSO by considering quinine sulfate dihydrate as the fluorescence standard. Interestingly, we have observed 0.48 as the quantum yield of **5**, while the quantum yield (Φ) of **4a**, initially recorded in DMSO, was Φ = 0.61 (Figure 4). The Stokes shift of **5** is 62 nm, while it is 111 nm for compound **4a** that contains the 1, 3-dimethylbarbituric acid moiety (the UV and fluorescence spectra of **5** are available in the Supporting Information). From this study, we confirmed that the incorporation of the barbituric acid moiety increases the fluorescence property of imidazopyridine.

Finally, based on our research findings and literature reports, we have proposed a plausible reaction pathway for the iodine-catalyzed three-component synthesis of **4** in Scheme 2. It is believed that initially, acetophenone derivative **1** reacts with iodine to produce intermediate [**A**] and byproduct HI. This HI in the presence of DMSO regenerates I_2 for the next cycle. After this, in the presence of DMSO, **A** transforms into the corresponding phenylglyoxal **B**, which upon reaction with **2**by Knoevenagel condensation provides **C**. The aza-Michael attack of **3** on **C** provides intermediate **D**, which upon cyclization provides **E**, which after loss of H_2O gives desired product **4**.

CONCLUSIONS

In summary, we have developed a metal-free one-pot methodology for the synthesis of pyrimidine-linked imidazopyridines using iodine catalysis in DMSO medium. This reaction involves a one-pot C−H oxidation, followed by the formation of three new bonds (one C−C and two C−N). The salient features of this methodology are a wide substrate scope, good to very good yields, no need of column chromatographic purification, and the presence of more than one bioactive moieties in the products. In addition to these, we have found

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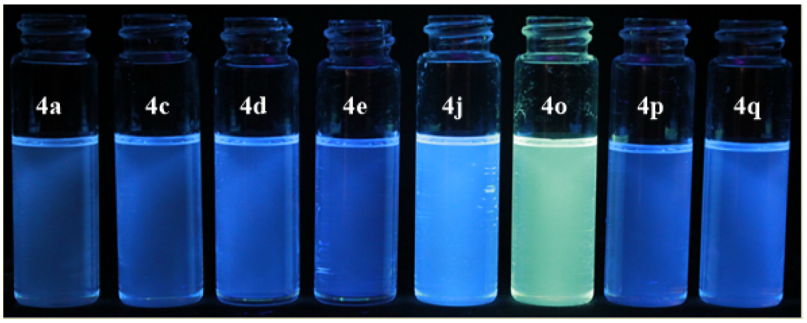


Figure 3. Photograph of some of the highly fluorescent compounds in DMSO medium under UV light.

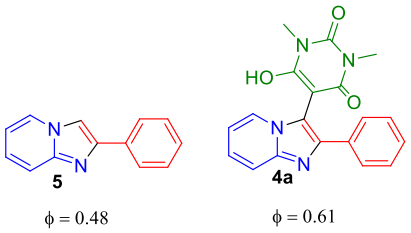


Figure 4. Comparison of quantum yields of **5** and **4a**.

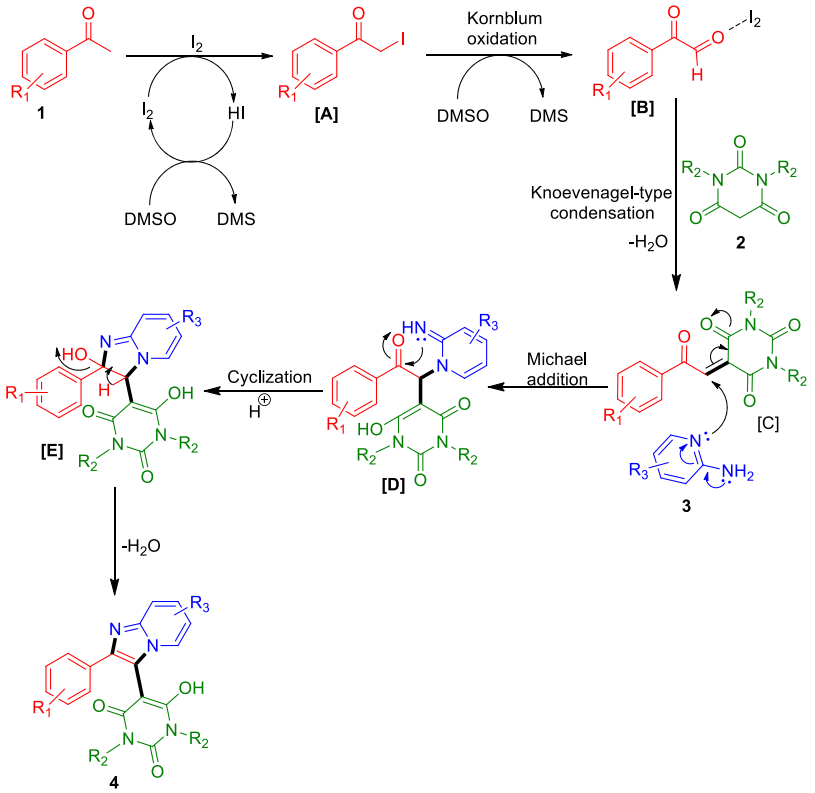
that most of the synthesized products exhibit very good to excellent fluorescence quantum yields. We have carried out the photophysical studies of all the products in aqueous medium under basic conditions as well as in DMSO medium.

EXPERIMENTAL SECTION

General Information. All the starting materials were purchased from commercial sources (Sigma-Aldrich, Merck, and Alfa-Aesar) and used as such without further purification. Reactions were monitored by TLC. Melting points were determined using an SRS EZ-Melt automated melting point apparatus by capillary methods and uncorrected. The NMR spectra were recorded using Bruker 400 MHz and JEOL 500 MHz spectrometers in DMSO-d_6 with tetramethyl silane as the internal standard or adding NaOH in D_2O. Chemical shift values are reported in δ values (ppm) downfield from tetramethyl silane. HRMS analysis was carried out using a Bruker Impact HD mass spectrometer (Impact HD UHRTOF, ESI with the positive mode) mass spectrometer.

Experimental Procedure. In a 10.0 mL round-bottom flask fitted with a reflux condenser, 0.5 mmol of acetophenone derivative (**1**), 10 mol % of I_2 (12.69 mg), and 2.0 mL of DMSO were added, and the solution was kept under heating at 110 °C with constant stirring until the reactant **1** was totally consumed (monitored by TLC). Then, barbituric acid derivative (**2**) (0.5 mmol) was added to the mixture and stirred for 5 min. Subsequently, 2-aminopyridine (**3**) (0.5 mmol) was added to the flask, and the mixture was kept at the same temperature with constant stirring. After the completion of the reaction, the reaction mixture was cooled to room temperature, 10 mol % sodium thiosulfate solution (10.0 mL) was added, the solid

Scheme 2. Proposed Reaction Pathway for the Formation of Iodine-Catalyzed Pyrimidine-Linked Imidazopyridines



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mass was filtered off, and it was washed with hot ethyl acetate to get the pure three-component product **4**.

6-Hydroxy-1,3-dimethyl-5-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4a).[9b,d] White solid; 136 mg (78%); mp above 400 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, J = 4.0 Hz, 1H), 7.92 (t, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.44−7.39 (m, 2H), 3.14 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.9, 153.1, 144.3, 138.4, 132.8, 131.8, 129.3, 128.9, 128.3, 127.8, 127.3, 121.8, 116.2, 111.5, 72.5, 27.2 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{17}N_4O_3$ [M + H]$^+$, 349.1296; found, 349.1314.

6-Hydroxy-1,3-dimethyl-5-(2-(*p*-tolyl)imidazo[1,2-*a*]-pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4b).[9b] Light yellow solid; 147 mg (80%); charred at 375 °C. ^{1}H NMR (400 MHz, saturated solution of NaOH in D_2O): δ 7.88 (d, J = 4.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 8.0 Hz, 1H), 3.26 (s, 6H), 2.32 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, saturated solution of NaOH in D_2O): δ 168.4, 164.8, 154.6, 145.2, 142.2, 138.2, 131.2, 129.3, 126.8, 126.5, 124.6, 115.4, 112.7, 80.1, 27.9, 20.2 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{19}N_4O_3$ [M + H]$^+$, 363.1452; found, 363.1454.

5-(2-(4-Ethylphenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4 (1*H*,3*H*)-dione (4c). Light orange solid; 152 mg (81%); charred at 293−295 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.71 (d, J = 4.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.78 (t, J = 8.0 Hz, 1H), 3.11 (s, 6H), 2.54−2.52 (m, 2H), 1.09 (t, J = 8.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 164.5, 161.6, 155.2, 145.2, 144.5, 142.9, 133.4, 129.1, 128.3, 126.6, 126.0, 118.4, 116.8, 114.8, 113.2, 79.2, 29.2, 29.0, 16.6 ppm. HRMS (ESI-TOF): m/z: [M + H]$^+$ calcd for $C_{21}H_{21}N_4O_3$, 377.1608; found, 377.1634.

6-Hydroxy-5-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4d). White solid; 161 mg (85%); charred at 384 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.74 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 4.0 Hz, 1H) 7.49 (d, J = 12.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 6.79−6.76 (m, 1H), 3.70 (s, 3H), 3.13 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.7, 159.2, 154.7, 144.6, 142.3, 129.3, 128.9, 125.8, 125.6, 118.3, 116.5, 114.6, 112.4, 78.1, 56.1, 28.6 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{19}N_4O_4$ [M + H]$^+$, 379.1401; found, 379.1402.

6-Hydroxy-1,3-dimethyl-5-(2-(3,4,5-trimethoxyphenyl)-imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4e). Greenish white solid; 186 mg (85%); charred at 354 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.75 (d, J = 4.0 Hz, 1H), 7.50 (d, J = 12.0 Hz, 1H), 7.24−7.20 (m, 1H), 7.17 (s, 2H), 6.80 (t, J = 8.0 Hz, 1H), 3.68 (s, 6H), 3.62 (s, 3H), 3.11 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O) 163.9, 154.7, 153.4, 144.7, 142.2, 137.1, 131.8, 126.1, 119.2, 116.7, 112.8, 105.4, 78.2, 61.4, 56.5, 28.6 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{23}N_4O_6$, 439.1612; found, 439.1605.

6-Hydroxy-1,3-dimethyl-5-(2-(3,4,5-trimethoxyphenyl)-imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4f). Light brown solid; 165 mg (84%); charred at 350 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.69 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.34 (dd, J = 8 Hz, 2 Hz, 1H), 7.28 (d, J = 4.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H) 6.84 (d, J = 8.0 Hz, 1H), 6.78 (t, J = 8.0 Hz, 1H), 5.90 (s, 2H), 3.11 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.7, 154.7, 147.9, 147.1, 144.6, 142.1, 130.4, 125.9, 121.9, 118.5, 116.6, 112.6, 109.3, 108.3, 101.8, 78.0, 28.6 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{17}N_4O_5$, 393.1193; found, 393.1189.

5-(2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4g). Light yellow solid; 141 mg (74%); charred at 390−393 °C. ^{1}H NMR (400 MHz, saturated solution of NaOH in D_2O): δ 7.92−7.89 (m, 1H), 7.80−7.79 (m, 1H), 7.78−7.77 (m, 1H), 7.62−7.59 (m, 1H), 7.44−7.39 (m, 3H), 6.97−6.94 (m, 1H), 3.29 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, saturated solution of NaOH in D_2O): δ 164.7, 154.6, 145.3, 141.2, 132.9, 132.7, 128.7, 128.2, 126.7, 124.8, 116.3, 115.5, 112.8, 79.9, 27.9 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{16}ClN_4O_3$ [M + H]$^+$, 383.0905; found, 383.0890.

5-(2-(3,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4h). White solid; 150 mg (72%); mp above 400 °C. ^{1}H NMR (400 MHz, saturated solution of NaOH in D_2O): δ 7.89 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.0, 4.0 Hz, 1H), 7.57 (d, J = 12.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 6.93−6.90 (m, 1H), 3.25 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 162.3, 153.8, 143.9, 138.9, 136.9, 131.1, 130.7, 129.2, 128.8, 127.3, 126.0, 125.1, 120.5, 116.5, 111.7, 76.3, 27.8 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{15}Cl_2N_4O_3$ [M + H]$^+$, 417.0516; found, 417.0499.

5-(2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4i). Off-white solid; 149 mg (70%); mp above 400 °C. ^{1}H NMR (400 MHz, saturated solution of NaOH in D_2O): δ 7.91 (d, J = 4.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.62−7.56 (m, 3H), 7.41 (t, J = 8.0 Hz, 1H), 6.97−6.94 (m, 1H), 3.29 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 162.3, 153.8, 143.9, 140.5, 135.6, 131.3, 129.4, 125.8, 124.6, 120.1, 119.9, 116.4, 111.4, 76.4, 27.7. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{16}BrN_4O_3$ [M + H]$^+$, 427.0400; found, 427.0407.

6-Hydroxy-1,3-dimethyl-5-(2-(3-(trifluoromethyl)phenyl)-imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4j). Light yellow solid; 141 mg (68%); charred at 368 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 8.05 (s, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.53−7.50 (m, 3H), 7.26 (t, J = 8.0 Hz, 1H), 6.84−6.81 (m, 1H), 3.11 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 164.1, 154.9, 145.3, 140.9, 136.9, 131.7, 130.6, 130.3, 126.9, 126.9, 126.4, 124.68−124.60 (m), 124.17, 120.00, 117.09, 113.31, 78.51, 40.18, 39.96, 39.75, 39.52, 39.31, 39.09, 38.88, 28.82 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}F_3N_4O_6$, 417.1169; found, 417.1173.

6-Hydroxy-1,3-dimethyl-5-(2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4k). Yellow solid; 132 mg (67%); mp above 400 °C. ^{1}H NMR (400 MHz, saturated solution of NaOH in D_2O): δ 8.19 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 12.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.96−6.93 (m, 1H), 3.29 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ 164.5, 154.5, 146.4, 145.5, 141.2, 139.9, 127.3, 127.2, 125.0, 123.9, 118.3, 115.8, 113.1, 79.7, 27.9 ppm. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{16}N_5O_5$ [M + H]$^+$, 394.1146; found, 394.1136.

6-Hydroxy-5-(2-(4-methoxy-3-nitrophenyl)imidazo[1,2-*a*]-pyridin-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4l). Yellow solid; 151 mg (71%); charred at 320 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 8.24 (d, J = 2.4 Hz, 1H), 8.07 (dd, J = 8.8, 2.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.29−7.22 (m, 2H), 6.81 (t, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.12 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.9, 154.7, 152.5, 145.0, 139.9, 139.6, 134.4, 128.8, 126.5, 126.3, 124.7, 119.4, 116.8, 115.3, 113.0, 78.2, 57.7, 28.7 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}N_5O_6$, 424.1252; found, 424.1262.

6-Hydroxy-1,3-dimethyl-5-(2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4m). White solid; 149 mg (75%); mp above 400 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 8.02 (s, 1H), 7.82−7.73 (m, 4H), 7.52 (t, J = 4.0 Hz, 2H) 7.34−7.31 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H) 6.82−6.79 (m, 1H), 3.13 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 164.0, 154.9, 145.1, 142.4, 134.1, 133.8, 133.2, 129.2,

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128.64, 128.58, 127.4, 127.1, 126.7, 126.6, 126.3, 126.1, 119.7, 116.9, 112.9, 78.5, 28.8 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}N_4O_3$, 399.1452; found, 399.1441.

5-(2-(9*H*-Fluoren-3-yl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4n). Off-white solid; 155 mg (71%); charred at 379 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 8.26 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.81−7.75 (m, 4H), 7.54 (d, J = 8.0 Hz, 1H), 7.46−7.40 (m, 2H), 7.25 (t, J = 8.0 Hz, 1H), 6.83−6.80 (m, 1H), 4.99 (s, 2H) 3.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.6, 154.6, 144.7, 144.1, 143.9, 142.6, 141.9, 140.8, 134.9, 127.9, 127.8, 126.9, 126.2, 125.9, 125.7, 124.8, 120.8, 120.5, 119.3, 116.6, 112.5, 78.1, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{21}N_4O_3$, 437.1608; found, 437.1637.

5-(2-([1,1′-Biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4o). Pale yellow solid; 165 mg (78%); charred at 396 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.90 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 4.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H) 6.82−6.79 (m, 1H), 3.13 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.7, 154.7, 144.8, 141.9, 140.7, 139.4, 135.4, 130.1, 128.55, 128.47, 127.3, 125.9, 119.4, 116.7, 112.6, 78.1, 28.6 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}N_4O_3$, 425.1608; found, 425.1602.

6-Hydroxy-1,3-dimethyl-5-(6-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4p).[9b] Light brown solid; 143 mg (79%); charred at 398 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.86 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.42 (d, J = 12.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 3.12 (s, 6H), 2.23 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 162.7, 154.0, 143.0, 141.7, 136.4, 128.5, 127.5, 127.4, 126.9, 123.0, 120.6, 119.2, 115.9, 76.8, 27.9, 18.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_3$, 363.1452; found, 363.1448.

6-Hydroxy-5-(2-(4-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4q). Light pink solid; 165 mg (84%); charred at 375 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.76 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 12.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 3.72 (s, 3H), 3.11 (s, 6H), 2.21 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.3, 158.9, 154.4, 143.4, 142.0, 129.0, 128.9, 127.9, 123.1, 121.2, 118.1, 115.9, 114.3, 77.7, 55.8, 28.3, 18.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{21}N_4O_4$, 393.1557; found, 393.1585.

5-(7-Chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4r). White solid; 167 mg (81%); mp above 400 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.77 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 4.0 Hz, 1H), 7.58 (s, 1H), 6.88 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 4.0 Hz, 1H), 3.72 (s, 3H), 3.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.1, 159.2, 154.3, 143.8, 142.9, 130.0, 129.1, 128.3, 126.8, 118.9, 114.9, 114.4, 112.9, 77.1, 55.8, 28.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}ClN_4O_4$, 413.1011; found, 413.1009.

5-(6-Bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4s). Brown solid; 183 mg (80%); charred at 392−394 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.84 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 3.72 (s, 3H), 3.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 163.6, 159.4, 154.6, 143.3, 143.0, 129.4, 128.3, 128.1, 119.0, 118.9, 117.7, 114.7, 106.3, 77.6, 56.0, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}BrN_4O_4$, 457.0506; found, 457.0515.

5-(8-Chloro-2-phenyl-6-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4t). Light green solid; 160 mg (71%); charred at 365 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 8.09 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.31−7.28 (m, 2H), 7.25−7.22 (m, 1H), 3.08 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 164.9, 155.4, 146.1, 142.7, 134.9, 129.9, 129.6, 128.8, 125.9, 123.5, 123.2, 122.44−122.36 (m), 121.1, 116.3, 79.0, 29.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{15}ClF_3N_4O_3$, 451.0779; found, 451.0784.

6-Hydroxy-5-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4u).[9d] Light yellow solid; 121 mg (69%); charred at 366 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 7.79 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 6.76−6.73 (m, 1H), 4.98 (s, 2H), 3.70 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 + saturated solution of NaOH in D_2O): δ 172.3, 162.0, 159.1, 144.7, 141.7, 129.6, 129.3, 126.1, 125.4, 120.1, 116.4, 114.6, 112.2, 79.9, 56.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_4O_4$, 351.1088; found, 351.1100.

5-(2-(2-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4v). White solid; 139 mg (57%); charred at 364−366 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.51 (s, 1H), 8.30 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.52−7.49 (m, 1H), 7.44 (t, J = 8.0 Hz, 2H), 3.06 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 161.7, 153.0, 138.1, 132.8, 132.6, 132.3, 131.4, 129.9, 129.9, 128.2, 127.7, 127.4, 123.9, 116.1, 111.6, 72.0, 27.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}ClN_4O_3$, 383.0905; found, 383.0904.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01332.

NMR spectra of all products and UV and fluorescence spectra of all compounds in aqueous and DMSO media (PDF)

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Notes

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