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Synthesis of 2-Aminoquinazolinones via Carbonylative Coupling of *ortho*-Iodoanilines and Cyanamide

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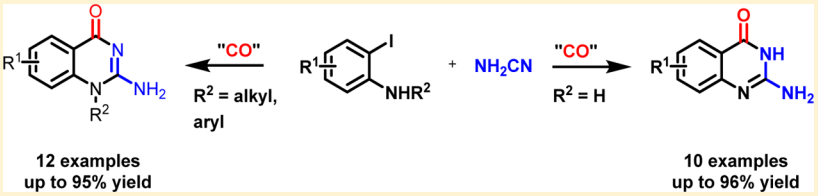
Supporting Information



ABSTRACT: Herein, we describe a convenient and efficient synthesis of 2-aminoquinazolin-4(3*H*)-ones and N1-substituted 2-aminoquinazolin-4(1*H*)-ones by a domino carbonylation/cyclization process. The reaction proceeds via carbonylative coupling of readily available *ortho*-iodoanilines with cyanamide followed by in situ ring closure of an *N*-cyanobenzamide intermediate. The products were easily isolated by precipitation in moderate to excellent yields for a wide range of substrates, making this a highly attractive method for the synthesis of 2-aminoquinazolinones.

INTRODUCTION

The quinazolinone structure is one of the most frequently encountered heterocycles in small-molecule drugs,[1] displaying a broad range of biological activities such as antimalarial,[2] antitumor (thymidylate synthase inhibitors),[3] protein kinase inhibition,[4] anti-inflammatory,[5,6] antiviral,[7] antihypertensive,[8] and anticonvulsant.[9] Several synthetic methods are available for the preparation of quinazolinones and 2-aminoquinazolinones,[10,11] including fusion of anthranilic acid with amides,[12] amidation of 2-aminobenzoic acids and its derivatives,[13,14] reaction of resin-bound isothioureas with isatoic anhydrides,[15] and acylation of *ortho*-fluorobenzoic acids with substituted guanidines and subsequent ring closure.[16] Furthermore, 1-aryl-2-aminoquinazolin-4-ones and 2-(arylamino)quinazolin-4-ones have been obtained from the reaction of *N*-cyanoimidates and arylamines.[17] However, these reactions are often performed under harsh reaction conditions and require multistep procedures or complex intermediates, and there is still a need for new and efficient methods to prepare this important ring system.

Pd-catalyzed carbonylation reactions such as aminocarbonylation, cross-coupling reactions, and carbonylation of alkenes are now essential tools for synthetic and medicinal chemists, and significant effort has been invested into developing safer methods for handling the toxic carbon monoxide gas.[18−20] In the past decade, several nongaseous CO sources have been reported for in situ and ex situ use.[21] For example, formates, formamides, aldehydes, and formic acid have been reported as CO sources.[20,22−24] The Pd-catalyzed decomposition of 9-methylfluorene-9-carbonyl chloride (COgen)[25] and the liberation of CO from silacarboxylic acids[26] allow the use of substoichiometric amounts of CO as well as a possibility to label the carbonyl carbon. Recently, the base-mediated decomposition of oxalyl chloride[27,28] and chloroform[29] has been reported as efficient CO-generating strategies for carbonylation chemistry. Finally, metal carbonyls such as $Mo(CO)_6$ offer a convenient and easy-to-handle solid source of CO suitable for in situ and ex situ gas release.[30−34]

Pd-catalyzed carbonylation reactions have been proven to be useful in the synthesis of various heterocyclic ring systems.[35] There are numerous reports where aryl halides equipped with *ortho*-heteroatoms have been used in carbonylation reactions to synthesize various heterocycles, such as indoles,[36] quinolones,[37] and chromones.[38] We have previously utilized this approach to prepare 4-quinolones under mild conditions using a carbonylative Sonogashira coupling reaction of *ortho*-iodoanilines followed by intramolecular cyclization.[39]

There are a few reports employing Pd-catalyzed carbonylative methods to prepare quinazolin-4(3*H*)-ones using gaseous CO.[35] The most prominent approach was developed by Larksarp and Alper involving the cyclocarbonylation of *ortho*-iodoanilines with carbodiimides and ketenimines[40] to obtain 2-aminoquinazolin-4(3*H*)-ones and 2-alkylquinazolin-4(3*H*)-ones, respectively (Scheme 1a). This methodology was further developed by the same group to include carbonylation of *N*-(2-iodophenyl)-*N*′-phenylcarbodiimides[41] in the presence of secondary amines and phenols to give the corresponding 2-aminoquinazolin-4(3*H*)-ones and 2-phenoxyquinazolin-4(3*H*)-ones (Scheme 1b). Based on this work, Roberts et al. developed a molybdenum-catalyzed cyclocarbonylation of carbodiimides using microwave irradiation, giving 2-aminoquinazolin-4(3*H*)-

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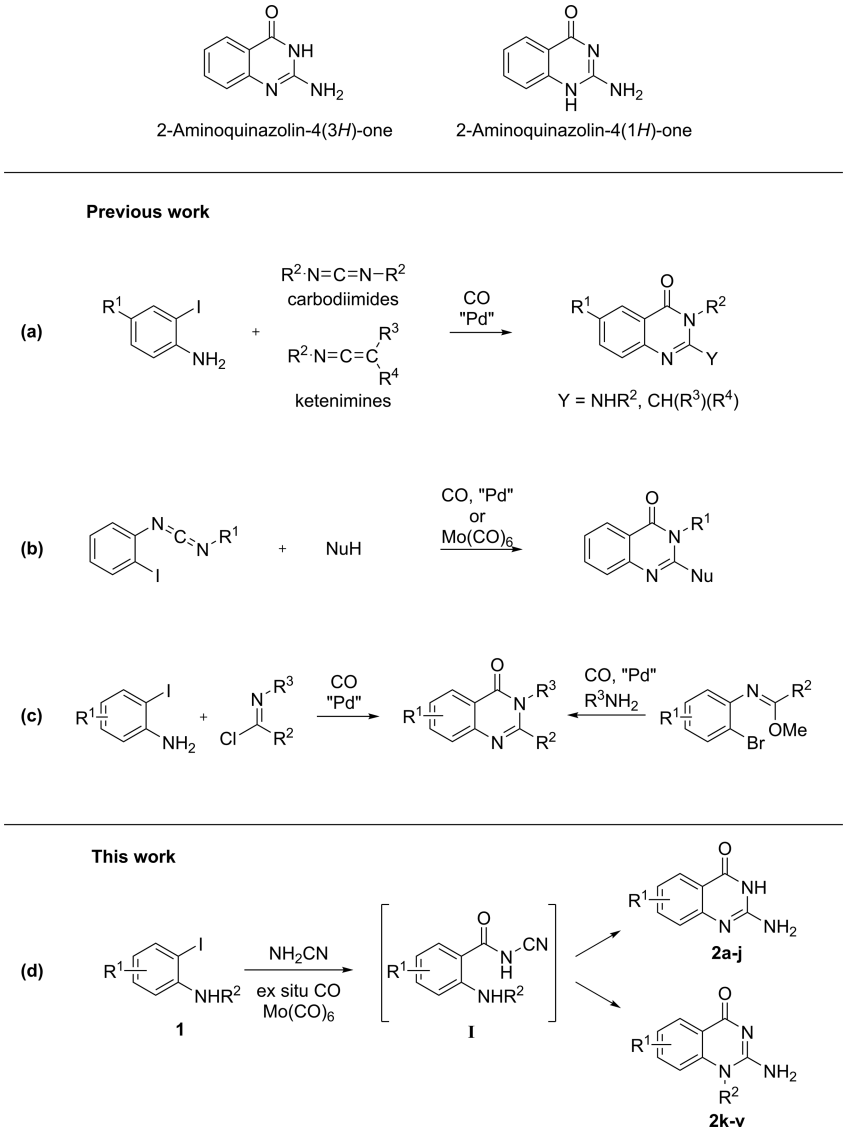
Scheme 1. Synthesis of Quinazolinones by Carbonylative Coupling of *ortho*-Iodoanilines



ones in moderate to good yields (Scheme 1b).[42] By using $Mo(CO)_6$ as both catalyst and CO source, the use of gaseous CO could be avoided. Moreover, 2-substituted quinazolinones have been prepared by coupling *ortho*-iodoanilines with imidoyl chlorides[43] or by the aminocarbonylation of *N*-(*ortho*-bromophenyl)imidates with various amines[44] (Scheme 1c). However, these methods all suffer from a number of drawbacks, including the use of high CO pressures, high reaction temperatures, complex noncommercially available starting materials, and the formation of regioisomeric mixtures. Additionally, these methods are limited to the preparation of aminoquinazolin-4(3*H*)-ones and consequently do not allow the introduction of N1-substituents. We have previously reported the carbonylative coupling of aryl iodides with cyanamide to yield *N*-cyanobenzamides,[45] and we reasoned that the use of readily available *ortho*-iodoanilines (**1**) would afford an *ortho*-amino-*N*-cyanobenzamide intermediate **I** (Scheme 1d), which could then undergo cyclization to give a 2-aminoquinazolin-4(3*H*)-one (Scheme 1d). This approach offers a number of significant advantages including (i) the use of readily available cyanamide as the N−C−N source, (ii) increased flexibility as both unsubstituted 2-aminoquinazolin-4(3*H*)-ones or *N*1-substituted 2-aminoquinazolin-4(1*H*)-ones can be accessed depending on the choice of *ortho*-iodoaniline, and (iii) no requirement for high CO pressures or the use of CO gas. Herein, we describe the development of a facile, convenient carbonylative synthesis of 2-aminoquinazolinones (**2**) from cyanamide and *ortho*-iodoanilines.

RESULTS AND DISCUSSION

Initially, we sought to investigate if an aminocarbonylation with cyanamide could proceed in the presence of a potentially problematic *ortho*-aniline group. To test this, 2-iodoaniline (**1a**) and cyanamide (3 equiv) were heated in 1,4-dioxane at 65 °C for 20 h using $Pd(PPh_3)_4$ and triethylamine as the catalyst and base, respectively, similar to the conditions reported by Mane et al.[45] To our delight, the carbonylation proceeded smoothly even with this challenging substrate, and full conversion of the starting material was observed after 20 h at 65 °C (LCMS). Further studies revealed that the reaction produced a mixture of the fully cyclized 2-aminoquinazolin-4(3*H*)-one **2a** (24% isolated yield, analyzed by LCMS and NMR) and the linear *N*-cyanobenzamide intermediate **I** (37% isolated yield, analyzed by LCMS and NMR). This indicated that the carbonylative

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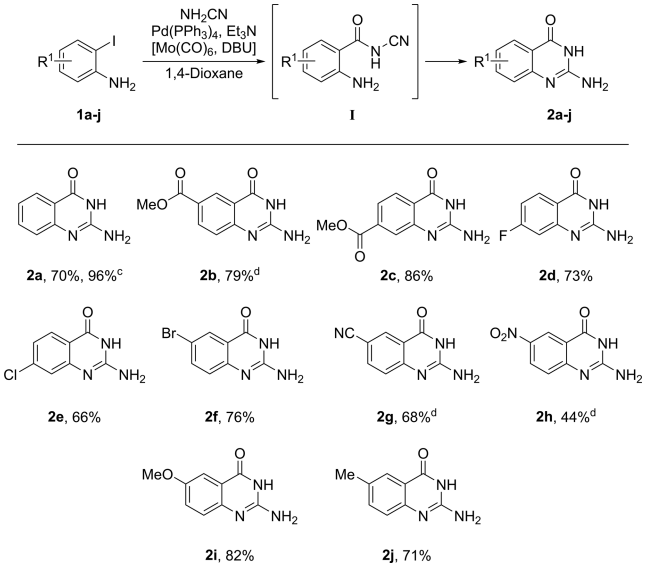
coupling was compatible with an *ortho*-heteroatom on the iodide substrate; however, the subsequent ring closure required additional attention. Therefore, the carbonylative reaction was repeated using the conditions described above, and to complete the cyclization process, the reaction mixture in chamber 1 was transferred to a microwave vial and heated at 140 °C for 20 min. These conditions led to full conversion of intermediate **I**, and 2-aminoquinazolin-4(3*H*)-one (**2a**) was obtained in 70% isolated yield (Scheme 2). Notably, **2a** could conveniently be

Scheme 2. Substrate Scope for the Synthesis of 2-Aminoquinazolin-4(3*H*)-ones (2a–j) from Unsubstituted *ortho*-Iodoanilines (1a–j)[a,b]



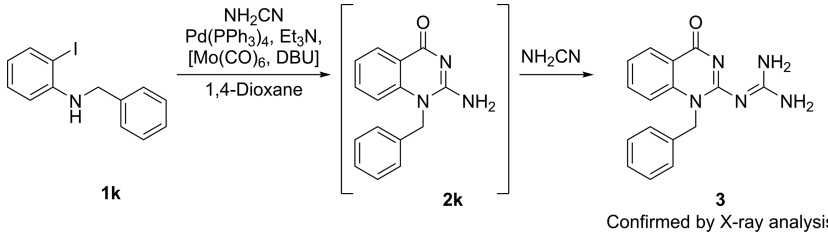
[a]Isolated yield. [b]Reaction conditions: Chamber 1: *ortho*-iodoaniline (0.5 mmol), cyanamide (3 equiv), $Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), 1,4-dioxane (3 mL), 65 °C, 20 h. Chamber 2: $Mo(CO)_6$ (1 equiv), DBU (3 equiv), 1,4-dioxane (3 mL), 65 °C, 20 h. The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 20 min. [c]2-Iodoaniline (1 mmol). [d]The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 40 min.

isolated by precipitation in aqueous sodium bicarbonate solution without further purification, and when the experiment was repeated on a 1 mmol scale, the isolated yield was increased to an excellent 96%.

To investigate the generality of the reaction, a diverse set of *ortho*-iodoanilines was tested to explore the scope and limitations with respect to aryl substituents (Scheme 2). Gratifyingly, the carbonylative coupling with cyanamide followed by intramolecular cyclization proved to be general for a wide scope of substrates with isolated yields of up to 86% (Scheme 2). Methyl-ester-substituted *ortho*-iodoanilines (**1b** and **1c**) furnished the 6- and 7-substituted 2-aminoquinazolin-4(3*H*)-ones (**2b** and **2c**) in 79 and 86% isolated yield, respectively. The fluoro-, chloro-, and bromo-substituted *ortho*-iodoanilines (**1d–f**) provided the corresponding 2-aminoquinazolin-4(3*H*)-ones (**2d–f**) in 66–76% isolated yield. As expected, the bromo-substituent in **1f** was fully orthogonal to the iodide at the moderate reaction temperature, and no activation of the C–Br bond was detected (LCMS). The introduction of strongly electron-withdrawing groups *para* to the aniline (e.g., **1b**, **1g**, and **1h**) reduced the rate of cyclization due to the lower nucleophilicity of the aniline. In these reactions, the carbonylative coupling proceeded smoothly with full conversion to the *N*-cyanobenzamide intermediate, but the subsequent ring closure was sluggish, and for **2b**, **2g**, and **2h**, longer reaction times were needed to drive the cyclization to completion. With the nitrile- and nitro-substituted 2-aminoquinazolin-4(3*H*)-ones, this also led to competing side reactions, and **2g** and **2h** were isolated in reduced yields of 68 and 44%, respectively. In contrast, the presence of an electron-donating methoxy group in the *para* position led to complete cyclization at 65 °C, and the corresponding 2-aminoquinazolin-4(3*H*)-one (**2i**) was obtained in 82% isolated yield. However, the inductively electron-donating methyl group still required additional heating, and 2-iodo-4-methylaniline gave the corresponding product (**2j**) in 71% isolated yield.

To further expand the reaction scope, we sought to explore the use of *N*-substituted anilines as substrates to introduce additional diversity at the *N*1-position of the quinazolinone ring system. However, when *N*-benzyl-2-iodoaniline (**1k**) was used as a substrate under the standard conditions from Scheme 2, the formation of significant quantities of a side product was noted during the carbonylation step. At first, we suspected that this byproduct might be related to elevated reaction temperatures, but further analysis revealed that the formation of byproduct was closely related to the amount of cyanamide in the reaction. Indeed, the byproduct had an m/z ratio that corresponded to the expected product mass plus cyanamide (Scheme 3), and NMR spectroscopy analysis was not sufficient to fully elucidate the structure of this product. However, we were able to crystallize the compound and obtain an X-ray structure. The crystal structure revealed the guanidine-substituted quinazolinone **3** (Figure 1), resulting from the nucleophilic attack of the exocyclic amine group in the aminoquinazolinone intermediate at the electrophilic center in cyanamide. This side product was never observed for the reaction with *ortho*-iodoanilines **1a–j**, suggesting that the exocyclic amine in N1-substituted 2-aminoquinazolinones is more nucleophilic compared to the unsubstituted 2-aminoquinazolinones.

Scheme 3. Formation of Guanidine-Substituted Byproduct (3) Resulting from Excess Cyanamide



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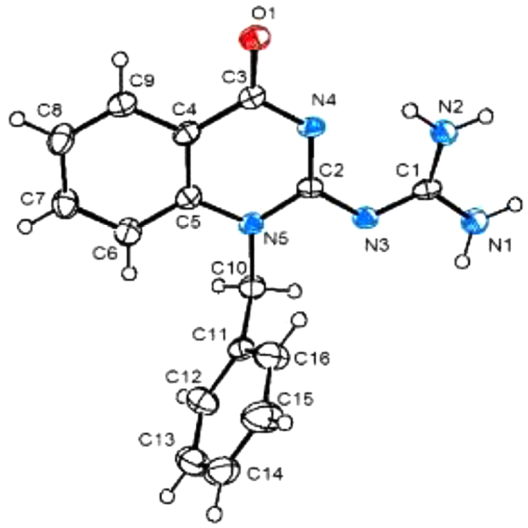
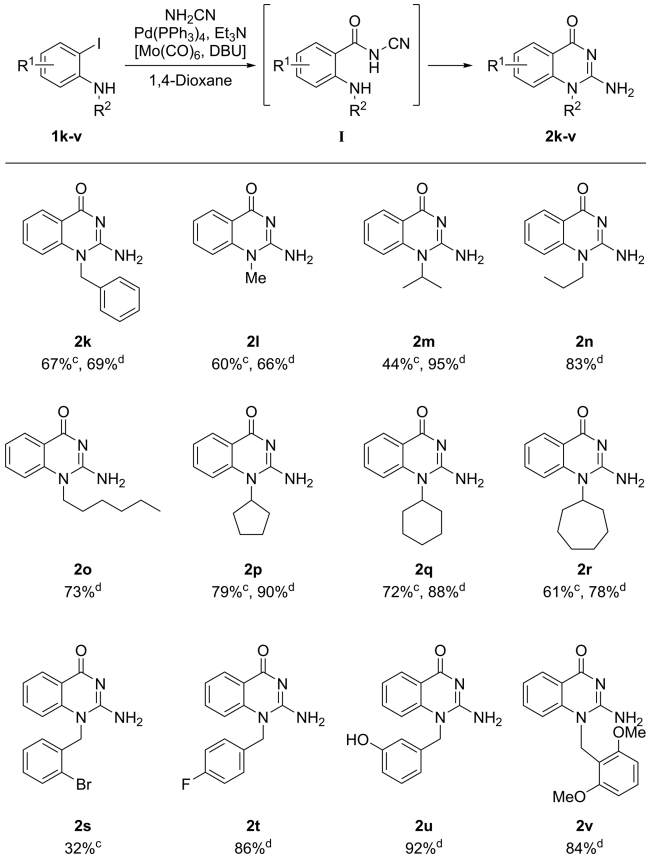


Figure 1. Structure of byproduct **3** formed in the reaction of *N*-benzyl-2-iodoaniline (**1k**) with excess cyanamide (at the 50% probability level).

By decreasing the amount of cyanamide to 1.2 equiv but keeping the same reaction temperatures used for the synthesis of **2a**–**j** (Scheme 2), the formation of the guanidine byproduct was avoided and 2-amino-*N*-benzylquinazolinon-4(1*H*)-one (**2k**) was isolated in 67% yield (Scheme 4, method A). We reasoned that additional steric hindrance from the benzyl group might hamper the reactivity of the aryl iodide in the Pd-mediated oxidative addition and result in a lower yield. Therefore, the reaction temperature during the carbonylative coupling was increased to 85 °C (Scheme 4, method B). Under these conditions, full consumption of the *N*-cyanobenzamide intermediate was obtained in one step, and no further heating was required. While this made the method more convenient, it did not improve the yield, and **2k** was isolated in 69% yield. Still, encouraged by this development, both methods A and B were tested in the reaction with *N*-methyl-2-iodoaniline (**1l**). Interestingly, for this substrate, a slight increase in yield was observed when the higher temperature was used in the carbonylation step (60% method A, 66% method B). When the two methods were applied to *N*-isopropylaniline (**1m**), a substantially lower yield was observed when the intermediate was cyclized at a higher temperature (44%, method A, microwave irradiation at 140 °C) rather than during the carbonylation step (95%, method B, 85 °C). At higher temperatures, the formation of intractable solid material was observed, suggesting that the *N*-substituted 2-aminoquinazolin-4(1*H*)-one isomer may be more susceptible to thermally induced degradation than the corresponding 2-aminoquinazolin-4(3*H*)-one. With these two methods in hand, we wanted to explore the scope of *N*-substituted *ortho*-iodoanilines (**1k**–**v**) in the synthesis of *N*-substituted 2-aminoquinazolin-4(1*H*)-ones (**2k**–**v**, Scheme 4). Generally, the *N*-alkyl-substituted *ortho*-iodoanilines (**1l**–**o**) performed well in the reaction using method B, returning isolated yields of 66–95%. Interestingly, compounds with small aliphatic substituents (**2l**–**n**) were found to be unstable upon prolonged exposure to air, leading to a change in color and physical appearance. Cyclopentyl, cyclohexyl, and cycloheptyl *N*-substituted *ortho*-iodoanilines (**1p**–**r**) gave moderate to good yields using method A (61–79%) and good to excellent yields using method B (78–90%).

Scheme 4. Substrate Scope for the Synthesis of N-Substituted 2-Aminoquinazolin-4(1*H*)-ones (2k–v) from N-Substituted *ortho*-Iodoanilines (1k–v)[a,b]



[a]Isolated yield. [b]Reaction conditions: Chamber 1: *ortho*-iodoaniline (0.5 mmol), cyanamide (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), 1,4-dioxane (3 mL). Chamber 2: $Mo(CO)_6$ (1 equiv), DBU (3 equiv), 1,4-dioxane (3 mL). [c]Method A: (a) 65 °C, 20 h. (b) The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 20 min. [d]Method B: 85 °C, 20 h.

In general, the differences between the two methods were smaller for the cycloalkyl-substituted compounds, indicating that they may be less sensitive toward heat. Given that the aryl bromide (**1f**, Scheme 2) was tolerated, we wanted to investigate if *N*-(2-bromobenzyl)-2-iodoaniline (**1s**) could be used to synthesize 2-amino-1-(2-bromobenzyl)quinazolin-4(1*H*)-one (**2s**). Disappointingly, **2s** was isolated in only 32% yield using method A, and when the carbonylation was carried out at 85 °C (method B), an unidentified byproduct without the bromine isotope pattern was formed. The reaction, however, performed well for other *N*-benzyl-substituted 2-iodoanilines (**1t**–**v**), and *N*-(4-fluorobenzyl)-, *N*-(3-hydroxybenzyl)-, and *N*-(2,6-dimethoxybenzyl)-2-aminoquinazolin-4(1*H*)-ones (**2t**–**v**) were isolated in high yields (84–92%).

Since method B is carried out in one step and requires less cyanamide, we were encouraged to explore this method using **1a**. Unfortunately, **2a** was isolated in 61% compared to 70% for the method used in Scheme 2. However, increasing the amount of cyanamide to 3 equiv afforded an equivalent isolated yield of **2a** (71%). The two developed methods complement each other, where method B allows for the quinazolinones to be prepared directly in one step and method A is better suited for

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substrates with potentially palladium-sensitive functional groups, such as bromides.

CONCLUSION

In summary, we have developed a novel synthesis of 2-aminoquinazolin-4(3*H*)-ones and *N*1-substituted 2-aminoquinazolin-4(1*H*)-ones using a carbonylative coupling of *ortho*-iodoanilines with cyanamide. The final products were obtained from ring closure of the *N*-cyanobenzamide intermediates either by an additional heating step or directly during the carbonylation reaction. With the developed protocol, both unsubstituted and *N*1-substituted quinazolinones with a free exocyclic amino group can be prepared selectively in moderate to excellent yields. Given that cyclized products can be readily isolated by precipitation, this strategy represents a convenient and highly attractive method for the synthesis of 2-aminoquinazolinones.

EXPERIMENTAL SECTION

General Information. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed on silica gel 60 (40−63 μm). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts for ^{1}H NMR and ^{13}C NMR are referenced to TMS via residual solvent signals (^{1}H, MeOD at 3.31 ppm, $CDCl_3$ at 7.26 ppm, and DMSO-d_6 at 2.50 ppm; ^{13}C, MeOD at 49.0 ppm, $CDCl_3$ at 77.0 ppm, and DMSO-d_6 at 39.5 ppm). The data are reported as follows: s = singlet, d = doublet, t = triplet, q = quintet, sext = sextet, m = multiplet, coupling, constant(s), integration. NMR spectra for **2a**−**v** were recorded in DMSO-d_6 at 50 °C to avoid peak broadening resulting from tautomerism. Analytical HPLC/ESI-MS was performed using electrospray ionization (ESI) and a C18 column (50 × 3.0 mm, 2.6 μm particle size, 100 Å pore size) with CH_3CN/H_2O in 0.05% aqueous HCOOH as the mobile phase at a flow rate of 1.5 mL/min. LC purity analyses were run using a gradient of 5−100% CH_3CN/H_2O in 0.05% aqueous HCOOH as the mobile phase at a flow rate of 1.5 mL/min for 5 min on a C18 column unless otherwise stated. Accurate mass values were determined using a mass spectrometer equipped with an ESI source and time-of-flight (TOF) mass analyzer. Compounds **1j**,[46] **1k**,[47] **1l**,[48] **1m**,[49] **1s**,[50] **2a**,[51] and **2l**[52] are known, and spectral data were in agreement with the proposed structures and matched those reported in the literature.

*2-Iodo-4-methylaniline (**1j**).* Prepared following a literature procedure[53] to yield **1j** as a beige solid (759 mg, 64%).

*N-Benzyl-2-iodoaniline (**1k**).* Prepared following a literature procedure[53] to yield **1k** as a colorless oil (224 mg, 67%).

*2-Iodo-N-Methylaniline (**1l**).* Prepared following a literature procedure[54] to yield **1l** as a yellow oil (808 mg, 72%).

*2-Iodo-N-isopropylaniline (**1m**).* Prepared following a literature procedure[55] to yield **1m** as a colorless oil (867 mg, 84%).

*2-Iodo-N-propylaniline (**1n**).* Acetic acid (0.86 mL, 15 mmol) and sodium triacetoxyborohydride (2.50 g, 11.8 mmol) were added to a solution of 2-iodoaniline (1.10 g, 5.04 mmol) and propionaldehyde (0.43 mL, 6.0 mmol) in dry dichloromethane (70 mL), and the reaction mixture was stirred at ambient temperature overnight. After the reaction was deemed complete (TLC), the mixture was poured into saturated $NaHCO_3$ (aq) (50 mL) and then extracted into dichloromethane (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (100:1) to give **1n** as a colorless oil (967 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 6.56 (dd, J = 8.2, 1.5 Hz, 1H), 6.43 (ddd, J = 7.3, 1.5 Hz, 1H), 4.15 (br s, 1H), 3.13 (td, J = 7.0, 5.3 Hz, 2H), 1.70 (sext, J = 7.3 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.5, 139.1, 129.5, 118.4, 110.7, 85.5, 46.1, 22.6, 11.8; HRMS (ESI-TOF) calcd for $C_9H_{13}NI$ $[M + H]^+$ 262.0093 m/z, found 262.0093; LC purity (254 nm) = >98%.

*N-Hexyl-2-iodoaniline (**1o**).* To a solution of 2-iodoaniline (1.11 g, 5.05 mmol) and hexanal (0.74 mL, 6.02 mmol) in dry dichloromethane (70 mL) were added acetic acid (0.86 mL, 15.0 mmol) and sodium triacetoxyborohydride (2.46 g, 11.6 mmol). The reaction was stirred at ambient temperature overnight. The reaction was poured into saturated $NaHCO_3$ (aq) (50 mL) and then extracted into dichloromethane (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (100:1) to give **1o** as a colorless oil (1.13 g, 74%): ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (ddd, J = 8.1, 7.2, 1.5 Hz, 1H), 6.56 (dd, J = 8.2, 1.5 Hz, 1H), 6.42 (ddd, J = 7.8, 7.2, 1.5 Hz, 1H), 4.12 (br s, 1H), 3.14 (td, J = 7.1, 5.2 Hz, 2H), 1.73−1.63 (m, 2H), 1.48−1.30 (m, 6H), 0.95−0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 147.6, 139.1, 129.5, 118.4, 110.7, 85.5, 44.4, 31.7, 29.3, 27.0, 22.8, 14.2; HRMS (ESI-TOF) calcd for $C_{12}H_{19}NI$ $[M + H]^+$ 304.0562 m/z, found 304.0571; LC purity (254 nm) = >98%.

*N-Cyclopentyl-2-iodoaniline (**1p**).* Acetic acid (0.57 mL, 10 mmol) was added to a solution of 2-iodoaniline (1.10 g, 5.03 mmol) and cyclopentanone (0.69 mL, 7.8 mmol) in dry dichloromethane (10 mL), and the reaction mixture was stirred at ambient temperature for 2 h. Sodium triacetoxyborohydride (1.82 g, 8.56 mmol) was added, and the reaction mixture was stirred at ambient temperature for 20 h; 1 M NaOH (aq) (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (gradient 0−1% ethyl acetate) to give **1p** as a colorless oil (751 mg, 52%): ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 7.8, 1.5 Hz, 1H), 7.21 (ddd, J = 8.3, 7.2, 1.5 Hz, 1H), 6.62 (dd, J = 8.2, 1.5 Hz, 1H), 6.43 (ddd, J = 7.7, 7.3, 1.5 Hz, 1H), 4.17 (br s, 1H), 3.83 (h, J = 5.9 Hz, 1H), 2.11−2.01 (m, 2H), 1.85−1.51 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.1, 139.1, 129.4, 118.2, 111.4, 55.0, 33.6, 24.2; HRMS (ESI-TOF) calcd for $C_{11}H_{15}NI$ $[M + H]^+$ 288.0249 m/z, found 288.0255; LC purity (254 nm) = 97%.

*N-Cyclohexyl-2-iodoaniline (**1q**).* Anhydrous $MgSO_4$ (5.82 g, 48.3 mmol) was added to a solution of 2-iodoaniline (1.06 g, 4.85 mmol) in acetic acid (25 mL). Cyclohexanone (0.52 mL, 5.0 mmol) was added dropwise, and the suspension was stirred at ambient temperature for 2.5 h. Sodium triacetoxyborohydride (2.25 g, 10.6 mmol) was added, and the resulting mixture was stirred at ambient temperature overnight. The slurry was filtered off, and the filtrate was diluted with additional ethyl acetate (50 mL); 1 M NaOH (aq) (20 mL) was added. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (100:1) to give **1q** as a colorless oil (1.10 g, 75%): ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, J = 7.9, 1.5 Hz, 1H), 7.17 (ddd, J = 8.2, 7.2, 1.5 Hz, 1H), 6.58 (ddd, J = 8.2, 1.5, 0.6 Hz, 1H), 6.39 (ddd, J = 7.8, 7.2, 1.5 Hz, 1H), 4.10 (br d, J = 7.0 Hz, 1H), 3.31 (m, 1H), 2.08−1.99 (m, 2H), 1.82−1.73 (m, 2H), 1.64 (m, 1H), 1.45−1.22 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 146.6, 139.3, 129.5, 118.2, 111.3, 85.9, 52.0, 33.2, 26.0, 24.9; HRMS (ESI-TOF) calcd for $C_{12}H_{17}NI$ $[M + H]^+$ 302.0406 m/z, found 302.0411; LC purity (254 nm) = >98%.

*N-(2-Iodophenyl)cycloheptanamine (**1r**).* Acetic acid (0.57 mL, 10 mmol) was added to a solution of 2-iodoaniline (1.11 g, 5.07 mmol) and cycloheptanone (0.92 mL, 7.8 mmol) in dry dichloromethane (10 mL), and the reaction mixture was stirred at ambient temperature for 2 h. Sodium triacetoxyborohydride (1.82 g, 8.56 mmol) was added, and the reaction mixture was stirred at ambient temperature for 20 h; 1 M NaOH (aq) (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (gradient 0−1% ethyl acetate) to give **1r** as a colorless oil (831

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mg, 52%): ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H), 6.51 (m, 1H), 6.41 (m, 1H), 4.17 (s, 1H), 3.52 (m, 1H), 2.06−1.96 (m, 2H), 1.79−1.47 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 146.4, 139.3, 129.4, 118.1, 111.3, 86.0, 54.0, 34.7, 28.4, 24.4; HRMS (ESI-TOF) calcd for $C_{13}H_{19}NI$ $[M + H]^+$ 316.0562 m/z, found 316.0576; LC purity (254 nm) = 93%.

*N-(2-Bromobenzyl)-2-iodoaniline (**1s**).* Prepared following a literature procedure[50] to yield **1s** as a white solid (1.77 g, 90%).

*N-(4-Fluorobenzyl)-2-iodoaniline (**1t**).* Acetic acid (0.43 mL, 7.5 mmol) was added to a solution of 2-iodoaniline (1.06 g, 4.86 mmol) and 4-fluorobenzaldehyde (0.80 mL, 7.5 mmol) dissolved in methanol (5 mL), and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, and sodium cyanoborohydride (549 mg, 8.74 mmol) was added. The reaction was stirred from 0 °C to ambient temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq) (25 mL) and then extracted into diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (100:1) to give **1t** as a white solid (1.05 g, 66%): ^{1}H NMR ($CDCl_3$) δ 7.68 (dd, J = 7.8, 1.5 Hz, 1H), 7.36−7.29 (m, 2H), 7.16 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.08−7.00 (m, 2H), 6.57−6.40 (m, 2H), 4.60 (br t, 1H), 4.37 (d, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 245.4 Hz), 147.0, 139.2, 134.4 (d, $^4J_{CF}$ = 3.1 Hz), 129.6, 128.9 (d, $^3J_{CF}$ = 8.1 Hz), 119.2, 115.7 (d, $^2J_{CF}$ = 21.5 Hz), 111.1, 85.5, 47.8; HRMS (ESI-TOF) calcd for $C_{13}H_{12}NFI$ $[M + H]^+$ 327.9999 m/z, found 328.0004; LC purity (254 nm) = >98%.

*3-(((2-Iodophenyl)amino)methyl)phenol (**1u**).* Acetic acid (0.46 mL, 8.0 mmol) was added to a solution of 2-iodoaniline (1.18 g, 5.41 mmol) and 3-hydroxybenzaldehyde (1.02 g, 8.34 mmol) dissolved in methanol (5 mL), and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, and sodium cyanoborohydride (408 mg, 6.49 mmol) was added. The reaction was stirred from 0 °C to ambient temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq) (25 mL) and then extracted into diethyl ether (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (gradient 10−20% ethyl acetate) to give **1u** as a white solid (1.50 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.68 (dd, J = 7.7, 1.5 Hz, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.83 (br s, 1H), 6.74 (dd, J = 8.1, 2.6 Hz, 1H), 6.51 (dd, J = 8.1, 1.5 Hz, 1H), 6.45 (m, 1H), 4.81 (s, 1H, OH), 4.63 (br s, 1H, NH), 4.37 (d, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 156.1, 147.1, 140.9, 139.2, 130.2, 129.6, 119.6, 119.1, 114.4, 114.0, 111.2, 85.4, 48.2; HRMS (ESI-TOF) calcd for $C_{13}H_{13}NOI$ $[M + H]^+$ 326.0042 m/z, found 326.0036; LC purity (254 nm) = >98%.

*N-(2,6-Dimethoxybenzyl)-2-iodoaniline (**1v**).* Acetic acid (0.22 mL, 3.8 mmol) was added to a solution of 2-iodoaniline (566 mg, 2.58 mmol) and 2,6-dimethoxybenzaldehyde (536 mg, 3.23 mmol) dissolved in methanol (5 mL), and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, and sodium cyanoborohydride (231 mg, 3.84 mmol) was added. The reaction was stirred from 0 °C to ambient temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq) (25 mL) and then extracted into diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography using pentane/ethyl acetate (gradient 1−10% ethyl acetate) to give **1v** as a white solid (806 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.17 (m, 1H), 6.91 (dd, J = 8.2, 1.5 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 6.38 (m, 1H), 4.92 (br t, NH), 4.44 (d, J = 5.6 Hz, 2H), 3.88 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.8, 148.0, 139.0, 129.4, 128.9, 118.5, 115.0, 111.6, 104.0, 86.0, 55.9, 37.1; HRMS (ESI-TOF) calcd for $C_{15}H_{17}NO_2I$ $[M + H]^+$ 370.0304 m/z, found 370.0318; LC purity (254 nm) = >98%.

*2-Amino-N-cyanobenzamide Triethylamine Salt (Intermediate **I**).* To chamber 1 of an oven-dried, bridged two-chamber system[31] were added 2-iodoaniline (114 mg, 0.52 mmol), cyanamide (71 mg, 1.7 mmol), and $Pd(PPh_3)_4$ (33 mg, 5 mol %). $Mo(CO)_6$ (152 mg, 0.55 mmol) was added to chamber 2. The two chambers were capped with a gastight cap, and the atmosphere was exchanged for nitrogen. 1,4-Dioxane (3 mL) was added through the septa to both chambers followed by the addition of Et_3N (0.14 mL, 1.0 mmol) to chamber 1 and finally DBU (0.23 mL, 1.5 mmol) to chamber 2. The two-chamber system was immediately heated under vigorous stirring in a heating block at 65 °C for 20 h. The precipitate was filtered off, and the filtrate was purified by silica column chromatography using acetone/methanol with 2% triethylamine (gradient 1−5% methanol). Intermediate **I** was obtained as a colorless oil (50 mg, 37%): ^{1}H NMR (DMSO-d_6) δ 8.94 (br s, 1H), 7.76 (ddd, J = 7.9, 1.8, 0.5 Hz, 1H), 6.98 (m, 1H), 6.69 (br s, 2H), 6.54 (m, 1H), 6.36 (m, 1H), 3.09 (q, J = 7.3 Hz, 6H), 1.17 (t, J = 7.3 Hz, 9H); ^{13}C NMR (DMSO-d_6) δ 177.1, 149.8, 130.9, 130.5, 122.2, 118.6, 115.6, 113.8, 45.8, 8.7; HRMS (ESI-TOF) calcd for $C_8H_8N_3O$ $[M + H]^+$ 162.0667 m/z, found 162.0667; LC purity (254 nm) = 98%.

General Procedure for the Synthesis of 2-Aminoquinazolin-4(3*H*)-ones (2a−j). To chamber 1 of an oven-dried, bridged two-chamber system[31] were added *ortho*-iodoaniline (0.5 mmol), cyanamide (63 mg, 1.5 mmol), and $Pd(PPh_3)_4$ (29 mg, 5 mol %). $Mo(CO)_6$ (132 mg, 0.5 mmol) was added to chamber 2. The two chambers were capped with a gastight cap, and the atmosphere was exchanged for nitrogen. 1,4-Dioxane (3 mL) was added through the septa to both chambers followed by the addition of Et_3N (0.14 mL, 1.0 mmol) to chamber 1 and finally DBU (0.23 mL, 1.5 mmol) to chamber 2. The two-chamber system was immediately heated under vigorous stirring in a heating block at 65 °C for 20 h. After 20 h, the reaction mixture in chamber 1 was transferred to a microwave vial (Biotage 2−5 mL) and heated under microwave irradiation at 140 °C for 20 min. The reaction mixture was poured into $NaHCO_3$ (aq) (30 mL) and collected by filtration. The solid was washed with water (10 mL) and ethyl acetate (10 mL) to give the pure compound.

*2-Aminoquinazolin-4(3H)-one (**2a**):*[51] Prepared from 1.0 mmol **1a**; tan solid (154 mg, 96%); ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 1H), 7.53 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.10−7.02 (m, 1H), 6.53 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 164.2, 153.5, 150.8, 133.3, 125.7, 123.0, 120.8, 117.2; LC purity (254 nm) = >98%.

*Methyl 2-Amino-4-oxo-3,4-dihydroquinazoline-6-carboxylate (**2b**):* The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 40 min; tan solid (82 mg, 79%); ^{1}H NMR (DMSO-d_6) δ 8.49 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.7, 2.2 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.84 (br s, 2H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.6, 163.6, 155.11, 155.03, 133.2, 128.1, 123.6, 121.4, 116.6, 51.6; HRMS (ESI) calcd for $C_{10}H_{10}N_3O_3$ $[M + H]^+$ 220.0722 m/z, found 220.0721; LC purity (254 nm) = >98%.

*Methyl 2-Amino-4-oxo-3,4-dihydroquinazoline-7-carboxylate (**2c**):* Tan solid (94 mg, 86%); ^{1}H NMR (DMSO-d_6) δ 7.99 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.56 (dd, J = 8.2, 1.7 Hz, 1H), 6.64 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.9, 164.0, 154.6, 151.2, 133.9, 126.3, 124.5, 120.3, 120.0, 52.1; HRMS (ESI-TOF) calcd for $C_{12}H_{13}N_4O_3$ $[M + CH_3CN + H]^+$ 261.0988 m/z, found 261.0983; LC purity (254 nm) = >98%.

*2-Amino-7-fluoroquinazolin-4(3H)-one (**2d**):* Tan solid (64 mg, 73%); ^{1}H NMR (DMSO-d_6) δ 10.95 (br s, 1H), 7.99−7.90 (m, 1H), 6.96−6.86 (m, 2H), 6.47 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 165.9 (d, $^1J_{CF}$ = 248.8 Hz), 161.5, 152.7, 128.6 (d, $^3J_{CF}$ = 11.5 Hz), 114.1 (d, $^4J_{CF}$ = 1.7 Hz), 109.5 (d, $^2J_{CF}$ = 23.6 Hz), 108.3 (d, $^2J_{CF}$ = 21.3 Hz); one carbon missing; HRMS (ESI) calcd for $C_8H_7N_3OF$ $[M + H]^+$ 180.0573 m/z, found 180.0566; LC purity (254 nm) = >98%.

*2-Amino-7-chloroquinazolin-4(3H)-one (**2e**):* Off-white solid (70 mg, 66%); ^{1}H NMR (DMSO-d_6) δ 10.99 (br s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.21 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.49 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 161.6, 152.7, 138.5, 127.7, 122.6, 121.3, 115.9; one carbon missing; HRMS (ESI) calcd for $C_8H_7N_3OCl$ $[M + H]^+$ 196.0278 m/z, found 196.0272; LC purity (254 nm) = >98%.

*2-Amino-6-bromoquinazolin-4(3H)-one (**2f**):* Tan solid (91 mg, 76%); ^{1}H NMR (DMSO-d_6) δ 11.13 (br s, 1H), 8.00−7.93 (m, 1H), 7.67 (dd, J = 8.7, 2.5 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.46 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 161.6, 152.5, 149.8, 136.3, 127.7, 125.8,

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118.7, 112.7; HRMS (ESI) calcd for $C_8H_7N_3OBr$ $[M + H]^+$ 239.9772 *m/z*, found 239.9774; LC purity (254 nm) = >98%.

*2-Amino-4-oxo-3,4-dihydroquinazoline-6-carbonitrile (**2g**):* The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 40 min; beige solid (63 mg, 68%); ^{1}H NMR (DMSO-d_6) δ 11.18 (br s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 8.6, 2.1 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.76 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 160.8, 154.3 (br s due to tautomerism), 153.7, 135.8, 131.2, 124.8, 118.7, 117.2, 102.8; HRMS (ESI) calcd for $C_9H_7N_4O$ $[M + H]^+$ 187.0620 *m/z*, found 187.0619; LC purity (254 nm) = >98%.

*2-Amino-6-nitroquinazolin-4(3H)-one (**2h**):* The reaction mixture in chamber 1 was heated under microwave irradiation at 140 °C for 40 min; yellow solid (47 mg, 44%); ^{1}H NMR (DMSO-d_6) δ 8.62 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 9.1, 2.8 Hz, 1H), 7.27 (d, J = 9.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 162.0, 156.7 (br s due to tautomerism), 154.8, 140.5, 128.3, 124.9, 122.7, 116.3; HRMS (ESI) calcd for $C_{10}H_{10}N_5O_3$ $[M + CH_3CN + H]^+$ 248.0784 *m/z*, found 248.0791; LC purity (254 nm) = >98%.

*2-Amino-6-methoxyquinazolin-4(3H)-one (**2i**):* Tan solid (95 mg, 82%); ^{1}H NMR (DMSO-d_6) δ 7.31 (s, 1H), 7.34−7.09 (m, 2H), 6.48 (br s, 2H, NH_2), 3.77 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.2, 153.9, 152.5, 145.5 (br s due to tautomerism), 124.9, 123.4, 117.4, 106.1, 55.3; HRMS (ESI) calcd for $C_9H_{10}N_3O_2$ $[M + H]^+$ 192.0773 *m/z*, found 192.0781; LC purity (254 nm) = 98%.

*2-Amino-6-methylquinazolin-4(3H)-one (**2j**):* Off-white solid (66 mg, 71%); ^{1}H NMR (DMSO-d_6) δ 10.78 (br s, 1H), 7.70 (s, 1H), 7.39 (dd, J = 8.4, 2.2 Hz, 1H), 7.16−7.06 (m, 1H), 6.18 (br s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD + 1 drop conc HCl) δ 159.2, 150.9, 137.4, 136.2, 135.6, 127.2, 117.0, 115.2, 20.5; HRMS (ESI) calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0824 *m/z*, found 176.0830; LC purity (254 nm) = >98%.

General Procedure for the Synthesis of 2-Aminoquinazolin-4(1*H*)-ones (2k−v). To chamber 1 of an oven-dried, bridged two-chamber system[31] were added *ortho*-iodoaniline (0.5 mmol), cyanamide (25 mg, 0.6 mmol), and $Pd(PPh_3)_4$ (29 mg, 5 mol %). $Mo(CO)_6$ (132 mg, 0.5 mmol) was added to chamber 2. The two chambers were capped with a gastight cap, and the atmosphere was exchanged for nitrogen. 1,4-Dioxane (3 mL) was added through the septa to both chambers followed by the addition of Et_3N (0.14 mL, 1.0 mmol) to chamber 1 and finally DBU (0.23 mL, 1.5 mmol) to chamber 2. The two-chamber system was immediately heated under vigorous stirring in a heating block at 65 °C for 20 h (method A). After 20 h, the reaction mixture in chamber 1 was transferred to a microwave vial (Biotage 2−5 mL) and heated under microwave irradiation at 140 °C for 20 min or (method B) 85 °C for 20 h. The reaction mixture was poured into isohexane (30 mL) and collected by filtration. The solid was washed with water (10 mL) and ethyl acetate (10 mL) to give the pure compound.

*2-Amino-1-benzylquinazolin-4(1H)-one (**2k**).* Method A: tan solid (81 mg, 67%). Method B: tan solid (82 mg, 69%); ^{1}H NMR (DMSO-d_6) δ 7.99 (dd, J = 7.7, 1.7 Hz, 1H), 7.51 (ddd, J = 8.8, 7.1, 1.8 Hz, 1H), 7.39−7.32 (m, 2H), 7.31−7.16 (m, 7H), 5.37 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.2, 156.3, 140.7, 135.5, 132.4, 128.5, 127.1, 126.9, 125.9, 122.7, 119.0, 114.5, 47.1; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_3O$ $[M + H]^+$ 252.1137 *m/z*, found 252.1138; LC purity (254 nm) = >98%.

*2-Amino-1-methylquinazolin-4(1H)-one (**2l**).*[52] Method A: beige solid (51 mg, 60%). Method B: white solid (56 mg, 66%); ^{1}H NMR (DMSO-d_6) δ 8.04 (dd, J = 7.8, 1.7 Hz, 1H), 7.79 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.40 (m, 1H), 3.57 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.2, 153.9, 140.7, 134.2, 126.9, 123.9, 117.7, 115.1, 32.7; HRMS (ESI-TOF) calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0824 *m/z*, found 176.0817; LC purity (254 nm) = >98%.

*2-Amino-1-isopropylquinazolin-4(1H)-one (**2m**).* Method A: tan solid (46 mg, 44%). Method B: tan solid (96 mg, 95%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 7.8 Hz, 1H), 7.80−7.70 (m, 2H), 7.39 (m, 1H), 4.89 (m, 1H), 1.61 (d, J = 7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 163.6, 153.6, 139.4, 134.0, 127.4, 124.2, 118.8, 117.3, 50.4, 19.4; HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O$ $[M + H]^+$ 204.1137 *m/z*, found 204.1127; LC purity (254 nm) = >98%.

*2-Amino-1-propylquinazolin-4(1H)-one (**2n**).* Method B: white solid (89 mg, 83%); ^{1}H NMR (DMSO-d_6) δ 8.04 (m, 1H), 7.75 (m, 1H), 7.60 (m, 1H), 7.36 (m, 1H), 4.06−3.96 (m, 2H), 1.74−1.60 (m, 2H), 1.07−0.93 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 165.0, 154.2, 140.1, 134.2, 127.3, 123.8, 118.1, 115.1, 45.5, 19.9, 10.4; HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O$ $[M + H]^+$ 204.1137 *m/z*, found 204.1131; LC purity (254 nm) = 98%.

*2-Amino-1-hexylquinazolin-4(1H)-one (**2o**).* Method B: white solid (87 mg, 73%); ^{1}H NMR (DMSO-d_6) δ 8.02 (dd, J = 7.8, 1.7 Hz, 1H), 7.71 (ddd, J = 8.7, 7.2, 1.8 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.31 (m, 1H), 4.16−3.96 (m, 2H), 1.69−1.58 (m, 2H), 1.47−1.37 (m, 2H), 1.36−1.25 (m, 4H), 0.92−0.83 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 165.3, 154.6, 140.1, 133.3, 127.1, 123.1, 118.4, 114.4, 44.0, 30.8, 26.5, 25.1, 21.8, 13.6; HRMS (ESI-TOF) calcd for $C_{14}H_{20}N_3O$ $[M + H]^+$ 246.1606 *m/z*, found 246.1603; LC purity (254 nm) = >98%.

*2-Amino-1-cyclopentylquinazolin-4(1H)-one (**2p**).* Method A: gray solid (92 mg, 79%). Method B: tan solid (106 mg, 90%); ^{1}H NMR (DMSO-d_6) δ 8.07 (dd, J = 7.7, 1.7 Hz, 1H), 7.75 (m, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.39 (m, 1H), 4.93 (q, J = 9.2 Hz, 1H), 2.23−1.97 (m, 6H), 1.79−1.66 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 163.1, 154.3, 138.5, 133.3, 127.4, 123.9, 119.0, 116.8, 58.3, 26.9, 24.1; HRMS (ESI-TOF) calcd for $C_{13}H_{16}N_3O$ $[M + H]^+$ 230.1293 *m/z*, found 230.1285; LC purity (254 nm) = >98%.

*2-Amino-1-cyclohexylquinazolin-4(1H)-one (**2q**).* Method A: gray solid (88 mg, 72%). Method B: white solid (108 mg, 88%); ^{1}H NMR (DMSO-d_6) δ 8.03 (dd, J = 7.7, 1.7 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.73 (ddd, J = 8.8, 7.1, 1.8 Hz, 1H), 7.38 (m, 1H), 4.51−4.16 (m, 1H), 2.43−2.29 (m, 2H), 1.90−1.77 (m, 4H), 1.69−1.12 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 163.6, 154.0, 139.8, 133.7, 127.3, 124.2, 119.1, 117.8, 59.4, 28.3, 25.6, 24.1; HRMS (ESI-TOF) calcd for $C_{14}H_{18}N_3O$ $[M + H]^+$ 244.1450 *m/z*, found 244.1440; LC purity (254 nm) = >98%.

*2-Amino-1-cycloheptylquinazolin-4(1H)-one (**2r**).* Method A: tan solid (77 mg, 61%). Method B: tan solid (97 mg, 78%); ^{1}H NMR (DMSO-d_6) δ 8.02 (dd, J = 7.9, 1.7 Hz, 1H), 7.70 (m, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.33 (m, 1H), 4.55 (m, 1H), 2.44−2.29 (m, 2H), 2.01−1.88 (m, 2H), 1.88−1.76 (m, 2H), 1.77−1.53 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 164.4, 153.9, 139.3, 133.1, 127.2, 123.5, 119.1, 116.8, 59.9, 30.6, 27.1, 26.0; HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_3O$ $[M + H]^+$ 258.1606 *m/z*, found 258.1614; LC purity (254 nm) = 96%.

*2-Amino-1-(2-bromobenzyl)quinazolin-4(1H)-one (**2s**).* Method A: off-white solid (53 mg, 32%); ^{1}H NMR (DMSO-d_6) δ 8.02 (dd, J = 7.8, 1.7 Hz, 1H), 7.74 (dd, J = 7.7, 1.5 Hz, 1H), 7.53 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 7.34−7.22 (m, 3H), 6.91 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 7.6, 1.9 Hz, 1H), 5.27 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.5, 156.5, 140.5, 134.0, 133.1, 133.0, 129.4, 128.3, 127.2, 126.4, 123.2, 122.1, 119.1, 114.2, 48.7; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_3OBr$ $[M + H]^+$ 330.0242 *m/z*, found 330.0246; LC purity (254 nm) = 95%.

*2-Amino-1-(4-fluorobenzyl)quinazolin-4(1H)-one (**2t**).* Method B: white solid (120 mg, 86%); ^{1}H NMR (DMSO-d_6) δ 7.99 (dd, J = 7.7, 1.7 Hz, 1H), 7.53 (m, 1H), 7.31−7.12 (m, 8H), 5.35 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.8, 161.8 (d, $^1J_{CF}$ = 243.1 Hz), 156.8, 141.1, 133.2, 132.2 (d, $^4J_{CF}$ = 2.9 Hz), 128.6 (d, $^3J_{CF}$ = 8.2 Hz), 127.5, 123.5, 119.5, 116.0 (d, $^2J_{CF}$ = 21.5 Hz), 115.1, 47.0; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_3OF$ $[M + H]^+$ 270.1043 *m/z*, found 270.1048; LC purity (254 nm) = >98%.

*2-Amino-1-(3-hydroxybenzyl)quinazolin-4(1H)-one (**2u**).* Method B: pale yellow solid (127 mg, 92%); ^{1}H NMR (DMSO-d_6) δ 9.32 (br s, 1H, OH), 7.99 (m, 1H), 7.52 (m, 1H), 7.30−7.19 (m, 2H), 7.14 (m, 1H), 6.69−6.62 (m, 2H), 6.56 (m, 1H), 5.28 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 167.5, 157.7, 156.5, 140.8, 137.1, 132.7, 129.8, 127.0, 123.0, 119.0, 116.7, 114.8, 114.2, 112.6, 47.1; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_3O_2$ $[M + H]^+$ 268.1086 *m/z*, found 268.1092; LC purity (254 nm) = 98%.

*2-Amino-1-(2,6-dimethoxybenzyl)quinazolin-4(1H)-one (**2v**).* Method B: off-white solid (137 mg, 84%); ^{1}H NMR (DMSO-d_6) δ 7.91 (m, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.25 (t, J = 8.3 Hz, 1H), 7.16 (m, 1H), 7.07 (br s, NH_2), 6.67 (d, J = 8.3 Hz, 2H), 5.23 (s, 2H), 3.74 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 167.2, 158.0, 156.8, 140.8, 131.8, 129.6, 126.6, 122.3, 119.1, 114.6, 110.8, 104.4, 55.8, 39.0

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(overlaps with residual solvent signal); HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_3O_3$ $[M + H]^+$ 312.1348 *m/z*, found 312.1352; LC purity (254 nm) = >98%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00249.

Copies of ^1H and ^{13}C NMR spectra, chromatograms for all compounds obtained, and X-ray crystallographic data (PDF)

X-ray crystallographic data for **3** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.
(2) McLaughlin, N. P.; Evans, P.; Pines, M. *Bioorg. Med. Chem.* **2014**, *22*, 1993−2004.
(3) Pendergast, W.; Johnson, J. V.; Dickerson, S. H.; Dev, I. K.; Duch, D. S.; Ferone, R.; Hall, W. R.; Humphreys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279−2291.
(4) Zhang, H.; Xin, M.-H.; Xie, X.-X.; Mao, S.; Zuo, S.-J.; Lu, S.-M.; Zhang, S.-Q. *Bioorg. Med. Chem.* **2015**, *23*, 7765−7776.
(5) Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. a.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860−3873.
(6) Alagarsamy, V.; Dhanabal, K.; Parthiban, P.; Anjana, G.; Deepa, G.; Murugesan, B.; Rajkumar, S.; Beevi, A. J. *J. Pharm. Pharmacol.* **2007**, *59*, 669−677.
(7) Chen, M.; Li, P.; Hu, D.; Zeng, S.; Li, T.; Jin, L.; Xue, W.; Song, B. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 168−173.
(8) Chern, J.; Tao, P.; Wang, K.; Gutcait, A.; Liu, S.; Yen, M.; Chien, S.; Rong, J. *J. Med. Chem.* **1998**, *41*, 3128−3141.
(9) Zappalà, M.; Grasso, S.; Micale, N.; Zuccalà, G.; Menniti, F. S.; Ferreri, G.; De Sarro, G.; De Micheli, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4427−4430.
(10) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153−10202.
(11) He, L.; Li, H.; Chen, J.; Wu, X.-F. *RSC Adv.* **2014**, *4*, 12065−12077.
(12) Alexandre, F. R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911−3913.
(13) Somers, F.; Ouedraogo, R.; Rigo, B.; Delarge, J.; Lebrun, P. *J. Med. Chem.* **2001**, *44*, 2575−2585.
(14) Wilson, L. J. *Org. Lett.* **2001**, *3*, 585−588.
(15) Yang, R.; Kaplan, A. *Tetrahedron Lett.* **2000**, *41*, 7005−7008.
(16) Fray, M. J.; Mathias, J. P.; Nichols, C. L.; Po-Ba, Y. M.; Snow, H. *Tetrahedron Lett.* **2006**, *47*, 6365−6368.
(17) Gu, L.; Guo, Z.; He, L.; Qi, Q. *Synthesis* **2013**, *45*, 2533−2544.
(18) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515−5548.
(19) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133.
(20) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580−5588.
(21) Gautam, P.; Bhanage, B. M. *Catal. Sci. Technol.* **2015**, *5*, 4663−4702.
(22) Schareina, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1205−1209.
(23) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806−3807.
(24) Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2794−2797.
(25) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061−6071.
(26) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114−18117.
(27) Hansen, S. V. F.; Ulven, T. *Org. Lett.* **2015**, *17*, 2832−2835.
(28) Markovič, M.; Lopatka, P.; Koóš, P.; Gracza, T. *Org. Lett.* **2015**, *17*, 5618−5621.
(29) Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236−3239.
(30) Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, *23*, 685−698.
(31) Nordeman, P.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2012**, *77*, 11393−11398.
(32) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750−5753.
(33) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2004**, *6*, 121−125.
(34) Kaiser, N. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109−111.
(35) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1−35.
(36) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215−PR283.
(37) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373−376.
(38) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773−6784.
(39) Åkerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464−1471.
(40) Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773−2777.
(41) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 1188−1191.
(42) Roberts, B.; Liptrot, D.; Luker, T.; Stocks, M. J.; Barber, C.; Webb, N.; Dods, R.; Martin, B. *Tetrahedron Lett.* **2011**, *52*, 3793−3796.
(43) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 829−832.
(44) Sadig, J. E. R.; Foster, R.; Wakenhut, F.; Willis, M. C. *J. Org. Chem.* **2012**, *77*, 9473−9486.
(45) Mane, R. S.; Nordeman, P.; Odell, L. R.; Larhed, M. *Tetrahedron Lett.* **2013**, *54*, 6912−6915.
(46) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804−5812.
(47) Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 1732−1735.
(48) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791−1801.
(49) Reddy, T. J.; Leclair, M.; Proulx, M. *Synlett* **2005**, 583−586.
(50) Jiang, M.; Li, J.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. *Org. Lett.* **2012**, *14*, 1420−1423.
(51) Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, *2009*, 2679−2688.
(52) Ozaki, K.-I.; Yamada, Y.; Oine, T. *Chem. Pharm. Bull.* **1983**, *31*, 2234−2243.
(53) Roman, D. S.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3242−3245.
(54) Cai, Q.; Yan, J.; Ding, K. *Org. Lett.* **2012**, *14*, 3332−3335.
(55) Lee, K. L.; Foley, M. A.; Chen, L.; Behnke, M. L.; Lovering, F. E.; Kirincich, S. J.; Wang, W.; Shim, J.; Tam, S.; Shen, M. W. H.; Khor, S.; Xu, X.; Goodwin, D. G.; Ramarao, M. K.; Nickerson-Nutter, C.; Donahue, F.; Ku, M. S.; Clark, J. D.; McKew, J. C. *J. Med. Chem.* **2007**, *50*, 1380−1400.

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