JOC The Journal of Organic Chemistry

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$FeCl_3$-Catalyzed Cross-Dehydrogenative Coupling between Imidazoheterocycles and Oxoaldehydes

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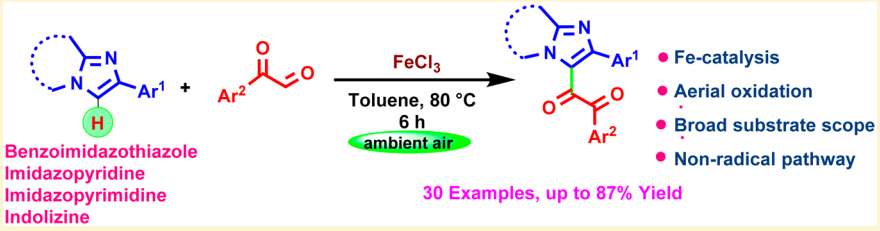
Supporting Information

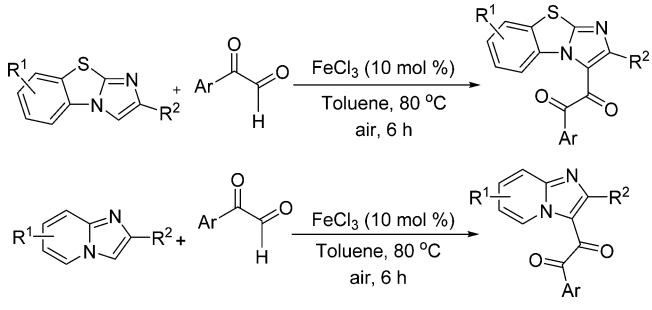


ABSTRACT: An Fe(III)-catalyzed efficient dicarbonylation of imidazoheterocycles has been developed through cross-dehydrogenative coupling between imidazoheterocycles and oxoaldehydes under ambient air in high yields. The present protocol is also applicable to indolizines. Imidazopyridine produced bisimidazopyridine with arylaldehyde. Experimental results suggest that the reactions proceed through the nonradical pathway.

Transition-metal-catalyzed C−H functionalization has become one of the fundamental methods in organic synthesis and gained a huge impact on medicinal chemistry, synthetic organic chemistry, and material science.[1] As such, advances that achieve the selective C−H bond activation for new C−C bond formation based on recently developed cross-dehydrogenative coupling (CDC) reaction have received special attention.[2] These methods avoid the prefunctionalization of starting materials which make the synthetic routes straightforward and more efficient. Transition metals such as Pd, Cu, Ag, Rh, and Ru have been extensively studied for CDC due to their high efficiency. However, the exploration of iron catalysis in CDC reactions is in high demand due to its low price, ready availability, sustainability, nontoxicity, and environmentally friendly properties.[3]

Benzo[*d*]imidazo[2,1-*b*]thiazole and imidazo[1,2-*a*]pyridines are important fused bicyclic nitrogen-containing heterocycles and have gained much attention of the synthetic organic chemists due to their wide applications in the field of organic and biological chemistry.[4] These scaffolds have been used as antitumor agents, antimicrobial agents, antibacterial agents, and antiallergic agents.[5] 1,2-Dicarbonyl derivatives are important building blocks for the construction of biologically active compounds, and generally, these are prepared from 1,2-diols, alkyne, and alkene by oxidation.[6] There are few efficient methods for 1,2-dicarbonylation of phenols, indoles, imidazopyridines, etc.[7] Recently, Cao et al. developed a copper-catalyzed regioselective double carbonylation of imidazo[1,2-*a*]pyridines with *N*,*N*-disubstituted acetamide or acetone using molecular oxygen.[7b,f] The Atmakur group described the same transformation by using molecular iodine in DMSO in the presence of a catalytic amount of PTSA.[7c] In addition, direct aerobic oxidative cross-dehydrogenative coupling of aryl acetaldehydes and imidazoheterocycles was developed by Sakhuja et al.[7d] Installation of a 1,2-dicarbonyl functionality in the benzo[*d*]imidazo[2,1-*b*]thiazoles as well as other imidazoheterocycles might render these compounds more valuable in the subject of drug discovery and material based applications. However, to the best of our knowledge, there is no such method for the direct 1,2-dicarbonylation of imidazoheterocycles by using an iron catalyst. In continuation of our research on imidazoheterocycles,[8] herein we report a direct method for 1,2-dicarbonylation of imidazoheterocycles using oxoaldehydes through cross-dehydrogenative coupling reaction by iron catalysis (Scheme 1).

Scheme 1. 1,2-Dicarbonylation of Imidazoheterocycles

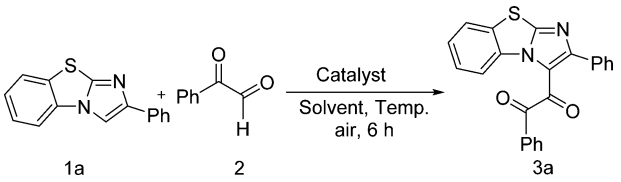


Received: August 25, 2016
Published: October 4, 2016

DOI: 10.1021/acs.joc.6b02091
J. Org. Chem. 2016, 81, 10088−10093

The study was initiated by investigating the reaction of 2-phenyl-benzo[*d*]imidazo[2,1-*b*]thiazole **1a** and phenylglyoxal **2** employing 10 mol % of $FeCl_3$ in 1,4-dioxane at 80 °C under ambient air. Gratifyingly, the coupling product, 1-phenyl-2-(2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)ethane-1,2-dione (**3a**), was obtained in 75% yield after 6 h (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

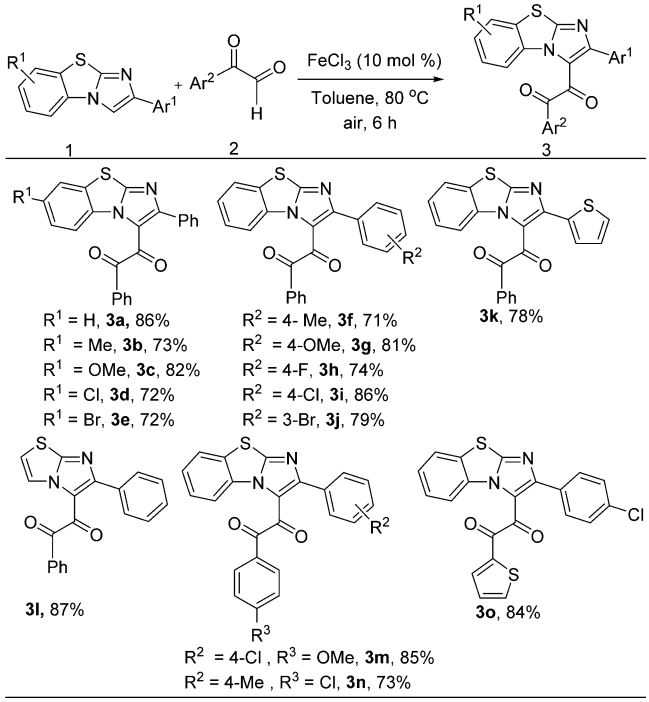
entry	catalyst (mol %)	solvent	temp (°C)	yields (%)
1	$FeCl_3$ (10 mol %)	1,4-dioxane	80	75
2	$FeCl_3$ (10 mol %)	toluene	80	86 (trace)[b]
3	$FeCl_3$ (10 mol %)	CH_3CN	80	55
4	$FeCl_3$ (10 mol %)	1,2-DCB	80	64
5	$FeCl_3$ (10 mol %)	chlorobenzene	80	69
6	$FeCl_3$ (10 mol %)	DMSO	80	58
7	$FeCl_3$ (10 mol %)	DMF	80	22
8	$FeCl_3$ (10 mol %)	NMP	80	17
9	$FeBr_3$ (10 mol %)	toluene	80	48
10	$FeBr_2$ (10 mol %)	toluene	80	trace
11	$FeSO_4$ (10 mol %)	toluene	80	NR
12	$Fe(NO_3)_3{\cdot}9H_2O$ (10 mol %)	toluene	80	trace
13	$Cu(OAc)_2{\cdot}H_2O$ (10 mol %)	toluene	80	42
14	$FeCl_3$ (20 mol %)	toluene	80	87
15	$FeCl_3$ (5 mol %)	toluene	80	45[c]
16	$FeCl_3$ (10 mol %)	toluene	100	81
17	$FeCl_3$ (10 mol %)	toluene	110	78
18	$FeCl_3$ (10 mol %)	toluene	70	72
19		toluene	80	NR

[a]Reaction conditions: Carried out with 0.2 mmol of **1a** and 0.2 mmol of **2** in the presence of catalyst in 2 mL of solvent. [b]Under an argon atmosphere. [c]Reaction time 12 h.

Encouraged by this result, we carried out the reaction in different conditions to optimize the reaction, and the results are summarized in Table 1. To interpret the solvent effects, the reaction was examined in various solvents (Table 1, entries 2–8). To our delight, the desired product was obtained in high yield (86%) in toluene. Only a trace amount of product was formed under an argon atmosphere (Table 1, entry 2). Other common solvents such as acetonitrile, 1,2-DCB, chlorobenzene, DMSO, DMF, and NMP were not so effective. Various iron salts such as $FeBr_3$, $FeBr_2$, $FeSO_4$, and $Fe(NO_3)_3{\cdot}9H_2O$ were also investigated. These were found to be less effective for this transformation (Table 1, entries 9–12). $Cu(OAc)_2{\cdot}H_2O$ is not also effective for this transformation (Table 1, entry 13). A higher amount of catalyst loading (20 mol %) did not improve the yield further (Table 1, entry 14), but on decreasing the amount of catalyst (5 mol %), the yield was decreased significantly (Table 1, entry 15). The yield of the reaction was decreased on increasing as well as decreasing the temperature (Table 1, entries 16–18). The reaction did not proceed at all in the absence of any catalyst (Table 1, entry 19). Finally, the optimized reaction conditions was achieved using 10 mol % of $FeCl_3$ in toluene at 80 °C for 6 h under ambient air (Table 1, entry 2).

After optimizing the reaction conditions, we turned our attention toward the substrate scope. As shown in Scheme 2, a series of C-3 dicarbonylated benzo[*d*]imidazo[2,1-*b*]thiazoles were obtained under the present reaction conditions in good to excellent yields (**3a**–**3k**). Benzo[*d*]imidazo[2,1-*b*]thiazoles with electron-donating −Me and −OMe substituents on the benzene ring afforded the corresponding C-3 dicarbonylated benzo[*d*]imidazo[2,1-*b*]thiazoles in excellent yields (**3b** and **3c**). The chloro- and bromo-substituted benzo[*d*]imidazo[2,1-*b*]thiazoles proceeded well without dehalogenation (**3d** and **3e**). Furthermore, the effect of a C-2 substituent on the phenyl ring was examined. Electron-donating substituents like −Me and −OMe as well as electron-withdrawing substituents like −F, −Cl, and −Br on the phenyl ring at the 2-position of the benzo[*d*]imidazo[2,1-*b*]thiazole moiety efficiently reacted with phenylglyoxal to produce the respective C-3 dicarbonylated benzo[*d*]imidazo[2,1-*b*]thiazoles derivatives (**3f**–**3j**). Benzo-[*d*]imidazo[2,1-*b*]thiazoles with a heteroaryl moiety like thiophene at the C-2 position also afforded the desired product in good yield (**3k**). Imidazo[2,1-*b*]thiazole was also tested under the optimized reaction conditions. To our delight, the corresponding product was obtained in excellent yield (**3l**). Methoxy- and chloro-substituted phenylglyoxals also reacted well (**3m** and **3n**). Moreover, heteroaryl oxoaldehyde also afforded the desired product in good yield (**3o**).

Scheme 2. Substrate Scope of the Present Method[a]

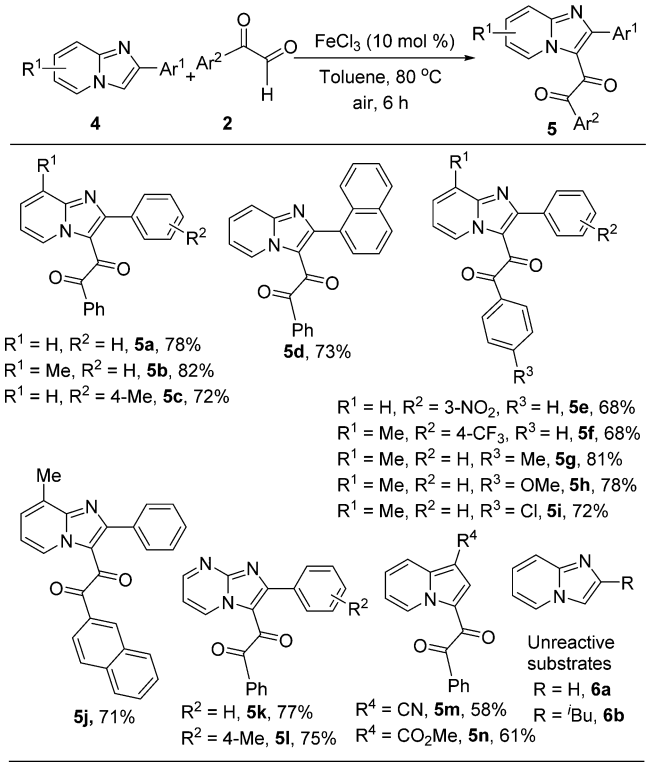


[a]Reaction conditions: 0.2 mmol of **1** and 0.2 mmol of **2** in the presence of 10 mol % $FeCl_3$ in 2 mL of toluene at 80 °C for 6 h.

To extend the scope of the present methodology, we explored on imidazo[1,2-*a*]pyridine to synthesize C-3 dicarbonylated imidazo[1,2-*a*]pyridine derivatives (Scheme 3). To our delight, the desired products (**5**) were obtained in good to excellent yields. Imidazo[1,2-*a*]pyridine bearing a −Me substituent on the pyridine ring efficiently reacted with

DOI: 10.1021/acs.joc.6b02091
J. Org. Chem. 2016, 81, 10088–10093

Scheme 3. Substrate Scope[a]

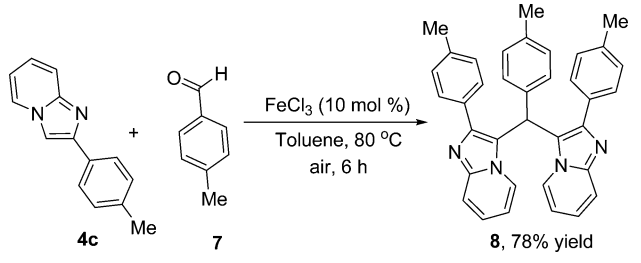


[a]Reaction conditions: 0.2 mmol of **4** and 0.2 mmol of **2** in the presence of 10 mol % $FeCl_3$ in 2 mL of toluene at 80 °C for 6 h.

phenylglyoxal to afford the product with high yield (**5b**). The imidazo[1,2-*a*]pyridine bearing a naphthyl substituent at the C-2 position produced the desired product with good yield (**5d**). Strong electron-withdrawing groups like $-NO_2$ and $-CF_3$ in the phenyl ring also successfully gave the desired products without any difficulties (**5e** and **5f**). The single crystal X-ray analysis of **5e** was performed to confirm the structure.[9] Other oxoglyoxals also reacted well under the present reaction conditions (**5g**, **5h**, **5i**, and **5j**). Imidazo[1,2-*a*]pyrimidines reacted smoothly to afford the desired products (**5k** and **5l**). It is noteworthy to mention that indolizines were also reacted well under the present reaction conditions (**5m** and **5n**). However, simple imidazo[1,2-*a*]pyridine (**6a**) and aliphatic-substituted imidazo[1,2-*a*]pyridine (**6b**) did not react under the present reaction conditions.

To check the feasibility of simple aldehyde, benzaldehyde (**7**) was examined (Scheme 4). However, CDC reaction did not occur at all. Bisimidazopyridine (**8**) was obtained under the present reaction conditions.

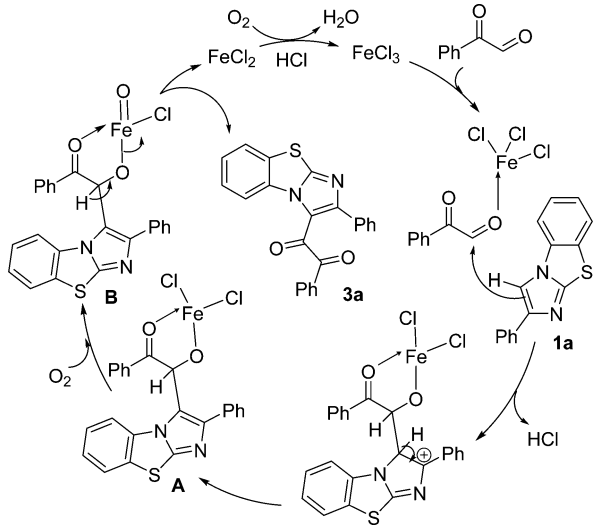
Scheme 4. Formation of Bisimidazopyridine



A few control experiments were carried out to get a better understanding on the mechanistic pathway of the reaction (see the Supporting Information). The reaction proceeded in equal ease in the presence of radical scavengers like TEMPO, BHT, and BQ, which signifies that the reaction probably proceeds through a nonradical pathway. When the reaction was carried out using phenylglyoxalic acid instead of phenylglyoxal, no formation of the desired product was observed, which indicates that the reaction does not proceed through the formation of phenylglyoxalic acid through oxidation of aldehyde.

On the basis of the above experimental results and our previous experiences in iron catalysis,[8b,d,e] a nonradical pathway is proposed (Scheme 5). Initially, $FeCl_3$-catalyzed addition of

Scheme 5. Probable Mechanistic Pathway



phenylglyoxal to benzo[*d*]imidazo[2,1-*b*]thiazole occurs at the C-3 postion to produce the Fe(III)-chelated benzo[*d*]imidazo-[2,1-*b*]thiazole intermediate **A**. Probably at this stage, Fe(III) is converted to Fe(IV) oxo complex **B** via aerial oxidation.[10] Finally, **3a** is obtained via reductive elimination and Fe(II) is oxidized to Fe(III) in the presence of oxygen to complete the catalytic cycle.

In conclusion, we have demonstrated that $FeCl_3$ is a highly effective catalyst for the synthesis of 1,2-dicarbonylated benzo[*d*]imidazo[2,1-*b*]thiazoles through the cross-dehydrogenative coupling of benzo[*d*]imidazo[2,1-*b*]thiazoles and oxoaldehydes under ambient air. An array of C-3 dicarbonylated derivatives with broad functionalities have been synthesized in high yields. The present methodology is also useful for the synthesis of C-3 dicarbonylated imidazo[1,2-*a*]pyridine and indolizine derivatives. Experimental results suggest that the reaction proceeds through a nonradical pathway. Benzaldehyde afforded bisimidazoheterocycle under the present reaction conditions. To the best of our knowledge, this is the first report of an iron catalyst for the direct dicarbonylation of imidazoheterocycles through CDC reaction. We believe that the present methodology opens a new door to synthesize important building blocks of C-3 dicarbonylated imidazoheterocycles.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification. ^1H NMR

DOI: 10.1021/acs.joc.6b02091
J. Org. Chem. 2016, 81, 10088−10093

spectra were determined on a 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ), and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), and coupling constants (J) were given in Hz. $^{13}C\{^1H\}$ NMR spectra were recorded at 100 MHz in $CDCl_3$ solution. Chemical shifts as internal standard are referenced to $CDCl_3$ (δ = 7.26 for ^1H and δ = 77.16 for $^{13}C\{^1H\}$ NMR) as internal standard. TLC was done on silica gel coated glass slides. All solvents were dried and distilled before use. Commercially available solvents were freshly distilled before the reaction. All reactions involving moisture-sensitive reactants were executed using oven-dried glassware. X-ray single crystal data were collected using Mo Kα (λ = 0.71073 Å) radiation with a CCD area detector. All the imidazoheterocycles were prepared by our reported methods.[8c,e]

Typical Experimental Procedure for the Synthesis of 3a. A mixture of 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (**1a**, 41 mg, 0.20 mmol), phenylglyoxal (**2**, 30.4 mg, 0.20 mmol), and $FeCl_3$ (3.3 mg, 10 mol %) in toluene (2 mL) was stirred at 80 °C under air for 6 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and extracted with ethyl acetate/water. The organic phase was dried over anhydrous Na_2SO_4. The crude residue was obtained after evaporation of the solvent in vacuum and purified by column chromatography on silica gel (60−120 mesh) using *n*-hexane/EtOAc (9:1) as the eluent to afford pure **3a** as a light yellow solid (66 mg, 86% yield).

*1-Phenyl-2-(2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)ethane-1,2-dione (**3a**).*[7d] Light yellow solid (86%, 66 mg); m.p.: 179−180 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.21−9.19 (m, 1H), 7.78−7.76 (m, 1H), 7.72−7.70 (m, 2H), 7.58−7.54 (m, 2H), 7.48−7.44 (m, 1H), 7.39−7.35 (m, 2H), 7.29−7.20 (m, 3H), 7.07−7.03 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.5, 183.5, 160.6, 155.4, 134.2, 134.1, 133.4, 132.8, 130.3, 130.1, 129.67, 129.64, 128.6, 128.5, 128.0, 126.9, 126.1, 123.8, 118.9. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{23}H_{14}N_2O_2S$: 383.0854; found: 383.0846.

*1-(7-Methyl-2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3b**).* Light yellow solid (73%, 58 mg); m.p.: 123−124 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, J = 8.8 Hz, 1H), 7.71−7.69 (m, 2H), 7.55 (t, J = 8.4 Hz, 2H), 7.39−7.33 (m, 3H), 7.27 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 8.0 Hz, 2H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.5, 183.4, 160.3, 155.2, 136.3, 134.2, 133.4, 132.9, 132.1, 130.3, 130.1, 129.6, 129.5, 128.6, 128.0, 128.0, 125.2, 123.7, 118.5, 21.4; Anal. Calcd for $C_{24}H_{16}N_2O_2S$: C, 72.71; H, 4.07; N, 7.07%; Found: C, 72.92; H, 4.12; N, 6.91%.

*1-(7-Methoxy-2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3c**).* Light yellow solid (82%, 67 mg); m.p.: 119−120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, J = 9.2 Hz, 1H), 7.71−7.69 (m, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 8.4 Hz, 2H), 7.27−7.19 (m, 4H), 7.10−7.02 (m, 3H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.5, 183.4, 159.9, 157.9, 154.6, 134.1, 133.4, 132.9, 131.5, 130.3, 129.6, 129.5, 128.6, 128.3, 127.9, 125.1, 119.7, 114.1, 107.7, 56.0; Anal. Calcd for $C_{24}H_{16}N_2O_3S$: C, 69.89; H, 3.91; N, 6.79%; Found: C, 70.01; H, 4.10; N, 6.62%.

*1-(7-Chloro-2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3d**).* Light yellow solid (72%, 60 mg); m.p.: 144−145 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.71−7.69 (m, 2H), 7.59−7.54 (m, 1H), 7.52−7.50 (m, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.28−7.20 (m, 3H), 7.07−7.03 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.2, 183.6, 160.5, 155.0, 134.3, 133.2, 132.7, 132.6, 131.8, 131.5, 130.3, 129.7, 129.6, 128.6, 128.0, 127.3, 125.3, 123.4, 119.8; Anal. Calcd for $C_{23}H_{13}ClN_2O_2S$: C, 66.27; H, 3.14; N, 6.72%; Found: C, 66.18; H, 3.21; N, 6.51%.

*1-(7-Bromo-2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3e**).* Light yellow solid (72%, 66 mg); m.p.: 166−167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.72−7.65 (m, 3H), 7.57 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.28−7.21 (m, 3H), 7.06 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.2, 183.6, 160.6, 155.0, 134.3, 133.2, 133.1, 132.6, 131.8, 130.3, 130.1, 129.7, 129.6, 128.6, 128.0, 126.3, 125.4, 120.1, 119.2; Anal. Calcd for $C_{23}H_{13}BrN_2O_2S$: C, 59.88; H, 2.84; N, 6.07%; Found: C, 59.72; H, 2.91; N, 6.19%.

*1-Phenyl-2-(2-(p-tolyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-ethane-1,2-dione (**3f**).* Light yellow solid (71%, 56 mg); m.p.: 95−96 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (d, J = 8.4 Hz, 1H), 7.78−7.75 (m, 1H), 7.71−7.69 (m, 2H), 7.58−7.53 (m, 2H), 7.45 (t, J = 8.0 Hz, 4H), 7.37 (t, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 7.6 Hz, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.4, 183.3, 160.6, 155.2, 139.5, 134.0, 133.2, 130.1, 130.0, 129.8, 129.7, 129.4, 128.5, 128.3, 126.7, 125.8, 125.1, 123.6, 118.7, 21.2; Anal. Calcd for $C_{24}H_{16}N_2O_2S$: C, 72.71; H, 4.07; N, 7.07%; Found: C, 72.88; H, 4.21; N, 6.91%.

*1-(2-(4-Methoxyphenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3g**).* Light yellow solid (81%, 67 mg); m.p.: 96−97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, J = 8.4 Hz, 1H), 7.76−7.71 (m, 3H), 7.56−7.52 (m, 2H), 7.46−7.42 (m, 1H), 7.39−7.35 (m, 2H), 7.20−7.18 (m, 2H), 6.56 (dd, J = 6.8 Hz, 2.0 Hz, 2H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.6, 183.5, 160.8, 160.6, 155.4, 134.2, 134.1, 133.4, 131.8, 130.1, 129.9, 129.5, 128.5, 126.8, 125.9, 125.2, 123.7, 118.8, 113.5, 55.3; Anal. Calcd for $C_{24}H_{16}N_2O_3S$: C, 69.89; H, 3.91; N, 6.79%; Found: C, 70.05; H, 4.11; N, 6.57%.

*1-(2-(4-Fluorophenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3h**).* Light yellow solid (74%, 59 mg); m.p.: 139−140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.71−7.69 (m, 2H), 7.59−7.53 (m, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.25−7.21 (m, 2H), 6.74 (t, J = 8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.6, 183.3, 163.5 ($J_{C\text{-}F}$ = 249 Hz), 159.3, 155.4, 134.4, 134.0, 133.1, 132.3 ($J_{C\text{-}F}$ = 8 Hz), 130.0, 129.5, 128.8 ($J_{C\text{-}F}$ = 3 Hz), 128.7, 126.9, 126.1, 125.3, 123.8, 118.8, 115.0 ($J_{C\text{-}F}$ = 21 Hz); Anal. Calcd for $C_{23}H_{13}FN_2O_2S$: C, 68.99; H, 3.27; N, 7.00%; Found: C, 68.91; H, 3.14; N, 6.81%.

*1-(2-(4-Chlorophenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3i**).* Light yellow solid (86%, 72 mg); m.p.: 166−168 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.17 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.71−7.67 (m, 2H), 7.60−7.53 (m, 2H), 7.50−7.38 (m, 3H), 7.19−7.17 (m, 2H), 7.02 (d, J = 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.6, 183.2, 159.0, 155.4, 135.9, 134.5, 134.0, 133.2, 131.6, 131.2, 130.0, 129.5, 128.7, 128.1, 126.9, 126.2, 125.3, 123.8, 118.8; Anal. Calcd for $C_{23}H_{13}ClN_2O_2S$: C, 66.27; H, 3.14; N, 6.72%; Found: C, 66.11; H, 3.02; N, 6.87%.

*1-(2-(3-Bromophenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-phenylethane-1,2-dione (**3j**).* Light yellow solid (79%, 73 mg); m.p.: 115−116 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 3H), 7.53−7.45 (m, 2H), 7.39−7.33 (m, 3H), 7.27 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.4, 183.2, 158.4, 155.4, 134.9, 134.6, 134.0, 133.17, 133.13, 132.6, 130.1, 129.67, 129.63, 128.98, 128.90, 127.0, 126.2, 125.3, 123.8, 122.3, 118.9; Anal. Calcd for $C_{23}H_{13}BrN_2O_2S$: C, 59.88; H, 2.84; N, 6.07%; Found: C, 59.79; H, 2.98; N, 6.12%.

*1-Phenyl-2-(2-(thiophen-2-yl)benzo[d]imidazo[2,1-b]thiazol-3-yl)ethane-1,2-dione (**3k**).* Yellow solid (78%, 60 mg); m.p.: 106−107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.12 (d, J = 8.8 Hz, 1H), 7.81−7.75 (m, 3H), 7.59−7.52 (m, 2H), 7.47−7.39 (m, 3H), 7.29−7.28 (m, 1H), 6.93−6.92 (m, 1H), 6.70−6.68 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.5, 183.4, 155.6, 153.0, 134.4, 134.1, 133.9, 133.4, 132.0, 130.1, 129.7, 129.6, 128.8, 127.0, 126.9, 126.2, 125.7, 123.9, 118.9; Anal. Calcd for $C_{21}H_{12}N_2O_2S_2$: C, 64.93; H, 3.11; N, 7.21%; Found: C, 65.01; H, 3.25; N, 7.05%.

*1-Phenyl-2-(6-phenylimidazo[2,1-b]thiazol-5-yl)ethane-1,2-dione (**3l**).*[7d] Light yellow solid (87%, 58 mg); m.p.: 158−159 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 4.4 Hz, 1H), 7.75−7.72 (m, 2H), 7.57−7.52 (m, 1H), 7.39−7.36 (m, 2H), 7.30−7.22 (m, 3H), 7.11−7.07 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.7, 183.1, 158.5, 156.2, 134.3, 133.2, 132.8, 129.8, 129.5, 129.5, 128.7, 128.0, 122.0, 121.9, 115.0.

*1-(2-(4-Chlorophenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-(4-methoxyphenyl)ethane-1,2-dione (**3m**).* Light yellow solid (85%, 76 mg); m.p.: 174−176 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69−7.65 (m, 2H), 7.57−7.52

DOI: 10.1021/acs.joc.6b02091
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(m, 1H), 7.47−7.43 (m, 1H), 7.22−7.18 (m, 2H), 7.06−7.03 (m, 2H), 6.89−6.85 (m, 2H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 190.3, 183.5, 164.7, 158.8, 155.2, 135.7, 134.0, 132.0, 131.6, 131.3, 130.0, 128.0, 126.9, 126.4, 126.1, 125.5, 123.8, 118.8, 114.0, 55.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{15}ClN_2O_3S$: 447.0570; found: 447.0566.

*1-(4-Chlorophenyl)-2-(2-(p-tolyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)ethane-1,2-dione (**3n**).* Light yellow solid (73%, 63 mg); m.p.: 96−97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (d, J = 8.4 Hz, 1H), 7.78−7.76 (m, 1H), 7.66−7.64 (m, 2H), 7.58−7.55 (m, 1H), 7.48−7.46 (m, 1H), 7.38−7.35 (m, 2H), 7.19−7.13 (m, 2H), 6.88 (d, J = 7.6 Hz, 2H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 190.2, 182.8, 161.0, 155.5, 139.9, 131.8, 130.9, 130.2, 129.8, 129.2, 128.9, 128.8, 128.6, 127.8, 126.9, 126.1, 123.8, 120.7, 118.8, 21.4; Anal. Calcd for $C_{24}H_{15}ClN_2O_2S$: C, 66.90; H, 3.51; N, 6.50; Found: C, 66.85; H, 3.58; N, 6.62%.

*1-(2-(4-Chlorophenyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)-2-(thiophen-2-yl)ethane-1,2-dione (**3o**).* Light yellow solid (84%, 71 mg); m.p.: 102−104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.26 (d, J = 8.4 Hz, 1H), 8.03−7.99 (m, 3H), 7.80−7.75 (m, 1H), 7.71−7.67 (m, 1H), 7.54−7.52 (m, 2H), 7.41−7.36 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 183.4, 181.7, 158.8, 155.2, 140.2, 136.6, 135.8, 133.8, 131.6, 131.2, 129.9, 128.9, 128.5, 128.3, 126.9, 126.1, 124.5, 123.8, 118.4; Anal. Calcd for $C_{21}H_{11}ClN_2O_2S_2$: C, 59.64; H, 2.62; N, 6.62%; Found: C, 59.83; H, 2.70; N, 6.78%.

General Procedure for the Synthesis of 5a. A mixture of 2-phenylimidazo[1,2-*a*]pyridine (**4a**, 39 mg, 0.20 mmol), phenylglyoxal (**2**, 30.4 mg, 0.20 mmol), and $FeCl_3$ (3.3 mg, 10 mol %) in toluene (2 mL) was stirred at 80 °C under air for 6 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and extracted with ethyl acetate/water. The organic phase was dried over anhydrous Na_2SO_4. The crude residue was obtained after evaporation of the solvent in vacuum and purified by column chromatography on silica gel (60−120 mesh) using *n*-hexane/EtOAc (3:1) as the eluent to afford pure product **5a** as yellow solid (51 mg, 78% yield).

*1-Phenyl-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (**5a**).*[7d] Yellow solid (78%, 51 mg); m.p.: 121−122 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.83 (d, J = 6.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.73−7.70 (m, 2H), 7.67−7.63 (m, 1H), 7.58−7.54 (m, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.31−7.20 (m, 4H), 7.09 (t, J = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.4, 184.6, 158.7, 148.4, 134.1, 133.4, 132.9, 131.0, 130.1, 129.6, 129.5, 129.3, 128.7, 128.6, 127.9, 117.7, 115.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{14}N_2O_2$: 327.1134; found: 327.1108.

*1-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (**5b**).*[7f] White solid (82%, 56 mg); m.p.: 114−115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J = 6.8 Hz, 1H), 7.69−7.67 (m, 2H), 7.57−7.52(m, 1H), 7.47−7.44 (m, 1H), 7.38−7.34 (m, 2H), 7.28−7.21 (m, 3H), 7.14 (t, J = 7.2 Hz, 1H), 7.09−7.05 (m, 2H), 2.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.7, 184.8, 158.3, 148.6, 134.1, 133.5, 133.1, 130.3, 130.2, 129.6, 129.4, 128.6, 128.5, 128.0, 127.1, 119.5, 115.9, 17.1.

*1-Phenyl-2-(2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (**5c**).*[7d] Yellow solid (72%, 49 mg); m.p.: 111−112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (d, J = 6.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.73−7.71 (m, 2H), 7.66−7.61 (m, 1H), 7.58−7.54 (m, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.22−7.17 (m, 3H), 6.88 (d, J = 8.0 Hz, 2H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.5, 184.7, 159.0, 148.5, 139.6, 134.1, 133.6, 131.0, 130.1, 130.0, 129.7, 129.4, 128.7, 128.5, 119.0, 117.7, 115.8, 21.4.

*1-(2-(Naphthalen-1-yl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (**5d**).* Yellow solid (73%, 55 mg); m.p.: 143−144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.85 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70−7.61 (m, 5H), 7.56−7.50 (m, 2H), 7.46−7.42 (m, 1H), 7.33−7.27 (m, 3H), 7.23 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.2, 184.8, 158.6, 148.6, 134.2, 133.6, 133.5, 132.3, 131.1, 130.9, 130.4, 129.6, 129.4, 128.6, 128.3, 128.1, 127.7, 126.9, 126.5, 126.4, 119.2, 117.8, 115.9; Anal. Calcd for $C_{25}H_{16}N_2O_2$: C, 79.77; H, 4.28; N, 7.44%; Found: C, 79.93; H, 4.14; N, 7.35%.

*1-(2-(3-Nitrophenyl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (**5e**).*[7d] White solid (68%, 50 mg); m.p.: 197−198 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (d, J = 6.8 Hz, 1H), 8.13−8.10 (m, 1H), 8.03 (t, J = 2.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.73−7.68 (m, 4H), 7.60−7.57 (m, 1H), 7.42−7.37 (m, 3H), 7.31−7.27 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.4, 184.1, 155.6, 148.4, 147.3, 135.9, 135.0, 134.9, 133.0, 131.5, 129.5, 129.4, 129.3, 129.1, 125.2, 124.2, 119.2, 118.0, 116.5.

*1-(8-Methyl-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (**5f**).* Light yellow solid (68%, 55 mg); m.p.: 106−107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J = 6.4 Hz, 1H), 7.63−7.61 (m, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.38−7.31 (m, 6H), 7.17 (t, J = 7.2 Hz, 1H), 2.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.9, 184.5, 156.3, 148.5, 135.6 ($J_{C\text{-}F}$ = 222 Hz), 133.2, 130.9 ($J_{C\text{-}F}$ = 36 Hz), 130.2, 129.5, 128.8, 128.5, 128.1, 127.1, 125.0 ($J_{C\text{-}F}$ = 45 Hz), 124.8 ($J_{C\text{-}F}$ = 4 Hz), 122.5, 119.6, 116.3, 17.1; Anal. Calcd for $C_{23}H_{15}F_3N_2O_2$: C, 67.65; H, 3.70; N, 6.86%; Found: C, 67.88; H, 3.84; N, 6.81%.

*1-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-(p-tolyl)-ethane-1,2-dione (**5g**).* Light yellow solid (81%, 57 mg); m.p.: 149−151 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J = 6.8 Hz, 1H), 7.59−7.57 (m, 2H), 7.45−7.43 (m, 1H), 7.29−7.27 (m, 2H), 7.24−7.22 (m, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.14−7.06 (m, 3H), 2.71 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.3, 185.0, 158.2, 148.5, 145.2, 133.2, 131.2, 130.3, 130.0, 129.8, 129.6, 129.3, 127.96, 127.91, 127.1, 119.5, 115.8, 21.9, 17.1; Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90; Found: C, 77.81; H, 5.09; N, 7.97%.

*1-(4-Methoxyphenyl)-2-(8-methyl-2-phenylimidazo[1,2-a]-pyridin-3-yl)ethane-1,2-dione (**5h**).* Light yellow solid (78%, 57 mg); m.p.: 118−120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 9.2 Hz, 2H), 7.44 (d, J = 6.8 Hz, 1H), 7.30−7.28 (m, 2H), 7.25−7.22 (m, 1H), 7.14−7.08 (m, 3H), 6.84 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 190.4, 185.2, 164.4, 158.1, 148.5, 139.4, 133.2, 132.1, 130.2, 130.0, 129.3, 127.9, 127.1, 126.8, 115.8, 114.2, 114.0, 55.6, 17.2; Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56; Found: C, 74.81; H, 4.84; N, 7.61%.

*1-(4-Chlorophenyl)-2-(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (**5i**).* Light yellow solid (72%, 53 mg); m.p.: 111−112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, J = 6.8 Hz, 1H), 7.63−7.60 (m, 2H), 7.48−7.46 (m, 1H), 7.36−7.33 (m, 2H), 7.28−7.25 (m, 3H), 7.17−7.09 (m, 3H), 2.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 190.4, 184.0, 158.4, 140.7, 139.4, 133.1, 131.9, 130.9, 130.4, 130.3, 129.5, 129.0, 128.09, 128.07, 127.1, 116.0, 114.2, 17.1; Anal. Calcd for $C_{22}H_{15}ClN_2O_2$: C, 70.50; H, 4.03; N, 7.47; Found: C, 70.36; H, 4.11; N, 7.52%.

*1-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-(naphthalen-2-yl)ethane-1,2-dione (**5j**).* Light yellow solid (71%, 67 mg); m.p.: 130−132 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (d, J = 6.8 Hz, 1H), 8.31 (s, 1H), 7.87 (t, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.67−7.60 (m, 2H), 7.56−7.52 (m, 1H), 7.48−7.46 (m, 1H), 7.28−7.26 (m, 2H), 7.21−7.15 (m, 2H), 7.00 (t, J = 8.0 Hz, 2H), 2.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 191.7, 184.7, 158.4, 148.6, 139.4, 136.1, 133.2, 132.6, 132.3, 131.0, 130.2, 129.9, 129.4, 129.2, 128.6, 128.0, 127.2, 127.0, 124.5, 124.1, 119.6, 115.9, 114.2, 17.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{18}N_2O_2$: 391.1447; found: 391.1442.

*1-Phenyl-2-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)ethane-1,2-dione (**5k**).*[7d] White solid (77%, 50 mg); m.p.: 170−171 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 10.03−10.01 (m, 1H), 8.88−8.87 (m, 1H), 7.74−7.72 (m, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.42−7.34 (m, 4H), 7.29−7.26 (m, 2H), 7.10 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz): δ 190.8, 185.3, 159.9, 154.9, 150.9, 136.9, 134.5, 133.1, 132.4, 130.2, 130.0, 129.7, 128.8, 128.1, 117.2, 111.8.

*1-Phenyl-2-(2-(p-tolyl)imidazo[1,2-a]pyrimidin-3-yl)ethane-1,2-dione (**5l**).* White solid (75%, 51 mg); m.p.: 165−167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 10.01−9.99 (m, 1H), 8.86−8.84 (m, 1H), 7.74−7.71 (m, 2H), 7.60−7.55 (m, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.24−7.22 (m, 3H), 6.88 (d, J = 8.0 Hz, 2H), 2.25 (s, 3H); $^{13}C\{^1H\}$

DOI: 10.1021/acs.joc.6b02091
J. Org. Chem. 2016, 81, 10088−10093

NMR (100 MHz): δ 190.9, 185.3, 160.1, 154.8, 151.0, 140.2, 136.9, 134.5, 133.2, 130.2, 129.7, 129.5, 128.9, 128.7, 117.1, 111.7, 21.4; Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31%; Found: C, 73.94; H, 4.29; N, 12.18%.

*3-(2-Oxo-2-phenylacetyl)indolizine-1-carbonitrile (**5m**).* Yellow solid (58%, 32 mg); m.p.: 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (d, *J* = 7.2 Hz, 1H), 8.06−8.04 (m, 2H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 7.69−7.65 (m, 1H), 7.62−7.58 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.28−7.24 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz): δ 191.8, 181.7, 141.9, 135.0, 133.0, 130.4, 130.3, 130.0, 129.3, 129.0, 120.7, 117.9, 117.0, 114.4, 87.1; Anal. Calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.68; N, 10.21%; Found: C, 74.21; H, 3.41; N, 10.40%.

*Methyl 3-(2-Oxo-2-phenylacetyl)indolizine-1-carboxylate (**5n**).* Yellow solid (61%, 37 mg); m.p.: 118−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (d, *J* = 6.8 Hz, 1H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.06−8.04 (m, 2H), 7.92 (s, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.56−7.48 (m, 3H), 7.19 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz): δ 192.5, 182.3, 164.0, 140.9, 134.7, 133.3, 130.3, 129.7, 129.6, 129.2, 129.0, 120.2, 119.8, 116.4, 107.9, 51.5; Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56%; Found: C, 70.47; H, 4.17; N, 4.72%.

General Procedure for the Synthesis of 8. A mixture of 2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**4c**, 42 mg, 0.20 mmol), 4-methylbenzaldehyde (**7**, 24 mg, 0.20 mmol), and $FeCl_3$ (3.3 mg, 10 mol %) in toluene (2 mL) was stirred at 80 °C under air for 6 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and extracted with ethyl acetate/water. The organic phase was dried over anhydrous Na_2SO_4. The crude residue was obtained after evaporation of the solvent in vacuum and purified by column chromatography on silica gel (60−120 mesh) using *n*-hexane/EtOAc (3:1) as the eluent to afford pure **8** as yellow solid (74 mg, 71% yield).

*3,3′-(p-Tolylmethylene)bis(2-(p-tolyl)imidazo[1,2-a]pyridine) (**8**).* Brown gummy mass (71%, 74 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.57 (m, 2H), 7.21−7.16 (m, 6H), 7.09−7.05 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 4H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.45 (s, 1H), 6.40−6.36 (m, 2H), 2.23 (s, 3H), 2.21 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz): δ 145.5, 144.8, 137.5, 137.4, 132.8, 131.1, 129.9, 128.7, 128.6, 127.9, 124.3, 124.2, 118.2, 117.3, 112.0, 38.2, 21.17, 21.12; Anal. Calcd for $C_{36}H_{30}N_4$: C, 83.37; H, 5.83; N, 10.80%; Found: C, 83.28; H, 5.71; N, 11.01%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02091.

Scanned copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds (PDF)

Crystallographic data for compound **5e** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.H. acknowledges the financial support from DST, GoWB (Grant no. 700(Sanc.)/ST/P/S&T/4G-2/2014). S.S. thanks UGC, New Delhi, and S.M. thanks CSIR, New Delhi, for their fellowships.

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DOI: 10.1021/acs.joc.6b02091
J. Org. Chem. 2016, 81, 10088−10093