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Copper-Catalyzed Direct Amination of Ortho-Functionalized Haloarenes with Sodium Azide as the Amino Source

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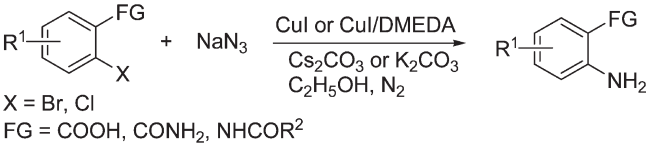

A simple copper-catalyzed direct amination of ortho-functionalized haloarenes (2-halobenzoic acid, 2-halobenzamide, and *N*-(2-bromophenyl)acetamide derivatives) has been developed with use of NaN_3 as the amino source in ethanol, and the corresponding ortho-functionalized aromatic amines were synthesized in good to excellent yields. The protocol undergoes one-pot Ullmann-type coupling of ortho-functionalized haloarenes with NaN_3 to lead to ortho-functionalized azidoarenes, followed by reduction with ethanol.

Introduction

Nitrogen-containing heterocyclic compounds in the form of biologically active drugs or agents play an important role in the pharmaceutical and agrochemical industries.[1] Quinazolinone derivatives are now known to show various useful biological and medicinal activity, such as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, anti-inflammatory, and antitumor.[2,3] Moreover, some therapeutic agents containing the core structure have been on the market or are in clinical trials for the treatment of cancer.[4] Although some methods for syntheses of quinazolinone derivatives have been developed, their preparation depends on the availability of the requisite 2-aminobenzoic acid derivatives (Figure 1, structure **A**)[2,5,6] or 2-aminobenzamide derivatives (Figure 1, structure **B**).[7] Dihydroquinazolinones display a broad range of biological, medicinal, and pharmacological properties and are constituents of antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating agents,[8] and 2-aminobenzamide derivatives (Figure 1, structure **B**) are important building blocks for their synthesis.[9] Benzimidazoles have attracted much attention for their wide applications as enzyme inhibitors,[10]

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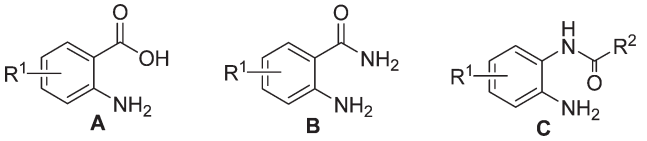


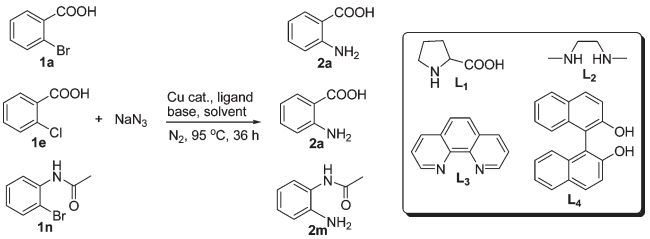
FIGURE 1. 2-Aminobenzoic acid, 2-aminobenzamide, and *N*-(2-aminophenyl)acetamide derivatives as intermediates of some important nitrogen-containing heterocyclic compounds.

drugs,[11] organic light emitting diodes (OLEDs),[12] and polymers.[13] Among the previous methods,[14] the condensation of 1,2-diaminoarene derivatives with carbonyl compounds is perhaps the most common.[15,16] Therefore, it is very desirable to develop readily prepared 1,2-diaminoarene derivatives (Figure 1, structure **C**). Recently, copper-catalyzed Ullmann *N*-arylations have produced great progress,[17] and the *N*-arylation strategy has been used to make aryl azides.[18] The wide applications of 2-aminobenzoic acid, 2-aminobenzamide, and *N*-(2-aminophenyl)acetamide derivatives have stimulated our research into the development of new strategies for their synthesis. In continuation of our endeavors to develop copper-catalyzed cross couplings,[19] herein, we report a simple, convenient copper-catalyzed direct amination of ortho-functionalized haloarenes using NaN_3 as the amino source under mild conditions.

Results and Discussion

Initially, 2-bromobenzoic acid was chosen as the model substrate to optimize reaction conditions including the catalysts, bases, and solvents under nitrogen atmosphere as shown in Table 1. Interestingly, reaction of 2-bromobenzoic acid with NaN_3 in ethanol at 95 °C afforded 2-aminobenzoic acid rather than 2-azidobenzoic acid with use of 10 mol % CuI as the catalyst, 20 mol % of L-proline as the ligand, and 2 equiv of K_2CO_3 as the base (relative to amount of 2-bromobenzoic acid) (entry 1). Other ligands were tested (entries 2−4), and *N*,*N*′-dimethylethylenediamine (DMEDA) was proven to be most effective (entry 2). Reaction of 2-bromobenzoic acid with NaN_3 provided 83% yield in the absence of ligand (entry 5). We attempted various copper salts (compare entries 5−9), and CuI

TABLE 1. Copper-Catalyzed Amination of 2-Bromobenzoic Acid, 2-Chlorobenzoic Acid, and *N*-(2-Bromophenyl)acetamide with NaN_3 As the Amino Source: Optimization of Conditions[a]



entry	substrate	cat.	ligand	base	solvent	yield (%)
1	**1a**	CuI	L_1	K_2CO_3	C_2H_5OH	73
2	**1a**	CuI	L_2	K_2CO_3	C_2H_5OH	88
3	**1a**	CuI	L_3	K_2CO_3	C_2H_5OH	68
4	**1a**	CuI	L_4	K_2CO_3	C_2H_5OH	69
5	**1a**	CuI		K_2CO_3	C_2H_5OH	83
6	**1a**	CuBr		K_2CO_3	C_2H_5OH	80
7	**1a**	CuCl		K_2CO_3	C_2H_5OH	62
8	**1a**	Cu_2O		K_2CO_3	C_2H_5OH	65
9	**1a**	$Cu(OAc)_2$		K_2CO_3	C_2H_5OH	70
10	**1a**			K_2CO_3	C_2H_5OH	trace
11	**1a**	CuI		Cs_2CO_3	C_2H_5OH	91
12	**1a**	CuI		K_3PO_4	C_2H_5OH	85
13	**1a**	CuI		Cs_2CO_3	CH_3OH	89
14	**1a**	CuI		Cs_2CO_3	$PhCH_2OH$	trace
15	**1a**	CuI		Cs_2CO_3	2-propanol	trace
16	**1a**	CuI		Cs_2CO_3	*tert*-butanol	trace
17	**1a**	CuI		Cs_2CO_3	DMSO	25
18	**1e**	CuI		Cs_2CO_3	C_2H_5OH	51
19	**1e**	CuI	L_2	Cs_2CO_3	C_2H_5OH	90
20	**1n**	CuI		Cs_2CO_3	C_2H_5OH	0
21	**1n**	CuI	L_2	K_2CO_3	C_2H_5OH	52
22	**1n**	CuI	L_1	K_2CO_3	C_2H_5OH	45
23	**1n**	CuI	L_2	Cs_2CO_3	C_2H_5OH	47

[a] Reaction condition: NaN_3 (4 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), solvent (5 mL), reaction temperature (95 °C) under nitrogen atmosphere, reaction time (36 h).

showed the highest activity (entry 5). No target product was observed in the absence of copper catalyst (entry 10). The bases were also investigated, and Cs_2CO_3 gave the highest yield (compare entries 5, 11, and 12). Other solvents were screened (entries 13−17), ethanol was proven to be best (entry 11), and DMSO provided 25% yield for unknown reasons (entry 17). When 2-chlorobenzoic acid was used as the substrate, only 51% yield of the target product was obtained under the same condition as entry 11 (entry 18). The reactivity greatly increased when 20 mol % of DMEDA was used as the ligand (entry 19). Reaction of *N*-(2-bromophenyl)acetamide with NaN_3 did not work under the same condition as entry 11 (entry 20). We also attempted different bases and ligands (compare 21−23), and a moderate yield was provided with use of 2 equiv of K_2CO_3 as the base and 20 mol % of DMEDA as the ligand (entry 21). Reaction temperature was also changed, and 95 °C was the best choice.

The scope of copper-catalyzed amination of the 2-halobenzoic acid and 2-halobenzamide derivatives was investigated with use of NaN_3 as the amino source under the optimized conditions. Amination of the 2-bromobenzoic acid and 2-bromobenzamide derivatives was performed with 10 mol % of CuI as the catalyst and 2 equiv of Cs_2CO_3 as the base. For 2-chlorobenzoic acid and 2-chlorobenzamide derivatives (see entries 5, 6, 12, and 13), an additional ligand, 20 mol % of DMEDA, was required to promote their reactivity because of lower activity of the C−Cl bond. As shown in Table 2, most of the examined

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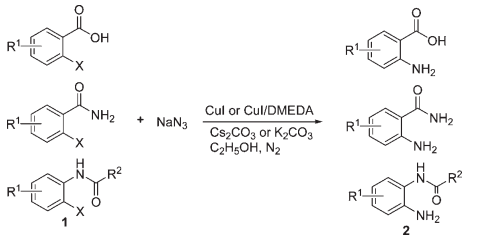
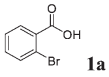
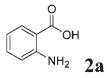
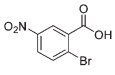
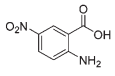
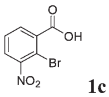
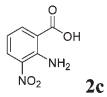
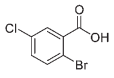
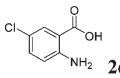
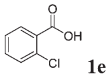
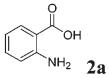
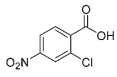
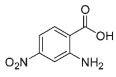
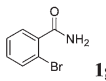
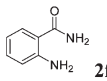
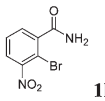
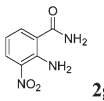
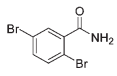
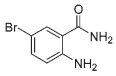
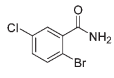
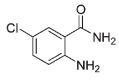
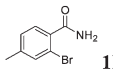
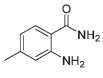
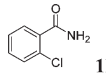
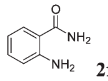
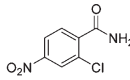
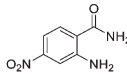
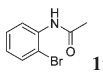
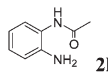
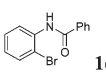
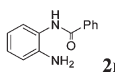
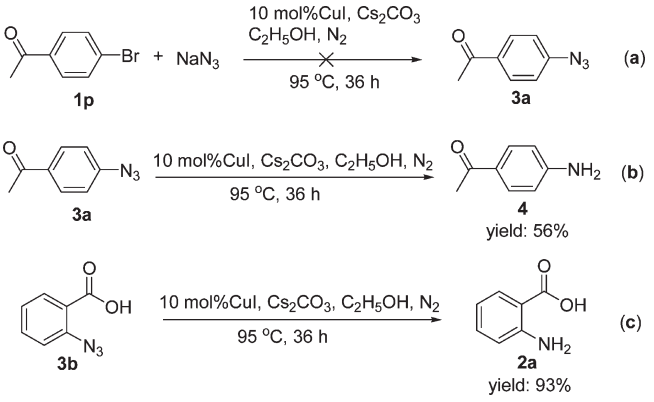
TABLE 2. Copper-Catalyzed Synthesis of Ortho-Functionalized Aromatic Amines[a]



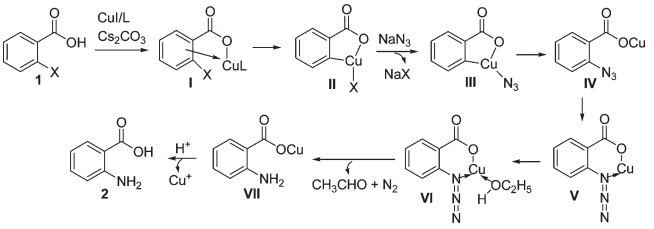
entry	1	time (h)	2	yield (%)
1	 **1a**	36	 **2a**	91
2	 **1b**	30	 **2b**	79
3	 **1c**	30	 **2c**	95
4	 **1d**	48	 **2d**	68
5	 **1e**	30	 **2a**	90[b]
6	 **1f**	48	 **2e**	62[b]
7	 **1g**	36	 **2f**	79
8	 **1h**	36	 **2g**	71
9	 **1i**	48	 **2h**	64
10	 **1j**	56	 **2i**	66
11	 **1k**	48	 **2j**	65
12	 **1l**	36	 **2f**	70[b]
13	 **1m**	42	 **2k**	43[b]
14	 **1n**	36	 **2l**	52[b]
15	 **1o**	12	 **2m**	68[b,c]

[a]Reaction condition: ortho-functionalized haloarene (1 mmol), NaN_3 (4 mmol), CuI (0.1 mmol), Cs_2CO_3 (2 mmol for entries 1−13), K_2CO_3 (2 mmol for entries 14 and 15), C_2H_5OH (5 mL), reaction temperature (95 °C) under nitrogen atmosphere. [b]Addition of *N*,*N*′-dimethylethylenediamine (0.2 mmol). [c]Reaction temperature (78 °C).

SCHEME 1. Treatment of 1-(4-Bromophenyl)ethanone with NaN_3 (a) and Reactions of 1-(4-Azidophenyl)ethanone (b) and 2-Azidobenzoic Acid (c) under Our Standard Conditions



SCHEME 2. Possible Formation Mechanism of 2-Aminobenzoic Acid



2-halobenzoic acid and 2-halobenzamide derivatives provided good to excellent yields at 95 °C. When 2,5-dibromobenzamide was used as the substrate, the amination selectively occurred on the ortho-site C−Br bond of $-CO-NH_2$, which implied an ortho-substituent effect of the amide group.[19e]

To explore the amination mechanism of 2-halobenzoic acid derivatives, the following control experiments were performed under our standard condition as shown in Scheme 1. Reaction of 1-(4-bromophenyl)ethanone with NaN_3 did not work because of the absence of an ortho-substituent group (Scheme 1a). Treatment of 1-(4-azidophenyl)ethanone (**3a**) provided product **4** in moderate yield (56%) (Scheme 1b), and the result showed that aromatic azides could be transferred into the corresponding aromatic amines under our standard condition. 2-Azidobenzoic acid produced 2-aminobenzoic acid in 93% yield (Scheme 1c), which indicated a copper-catalyzed ortho-substituent effect[19f] of the carboxyl group during transformation of azide to amine.

A possible formation mechanism of 2-aminobenzoic acid derivatives was proposed in Scheme 2 according to the results above. Coordination of 2-halobenzoic acid (**1**) with CuI first forms **I** in the presence of base (Cs_2CO_3). Oxidation addition of **I** provides coordinate **II**, and exchange of X^- in **II** with N_3^- of NaN_3 gives **III**. Reduction elimination of **III** leads to **IV**, coordination of **IV** with copper gives **V**, and a complex of **V** with ethanol provides **VI**. Oxidation−reduction reaction of **VI** in the presence of base leads to amination product **VII** with leaving acetaldehyde and N_2, and the similar copper-catalyzed oxidation of alcohols to aldehydes was previously investigated.[20] Acidification of **VII** affords the target product (**2**) with release of copper catalyst.

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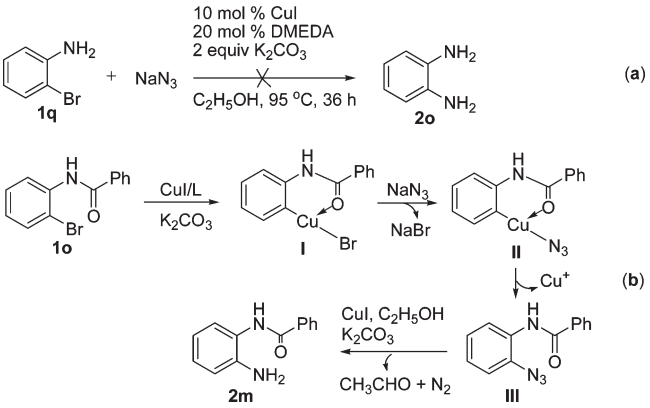
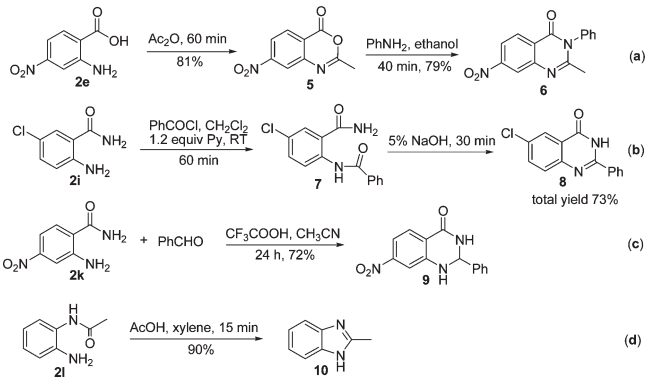
SCHEME 3. (a) Treatment of 2-Bromobenzenamine (1q) with NaN_3 under Our Standard Condition and (b) Possible Mechanism for Amination of *N*-(2-Bromophenyl)benzamide (1o)



SCHEME 4. Application of the Synthesized Ortho-Functionalized Aromatic Amines in Synthesis of Nitrogen-Containing Heterocyclic Compounds



The amination mechanism of 2-halobenzamide derivatives could be similar to the result above and the previous report.[19e]

N-(2-Bromophenyl)acetamide (**1n**) and *N*-(2-bromophenyl)benzamide (**1o**) also provided the corresponding amination products in moderate yields (entries 14 and 15 in Table 2) under our catalytic condition (10 mol % of CuI as the catalyst, 2 equiv of K_2CO_3 as the base, and 20 mol % of DMEDA as the ligand). However, 2-bromobenzenamine (**1q**) could not react with NaN_3 under the same condition (Scheme 3a), and the results showed an ortho-substituent effect of the −NHCOPh group in **1o** during azidation as shown in Scheme 3b. Coordination of *N*-(2-bromophenyl)benzamide (**1o**) with CuI and the following oxidation addition forms **I**, and treatment of **I** with NaN_3 gives **II**. Reduction elimination of **II** affords *N*-(2-azidophenyl)benzamide (**III**) with leaving copper catalyst. *N*-(2-Azidophenyl)benzamide undergoes a similar oxidation−reduction process to that shown in Scheme 2 to give the target product (**2m**) under our catalytic condition.

The amination reactions in Table 2 could tolerate various functional groups including nitro (entries 2, 3, 6, 8, and 13), C−Cl bond (entries 4 and 10), C−Br bond (entry 9), carboxyl (entries 1−6), and amide (entries 7−15) in the substrates.

We attempted synthesis of some nitrogen-containing heterocyclic compounds by using the synthesized ortho-functionalized aromatic amines as the materials as shown in Scheme 4. Reaction of 2-amino-4-nitrobenzoic acid (**2e**) with

Ac_2O afforded compound **5** in 81% yield, and the treatment of **5** with aniline in ethanol gave 2-methyl-7-nitro-3-phenylquinazolin-4(3*H*)-one (**6**) in 79% yield according to the previous procedure (Scheme 4a).[21] Reaction of 2-amino-5-chlorobenzamide (**2i**) with benzoyl chloride provided **7**, and treatment of **7** in 5% NaOH aqueous solution afforded 6-chloro-2-phenylquinazolin-4(3*H*)-one (**8**) in 73% total yield (Scheme 4b).[22] Reaction of 2-amino-5-nitrobenzamide (**2k**) with benzaldehyde in the presence of CF_3COOH produced the corresponding dihydroquinazolinone (**9**) in 72% yield (Scheme 4c).[23] Treatment of *N*-(2-aminophenyl)acetamide (**2*l***) in acetic acid afforded 2-methyl-1*H*-benzoimidazole (**10**) in 90% yield (Scheme 4d).[15c]

Conclusion

We have developed a simple copper-catalyzed amination of *o*-functionalized haloarenes (2-halobenzoic acid, 2-halobenzamide, and *N*-(2-bromophenyl)acetamide derivatives) using NaN_3 as the amino source in ethanol, and the corresponding 2-aminobenzoic acid, 2-aminobenzamide, and *N*-(2-aminophenyl)acetamide derivatives were obtained in good to excellent yields. The protocol undergoes one-pot Ullmann-type coupling of ortho-functionalized haloarenes with NaN_3 to give ortho-functionalized azidoarenes, followed reduction with ethanol, and ethanol acted as solvent and reductive agent. The method is of economical and practical advantages, and the synthesized compounds can be widely used in the synthesis of various nitrogen-containing heterocyclic compounds.

Experimental Section

General Experimental Procedures. All reactions were carried out under nitrogen atmosphere in sealed tubes. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or were recorded with tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm).

General Procedure for Synthesis of Compounds 2a−m. A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with CuI (0.1 mmol, 19 mg), NaN_3 (4 mmol, 260 mg), Cs_2CO_3 (2 mmol, 652 mg for entries 1−13 in Table 2) or K_2CO_3 (2 mmol, 276 mg for entries 14 and 15 in Table 2), and 2-halobenzoic acid, 2-halobenzamide, or *N*-(2-bromophenyl)acetamide derivative (1 mmol). The tube was evacuated twice and backfilled with nitrogen. Ethanol (5 mL) and *N*,*N*′-dimethylethylenediamine (DMEDA) (0.2 mmol, 18 mg for entries 5, 6, 12, 13, 14, and 15 in Table 2) were sequentially added at room temperature under a stream of nitrogen, and the tube was sealed and put into a preheated oil bath at 95 °C for 12−56 h under a positive pressure of nitrogen. After the resulting solution was cooled to room temperature, the solvent was removed under rotary evaporation. Five milliliters of HCl (1 N) was added to acidify the solution (pH 2−3), and the solution was extracted with ethyl acetate (3 × 5 mL) for 2-halobenzoic acid derivative substrates (entries 1−6 in Table 2). The combined organic phase was concentrated, and the residue was purified by column chromatography on silica gel to provide the desired product. For 2-halobenzamide or *N*-(2-bromophenyl)acetamide derivative substrtates, the resulting solution was filtered, and the solid was washed with ethanol. The combined ethanol solution was concentrated, and the residue was purified by column chromatography on silica gel to provide the desired product.

2-Aminobenzoic acid (2a).[24] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 125 mg (91%), using 2-bromobenzoic acid as the substrate; 123 mg (90%), using 2-chlorobenzoic acid as the substrate. Yellow solid, mp 145 °C (lit.[24] mp 145 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.59 (s, br, 2H), 7.68 (d, 1H, J = 7.9 Hz), 7.22 (t, 1H, J = 7.5 Hz), 6.76 (d, 1H, J = 8.2 Hz), 6.50 (t, 1H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.1, 152.0, 134.3, 131.7, 116.8, 115.1, 110.1. ESIMS $[M + H]^+$ m/z 138.1.

2-Amino-5-nitrobenzoic acid (2b).[25] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 144 mg, 79%. Yellow solid, mp 278 °C (lit.[25] mp 279−280 °C, dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.32 (s, br, 1H), 8.60 (d, 1H, J = 2.2 Hz), 8.08 (d, 1H, J = 9.3 Hz), 7.88 (s, br, 2H), 6.88 (d, 1H, J = 9.3 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.1, 156.1, 135.0, 128.7, 128.6, 116.5, 108.5. ESIMS $[M + H]^+$ m/z 183.1.

2-Amino-3-nitrobenzoic acid (2c).[26] Eluent: petroleum ether/ethyl acetate (1:2). Yield: 174 mg (95%). Yellow solid, mp 209 °C (lit.[26] mp 208 −209 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.46 (s, br, 1H), 8.51 (s, br, 2H), 8.30 (d, 1H, J = 8.3 Hz), 8.23 (d, 1H, J = 7.7 Hz), 6.72 (t, 1H, J = 8.1 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.7, 146.8, 139.7, 132.5, 131.7, 114.8, 113.9. ESIMS $[M + H]^+$ m/z 183.1.

2-Amino-5-chlorobenzoic acid (2d).[27] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 133 mg (77%). Pale yellow crystal, mp 204 °C (lit.[27] mp 204 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (s, br, 2H), 7.61 (d, 1H, J = 2.0 Hz), 7.24 (d, 1H, J = 8.9 Hz), 6.77 (d, 1H, J = 8.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.0, 150.8, 134.0, 130.4, 118.8, 118.0, 110.9. ESIMS $[M + H]^+$ m/z 172.1.

2-Amino-4-nitrobenzoic acid (2e).[28] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 113 mg 62%. Yellow solid, mp 264 °C (lit.[28] mp 264 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.93 (d, 1H, J = 8.3 Hz), 7.44 (d, 1H, J = 1.7 Hz), 7.33 (s, br, 2H), 7.16 (d, 1H, J = 8.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.0, 151.3, 149.2, 133.3, 125.3, 109.5, 108.1. ESIMS $[M + H]^+$ m/z 183.1.

2-Aminobenzamide (2f).[29] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 108 mg (79%) with 2-bromobenzamide as the substrate; 96 mg (70%) with 2-chlorobenzamide as the substrate. White crystal, mp 110 °C (lit.[29] mp 109−110 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.71 (s, br, 1H), 7.52 (d, 1H, J = 7.6 Hz), 7.12 (t, 1H, J = 7.6 Hz), 7.04 (s, br, 1H), 6.67 (d, 1H, J = 7.9 Hz), 6.55 (s, br, 2H), 6.46 (t, 1H, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.3, 150.2, 131.9, 128.7, 116.4, 114.4, 113.7. ESIMS $[M + H]^+$ m/z 137.2.

2-Amino-3-nitrobenzamide (2g).[26] Eluent: petroleum ether/ethyl acetate (1:1). Yield: 128 mg (71%). Yellow solid, mp 237 °C (lit.[26] mp 234 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.49 (s, br, 2H), 8.19 (d, 1H, J = 8.6 Hz), 8.16 (s, br, 1H), 7.96 (d, 1H, J = 7.6 Hz), 7.63 (s, br, 1H), 6.69 (t, 1H, J = 7.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.0, 146.1, 136.4, 132.1, 129.4, 118.8, 113.7. ESIMS $[M + H]^+$ m/z 182.1.

2-Amino-5-bromobenzamide (2h).[30] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 138 mg (64%). White solid, mp 188 °C

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(lit.[30] mp 187−189 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.85 (s, br, 1H), 7.70 (d, 1H, J = 2.1 Hz), 7.25 (d, 1H, J = 8.9 Hz), 7.17 (s, br, 1H), 6.72 (s, br, 2H), 6.66 (d, 1H, J = 8.6 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.5, 149.9, 134.8, 131.3, 119.0, 115.7, 105.2. ESIMS $[M + H]^+$ m/z 214.1, 216.1.

2-Amino-5-chlorobenzamide (2i).[31] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 112 mg (66%). White solid, mp 174 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88 (s, br, 1H), 7.61 (d, 1H, J = 2.1 Hz), 7.14−7.22 (m, 2H), 6.71−6.74 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ170.6, 149.6, 132.1, 128.5, 118.6, 118.0, 115.0. ESIMS $[M + H]^+$ 171.2.

2-Amino-4-methylbenzamide (2j).[6b] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 98 mg (65%). White solid, mp 148 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.67 (s, br, 1H), 7.44 (d, 1H, J = 6.12 Hz), 6.94 (s, 1H), 6.56 (s, 2H), 6.47 (s, 1H), 6.28 (d, 1H, J = 6.12 Hz), 2.16 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.8, 150.9, 142.1, 129.4, 117.0, 116.1, 111.6, 21.6. ESIMS $[M + H]^+$ 151.2.

2-Amino-4-nitrobenzamide (2k).[32] Eluent: petroleum ether/ethyl acetate (1:1). Yield: 77 mg (43%). Yellow solid, mp 222−224 °C (lit.[32] mp 221−223 °C dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.06 (s, br, 1H), 7.74 (d, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 2.4 Hz), 7.47 (s, br, 1H), 7.24 (d, 1H, J = 8.6 Hz), 7.03 (s, br, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.2, 151.2, 150.0, 130.8, 119.3, 110.7, 108.4. ESIMS $[M + H]^+$ 182.3.

***N*-Acetyl-2-aminoaniline (2l).**[33] Eluent: petroleum ether/ethyl acetate (1:2). Yield: 78 mg (52%). White solid, mp 128 °C (lit.[33] mp 130 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.11 (s, 1H), 7.15 (d, 1H, J = 7.9 Hz), 6.88 (t, 1H, J = 8.4 Hz), 6.70 (d, 1H, J = 7.9 Hz), 6.53 (t, 1H, J = 8.2 Hz), 4.88 (s, br, 2H), 2.03 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.7, 142.4, 126.3, 125.9, 124.1, 116.7, 116.3, 23.8. ESIMS $[M + H]^+$ m/z 151.1.

***N*-(2-Aminophenyl)benzamide (2m).**[34] Eluent: petroleum ether/ethyl acetate (1:1). Yield: 145 mg (68%). White solid, mp 149−151 °C (lit.[34] mp 148 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.68 (s, 1H), 8.00 (d, 2H, J = 7.2 Hz), 7.50−7.57 (m, 3H), 7.19 (d, 1H, J = 7.6 Hz), 6.97 (t, 1H, J = 7.5 Hz), 6.80 (d, 1H, J = 7.9 Hz), 6.61 (t, 1H, J = 7.5 Hz), 4.91 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.9, 143.7, 135.2, 131.9, 128.8, 128.3, 127.2, 127.0, 123.9, 116.8, 116.7. ESIMS $[M + H]^+$ m/z 213.2.

4-Aminoacetophenone (4).[29] Eluent: petroleum ether/ethyl acetate (5:1). Yield: 75 mg (56%). White solid, mp 104 °C (lit.[29] mp 104−106 °C) .^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, 2H, J = 8.6 Hz), 6.63 (d, 2H, J = 8.6 Hz), 4.21 (s, br, 2H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.7, 151.5, 130.9, 127.7, 113.8, 26.2. ESIMS $[M + H]^+$ m/z 136.1.

2-Methyl-3-phenyl-7-nitro-4(*3H*)-quinazolinone (6).[35] A suspension of 4-nitroanthranilic acid (364 mg, 2.0 mmol) was refluxed in Ac_2O (4 mL) for 1 h. The resulting solution was concentrated with the aid of a rotary evaporator, and the residue was added to a solution of aniline (2 mmol) in EtOH (4 mL) under vigorous stirring. The mixture was refluxed for 40 min, and then the solvent was evaporated to dryness. Water (10 mL) was added, and the insoluble residue was filtered off, washed with water, and dried.[21] Yield: 180 mg (64%) of a mild yellow powder, mp 207−210 °C (lit.[35] mp 205−207 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1H), 8.41 (d, 1H, J = 8.6 Hz), 8.20 (d, 1H, J = 8.6 Hz), 7.55−7.60 (m, 3H), 7.29 (d, 2H, J = 7.6 Hz), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 156.9, 151.8, 148.1, 137.1, 130.4, 129.9, 129.3, 129.1, 127.8, 125.0, 122.6, 120.3, 24.6. ESIMS $[M + H]^+$ m/z 282.1.

6-Chloro-2-phenylquinazolin-4(*3H*)-one (8).[22] To a solution of 2-amino-5-chlorobenzamide (1 mmol, 170 mg) and pyridine (1.2 mmol, 95 mg) in dichloromethane (3 mL) was added benzoyl chloride (1.2 mmol, 168 mg) slowly via syringe then the solution was stirred for 1 h at room temperature. The pale yellow solid formed was filtered and taken up in a solution of aqueous NaOH (5%, 3 mL) and refluxed for 30 min. The solution was cooled to room temperature and acidified to pH ∼3 with HCl (1 M). The solid was filtered and washed with water to yield the title compound as a white fibrous solid.[22] Total yield 187 mg (73%), mp 288 °C (lit.[19f] mp 286−288 °C). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 12.75 (s, 1H), 8.18 (d, 2H, J = 7.6 Hz), 8.09 (s, 1H), 7.87 (d, 1H, J = 2.8 Hz), 7.78 (d, 1H, J = 7.1 Hz), 7.56−7.61 (m, 3H). ^{13}C NMR (DMSO-d_6 150 MHz) δ 161.8, 153.3, 148.0, 135.2, 133.0, 132.1, 131.3, 130.2, 129.1, 128.4, 125.4, 122.7. ESIMS $[M + H]^+$ m/z 257.3.

2,3-Dihydro-7-nitro-2-phenyl-4(*1H*)-Quinazolinone (9).[23] To a room temperature solution of 4-nitroanthranilamide (1.19 mmol, 182 mg) and benzaldehyde (1.19 mmol, 106 mg) in 8 mL of MeCN was added 1−2 drops of trifluoroacetic acid. After the solution was stirred for 24 h at room temperature, the precipitate was collected and recrystallized from THF−hexanes to give **9** as a yellow solid. Yield 195 mg (72%), mp 220 °C (lit.[23] mp 219−221 °C). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.71 (s, 1H), 7.91 (s, 1H), 7.83 (d, H, J = 8.2 Hz), 7.62 (d, 1H, J = 2.0 Hz), 7.49 (d, 2H, J = 7.6 Hz), 7.43−7.36 (m, 4H), 5.91 (s, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ 162.3, 151.3, 148.7, 141.8, 129.6, 129.2, 129.0, 127.2, 119.7, 111.4, 109.4, 66.8. ESIMS $[M + H]^+$ m/z 270.1.

2-Methyl-*1H*-benzimidazole (10).[16] A mixture of the *N*-acetyl-2-aminoaniline (0.5 mmol, 75 mg), xylene (4 mL), and acetic acid (1.5 mL) was refluxed for 15 min. The solution was evaporated to dryness, the residue was purified by silica gel column chromatography with dichloromethane/methanol (9.5:0.5) as eluent, and 2-methyl-1*H*-benzimidazole (60 mg, 90%) was obtained.[16] Mp 177 °C (lit.[36] mp 175−176 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.98 (s, br, 1H), 7.55−7.57 (m, 2H), 7.21−7.23 (m, 2H), 2.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.4, 138.7, 122.3, 114.6, 15.0. ESIMS $[M + H]^+$ m/z 133.1.

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Supporting Information Available: ^{1}H, ^{13}C NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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