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Palladium-Catalyzed Intramolecular Cross-Dehydrogenative Coupling: Synthesis of Fused Imidazo[1,2-*a*]pyrimidines and Pyrazolo[1,5-*a*]pyrimidines

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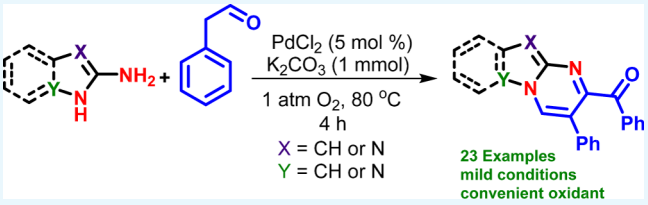
Supporting Information

ABSTRACT: A palladium-catalyzed intramolecular dehydrogenative coupling reaction was developed for the synthesis of fused imidazo[1,2-*a*]pyrimidines and pyrazolo[1,5-*a*]-pyrimidines. The developed protocol provides a practical approach for the synthesis of biologically important substituted pyrimidines from easily available substrates, with a broad substrate scope under mild reaction conditions.



INTRODUCTION

Cross-dehydrogenative coupling (CDC) that combines two C−H bonds to form a new carbon−carbon (C−C) bond has attracted much attention of organic chemists in the past decade.[1−6] Traditional cross-coupling reactions utilize prefunctionalized starting precursors as organohalides and/or organometallic derivatives. They lead to stoichiometric amounts of waste, whereas couplings via CDC of C(sp^2)−H bonds are economical and powerful tools to synthesize complex heterocycles.[7] These methods have been studied by employing various metal catalysts, organocatalysts, and photocatalysts to synthesize a wide range of organic molecules. In quest of other efficient and green organic transformations, direct functionalization of C−H bonds with metal catalyst plays a vital role in all areas of chemistry.[8−12] Among them, palladium-catalyzed CDC reactions have appeared as one of the most significant new approaches in organic synthesis.[13−23] A few protocols have been reported with palladium to access fused heterocycles via an intramolecular CDC.[7,24]

The use of direct oxidative intramolecular CDC for imine and enamine compounds for the construction of fused heterocycles is of interest. The reported CDC reactions contained a stoichiometric amount of oxidants, such as $PhI(OAc)_2$,[25] MnO_2,[26] TBHP,[27] $Cu(OAc)_2$,[28−31] AgOAc,[32] and others,[33,34] to maintain the catalytic cycle, which produced large amounts of waste and toxic byproducts. An elegant approach to avoid these limitations was the use of oxygen as a sole oxidant, which produced water as by-product after the reaction.[25]

The heteroaryl scaffold containing imidazo[1,2-*a*]pyrimidine is a masked form of the 2-aminoimidazole moiety, which showed prominent biological applications (Figure 1) as anxiolytic (A),[35] p38 kinase inhibitor (B),[36] anticonvulsant (C),[37] DPP4 inhibitor (D),[38] and androgen receptor antagonist (E).[39] The synthesis of imidazo[1,2-*a*]pyrimidines has been previously reported from nitrenoids in the presence of gold catalysts (Scheme 1a)[40] and from pyrimidyl arylamines or enamines with hypervalent iodine reagent (Scheme 1b).[41] Some of the reported methods need longer reaction times, require starting materials, which are synthesized in multiple steps, and have limited substrate scope. Thus, it is necessary to develop a simple and safer alternative method for these compounds. Herein, we report our initial results on the synthesis of imidazo[1,2-*a*]pyrimidines via a tandem reaction of amine and aldehyde derivatives under palladium catalysis, which involves oxidative CDC in the presence of air as an oxidant (Scheme 1c). To the best of our knowledge, this is the first report of using CDC reaction to produce fused imidazo[1,2-*a*]pyrimidine analogues.

RESULTS AND DISCUSSION

Our initial experiment commenced with the reaction of 1*H*-benzo[*d*]imidazol-2-amine (**1a**) and 2-phenylacetaldehyde (**2a**) in the presence of $CuCl_2$ and K_2CO_3 in toluene at 80 °C for 4 h, which resulted in the desired product, phenyl(3-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-2-yl)methanone (**3a**), with a yield of less than 10% (Table 1, entry 1). Other halogenated metal salts, such as Fe, Pd, Zn, and Sn, were scrutinized to increase the yield of **3a** (entries 2−6), and among them, $PdCl_2$ showed better results by giving 80% yield of **3a** (entry 4, Table 1). Next, we focused on screening different palladium salts, such as $Pd(OAc)_2$, $Pd(OH)_2$, and $Pd(TFA)_2$

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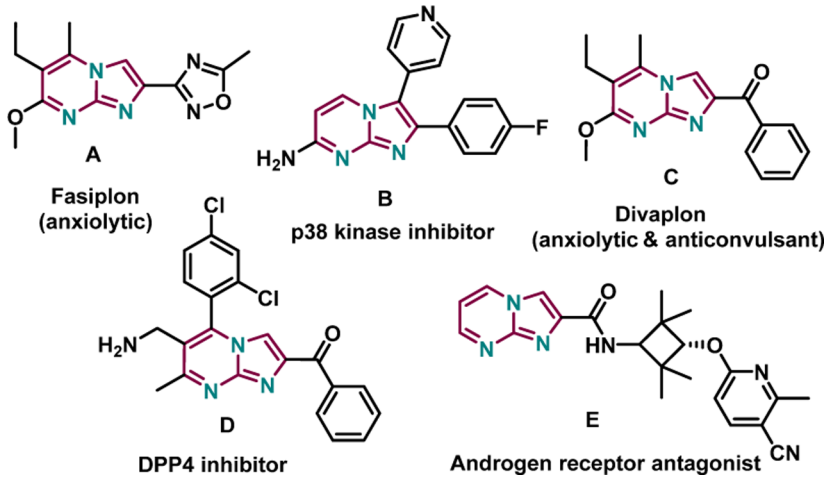
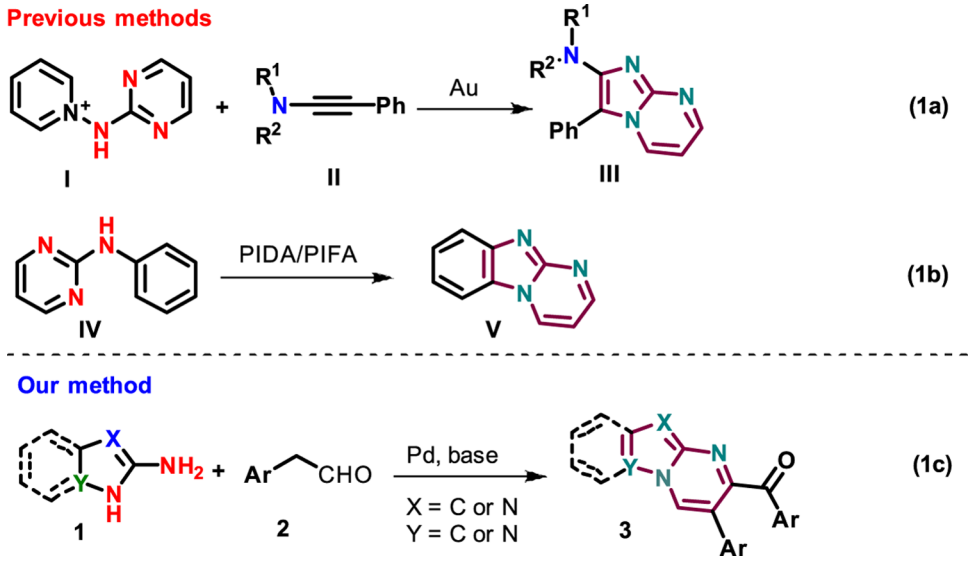


Figure 1. Biologically potent imidazo[1,2-*a*]pyrimidines.

Scheme 1. Various Pathways to Synthesize Imidazo[1,2-*a*]pyrimidine



(entries 7−9), to improve the yield of **3a** further and found that $PdCl_2$ was the best among all of these palladium catalysts. After choosing $PdCl_2$, various bases were also screened (entries 10−12), among which K_2CO_3 (entry 4) was found to give a higher yield of **3a**. The evaluation of reaction solvents, such as acetonitrile, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF) (entries 13−16), revealed that toluene is the preferred solvent for this reaction. The reaction temperature and the amount of the reagent were also optimized (entries 17−20). The reaction of 1*H*-benzo[*d*]-imidazol-2-amine **1a** and 2-phenylacetaldehyde **2a** (2 mmol) in the presence of $PdCl_2$ and K_2CO_3 in toluene at room temperature did not produce **3a** (entry 17). The yield of **3a** was not high at elevated temperature (entry 18). Importantly, lowering of the $PdCl_2$ to 2 mol % or increasing to 10 mol % had no impact on the reaction rate (entries 19 and 20, respectively). The reaction time was increased from 4 to 6 h, with no change in the yield (entry 21). Among all of these reaction conditions, the optimized condition was chosen as entry 4 in Table 1. The structure of **3a** was confirmed by X-ray crystallographic analysis (Table 1; files si_001 and si_002 of the Supporting Information).[42]

To examine the scope of the developed protocol, a series of imidazo[1,2-*a*]pyrimidine derivatives was synthesized by the reaction of differently substituted 1*H*-benzo[*d*]imidazol-2-amines **1** and 2-arylacetaldehyde **2**. The results are summarized in Table 2. The starting materials containing electron-donating groups gave higher yields (**3b−f**, **3h**, and **3m−p**) compared to those of materials containing electron-withdrawing groups (**3g**, **3i**, and **3j−l**). The reaction with a strong electron-withdrawing group, $-NO_2$ (**3q**), was detected in the crude reaction mixture using mass spectrometry; however, the isolation was not successful due to the stability of the compound. An aliphatic aldehyde was used instead of 2-phenylacetaldehyde for the reaction, which provided none of the desired compound (**3r**); our assumption was that the low stability of enamine may be the reason of failure.

To explore the applicability of the developed reaction further, we tested single-ring heterocycles, such as 1*H*-pyrazol-5-amine and 1*H*-imidazol-2-amine, as starting materials. The reaction succeeded and resulted in satisfactory yields of the corresponding fused heterocycles **5a−f** (Table 3). The formation of these products in good to excellent yields suggests the generality of the developed method.

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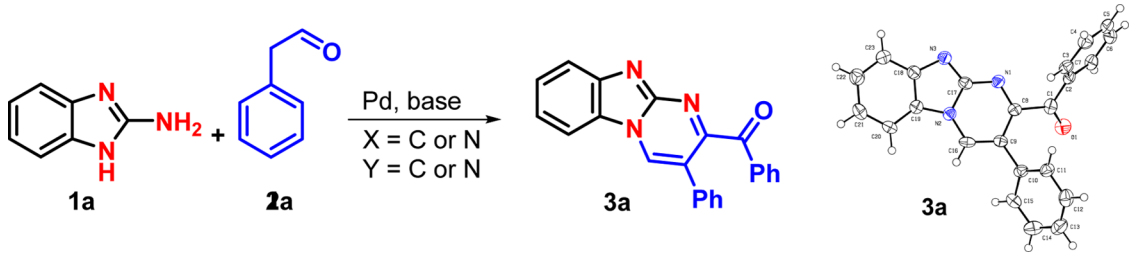
Table 1. Optimization of Reaction Conditions for the Synthesis of Imidazo[1,2-*a*]pyrimidines[a]



entry	catalyst	base	temp (°C)	solvent	yield (%)
1	$CuCl_2$	K_2CO_3	80	PhMe	<10
2	$FeCl_2$	K_2CO_3	80	PhMe	<10
3	$FeCl_3$	K_2CO_3	80	PhMe	<10
4	$PdCl_2$	K_2CO_3	80	PhMe	80
5	$ZnCl_2$	K_2CO_3	80	PhMe	30
6	$SnCl_2$	K_2CO_3	80	PhMe	26
7	$Pd(OAc)_2$	K_2CO_3	80	PhMe	47
8	$Pd(OH)_2$	K_2CO_3	80	PhMe	34
9	$Pd(TFA)_2$	K_2CO_3	80	PhMe	39
10	$PdCl_2$	Na_2CO_3	80	PhMe	64
11	$PdCl_2$	Cs_2CO_3	80	PhMe	71
12	$PdCl_2$	Li_2CO_3	80	PhMe	69
13	$PdCl_2$	K_2CO_3	80	CH_3CN	63
14	$PdCl_2$	K_2CO_3	80	DMF	58
15	$PdCl_2$	K_2CO_3	80	DMSO	61
16	$PdCl_2$	K_2CO_3	80	THF	43
17	$PdCl_2$	K_2CO_3	28	PhMe	0
18	$PdCl_2$	K_2CO_3	100	PhMe	76
19[b]	$PdCl_2$	K_2CO_3	80	PhMe	78
20[c]	$PdCl_2$	K_2CO_3	80	PhMe	80
21[d]	$PdCl_2$	K_2CO_3	80	PhMe	80
22	$PdCl_2$	K_2CO_3	60	PhMe	62
23[e]	$PdCl_2$	K_2CO_3	80	PhMe	78

[a] **1a** (1 mmol), **2a** (2 mmol), catalyst (5 mol %), base (2 mmol), 80 °C, 4 h. [b] $PdCl_2$ (2 mol %). [c] $PdCl_2$ (10 mol %). [d] 6 h. [e] $PdCl_2$ (3 mol %).

We performed functional group transformation of compound **3a** (Scheme 2) through reduction with $NaBH_4$ to produce alcohol **6a**. An attempt to synthesize the hydrazone derivative of compound **3a** resulted in the formation of compound **7**, which was confirmed by HRMS.

A plausible mechanism is proposed in Scheme 3 for the synthesis of imidazo[1,2-*a*]pyrimidine derivatives. In the proposed mechanism, the initial step involves the formation of intermediate **A** by the condensation of **4a** with **2a**, which then reacts with Pd(II) to generate intermediate **B**. The deprotonation of intermediate **B** leads to vinyl Pd intermediate **C**, which undergoes an intramolecular attack with imine to give seven-membered palladium cycle **D**. The 1,2-Pd migration in intermediate **D** produces six-membered aza cyclic compound **E**, which may result in the formation of intermediate **F** or **F′** after reductive palladium elimination. Intermediate **F′** could undergo a well-known Wacker−Tsuji type of oxidation in the presence of Pd (II). Pd(O) was oxidized by utilizing the oxygen to produce Pd(II), which further could lead to a π complex species in compound **G**. This compound is expected to undergo hydration in the presence of water, which may lead to compound **I**, and it could undergo reductive elimination of Pd to yield compound **J** that is finally oxidized to give the desired product, **5a**.

CONCLUSIONS

In conclusion, we have developed a simple, mild, and efficient method for the synthesis of fused imidazo[1,2-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidines via a tandem reaction of the corresponding 2-arylacetaldehyde and azole-amine in the presence of $PdCl_2$. The developed protocol will be not only applicable as a versatile method for the mentioned heterocycles but also useful to construct complex derivatives.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all of the reactions for the preparation of the substrates were performed in oven-dried glassware with freshly distilled solvents. The solvents were dried under standard methods. All other commercial reagents were used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometers using chloroform-d ($CDCl_3$) as the internal standard. Multiplicities were denoted as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). Aluminum-backed plates precoated with silica gel 60F254 were used for thin-layer chromatography and were visualized with a UV lamp. The melting points were uncorrected. MS and HRMS were obtained on QTOF Bruker Impact II using electrospray ionization (ESI) source. X-ray was recorded on Bruker D8

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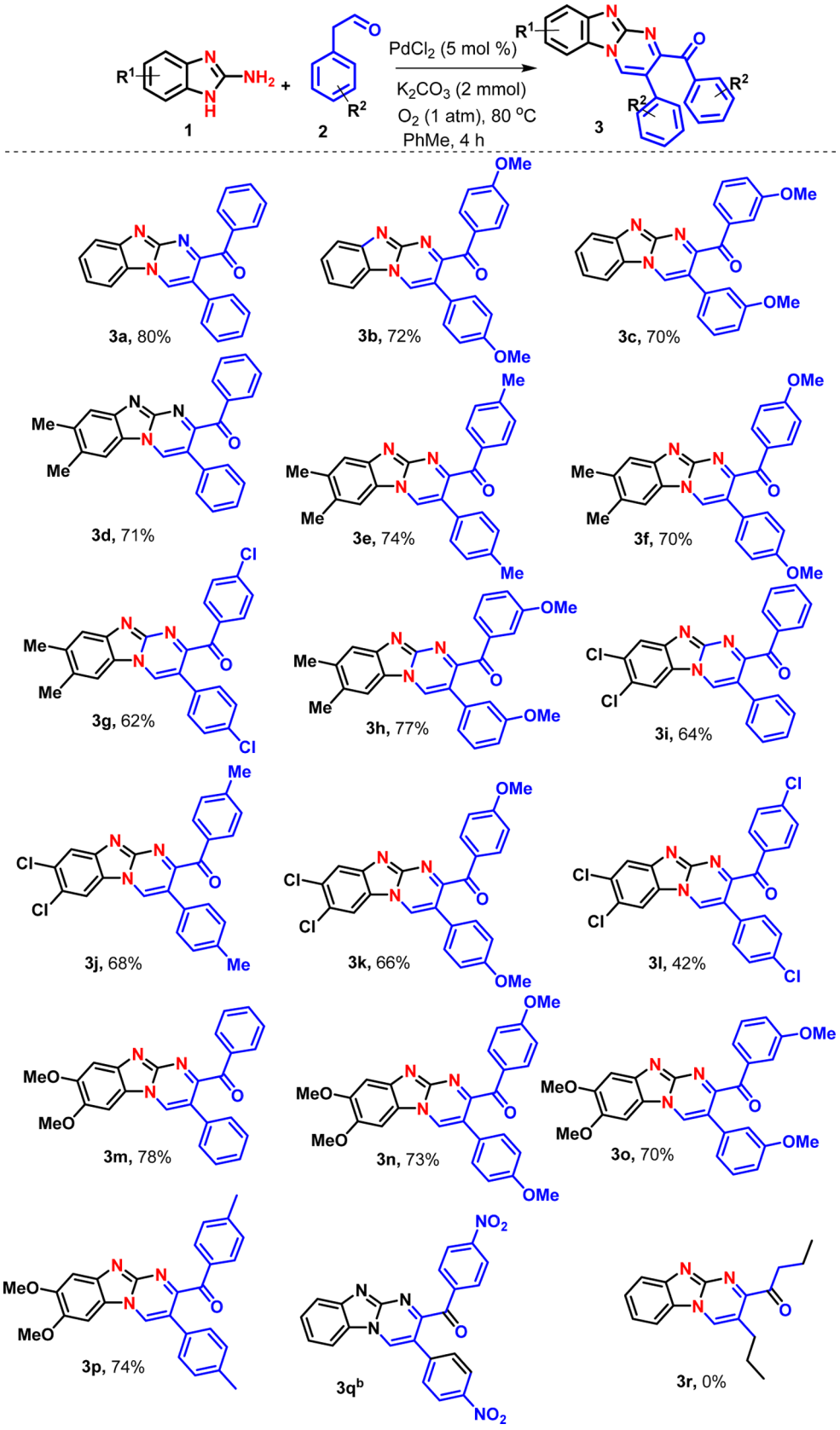
Table 2. Synthesis of Imidazo[1,2-*a*]pyrimidines by CDC[a,b]



[a]Compound **1a** (1 mmol), compound **2a** (2 mmol), catalyst (5 mol %), base (2 mmol), 80 °C, 4 h. [b]High resolution mass spectra (HRMS) showed peak of comp **3q**.

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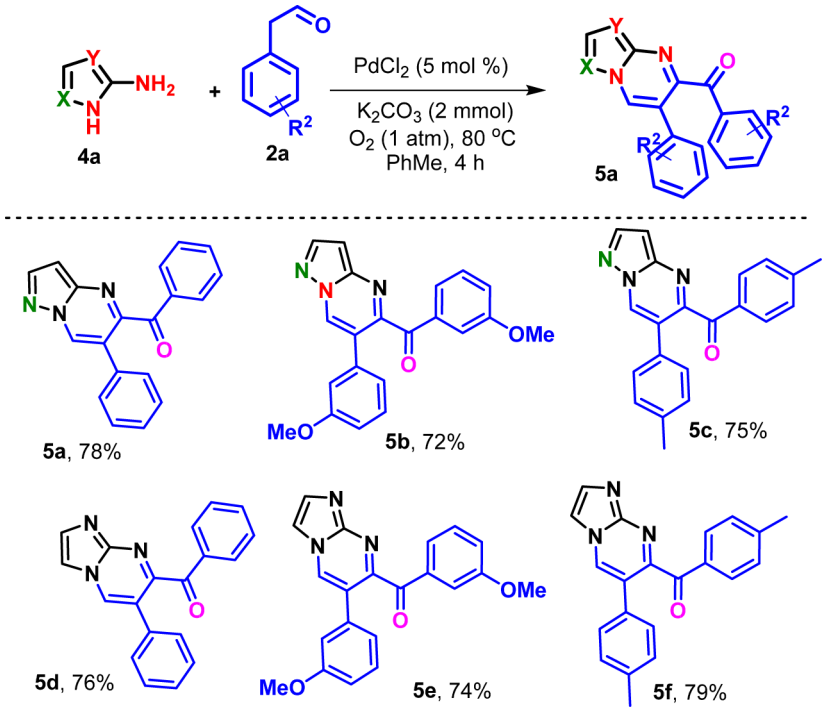
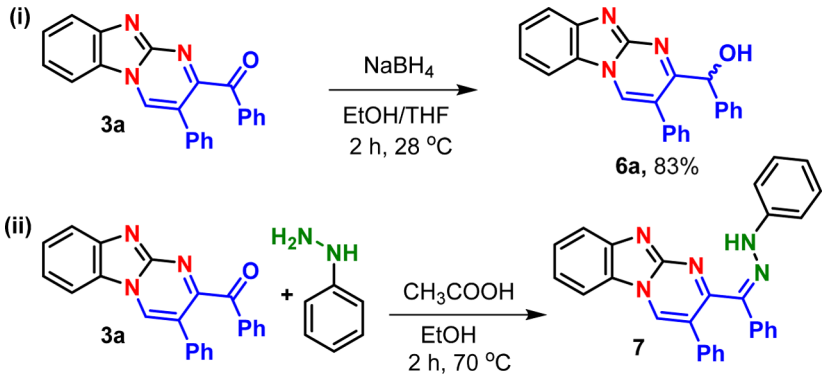
Table 3. Direct Way to Synthesize Fused Bicyclic Systems[a]



[a]Compound **4a** (1 mmol), **2a** (2 mmol), catalyst (5 mol %), base (2 mmol), 80 °C, 4 h.

Scheme 2. Applications of Compound 3a



venture gallium liquid metal jet single-crystal diffraction system. Flash column chromatography was carried out over silica gel 60 (230−400 mesh).

Experimental Procedures and Spectral Data. *General Procedure for the Synthesis of Fused Imidazo[1,2-a]-pyrimidines.* A suspension of *1H*-benzo[*d*]imidazol-2-amine **1** (100 mg, 1.00 mmol, 1.00 equiv), 2-phenylacetaldehyde **2** (180.4 mg, 2 equiv), $PdCl_2$ (6.65 mg, 0.037 mmol, 5 mol%), and K_2CO_3 (101 mg, 2.00 equiv) in anhydrous toluene (5.0 mL) was stirred at 80 °C for 4 h under oxygen atmosphere (1 atm). At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield product **3a**. Similar procedures were followed to synthesize compounds **3b−p** and **5a−e** (Supporting Information).

*Phenyl(3-phenylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)-methanone (**3a**).* This compound was obtained as a yellow solid (80%) with mp 204.4−206.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.00−7.91 (m, 4H), 7.60−7.56 (m, 2H), 7.44−7.41 (m, 3H), 7.31 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 160.7, 148.4, 145.2, 135.0, 134.2, 133.5, 133.2, 130.6, 129.0, 128.9, 128.7, 128.5, 127.1, 122.8, 120.8, 111.1; HRMS (ESI) calcd $[C_{23}H_{16}N_3O]$ $[M + H]^+$: 350.1294, found: 350.1291.

*(4-Methoxyphenyl)(3-(4-methoxyphenyl)benzo[4,5]-imidazo[1,2-a]pyrimidin-2-yl)methanone (**3b**).* This compound was obtained as a yellow solid (72%) with mp 190.7−192.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.97−7.89 (m, 4H), 7.57 (s, 1H), 7.42 (s, 1H), 7.24−7.23 (m, 2H), 6.90−6.83 (m, 4H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 164.5, 161.4, 159.9, 148.4, 145.1, 133.1, 132.8, 130.3, 128.3, 126.8, 125.9, 122.7, 120.8, 114.4, 114.0, 110.0, 55.6, 55.3; HRMS (ESI) calcd $[C_{25}H_{20}N_3O_3]$ $[M + H]^+$: 410.1505, found: 410.1500.

*(3-Methoxyphenyl)(3-(3-methoxyphenyl)benzo[4,5]-imidazo[1,2-a]pyrimidin-2-yl)methanone (**3c**).* This compound was obtained as a yellow solid (70%) with mp 202.3−204.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.10 (s, 1H), 8.00−7.99 (m, 1H), 7.64 (s, 1H), 7.56−7.48 (m 3H), 7.36 (t, J = 8.0 Hz, 1H), 7.30−7.26 (m, 1H), 7.16 (d, J = 8.0

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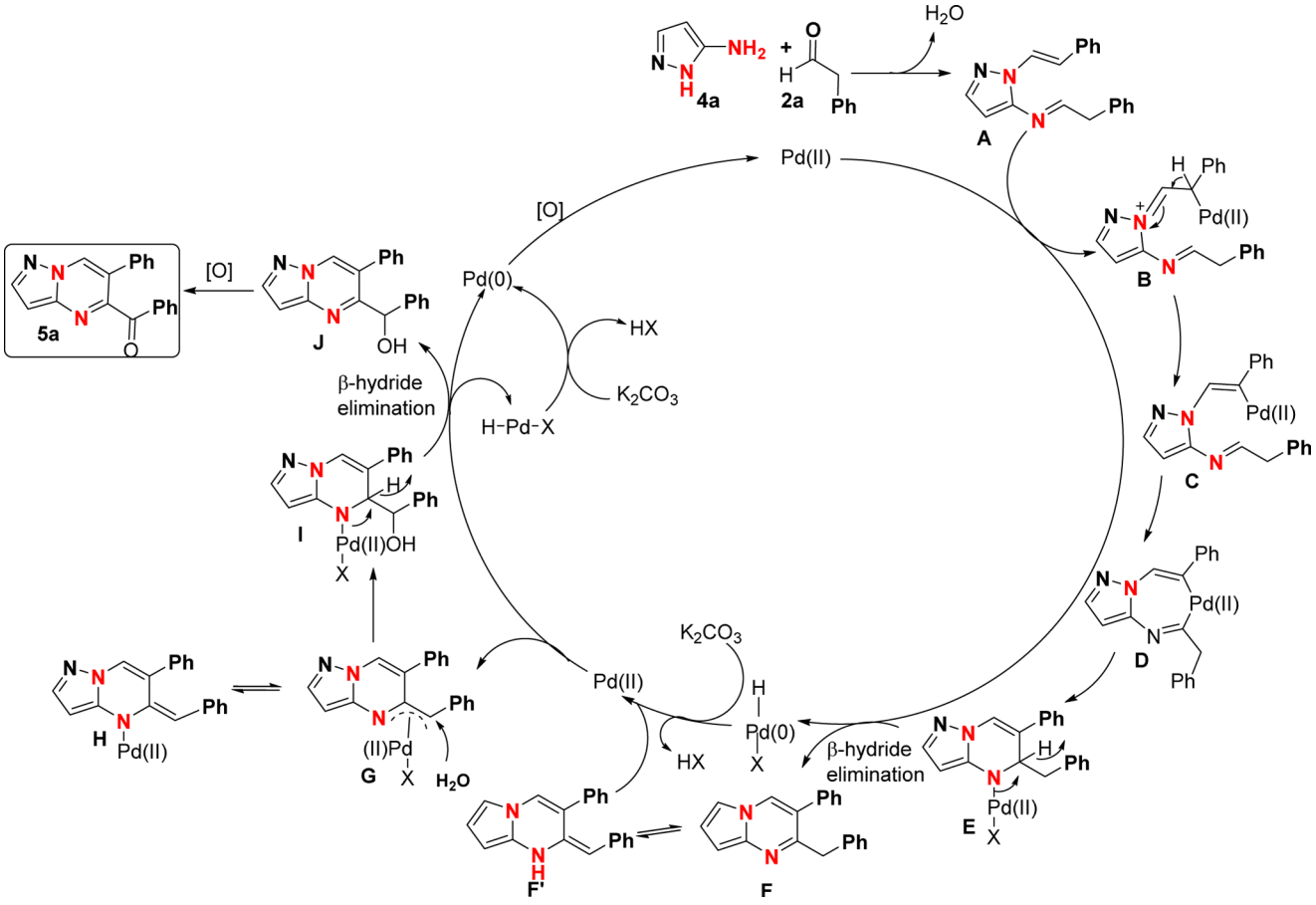
Scheme 3. Plausible Mechanism to Synthesize Imidazo[1,2-*a*]pyrimidine Derivatives



Hz, 1H), 6.94−6.89 (m, 3H), 3.83 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 160.8, 159.8, 136.4, 134.8, 132.9, 130.1, 129.7, 127.1, 124.0, 122.9, 121.3, 121.2, 120.9, 114.6, 114.3, 113.7, 110.9, 55.5, 55.2; HRMS (ESI) calcd $[C_{25}H_{20}N_3O_3]$ $[M + H]^+$: 410.1505, found: 410.1502.

(7,8-Dimethyl-3-phenylbenzo[4,5]imidazo[1,2-a]-pyrimidin-2-yl)(phenyl)methanone ***(3d)***. This compound was obtained as a yellow solid (71%) with mp 118.5−120.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.99 (s, 2H), 7.85−7.77 (m, 2H), 7.56−7.28 (m, 8H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 171.2, 159.0, 136.9, 135.2, 134.0, 133.8, 133.1, 132.8, 130.6, 128.9, 128.8, 128.6, 128.3, 120.7, 111.1, 20.8, 20.7; HRMS (ESI) calcd $[C_{25}H_{20}N_3O]$ $[M + H]^+$: 378.1607, found: 378.1605.

(7,8-Dimethyl-3-(p-tolyl)benzo[4,5]imidazo[1,2-a]-pyrimidin-2-yl)(p-tolyl)methanone ***(3e)***. This compound was obtained as a yellow solid (74%) with mp 114.7−116.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.92 (d, J = 8 Hz, 2H), 7.83 (s, 1H), 7.74 (s, 1H), 7.26−7.21 (m, 4H), 7.14 (d, J = 8 Hz, 2H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 159.7, 145.2, 138.4, 136.8, 132.8, 132.6, 132.5, 131.0, 130.8, 129.7, 129.4, 128.7, 120.7, 110.8, 21.9, 21.2, 20.9, 20.8; HRMS (ESI) calcd $[C_{27}H_{24}N_3O]$ $[M + H]^+$: 406.1920, found: 406.1914.

(4-Methoxyphenyl)(3-(4-methoxyphenyl)-7,8-dimethylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)methanone ***(3f)***. This compound was obtained as a yellow solid (70%) with mp 226.6−228.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.97 (d, J = 8 Hz, 2H), 7.77−7.70 (m, 2H), 7.23 (d, J = 8 Hz, 2H), 6.86 (dd, J = 8, 20 Hz, 4H), 3.86 (s, 3H), 3.76 (s, 3H), 2.47 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 164.4, 159.7, 133.1, 132.5, 130.1, 128.3, 126.1, 120.4, 114.3, 114.0, 110.8, 55.6, 55.3, 20.9, 20.8; HRMS (ESI) calcd $[C_{27}H_{24}N_3O_3]$ $[M + H]^+$: 438.1818, found: 438.1809.

(4-Chlorophenyl)(3-(4-chlorophenyl)-7,8-dimethylbenzo-[4,5]imidazo[1,2-a]pyrimidin-2-yl)methanone ***(3g)***. This compound was obtained as a yellow solid (62%) with mp 149.6−151.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.00 (s, 2H), 7.51 (s, 1H), 7.41 (s, 2H), 7.32 (d, J = 8 Hz, 2H), 7.26−7.23 (m, 3H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 157.8, 141.0, 137.2, 137.0, 134.8, 133.4, 133.3, 132.3, 132.0, 130.1, 129.2, 129.1, 119.7, 111.2, 20.9, 20.8; HRMS (ESI) calcd $[C_{25}H_{18}Cl_2N_3O]$ $[M + H]^+$: 446.0828, found: 446.0831.

(3-Methoxyphenyl)(3-(3-methoxyphenyl)-7,8-dimethylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)methanone ***(3h)***. This compound was obtained as a yellow solid (77%) with mp 166.8−168.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.57−7.53 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H); 7.15−7.12 (m, 1H), 6.88−6.82 (m, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 159.79, 159.77, 159.5, 148.0, 144.1, 136.9, 136.5, 135.1, 132.7, 132.6, 130.0, 129.6, 125.3, 124.0, 121.2, 121.0, 120.7, 120.5, 114.5, 114.0, 113.7, 110.8, 55.5, 55.2, 20.9, 20.8; HRMS (ESI) calcd $[C_{27}H_{24}N_3O_3]$ $[M + H]^+$: 438.1818, found: 438.1815.

(7,8-Dichloro-3-phenylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)(phenyl)methanone ***(3i)***. This compound was obtained as

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a yellow solid (64%) with mp 113.2−115.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.14−7.96 (m, 3H), 7.61−7.26 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 171.6, 161.8, 144.5, 134.5, 132.9, 130.55, 130.51, 129.1, 128.8, 128.7, 127.0, 122.1, 112.77, 112.74; HRMS (ESI) calcd $[C_{23}H_{14}Cl_2N_3O]$ $[M + H]^+$: 418.0515, found: 418.0502.

(7,8-Dichloro-3-(p-tolyl)benzo[4,5]imidazo[1,2-a]-pyrimidin-2-yl)(p-tolyl)methanone ***(3j)***. This compound was obtained as a pale brown solid (68%) with mp 267.7−269.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.17−8.12 (m, 2H), 7.88−7.86 (m, 2H); 7.26−7.12 (m, 6H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 162.2, 145.7, 138.9, 132.8, 132.3, 131.4, 130.7, 130.0, 129.8, 129.5, 128.6, 126.8, 122.1, 112.6, 21.9, 21.2; HRMS (ESI) calcd $[C_{25}H_{18}Cl_2N_3O]$ $[M + H]^+$: 446.0828, found: 446.0833.

(7,8-Dichloro-3-(4-methoxyphenyl)benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)(4-methoxyphenyl)methanone ***(3k)***. This compound was obtained as a pale brown solid (66%) with mp 210.5−212.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.08 (s, 2H); 7.91 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 6.89 (d, *J* = 8 Hz, 2H), 6.78 (d, *J* = 8 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 164.6, 162.5, 159.9, 132.9, 132.7, 131.2, 130.0, 127.7, 126.6, 125.1, 121.8, 121.6, 114.4, 114.1, 112.7, 55.6, 55.2; HRMS (ESI) calcd $[C_{25}H_{18}Cl_2N_3O_3]$ $[M + H]^+$: 478.0726, found: 478.0719.

(4-Chlorophenyl)(7,8-dichloro-3-(4-chlorophenyl)benzo-[4,5]imidazo[1,2-a]pyrimidin-2-yl)methanone ***(3l)***. This compound was obtained as a pale brown solid (42%) with mp 221.5−223.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.10−7.93 (m, 4H); 7.42−7.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 160.6, 141.4, 135.4, 133.4, 132.8, 131.9, 131.3, 130.1, 129.4, 129.3, 127.5, 122.0, 121.0, 112.7; HRMS (ESI) calcd $[C_{23}H_{12}Cl_4N_3O]$ $[M + H]^+$: 485.9735, found: 485.9738.

(7,8-Dimethoxy-3-phenylbenzo[4,5]imidazo[1,2-a]-pyrimidin-2-yl)(phenyl)methanone ***(3m)***. This compound was obtained as an orange solid (78%) with mp 196.7−198.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 1H); 7.46−7.42 (m, 4H), 7.35−7.31 (m, 5H), 4.02 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 157.1, 150.8, 147.9, 140.6, 135.4, 134.1, 134.0, 131.6, 130.7, 128.9, 128.6, 128.4, 121.1, 101.4, 92.5, 56.5, 56.4; HRMS (ESI) calcd $[C_{25}H_{20}N_3O_3]$ $[M + H]^+$: 410.1505, found: 410.1493.

(7,8-Dimethoxy-3-(4-methoxyphenyl)benzo[4,5]imidazo-[1,2-a]pyrimidin-2-yl)(4-methoxyphenyl)methanone ***(3n)***. This compound was obtained as a brown solid (73%) with mp 147.8−149.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.44−7.43 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 164.5, 159.7, 158.8, 151.1, 148.0, 146.5, 132.9, 132.1, 130.0, 127.9, 125.5, 121.5, 119.7, 114.3, 114.0, 100.1, 93.2, 56.6, 56.3, 55.6, 55.2; HRMS (ESI) calcd $[C_{27}H_{24}N_3O_5]$ $[M + H]^+$: 470.1717, found: 470.1704.

(7,8-Dimethoxy-3-(3-methoxyphenyl)benzo[4,5]imidazo-[1,2-a]pyrimidin-2-yl)(3-methoxyphenyl)methanone ***(3o)***. This compound was obtained as a yellow solid (70%) with mp 191.9−193.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 7.53 (br, 2H), 7.39−7.33 (m, 2H), 7.27 (s, 1H), 7.23 (t, *J* = 4.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.91−6.83 (m, 3H), 4.02 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 159.8, 159.7, 157.1, 136.6, 135.3, 131.7, 130.0, 129.6, 124.0, 121.3, 120.1, 120.8, 114.6, 113.9, 113.8, 92.6, 56.5, 56.4, 55.5, 55.2; HRMS (ESI) calcd $[C_{27}H_{24}N_3O_5]$ $[M + H]^+$: 470.1717, found: 470.1711.

(7,8-Dimethoxy-3-(p-tolyl)benzo[4,5]imidazo[1,2-a]-pyrimidin-2-yl)(p-tolyl)methanone ***(3p)***. This compound was obtained as a yellow solid (74%) with mp 232.2−234.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.76−7.69 (m, 2H), 7.23−7.21 (m, 3H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 164.3, 160.0, 159.6, 136.6, 133.0, 132.4, 130.0, 128.2, 126.1, 120.5, 114.3, 113.9, 110.8, 55.5, 55.2, 20.8, 20.7; HRMS (ESI) calcd $[C_{27}H_{24}N_3O_3]$ $[M + H]^+$: 438.1818, found: 438.1809.

Phenyl(6-phenylpyrazolo[1,5-a]pyrimidin-5-yl)methanone ***(5a)***. This compound was obtained as a yellow-brown solid (78%) with mp 148.2−149.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.23 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.58−7.57 (m, 1H), 7.46−7.43 (m, 2H), 7.32 (s, 5H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 155.1, 146.3, 146.1, 135.3, 134.7, 134.4, 134.1, 133.7, 130.4, 129.0, 128.9, 128.7, 128.5, 122.4, 98.1; HRMS (ESI) calcd $[C_{19}H_{14}N_3O]$ $[M + H]^+$: 300.1138, found: 300.1131.

(3-Methoxyphenyl)(6-(3-methoxyphenyl)pyrazolo[1,5-a]-pyrimidin-5-yl)methanone ***(5b)***. This compound was obtained as a yellow solid (72%) with mp 118.1−119.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.25−8.24 (m, 1H), 7.48−7.43 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27−7.23 (m, 1H), 7.16−7.13 (s, 1H), 6.91−6.86 (m, 3H), 6.83−6.82 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 159.85, 159.80, 146.4, 146.1, 136.6, 135.0, 134.6, 130.1, 129.7, 123.6, 122.2, 121.3, 121.0, 114.4, 114.3, 113.7, 98.1, 55.5, 55.1; HRMS (ESI) calcd $[C_{21}H_{18}N_3O_3]$ $[M + H]^+$: 360.1349, found: 360.1342.

p-Tolyl(6-(p-tolyl)pyrazolo[1,5-a]pyrimidin-5-yl)-methanone ***(5c)***. This compound was obtained as a yellowish solid (75%) with mp 181−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.69−7.68 (m, 1H), 7.26−7.24 (m, 2H), 7.20−7.18 (m, 2H), 7.15−7.13 (m, 2H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 155.8, 146.3, 145.1, 138.5, 137.1, 132.9, 132.8, 130.80, 130.78, 129.6, 129.3, 128.7, 123.6, 111.3, 21.8, 21.2; HRMS (ESI) calcd $[C_{21}H_{18}N_3O]$ $[M + H]^+$: 328.1451, found: 328.1445.

Phenyl(6-phenylimidazo[1,2-a]pyrimidin-7-yl)methanone ***(5d)***. This compound was obtained as a yellowish brown solid (76%) with mp 212.3−213.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.98−7.94 (m, 3H), 7.71 (s, 1H), 7.60−7.57 (s, 1H), 7.45−7.42 (m, 2H), 7.31−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 155.1, 146.3, 137.5, 135.4, 134.0, 133.8, 133.3, 130.5, 128.9, 128.6, 128.5, 123.5, 111.6; HRMS (ESI) calcd $[C_{19}H_{14}N_3O]$ $[M + H]^+$: 300.1138, found: 300.1129.

(3-Methoxyphenyl)(6-(3-methoxyphenyl)imidazo[1,2-a]-pyrimidin-7-yl)methanone ***(5e)***. This compound was obtained as a brown solid (74%) with mp 163−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.98 (s, 1H), 7.72−7.66 (m, 2H), 7.56−7.48 (m, 2H), 7.37−7.34 (m, 1H), 7.27−7.24 (m, 1H), 7.17−7.14 (m, 1H), 6.89−6.86 (s, 2H), 3.84 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 159.8, 155.4, 146.3, 137.4, 133.1, 132.0, 130.0, 129.6, 128.5, 123.9, 121.2, 120.8, 114.5, 114.2, 113.8, 111.6, 55.5, 55.2; HRMS (ESI) calcd $[C_{21}H_{18}N_3O_3]$ $[M + H]^+$: 360.1349, found: 360.1346.

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*p-Tolyl(6-(p-tolyl)imidazo[1,2-a]pyrimidin-7-yl)-methanone (**5f**).* This compound was obtained as a yellowish solid (79%) with mp 181.2−182.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.96 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.26−7.24 (m, 2H), 7.20−7.13 (s, 4H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 155.7, 146.4, 145.1, 138.5, 137.3, 133.0, 132.9, 130.86, 130.80, 129.6, 129.3, 128.7, 123.5, 111.3, 21.9, 21.2; HRMS (ESI) calcd $[C_{21}H_{18}N_3O]$ $[M + H]^+$: 328.1451, found: 328.1453.

Procedure for Reduction by Using $NaBH_4$. A suspension of compound **3a** (1 mmol) in THF/EtOH (4:2 mL) was cooled to 0 °C, and then slow portionwise addition of $NaBH_4$ (0.5 mmol) was done. The mixture was stirred at 0 °C for 20 min and at 28 °C for 4 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with water twice and finally with saturated brine solution once. The combined organic layers were dried over sodium sulfate and filtered. The volatiles were removed under pressure. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield product **6a**.

*Phenyl(3-phenylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)-methanol (**6a**).* This compound was obtained as a white solid (83%) with mp 189.5−191.3 °C; ^{1}H NMR (400 MHz, MeOD): δ 9.86 (s, 1H), 8.84 (d, J = 8.0 Hz, 1H), 8.00−7.93 (m, 1H), 7.90 (t, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.58−7.50 (m, 3H), 7.37−7.34 (s, 2H), 7.24−7.22 (m, 3H), 7.11−7.09 (m, 2H), 6.14 (s, 1H), 3.34−3.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 139.7, 136.5, 132.4, 129.8, 129.15, 128.6, 128.1, 128.0, 127.6, 126.9, 125.0, 113.9, 73.4; HRMS (ESI) calcd $[C_{23}H_{18}N_3O]$ $[M + H]^+$: 352.1451, found: 352.1441.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.6b00417.

X-ray analysis and NMR spectra (PDF)
Crystal structure data (CIF) (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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