Note

Copper-Catalyzed Radical Methylation/C-H Amination/ Oxidation Cascade for the Synthesis of Quinazolinones

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Copper-Catalyzed Radical Methylation/C-H Amination/ Oxidation Cascade for the Synthesis of Quinazolinones

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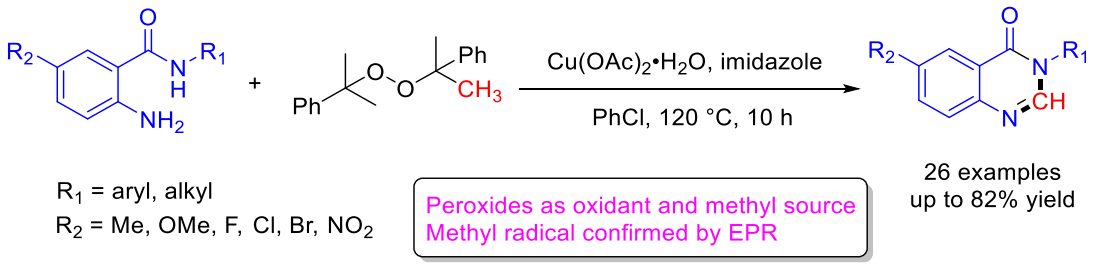
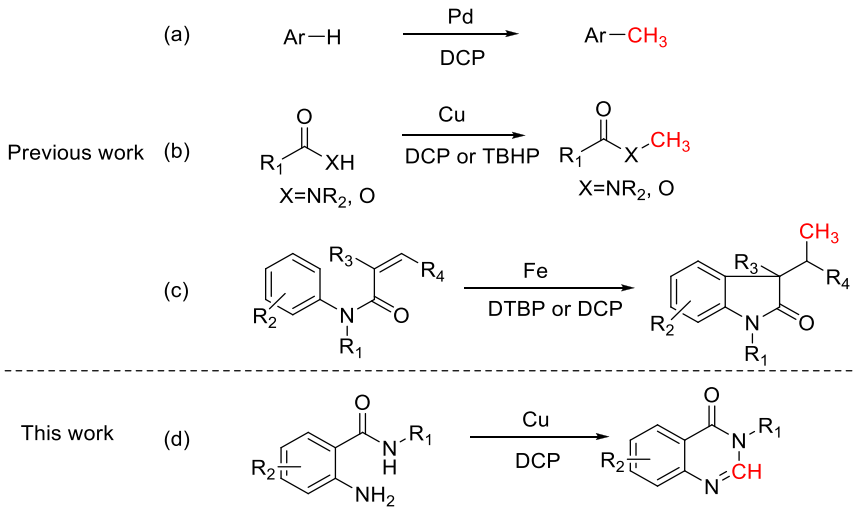


ABSTRACT: A copper-catalyzed radical methylation/sp^3 C-H amination/oxidation reaction for the facile synthesis of quinazolinone was developed. In this cascade reaction, dicumyl peroxide (DCP) acts not only as a useful oxidant, but also as an efficient methyl source. Notably, a methyl radical, generated from peroxide, was confirmed by electron paramagnetic resonance (EPR) for the first time.

The use of peroxides as methylation reagents has gained increasing attention in recent years. In 2008, Li developed a novel method for the direct methylation of aryl C-H bonds. In this reaction, dicumyl peroxide (DCP) was first used as both methylating reagents and hydrogen acceptor (Scheme 1a).[1a] Recently, a copper-catalyzed *N*-methylation of amides and *O*-methylation of carboxylic acids was developed with DCP as the methylating reagent by Chen's group (Scheme 1b).[1b] In the same year, Mao reported the copper-catalyzed methyl esterification of benzylic

alcohols, aldehydes, and acids using TBHP as the methylating reagent (Scheme 1b).[1c] Very recently, Cheng and Li respectively reported the iron-catalyzed radical arylmethylation of activated alkenes using di-tert-butylperoxide (DTBP) or DCP as the methyl source, leading to the biologically active product 3-ethyl-3-substituted indolin-2-one (Scheme 1c).[1d, 1e] In light of these results above, we reasoned that peroxides could be used as a methyl source for the construction of other useful compounds.

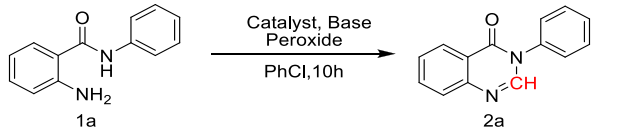


Scheme 1. The radical methylation reaction.

On the other hand, transition-metal-catalyzed oxidative amination of sp^3 C-H bond has emerged as a powerful and versatile method to form C-N bonds for its straightforward and atom-economical advantages, avoiding tedious prefunctionalized processes.[2] In particular, copper as an inexpensive and less toxic metal catalyst, has been widely used to catalyze the sp^3 C-H amination reaction.[3] Our group has also been focused on developing sp^3 C-H amination for the synthesis of heterocycles.[4] Notably, quinazolinone as an important structural unit has been widely found in many natural products and pharmaceuticals.[5] Many great efforts have been made towards their construction starting from a variety of substrates,[6] among which 2-amino benzamide is

probably the most typical one. Herein, we demonstrated a facile method for the synthesis of *N*-substituted quinazolinones starting from anthranilamides using DCP as the methyl source (Scheme 1d). This reaction involved a tandem *N*-methylation-sp^3 C-H amination-oxidation process in the presence of a copper catalyst.

Table 1. Optimization of reaction conditions. [a]



Entry	Catalyst	Base	Peroxide	T(℃)	Yield[b] (%)
1	$Cu(OAc)_2•H_2O$	—	DCP	120	20[c]
2	$Cu(OAc)_2•H_2O$	Imidazole	DCP	120	65[c]
3	$Cu(OAc)_2•H_2O$	NEt_3	DCP	120	25[c]
4	$Cu(OAc)_2•H_2O$	DBU	DCP	120	28[c]
5	$Cu(OAc)_2•H_2O$	Pyridine	DCP	120	35[c]
6	$Cu(OAc)_2•H_2O$	DMAP	DCP	120	50[c]
7	**$Cu(OAc)_2•H_2O$**	**Imidazole**	**DCP**	**120**	**82 (74)[d]**
8	—	Imidazole	DCP	120	50
9	$Cu(OAc)_2•H_2O$	Imidazole	DCP	120	74[e]
10	CuCl	Imidazole	DCP	120	70
11	$Cu(OTf)_2$	Imidazole	DCP	120	54
12	$Cu(OAc)_2•H_2O$	Imidazole	TBHP	120	20
13	$Cu(OAc)_2•H_2O$	Imidazole	TBPB	120	n.d.
14	$Cu(OAc)_2•H_2O$	Imidazole	DTBP	120	40
15	$Cu(OAc)_2•H_2O$	Imidazole	DCP	110	70
16	$Cu(OAc)_2•H_2O$	Imidazole	DCP	130	72
17	$Cu(OAc)_2•H_2O$	Imidazole	DCP	120	69[f]
18	$Cu(OAc)_2•H_2O$	Imidazole	DCP	120	56[g]
19	$Cu(OAc)_2•H_2O$	Imidazole	DCP	120	79[h]

[a] Reaction conditions: **1a** (0.2 mmol), peroxide (0.6 mmol), catalyst (0.04 mmol), base (0.4 mmol), PhCl (0.5 mL), 10 h. [b] Isolated yield. [c] PhCl (1.0 mL). [d] The data in parentheses is the result when **1a** was 0.5 mmol and the reaction time was 24 h. [e] 10 mol% $Cu(OAc)_2•H_2O$ was used. [f] Under N_2.

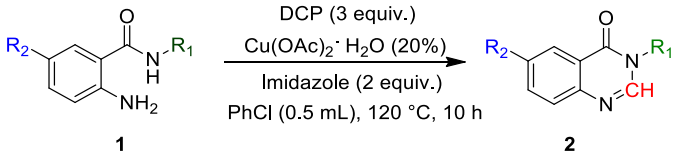
[g] DCP (1 equiv.) was used. [h] DCP (2 equiv.) was used. (NEt_3 = Triethylamine, DBU = 1,8-Diaza-7-bicyclo[5.4.0]undecene, DMAP = 4-(*N*,*N*-Dimethylamino)pyridine, TBHP = tert-butyl hydroperoxide (70% in aqueous), TBPB = Benzoyl tert-butyl peroxide, DTBP = di-tert-butylperoxide, n.d. = not detected.)

Initially, we began our study with the reaction of 1 equiv. of 2-amino-*N*-phenyl-benzanilide (**1a**) and 3 equiv. of DCP as the oxidant in the presence of 20 mol% of $Cu(OAc)_2•H_2O$ as the catalyst. When the reaction mixture was stirred in 1 mL of PhCl at 120 ℃ for 10 h under air, 3-phenyl-4(3*H*)-quinazolinone (**2a**) was obtained only in 20% yield (Table 1, entry 1). To improve the reaction yield, 2 equiv. of bases were employed. To our delight, imidazole gave the best result with 65% yield (Table 1, entries 2-6). Besides, reducing the volume of solvent from 1 mL to 0.5 mL obviously increased the yield to 82% (Table 1, entry 7). In the absence of copper salt, the corresponding product **2a** was obtained in 50% yield, while reducing the amount of $Cu(OAc)_2•H_2O$ to 10 mol% also decreased the yield, which showed that copper catalysts played an important role in this transformation (Table 1, entries 8-9). Other copper catalysts such as CuCl, $Cu(OTf)_2$ gave lower yields (Table 1, entries 10-11). Subsequently, various oxidants such as TBHP, TBPB and DTBP were also examined, but failed to give better results (Table 1, entries 12-14). After a brief survey of reaction temperature, the optimal reaction temperature was 120 ℃ (Table 1, entries 15-16). Considering the atom-economy synthesis, we reduced the amount of DCP to 2.0 and 1.0 equiv. and lower reaction yields were observed (Table 1, entries 18-19). Thus, the optimal reaction conditions were determined as described in entry 7.

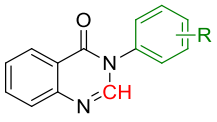
To examine the substrate scope of this protocol, the optimized reaction conditions were then applied to the synthesis of a variety of quinazolinones (Table 2). Firstly, when R_1 was an aromatic

substituent, the corresponding products (**2aa-oa**) were obtained in moderate to good yields. It is noted that *o*-amino-benzanilide bearing electron-withdrawing groups (4-CF_3, 4-Cl or 4-F) on the phenyl ring of R_1 gave the desired products in higher yields than electron-donating groups (4-CH_3, 4-OCH_3, 4-*n*-Bu or 4-*t*-Bu) on the phenyl ring. Similarly, the effect of steric hindrance on the phenyl ring of R_1 had little influence on the reaction. Subsequently, substrates with aliphatic substituents, such as benzyl, isopropyl, *n*-butyl and cyclohexyl (**2qa-ta**), can be employed in this reaction to give the corresponding products smoothly in spite of slightly lower yields. Finally, *o*-amino-benzanilides with various R_2 substitutes were also employed in this reaction, giving the desired products **2ab-ag** in moderate yields.

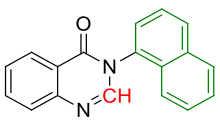
Table 2. Synthesis of various quinazolinones. [a]



1 **2**

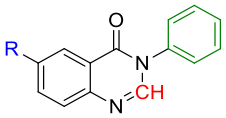


2aa, R= 2-CH_3, 75%
2ba, R= 3-CH_3, 61%
2ca, R= 4-CH_3, 65%
2da, R= 2-OCH_3, 60%
2ea, R= 3-OCH_3, 70%
2fa, R= 4-OCH_3, 66%
2ga, R= 2-CF_3, 64%
2ha, R= 3-CF_3, 81%
2ia, R= 4-CF_3, 78%
2ja, R= 2-Cl , 63%
2ka, R= 4-Cl, 70%
2la, R= 3-F, 72%
2ma, R= 4-F, 82%
2na, R= 4-*n*-butyl, 73%
2oa, R= 4-*t*-butyl, 68%



2pa, 63%

2qa, R= CH_2Ph, 42%
2ra, R= isopropyl, 37%
2sa, R= *n*-butyl, 40%
2ta, R= cyclohexyl, 35%



2ab, R= CH_3, 72%
2ac, R= OCH_3, 52%
2ad, R= F, 69%
2ae, R= Cl, 68%
2af, R= Br, 75%
2ag, R= NO_2, 65%

[a] Reaction conditions: **1a** (0.2 mmol), DCP (0.6 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.04 mmol), Imidazole (0.4 mmol), PhCl (0.5 mL), 120 ℃, 10 h. [b] Isolated yield.

To gain an insight into the reaction mechanism, the active intermediates were studied (Scheme 2). Firstly, we observed that the reaction was obviously inhibited in the presence of 3.0 equiv. radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The radical trapping product **3** was also detected by GC-MS (see SI for details). The methyl radical was further trapped by 5,5-dimethyl-1-proline-*N*-oxide (DMPO) in the EPR experiments.[7] In Figure 1, EPR spectra of the signal **a,** i.e. the DMPO-CH_3 adduct radical, was identified by the characteristic hyperfine constants for the nitrogen and proton A_{14N} = 15.6 G and A_{1H} = 23.2 G, respectively. Another signal **b** was assigned to oxidized DMPO with an A_{14N} = 14.9 G for the nitrogen, which was possibly oxidized by DCP, although the precise mechanism was not clear. This observation implied that the reaction presumably involved a free methyl radical.

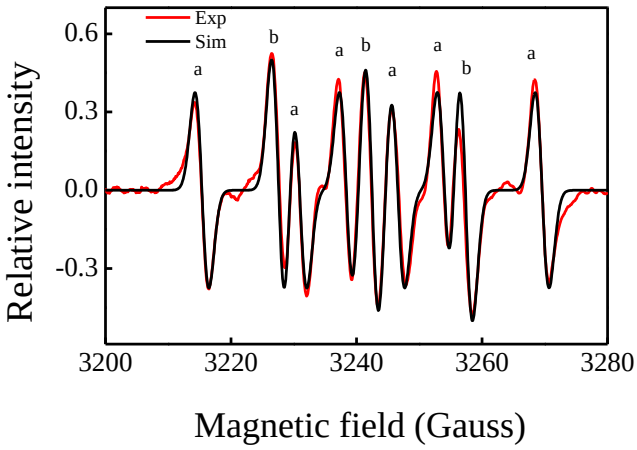
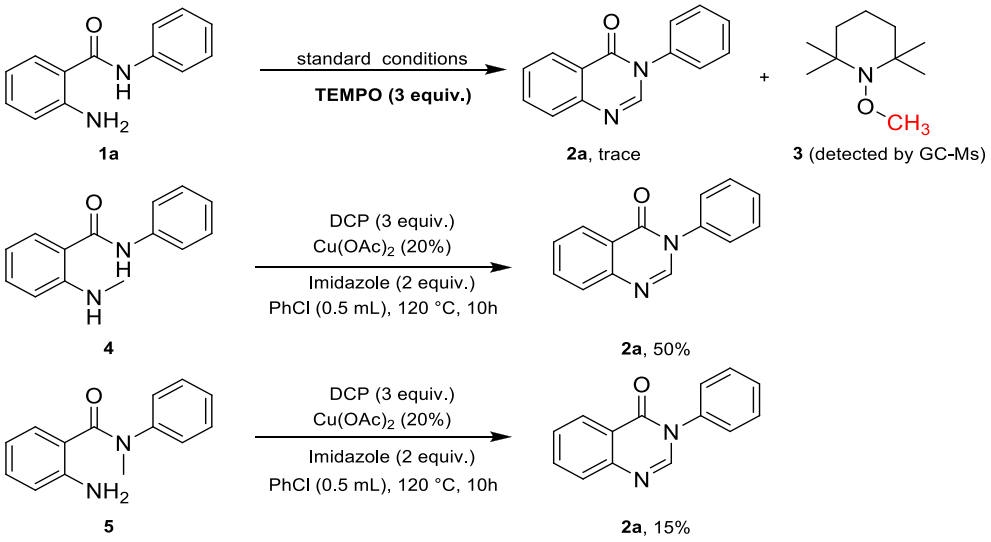


Figure 1. EPR spectra (X band, 9.07 GHz, room temperature) for reaction mixtures in the presence of the radical trapper DMPO (0.5 mol/L). In the spectra, **a** is assigned to the DMPO-CH_3 radical, while **b** is assigned to oxidized DMPOX (Sim = simulation, Exp = experiment).

Moreover, the possible intermediates of this reaction were also investigated. When 2-(methylamino)-*N*-phenylbenzamide **4** and 2-amino-*N*-methyl-*N*-phenylbenzamide **5** were carried out under the standard reaction conditions, the desired product **2a** was obtained in 50% and 15% yield respectively. These results indicated that both **4** and **5** are intermediates. And the compound **4** may be the major intermediate.



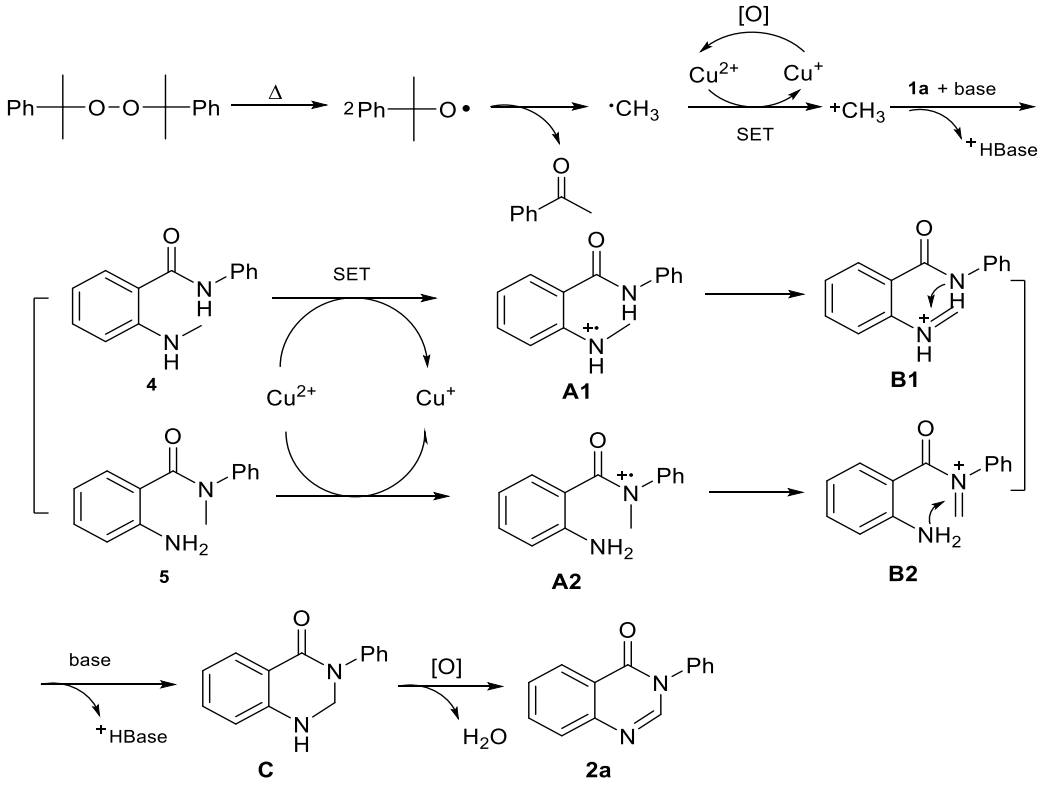
Scheme 2. Control experiments.

On the basis of the results above and previous reports,[1b] a plausible mechanism is proposed (Scheme 3). Initially, the thermal cleavage of DCP produces a tert-butoxy radical, which is converted to a methyl radical by the loss of one equivalent of acetophenone. Then methyl radical is transformed into methyl cation via a single electron transfer (SET) process in the presence of Cu^{2+}. The intermediate **4** or **5** can be formed via the nucleophilic attack of **1a** to methyl cation. The intermediate **4** then generates radical **A1** via a SET process in the presence of Cu^{2+}. Then intermediate **B1** is formed through removing a hydrogen radical from **A1**. **B1** can be further subjected to intramolecular nucleophilic attack to give the amination product **C**. Finally, the further oxidation of **C** gives the quinazolinone **2a**. Meanwhile, the product **2a** is probably

generated from **5** via a minor pathway. In entire pathway, imidazole is used as base to accept hydrogen.

CONCLUSION

In summary, we have developed a facile method for the synthesis of quinazolinones from anthranilamides. The reaction undergoes a copper-catalyzed tandem radical methylation/sp^3 C-H amination/oxidation pathway. It is noted that DCP was not only an oxidant, but also an efficient methylation reagent. Meanwhile, this reaction has wide substrate scope and good functional group tolerance, which represents a new avenue for practical multiple C-N bond formation. Further investigation to synthesize other heterocycles by this method is currently in progress.



Scheme 3. Proposed mechanism.

Experiment Section

General Information: Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. ^{1}H NMR, ^{13}C NMR using TMS as internal reference (^{1}H NMR 400 MHz, ^{13}C NMR 100 MHz).

General procedure for the synthesis of quinazolinones: 2-amino-*N*-phenyl-benzanilide **1a** (0.2 mmol, 42.4 mg), DCP (0.6 mmol, 162 mg), $Cu(OAc)_2 \cdot H_2O$ (0.04 mmol, 8 mg) and imidazole (0.4 mmol, 27.2 mg) in PhCl (0.5 mL) were heated at 120 ℃ for 10 h in air. The completion of the reaction was monitored by TLC and purified by column chromatography over silica gel to give the pure product **2a** as an orange solid (36 mg, 82 % yield).

Preparation of substrates

Synthesis of 1a, 1aa-fa, 1ha-oa

Isatoic anhydride (815 mg, 5 mmol) was dissolved in EtOH (10 mL) with aniline (916 uL, 5 mmol) and I_2 (127 mg, 0.5 mmol). The mixture was stirred under reflux in air overnight. Then the reaction mixture was concentrated in vacuo. Washed with EtOAc and $Na_2S_2O_3$ saturated solution for three times, then the organic layer washed with brine and dried over anhydrous Na_2SO_4. The organic phase was concentrated in vacuum and purified by chromatographic column on silica gel, giving 2-Amino-*N*-phenylbenzamide (**1a**) as a light yellow solid (715 mg, yield 67%).[8]

1aa-fa, 1ha-oa was synthesized according to the procedure for **1a**.

Synthesis of 1ga, 1pa

o-nitrobenzoic acid (835 mg, 5 mmol) were dissolved in dry DCM (5 mL) under N_2. After cooling to 0 ℃, thionyl chloride (726 uL, 10 mmol) with DCM (5 mL) solution was added slowly. The mixture was then allowed to warm to 40 ℃ for 3-6 h. Subsequently, the reaction mixture concentrated in vacuo to leave the crude product as a light yellow oil.[4e]

o-nitrobenzoyl chloride (5 mmol) in $CHCl_3$ was treated with 2-trifluoromethyl phenylamine (628 uL, 5 mmol) under N_2 atmosphere at reflux for 3 h. Upon cooling, the reaction mixture was diluted with $CHCl_3$ and washed consecutively with aq 1 M HCl and saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture was used for next step without further purification.[9]

Eight drops of concentrated HCl were added to the solution of *N*-(2-trifluoromethylphenyl)-2-nitrobenzamide (5 mmol) in EtOH (16 mL) and water (4 mL) with iron powder (1.12 g, 20 mmol). The reaction was refluxed at 80 ℃ for 2 h, filtrated through silica gel and the filtrate was concentrated under reduced pressure. Then washed with EtOAc and saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum under reduced pressure and purified by chromatographic column on silica gel, giving *N*-(2-trifluoromethylphenyl)-2-aminobenzamide (**1ga**) as a light yellow solid (642 mg, the total yield of three steps was 46%).[4e]

1pa was synthesized according to the procedure for **1ga**.

Synthesis of 1qa-1ta

Isatoic anhydride (815 mg, 5 mmol) in DMF was treated with benzylamine (547 uL, 5 mmol) at 50-60 ℃ for 1 h. After the completion, the mixture was washed with EtOAc and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum under reduced pressure and purified by chromatographic column on silica gel, giving 2-amino-*N*-(phenylmethyl)-benzamide (**1qa**) as a white solid (1100 mg, yield 98 %).[10]

1ra-1ta was synthesized according to the procedure for **1qa**.

Synthesis of 1ab-1ag

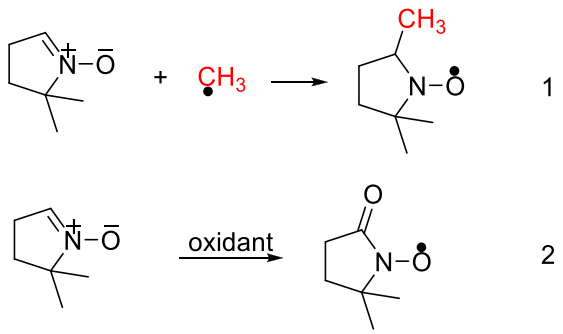
CrO_3 (833 mg, 8.33 mmol) was added portionwise to a hot (90 ℃) suspension of the 5-Methylisatin (806 mg, 5 mmol) in glacial AcOH (4 ml) and Ac_2O (4 ml). The mixture was heated at 90 ℃ for 2 h. After cooling at room temperature, the suspension was diluted with water (50 ml) and the solid collected and abundantly washed with H_2O. The obtained mixture was used for next step without further purification (796 mg, yield 90%).[11]

The mixture was dissolved in EtOH (10 mL) with aniline (916 uL, 5 mmol) and I_2 (127 mg, 0.5 mmol). The mixture was stirred under reflux in air overnight. Then the reaction mixture was concentrated in vacuo. Washed with EtOAc and saturated $Na_2S_2O_3$ solution for three times, washed with brine and dried over anhydrous Na_2SO_4. The organic phase was concentrated in vacuum and purified by chromatographic column on silica gel, giving 2-amino-5-methyl-*N*-phenylbenzamide (**1ab**) as a light yellow solid (780 mg, yield 69 %).[8]

1ac-ag was synthesized according to the procedure for **1ab**.

Further investigation about mechanism

Experimental details for the capture of radical: An 10 mL reaction tube was equipped with a magnet stirrer, than 2-Amino-*N*-phenylbenzamide (**1a**) (0.2 mmol, 42.4 mg), DCP (0.6 mmol, 162 mg), $Cu(OAc)_2•H_2O$ (0.04 mmol, 8 mg) and imidazole (0.4 mmol, 27.2 mg) in mesitylene (0.5 mL) were heated at 120 ℃ for 1 h in air. 50 uL solution was taken out into a small tube, mixed well with 0.3 ml DMPO aqueous solution. Then this mixture was quick-freezed with liquid nitrogen and analyzed by EPR. The EPR measurements were performed at room temperature.



Scheme 4. The reaction of DMPO

The intermediate radical **1** trapped by DMPO was characterized by the hyperfine coupling (hfc). The hyperfine constants for the nitrogen and proton in **a** were A_{14N} = 15.6 G and A_{1H} = 23.2 G, respectively. And DMPO can be readily oxidized by DCP. The oxidized DMPO with an A_{14N} = 14.9 G for the nitrogen (Scheme 4).

Characterization Data for the Products

3-phenyl-4(3*H*)-Quinazolinone (2a)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether: ethyl acetate = 3:1) to give light yellow solid (36 mg**,** 82%). m.p. 136-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.39-8.36 (d, *J* = 12 Hz, 1 H), 8.14 (s, 1 H), 7.83-7.76 (m, 2H), 7.58-7.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 147.9, 146.1, 137.5, 134.6, 129.7, 129.2, 127.7, 127.6, 127.2, 127.2, 122.4.

3-(2-methylphenyl)-4(3*H*)-Quinazolinone (2aa)[12]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light red solid (35 mg, 75%). m.p. 136-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38-8.37 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 1 H), 7.82-7.78 (m, 2H), 7.58-7.53 (m, 1H), 7.42-7.36 (m, 3H), 7.26-7.24 (d, *J* = 7.3 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm) 160.5, 148.1, 146.4, 136.7, 135.9, 134.6, 131.4, 129.8, 127.9, 127.6, 127.6, 127.4, 127.2, 122.4, 17.8.

3-(3-methylphenyl)-4(3*H*)-Quinazolinone (2ba)[12]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light red solid (29 mg, 61%). m.p. 136-137 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37-8.35 (d, *J* = 8.4 Hz，1H), 8.15 (s, 1H), 7.80-7.77 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.41 (m, 1H), 7.31-7.29 (d, *J* = 7.6 Hz，1H), 7.23-7.20 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.7, 147.5, 146.3, 139.9, 137.3, 134.7, 130.0, 129.5, 127.7, 127.6, 127.3, 127.2, 124.0, 122.3, 21.4.

3-(4-methylphenyl)-4(3*H*)-Quinazolinone (2ca)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light red solid (31 mg, 65%). m.p. 150-151 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36-8.34 (d, *J* = 7.8 Hz, 1H), 8.14 (s, 1H), 7.80-7.76 (m, 2H), 7.56-7.52 (m, 1H), 7.35-7.28 (m, 4H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 147.5, 146.4, 139.3, 134.8, 134.6, 130.3, 127.7, 127.4, 127.2, 126.7, 122.3, 21.2.

3-(2-methoxyphenyl)-4(3*H*)-Quinazolinone (2da)[12]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give red solid (30 mg, 60%). m.p. 156-157 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37-8.35 (d, *J* = 8.5 Hz, 1H), 7.98 (s, 1H), 7.79-7.77 (m, 2H), 7.54-7.45 (m, 2H), 7.35-7.33 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 7.12-7.07 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.7, 154.7, 148.0, 147.2, 134.4, 130.9, 129.1, 127.5, 127.3, 127.2, 126.0, 122.7, 121.0, 112.3, 55.8.

3-(3-methoxyphenyl)-4(3*H*)-Quinazolinone (2ea)[12]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (35 mg**,** 70%). m.p. 164-166 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37-8.35 (d, *J* = 7.8 Hz, 1H), 8.12 (s, 1H), 7.80-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.46-7.42 (m, 1H), 7.03-6.97 (m, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.7, 160.4, 147.9, 146.1, 138.5, 134.6, 130.4, 127.7, 127.6, 127.2, 122.4, 119.1, 115.1, 112.9, 55.6.

3-(4-methoxyphenyl)-4(3*H*)-Quinazolinone (2fa)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (33 mg, 66%). m.p. 209-210 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35-8.33 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.80-7.74 (m, 2H), 7.55-7.51 (m, 1H), 7.34-7.32 (d, *J* = 8.7 Hz, 2H), 7.04-7.02 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.0, 159.9, 147.9, 146.5, 134.5, 130.2, 128.2, 127.6, 127.5, 127.1, 122.4, 114.8, 55.6.

3-[2-(trifluoromethyl)phenyl]-4(3*H*)-Quinazolinone (2ga):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (37 mg**,** 64%). m.p. 157-158 ℃. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 8.36-8.34 (d, *J* = 7.8 Hz , 1H), 7.98 (s, 1H), 7.90-7.88 (m, 1H), 7.85-7.75 (m, 3H)， 7.70-7.66 (m, 1H), 7.59-7.55 (m, 1H), 7.48-7.46 (d, *J* = 7.7 Hz , 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.9, 147.7, 145.6, 135.2, 134.9, 133.5, 131.0, 130.3, 128.6 (q, *J* = 31 Hz), 127.9, 127.7 (q, *J* = 4.4 Hz), 127.7, 127.2, 122.8 (q, *J* = 272 Hz), 122.1. HRMS (ESI) m/z calcd for $C_{15}H_{10}F_3N_2O$ $[M+H]^+$ 291.0745, found 291.0746; IR (film, ν/cm^{-1}): 3015, 1690, 1607, 1317, 1176, 1128, 879, 772.

3-[3-(trifluoromethyl)phenyl]-4(3*H*)-Quinazolinone (2ha)[13]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (47 mg, 81%). m.p. 142-143 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35-8.32 (dd, J_1 = 7.2 Hz, J_2 = 0.76 Hz, 1H), 8.10 (s, 1H), 7.82-7.63 (m, 6H), 7.57-7.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 146.7, 144.2, 136.9, 133.9, 131.2 (q, *J*= 33 Hz), 129.5, 129.3, 126.9, 126.7, 126.1, 124.9 (q, *J* = 3.6 Hz), 123.2 (q, *J* = 3.7 Hz), 122.3 (q, *J* = 271 Hz), 121.1.

3-[4-(trifluoromethyl)phenyl]-4(3*H*)-Quinazolinone (2ia)[14]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid **(**45 mg, 78%). m.p. 206-207 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35-8.33 (d, *J* = 7.92 Hz, 1H), 8.11 (s, 1H), 7.83-7.80 (m, 3H), 7.77-7.75 (m, 1 H), 7.61-7.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.5, 147.7, 145.1, 140.4, 134.9, 131.3 (q, *J* = 33 Hz), 128.0, 127.7, 127.5, 127.2, 126.8 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 271 Hz), 122.1.

3-(2-chlorophenyl)-4(3*H*)-Quinazolinone (2ja):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give yellow solid (32 mg, 63%). m.p. 174-175 ℃. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 8.38-8.36 (d, *J* = 7.7 Hz, 1H), 7.99 (s, 1H), 7.85-7.79 (m, 2H), 7.63-7.54 (m, 2H), 7.50-7.44 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.1, 147.6, 145.9, 134.9, 134.8, 132.4, 131.0, 130.7, 129.8, 128.1, 127.8, 127.5, 127.3, 122.3. HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2O$ $[M+H]^+$ 257.0482, found 257.0489; IR (film, ν/cm^{-1}): 3244, 1687, 1608, 1474, 1307, 696, 541.

3-(4-chlorophenyl)-4(3*H*)-Quinazolinone (2ka)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (36 mg, 70%). m.p. 188-189 ℃. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 8.35-8.33 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 7.82-7.75 (m, 2H), 7.57-7.51 (m, 3H), 7.39-7.37 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.6, 147.7, 145.6, 135.9, 135.2, 134.8, 129.9, 128.3, 127.8, 127.7, 127.2, 122.2.

3-(3-fluorophenyl)-4(3*H*)-Quinazolinone (2la):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (35 mg, 72%). m.p. 158-160 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36-8.34 (dd, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 1H), 8.15 (m, 1H), 7.84-7.77 (m, 2H), 7.58-7.50 (m, 2H), 7.24-7.19 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.1, 161.6, 160.4, 147.3, 145.7, 138.6 (d, *J* = 10 Hz), 134.9, 131.0 (d, *J* = 9 Hz), 127.9, 127.3 (d, *J* = 16 Hz), 122.7 (d, *J* = 3 Hz), 122.1, 116.4 (d, *J* = 21 Hz), 114.9(d, *J* = 24 Hz). HRMS (ESI) m/z calcd for $C_{14}H_{10}FN_2O$ $[M+H]^+$ 241.0777, found 241.0783; IR (film, ν/cm^{-1}): 3065, 1678, 1598, 1455,1398, 1292, 1255, 1166, 863, 825, 764, 448.

3-(4-fluorophenyl)-4(3*H*)-Quinazolinone (2ma)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (39 mg, 82%). m.p. 164-166 ℃. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 8.35-8.33 (d, *J* = 7.9 Hz, 1H), 8.09 (s, 1H), 7.82-7.74 (m, 2H), 7.56-7.53 (m, 1H), 7.43-7.40 (m, 2H), 7.27-7.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8, 160.3, 159.8, 146.8, 144.8, 133.7, 132.4 (d, *J* = 3.1 Hz), 127.9 (d, *J* = 8.8 Hz), 126.7 (d, *J* = 15 Hz), 126.1, 121.2, 115.6 (d, *J* = 23 Hz).

3-[4-(n-butyl)phenyl]-4(3*H*)-Quinazolinone (2na):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (41 mg, 73%). m.p. 101-102 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37-8.35 (d, *J* = 7.9 Hz, 1H), 8.16 (s, 1H), 7.80-7.77 (m, 2H), 7.56-7.52 (m, 1H), 7.36-7.30 (m, 4H), 2.70-2.67 (t, 2H), 1.68-1.61 (q, 2H), 1.44-1.37 (s, 2H), 0.97-0.93 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.7, 146.3, 145.4, 143.2, 133.9, 133.6, 128.6, 126.7, 126.2, 125.7, 121.3, 34.3, 32.4, 21.3, 12.9. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2ONa$ $[M+Na]^+$ 301.1317, found 301.1322; IR (film, ν/cm^{-1}): 2925, 1677, 1601, 1474, 1324, 1287, 1263, 1096, 1022, 798, 772, 477.

3-[4-(1,1-dimethylethyl)phenyl]-4(3*H*)-Quinazolinone (2oa):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light red solid (38 mg, 68%). m.p. 120-121 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (s, 1H), 8.22-8.19 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H), 7.90-7.86 (m, 1H), 7.75-7.73 (d, *J* = 8.1 Hz, 1H), 7.61-7.56 (m, 3H), 7.47-7.45 (m, 2H)，1.34（s, 3H）. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.5, 151.7, 148.2, 147.7, 135.5, 135.1, 127.9, 127.8, 127.4, 126.9, 126.5, 122.4, 34.9, 31.5. HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1497, found 279.1504; IR (film, ν/cm^{-1}): 2961, 1686, 1606, 1512, 1469, 1294, 1262, 771.

3-(1-naphthalenyl)-4(3*H*)-Quinazolinone (2pa):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give yellow solid (34 mg, 63%). m.p. 93-95 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42-8.40 (d, *J* = 7.9 Hz, 1H), 8.10 (s, 1H), 8.04-8.02 (d, *J* = 8.2 Hz, 1H), 7.98-7.96 (d, *J* = 7.9 Hz, 1H), 7.88-7.83 (m, 2H), 7.63-7.50 (m, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.1, 148.2, 146.9, 134.8, 134.4, 134.1, 130.3, 129.8, 128.7, 127.8, 127.8, 127.7, 127.3,

126.9, 126.0, 125.5, 122.4, 122.0. HRMS (ESI) m/z calcd for $C_{18}H_{13}N_2O$ $[M+H]^+$ 273.1028, found 273.1034; IR (film, ν/cm^{-1}): 3475, 2922, 1687, 1604, 1456, 1266, 774, 741, 699, 497.

3-(phenylmethyl)-4(3*H*)-Quinazolinone (2qa)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (20 mg, 42%). m.p. 117-118 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33-8.31 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.77-7.69 (m, 2H), 7.52-7.48 (m, 1H), 7.35-7.29 (m, 5H), 5.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.1, 148.0, 146.4, 135.7, 134.3, 129.1, 128.3, 128.0, 127.5, 127.4, 126.9, 122.2, 49.6.

3-(1-methylethyl)-4(3*H*)-Quinazolinone (2ra)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (14 mg, 37%). m.p. 98-100 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32-8.30 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.77-7.69 (m, 2H), 7.52-7.48 (m, 1H), 5.23-5.16 (m, 1H), 1.50-1.49 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.7, 147.5, 143.6, 134.1, 127.3, 127.2, 126.9, 121.9, 46.0, 21.9.

3-butyl-4(3*H*)-Quinazolinone (2sa)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (16 mg, 40%). m.p. 70-72 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33-8.30 (d, *J* = 7.9 Hz, 1H), 8.10 (s, 1H), 7.78-7.71 (m, 2H), 7.53-7.49 (m, 1H), 4.03-4.00 (t, 2H), 1.82-1.75 (q, 2H), 1.45-1.39 (s, 2H), 0.99-0.96 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.9, 147.7, 146.7, 134.2, 127.3, 127.1, 126.7, 122.1, 46.9, 31.4, 19.9, 13.6.

3-cyclohexyl-4(3*H*)-Quinazolinone (2ta)[6b]:

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (16 mg, 35%). m.p. 118-119 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24-8.22 (dd, J_1 = 7.1 Hz, J_2 = 0.9 Hz, 1H), 8.05 (s, 1H), 7.68-7.60 (m, 2H), 7.42-7.38 (m, 1H), 4.76-4.70 (m, 1H), 1.93-1.84 (m, 4H), 1.72-1.68 (m, 1H), 1.61-1.39 (m, 4H), 1.22-1.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 146.4, 142.9, 133.1, 126.2, 126.1, 125.9, 120.9, 52.3, 31.5, 24.9, 24.3.

6-methyl-3-phenyl-4(3*H*)-Quinazolinone (2ab):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give light yellow solid (34 mg, 72%). m.p. 107-108 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 (s, 1H), 8.08 (s, 1H), 7.68-7.60 (m, 2H), 7.57-7.47 (m, 3H), 7.43-7.41 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 145.8, 145.4, 138.0, 137.6, 136.0, 129.6, 129.1, 127.4, 127.0, 126.6, 122.1, 21.4. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$ 237.1028, found 237.1032; IR (film, ν/cm^{-1}): 3282, 3049, 2921, 1687, 1642, 1611, 1547, 1496, 834, 754.

6-methoxy-3-phenyl-4(3*H*)-Quinazolinone (2ac):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give yellow solid (26 mg, 52%). m.p. 167-168 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.73-7.69 (m, 2H), 7.56-7.54 (m, 3H), 7.44-7.38 (m, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 158.1, 143.0, 141.2, 136.6, 128.6, 128.1, 128.03, 125.9, 123.7, 122.2, 105.6, 54.9. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$

253.0977, found: 253.0979; IR (film, ν/cm^{-1}): 3333, 3125, 2962, 2926, 1680, 1617, 1552, 1350, 1025, 802, 751, 568.

6-fluoro-3-phenyl-4(3*H*)-Quinazolinone (2ad):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (33 mg, 69%). m.p. 205-206 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (s, 1H), 8.00-7.98 (m, 1H), 7.80-7.76 (m, 1H), 7.58-7.48 (m, 4H), 7.43-7.41 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7, 160.2, 160.1 (d, *J* = 3.3 Hz), 145.4 (d, *J* = 2 Hz), 144.5, 137.3, 130.0 (d, *J* = 8 Hz), 129.7, 129.3, 126.9, 123.1 (d, *J* = 24 Hz), 112.2 (d, *J* = 23 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{10}FN_2O$ $[M+H]^+$ 241.0777, found 241.0778; IR (film, ν/cm^{-1}): 3113, 3053, 3029, 2916, 2853, 1594, 1483, 1284, 647, 500, 422.

6-chloro-3-phenyl-4(3*H*)-Quinazolinone (2ae):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give yellow solid (35 mg, 68%). m.p. 190-191 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (s, 1H), 8.12 (s, 1H), 7.73-7.70 (m, 2H), 7.58-7.48 (m, 3H), 7.43-7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.7, 146.4, 146.3, 137.2, 135.0, 133.6, 129.8, 129.3, 129.3, 126.9, 126.6, 123.5. HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2O$ $[M+H]^+$ 257.0482, found 257.0482; IR (film, ν/cm^{-1}): 3043, 2920, 1677, 1611, 1592,1472, 1180, 832, 766, 644, 622.

6-bromo-3-phenyl-4(3*H*)-Quinazolinone (2af):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give white solid (45 mg, 75%). m.p. 185-186 ℃. ^{1}H NMR (400

MHz, $CDCl_3$) δ (ppm) 8.486-8.480 (d, *J* = 2.3 Hz, 1H), 8.12 (s, 1H), 7.89-7.86 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H), 7.65-7.63(d, *J* = 8.6 Hz, 2H), 7.58-7.48 (m, 3H), 7.42-7.40 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 146.7, 146.4, 137.8, 137.2, 129.8, 129.7, 129.4, 129.3, 126.9, 123.8, 121.3. HRMS (ESI) m/z calcd for $C_{14}H_{10}BrN_2O$ $[M+H]^+$ 300.9977, found 300.9977; IR (film, ν/cm^{-1}): 3061, 2922, 1679, 1591, 1508, 1267, 875, 749, 611, 486.

6-nitro-3-phenyl-4(3*H*)-Quinazolinone (2ag):

Synthesized according to typical procedure and purified by column chromatography (petroleum ether : ethyl acetate = 3 : 1) to give yellow solid (35 mg, 65%). m.p. 223-224 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.22-9.21 (d, *J* = 2.6 Hz, 1H), 8.60-8.57 (dd, J_1 = 8.9 Hz, J_2 = 2.6 Hz, 1H), 8.26 (s, 1H), 7.92-7.89 (d, *J* = 8.9 Hz, 1H), 7.61-7.52 (m, 3H), 7.45-7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 151.9, 148.9, 146.4, 136.7, 129.9, 129.7, 129.4, 128.7, 126.8, 123.8, 122.8. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3O_3$ $[M+H]^+$ 268.0722, found 268.0727; IR (film, ν/cm^{-1}): 3023, 1743, 1683, 1615, 1568, 1398, 1273, 1098, 913, 849, 749, 547, 467.

ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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