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Approach to the Synthesis of 2,3-Disubstituted-3*H*-quinazolin-4-ones Mediated by Ph_3P-I_2

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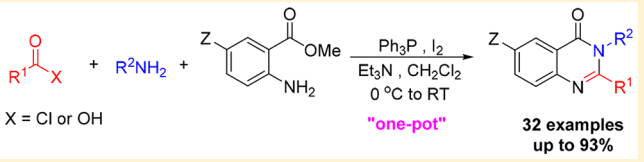
Supporting Information

ABSTRACT: Readily available *N*-substituted amides or their requisite carboxylic acids or acid chlorides have been used to construct 2,3-disubstituted-3*H*-quinazolin-4-ones in a one-pot procedure. Key transformation in this convergent approach involves Ph_3P-I_2-mediated formation of amidine upon condensation of an amide or the intermediate amide with methyl anthranilate. Cyclization of the amidine-tethered anthranilate then affords 2,3-disubstituted-3*H*-quinazolin-4-ones in good to excellent yields under mild conditions.



INTRODUCTION

Quinazoline-4(3*H*)-ones represent a unique class of heterocycles that attracted considerable attention among organic and medicinal chemists.[1] Both naturally occurring and synthetic quinazolinones, especially the 2,3-disubstituted derivatives, have been shown to exhibit a broad spectrum of pharmacological and biological activities, including antibacterial, antifungal, antimalaria, antiviral, anti-inflammatory, antidiabetic, antituberculosis, and antitumor properties.[2] Their potent inhibitory effects on thymidylate synthase, poly(ADP-ribose) polymerase (PARP), cholecystokinin, and thyrosine kinase have also been reported.[3]

Currently, several approved drugs with sedative, hypnotic, and anxiolytic properties, such as methaqualone, mebroqualone, mecloqualone, etaqualone, and piriqualone, are on the market for treatment of insomnia and for use as a sedative and muscle relaxant (Figure 1). Tryptanthrin is a plant alkaloid with anti-inflammatory and anticancer activities. Idelalisib, ispinesib, and raltitrexed have been in the market or are currently in clinical trials for treatment of cancers.[2]

Owing to their remarkable properties as potential therapeutic candidates, numeral synthetic methods have been developed toward this compound class.[2,4] Representative examples of these methodologies include (i) condensation of 2-aminobenzamides with aldehydes or 1,3-diketones;[5] (ii) oxidation/cyclization reaction of 2-aminobenzamides derived from isatoic anhydride with aldehydes,[6] benzyl halides,[7] benzyl alcohols,[8] or orthoesters;[9] (iii) amidation of benzoxazinones with arylamines;[10] (iv) reductive cyclization of 2-nitrobenzamides with carbonyl compounds;[11] (v) palladium-catalyzed cyclocarbonylation of *o*-haloanilines with *N*-toluenesulfonyl aldimines[12] or imidoyl chlorides;[13] (vi) metal-catalyzed arylation of quinazolinones with aryl halides;[14] (vii) intramolecular dehydrative cyclization of the diamide derivatives of anthranilic acid;[15] and (viii) condensation of methyl anthranilate with an imidoyl chloride prepared by reacting lactam-HCl salts with $POCl_3$ (Scheme 1).[16]

Although these methods have their own merits, most of them still suffer from various limitations, such as requirement of multistep procedure, costly and toxic reagents/or catalysts, harsh reaction conditions, and long reaction times. Additionally, some of the starting materials are not readily available and are difficult to prepare, while the conditions are only applicable for limited substrate scope. Considering the importance of this class of molecules, the development of new mild and economic methods that enable a convenient access to diverse quinazolin-4(3*H*)-ones from simple and readily accessible precursors is highly desirable.

Recently, our group has reported that amidines could be efficiently synthesized from amides using a combination of triphenylphosphine (Ph_3P) and iodine (I_2) under mild conditions.[17] In a continuing study, this method was extended toward the synthesis of 2,3-disubstituted-3*H*-quinazolin-4-ones (Scheme 1). Although the Ph_3P-I_2 system has previously been applied in the synthesis of quinazolinone derivatives from the diamides of anthranilic acid (Scheme 1, route vii),[15b−d] to the best of our knowledge, this reagent system has never been applied in the condensation of readily available methyl anthranilate and amides. We thus presented here a detailed study of the reaction between amides and methyl anthranilate mediated by the Ph_3P-I_2 system.

RESULTS AND DISCUSSION

First, the formation of 2,3-disubstituted-3*H*-quinazolin-4-one was explored using *N*-methylbenzamide in reaction with methyl anthranilate as model substrates. According to the previously reported procedure for amidine synthesis,[17] the reaction carried out using Ph_3P (1.5 equiv), I_2 (1.5 equiv), and triethylamine (5

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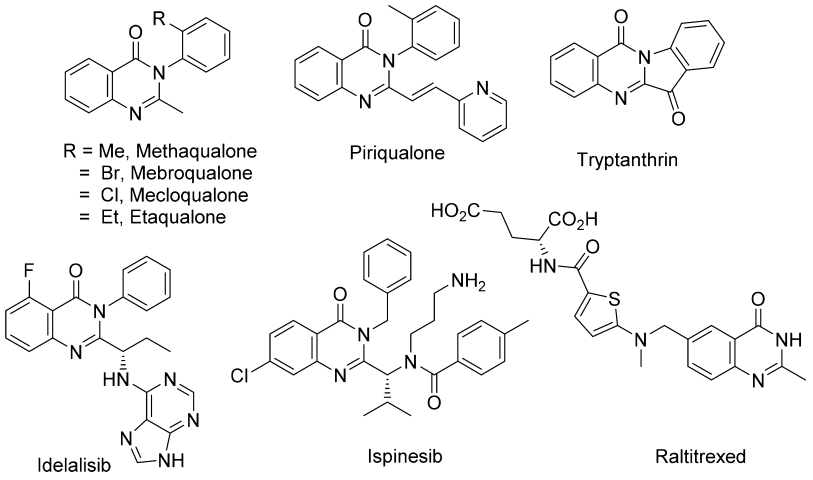
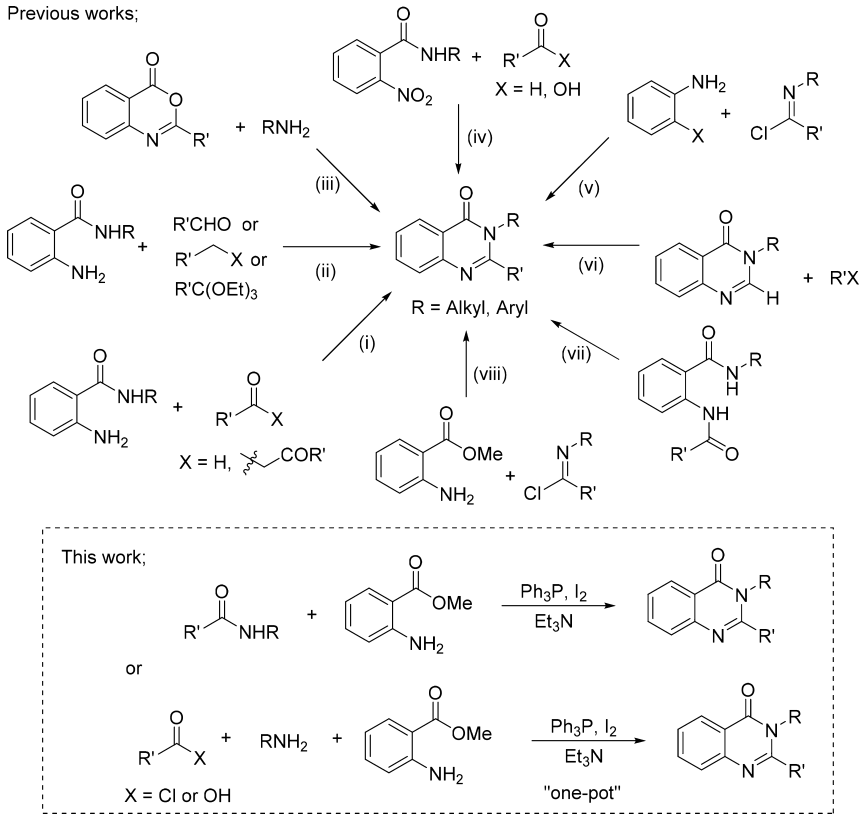


Figure 1. Examples of bioactive 2,3-disubstituted quinazoline-4(3*H*)-ones.

Scheme 1. Reported Methods and the Present Strategy for the Synthesis of 2,3-Disubstituted-3*H*-quinazolin-4-ones



equiv) in dichloromethane was found to provide the corresponding quinazolinone product in good yield at room temperature (Table 1, Entry 1). The efficiency of the reaction significantly decreased when replacing I_2 with other halogenated additives, such as carbon tetrachloride, *N*-chlorosuccinimide (NCS), bromine, and *N*-bromosuccinimide (NBS) (Table 1, Entries 2−5). Only trace amount of the product was observed when the reaction was conducted with more polar solvents including THF and acetonitrile (Table 1, Entries 6, 7). Attempt to improve the product yield by increasing the reaction temperatures in 1,2-dichloroethane or toluene also failed to give satisfactory results possibly due to insolubility of polar intermediates as well as their decomposition at elevated temperature (Table 1, Entries 8, 9). Additionally, other variation of the reactant and reagent quantities, addition order, and reaction time did not lead to significant enhancement of the final outcomes.

After having established the optimum reaction conditions, the scope of the reaction was then examined using a variety of *N*-aryl and *N*-alkyl substituted amides. These compounds were subjected to our conditions without further modification. According to Table 2, the reaction was applicable to a broad range of amide substrates as several 2,3-disubstituted quinazolinone derivatives were prepared in satisfactory yields.

In the reaction with *N*-methylbenzamide, anthranilate esters containing -Cl or -I group were less reactive giving the corresponding quinazolinones in lower yields than the parent methyl anthranilate (Entries 1−3). Benzamide bearing *N*-aryl

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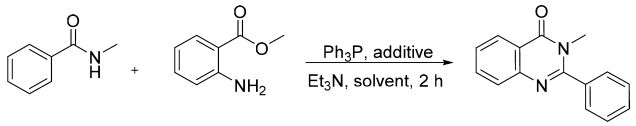
Table 1. Optimization of the Reaction Conditions[a]



entry	additive	solvent	temperature (°C)	yield (%)
1	I_2	CH_2Cl_2	25	84
2	CCl_4	CH_2Cl_2	25	48
3	NCS	CH_2Cl_2	25	NR
4	Br_2	CH_2Cl_2	25	NR
5	NBS	CH_2Cl_2	25	NR
6	I_2	THF	25	trace
7	I_2	CH_3CN	25	trace
8	I_2	DCE	80	77
9	I_2	toluene	110	18

[a]Reaction conditions: *N*-methylbenzamide (0.28 mmol), methyl anthranilate (0.34 mmol), Ph_3P (0.42 mmol), additive (0.42 mmol), and Et_3N (1.4 mmol), solvent 2 mL, 0 °C–RT for 2 h. DCE = 1,2-dichloroethane. NR = no reaction

substituent, such as benzanilide, also provided lower yield of the cyclized product **2d** possibly due to the low reactivity of the arylamido nitrogen (Entry 4). In most of the cases, the reaction of *N*-benzylbenzamide derivatives with methyl anthranilate proceeded smoothly to give the cyclized products in good yields (Entries 5–9). While the substrate bearing strong electron-withdrawing nitro group gave low product yield (entry 6), other *N*-benzylbenzamides substituted with *p*-Br, (Entry 7), *o*-Cl (Entry 8) as well as sterically hindered *o*-Me group (entry 9) provided the corresponding quinazolinones **2g–2i** in high yields. The reaction also proceeded smoothly with *N*-benzyl amides containing conjugated cinnamyl group (Entry 10) or alkyl moiety (Entries 11 and 12).

Further, the effect of substituents on the *N*-aryl ring of the acetamides was investigated as shown in Entries 13–17. Various *N*-arylacetamide substrates efficiently participated in the reaction providing the products in good yields. The presence of electron-donating groups in *N*-aryl substituent, such as *o*-CH_3 and *p*-OEt, gave higher yields of quinazolinones (Entries 13 and 14) when comparing with the substrate having an electron-withdrawing group, such as *p*-Cl (Entry 15). In the case of *N*-(4-nitrophenyl)acetamide (Entry 16), no conversion was observed which should be mainly due to the poor nucleophilicity of the aryl amido group. The reaction condition was compatible with the methyl ester group in *N*-arylacetamide albeit with low yield due to incomplete cyclization of the formed amidine intermediate (Entry 17). Nevertheless, the isolation of this uncyclized product suggested that the formation of amidine-tethered anthranilate is the key step toward quinazolinone.

Evidently, both electronic and steric effects play crucial rule in controlling amidine formation and the cyclization process. The formation of intermediate amidine is less favorable when the electron-withdrawing substituent is presented on the aromatic ring of aryl amides, while its presence on *N*-aryl group on the amide substrates makes the aryl amido nitrogen less nucleophilic leading to ineffective cyclization. Sterically hindered group also disfavors the ring closing reaction.

It is noted that attempt to use primary amides, such as benzamide or acetanilide, to form quinazolinones failed to yield the desired products. This may in part be due to low solubility of these substrates as well as the low acidity of the amide proton which make it difficult to form reactive intermediate under the applied conditions.[18]

Multicomponent reactions have attracted considerable interest for their high synthetic efficiency. In order to avoid chromatographic purification of the requisite amide, a one-pot three-component reaction toward quinazolinones was investigated. The in situ generated intermediate amide should undergo activation with $Ph_3P–I_2$, before reacting with methyl anthranilate to yield the 2,3-disubstituted quinazolin-4-ones.

Since no coupling reagent is necessary for the reaction of acid chloride with an amine, the one-pot synthesis of quinazolinones was carried out by sequentially mixing equimolar ratio of both substrates to provide an amide, followed by coupling with methyl anthranilate in the presence of $Ph_3P–I_2$. As shown in Scheme 2, the reaction using different acid chlorides and amines proceeded well to give the corresponding quinazolinones in good yields. Remarkably, the sedative drug, methaqualone, was directly obtained in 84% yield. This result is comparable to the above-described method where amide was obtained and purified from a separate step (Table 2, Entry 13) indicating no interference from the first amide bond formation.

To our delight, the reaction could also be carried out starting directly from a carboxylic acid. In this case, a one-pot procedure toward quinazolinones was performed by increasing the amount of the dehydrating agent. As shown in Scheme 3, the three-component reaction of carboxylic acids, amines, and methyl anthranilate proceeded smoothly to afford the corresponding quinazoline-4(3*H*)-ones in reasonable yields. By adding Ph_3P (2.5 equiv), I_2 (2.5 equiv), and 6 equiv of triethylamine in one portion during the amide bond forming step, the in situ generated *N*-benzyl benzamide reacted with methyl anthranilate to provide the product **4a** in good yield. Nevertheless, the intermediate amide derived from an electron-deficient nitro substituted acid gave low conversion toward **4b**. Noteworthy that 3-styrylquinazolinone derivative **4c**, a carbon analog of piriqualone, could be readily prepared in satisfactory yield in one-pot. 2,3-Diaryl (3*H*)-quinazolin-4-one **4d** was also obtained in good yield from heteroaromatic acid.

The synthesis of 2,3-dialkyl-substituted quinazolinones starting directly from a carboxylic acid was proven to be much more difficult giving low to moderate yields of the products **4e–4j**. In these cases, amide bond forming step seems to be the main problem. According to our previous study in the Ph_3P/I_2-mediated synthesis of amides,[19] the reaction between aliphatic acids and aliphatic amines is generally slow with incomplete conversion. Thus, the remained reactants from the first amide bond forming may interfere with the following reaction with methyl anthranilates. Indeed, compound **4e** was obtained in 63% yield when starting from the requisite amide prepared and isolated from a separate step. It was also observed that the yields were improved when the reagents were added in two portions during the activation of a carboxylic acid to form an amide and 30 min before treatment of the formed amide with anthranilate.

It should be noted that the reported conditions for synthesis of 2,3-dialkyl-substituted quinazolinones often required elevated temperatures and long reaction times.[20] Low yield or no product formation has been observed in several cases including those metal-catalyzed reactions.[13,14,21] Additionally, although several one-pot three-component reactions toward substituted quinazolinone have been reported,[22] these methods still suffer from harsh reaction conditions, expensive reagents, and/or limited substrate scope. To the best of our knowledge, a mild

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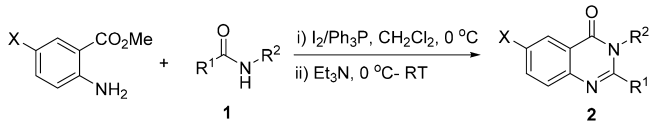
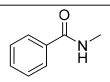
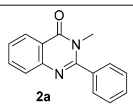
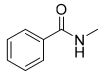
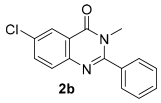
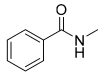
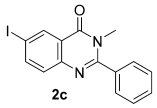
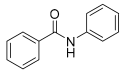
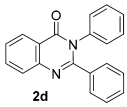
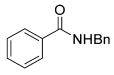
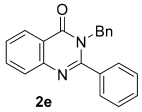
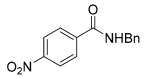
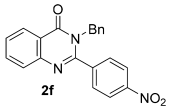
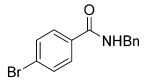
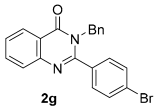
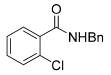
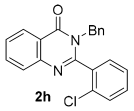
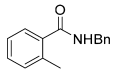
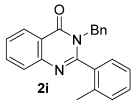
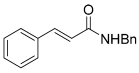
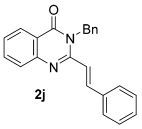
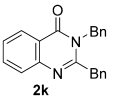
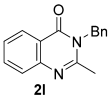
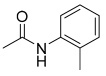
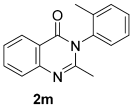
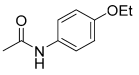
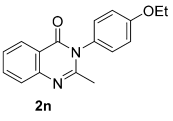
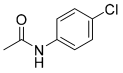
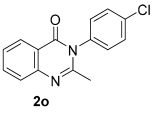
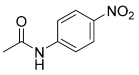
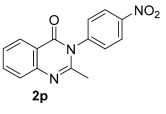
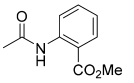
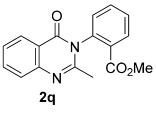
Table 2. Synthesis of 2,3-Substituted-3*H*-quinazolin-4-ones Using $Ph_3P/I_2/Et_3N$



Entry	X	Amide **1**	Product **2**	Time (h)	Yield (%)
1	H		 **2a**	2	84
2	Cl		 **2b**	2	71
3	I		 **2c**	2	74
4	H		 **2d**	2	72
5	H		 **2e**	1.5	89
6	H		 **2f**	O/N	35
7	H		 **2g**	2	82
8	H		 **2h**	2	88
9	H		 **2i**	5	82
10	H		 **2j**	2	72
11	H		 **2k**	3	78
12	H		 **2l**	1	93
13	H		 **2m**	1.5	85
14	H		 **2n**	1.5	89
15	H		 **2o**	4	83
16	H		 **2p**	O/N	NR
17	H		 **2q**	O/N	37(48)[b]

[a]Reaction conditions: amide (0.28 mmol), methyl anthranilates (0.34 mmol), Ph_3P (0.42 mmol), iodine (0.42 mmol) and Et_3N (1.4 mmol), CH_2Cl_2 2 mL, 0 °C–RT. [b]Yield of noncyclized product.

method for direct access to broad scope of quinazolinone derivatives in one-pot from readily available reactants is unprecedented.

Based on the above results, it is highly likely that the amido oxygen would undergo initial phosphorylation, followed by converting to imidoyl iodide before reacting with methyl anthranilate. To obtain more evidence for the formation of phosphorus-containing intermediates as well as imidoyl iodide, further experiments were conducted using NMR studies to follow the progress of the reaction between *N*-methylbenzamide and methyl anthranilate.

According to $^{31}P\{^1H\}$ NMR spectra of the reaction mixture (see Figure S1 in ESI), addition of *N*-methylbenzamide into the $Ph_3P–I_2$ solution caused a significant shift of the signal at 44.4 ppm corresponded to triphenylphosphonium iodide to 36.3 ppm. This result indicates the formation of a new phosphonium species which could be resulted from the phosphorylation of the amido oxygen. After treatment with triethylamine, this signal rapidly disappeared with a release of Ph_3PO (29.1 ppm)[19] suggesting the formation of imidoyl iodide at this stage. Subsequent adding with methyl anthranilate caused no significant change in the $^{31}P\{^1H\}$ NMR spectrum excluding the formation of other possible intermediates such as aryliminophosphoranes which should appear at ca. 3–8 ppm.[23]

The ^1H and ^{13}C NMR spectra of crude reaction after 10 min treatment with methyl anthranilate also provide useful information (see Figure S2 in ESI). Four kinds of methyl group including -NCH_3 group of amides, -NCH_3 group of

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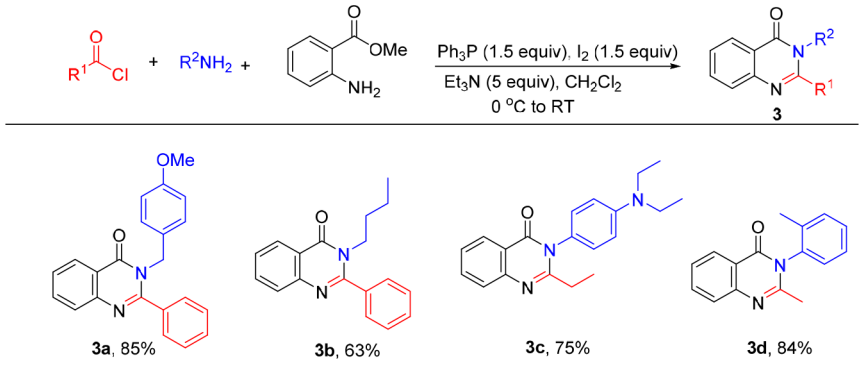
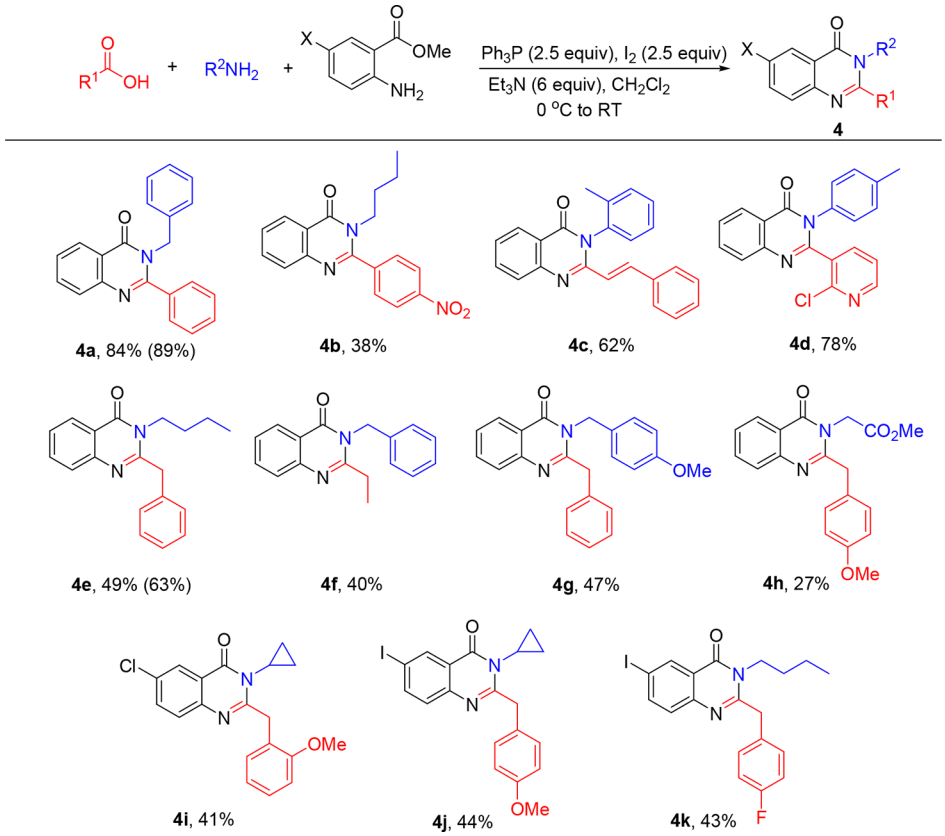
Scheme 2. Ph_3P-I_2-Mediated Synthesis of 2,3-Disubstituted-3*H*-quinazolin-4-ones from Acid Chlorides



Scheme 3. Ph_3P-I_2-Mediated Synthesis of 2,3-Disubstituted-3*H*-quinazolin-4-ones from Carboxylic Acids[a]

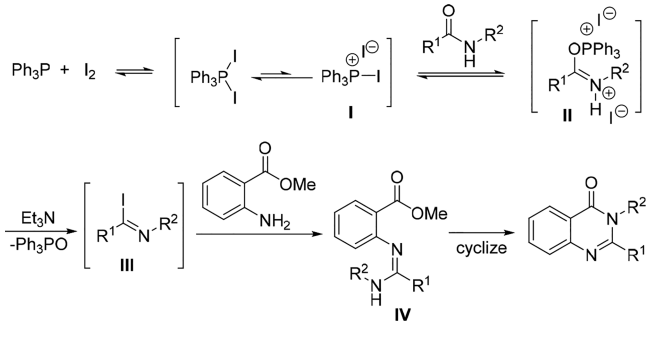


[a]The yield obtained from an amide was given in parentheses.

imidoyl iodide, -NCH_3 of the desired quinazolinone product, and -OCH_3 of methyl anthranilate were observed at 2.96, 3.37, 3.49, 3.83 ppm, respectively. The $^{13}C\{^1H\}$ NMR spectrum strongly supports the inclusion of imidoyl iodide intermediate ($CH_3N{=}CIPh$) at 109.8 ppm.[24]

On the basis of these data, the mechanism for the formation of quinazolinones was proposed as shown in Scheme 4. Treatment of Ph_3P with I_2 provides reactive triphenylphosphonium iodide **I**. Phosphorylation at the oxygen atom of the starting amide yields imidinium intermediate **II**. This species is then converted into imidoyl iodide **III** in the presence of base. Displacement of iodide of **III** with an amine function of methyl anthranilate leads to the intermediate amidine **IV** before an intramolecular cyclization to furnish quinazolinone product.

Scheme 4. Proposed Mechanism for the Ph_3P-I_2-Mediated Synthesis of Substituted Quinazolinones



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CONCLUSIONS

In summary, we have developed a facile and cost-effective method for convergent synthesis of 2,3-disubstituted-3*H*-quinazolin-4-ones through Ph_3P-I_2-mediated amidine formation/cyclization sequence. A variety of quinazolinones could be readily obtained in one-pot under mild conditions from readily available starting materials and inexpensive reagents. This convergent approach provides a useful alternative for quinazolinone formation circumventing many issues associated with previously reported processes.

EXPERIMENTAL SECTION

Experimental Procedure. *Material and Methods.* All reagents were purchased from Sigma-Aldrich Co., USA, and used without further purification. The reaction was monitored by thin-layer chromatography carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (254 nm). Melting points were determined using Mettler Toledo DSC equipment at a heating rate of 6 °C/min and are uncorrected. NMR spectra were determined using a Bruker AVANCE (400 MHz for ^{1}H). Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS. Splitting patterns are described as singlet (s), doublet (d), triplet (*t*), quartet (q), quintet (qui), sextet (sex), multiplet (m), broad (br), doublet of doublets (dd), triplet of doublets (td), and doublet of doublet of doublets (ddd). High resolution mass spectra (HRMS) were recorded using the LC-DAD-ESI-MS/MS system consisted of a Waters Alliance 2695 LC-DAD and a Q-TOF 2 (quadrupole mass filter-time-of-flight) mass spectrometer with a Z-spray ES source.

General Procedure for the Synthesis of 2,3-Disubstituted-3H-quinazolin-4-ones from Amides or Acid Chlorides. To a solution of amide (0.28 mmol) in CH_2Cl_2 (2 mL) was added iodine (107 mg, 0.42 mmol) and triphenylphosphine (111 mg, 0.42 mmol) in one portion at 0 °C. Triethylamine (0.20 mL, 1.40 mmol) was subsequently added into the mixture with continuous stirring at 0 °C for 30 min. After that, methyl anthranilate (0.34 mmol) was added and the reaction mixture was allowed to warm up to room temperature and stirred until completion of the reaction. The crude mixture was concentrated under reduced pressure then purified by column chromatography (CC) using 5−20% ethyl acetate in hexane. A one-pot method starting from acid chloride was also carried out according to the above-described procedure except that acid chloride (0.28 mmol) was reacted with an amine (0.28 mmol) in CH_2Cl_2 (2 mL) to generate amide in situ before treatment with Ph_3P-I_2 reagent.

General Procedure for the Synthesis of 2,3-Disubstituted-3H-quinazolin-4-ones from Carboxylic Acids. To a solution of a carboxylic acid (0.28 mmol) in CH_2Cl_2 (2 mL) was added an amine (0.28 mmol), followed by iodine (178 mg, 0.70 mmol) and triphenylphosphine (184 mg, 0.70 mmol) in one portion at 0 °C. Triethylamine (0.23 mL, 1.68 mmol) was then added into the reaction mixture which was allowed to stir at room temperature until the disappearance of the acid as indicated by TLC. Subsequently, methyl anthranilate (0.34 mmol) was added at 0 °C and the reaction mixture was further stirred at room temperature until completion of the reaction. The crude mixture was concentrated under reduced pressure then purified by column chromatography (CC) using 5−20% ethyl acetate in hexane.

3-Methyl-2-phenylquinazolin-4(3H)-one.[25] Table 2, entry 1, compound **2a**; white solid; (0.0557 g, 84% yield); mp 132−133 °C (lit.[25] mp 131−132 °C); R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1H), 7.77−7.71 (m, 2H), 7.58−7.47 (m, 6H), 3.49 (s, 3H).

6-Chloro-3-methyl-2-phenylquinazolin-4(3H)-one. Table 2, entry 2, compound **2b**; white solid; (0.0541 g, 71% yield); mp 130−133 °C; R_f 0.27 (10% EtOAc/hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 1.4 Hz, 1H), 7.65 (d, J = 1.4 Hz, 2H), 7.56−7.50 (m, 5H), 3.48 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 161.8, 156.4, 145., 135.2, 134.8, 132.8, 130.3, 129.3, 129.0, 128.1, 126.1, 121.6, 34.5; TOF-HRMS calcd for $C_{15}H_{12}{}^{37}ClN_2O$ $(M+H)^+$ 273.0608, found 273.0614, for $C_{15}H_{16}{}^{35}ClN_2O$ $(M+H)^+$271.0638, found 271.0637.

6-Iodo-3-methyl-2-phenylquinazolin-4(3H)-one.[26] Table 2, entry 3, compound **2c**; white solid; (0.0656 g, 74% yield); mp 137−138 °C; R_f 0.23 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.6, 2.0 Hz, 1H), 7.62−7.48 (m, 5H), 7.45 (d, J = 8.6 Hz, 1H), 3.48 (s, 3H).

2,3-Diphenylquinazolin-4(3H)-one.[13] Table 2, entry 4, compound **2d**; yellow solid; (0.0604 g, 72% yield); mp 156−157 °C (lit.[13] mp 158−159 °C); R_f 0.37 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.0 Hz, 1H), 7.85−7.78 (m, 2H), 7.53 (ddd, J = 8.0, 6.0, 2.0 Hz, 1H), 7.36−7.14 (m, 10H).

3-Benzyl-2-phenylquinazolin-4(3H)-one.[6b] Table 2, entry 5, compound **2e**; yellow solid; (0.0778 g, 89% yield and 0.0735 g, 84% yield for **4a**); mp 136−138 °C (lit.[6b] mp 137−139 °C); R_f 0.27 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.6 Hz, 1H), 7.81−7.75 (m, 2H), 7.55−7.33 (m, 6H), 7.22−7.19 (m, 3H), 6.94−6.92 (m, 2H), 5.28 (s, 2H).

3-Benzyl-2-(4-nitrophenyl)quinazolin-4(3H)-one.[14a] Table 2, entry 6, compound **2f**; yellow solid; (0.0350 g, 35% yield); mp 120−122 °C (lit.[14a] mp 121−123 °C); R_f 0.23 (20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.0, 1.6 Hz, 1H), 8.23 (d, J = 8.8 Hz, 2H), 7.83 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.75 (dd, J = 8.0, 1.6 Hz, 1H), 7.59 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.25−7.21 (m, 3H), 6.89−6.87 (m, 2H), 5.24 (s, 2H).

3-Benzyl-2-(4-bromophenyl)quinazolin-4(3H)-one.[27] Table 2, entry 7, compound **2g**; white solid; (0.0901 g, 82% yield); mp 142−143 °C (lit.[27] mp 144−145 °C) ; R_f 0.35 (20% EtOAc/hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.81−7.73 (m, 2H), 7.56−7.51 (m, 3H), 7.24−7.20 (m, 5H), 6.94−6.92 (m, 2H), 5.25 (s, 2H).

3-Benzyl-2-(2-chlorophenyl)quinazolin-4(3H)-one. Table 2, entry 8, compound **2h**; colorless oil; (0.0857 g, 88% yield); R_f 0.38 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.2, 1.6 Hz, 1H), 7.82−7.75 (m, 2H), 7.56 (ddd, J = 8.2, 6.6, 1.6 Hz, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 7.41 (td, J = 8.0, 1.6 Hz, 1H), 7.23−7.13 (m, 4H), 7.07 (dd, J = 8.0, 1.6 Hz, 1H), 6.87−6.85 (m, 2H), 5.77 (d, J = 15.2 Hz, 1H), 4.62 (d, J = 15.2 Hz, 1H).; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.3, 153.7, 147.3, 136.3, 134.7, 134.4, 132.4, 131.2, 130.5, 129.7, 128.5, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 121.3, 48.1; TOF-HRMS calcd for $C_{21}H_{16}{}^{37}ClN_2O$ $(M+H)^+$ 349.0921, found 349.0913, for $C_{21}H_{16}{}^{35}ClN_2O$ $(M+H)^+$ 347.0951, found 347.0896.

3-Benzyl-2-(o-tolyl)quinazolin-4(3H)-one.[14a] Table 2, entry 9, compound **2i**; colorless solid; (0.0753 g, 82% yield); mp 110−111 °C (lit.[14a] mp 112−113 °C); R_f 0.40 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.0, 1.6 Hz, 1H), 7.81−7.74 (m, 2H), 7.54 (ddd, J = 8.0, 6.6, 1.6 Hz, 1H), 7.37 (td, J = 7.6, 1.6 Hz, 1H), 7.24−7.12 (m, 6H), 6.86 (dd, J = 7.6, 1.6 Hz, 2H), 5.24 (d, J = 14.8 Hz, 1H), 5.09 (d, J = 14.8 Hz, 1H), 1.96 (s, 3H).

(E)-3-Benzyl-2-styrylquinazolin-4(3H)-one.[28] Table 2, entry 10, compound **2j**; white solid; (0.0684 g, 72% yield); mp 138−139 °C (lit.[28] mp 138−140 °C); R_f 0.24 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 15.6 Hz, 1H), 7.79−7.75 (m, 2H), 7.49−7.44 (m, 3H), 7.39−7.26 (m, 8H), 7.03 (d, J = 15.6 Hz, 1H), 5.52 (s, 2H).

2,3-Dibenzylquinazolin-4(3H)-one.[20d] Table 2, entry 11, compound **2k**; yellow solid; (0.0716 g, 78% yield); mp 168−169 °C (lit.[20d] mp 167−168 °C); R_f 0.32 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 8.0, 1.6 Hz, 1H), 7.82−7.75 (m, 2H), 7.51 (ddd, J = 8.0, 6.6, 1.6 Hz, 1H), 7.36−7.23 (m, 8H), 7.16 (d, J = 7.2 Hz, 2H), 5.27 (s, 2H), 4.11 (s, 2H).

3-Benzyl-2-methylquinazolin-4(3H)-one.[29] Table 2, entry 12, compound **2l**; colorless solid; (0.0654 g, 93% yield); mp 120−121 °C (lit.[29] mp 123−124 °C); R_f 0.28 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 8.0, 1.6 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.34−7.24 (m, 3H), 7.19 (d, J = 7.2 Hz, 3H), 5.39 (s, 2H), 2.54 (s, 3H).

2-Methyl-3-(o-tolyl)quinazolin-4(3H)-one.[29] Table 2, entry 13, compound **2m**; yellow solid; (0.0598 g, 85% yield and 0.0590 g, 84% yield for **3d**); mp 121−123 °C (lit.[29] mp 119−121 °C) ; R_f 0.33 (30%

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EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J = 8.0, 1.6 Hz, 1H), 7.77 (ddd, J = 8.2, 7.2, 1.6 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.47 (ddd, J = 8.2, 7.2, 1.6 Hz, 2H), 7.43−7.30 (m, 4H), 7.16 (d, J = 7.2 Hz, 1H), 2.18 (s, 3H), 2.12 (s, 3H).

3-(4-Ethoxyphenyl)-2-methylquinazolin-4(3H)-one.[30] Table 2, entry 14, compound **2n**; yellow solid; (0.0699 g, 89% yield); mp 146−147 °C (lit.[30] mp 152−154 °C); R_f 0.26 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.08 (q, J = 6.8 Hz, 2H), 2.24 (s, 3H), 1.44 (t, J = 6.8 Hz, 3H).

3-(Chlorophenyl)-2-methylquinazolin-4(3H)-one.[29] Table 2, entry 15, compound **2o**; a white solid; (0.0631 g, 83% yield); mp 155−156 °C (lit.[29] mp 157−158 °C); R_f 0.30 30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 7.76 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.66 (dd, J = 8.0, 1.6 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.46 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 2.24 (s, 3H).

Methyl 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)benzoate.[31] Table 2, entry 17, compound **2q**; yellow solid; (0.0306 g, 37% yield); mp 118−119 °C (lit.[31] mp 114−115 °C) ; R_f 0.39 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.78−7.68 (m, 3H), 7.60 (t, J = 7.6 Hz, 1H),7.44 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 3.69 (s, 3H), 2.19 (s, 3H).

Methyl (Z)-2-(N′-(2-(methoxycarbonyl)phenyl)acetimidamido)-benzoate. Table 2, entry 17, noncyclized product; yellow oil; (0.0442 g, 48% yield); R_f 0.41 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.30−7.24 (m, 3H), 6.98 (t, J = 7.6 Hz, 2H), 6.68 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H), 2.15 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 169.0, 167.6, 158.6, 149.7, 148.2, 136.0, 133.0, 130.7, 130.5, 129.3, 123.16, 123.12, 123.07, 122.3, 121.4, 55.1, 52.1, 24.5; TOF-HRMS calcd for $C_{18}H_{19}N_2O_4$ $(M+H)^+$ 327.1345, found 327.1349.

3-(4-Methoxybenzyl)-2-phenylquinazolin-4(3H)-one.[20d] Scheme 2, compound **3a**; white solid; (0.0818 g, 85% yield); mp 187−189 °C (lit.[20d] mp 187−189 °C); R_f 0.30 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.0 Hz, 1H), 7.78−7.73 (m, 2H), 7.53−7.35 (m, 6H), 6.85 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 5.21 (s, 2H), 3.73 (s, 3H).

3-Butyl-2-phenylquinazolin-4(3H)-one.[13] Scheme 2, compound **3b**; white solid; (0.0493 g, 63% yield); mp 113−114 °C (lit.[13] mp 112−113 °C); R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.6 Hz, 1H), 7.77−7.71 (m, 2H), 7.54−7.47 (m, 6H), 3.97 (t, J = 7.6 Hz, 2H), 1.62−1.55 (m, 2H), 1.17 (sex, J = 7.6 Hz, 2H), 0.75 (t, J = 7.6 Hz, 3H).

3-(4-(Diethylamino)phenyl)-2-ethylquinazolin-4(3H)-one. Scheme 2, compound **3c**; yellow solid; (0.0678 g, 75% yield); mp 165−167 °C; R_f 0.54 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.0, 1.6 Hz, 1H), 7.75−7.68 (m, 2H), 7.42 (ddd, J = 8.0, 6.6, 1.6 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 3.39 (q, J = 7.2 Hz, 4H), 2.53 (q, J = 7.2 Hz, 2H), 1.24−1.19 (m, 9H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 163.1, 159.3, 148.1, 147.7, 134.3, 128.8, 127.2, 127.0, 126.3, 124.5, 121.0, 112.0, 44.5, 29.5, 12.6, 11.5; TOF-HRMS calcd for $C_{20}H_{24}N_3O$ $(M+H)^+$, 322.1919, found 322.1922.

3-Butyl-2-(4-nitrophenyl)quinazolin-4(3H)-one.[21d] Scheme 3, compound **4b**; yellow solid; (0.0347 g, 38% yield); mp 131−132 °C (lit.[21d] mp 126−128 °C); R_f 0.21 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.8 Hz, 2H), 8.33 (dd, J = 8.0, 1.6 Hz, 1H), 7.80−7.73 (m, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H), 7.53 (td, J = 8.0, 1.6 Hz, 1H), 3.94 (t, J = 7.2 Hz, 2H), 1.61−1.54 (m, 1H), 1.18 (sex, J = 7.2 Hz, 1H), 0.77 (t, J = 7.2 Hz, 2H).

(E)-2-styryl-3-(o-tolyl)quinazolin-4(3H)-one.[28] Scheme 3, compound **4c**; brown solid; (0.0591 g, 62% yield); mp 160−162 °C (lit.[28] mp 162−164 °C); R_f 0.31 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dt, J = 8.0, 1.2 Hz, 1H), 8.02 (d, J = 15.6 Hz, 1H), 7.83−7.80 (m, 2H), 7.51−7.40 (m, 3H), 7.34−7.28 (m, 5H), 7.23 (d, J = 7.6 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 2.14 (s, 3H).

2-(2-Chloropyridin-3-yl)-3-(p-tolyl)quinazolin-4(3H)-one. Scheme 3, compound **4d**; colorless crystal; (0.0762 g, 78% yield); mp 157−159 °C; R_f 0.23 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 8.0, 1.6 Hz, 1H), 8.28 (dd, J = 5.0, 1.6 Hz, 1H), 7.81 (m, 2H), 7.63 (dd, J = 7.6, 2.0 Hz, 1H), 7.56 (ddd, J = 8.0, 6.8, 1.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.15 (dd, J = 7.6, 5.0 Hz, 1H), 7.12−7.06 (m, 1H), 6.92 (br s, 1H), 2.25 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 161.9, 151.5, 150.3, 148.7, 147.2, 139.3, 139.0, 134.9, 133.7, 131.4, 130.2, 129.7, 128.5, 128.0, 127.9, 127.8, 127.3, 121.8, 121.5, 21.2; TOF-HRMS calcd for $C_{20}H_{15}{}^{37}ClN_3O$ $(M+H)^+$ 350.0874, found 350.0857, for $C_{20}H_{15}{}^{35}ClN_3O$ $(M+H)^+$ 348.0904, found 348.0896.

2-Benzyl-3-butylquinazolin-4(3H)-one.[20b] Scheme 3, compound **4e**; colorless crystal; (0.0404 g, 49% yield); mp 125−127 °C (lit.[20b] mp 127 °C); R_f 0.48 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.2, 1.6 Hz, 1H), 7.76−7.69 (m, 2H), 7.46 (ddd, J = 8.2, 6.8, 1.6 Hz, 1H), 7.34−7.25 (m, 5H), 4.25 (s, 2H), 3.96 (t, J = 7.2 Hz, 2H), 1.54 (m, 2H), 1.34 (sex, J = 7.2 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H).

3-Benzyl-2-ethylquinazolin-4(3H)-one.[20b] Scheme 3, compound **4f**; colorless crystal; (0.0296 g, 40% yield); mp 117−119 °C; R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, J = 8.0, 1.2 Hz, 1H), 7.74 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.68 (dd, J = 8.0, 1.2 Hz, 1H), 7.46 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.34−7.23 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 5.42 (s, 3H), 2.77 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H).

2-Benzyl-3-(4-methoxybenzyl)quinazolin-4(3H)-one. Scheme 3, compound **4g**; colorless oil; (0.0473 g, 47% yield); R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 8.0, 1.6 Hz, 1H), 7.80−7.72 (m, 2H), 7.50 (ddd, J = 8.0, 6.8, 1.6 Hz, 1H), 7.36−7.23 (m, 5H), 7.11 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.19 (s, 2H), 4.14 (s, 2H), 3.78 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.9, 159.2, 155.6, 147.4, 135.4, 134.5, 129.2, 128.3, 128.2, 127.8, 127.5, 127.3, 127.2, 126.9, 120.7, 114.5, 55.4, 45.9, 42.3; TOF-HRMS calcd for $C_{23}H_{21}N_2O_2$ $(M+H)^+$ 357.1603, found 357.1596.

Methyl 2-(2-(4-methoxybenzyl)-4-oxoquinazolin-3(4H)-yl)-acetate one. Scheme 3, compound **4h**; brown solid; (0.0259 g, 27% yield); mp 112−114 °C; R_f 0.40 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 8.0,1.6 Hz, 1H), 7.78−7.74 (m, 2H), 7.48 (ddd, J = 8.0, 6.8, 1.6 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.77 (s, 2H), 4.09 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 168.0, 162.3, 159.0, 154.7, 147.2, 134.6, 132.0. 129.4, 127.3, 127.0, 126.3, 120.2, 114.5, 55.3, 52.7, 44.9, 41.9; TOF-HRMS calcd for $C_{19}H_{19}N_2O_4$ $(M+H)^+$ 339.1345, found 339.1336.

6-Chloro-3-cyclopropyl-2-(2-methoxybenzyl)quinazolin-4(3H)-one. Scheme 3, compound **4i**; yellow solid; (0.0394 g, 41% yield); mp 160−162 °C; R_f 0.36 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.26−7.22 (m, 1H), 7.08 (dd,, J = 7.6, 1.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 2.75−2.69 (m, 1H), 1.26−1.23 (m, 2H), 0.94−0.89 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.6, 158.8, 157.1, 145.7, 134.4, 132.1, 129.7, 128.7, 128.4, 126.0, 124.7, 122.3, 120.9, 110.6, 55.5, 36.2, 27.6, 10.6; TOF-HRMS calcd for $C_{19}H_{18}{}^{37}ClN_2O_2$ $(M+H)^+$ 343.1027, found 343.1012, for $C_{19}H_{18}{}^{35}ClN_2O_2$ $(M+H)^+$ 341.1057, found 341.1046.

3-Cyclopropyl-6-iodo-2-(4-methoxybenzyl)quinazolin-4(3H)-one. Scheme 3, compound **4j**; yellow solid; (0.0536 g, 44% yield); mp 138−140 °C; R_f 0.23 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 8.8, 2.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.33 (s, 2H), 3.76 (s, 3H), 2.63−2.57 (m, 1H), 1.29−1.24 (m, 2H), 0.93−0.90 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.0, 158.8, 146.2, 142.8, 135.4, 129.6, 128.8, 127.2, 122.22, 114.3, 90.8, 55.3, 41.5, 27.4, 10.9; TOF-HRMS calcd for $C_{19}H_{18}IN_2O_2$ $(M+H)^+$, 433.0413, found 433.0406.

3-Butyl-2-(4-fluorobenzyl)-6-iodoquinazolin-4(3H)-one. Scheme 3, compound **4k**; colorless oil; (0.0529 g, 43% yield); R_f 0.33 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.4, 2.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.23−

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7.20 (m, 2H), 7.04−6.98 (m, 2H), 4.17 (s, 2H), 4.03−3.73 (m, 2H), 3.93 (t, J = 7.6 Hz, 2H), 1.35 (sex, J = 7.6 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 163.3, 160.9, 155.6, 146.4, 142.9, 135.6, 130.9, 129.8, 129.7, 129.0, 122.4, 116.1, 115.9, 91.0, 44.4, 41.6, 30.7, 20.2, 13.7; TOF-HRMS calcd for $C_{19}H_{19}FIN_2O$ $(M+H)^+$ 437.0526, found 437.0524.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01322.

Copies of ^1H NMR of all products and ^{13}C NMR spectra for new compound (PDF)

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Notes

The authors declare no competing financial interest.

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