JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Regioselective Synthesis of Fused Imidazo[1,2-*a*]pyrimidines via Intramolecular C−N Bond Formation/6-*Endo-Dig* Cycloisomerization

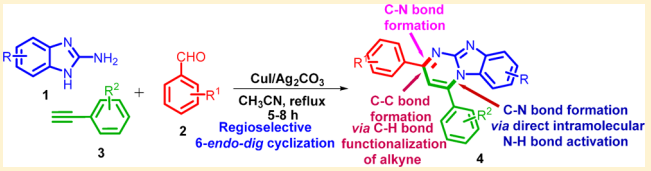
Atul Kumar,*[†] Mukesh Kumar,[†] Shivam Maurya,[†] and Ranjana S. Khanna[‡]

[†]Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Lucknow 226031 India

[‡]Department of Chemistry, Faculty of Science, BHU, Varanasi 221005, India

Supporting Information

ABSTRACT: An efficient regioselective cascade synthesis of *N*-fused imidazo heterocycles has been developed. This cascade transformation proceeds via a transition-metal (copper/silver) catalyzed coupling reaction between 2-aminobenzimidazole, aldehydes, and alkynes leading to the formation of propargylamine intermediate, which regioselectively undergoes 6-*endo-dig* cyclization through intramolecular N−H bond activation interceded C−N bond formation leading to highly functionalized imidazo[1,2-*a*]pyrimidines in good to excellent yields.



INTRODUCTION

Nitrogen-containing fused heterocyclic molecules can be extremely valuable for obtaining biological leads and exploring drug discovery programs.[1] Imidazo-fused heterocyclic fragments are important in pharmaceutical and biomedical research since these scaffolds occur in several natural and biologically active molecules and exhibit promising biological profiles such as anticancer, antimicrobial, and antitubercular agents, benzodiazepine receptor agonists, and calcium channel blockers.[2] Imidazo-fused fragments also constitute the core structure of several currently marketed drugs,[3−6] and imidazo-fused pyrimidines also have immense importance in the pharmaceutical industry owing to their broad range of interesting pharmacological activity. Several anxiolytic drugs such as fasiplon, taniplon, and divaplon holding imidazopyrimidine fragments are currently used in clinics.[7] Therefore, the availability of efficient and practical synthetic routes to generate heterocyclic units for the synthesis of natural and biomimetic compounds is of great demand. One of the ways to achieve this goal is the development of cascade reactions that allow the sequential transformations of two or more reactions in the same reaction vessel, thereby minimizing the number of laboratory operations, the generation of waste chemicals, time, and cost. Several synthetic type of methods have been described for the synthesis of these heterocycles.[8] In 2007, Yan and Liu reported a Au(III)-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes for the synthesis of aminoindolizines.[9] In 2010, Gevorgyan et al. reported the Cu-promoted synthesis of imidazopyridine via *exo-dig* cycloisomerization using aldehydes, 2-aminopyridines, and alkynes.[10] Ji et al. described an approach toward the synthesis of complex butenolides from alkynes, amines, and glyoxylic acids in the presence of gold catalysts.[11] More recently, Guchhait et al. reported the synthesis of imidazo-fused heterocycles involving 2-aminopyridines, alkynes, and aldehydes using copper sulfate/glucose via *exo-dig* cyclization.[12] All these methods lead to the formation of five-membered ring systems.

However, an efficient synthesis of multisubstituted imidazopyrimidines with high regioselectivity still remains a challenge. To the best of our knowledge, synthesis of fused imidazopyrimidines via intramolecular N−H bond activation mediated C−N bond formation through regioselective 6-*endo-dig* cycloisomerization in the presence of Cu/Ag bimetallic catalyst system has not yet been explored. Functionalized imidazopyrimidine is an important pharmacophore and is extensively found in many biologically active molecules. In particular, aryl- and heteroarylimidazo[1,2-*a*]pyrimidines have significant importance in the pharmaceutical industry owing to their broad range of interesting pharmacological activity.[13]

As part of our ongoing efforts in the synthesis of *N*-containing heterocycles,[14] for the first time herein we describe a highly efficient, regioselective approach for the synthesis of functionalized imidazo[1,2-*a*]pyrimidine derivatives from 2-aminobenzimidazole, benzaldehydes, and alkynes using a Cu/Ag coinage bimetallic catalyst system through a multicomponent cascade coupling (MCC) reaction involving 6-*endo-dig* intramolecular N−H bond activation interceded C−N bond formation and cycloisomerization (Scheme 1).

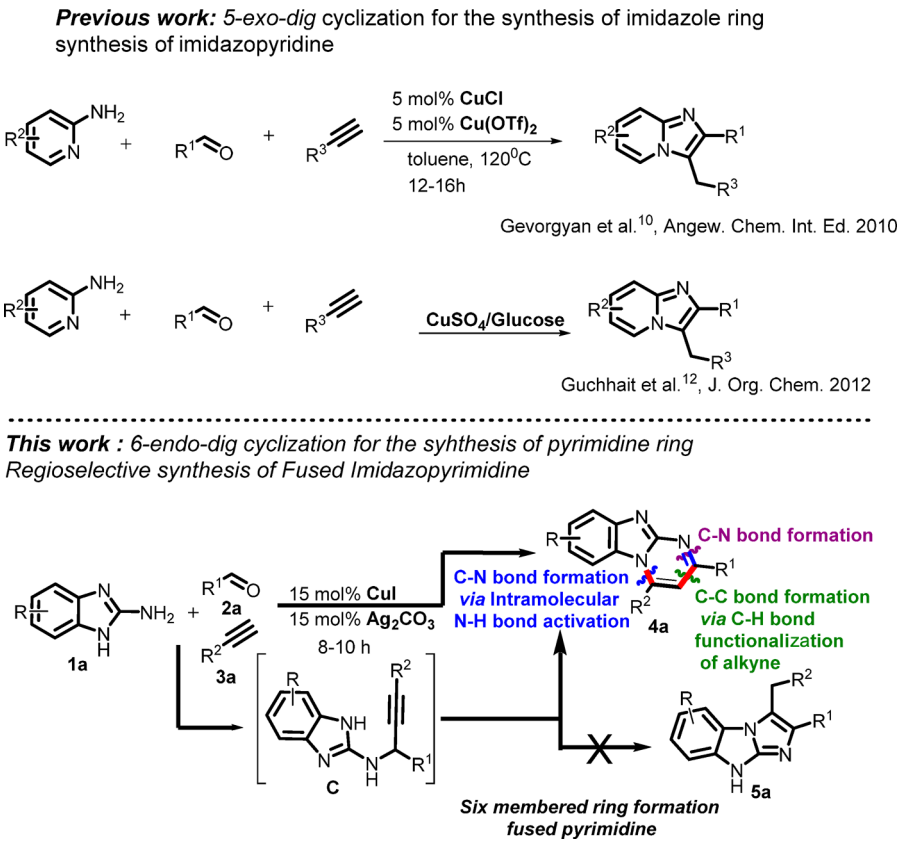
RESULTS AND DISCUSSION

We commenced this project by investigating the reaction of 2-aminobenzimidazole (**1a**), 4-chlorobenzaldehyde (**2a**), and phenylacetylene (**3a**) in the absence of catalyst in MeCN at 81−83 °C, but no desired compound was identified (Table 1, entry 1). When the same reaction was carried out in toluene at

Received: May 6, 2014

   dx.doi.org/10.1021/jo5007762 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

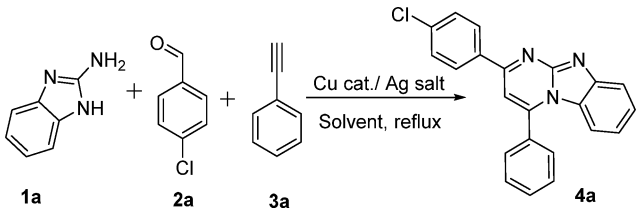
Scheme 1. Comparison between Previous Approach and Our Approach



81−83 °C in the presence of CuI (15 mol %) and $Cu(OTf)_2$/$CuSO_4$ (15 mol %) following previously reported protocols,[10a,12] unfortunately the reaction failed to provide desired coupling product and instead gave previously reported exocyclic analogues **5** (Table 1, entry 2).[10a,12] Fortunately, the reaction produced the desired coupling product **4a** in 72% yield in MeCN when we used the combination of CuI (15 mol %) and Ag_2CO_3 (15 mol %) at refluxing temperature (81−83 °C) for 8 h in place of Cu(I) and Cu(II) salt combination (Table 1, entry 3). The above result prompted us to examine other silver salts. In light of these results, a series of other silver salts were evaluated in combination with CuI (15 mol %), and only Ag_2CO_3 displayed the best results (Table 1, entries 8−11). We have also used some other copper salts in combination with silver carbonate, and we found copper iodide to be the best (Table 1 entries 12−16). Several solvents were also screened for this reaction, and MeCN was seen to be the best (Table 1, compare entries 3 and 4−7). Catalyst loadings have also been studied for developing an efficient combination for a bimetallic catalyst catalyst system. We first modulated loading of Cu, keeping the Ag loading constant and decreasing the amount of CuI loading, resulting in a decreased yield of desired product (Table 1, compare entries 3, 18, and 19), whereas reducing the amount of silver salt with a constant loading of CuI also furnished a lower yield of the product **4a** (Table 1, compare entries 3, 20, and 21). Control experiments showed that both CuI and Ag_2CO_3 catalysts are necessary for this reaction (see the Supporting Information, Table 1, entries 22 and 23). In control experiments, we found a lower yield of coupling product when we decreased the amount of both catalysts (Table 1, entry 17). After the various combinations of copper and silver catalysts were screened, we finally found the optimal reaction conditions [Cu (15 mol %)/Ag (15 mol %) in CH_3CN] at which coupling product **4a** was obtained in 72% yield. It is worth mentioning that the reaction was successful only when the bimetallic Cu/Ag catalyst system was used. The obtained poly-heterocyclic product of the reaction was fully characterized by ^1H and ^{13}C NMR methods and mass spectrometric data. The disappearance of the two characteristic peaks of propargylamine (**C**) in the ^{13}C NMR spectrum confirmed the formation of either compound **4a** or **5a**, but initially it was difficult to confirm the structure of the regioisomer as either **4a** or **5a** (Scheme 1). X-ray crystallographic analysis of the product confirmed the formation of **4a** (see the Supporting Information). To demonstrate the generality of this method, the substrate scope of the reaction was investigated under optimized conditions, and results are illustrated in Figure 1. First, a wide range of aromatic aldehydes **2a** bearing electron-neutral, electron-withdrawing, and electron-donating groups could be employed as coupling partners with 2-aminobenzimidazole **1a**, which were smoothly transformed to the corresponding benzoimidazo[1,2-*a*]pyrimidines **4a** with alkyne **3a** in good to moderate yields (Figure 1, entries **4a**−**k**). All *para*-, *meta*-, and *ortho*-substituted aldehydes were easily converted into the desired products, which indicated that steric bulk did not significantly affect the reactivity. Aldehydes bearing dioxo groups furnished the corresponding products in moderate yield (Figure 1, entries **4l**−**m**). Moreover, aliphatic aldehydes also reacted smoothly to give the desired coupling products in good yields (Figure 1, entries **4n**−**p**). Unfortunately, aromatic nitrogen-containing aldehydes such as pyridine-4-carboxyaldehyde and *N*,*N*-dimethylbenzaldehyde failed to provide the desired coupling products. Substituted 2-aminobenzimidazoles smoothly coupled with aldehydes and

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



entry	Cu (mol %)	Ag (mol %)	solvent	time (h)	yield[c] (%)
1			MeCN	8	
2	CuI (15)	*b*	toluene	8	
3	**CuI (15)**	**Ag_2CO_3 (15)**	**MeCN**	**8**	**72**
4	CuI (15)	Ag_2CO_3 (15)	THF	8	45
5	CuI (15)	Ag_2CO_3 (15)	DMF	8	15
6	CuI (15)	Ag_2CO_3 (15)	DMSO	10	10
7	CuI (15)	Ag_2CO_3 (15)	DMA	10	15
8	CuI (15)	AgOAc (15)	MeCN	8	25
9	CuI (15)	$AgNO_3$ (15)	MeCN	8	40
10	CuI (15)	Ag_2O (15)	MeCN	8	20
11	CuI (15)	AgI (15)	MeCN	8	20
12	CuCl (15)	Ag_2CO_3 (15)	MeCN	8	40
13	CuBr (15)	Ag_2CO_3 (15)	MeCN	12	38
14	$CuCl_2$ (15)	Ag_2CO_3 (15)	MeCN	12	nd
15	Cu_2O (15)	Ag_2CO_3 (15)	MeCN	12	nd
16	$Cu(OTf)_2$(15)	Ag_2CO_3 (15)	MeCN	8	nd
17	CuI (10)	Ag_2CO_3 (10)	MeCN	10	65
18	CuI (10)	Ag_2CO_3 (15)	MeCN	10	50
19	CuI (5)	Ag_2CO_3 (15)	MeCN	10	48
20	CuI (15)	Ag_2CO_3 (10)	MeCN	10	52
21	CuI (15)	Ag_2CO_3 (5)	MeCN	10	45

[a]Reaction conditions: All reactions were performed with 2-aminobenzimidazole **1a** (1.0 mmol), 4-chlorobenzaldehyde **2a** (1.0 mmol), and phenylacetylene **3a** (2.0 mmol) in 5 mL of solvent under refluxing conditions. [b]Copper triflate/copper sulfate. [c]Isolated yield. nd = not detected.

alkynes to afford the desired coupling products **4r–v** in good yields (Figure 1, entries **4r–v**). Next we evaluated the scope of several alkynes, which were reacted under optimized reaction conditions, and results are shown in Figure 2. Aromatic alkynes bearing methyl groups at the *para*- and *meta*-position afforded the corresponding products in good yields (Figure 2, entries **4z** and **4aa**). Methyl propiolate, pent-1-yne, and ethynyltrimethylsilane furnished the corresponding products in better yield (Figure 2, entries **4w**, **4x**, and **4y**). Furthermore, we have used benzyl-protected hydroxyl benzaldehyde for the synthesis of imidazo[1,2-*a*]pyrimidine and found that it is well tolerated and afforded good yield (Figure 1, entry **4q**). The tolerance of functional groups such as chloro, fluoro, bromo, nitro, methoxy, and cyano in this method provides an opportunity for further chemical transformations. Several pharmaceutically relevant scaffolds could be easily generated with the help of this protocol into *N*-fused imidazopyrimidines. The proposed mechanism for the formation of imidazopyrimidine **4a** is illustrated in Scheme 3. First, the Cu(I) salt reacts with the terminal alkyne to form copper acetylide. The imine (**A**) formed in situ is attacked by the copper acetylide, resulting in the Cu complex intermediate (**B**) followed by elimination of copper via reductive elimination, producing alkynyl moiety (**C**). The formed alkynyl moiety (**C**) is coordinated to the silver salt to generate complex (**D**), which underwent intramolecular N–H bond activation and regioselectively attacked at the electron-deficient center of triple bond via 6-*endo-dig* cyclization leading to C–N bond formation and gave vinyl silver species (**E**). Complex **E** then subsequently undergoes demetalation as well as auto-oxidation leading to the formation of **4a**.

On the basis of the above results illustrated in Figures 1 and 2, the reactions displayed very high regioselectivity. Only the six-membered ring imidazopyrimidine formed via 6-*endo-dig* cyclization. Most likely, the reaction via 6-*endo-dig* cyclization can produce a stable product and undergo a similar mechanism, which has been supported in the literature.[15]

On the basis of the crystallographic results (see the Supporting Information), the formation of product **5** was ruled out by path C_1', clearly suggesting that product **4a** must be formed by intramolecular attack of the nitrogen onto the carbon–carbon triple bond (Scheme 3, path C_2').

On the application of this protocol we have synthesized 2-(4-chlorophenyl)-4-phenyl-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidine (Scheme 2). To further demonstrate the advantage of this method, we attempted scale-up synthesis of imidazo[1,2-*a*]pyrimidine **4a** using of 2-aminobenzimidazole (1a) with *p*-chlorobenzaldehyde (**2a**) and phenylacetylene (**3a**), and 65% yield was afforded (Scheme 4).

CONCLUSION

In conclusion, we have developed a Cu/Ag-catalyzed three-component cascade coupling cyclization reaction, which can be tuned to proceed via tandem C–H bond functionalization of alkynes followed by intramolecular N–H activation mediated C–N bond formation through regioselective 6-*endo-dig* cycloisomerization sequence to afford substituted imidazopyrimidines. This methodology is amenable to one-pot efficient synthesis of thiazolopyrimidine framework. The products generated herein tolerate functional groups viable for further derivatization. From a synthetic point of view, and taking into deliberation the easily availability of the starting materials, the experimental simplicity of the reactions, and the importance of pyrimidines, especially in medicinal chemistry and material science, this methodology may become a very helpful device for synthetic as well as medicinal chemists.

EXPERIMENTAL SECTION

Typical Procedure for the Synthesis of Benzoimidazo[1,2-*a*]pyrimidines (4a). 2-Aminobenzimidazole (**1a**) (133.1 mg, 1.0 mmol), *p*-chloro-benzaldehyde (**2a**) (140 mg, 1.0 mmol), and phenylacetylene (**3a**) (0.220 mL, 2.0 mmol) was dissolved in 5 mL of acetonitrile in a round-bottom flask, CuI (38 mg, 20 mol %) was added, the mixture was stirred at room temperature for 10 min under nitrogen, silver carbonate (54 mg, 20 mol %) was added, and the reaction mixture was refluxed (81–83 °C) until full consumption of 2-aminobenzimidazole as monitored through TLC. Upon completion (6–8 h) of the reaction, the mixture was filtered on Celite. The filtrate was concentrated under reduced pressure to give the crude material, which was purified by column chromatography on silica gel (eluent: EtOAc/hexane) and afforded benzoimidazopyrimidine **4a** in 72–60% yield.

Typical Procedure for the Synthesis of 2-(4-Chlorophenyl)-4-phenyl-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (7). 2-Aminobenzothiazole (**6**) (150.1 mg, 1.0 mmol), *p*-chlorobenzaldehyde (**2a**) (140 mg, 1.0 mmol), and phenylacetylene (**3a**) (0.220 mL, 2.0 mmol) was dissolved in 5 mL of acetonitrile in a round-bottom flask, CuI (38 mg, 20 mol %) was added, the mixture was stirred at room temperature for 10 min under nitrogen, silver carbonate (54 mg, 20 mol %) was added, and the reaction mixture (81–83 °C) was refluxed until full consumption of 2-aminobenzothiazole as monitored through TLC. Upon completion (6–8 h) of the reaction, the mixture was

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX–XXX

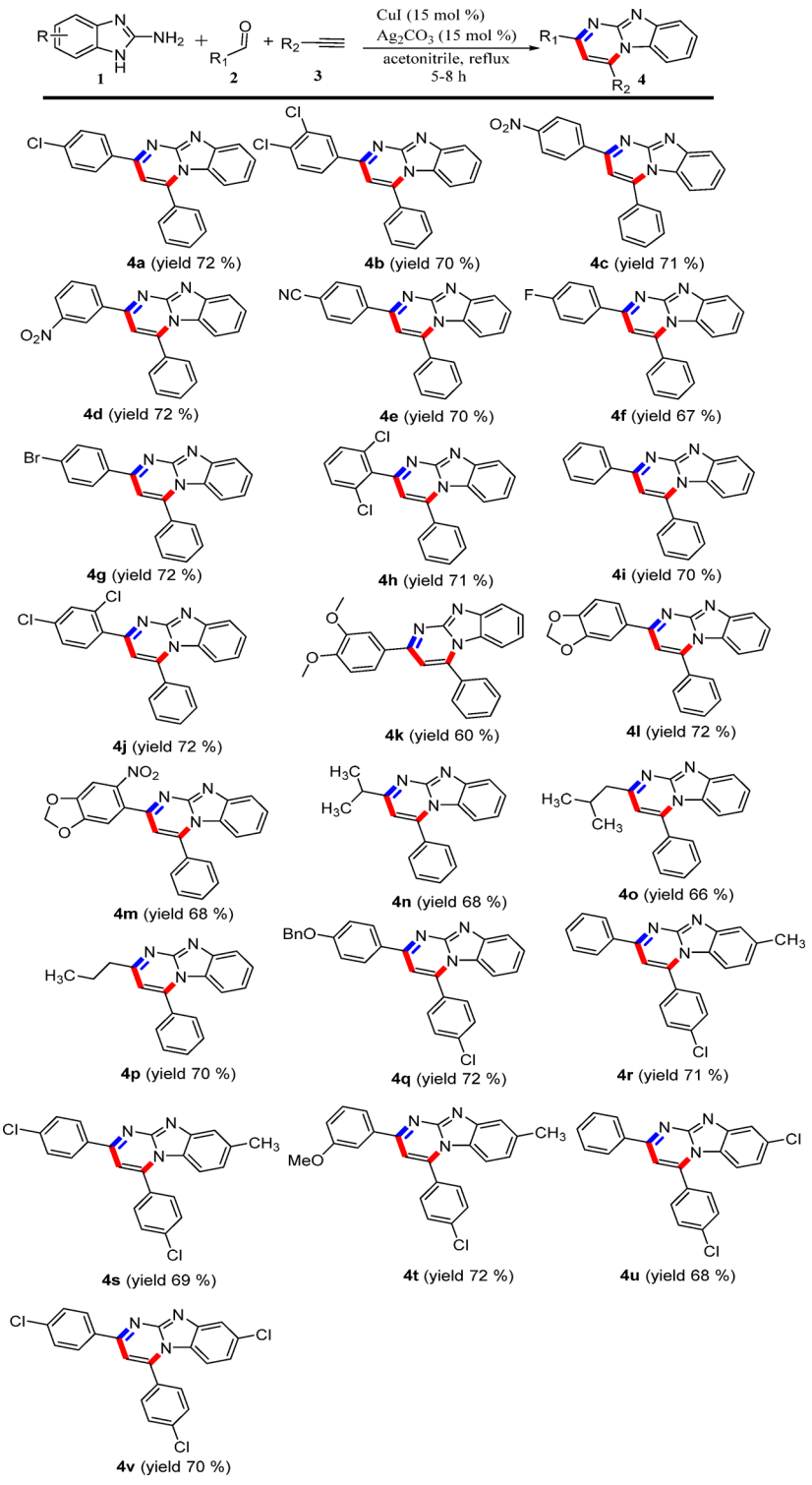


Figure 1. Synthesis of imidazopyrimidine derivatives using different aldehydes.

filtered on Celite. The filtrate was concentrated under reduced pressure to give the crude material, which was purified by column chromatography on silica gel (eluent: EtOAc/hexane), and afforded 2-(4-chlorophenyl)-4-phenyl-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (7) in 70% yield.

2-(4-Chlorophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4a): yield 256.1 mg (72%); physical state: solid; mp = 197−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, J = 8.3 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.46 (t, J = 8.5 Hz, 3H), 7.66 (t, J = 7.7 Hz, 5H), 7.93 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.8, 114.5, 120.2, 121.3, 126.0, 127.4, 128.3, 129.0, 129.2, 129.4, 131.1, 132.4, 135.1, 137.6, 145.5, 149.5, 159.7; IR (KBr) 3429, 2921, 2854, 1013, 827, 768 cm^{-1}; ESI MS (m/z) = 356 (M + H)$^+$. Anal. Calcd for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 74.28; H, 3.98; N, 11.80.

2-(3,4-Dichlorophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4b): yield 273.1 mg (70%); physical state: solid; mp = 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 1H), 7.00−6.98 (m, 2H), 7.20 (s, 1H), 7.32−7.30 (m, 2H), 7.72−7.43 (m, 6H), 7.97 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.4, 112.0,

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX−XXX

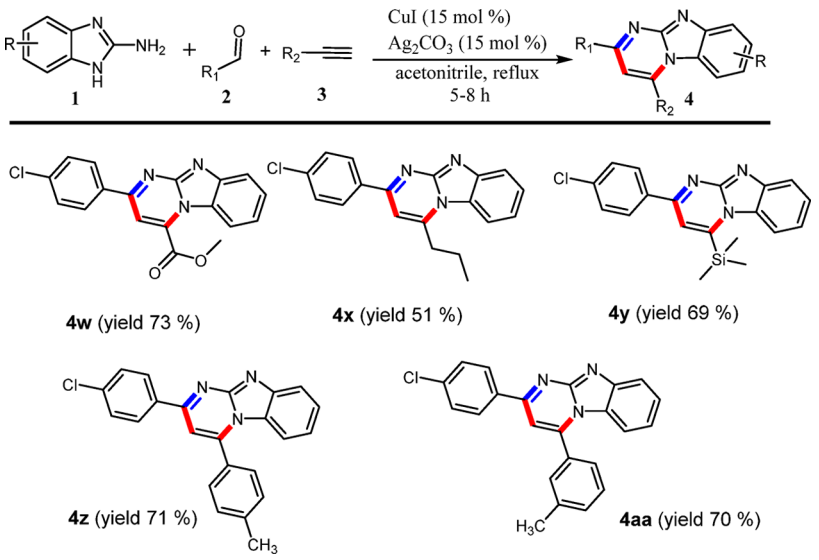
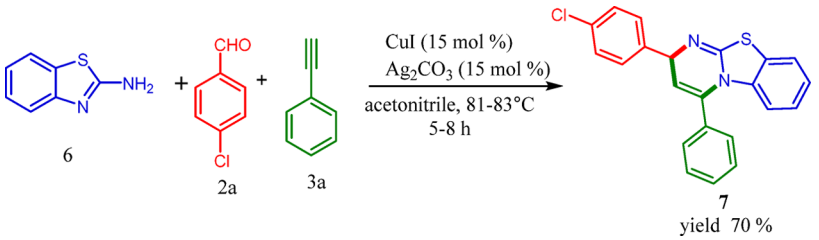


Figure 2. Synthesis of imidazopyrimidine analogues using different alkynes.

Scheme 2. Synthesis of Thiazolopyrimidine



115.3, 119.8, 122.4, 126.6, 127.8, 128.5, 129.8, 129.9, 130.9, 131.8, 132.5, 133.9, 134.4, 137.4, 139.1, 144.4, 151.6, 162.1; IR (KBr) 3428, 2920, 2853, 1010, 824, 765 cm^{-1}; ESI MS (m/z) = 390 $(M + H)^+$. Anal. Calcd for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.72; H, 3.35; N, 10.78.

2-(4-Nitrophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4c): yield 260.1 mg (71%); physical state: solid; mp =199−201 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 7.6 Hz, 2H), 7.31 (s, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.70 (br, 3H), 8.01 (d, J = 7.5 Hz, 1H), 8.47 (dd, J = 8.1, 7.9 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.3, 114.6, 116.3, 122.5, 124.8, 125.4, 129.6, 130.2, 133.4, 135.5, 138.8, 143.7, 152.5, 153.4, 160.2; IR (KBr) 3375, 2922, 2854, 1377, 1217, 767 cm^{-1}; ESI MS (m/z) = 367 $(M + H)^+$. Anal. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found: C, 72.11; H, 3.84; N, 15.31.

2-(3-Nitrophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4d): yield 263.7 mg (72%); Physical state: solid; mp =200−202 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J = 8.3 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.78−7.71 (m, 6H), 8.02 (d, J = 6.9 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1H), 8.78 (d, J = 7.2 Hz, 1H), 9.07 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.4, 100.4, 106.1, 107.4, 108.1, 111.2, 112.1, 114.0, 115.2, 115.7, 117.1, 117.8, 119.2, 123.9, 131.3, 134.4, 136.0,143.8; IR (KBr) 3415, 2924, 2852, 1371, 835, 770 cm^{-1}; ESI MS (m/z) = 367 $(M + H)^+$. Anal. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found: C, 72.11; H, 3.85; N, 15.30.

4-(4-Phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-2-yl)-benzonitrile (4e): yield 242.4 mg (70%); Physical state: solid; mp = 195−197 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.1 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.42 (s, 1H), 7.51 (br, 1H), 7.74−7.56 (m, 5H), 7.84 (d, J = 7.2 Hz, 2H), 8.01 (br, 1H), 8.42 (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.1, 113.5, 114.7, 118.3, 121.8, 126.4, 128.3, 129.5, 131.4, 132.6, 142.8, 148.2, 151.7, 160.6; IR (KBr) 3436, 2921, 2853, 2245, 1218, 822, 769 cm^{-1}; ESI MS (m/z) = 347 $(M + H)^+$. Anal. Calcd for $C_{23}H_{14}N_4$: C, 79.75; H, 4.07; N, 16.17. Found: C, 79.77; H, 4.05; N, 16.18.

2-(4-Fluorophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4f): yield 227.3 mg (67%); physical state: solid; mp = 193−195 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, J = 8.1 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 7.25−7.17 (m, 3H), 7.47 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.8 Hz, 5H), 7.97 (d, J = 8.2 Hz, 1H), 8.33 (q, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 110.2, 119.5, 120.7, 120.9, 124.4, 125.9, 130.6, 133.4, 134.2, 135.1, 135.2, 136.0, 137.3, 137.8, 154.6, 164.6; IR (KBr) 3428, 2922, 2851, 1218, 1015, 828, 766 cm^{-1}; ESI MS (m/z) = 340 $(M + H)^+$. Anal. Calcd for $C_{22}H_{14}FN_3$: C, 77.86; H, 4.16; N, 12.38. Found: C, 77.88; H, 4.13; N, 12.39.

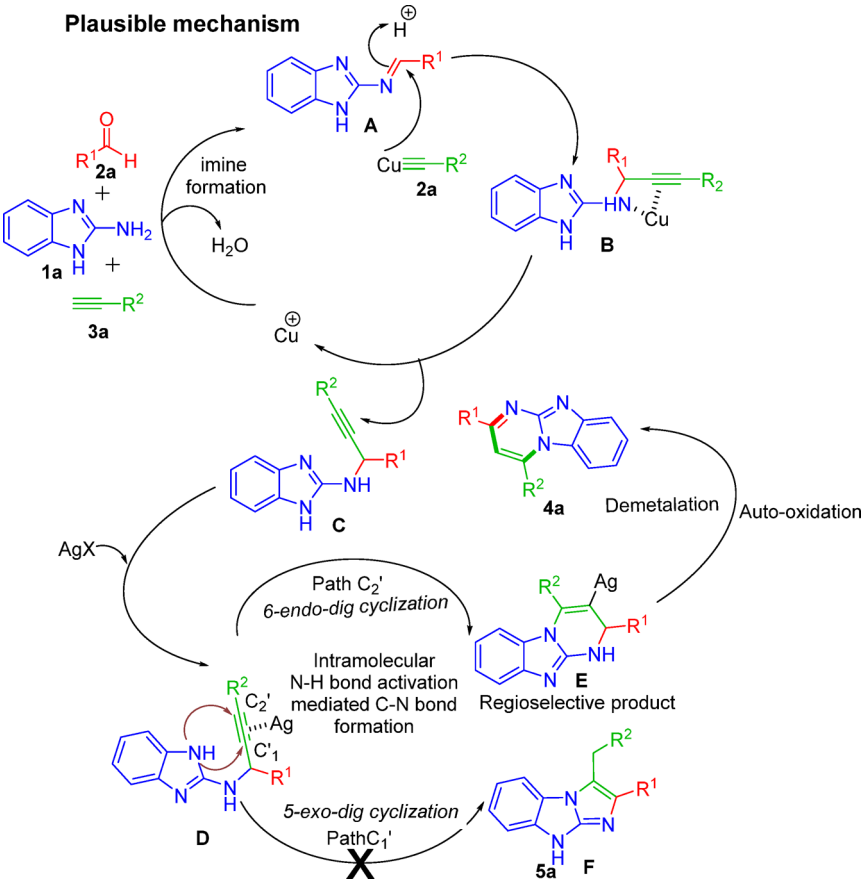
2-(4-Bromophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4g): yield 288.1 mg (72%); physical state: solid; mp = 207−209 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.65−7.57 (m, 7H), 7.90 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.6, 114.6, 116.4, 122.4, 125.4, 127.9, 128.1, 129.6, 132.2, 133.4, 135.5, 136.2, 138.4, 152.5, 153.4, 160.0; IR (KBr) 3431, 2920, 2855, 1217, 1012, 827, 768 cm^{-1}; ESI MS (m/z) = 400 $(M + H)^+$. Anal. Calcd for $C_{22}H_{14}BrN_3$: C, 66.01; H, 3.53; N, 10.50. Found: C, 65.99; H, 3.54; N, 10.51.

2-(2,6-Dichlorophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4h): yield 277.1 mg (71%); physical state: solid; mp = 206−208 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 6.9 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 7.36 (s, 1H), 7.67−7.45 (m, 8H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 104.6, 109.5, 114.8, 119.2, 120.6, 121.5, 126.2, 127.4, 128.3, 128.4, 128.9, 129.4, 129.6, 130.6, 131.2, 132.1, 134.1, 135.7, 136.7, 145.3, 149.4, 160.3; IR (KBr) 3424, 2919, 2854, 1217, 1011, 829, 771 cm^{-1}; ESI MS (m/z) = 390 $(M + H)^+$. Anal. Calcd for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.72; H, 3.34; N, 10.79.

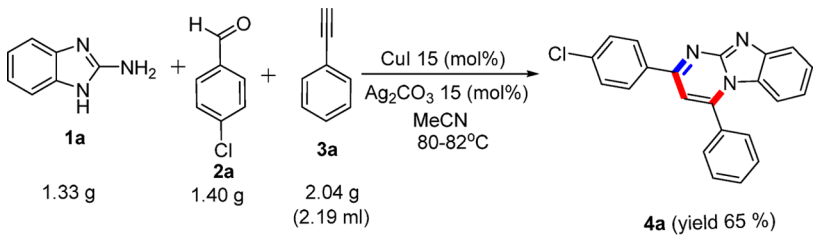
2,4-Diphenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4i): yield 224.8 mg (70%); physical state: solid; mp = 194−196 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.64 (br, 1H), 6.99 (d, J = 6.9 Hz, 1H), 7.20 (s,

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Proposed Mechanism



Scheme 4. Scale-up Synthesis of Imidazopyrimidine (4a) from 2-Aminobenzimidazole (1a), *p*-Chlorobenzaldehyde (2a), and Phenylacetylene (3a)



1H), 7.61−7.39 (m, 9H), 7.93 (br, 1H), 8.25 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.4, 114.9, 116.2, 122.5, 125.4, 128.2, 129.0, 132.6, 133.3, 135.5, 138.4, 152.1, 153.4, 160.3; ESI MS (m/z) = 322 (M + H)$^+$. Anal. Calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.19; H, 4.72; N, 13.06.

2-(2,4-Dichlorophenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4j): yield 280.9 mg (72%); physical state: solid; mp = 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 8.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.54−7.43 (m, 4H), 7.68 (br, 4H), 8.02 (dd, J = 7.9, 8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.4, 114.7, 120.4, 121.5, 126.2, 127.8, 128.3, 129.4, 130.2, 131.2, 132.2, 133.0, 136.6, 145.7, 151.5, 160.4; IR (KBr) 3427, 2924, 2850, 1009, 828, 767 cm^{-1}; ESI MS (m/z) = 390 (M + H)$^+$. Anal. Calcd for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.72; H, 3.35; N, 10.78.

2-(3,4-Dimethoxyphenyl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4k): yield 228.8 mg (60%); physical state: solid; mp = 205−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.05 (s, 3H), 6.68 (d, J = 7.4 Hz, 1H), 7.25−6.96 (m, 4H), 7.46 (s, 1H), 7.73−7.68 (m, 5H), 7.97 (d, J = 7.8 Hz, 1H), 8.14 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8, 102.1, 113.6, 114.2, 166.2, 122.5, 123.1, 125.4, 128.3, 129.6, 130.6, 133.3, 135.5, 138.8, 150.1, 151.9, 154.8, 161.0; IR (KBr) 3436, 2951, 2922, 2855, 1113, 849, 762 cm^{-1}; ESI MS (m/z) = 382 (M + H)$^+$. Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.58; H, 5.01; N, 11.04.

2-(Benzo[*d*][1,3]dioxol-5-yl)-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4l): yield 263.1 mg (72%); physical state: solid; mp = 198−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 2H), 6.58 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 7.07 (s, 1H), 7.35 (br, 1H), 7.70−7.56 (m, 6H), 7.82 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.7, 104.9, 107.8, 108.4, 114.4, 119.9, 120.9, 122.7, 125.7, 128.4, 129.3, 131.0, 132.5, 148.5, 149.0, 150.5, 160.3; IR (KBr) 3430, 2928, 2910, 2854, 1106, 834, 771 cm^{-1}; ESI MS (m/z) = 366 (M + H)$^+$. Anal. Calcd for $C_{23}H_{15}N_3O_2$: C, 75.60; H, 4.14; N, 11.50. Found: C, 75.59; H, 4.12; N, 11.52.

2-(6-Nitrobenzo[*d*][1,3]dioxol-5-yl)-4-phenylbenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4m): yield 279.1 mg (68%); physical state: solid; mp = 205−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 6.72 (s, 1H), 6.77 (s, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.28 (s, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.567 (s, 1H), 7.72−7.64 (m, 5H), 8.03

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX−XXX

(d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 105.6, 101.1, 110.5, 114.7, 120.4, 121.6, 126.1, 128.3, 129.4, 130.5, 131.3, 131.9, 142.8, 148.9, 151.7, 160.7; IR (KBr) 3429, 2930, 2915, 2855, 1109, 821, 769 cm^{-1}; ESI MS (m/z) = 411 (M + H)$^+$. Anal. Calcd for $C_{23}H_{14}N_4O_4$: C, 67.31; H, 3.44; N, 13.65. Found: C, 67.33; H, 3.42; N, 13.66.

2-Isopropyl-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4n): yield 195.4 mg (68%); physical state: solid; mp = 192−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, J = 6.2 Hz, 6H), 3.21 (br, 1H), 6.68 (s, 2H), 7.04 (t, J = 7.6 Hz, 1H), 7.44 (br, 1H), 7.68−7.62 (m, 5H), 7.96 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 37.1, 106.9, 114.4, 120.1, 120.7, 125.5, 127.8, 128.3, 128.8, 129.3, 130.9, 132.7, 148.9, 173.5; IR (KBr) 3427, 2954, 2921, 2851, 1101, 846, 766 cm^{-1}; ESI MS (m/z) = 288 (M + H)$^+$. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.42; H, 5.97; N, 14.61.

2-Isobutyl-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4o): yield 198.9 mg (66%); physical state: solid; mp = 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.4 Hz, 6H), 2.39−2.34 (m, 1H), 2.84 (d, J = 7.0 Hz, 2H), 6.69−6.63 (m, 2H), 7.04 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.68−7.61 (m, 5H), 7.98 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 28.4, 47.9, 108.9, 114.5, 120.2, 120.8, 125.6, 127.8, 128.3, 129.3, 130.9, 132.3, 144.9, 148.5, 168.4; IR (KBr) 3427, 2954, 2920, 2854, 1100, 848, 765 cm^{-1}; ESI MS (m/z) = 302 (M + H)$^+$. Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.71; H, 6.34; N, 13.92.

4-Phenyl-2-propylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (4p): yield 201.1 mg (70%); physical state: solid; mp = 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 6.9 Hz, 3H), 1.96 (q, J = 7.3 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H), 6.63 (s, 1H), 6.66 (s, 1H), 7.02 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.1 Hz, 1H), 7.66−7.59 (m, 5H), 7.95 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ13.9, 21.6, 40.8, 108.5, 114.4, 120.2, 120.8, 125.6, 127.4, 128.3, 129.3, 130.9, 132.4, 144.9, 148.6, 152.1, 168.9; IR (KBr) 3427, 2954, 2920, 2854, 1100, 848, 765 cm^{-1}; ESI MS (m/z) = 288 (M + H)$^+$. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.42; H, 5.96; N, 14.61.

2-(4-(Benzyloxy)phenyl)-4-(4-chlorophenyl)benzo[4,5]-imidazo[1,2-*a*]pyrimidine (4q): yield 332.5 mg (72%); physical state: solid; mp = 207−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 2 H), 7.06 (s, 2 H), 7.14−7.27 (m, 3 H), 7.50−7.64 (m, 7 H), 7.64−7.77 (m, 4 H), 7.77−7.90 (m, 1 H), 8.20 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.11, 109.72, 115.48, 116.18, 119.02, 120.07, 121.89, 122.74, 123.86, 126.76, 127.39, 127.49, 127.58, 127.95, 128.04, 128.57, 128.61, 128.80, 129.08, 129.44, 132.25, 134.02, 134.90, 136.51, 138.52, 141.41, 148.52, 158.87; IR (KBr) 3425, 2931, 2916, 2856, 1250, 1108, 833, 749 cm^{-1}. ESI MS (m/z) = 462 (M + H)$^+$. Anal. Calcd for $C_{29}H_{20}ClN_3O$: C, 75.40; H, 4.36; N, 9.10. Found: C, 75.42; H, 4.37; N, 9.09.

4-(4-Chlorophenyl)-8-methyl-2-phenylbenzo[4,5]imidazo-[1,2-*a*]pyrimidine (4r). The general procedure was followed using 5-methyl-1*H*-benzo[*d*]imidazol-2-amine (147.1 mg, 1.0 mmol): yield 262.5 mg (71%); physical state: solid; mp = 204−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 6.58 (s, 1 H), 6.69−6.75 (m, 1 H), 6.81 (dd, J = 8.3, 1.2 Hz, 2 H), 7.11−7.17 (m, 2 H), 7.25−7.33 (m, 3 H), 7.42−7.49 (m, 1 H), 7.57−7.71 (m, 1 H), 7.94−8.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.84, 105.56, 112.08, 114.32, 118.25, 120.09, 120.34, 121.40, 126.06, 127.25, 129.78, 129.89, 130.88, 137.41, 137.85, 145.46, 147.98, 151.93, 160.24, 160.72; IR (KBr) 3428, 2921, 2850, 1079, 760, 669 cm^{-1}; ESI MS (m/z) = 370 (M + H)$^+$. Anal. Calcd for $C_{23}H_{16}ClN_3$: C, 74.69; H, 4.36; N, 11.36. Found: C, 74.71; H, 4.34; N, 11.37.

2,4-Bis(4-chlorophenyl)-8-methylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4s). The general procedure was followed using 5-methyl-1*H*-benzo[d]imidazol-2-amine (147.1 mg, 1.0 mmol): yield 278.9 mg (69%); physical state: solid; mp = 203−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 6.50−6.67 (m, 1 H), 6.69−6.83 (m, 2 H), 6.93−7.19 (m, 4 H), 7.27−7.37 (m, 3 H), 7.61−7.71 (m, 1 H), 7.94−8.04 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.88, 105.66, 114.37, 120.22, 121.52, 126.20, 127.21, 127.81, 129.05, 129.84, 130.80, 131.50, 136.42, 137.51, 145.25, 148.21, 151.94, 161.28; IR (KBr) 3430, 2923, 2854, 1091, 844, 758 cm^{-1}; ESI MS (m/z) = 405 (M + H)$^+$. Anal. Calcd for $C_{23}H_{15}Cl_2N_3$: C, 68.33; H, 3.74; N, 10.39. Found: C, 68.35; H, 3.71; N, 10.40.

4-(4-Chlorophenyl)-2-(3-methoxyphenyl)-8-methylbenzo-[4,5]imidazo[1,2-*a*]pyrimidine (4t). The general procedure was followed using 5-methyl-1*H*-benzo[d]imidazol-2-amine (147.1 mg, 1.0 mmol): yield 287.9 mg (72%); physical state: solid; mp = 205−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.95 (s, 3 H), 6.66 (d, J = 8.5 Hz, 1 H), 6.90−6.95 (m, 1 H), 7.10 (ddd, J = 8.2, 2.6, 0.7 Hz, 1 H), 7.19−7.23 (m, 1 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.61−7.66 (m, 2 H), 7.66−7.70 (m, 2 H), 7.74−7.77 (m, 2 H), 7.98−8.02 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.85, 55.58, 105.30, 112.02, 113.83, 118.17, 119.89, 120.04, 123.13, 125.30, 127.82, 129.64, 129.75, 129.87, 130.98, 136.31, 137.34, 137.98, 145.87, 147.70, 152.06, 160.25, 160.29; IR (KBr) 3429, 2923, 2854, 1384, 1217, 1067, 770 cm^{-1}; ESI MS (m/z) = 400 (M + H)$^+$. Anal. Calcd for $C_{24}H_{18}ClN_3O$: C, 72.09; H, 4.54; N, 10.51. Found: C, 72.07; H, 4.55; N, 10.52.

8-Chloro-4-(4-chlorophenyl)-2-phenylbenzo[4,5]imidazo-[1,2-*a*]pyrimidine (4u). The general procedure was followed using 5-chloro-1*H*-benzo[d]imidazol-2-amine (167.5 mg, 1.0 mmol): yield 264.5 mg (68%); physical state: solid; mp = 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.9, 2.0 Hz, 1 H), 7.45−7.53 (m, 1 H), 7.61−7.65 (m, 3 H), 7.68 (d, J = 1.0 Hz, 1 H), 7.81−7.88 (m, 3 H), 7.92−7.98 (m, 2 H), 8.43−8.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.07, 114.29, 115.99, 116.20, 120.42, 121.48, 126.14, 127.24, 129.83, 129.91, 130.00, 130.83, 132.68, 137.51, 145.51, 148.23, 151.88, 159.84, 163.72; IR (KBr) 3423, 2955, 2915, 1215, 1103, 929, 758, 669 cm^{-1}; ESI MS (m/z) = 391 (M + H)$^+$. Anal. Calcd for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.72; H, 3.35; N, 10.78.

8-Chloro-2,4-bis(4-chlorophenyl)benzo[4,5]imidazo[1,2-*a*]-pyrimidine (4v). The general procedure was followed using 5-chloro-1*H*-benzo[d]imidazol-2-amine (167.5 mg, 1.0 mmol): yield 297.2 mg (70%); physical state: solid; mp = 203−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J = 8.9, 2.0 Hz, 1 H), 7.17−7.24 (m, 4 H), 7.62−7.66 (m, 2 H), 7.68−7.74 (m, 2 H), 7.81−7.88 (m, 1 H), 8.24−8.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.54, 116.05, 116.27, 119.66, 121.05, 122.01, 126.91, 129.72, 129.77, 129.99, 130.17, 130.35, 131.94, 132.30, 137.80, 137.92, 143.68, 146.00, 148.18, 152.49, 160.39; IR (KBr) 3429, 2956, 2919, 1158, 1064, 757, 669 cm^{-1}; ESI MS (m/z) = 425 (M + H)$^+$. Anal. Calcd for $C_{22}H_{12}Cl_3N_3$: C, 62.22; H, 2.85; N, 9.89. Found: C, 62.21; H, 2.84; N, 9.91.

Methyl 2-(4-chlorophenyl)benzo[4,5]imidazo[1,2-*a*]-pyrimidine-4-carboxylate (4w): yield 246.5 mg (73%); physical state: solid; mp = 192−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.39 (br, 2H), 7.52 (d, J = 7.1 Hz, 2H), 7.75 (dd, J = 5.2, 5.4, Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 9.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 105.6, 112.2, 120.3, 124.4, 124.7, 129.4, 131.4, 132.8, 133.4, 136.2, 139.8, 142.4, 154.7, 165.6, 167.4; IR (KBr) 3436, 2923, 2856, 1730, 1310, 821, 770 cm^{-1}; ESI MS (m/z) = 338 (M + H)$^+$. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44. Found: C, 64.04; H, 3.56; N, 12.45.

2-(4-Chlorophenyl)-4-propylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4x): yield 164.1 mg (51%); physical state: solid; mp = 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.52−1.62 (m, 2H), 2.82 (t, J = 7.6, Hz, 2H), 7.04−7.20 (m, 2 H) 7.20−7.30 (m, 1 H) 7.30−7.47 (m, 3 H) 7.96 (d, J = 7.7 Hz, 2 H) 8.16 (dd, J = 7.8, 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02, 24.84, 36.47, 109.82, 112.65, 123.89, 128.39, 128.81, 128.92, 129.59, 130.37, 131.56, 133.27, 135.39, 136.31, 142.41, 149.72, 157.98; IR (KBr) 3428, 2953, 2921, 2853, 1100, 849, 764 cm^{-1}; ESI MS (m/z) = 322 (M + H)$^+$. Anal. Calcd for $C_{19}H_{16}ClN_3$: C, 70.91; H, 5.01; N, 13.06. Found: C, 70.92; H, 4.99; N, 13.08.

2-(4-Chlorophenyl)-4-(trimethylsilyl)benzo[4,5]imidazo[1,2-*a*]pyrimidine (4y): yield 242.8 mg (69%); physical state: solid; mp = 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.23 (s, 9H), 7.18−7.16 (m, 2H), 7.51 (d, J = 8.2 Hz, 3H), 7.79 (s, 1H), 7.97 (d, J = 8.3 Hz, 2H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.7, 124.3, 127.3, 134.5, 134.6, 136.2, 136.3, 139.2, 140.1, 142.6, 143.7, 144.6, 160.6, 169.3, 197.3; IR (KBr) 3422, 2910, 2849, 1006, 826, 759 cm^{-1}; ESI MS (m/z) = 352 (M + H)$^+$. Anal. Calcd for

dx.doi.org/10.1021/jo5007762 | J. Org. Chem. XXXX, XXX, XXX−XXX

$C_{19}H_{18}ClN_3Si$: C, 64.85; H, 5.16; N, 11.94. Found: C, 64.86; H, 5.14; N, 11.96.

2-(4-Chlorophenyl)-4-*p*-tolylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4z): yield 262.5 mg (71%); physical state: solid; mp = 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 6.80 (d, J = 8.1 Hz, 1H), 7.08 (t, J = 7.9 Hz, 1H), 7.19 (s, 1H), 7.55−7.47 (m, 7H), 7.98 (d, J = 7.2 Hz, 1H), 8.26 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 104.8, 114.5, 119.2, 120.8, 125.5, 127.8, 128.6, 128.8, 129.6, 141.0, 148.9, 151.7, 160.7; IR (KBr) 3437, 2920, 2853, 1012, 820, 761 cm^{-1}; ESI MS (m/z) = 370 (M + H)$^+$. Anal. Calcd for $C_{23}H_{16}ClN_3$: C, 74.69; H, 4.36; N, 11.36. Found: C, 74.71; H, 4.33; N, 11.37.

2-(4-Chlorophenyl)-4-*m*-tolylbenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4aa): yield 258.8 mg (70%); physical state: solid; mp = 201−203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3H), 6.75 (br, 1H), 7.03 (s, 1H), 7.24 (br, 2H), 7.50−7.43 (m, 6H), 7.99 (br, 1H), 8.24 (br, 2H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6) δ 26.2, 109.9, 119.6, 124.4, 126.1, 130.2, 130.7, 133.6, 133.9, 134.1, 136.9, 140.1, 141.9, 144.1, 154.9, 164.4; IR (KBr) 3440, 2919, 2855, 1009, 821, 765 cm^{-1}; ESI MS (m/z) = 370 (M + H)$^+$. Anal. Calcd for $C_{23}H_{16}ClN_3$: C, 74.69; H, 4.36; N, 11.36. Found: C, 74.70; H, 4.35; N, 11.34.

2-(4-Chlorophenyl)-4-phenyl-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidine (7): yield 262.4 mg (70%); physical state: solid; mp = 203−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, J = 4.1 Hz, 1H), 6.03 (d, J = 4.1 Hz, 1H), 6.62 (d, J = 7.4 Hz, 1H), 7.01 (q, J = 7.2 Hz, 2H) 7.22−7.17 (m, 8H), 7.61 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 59.6, 104.4, 111.8, 121.7, 123.0, 123.2, 126.1, 127.0, 128.2, 128.3, 129.3, 133.7, 136.4, 138.6, 139.5, 141.7, 161.1; IR (KBr) 3439, 2928, 2855, 1112, 845, 773 cm^{-1}; ESI MS (m/z) = 375 (M + H)$^+$. Anal. Calcd for $C_{22}H_{15}ClN_2S$: C, 70.48; H, 4.03 N, 7.47. Found: C, 70.50; H, 4.01 N, 7.46.

***N*-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)-1*H*-benzo-[d]imidazol-2-amine (C).** The reaction using 2-aminobenzimidazole (**1a**) (133.1 mg, 1.0 mmol), 4-chlorobenzaldehyde (**2a**) (140 mg, 1.0 mmol), and phenylacetylene (**3a**) (0.220 mL, 2.0 mmol) in the presence of only CuI (15 mol %) in acetonitrile was subjected to refluxing temperature (81−83 °C) afforded intermediate **C**: yield 75.14 mg (21%); physical state: gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (br, 1H), 5.49 (s, 1 H), 6.98−7.03 (m, 2 H), 7.04−7.08 (m, 3 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.62−7.65 (m, 2 H), 7.84 (s, 1 H), 7.82 (s, 1 H), 8.17−8.20 (m, 2 H), 8.44 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.64, 84.54, 88.92, 112.12, 120.64, 121.57, 123.61, 128.04, 129.23, 129.34, 129.85, 129.93, 130.60, 132.02, 133.34, 136.11, 136.86, 137.40, 139.53, 139.56, 140.24, 148.12; IR (KBr) 3479, 3403, 3050, 2941, 1615, 784, 692 cm^{-1}; ESI MS (m/z) = 358 (M + H)$^+$. Anal. Calcd for $C_{22}H_{16}ClN_3$: C, 73.84; H, 4.51; N, 11.74. Found: C, 73.82; H, 4.52; N, 11.75.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization of reaction conditions, copies of ^{1}H and ^{13}C NMR spectra for all compounds, and X-ray crystallographic data for compound **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dratulsax@gmail.com.Fax: (+) 91-5222623405. Tel: 91-522-2612411.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.K. and S.M. are thankful to CSIR-UGC for financial support. We thank the SAIF division, CDRI, for providing the spectroscopic and analytical data and Dr. Ranjana S. Khanna for the X-ray data. We acknowledge CSIR Network Project BSC0108 for financial support. CDRI communication no. 8737.

■ REFERENCES

(1) (a) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discovery* **2007**, *6*, 881. (b) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473.

(2) (a) Kaminski, J. J.; Wallmark, B.; Briving, C.; Andersson, B. M. *J. Med. Chem.* **1991**, *34*, 533. (b) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. (c) Margiotta, N.; Ostuni, R.; Ranaldo, R.; Denora, N.; Laquintana, V.; Trapani, G.; Liso, G.; Natile, G. *J. Med. Chem.* **2007**, *50*, 1019. (d) Veron, J. B.; Allouchi, H.; Enguehard Gueiffier, C.; Snoeck, R.; De Clercq, G. A. E.; Gueiffier, A. *Bioorg. Med. Chem.* **2008**, *16*, 9536.

(3) (a) George, P. G.; Rossey, G.; Sevrin, M.; Arbilla, S.; Depoortere, H.; Wick, A. E. *L. E. R. S. Monogr. Ser.* **1993**, *8*, 49. (b) Berson, A.; Descatoire, V.; Sutton, A.; Fau, D.; Maulny, B.; Vadrot, N.; Feldmann, G.; Berthon, B.; Tordjmann, T.; Pessayre, D. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 793. (c) Saletu, J.; Grunberger, B.; Linzmayer, L. *Int. Clin. Psychopharmacol.* **1986**, *1*, 145.

(4) (a) Harrison, T. S.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65. (b) Hanson, S. M.; Morlock, E. V.; Satyshur, K. A.; Czajkowski, C. *J. Med. Chem.* **2008**, *51*, 7243. (c) Monti, J. M.; Warren, S. D.; Pandi-Perumal, S. R.; Langer, S. Z.; Hardeland, R. *Clin. Med. Ther.* **2009**, *1*, 123.

(5) (a) Boerner, R. J.; M?ller, H. J. *Psychopharmakother.* **1997**, *4*, 145. (b) Sanger, D. J. *Behav. Pharmacol.* **1995**, *6*, 116.

(6) (a) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.

(7) (a) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060. (b) Clements-Jewery, S.; Danswan, G.; Gardner, C. R.; Matharu, S. S.; Murdoch, R.; Tully, W. R.; Westwood, W. *J. Med. Chem.* **1988**, *31*, 1220.

(8) (a) Gudmundsson, K. S.; Johns, B. A. *Org. Lett.* **2003**, *5*, 1369. (b) Denora, N.; Laquintana, V.; Pisu, M. G.; Dore, R.; Murru, L.; Latrofa, A.; Trapani, G.; Sanna, E. *J. Med. Chem.* **2008**, *51*, 6876. (c) Trapani, G.; Laquintana, V.; Denora, N.; Trapani, A.; Lopedota, A.; Latrofa, A.; Franco, M.; Serra, M.; Pisu, M. G.; Floris, I.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **2005**, *48*, 292. (d) Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, D. P.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **2005**, *70*, 6034. (e) Al-Tel, T. H.; Al-Qawasmeh, R. A.; Voelter, W. *Eur. J. Org. Chem.* **2010**, 5586.

(9) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323.

(10) (a) Chernyak, N.; Gevorgyan, V. *Angew. Chem.* **2010**, *122*, 2803. (b) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743. (c) Chernyak, D.; Chernyak, N.; Gevorgyana, V. *Adv. Synth. Catal.* **2010**, *352*, 961.

(11) Zhang, Q.; Cheng, M.; Hu, X.; Li, B.-G.; Ji, J.-X. *J. Am. Chem. Soc.* **2010**, *132*, 7256.

(12) Guchhait, S. K.; Chandgude, A. L.; Priyadarshani, G. *J. Org. Chem.* **2012**, *77*, 4438.

(13) (a) Moraski, G. C.; Markley, L. D.; Hipskind, P. A.; Boshoff, H.; Cho, S.; Franzblau, S. G.; Miller, M. J. *ACS Med. Chem. Lett.* **2011**, *2*, 466. (b) Blackaby, W. P.; Atack, J. R.; Bromidge, F.; Castro, J. L.; Goodacre, S. C.; Hallett, D. J.; Lewis, R. T.; Marshall, G. R.; Pike, A.; Smith, A. J.; Street, L. J.; Tattersall, D. F. D.; Wafford, K. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1175. (c) Almansa, C.; De Arriba, A. F.; Cavalcanti, F. L.; Gómez, L. A.; Miralles, A.; Merlos, M.; Garcýa-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350.

(14) (a) Kumar, A.; Gupta, G.; Srivastava, S. *Org. Lett.* **2011**, *13*, 6366. (b) Kumar, A.; Gupta, M. K.; Kumar, M. *Green Chem.* **2012**, *14*, 290. (c) Kumar, A.; Gupta, L. P.; Kumar, M. *RSC Adv.* **2013**, *3*, 18771. (d) Kumar, A.; Kumar, M.; Gupta, L. P.; Gupta, M. K. *RSC Adv.* **2014**, *4*, 9412.

(15) (a) Gilmore, K., IV. *Chem. Rev.* **2011**, *111*, 6513. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (c) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2005**, *7*, 3299.