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Synthesis of Quinazolin-4(3*H*)-ones via the Reaction of 2-Halobenzamides with Nitriles

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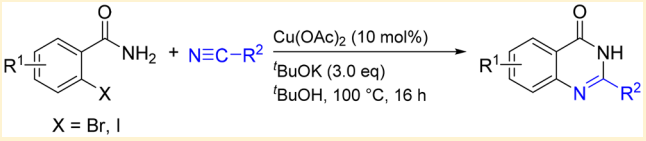
Supporting Information

ABSTRACT: This paper describes a convenient method to synthesize quinazolin-4(3*H*)-ones from simple and readily available 2-halobenzamides and nitriles. The Lewis acid Cu-catalyzed nucleophilic addition of 2-halobenzamide to nitriles followed by S_NAr reaction proceeds smoothly in the presence of ^{t}BuOK as a base to produce quinazolinone derivatives.



INTRODUCTION

Quinazolin-4(3*H*)-one structural motifs are frequently found in natural products[1] and bioactive compounds.[2] Compounds of this class are well-known for their anticancer,[3] anti-inflammatory,[4] and antimicrobial effects,[5] among others.[6] Therefore, the development of convenient and efficient methods to synthesize quinazolin-4(3*H*)-ones has attracted considerable attention. Studies over the past decade have synthesized quinazolin-4(3*H*)-one using various methods, including the condensation of 2-aminobenzamide with aryl aldehyde,[7] benzenecarboxylic acid,[8] and aroyl chloride;[9] Pd-catalyzed cyclocarbonylation with aryl halides;[10] transition-metal-catalyzed C−H amidation with benzyl alcohols or condensation with benzyl amine;[11] (^{t}BuO)$_2$(DTBP)/TsOH-mediated condensation with methylarenes or methylhetarenes;[12] CuCl-catalyzed condensation with methylhetarenes;[13] TFA-catalyzed condensation with ketoalkynes;[14] and redox condensation between *o*-substituted nitrobenzenes with amines in the presence of iron and cobalt catalysts.[15] Recent developments have been reported about the synthesis of quinazolin-4(3*H*)-ones via Cu-catalyzed Ullmann-type coupling reactions.[16] Fu and Jiang reported the Cu-catalyzed cascade reactions of amidine hydrochlorides with substituted 2-halobenzaldehydes, 2-halophenylketones, or methyl 2-halobenzoates (Scheme 1, eq 1); Fu et al. developed Cu-catalyzed cascade reactions of 2-halobenzamides with (aryl)methanamines or amino acids (Scheme 1, eq 2); Tripathi synthesized quinazolin-4(3*H*)-ones via Cu-catalyzed one-pot reaction of 2-bromobenzamides with aldehydes, alcohols, or methyl arenes, and $TMSN_3$ was used as a nitrogen source (Scheme 1, eq 3). In these reactions, Cu(I) salts are used as transition-metal catalysts for the Ullmann-type C−N coupling reaction, and specific ligands or oxidants are required for reductive elimination to construct C−N bonds.

In our recent study, we have synthesized isoquinolone, benzoxazole, and 1-naphthol derivatives through Lewis acid Cu(OAc)$_2$-catalyzed cyclization reactions under oxidant- and ligand-free conditions.[17−19] In the present work, the Lewis acid Cu(OAc)$_2$-catalyzed nucleophilic addition of 2-halobenzamides to nitriles followed by intramolecular S_NAr reaction proceeded under oxidant- and ligand-free conditions (Scheme 1, eq 4). Given this finding, systematic studies were conducted to optimize the conditions for this reaction, and the results are summarized in Table 1.

RESULTS AND DISCUSSION

In our initial studies, the reaction of 2-bromobenzamide (**1a**) and benzonitrile (**2a**) was chosen as a model reaction to optimize the reaction conditions. When **1a** and **2a** were treated with ^{t}BuOK in the absence of copper catalyst at 100 °C, the desired product 2-phenylquinazolin-4(3*H*)-one (**3a**) was obtained in only 14% yield. The failure in yield improvement through heating required us to add Lewis acid catalyst. Therefore, various Lewis acid copper catalysts, such as CuI, CuBr, CuCl, Cu(OAc)$_2$, and Cu(OTf)$_2$, were assessed (entries 2−6). Of these, Cu(OAc)$_2$ exhibited the best catalytic activity to give **3a** in 80% yield (entry 5). The base was subsequently screened using Cu(OAc)$_2$ as catalyst. Among the bases tested (NaOH, K_2CO_3, Cs_2CO_3, ^{t}BuONa, Et_3N, and ^{t}BuOK), the highest yield was obtained by using ^{t}BuOK as base (entry 5 vs entries 7−12). ^{t}BuOH, dioxane, toluene, DMF, and CH_3OH were then examined as solvents, and ^{t}BuOH was identified as the most suitable (entry 5 vs entries 13−16). Therefore, the subsequent cascade reactions of substrates **1** and **2** were performed using Cu(OAc)$_2$ as catalyst and ^{t}BuOK as base in ^{t}BuOH at 100 °C for 16 h.

The reactions of **1a** with nitriles **2a**−**l** were performed under optimized conditions to determine the scope of nitrile substrates. The results are summarized in Table 2. As described in Table 1, the desired product **3a** was obtained in 80% yield (entry 1). Good yields similar to that of **3a** were obtained when 4-methylbenzonitrile (**2b**) and 4-methoxybenzonitrile (**2c**) were examined under optimized reaction conditions (entries 2 and 3). A relatively low yield (68%) of **3d** was obtained when 2-methylbenzonitrile (**2d**) was treated with **1a** (entry 4). This low

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Scheme 1. Synthesis of Quinazolin-4(3*H*)-ones

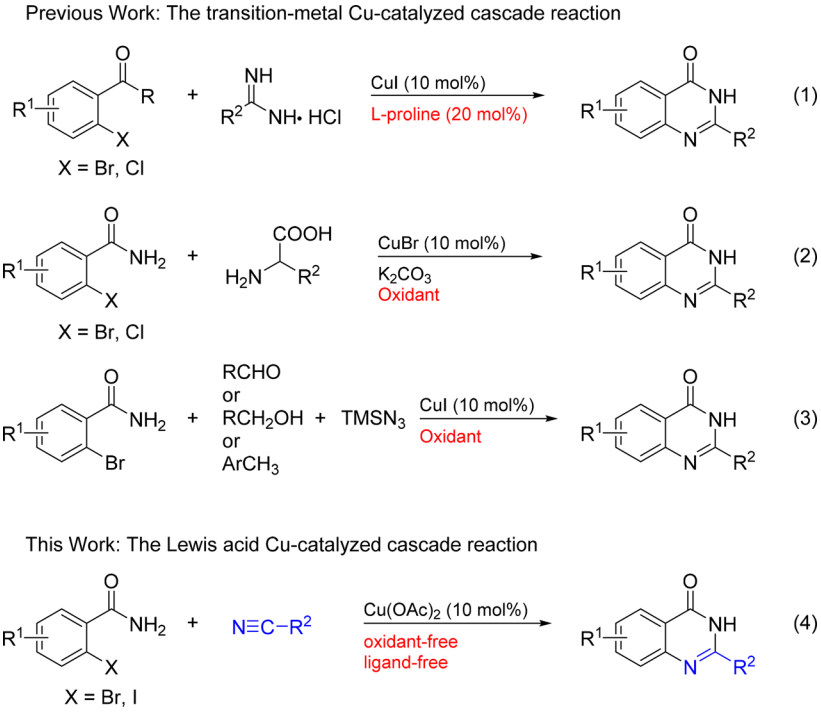
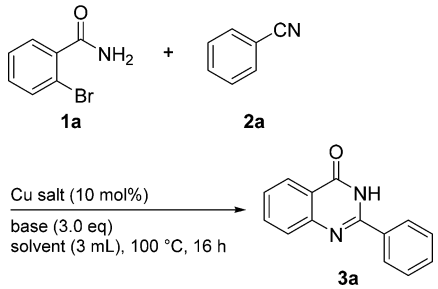


Table 1. Reaction Condition Screening[a]



entry	catalyst	base	solvent	yield (%)[b]
1	none	^{t}BuOK	^{t}BuOH	14
2	CuI	^{t}BuOK	^{t}BuOH	68
3	CuBr	^{t}BuOK	^{t}BuOH	62
4	CuCl	^{t}BuOK	^{t}BuOH	54
5	$Cu(OAc)_2$	^{t}BuOK	^{t}BuOH	80
6	$Cu(OTf)_2$	^{t}BuOK	^{t}BuOH	60
7	$Cu(OAc)_2$	none	^{t}BuOH	NR
8	$Cu(OAc)_2$	NaOH	^{t}BuOH	39
9	$Cu(OAc)_2$	K_2CO_3	^{t}BuOH	NR
10	$Cu(OAc)_2$	Cs_2CO_3	^{t}BuOH	NR
11	$Cu(OAc)_2$	^{t}BuONa	^{t}BuOH	31
12	$Cu(OAc)_2$	Et_3N	^{t}BuOH	NR
13	$Cu(OAc)_2$	^{t}BuOK	Dioxane	51
14	$Cu(OAc)_2$	^{t}BuOK	DMF	22
15	$Cu(OAc)_2$	^{t}BuOK	Toluene	18
16	$Cu(OAc)_2$	^{t}BuOK	CH_3OH	23

[a]Reaction conditions: 2-Bromobenzamide (**1a**, 0.5 mmol), benzonitrile (**2a**, 0.75 mmol), base (1.5 mmol), and copper catalyst (10 mol %) in solvent (3.0 mL) at 100 °C for 16 h. [b]Isolated yield was provided.

yield was attributed to the steric hindrance created by the *ortho*-methyl group in **2d**. However, the reaction of substrate **2e** containing an *ortho*-azyl group on the benzene ring generated the desired product **3e** in only 25% yield (entry 5). Reactions with arylnitriles **2f–I** bearing a halogen atom on the phenyl ring were also tolerated under the present cascade reaction (entries 6–9). The reaction of picolinonitrile (**2j**) was founded to be suitable for the present method to afford **3j** in 55% yield (entry 10). Aliphatic nitriles, acetonitrile (**2k**), and hexanenitrile (**2l**) were then used in this reaction. Quinazolinones **3k** and **3l** were obtained in 75% and 71% yields, respectively (entries 11 and 12).

We subsequently examined the scope of this reaction with various 2-halobenzamides under the optimized reaction conditions, and the results are summarized in Table 3. The reactions of 2-bromo-4-methylbenzamide (**1b**) with **2a** and **2b** proceeded smoothly to produce the corresponding products **3m** and **3n** in good yields (entries 1 and 2). A relatively low yield (60%) of **3o** was observed when 2-bromo-5-methoxybenzamide (**1c**) was treated with **2a** (entry 3). This result indicated that the reactivity of the arylamide substrate was remarkably influenced by the electronic properties of the aromatic ring. The reaction of **1c** with **2f** produced a low yield of quinazolinone **3p** due to the steric hindrance created by the *ortho*-halo group on **2f** and an electron-donating group linking on the aromatic ring in **1c** (entry 4). The secondary amides **1d** and **1e** were also utilized successfully for the synthesis of 2,3-disubstituted quinazolinones. Products **3q** and **3r** were obtained in 86% and 80% yields, respectively (entries 5 and 6). A low yield (35%) of **3s** was obtained when **2a** was treated with 3-bromoisonicotinamide (**1f**) (entry 7). This low yield was attributed to the ligating ability of nitrogen atom on pyridine that can lead to catalyst deactivation. In consideration of the good preliminary results with 2-bromobenzamides, the present method was then applied for 2-iodobenzamide (**1g**). The reactions of **1g** with **2a** were carried out under the same conditions, and the desired product **3a** was obtained in 85% yield (entry 8). However, no reaction was observed when 2-cholobenzamide (**1h**) was examined (entry 9).

On the basis of our experimental outcomes and previous reports, a plausible mechanism is proposed to account for the

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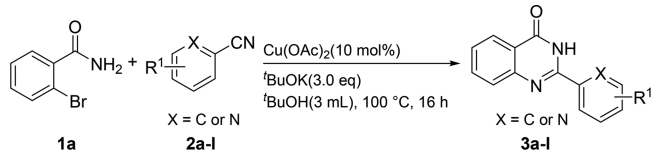
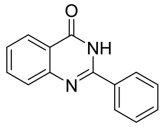
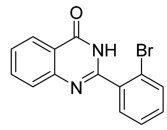
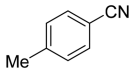
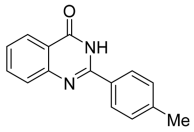
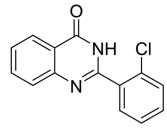
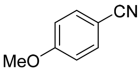
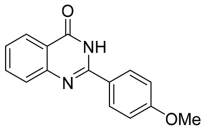
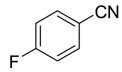
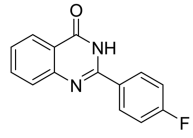
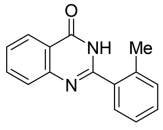
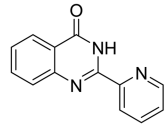
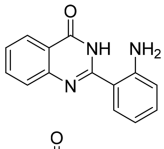
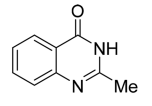
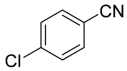
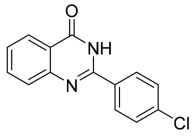
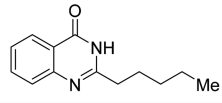
Table 2. Synthesis of Quinazolin-4(3*H*)-ones from Various Nitriles[a]



1a 2a-l 3a-l

Entry	Substrate 2	Product	Yield (%)[b]	Entry	Substrate 2	Product	Yield (%)[b]
1	 **2a**	 **3a**	80	7	 **2g**	 **3g**	35
2	 **2b**	 **3b**	79	8	 **2h**	 **3h**	57
3	 **2c**	 **3c**	85	9	 **2i**	 **3i**	60
4	 **2d**	 **3d**	61	10	 **2j**	 **3j**	55
5	 **2e**	 **3e**	25	11	CH_3CN **2k**	 **3k**	75
6	 **2f**	 **3f**	62	12	$CH_3(CH_2)_4CN$ **2l**	 **3l**	71

[a]Reaction conditions: 2-Bromobenzamide (**1a**, 0.5 mmol), benzonitrile (**2a**, 0.75 mmol), base (1.5 mmol), and copper catalyst (10 mol %) in solvent (3.0 mL) at 100 °C for 16 h. [b]Isolated yield was provided.

present catalytic cascade reaction (Scheme 2). Initially, coordination of the cyano group of **1a** to $Cu(OAc)_2$ generates complex **I**. Then, the nucleophilic addition of **2a** to complex **I** occurs to produce intermediate **II**, which subsequently undergoes intramolecular S_NAr reaction to afford intermediate **III**. Elimination of intermediate **III** generates the desired product **3a** with the liberation of Cu(OAc)Br. Finally, ion exchange of Cu(OAc)Br with KOAc generated in the initial step occurs.

CONCLUSION

A new method using simple and readily available starting materials has been developed to synthesize 2-substituted-4(3*H*)-quinazolinones. The Lewis acid Cu-catalyzed nucleophilic addition of 2-halobenzamides to nitriles and intramolecular S_NAr reaction proceeded smoothly in the presence of ^{t}BuOK as a base to produce quinazolinone derivatives. The affordability of the catalyst, the wide availability of the starting materials, and the simplicity of the procedure render the present methodology useful in organic synthesis.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. Solvents were purified by standard techniques without special instructions. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C); $CDCl_3$ (or DMSO-d_6) and TMS were used as a solvent and an internal standard, respectively. The chemical shifts are reported in ppm downfield (δ) from TMS, the coupling constants (J) are given in Hz. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; bs, broad singlet. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, 200−300 mesh).

Representative Procedure for the Synthesis of Quinazolinones. A mixture of 2-bromobenzamide (100.0 mg, 0.5 mmol), benzonitrile (77.3 mg, 0.75 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), ^{t}BuOK (168.3 mg, 1.5 mmol), and ^{t}BuOH (3.0 mL) was stirred at 100 °C under nitrogen atmosphere for 16 h. After cooling to room temperature, water was added to quench the reaction. The mixture was then extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The crude product was purified by column chromatography (eluent, ethyl acetate: petroleum ether = 1:15) to afford 2-phenylquinazolin-4(3*H*)-one as a white solid (88.8 mg, 80% yield).

Characterization Data of Products. *2-Phenylquinazolin-4(3H)-one (**3a**).*[20] White solid (0.089 g, 80% yield). Mp 233−235 °C (lit.[16] 233−235 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67(bs, 1H), 8.32−8.35 (m, 1H), 8.25−8.28 (m, 2H), 7.78−7.86 (m, 2H), 7.58−7.60 (m, 3H), 7.49−7.53 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 152.7, 149.1, 134.9, 133.2, 131.8, 129.0, 128.2, 127.9, 127.0, 126.3, 121.4.

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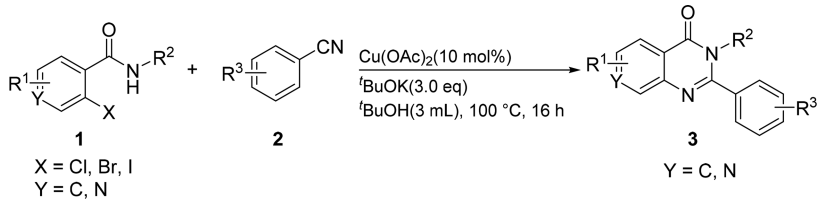
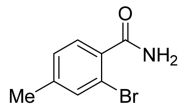
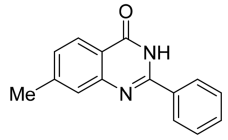
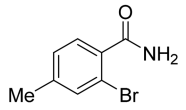
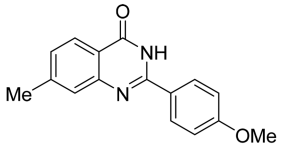
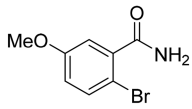
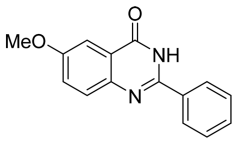
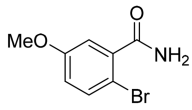
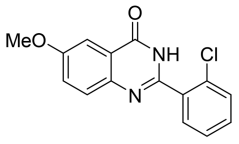
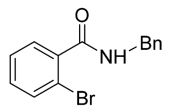
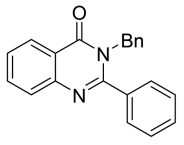
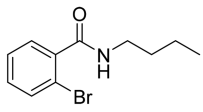
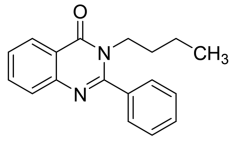
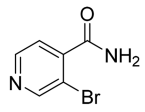
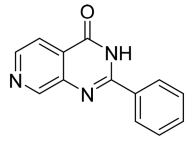
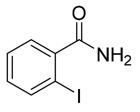
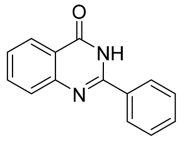
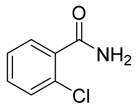
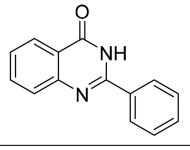
Table 3. Synthesis of Quinazolin-4(3*H*)-ones from Various 2-Halobenzamides[a]



Entry	Substrate **1**		Product **3**		Yield (%)[b]
1[c]		**1b**		**3m**	84
2[d]		**1b**		**3n**	75
3[c]		**1c**		**3o**	60
4[e]		**1c**		**3p**	41
5[c]		**1d**		**3q**	86
6[c]		**1e**		**3r**	80
7[c]		**1f**		**3s**	35
8[c]		**1g**		**3a**	85
9[c]		**1h**		**3a**	NR

[a]Reaction conditions: 2-Bromobenzamide (**1a**, 0.5 mmol), benzonitrile (**2a**, 0.75 mmol), base (1.5 mmol), and copper catalyst (10 mol %) in solvent (3.0 mL) at 100 °C for 16 h. [b]Isolated yield was provided. [c]Reacted with benzonitrile (**2a**, 0.75 mmol). [d]Reacted with 4-methoxybenzonitrile (**2c**, 0.75 mmol). [e]Reacted with 2-chlorobenzonitrile (**2f**, 0.75 mmol).

*2-(4-Methylphenyl)quinazolin-4(3H)-one (**3b**).*[20] White solid (0.093 g, 79% yield). Mp 261−264 °C (lit.[16] 261−263 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (bs, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.13−8.09 (m, 2H), 7.82−7.80 (m, 1H), 7.72 (m, 1H),

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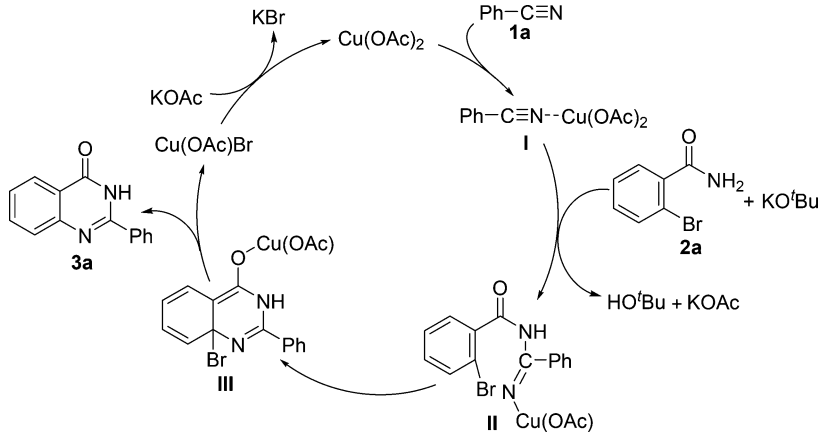
Scheme 2. Possible Reaction Mechanism



7.52−7.48 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 152.2, 148.8, 141.4, 134.5, 129.9, 129.2, 127.7, 127.4, 126.4, 125.8, 120.9, 21.0.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (**3c**).[20] White solid (0.107 g, 85% yield). Mp 247−248 °C (lit.[16] 245−246 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (bs, 1H), 8.23−8.16 (m, 2H), 8.13 (d, J = 7.9 Hz, 1H), 7.83−7.79 (m, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.50−7.48 (m, 1H), 7.08 (d, J = 7.9, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 152.7, 149.2, 141.9, 134.9, 130.3, 129.6, 128.1, 127.8, 126.8, 126.3, 121.4, 21.4.

2-(o-Tolyl)quinazolin-4(3H)-one (**3d**).[21] White solid (0.072 g, 61% yield). Mp 219−221 °C (lit.[19] 220−222 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (bs, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 3.6 Hz, 2H), 7.58 (m, 1H), 7.53−7.48 (m, 1H), 7.46−7.40 (m, 1H), 7.35 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 154.3, 148.7, 136.1, 134.4, 134.2, 130.5, 129.8, 129.1, 127.3, 126.6, 125.7, 125.6, 120.9, 19.5.

2-(2-Aminophenyl)quinazolin-4(3H)-one (**3e**).[22] Brownish solid (0.030 g, 25% yield). Mp 226−228 °C (lit.[18] 224−226 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (bs, 1H), 8.14 (dd, J = 1.6, 7.9 Hz, 1H), 7.84−7.80 (m, 1H), 7.78−7.70 (m, 2H), 7.53−7.45 (m, 1H), 7.26−7.18 (m, 1H), 7.08 (bs, 2H), 6.84 (d, J = 8.3 Hz, 1H), 6.65−6.57 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 154.0, 149.9, 148.5, 135.0, 132.3, 129.3, 127.4, 126.7, 126.2, 120.9, 117.1, 115.5, 112.8.

2-(4-Chlorophenyl)quinazolin-4(3H)-one (**3f**).[20] White solid (0.079 g, 62% yield). Mp 298−300 °C (lit.[16] 299−301 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (bs, 1H), 8.23−8.18 (m, 2H), 8.17−8.13 (dd, J = 0.8, 7.6 Hz, 1H), 7.87−7.83 (m, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.65−7.60 (m, 2H), 7.54 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 166.9, 139.4, 136.1, 133.1, 132.7, 130.6, 129.4, 128.6, 128.3, 127.5, 118.7.

2-(2-Bromophenyl)quinazolin-4(3H)-one (**3g**).[23] Light brown solid (0.052 g, 35% yield). Mp 175−177 °C (lit.[17] 175−177 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (bs, 1H), 8.18 (dd, J = 1.6, 8.0 Hz, 1H), 7.85 (m, 1H), 7.77 (dd, J = 1.2, 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 1.6, 7.2 Hz, 1H), 7.60−7.46 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 153.4, 148.6, 135.9, 134.7, 132.7, 131.7, 130.8, 127.8, 127.5, 127.2, 125.9, 121.3, 121.0.

2-(2-Chlorophenyl)quinazolin-4(3H)-one (**3h**).[23] White solid (0.072 g, 57% yield). Mp 172−173 °C (lit.[17] 172−174 °C). 1H NMR (400 MHz, DMSO-d_6) δ 12.64 (bs, 1H), 8.19 (dd, J = 1.2, 8.0 Hz, 1H), 7.85 (m, 1H), 7.73−7.66 (m, 2H), 7.65−7.53 (m, 3H), 7.49 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 152.2, 148.6, 134.6, 133.8, 131.6, 131.5, 130.8, 129.6, 127.5, 127.2, 127.1, 125.8, 121.3.

2-(4-Fluorophenyl)quinazolin-4(3H)-one (**3i**).[21] White solid (0.072 g, 60% yield). Mp 292−294 °C (lit.[19] 293−295 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.57 (bs, 1H), 8.32−8.21 (m, 2H), 8.16 (dd, J = 8.0, 1.7 Hz, 1H), 7.84 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.52 (m, 1H), 7.43−7.35 (m, 2H).; ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9(d, $^1J_{C-F}$ = 248.0 Hz), 162.2, 151.3, 148.5, 134.5, 130.2(d, $^3J_{C-F}$ = 9.0 Hz), 129.2, 127.3, 126.5, 125.7, 120.7, 115.5(d, $^2J_{C-F}$ = 22 Hz).

2-(2-Pyridyl)quinazoline-4(3H)-one (**3j**).[24] White solid (0.061 g, 55% yield). Mp 169−171 °C (lit.[28] 168−170 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (bs, 1H), 8.73 (s, 1H), 8.42 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 7.84 (t, J = 7.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (m, 1H), 7.54 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 150.0, 149.0, 148.7, 138.0, 134.7, 127.7, 127.3, 126.6, 126.2, 122.2, 122.0.

2-Methylquinazolin-4(3H)-one (**3k**).[25] White solid (0.060 g, 75% yield). Mp 238−240 °C (lit.[20] 235−239 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (bs, 1H), 8.06 (dd, J = 1.6, 8.0 Hz, 1H), 7.80−7.72 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46−7.41 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 154.7, 149.4, 134.7, 127.0, 126.3, 126.1, 121.1, 21.9.

2-Butylquinazolin-4(3H)-one (**3l**).[26] White solid (0.077 g, 71% yield). Mp 107−108 °C (lit.[21] 108−109 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.20 (bs, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.79−7.73 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.50−7.43 (m, 1H), 2.82 (t, J = 8.0 Hz, 2H), 1.93−1.84 (m, 2H), 1.54−1.45 (m, 2H), 1.25 (m, 2H) 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 157.2, 149.5, 134.7, 127.2, 126.2, 126.2, 120.4, 35.6, 29.7, 22.4, 13.8.

7-Methyl-2-phenylquinazolin-4(3H)-one (**3m**).[20] Light yellow solid (0.099 g, 84% yield). Mp 240−241 °C (lit.[16] 240−241 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (bs, 1H), 8.17 (d, J = 7.6 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.65−7.48 (m, 4H), 7.33 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 152.5, 148.9, 145.2, 132.9, 131.9, 128.1, 127.8, 127.2, 125.8, 118.7, 21.4.

2-(4-Methoxyphenyl)-7-methylquinazolin-4(3H)-one (**3n**).[20] Light yellow solid (0.094 g, 75% yield). Mp 248−250 °C (lit.[16] 246−248 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (bs, 1H), 8.21−8.14 (m, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.28 (dd, J = 1.6, 8.4 Hz, 1H), 7.11−7.03 (m, 2H), 3.84 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 161.9, 152.0, 149.1, 145.1, 129.5, 127.7, 127.0, 125.8, 124.9, 118.4, 114.1, 55.5, 21.4.

6-Methoxy-2-phenylquinazolin-4(3H)-one (**3o**).[20] White solid (0.076 g, 60% yield). Mp 250−252 °C (lit.[16] 249−251 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (bs, 1H), 8.16 (dd, J = 1.6, 7.6 Hz, 2H), 7.70 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 3.2 Hz, 1H), 7.58−7.50 (m, 3H), 7.44 (dd, J = 3.2, 8.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.12, 157.8, 150.2, 143.3, 132.9, 131.1, 129.3, 128.7, 127.6, 124.2, 121.9, 105.9, 55.7.

2-(2-Chlorophenyl)-6-methoxyquinazolin-4(3H)-one (**3p**). Light yellow solid (0.058 g, 41% yield). Mp 214−215 °C. IR (KBr) ν 3430, 3066, 1670, 1604, 1491, 1371, 1257, 1088, 1036, 891, 835, 766 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (bs, 1H), 7.69−7.64 (m, 2H), 7.63−7.59 (m, 1H), 7.58−7.53 (m, 2H), 7.51−7.43 (m, 2H), 3.90(s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 158.2, 150.1, 143.1, 134.0, 131.7, 131.6, 131.1, 129.7, 129.3, 127.3, 124.1, 122.2, 106.0,

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55.8; HRMS m/z (ESI, ion trap) calcd for $C_{15}H_{12}ClN_2O_2$ $(M + H)^+$ 287.0587, found 287.0587.

*3-Benzyl-2-phenylquinazolin-4(3H)-one (**3q**).*[27] White solid (0.134 g, 86% yield). Mp 143−145 °C (lit.[22] 131−133 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.0 Hz, 1H), 7.85−7.74 (m, 2H), 7.56−7.50 (m, 1H), 7.49−7.43 (m, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.23−7.16 (m, 3H), 6.96−6.89 (m, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 156.4, 147.3, 136.6, 135.3, 134.6, 129.9, 128.6, 128.5, 128.0, 127.6, 127.4, 127.2, 127.1, 127.0, 120.9, 48.8.

*3-Butyl-2-phenylquinazolin-4(3H)-one (**3r**).*[28] White solid (0.111 g, 80% yield). Mp 112−113 °C (lit.[23] 115−116 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.0 Hz, 1H), 7.79−7.70 (m, 2H), 7.57−7.46 (m, 6H), 3.98 (t, J = 7.6 Hz, 2H), 1.65−1.55 (m, 2H), 1.20−1.14 (m, 2H), 0.76 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 156.2, 147.2, 135.6, 134.3, 129.8, 128.8, 127.8, 127.4, 126.9, 126.8, 120.9, 45.7, 30.7, 19.9, 13.4.

*2-Phenylpyrido[3,4-d]pyrimidin-4(3H)-one (**3s**).*[29] White solid (0.039 g, 35% yield). Mp 264−266 °C (lit.[29] 266−267 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (bs, 1H), 9.12 (s, 1H), 8.65 (d, J = 5.2 Hz, 1H), 8.22−8.17 (m, 2H), 7.97 (dd, J = 0.8, 5.2 Hz, 1H), 7.64−7.54 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 154.5, 150.7, 145.7, 143.6, 132.6, 131.7, 128.6, 127.9, 125.9, 118.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01460.

Characterization for compounds, including copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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