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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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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(sp2)–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.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 MnO2,26 TBHP,27 Cu(OAc)2,28–31 AgOAc,32 and others33,34 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-aminimidazole 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).31 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 1H-benzo[d]imidazo[2-amine (1a) and 2-phenylacetalddehyde (2a) in the presence of CuCl2 and K2CO3 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, PdCl2 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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(entries 7−9), to improve the yield of 3a further and found that PdCl₂ was the best among all of these palladium catalysts. After choosing PdCl₂ various bases were also screened (entries 10−12), among which K₂CO₃ (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 1H-benzo[d]-imidazol-2-amine 1a and 2-phenylacetaldehyde 2a (2 mmol) in the presence of PdCl₂ and K₂CO₃ 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 PdCl₂ 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-α]pyrimidine derivatives was synthesized by the reaction of differently substituted 1H-benzo[d]imidazol-2-amine 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, −NO₂ (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 1H-pyrazol-5-amine and 1H-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.
We performed functional group transformation of compound 3a (Scheme 2) through reduction with NaBH4 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-arylaldehyde and azole-amine in the presence of PdCl2. 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 13C NMR spectra were recorded on Bruker 400 MHz spectrometers using chloroform-d (CDCl₃) 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.
Table 2. Synthesis of Imidazo[1,2-\(\alpha\)]pyrimidines by CDC\(^{\alpha,b}\)

<table>
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<tr>
<th>Compound</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Product</th>
<th>Yield</th>
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</thead>
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<td>OMe</td>
<td></td>
<td>3a</td>
<td>80%</td>
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<tr>
<td>3b</td>
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<td>Cl</td>
<td>Me</td>
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<td>71%</td>
</tr>
<tr>
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<td>OMe</td>
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<td>74%</td>
</tr>
<tr>
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<tr>
<td>3g</td>
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<td>Me</td>
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</tr>
<tr>
<td>3i</td>
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<td>Cl</td>
<td>3i</td>
<td>64%</td>
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<tr>
<td>3j</td>
<td>Cl</td>
<td>Cl</td>
<td>3j</td>
<td>68%</td>
</tr>
<tr>
<td>3k</td>
<td>OMe</td>
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<td>3n</td>
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<td>3o</td>
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<td>MeO</td>
<td>3o</td>
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</tr>
<tr>
<td>3p</td>
<td>MeO</td>
<td>MeO</td>
<td>3p</td>
<td>74%</td>
</tr>
<tr>
<td>3q(^\circ)</td>
<td>NO(_2)</td>
<td></td>
<td>3q(^\circ)</td>
<td>0%</td>
</tr>
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</table>

\(^{\alpha}\)Compound 1a (1 mmol), compound 2a (2 mmol), catalyst (5 mol %), base (2 mmol), 80 °C, 4 h. \(^{\circ}\)High resolution mass spectra (HRMS) showed peak of comp 3q.
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), PdCl2 (6.65 mg, 0.037 mmol, 5 mol%), and K2CO3 (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; 1H NMR (400 MHz, CDCl3): 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, 2H); 13C NMR (100 MHz, CDCl3): 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 [C23H16N3O] [M + H]+: 350.1294, found: 350.1291.

**Scheme 2. Applications of Compound 3a**
Hz, 1H), 6.94–6.89 (m, 3H), 3.83 (s, 3H), 3.71 (s, 3H); 13C NMR (100 MHz, CDCl3): 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, 55.3; HRMS (ESI) calcd [C25H20N3O3] [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; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 [C25H20N3O] [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; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): δ 191.9, 159.7, 145.2, 138.4, 136.8, 132.8, 132.6, 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 [C27H24N3O] [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; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 [C27H24N3O3] [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; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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, 119.7, 111.2, 20.9, 20.8; HRMS (ESI) calcd [C25H18Cl2N3O] [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; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 [C27H24N3O3] [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
a yellow solid (64%) with mp 113.2–115.1 °C; 1H NMR (400 MHz, CDCl3): δ 8.83 (s, 1H), 8.14–7.96 (m, 3H), 7.61–7.26 (m, 9H); 13C NMR (100 MHz, CDCl3): δ 191.7, 171.6, 161.8, 144.5, 134.5, 132.9, 130.55, 129.1, 128.8, 127.8, 127.0, 122.1, 112.77, 112.74; HRMS (ESI) calcd [C24H18Cl2N4O2] [M + H]+: 418.0851, found: 418.0802.

(7,8-Dichloro-3-(p-tolyI)benzo[4,5]imidazo[1,2-alpyrimidin-2-yl)](p-tolyl)methanone (3P). This compound was obtained as a yellow solid (74%) with mp 232.2–234.1 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 [C24H18N4O2] [M + H]+: 438.1818, found: 438.1809.

Phenyl[6-phenylpyrazolo[1,5-alpyrimidin-5-yl)methanone (5A). This compound was obtained as a yellow-brown solid (78%) with mp 148.2–149.5 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 [C19H14N3O2] [M + H]+: 300.1138, found: 300.1131.

(3-Methoxyphenyl)[6-(3-methoxyphenyl)pyrazolo[1,5-alpyrimidin-5-yl)methanone (5B). This compound was obtained as a yellow solid (72%) with mp 118.1–119.9 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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, 113.7, 98.1, 55.5, 55.1; HRMS (ESI) calcd [C26H21N4O3] [M + H]+: 360.1349, found: 360.1342.

p-Tolyl[6-(p-tolyl)pyrazolo[1,5-alpyrimidin-5-yl)methanone (5c). This compound was obtained as a yellowish solid (76%) with mp 212.3–213.8 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): δ 191.8, 158.5, 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 [C26H21N4O3] [M + H]+: 360.1345, found: 328.1445.

Phenyl[6-phenylimidazo[1,2-alpyrimidin-7-yl)methanone (5d). This compound was obtained as a yellowish brown solid (76%) with mp 212.3–213.8 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): δ 192.2, 155.1, 146.3, 137.5, 134.0, 133.8, 133.3, 130.5, 128.9, 128.5, 123.5, 111.6; HRMS (ESI) calcd [C19H14N3O2] [M + H]+: 300.1138, found: 300.1129.

(3-Methoxyphenyl)[6-(3-methoxyphenyl)imidazo[1,2-alpyrmidin-7-yl)methanone (5e). This compound was obtained as a brown solid (74%) with mp 163–166 °C; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): δ 192.0, 159.8, 155.4, 146.3, 137.4, 133.1, 130.2, 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 [C26H21N4O3] [M + H]+: 360.1349, found: 360.1346.
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 °C; 1H NMR (400 MHz, CDCl₃); 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); 13C NMR (100 MHz, CDCl₃); 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 [C₂₁H₁₈N₃O] [M + H]+: 328.1451, found: 328.1453.

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(42) CCDC number for comp 3a and 5a are 1455218 and 1481010.