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Palladium-Catalyzed One-Pot Synthesis of Quinazolinones via *tert*-Butyl Isocyanide Insertion

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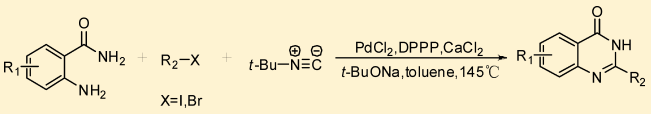
Supporting Information

ABSTRACT: A novel palladium-catalyzed three-component reaction for the synthesis of quinazolin-4(3*H*)-ones from readily available 2-aminobenzamides and aryl halides via a palladium-catalyzed isocyanide insertion/cyclization sequence has been developed. This methodology efficiently constructs quinazolin-4(3*H*)-ones in moderate to excellent yields with the advantages of operational simplicity.



INTRODUCTION

Quinazolinones, existing in many naturally occurring alkaloids,[1] are a significant class of heterocycles. They exhibit various kinds of biological activities, including antibacterial,[2] antifungal,[3] antimalarial,[4] anticancer,[5] antihypertensive,[6] antitubercular,[7] inhibitors of derived growth factor receptor phosphorylation,[8] anticonvulsant,[9] selective COX-II inhibitors,[10] and other activities.[11] Moreover, they are important building blocks in the synthesis of natural products[12] and bioactive compounds. As a result, numerous methods for the synthesis of quinazolinones based on the condensation of 2-aminobenzoic acids or their derivatives with aldehydes, acid chlorides, or carboxylic acid derivatives have been developed[13] (Scheme 1). Remarkably, carbon monoxide (CO) used as C1 source can be introduced to preparing carbonyl-containing compounds. For instance, the groups of Zhu[14a] and Beller[14b] have reported the construction of quinazolin-4(3*H*)-ones with moderate yield via palladium-catalyzed CO insertion (Scheme 1).

However, the drawbacks of long reaction time, high pressure, and toxicity limited the applications of CO reactions. Isocyanides, which are economic and stable kinds of liquid or solid compounds, are considered as an isoelectronic species of gaseous CO. Thus, they could be used as an easier handled and a safer alternative to odorless CO in palladium-catalyzed carbonylation reactions. Since the initial work of Passerini[15] and Ugi,[16] the utility of nucleophilicity and electrophilicity of isocyanides in multicomponent reactions (MCRs) has been widely explored. In the past decades, other reactive properties involving isocyanides, such as isocyanide insertion, have been attracting more attention. Many applications of isocyanide as a versatile C1 building block in palladium-catalyzed insertion into carbon–halogen bonds,[17] heteroatom–hydrogen bonds,[18a−c] carbon–hydrogen bonds,[19] and double carbon–metal bonds in carbenes[18d,e] have been reported, which provide a potential for synthesizing nitrogen-containing fine chemicals. Our group has successfully constructed the skeleton of isocoumarins, phthalides,[17n] and alkynones[17q] through palladium-catalyzed isocyanide insertion into C–X bonds. Lang,[17j,r] Shipman,[17s] and their co-workers provided a similar palladium-catalyzed three-component approach to forming *N*-containing heterocyclic compounds without further hydrolysis. In a continuation of our interest in forming potentially bioactive nitrogen heterocycles, we considered that quinazolin-4(3*H*)-ones could be prepared by establishing a C–N bond between easily accessible anthranilamide[20] and aryl halides via palladium-catalyzed isocyanide insertion under more convenient and mild conditions (Scheme 2).

RESULTS AND DISCUSSION

Initially, anthranilamide and iodobenzene were reacted with *tert*-butyl isocyanide in the presence of $PdCl_2$, DPPP, and Cs_2CO_3 in toluene, and the reaction conditions were modeled after the report of Shipman.[17s] When the reaction was performed at 120 °C for 8 h, the desired product 2-phenylquinazolin-4(3*H*)-one was formed in 27% yield because of the generation of amide[17i] (Table 1, entry 1). A slightly higher yield of **3a** was obtained in the presence of $CaCl_2$ as a dry agent (Table 1, entries 2–4); nevertheless, anthranilamide could not be converted totally. To our delight, complete transformation of anthranilamide was achieved (Table 1, entry 5) by increasing the amount of iodobenzene, *tert*-butyl isocyanide, and Cs_2CO_3. Higher temperature gave an even better yield of 62% (Table 1, entry 6). Further optimization led to an improved yield of 93% with changing the base to *t*-BuONa (Table 1, entries 7 and 8). Solvent screening revealed that toluene was the optimal solvent (Table 1, entries 9–11). A lower yield was obtained when other palladium catalysts such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were employed (Table 1, entries 12 and 13). After many trials with other commercially available ligands (Table 1, entries 14–18), DPPP gave the best yields of quinazolinone. Thus, we chose $PdCl_2$ (5%) and DPPP (10%) as the catalyst system, with *t*-BuONa (4 equiv) as base, $CaCl_2$

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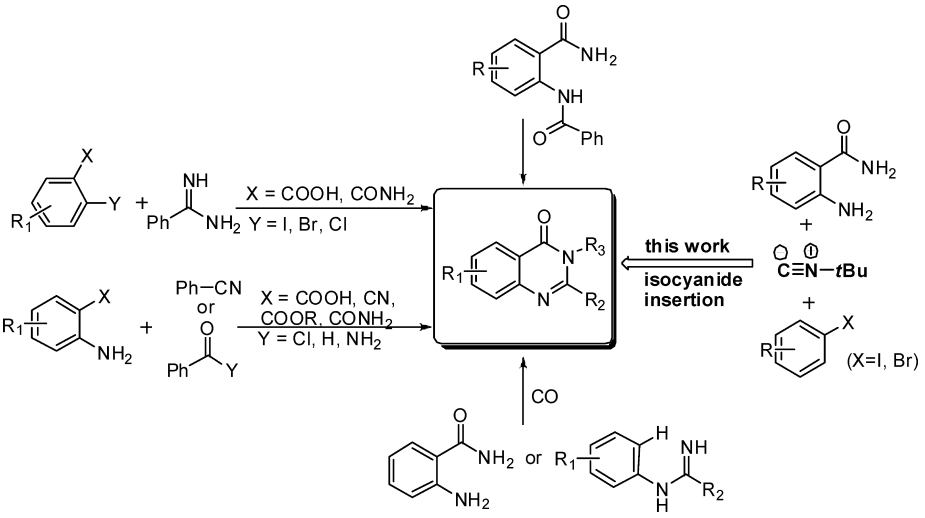
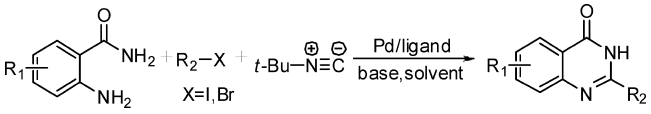
Scheme 1. Major Methods for Synthesis of Quinazolin-4(3*H*)-ones



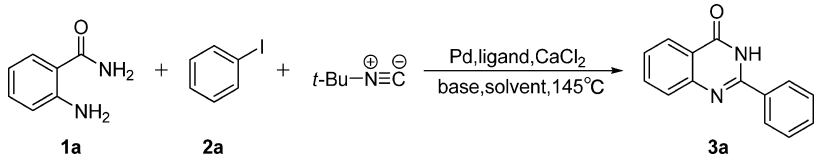
Scheme 2. Strategy to Quinazolin-4(3*H*)-ones via *tert*-Butyl Isocyanide Insertion



(2 equiv) as an additive, and toluene as solvent to continue our investigation.

Having optimized the reaction conditions, we next explored the scope of the reaction using anthranilamide and various aryl halides (Table 2). As indicated in Table 2, most aryl iodides with electron-donating groups give better results (Table 2, entries 1−4, 9 and 11) than the substrates with electron-withdrawing groups (Table 2, entries 6, 8, and 10). Due to a

Table 1. Condition Optimizations[a]



1a 2a 3a

entry	catalyst	ligand	base	solvent	temp (°C)	yield[b] (%)
1	$PdCl_2$	DPPP	Cs_2CO_3	toluene	120	27[c]
2	$PdCl_2$	DPPP	Cs_2CO_3	toluene	120	35[c,d]
3	$PdCl_2$	DPPP	Cs_2CO_3	toluene	120	29[c,e]
4	$PdCl_2$	DPPP	Cs_2CO_3	toluene	120	28[c,f]
5	$PdCl_2$	DPPP	Cs_2CO_3	toluene	120	53
6	$PdCl_2$	DPPP	Cs_2CO_3	toluene	145	62
7	$PdCl_2$	DPPP	AcONa	toluene	145	trace
8	$PdCl_2$	DPPP	*t*-BuONa	toluene	145	93
9	$PdCl_2$	DPPP	*t*-BuONa	dioxane	145	69
10	$PdCl_2$	DPPP	*t*-BuONa	DMSO	145	61
11	$PdCl_2$	DPPP	*t*-BuONa	DMF	145	trace
12	$Pd(OAc)_2$	DPPP	*t*-BuONa	toluene	145	53
13	$Pd_2(dba)_3$	DPPP	*t*-BuONa	toluene	145	39
14	$PdCl_2$	PCy_3	*t*-BuONa	toluene	145	28
15	$PdCl_2$	DPPB	*t*-BuONa	toluene	145	88
16	$PdCl_2$	DPPF	*t*-BuONa	toluene	145	73
17	$PdCl_2$	DPEPhos	*t*-BuONa	toluene	145	51
18	$PdCl_2$	(*R*)-BINAP	*t*-BuONa	toluene	145	80

[a]Reaction conditions: All reactions were performed with **1a** (0.7 mmol), **2a** (2.1 mmol), *tert*-butyl isocyanide (2.1 mmol), catalyst (5 mol %), ligand (10 mol %), base (4 equiv), and $CaCl_2$ (2 equiv) in 3.0 mL of solvent under nitrogen for 8 h in a round-bottom flask. DPPP = 1,3-bis(diphenylphosphino)propane, PCy_3 = tricyclohexylphosphine, DPPB = 1,4-bis(diphenylphosphino)butane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, DPEPhos = bis[(2-diphenylphosphino)phenyl]ether, (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [b]Isolated yield. [c]The reaction condtions were **1a** (0.7 mmol), **2a** (0.84 mmol), *tert*-butyl isocyanide (0.84 mmol), catalyst (5 mol %), ligand (10 mol %), and base (2 equiv) in 3.0 mL of solvent without $CaCl_2$. [d]Anhydrous $CaCl_2$ (2 equiv). [e]Anhydrous Na_2SO_4 (2 equiv). [f]Anhydrous $MgSO_4$ (2 equiv).

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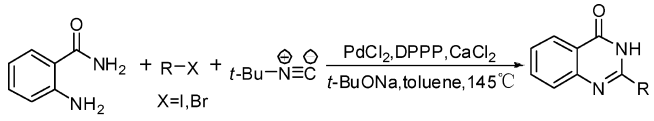
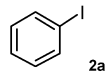
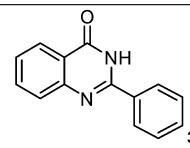
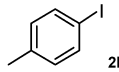
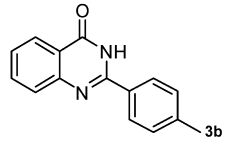
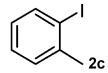
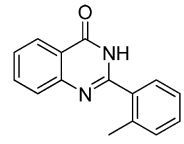
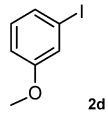
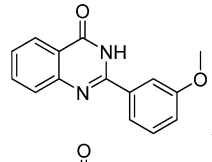
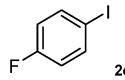
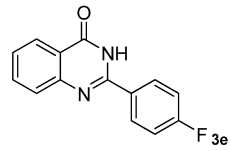
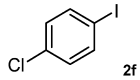
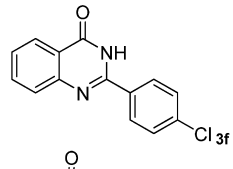
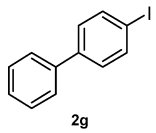
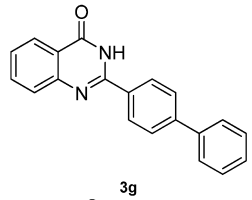
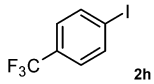
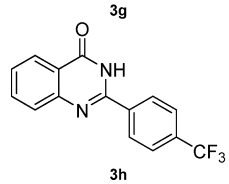
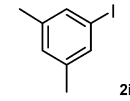
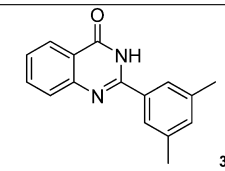
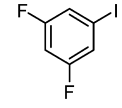
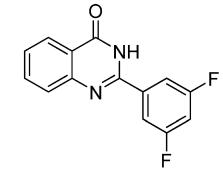
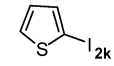
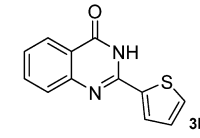
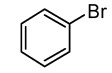
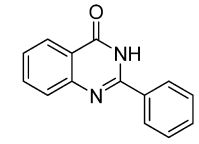
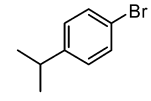
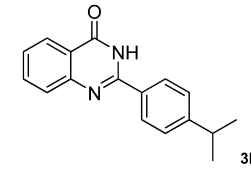
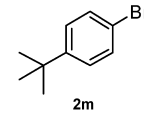
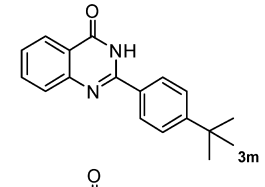
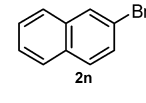
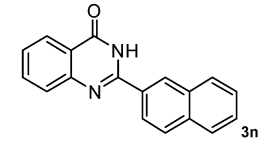
Table 2. Synthesis of Quinazolin-4(3*H*)-ones from Various Aryl Halides via Palladium-Catalyzed One-Pot Cyclization Reaction[a,b]



1a 2a-2n 3a-3n

entry	substrate	product	yield (%)
1	 2a	 3a	93
2	 2b	 3b	88
3	 2c	 3c	73
4	 2d	 3d	81
5	 2e	 3e	86
6	 2f	 3f	66
7	 2g	 3g	49
8	 2h	 3h	41
9	 2i	 3i	93
10	 2j	 3j	43
11	 2k	 3k	65
12			89
13	 2l	 3l	92
14	 2m	 3m	90
15	 2n	 3n	43[b]

[a]All reactions were performed under nitrogen, using anthranilamide (0.7 mmol), aryl halides (2.1 mmol), *tert*-butyl isocyanide (2.1 mmol), $PdCl_2$ (5 mol %), DPPP (10 mol %), *t*-BuONa (4 equiv), and $CaCl_2$ (2 equiv) in toluene (3.0 mL) at 145 °C for 8 h. [b]Reaction at 120 °C, 10 h

steric effect, the reaction of **1a** with *o*-methyliodobenzene (Table 2, entry 3) afforded a lower yield than *p*-methyliodobenzene (Table 2, entry 2). *m*-Methoxyiodobenzene provided the quinazolin-4(3*H*)-ones in good yield (Table 2, entry 4). However, as an electron-donating group, *p*-phenyliodobenzene gave a poor yield (Table 2, entry 7). As for electron-poor substituents, such as *p*-fluoro, *p*-chloro, and *p*-trifluoromethyl groups, the desired products were obtained in 41−86% yield (Table 2, entries 5, 6, and 8). In addition, the product of dimethyl-substituted aryl iodide was efficiently generated in 93% yield (Table 2, entry 9), but the substrate with a relevant 3,5-difluorophenyl group had a low yield (Table 2, entry 10). Heteroaromatic substrates were converted to the corresponding product in good yield (Table 2, entry 11). Besides, the yield of bromobenzene (Table 2, entry 12) was a little lower than that of iodobenzene. Some aryl bromides

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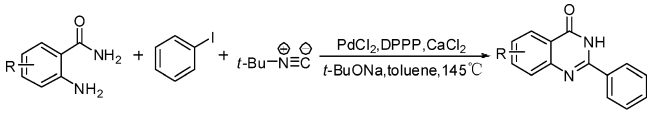
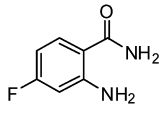
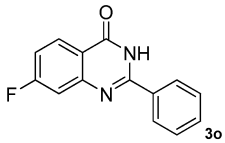
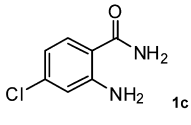
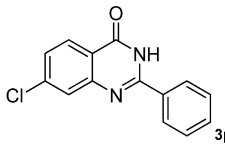
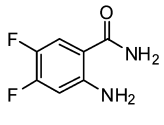
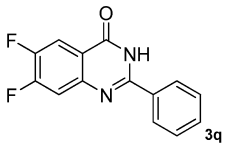
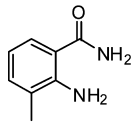
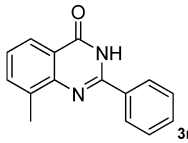
screened under our best conditions were transformed to the desired quinazolinones in moderate to excellent yield (Table 2, entries 13−15). ^{1}H NMR/^{13}C NMR spectra of **3l** revealed that there was tautomerism between quinazolin-4(3*H*)-one and quinazolin-4(1*H*)-one.

To extend the application of this reaction, we then investigated the reaction of various anthranilamides, and the results are summarized in Table 3. Both electron-rich (Table 3, entry 4) and electron-poor (Table 3, entries 1−3) substrates gave good yields, whereas difluoro-substituted anthranilamides gave an even lower yield (Table 3, entry 3).

Table 3. Synthesis of Quinazolin-4(3*H*)-ones from Various Anthranilamides via Palladium-Catalyzed One-Pot Cyclization Reaction[a]



1b-1e 2a 3o-3r

entry	substrate	product	yield (%)
1	 1b	 3o	85
2	 1c	 3p	75
3	 1d	 3q	41
4	 1e	 3r	75

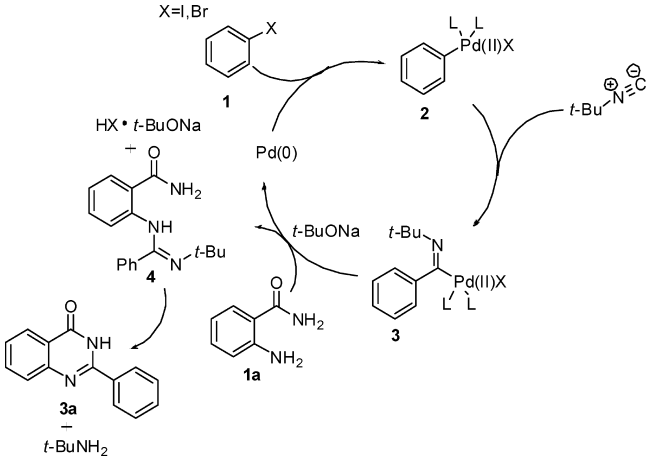
[a]All reactions were performed under nitrogen, using anthranilamides (0.7 mmol), iodobenzene (2.1 mmol), *tert*-butyl isocyanide (2.1 mmol), $PdCl_2$ (5 mol %), DPPP (10 mol %), *t*-BuONa (4 equiv), and $CaCl_2$ (2 equiv) in toluene (3.0 mL) at 145 °C for 8 h.

A plausible mechanism for this reaction is depicted in Scheme 3. Oxidative addition of aryl halides to the Pd(0) catalyst facilitates the formation of palladium complex **2**, followed by *tert*-butyl isocyanide insertion to get palladium(II) species **3**. Then, under the assistance of *t*-BuONa, the addition of 2-aminobenzamide gives the generation of **4**, which leads to the desired 4(3*H*)-quinazolinones after cyclization with losing *tert*-butylamine.

CONCLUSIONS

In summary, we have demonstrated a novel method for the preparation of quinazolin-4(3*H*)-ones from anthranilamides and aryl halides with isocyanide insertion in one step by an efficient palladium-catalyzed three-component reaction, which proceeded in reasonable to excellent yields. The strategy of constructing a C−N bond without further hydrolytic deamination offers a rapid and operationally simple route avoiding the use of toxic carbon monoxide under high pressure conditions for this class of compounds.

Scheme 3. Plausible Mechanism for the Synthesis of Quinazolin-4(3*H*)-ones



EXPERIMENTAL SECTION

General Remarks. Chemicals and reagents were purchased from commercial suppliers and used without further purification. All anhydrous solvents used in the reactions were dried and freshly distilled. TLC was performed on silica HSGF254 plates. Melting points were determined with a digital melting-point apparatus. ^{1}H and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with TMS as internal standard using a 400/101 MHz (^{1}H/^{13}C) or 600/151 MHz (^{1}H/^{13}C) spectrometer. Chemical shifts (δ) are given in ppm and *J* in Hz. HRMS or LRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

General Procedure for the Synthesis of Quinazolinones. 1 (0.7 mmol, 1 equiv), **2** (2.1 mmol, 3 equiv), *tert*-butyl isocyanide (2.1 mmol, 237 μL, 3 equiv), $PdCl_2$ (0.035 mmol, 6 mg, 5 mol %), DPPP (0.07 mmol, 29 mg, 10 mol %), *t*-BuONa (2.8 mmol, 269 mg, 4 equiv), anhydrous $CaCl_2$ (1.4 mmol, 156 mg, 2 equiv), and anhydrous toluene (3.0 mL) were added to a 25 mL round-bottom flask equipped with a magnetic stirring bar. The flask was purged with nitrogen and refluxed at 145 °C for 8 h. After completion of the reaction indicated by TLC, the mixture was filtered and the solvent was removed under vacuum. Then, the resulting mixture was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to provide the pure target product.

2-Phenylquinazolin-4(3H)-one (**3a**):[14b] White solid (145 mg, 93%); mp 239−240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H), 8.21 (t, *J* = 8.8 Hz, 3H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.66−7.51 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.2, 152.3, 148.8, 134.6, 132.7, 131.4, 128.6, 127.8, 127.5, 126.6, 125.9, 121.0. LRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}N_2O$ [M + H]$^+$, 223.1; found, 223.0.

2-p-Tolylquinazolin-4(3H)-one (**3b**):[14a] White solid (145 mg, 88%). mp 231−234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.45 (s, 1H), 8.11 (d, *J* = 6.8 Hz, 3H), 7.76 (dd, *J* = 20.5, 9.9 Hz, 2H), 7.49 (s, 1H), 7.32 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.8, 148.4, 141.0, 134.1, 129.4, 128.8, 127.3, 127.0, 125.9, 125.4, 120.5, 20.5. LRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}N_2O$ [M + H]$^+$, 237.1; found, 237.0.

2-o-Tolylquinazolin-4(3H)-one (**3c**):[14a] White solid (121 mg, 73%). mp 220−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.45 (s, 1H), 8.18 (d, *J* = 7.3 Hz, 1H), 7.82 (d, *J* = 6.8 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 5.7 Hz, 2H), 7.41 (d, *J* = 6.6 Hz, 1H), 7.34 (d, *J* = 7.1 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ

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161.9, 154.4, 148.8, 136.2, 134.5, 134.3, 130.6, 129.9, 129.2, 127.9, 126.7, 125.8, 125.7, 121.0, 19.6. LRMS (ESI): m/z calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$, 237.1; found, 237.1.

*2-(3-Methoxyphenyl)quinazolin-4(3H)-one (**3d**):*[14a] White solid (143 mg, 81%); mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.83−7.77 (m, 2H), 7.74 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 159.4, 152.0, 148.7, 134.6, 134.0, 129.8, 127.6, 126.6, 125.9, 121.1, 120.2, 117.6, 112.5, 55.4. LRMS (ESI): m/z calcd for $C_{15}H_{12}N_2O_2$ $[M + H]^+$, 253.1; found, 253.0.

*2-(4-Fluorophenyl)quinazolin-4(3H)-one (**3e**):*[13n] White solid (140 mg, 83%); mp 293−295 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.53 (s, 1H), 8.23 (s, 2H), 8.14 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 6.9 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 6.7 Hz, 1H), 7.37 (t, J = 8.0 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 165.3, 163.6, 162.7, 151.8, 149.1, 135.1, 130.8, 130.8, 129.7, 129.7, 127.9, 127.0, 126.3, 121.3, 116.1, 116.0. LRMS (ESI): m/z calcd for $C_{14}H_9FN_2O$ $[M + H]^+$, 241.1; found, 241.0.

*2-(4-Chlorophenyl)quinazolin-4(3H)-one (**3f**):*[13g] White solid (118 mg, 66%); mp 278−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.62 (s, 1H), 8.19 (d, J = 8.1 Hz, 2H), 8.15 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 151.5, 148.7, 136.4, 134.9, 132.9, 131.6, 129.8, 128.8, 127.6, 127.0, 126.0, 121.1. LRMS (ESI): m/z calcd for $C_{14}H_9ClN_2O$ $[M + H]^+$, 257.0; found, 256.9.

*2-(Biphenyl-4-yl)quinazolin-4(3H)-one (**3g**):*[23] White solid (102 mg, 49%); mp 265−267 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H), 8.30 (d, J = 7.9 Hz, 2H), 8.17 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.8 Hz, 3H), 7.76 (d, J = 5.9 Hz, 4H), 7.55−7.47 (m, 2H), 7.42 (d, J = 6.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 162.7, 152.4, 149.2, 143.3, 139.4, 135.1, 132.0, 129.5, 128.8, 128.6, 128.0, 127.3, 127.2, 127.0, 126.3, 121.5. LRMS (ESI): m/z calcd for $C_{20}H_{14}N_2O$ $[M + H]^+$, 299.1; found, 299.0.

*2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3H)-one (**3h**):*[14b] White solid (83 mg, 41%); mp 229−230 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (s, 1H), 8.35 (s, 2H), 8.16 (s, 1H), 8.05−7.62 (m, 4H), 7.54 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.2, 161.1, 151.2, 148.5, 148.2, 147.0, 147.0, 137.8, 137.8, 136.6, 136.6, 134.8, 134.8, 131.7, 129.0, 128.7, 128.6, 127.7, 127.7, 127.1, 126.1, 125.9, 125.5, 125.5, 125.3, 125.3, 123.1, 122.6, 121.2. LRMS (ESI): m/z calcd for $C_{15}H_9F_3N_2O$ $[M + H]$+, 291.1; found, 290.9.

*2-(3,5-Dimethylphenyl)quinazolin-4(3H)-one (**3i**):*[24] White solid (156 mg, 89%); mp 273−273 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1H), 8.14 (d, J = 7.1 Hz, 1H), 7.81 (s, 3H), 7.73 (d, J = 6.9 Hz, 1H), 7.51 (d, J = 6.3 Hz, 1H), 7.20 (s, 1H), 2.35 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.1, 152.4, 148.8, 137.8, 134.6, 132.7, 128.3, 127.4, 126.5, 125.8, 125.5, 121.0. LRMS (ESI): m/z calcd for $C_{16}H_{14}N_2O$ $[M + H]^+$, 251.1; found, 251.0.

*2-(3,5-Difluorophenyl)quinazolin-4(3H)-one (**3j**):* White solid (78 mg, 43%); mp 259−260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.19 (m, 1H), 8.00−7.73 (m, 4H), 7.67 (s, 1H), 7.58−7.31 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.1, 164.0, 163.6, 163.5, 162.5, 161.7, 161.5, 161.2, 161.1, 150.4, 148.6, 148.4, 147.4, 137.8, 137.8, 137.7, 137.6, 136.7, 136.6, 136.5, 135.3, 129.4, 129.1, 128.2, 127.7, 126.5, 126.4, 123.6, 121.7, 114.8, 114.7, 114.6, 114.5, 111.7, 111.6, 111.5, 111.4, 110.0, 109.8, 109.5, 107.6, 107.3, 107.0. IR (KBr): ν = 1684, 1594, 1337, 1123, 989, 864, 769, 670 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_8F_2N_2O$ $[M + H]^+$, 259.0677; found, 259.0691.

*2-(Thiophen-2-yl)quinazolin-4(3H)-one (**3k**):*[14b] Yellow solid (104 mg, 65%); mp 278−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.67 (s, 1H), 8.23 (s, 1H), 8.12 (d, J = 6.9 Hz, 1H), 7.87 (s, 1H), 7.80 (s, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.48 (s, 1H), 7.23 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 162.2, 149.1, 148.3, 137.8, 135.1, 132.6, 129.8, 128.9, 127.4, 126.8, 126.4, 121.3. LRMS (ESI): m/z calcd for $C_{12}H_8N_2OS$ $[M + H]^+$, 229.0; found, 229.0.

*2-(4-Isopropylphenyl)quinazolin-4(3H)-one (**3l**):*[25] Tautomer ratio (2:1), white solid (170 mg, 92%); mp 153−155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ12.51 (s, 3H), 8.21 (s, 1H, tautomer), 8.11 (m, 8H), 7.85 (d, J = 6.0 Hz, 1H, tautomer), 7.78 (s, 3H), 7.72 (d, J = 6.5 Hz, 2H), 7.63 (s, 1H, tautomer), 7.48 (s, 2H), 7.44−7.33 (m, 6H), 2.92 (d, J = 4.9 Hz, 3H), 1.19 (s, 18H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.4, 161.2, 155.5, 152.3, 152.1, 149.3, 148.8, 147.2, 134.7, 134.5, 131.9, 131.2, 130.3, 128.5, 128.3, 127.9, 127.4, 126.6, 126.4, 126.1, 125.9, 122.9, 120.9. LRMS (ESI): m/z calcd for $C_{17}H_{16}N_2O$ $[M + H]^+$, 265.1; found, 265.0.

*2-(4-tert-Butylphenyl)quinazolin-4(3H)-one (**3m**):*[14b] White solid (173 mg, 89%); mp 151−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (s, 1H), 8.13 (d, J = 7.5 Hz, 3H), 7.85−7.79 (m, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.58−7.49 (m, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 154.3, 152.2, 134.6, 130.9, 130.0, 128.4, 127.6, 126.5, 125.9, 125.4, 120.9. LRMS (ESI): m/z calcd for $C_{16}H_{14}N_2O$ $[M + H]^+$, 279.1; found, 279.0.

*2-(Naphthalen-2-yl)quinazolin-4(3H)-one (**3n**):*[14b] White solid (82 mg, 43%); mp 285−287 °C. ^{1}H NMR (400 MHz, DMSO): δ 12.86 (s, 1H), 8.25 (s, 1H), 8.17−8.01 (m, 3H), 7.99−7.80 (m, 4H), 7.70−7.44 (m, 5H). ^{13}C NMR (101 MHz, DMSO): δ 161.5, 149.7, 147.4, 135.6, 135.0, 134.2, 132.0, 131.5, 130.2, 129.7, 128.7, 128.5, 128.0, 127.4, 126.3, 125.2, 123.0.

*7-Fluoro-2-phenylquinazolin-4(3H)-one (**3o**):*[21] White solid (143 mg, 85%); mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.62 (s, 1H), 8.36−7.99 (m, 3H), 7.70−7.42 (m, 4H), 7.35 (t, J = 8.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.1, 164.6, 161.6, 153.7, 151.0, 150.8, 132.4, 131.7, 130.9, 129.0, 128.9, 128.6, 127.9, 118.0, 115.2, 114.9, 112.5, 112.3. LRMS (ESI): m/z calcd for $C_{14}H_9FN_2O$ $[M + H]^+$, 241.1; found, 241.0.

*7-Chloro-2-phenylquinazolin-4(3H)-one (**3p**):*[13d] White solid (134 mg, 75%); mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 8.15 (d, J = 7.9 Hz, 1H), 7.88−7.80 (m, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.53 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 151.4, 148.6, 136.4, 134.8, 134.3, 131.6, 129.7, 128.8, 126.9, 126.0, 121.0. LRMS (ESI): m/z calcd for $C_{14}H_9N_2O$ $[M + H]^+$, 257.0; found, 256.9.

*6,7-Difluoro-2-phenylquinazolin-4(3H)-one (**3q**):*[22] White solid (74 mg, 41%); mp 249−250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1H), 8.13 (d, J = 6.5 Hz, 2H), 8.05−7.93 (m, 1H), 7.72 (dd, J = 10.7, 6.8 Hz, 1H), 7.62−7.45 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.1, 155.3, 155.1, 153.4, 152.7, 152.6, 149.7, 149.6, 147.2, 147.1, 146.8, 146.7, 132.4, 131.6, 128.6, 127.8, 118.3, 118.2, 115.4, 115.2, 113.5, 113.3. LRMS (ESI): m/z calcd for $C_{14}H_8F_2N_2O$ $[M + H]^+$, 259.1; found, 258.8.

*8-Methyl-2-phenylquinazolin-4(3H)-one (**3r**):*[14a] White solid (124 mg, 75%); mp 248−249 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (s, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.98 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.3 Hz, 3H), 7.38 (t, J = 7.5 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 163.0, 151.5, 147.6, 136.1, 135.3, 133.4, 131.8, 129.1, 128.2, 126.5, 123.9, 121.3, 17.6. LRMS (ESI): m/z calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$, 237.1; found, 237.0.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. 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.

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