JOC The Journal of Organic Chemistry

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CuI-Catalyzed C−N Bond Formation and Cleavage for the Synthesis of Benzimidazo[1,2-*a*]quinazoline Derivatives

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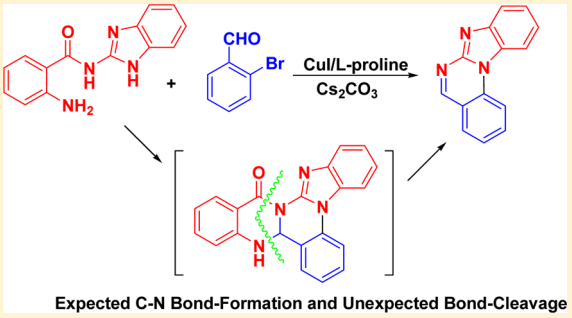
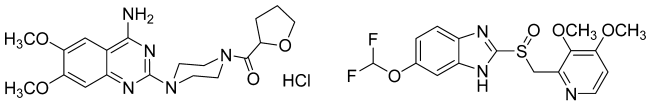
Supporting Information

ABSTRACT: A copper(I)-catalyzed domino reaction of *N*-(2-benzimidazolyl)-2-aminobenzamide and 2-halogenated benzaldehyde has been studied. The procedure is based on a sequential CuI-catalyzed Ullmann reaction (C−N bond formation) and two bond cleavage reactions and provides an efficient strategy for the synthesis of benzimidazo[1,2-*a*]quinazolines catalyzed by CuI/L-proline.



Quinazolines are an important class of heterocyclic compounds which have attracted considerable attention due to their diverse anticancer activities.[1] A well-known example is terazosin (Figure 1, left), which is an α-1-selective



Terazosin Pantoprazole

Figure 1. Drugs containing quinazoline or benzimidazole.

adrenoceptor blocking agent and is able to reduce a bladder outlet obstruction without affecting bladder contractility.[2] Therefore, it is a very good drug on the market used for the treatment of symptomatic benign prostatic hyperplasia in recent years.

In addition, benzimidazoles are also useful heterocyclic molecules, and the potential therapeutic applications of their derivatives include antimicrobial,[3] antitumor,[4] and antibacterial activities.[5] They are also used as inhibitors of PI3-kinase[6] and the potent antistaphylococcal agents with dual inhibitory mechanisms against DNA gyrase.[7] The most noteworthy is pantoprazole (Figure 1, right), and it is used for short-term treatment of erosion and ulceration of the esophagus caused by gastroesophageal reflux disease.[8]

The benzimidazoquinazoline moiety contains both quinazoline and benzimidazole heterocyclic skeletons, and it has been reported that its derivatives are potent immunosuppressors in doses as low as 0.1 mg/kg.[9] They have also recently been found to present promising antitumor activity serving to intercalate DNA, thereby effectively truncating proliferation of human tumor cell lines.[10] Therefore, much attention has been devoted to the syntheses of these potentially active fused heterocycles.[11] However, it should be noted that they are usually benzimidazo[2,1-*b*]quinazoline, benzimidazo[1,2-*c*]quinazoline, or benzimidazo[1,2-*b*]quinazoline but seldomly benzimidazo[1,2-*a*]quinazoline.[12]

It is well-known that transition metals, such as Cu, Fe, and Pd, are efficient catalysts to promote the C−N bond formation[13] (Ullmann reaction) and C−N bond cleavage.[14] We previously reported that CuBr could catalyze the Ullmann-type reaction of 2-amino-*N*′-arylbenzohydrazide and *o*-halogenated benzaldehyde to synthesize 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-ones in high yields.[15] Therefore, in order to obtain the desired fused heterocyle of 5*H*-benzo[4,5]-imidazo[1,2-*a*] quinazolino[3,2-*c*]quinazolin-17(5a*H*)-one, the reaction of *N*-(2-benzimidazolyl)-2-aminobenzamide **1a** and 2-bromobenzaldehyde **2a** was carried out in the presence of CuI/L-proline (Scheme 1). However, to our surprise, it unexpectedly gave benzimidazo[1,2-*a*]quinazoline **3a** with two C−N bond-cleavage reactions. Herein, we report the synthesis of benzimidazo[1,2-*a*]quinazoline derivatives via a Ullmann-type *N*-arylation reaction catalyzed by CuI/L-proline.

The reaction of *N*-(2-benzimidazolyl)-2-aminobenzamide **1a** with 2-bromobenzaldehyde **2a** was used as a model reaction to optimize reaction conditions (Scheme 1), and the results are summarized in Table 1. Initially, the reaction in toluene in the presence of CuCl (5 mol %) and K_2CO_3 (2 equiv) could afford the desired product **3a** in 51% yield. Adding the ligand of L-proline (10 mol %), the yield increased to 62%. Further investigation of various catalysts, CuI was found to be more effective than other Cu(I) species, and the reaction yield increased to 66% when CuI was employed (entries 2−4).

Received: March 31, 2014

dx.doi.org/10.1021/jo5007398 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. Model Reaction

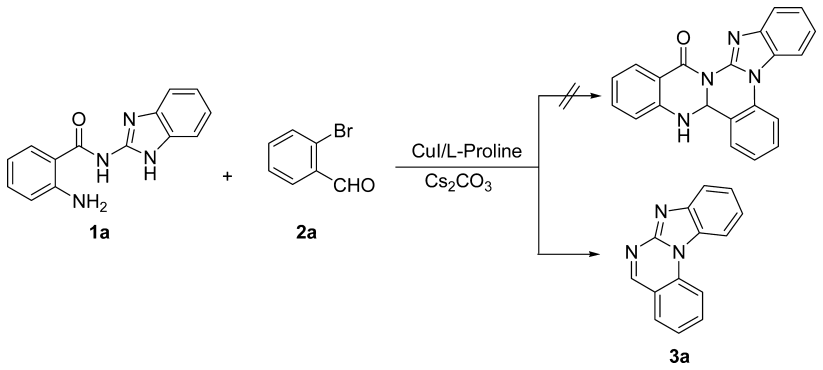


Table 1. Synthesis of 3a under Different Reaction Conditions[a]

entry	catalyst	solvent	ligand	base	yield[b] (%)
1	CuCl	toluene[c]		K_2CO_3	51
2	CuCl	toluene[c]	L-proline	K_2CO_3	62
3	CuBr	toluene[c]	L-proline	K_2CO_3	60
4	CuI	toluene[c]	L-proline	K_2CO_3	66
5	CuI	toluene[c]	L-proline	Na_2CO_3	56
6	CuI	toluene[c]	L-proline	$NaHCO_3$[d]	47
7	CuI	toluene[c]	L-proline	Et_3N	58
8	CuI	toluene[c]	L-proline	Cs_2CO_3	71
9	CuI	CH_3CN	L-proline	Cs_2CO_3	65
10	CuI	THF	L-proline	Cs_2CO_3	67
11	CuI	DMF[c]	L-proline	Cs_2CO_3	63
12	CuI	benzene	L-proline	Cs_2CO_3	64
13	CuI	dioxane	L-proline	Cs_2CO_3	76
14	CuI	dioxane	PPh_3	Cs_2CO_3	52
15	CuI	dioxane	$Me_2NCH_2CO_2H$	Cs_2CO_3	65

[a]Reagents and conditions: **1a** (0.252 g, 1.0 mmol), **2a** (0.185 g, 1.0 mmol), solvent (10 mL), base (2.0 mmol), catalyst (5 mol %), ligand (10 mol %), reflux. [b]Isolated yields. [c]100 °C. [d]$NaHCO_3$ (4 mmol).

Several bases such as Na_2CO_3, $NaHCO_3$, Et_3N, and Cs_2CO_3 were examined, and Cs_2CO_3 was found to give the best result (entries 4−8). Subsequently, different solvents including THF, CH_3CN, DMF, benzene, and dioxane were also evaluated, and a 76% yield was obtained when dioxane was used as a solvent (entry 13). In addition, lower yields were observed if other ligands were loaded (entries 14 and 15).

With these optimized conditions in hand, we surveyed the substrate scope of *N*-(2-benzimidazolyl)-2-aminobenzamides and *o*-halogenated benzaldehydes (Scheme 2, Table 2, entries 1−15). It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in the benzaldehydes. In all cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding products (**3a**−**m**) in good yields. The benzo[4,5]imidazo[1,2-*a*]thieno[2,3-*e*]pyrimidine **3n** was obtained when 3-bromothiophene-2-carbaldehyde was used as a reactant (Table 2, entry 16). All of the products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS, and the structure of **3a** was confirmed by X-ray diffraction analysis.

Scheme 2. Synthetic Route of 3

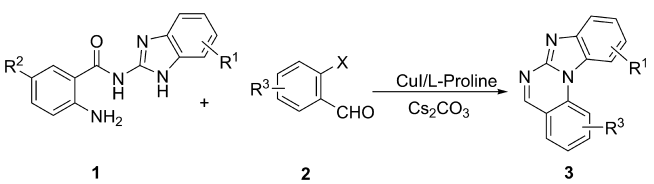


Table 2. Synthetic Results for the Products 3[a]

entry	X	R^1	R^2	R^3	products	time (h)	yield[b] (%)
1	Br	H	H	H	**3a**	18	76[c]
2	Br	H	CH_3	H		16	81[c]
3	Br	H	Cl	H		18	74[c]
4	Br	H	H	2-Cl	**3b**	16	78
5	Br	H	H	3-Cl	**3c**	20	80
6	F	H	H	4-Cl	**3d**	16	68
7	Br	H	H	2-F	**3e**	16	79
8	Br	H	H	3-F	**3f**	14	82
9	Br	H	H	4-F	**3g**	16	81
10	Br	H	H	3-OCH_3	**3h**	26	72
11	Cl	H	H	3-CF_3	**3i**	14	75
12	Br	H	H	2,3-$(OCH_3)_2$	**3j**	20	76
13	Br	H	H	2,3-OCH_2O	**3k**	24	67
14	Br	9,10-Me_2	H	H	**3l**	24	66
15	Br	9,10-Me_2	H	2-Cl	**3m**	19	75
16	Br	H	H	2-thienyl[d]	**3n**	20	82

[a]Reagents and conditions: **1** (1.0 mmol), CuI (10 mg, 0.05 mmol), L-proline (12 mg, 0.1 mmol), Cs_2CO_3 (652 mg, 2.0 mmol), dioxane (10 mL). [b]Isolated yields. [c]The corresponding 2-aminobenzoic acids were isolated in 56%, 62%, and 52% yields, respectively. [d]3-Bromothiophene-2-carbaldehyde was used as *o*-halogenated benzaldehyde.

We propose that four subsequent steps are involved in the formation of **3**, namely cyclization to dihydroquinazolinone **4** catalyzed by CuI, Ullmann reaction to 5*H*-benzo[4,5]imidazo[1,2-*a*]quinazolino[3,2-*c*]quinazolin-17(5*aH*)-one **5** in the presence of CuI/L-proline, and then cleavage of amide bond (Cs_2CO_3 and H_2O) in **5** occurs along with the ring-opening to **6**. At last, **6** takes place the second C−N bond-cleavage reaction in the presence of base (Cs_2CO_3) to give final product **3**. The key step is the C−N coupling in Ullmann reaction catalyzed by CuI/L-proline, and using L-proline as a ligand for copper(I) has been well reported by Zhao and Ma' groups.[16] The plausible reaction mechanism is outlined in Scheme 3.

In order to get more insight into the mechanism, the model reaction of **1a** and **2a** was treated with CuI in the absence of Cs_2CO_3, and the reaction formed the compound **4** in 86% yield at reflux (Scheme 4).

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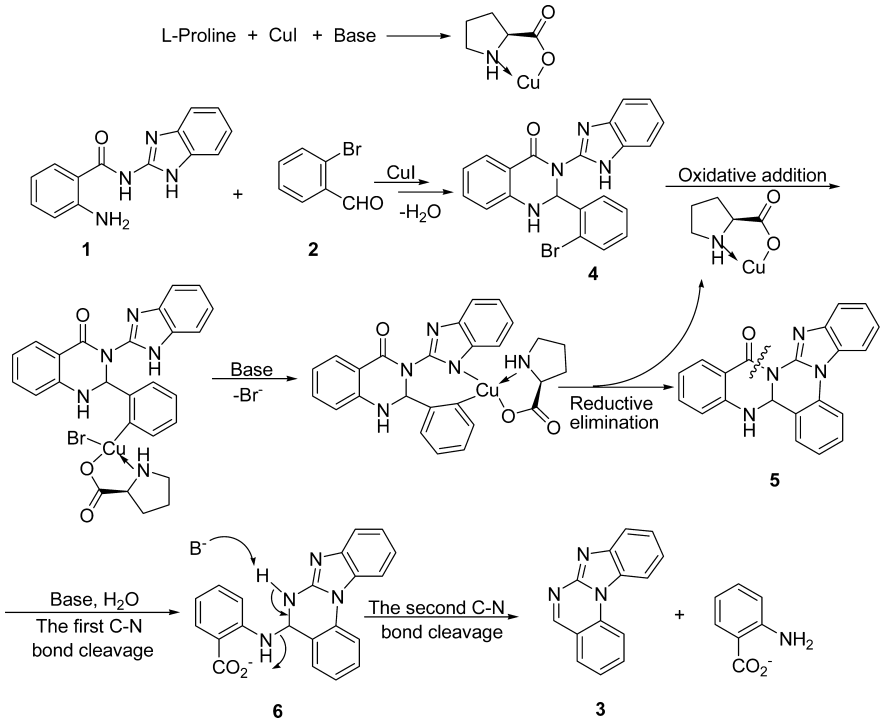
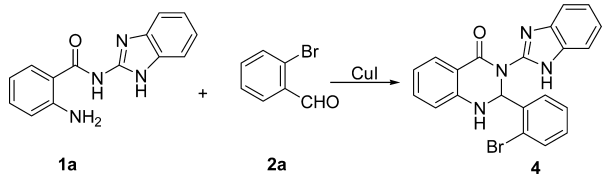
Scheme 3. Possible Reaction Mechanism



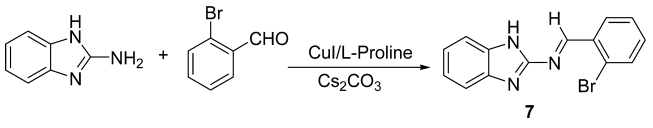
Scheme 4. Model Reaction in the Absence of Cs_2CO_3



In addition, the 2-aminobenzoic acid was isolated in 56% yield from the residue of the reaction. These data all supported the proposed four-step mechanism.

In our continued study, the Cu-catalyzed control experiment between 1*H*-benzo[*d*]imidazol-2-amine and 2-bromobenzaldehyde was tested at the same reaction. However, the desired product of **3a** was not detected by TLC with (*E*)-*N*-(2-bromobenzylidene)-1*H*-benzo[*d*]imidazol-2-amine **7** being obtained as the main product in 53% yield (Scheme 5); perhaps

Scheme 5. Control Experiment



the (*E*)-configuration prevented the further Ullmann reaction. This result indicated that this C−N bond cleavage reaction was a good and efficient method toward the synthesis of benzimidazo[1,2-*a*]quinazolines, in which the simple materials were hard to realize.

CONCLUSION

In conclusion, we found a novel and efficient method for the synthesis of benzimidazo[1,2-*a*]quinazoline derivatives using CuI/L-proline as a catalyst. The interesting reaction includes a sequential CuI-catalyzed Ullmann *N*-arylation (C−N bond formation) and two C−N bond-cleavage reactions.

EXPERIMENTAL SECTION

General Procedure for the Syntheses of Benzimidazo[1,2-*a*]quinazoline Derivatives 3. *N*-(2-Benzimidazolyl)-2-aminobenzamide (1.0 mmol), *o*-halogenated benzaldehyde (1.0 mmol), L-proline (12 mg, 0.1 mmol), CuI (10 mg, 0.05 mmol), Cs_2CO_3 (2.0 mmol, 652 mg), and dioxane (10 mL) were added into a 25 mL flask. The reaction mixture was stirred at reflux for 14−24 h before reaching completion, which was monitored by TLC. The product **3** was purified by column chromatography using ethyl acetate and petroleum ether (1:1) as eluent.

*Benzo[4,5]imidazo[1,2-a]quinazoline (**3a**).* Yield: 76% (166 mg). Pale yellow solid. Mp: 228−230 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.53−7.59 (m, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.97 (dd, J = 7.2 Hz, J' = 2.0 Hz, 1H), 8.06−8.10 (m, 1H), 8.28 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H), 8.64−8.66 (m, 1H), 8.76 (d, J = 8.8 Hz, 1H), 9.36 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 115.1, 115.6, 118.6, 120.5, 123.7, 125.1, 125.4, 129.1, 130.8, 135.7, 137.2, 143.5, 150.2, 159.7. IR (KBr): ν 3072, 3046, 3017, 1608, 1551, 1521, 1483, 1471, 1451, 1393, 1341, 1327, 1258, 1245, 1226, 1197, 1155, 1129, 1050, 1016, 953, 839, 765, 746, 703 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_{10}N_3$ [M + H]$^+$ 220.0875, found 220.0876.

*2-Chlorobenzo[4,5]imidazo[1,2-a]quinazoline (**3b**).* Yield: 78% (197 mg). Pale yellow solid. Mp: 241−242 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.55−7.63 (m, 2H), 7.78 (dd, J = 8.4 Hz, J'= 2.0 Hz, 1H), 7.98 (dd, J = 7.2 Hz, J'= 2.0 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.72−8.74 (m, 2H), 9.38 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 115.1, 115.2, 117.4, 120.6, 124.0, 125.4, 125.8, 129.0, 132.5, 138.0, 140.4, 143.6, 150.1, 159.0. IR (KBr): ν 3070, 3037, 2978, 2924, 1611, 1591, 1528, 1481, 1454, 1423, 1397, 1337, 1310, 1275, 1254, 1221, 1184, 1087, 1041, 1010, 957, 842, 819, 762, 726 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_8ClN_3Na$ [M + Na]$^+$ 276.0304, found 276.0299.

*3-Chlorobenzo[4,5]imidazo[1,2-a]quinazoline (**3c**).* Yield: 80% (202 mg). Pale yellow solid. Mp: 225−227 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.56−7.62 (m, 2H), 7.99 (d, J = 8.0 Hz, 1H), 8.08 (dd, J = 8.8 Hz, J'= 1.6 Hz, 1H), 8.45 (d, J = 1.6 Hz, 1H), 8.64 (d, J =

dx.doi.org/10.1021/jo5007398 | J. Org. Chem. XXXX, XXX, XXX−XXX

7.6 Hz, 1H), 8.81 (d, J = 9.2 Hz, 1H), 9.35 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 115.1, 117.8, 119.8, 120.7, 124.0, 125.3, 129.0, 129.1, 129.8, 135.1, 135.9, 143.5, 149.9, 158.6. IR (KBr): ν 3069, 3059, 3023, 2948, 1653, 1634, 1622, 1606, 1590, 1544, 1530, 1455, 1417, 1375, 1327, 1257, 1243, 1208, 1197, 1084, 1008, 955, 832, 821, 815, 762, 732 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_8ClN_3Na$ [M + Na]$^+$ 276.0304, found 276.0294.

*4-Chlorobenzo[4,5]imidazo[1,2-a]quinazoline (**3d**).* Yield: 68% (172 mg). Pale yellow solid. Mp: 266−267 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.58−7.65 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 8.02 (dd, J = 7.2 Hz, J'= 2.0 Hz, 1H), 8.06−8.10 (m, 1H), 8.02 (dd, J = 7.2 Hz, J'= 2.0 Hz, 1H), 8.82 (d, J = 8.4 Hz, 1H), 9.57 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 115.2, 115.4, 115.7, 120.8, 124.1, 125.5, 126.1, 129.1, 134.0, 136.2, 138.8, 143.8, 149.9, 155.1. IR (KBr): ν 3100, 3068, 3052, 3033, 1599, 1585, 1547, 1526, 1482, 1447, 1393, 1337, 1303, 1263, 1213, 1192, 1158, 1012, 973, 883, 841, 783, 760, 742 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_8ClN_3Na$ [M + Na]$^+$ 276.0304, found 276.0298.

*2-Fluorobenzo[4,5]imidazo[1,2-a]quinazoline (**3e**).* Yield: 79% (187 mg). Pale yellow solid. Mp: 272−275 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.52−7.60 (m, 3H), 7.95 (d, J = 7.6 Hz, 1H), 8.39 (dd, J = 8.4 Hz, J' = 6.4 Hz, 1H), 8.53 (d, J = 9.2 Hz, 1H), 8.69 (d, J = 8.0 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 102.7 (d, J_{F-C} = 27.2 Hz), 113.7 (d, J_{F-C} = 23.3 Hz), 115.1, 115.8 (d, J_{F-C} = 1.9 Hz), 120.5, 123.8, 125.3, 129.0, 133.9 (d, J_{F-C} = 11.3 Hz), 138.7 (d, J_{F-C} = 12.7 Hz), 143.6, 150.1, 158.9, 166.2 (d, J_{F-C} = 252.5 Hz). IR (KBr): ν 3099, 3074, 2987, 2946, 1625, 1596, 1556, 1536, 1492, 1455, 1435, 1402, 1348, 1269, 1247, 1223, 1167, 1110, 1049, 965, 931, 858, 843, 761, 740 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_8FN_3Na$ [M + Na]$^+$ 260.0600, found 260.0602.

*3-Fluorobenzo[4,5]imidazo[1,2-a]quinazoline (**3f**).* Yield: 82% (194 mg). Pale yellow solid. Mp: 223−225 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.53−7.60 (m, 2H), 7.91−7.98 (m, 2H), 8.17 (dd, J = 8.0 Hz, J' = 2.4 Hz, 1H), 8.63 (d, J = 8.0 Hz, 1H), 8.81 (dd, J = 8.8 Hz, J' = 4.0 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 114.9, 115.7 (d, J_{F-C} = 22.9 Hz), 118.1 (d, J_{F-C} = 8.0 Hz), 119.8 (d, J_{F-C} = 8.3 Hz), 120.7, 123.3 (d, J_{F-C} = 24.1 Hz), 123.9, 125.2, 129.1, 134.1 (d, J_{F-C} = 1.8 Hz), 143.5, 150.0, 158.5 (d, J_{F-C} = 242.5 Hz), 158.7. IR (KBr): ν 3050, 3024, 1556, 1525, 1476, 1454, 1428, 1387, 1343, 1262, 1253, 1194, 1143, 1031, 970, 929, 858, 827, 816, 761, 734 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_8FN_3Na$ [M + Na]$^+$ 260.0600, found 260.0587.

*4-Fluorobenzo[4,5]imidazo[1,2-a]quinazoline (**3g**).* Yield: 81% (192 mg). Pale yellow solid. Mp: 249−251 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.53−7.64 (m, 3H), 8.01 (d, J = 8.0 Hz, 1H), 8.10−8.15 (m, 1H), 8.64 (d, J = 8.8 Hz, 1H), 8.69 (d, J = 7.6 Hz, 1H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 108.6 (d, J_{F-C} = 16.8 Hz), 110.5 (d, J_{F-C} = 22.7 Hz), 110.6, 113.7, 121.5, 123.9, 125.3, 129.0, 135.7 (d, J_{F-C} = 10.1 Hz), 138.5 (d, J_{F-C} = 4.7 Hz), 143.8, 149.8, 151.6 (d, J_{F-C} = 6.8 Hz), 160.5 (d, J_{F-C} = 257.4 Hz). IR (KBr): ν 3100, 3076, 3053, 1628, 1614, 1590, 1548, 1529, 1485, 1465, 1455, 1341, 1272, 1265, 1251, 1224, 1202, 1156, 1125, 1065, 886, 863, 835, 786, 763, 744 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{14}H_9FN_3$ [M + H]$^+$ 238.0775, found 238.0782.

*3-Methoxybenzo[4,5]imidazo[1,2-a]quinazoline (**3h**).* Yield: 72% (179 mg). Pale yellow solid. Mp: 222−224 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.92 (s, 3H), 7.49−7.56 (m, 2H), 8.17 (dd, J = 8.8 Hz, J' = 2.8 Hz, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.93−7.95 (m, 1H), 8.57 (d, J = 7.6 Hz, 1H), 8.65 (d, J = 9.2 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 56.4, 112.2, 114.8, 117.0, 119.7, 120.5, 123.4, 124.1, 124.9, 129.0, 131.8, 143.5, 150.0, 156.4, 159.0. IR (KBr): ν 3054, 3031, 3007, 2982, 2946, 1620, 1597, 1557, 1522, 1481, 1467, 1453, 1421, 1388, 1378, 1353, 1265, 1252, 1199, 1189, 1040, 1016, 955, 898, 798, 763, 728 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{15}H_{11}N_3ONa$ [M + Na]$^+$ 272.0800, found 272.0782.

*3-(Trifluoromethyl)benzo[4,5]imidazo[1,2-a]quinazoline (**3i**).* Yield: 75% (215 mg). Pale yellow solid. Mp: >300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.61−7.64 (m, 2H), 8.01−8.03 (m, 1H), 8.17 (dd, J = 8.8 Hz, J' = 2.0 Hz, 1H), 8.68−8.71 (m, 1H), 8.81 (s, 1H), 8.98 (d, J = 9.2 Hz, 1H), 9.50 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 115.2, 117.0, 118.4, 120.8, 124.3, 125.2 (q, J_{F-C} = 32.9 Hz), 125.6, 128.3, 128.4, 129.2, 131.3, 139.4, 143.6, 150.1, 159.4. IR (KBr): ν 3087, 3060, 1649, 1628, 1613, 1592, 1567, 1533, 1479, 1455, 1430, 1388, 1347, 1321, 1248, 1203, 1167, 1151, 1115, 1075, 957, 939, 834, 819, 767, 737 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{15}H_8F_3N_3Na$ [M + Na]$^+$ 310.0568, found 310.0558.

*2,3-Dimethoxybenzo[4,5]imidazo[1,2-a]quinazoline (**3j**).* Yield: 76% (212 mg). Pale yellow solid. Mp: 222−225 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.92 (s, 3H), 4.17 (s, 3H), 7.47−7.56 (m, 2H), 7.73 (s, 1H), 7.83 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 8.0 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 56.4, 56.7, 96.9, 109.1, 112.5, 113.2, 121.1, 122.6, 124.8, 128.5, 133.9, 143.9, 146.8, 150.3, 155.4, 156.5. IR (KBr): ν 3051, 3037, 2984, 2937, 2829, 1616, 1598, 1555, 1529, 1455, 1395, 1283, 1251, 1200, 1159, 1142, 1115, 1048, 1011, 990, 961, 873, 856, 797, 761, 724 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{16}H_{13}N_3O_2Na$ [M + Na]$^+$ 302.0905, found 302.0905.

*Benzo[4,5]imidazo[1,2-a][1,3]dioxolo[4,5-g]quinazoline (**3k**).* Yield: 67% (176 mg). Pale yellow solid. Mp: 283−285 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.37 (s, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 8.36 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 96.2, 103.4, 103.7, 107.4, 113.8, 115.3, 120.1, 122.9, 123.8, 125.1, 135.0, 143.6, 145.5, 154.6, 157.6. IR (KBr): ν 3089, 3066, 3007, 2976, 2914, 1654, 1628, 1568, 1529, 1503, 1474, 1454, 1419, 1401, 1312, 1278, 1266, 1233, 1225, 1169, 1120, 1104, 1043, 944, 842, 828, 818, 767, 750 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{15}H_9N_3O_2Na$ [M + Na]$^+$ 286.0592, found 286.0588.

*9,10-Dimethylbenzo[4,5]imidazo[1,2-a]quinazoline (**3l**).* Yield: 66% (163 mg). Pale yellow solid. Mp: 255−257 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.43 (s, 3H), 2.50 (s, 3H), 7.66−7.69 (m, 1H), 7.72 (s, 1H), 8.06−8.10 (m, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.44 (s, 1H), 8.76 (d, J = 8.4 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR (($CDCl_3$, 100 MHz): δ_C 20.6, 21.1, 113.8, 114.7, 118.5, 121.1, 124.3, 129.1, 129.8, 133.0, 134.3, 135.1, 137.6, 142.4, 145.6, 157.3. IR (KBr): ν 3079, 3046, 3026, 2970, 2918, 2849, 1720, 1609, 1552, 1524, 1466, 1389, 1326, 1254, 1228, 1198, 1158, 1093, 1044, 1023, 1004, 991, 969, 860, 817, 766, 749 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{16}H_{14}N_3$ [M + H]$^+$ 248.1182, found 248.1192.

*2-Chloro-9,10-dimethylbenzo[4,5]imidazo[1,2-a]quinazoline (**3m**).* Yield: 75% (211 mg). Pale yellow solid. Mp: 249−251 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.51 (s, 3H), 2.58 (s, 3H), 7.88 (s, 1H), 7.93 (dd, J = 8.8 Hz, J'= 2.4 Hz, 1H), 8.02 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 8.44 (d, J = 8.8 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 20.6, 21.1, 113.6, 116.1, 119.4, 121.3, 127.4, 128.8, 129.7, 133.5, 134.2, 134.6, 135.9, 142.4, 149.3, 155.9. IR (KBr): ν 3044, 2920, 2861, 1612, 1586, 1533, 1455, 1380, 1324, 1303, 1248, 1211, 1159, 1127, 1098, 1024, 999, 950, 877, 863, 815, 756 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{16}H_{13}ClN_3$ [M + H]$^+$ 282.0793, found 282.0801.

*Benzo[4,5]imidazo[1,2-a]thieno[2,3-e]pyrimidine (**3n**).* Yield: 82% (185 mg). Pale yellow solid. Mp: 202−203 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.49−7.53 (m, 1H), 7.57−7.61 (m, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 4.8 Hz, 1H), 9.43 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 114.1, 116.9, 119.9, 120.3, 122.6, 125.5, 127.7, 139.1, 141.9, 143.4, 150.3, 151.3. IR (KBr): ν 3096, 3074, 2963, 2948, 1655, 1612, 1573, 1530, 1487, 1460, 1440, 1418, 1373, 1308, 1267, 1252, 1222, 1203, 1158, 1128, 1092, 1063, 1009, 888, 861, 833, 764, 730 cm^{-1}. HRMS (TOF, ESI, m/z): calcd for $C_{12}H_7N_3SNa$ [M + Na]$^+$ 248.0258, found 248.0251.

General Procedure for the Syntheses of 3-(1*H*-Benzo[*d*]-imidazol-2-yl)-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4). *N*-(2-Benzimidazolyl)-2-aminobenzamide (1.0 mmol), 2-bormobenzaldehyde (1.0 mmol), CuI (10 mg, 0.05 mmol), and dioxane (10 mL) were added into a 25 mL flask. The reaction mixture was stirred at reflux for 6 h before reaching completion, which was monitored by TLC. The solid was filtered off, the filtrate was cooled to room temperature, and product **4** was obtained in 86% yield by filtration.

dx.doi.org/10.1021/jo5007398 | J. Org. Chem. XXXX, XXX, XXX−XXX

3-(1H-Benzo[d]imidazol-2-yl)-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (4). Yield: 86% (360 mg). Pale yellow solid. Mp: 228−229 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.83−6.87 (m, 1H), 6.89 (d, J = 7.6 Hz, 1H), 7.07−7.13 (m, 2H), 7.14−7.17 (m, 1H), 7.20−7.26 (m, 2H), 7.35−7.39 (m, 1H), 7.41−7.43 (m, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.54−7.56 (m, 1H), 7.69−7.72 (m, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 8.0 Hz, J'= 1.2 Hz, 1H), 12.61 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 112.4, 114.5, 116.5, 118.0, 119.0, 122.0, 122.1, 122.3, 126.3, 127.7, 128.3, 128.6, 130.9, 133.6, 134.2, 135.7, 139.0, 140.1, 145.8, 146.7, 162.8.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **3a−n**, **4**, **7**, and 2-aminobenzoic acids and X-ray data for **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science foundation of China (20802061), a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, Qing Lan Project (10QLD008), and College Industrialization Project (JHB2012-31) of Jiangsu Province for financial support.

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