“On-Water” Synthesis of Quinazolinones and Dihydroquinazolinones Starting from o-Bromobenzonitrile

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Received: 31 July 2018; Accepted: 6 September 2018; Published: 12 September 2018

Abstract: A versatile and practical “on-water” protocol was newly developed to synthesize quinazolinones using o-bromobenzonitrile as a novel starting material. Studies have found that air as well as water plays an important role in synthesis of quinazolinones. Further investigation indicated that dihydroquinazolinones can be prepared with this protocol under the protection of N2. The protocol can be extended to other substrates and various quinazolinones and dihydroquinazolinones were obtained. o-Bromobenzamide, o-aminobenzonitrile, and o-aminobenzamide were also evaluated as starting materials, and the results further proved the versatility of this protocol, especially towards dihydroquinazolinones.

Keywords: quinazolinones; dihydroquinazolinones; “on-water” reaction; selective synthesis

1. Introduction

Quinazolinones and dihydroquinazolinones are important classes of nitrogen-containing heterocycles with an array of biological activities such as antitumor [1,2], anti-inflammatory [3], antibacterial [4,5], anticonvulsant [6], etc. As explicit examples, RVX-208 and balaglitazone, structurally based on quinazolin-4(3H)-one (Figure 1), are now under phase III clinical trials. The compound of RVX-208 is developed for the treatment of cardiovascular diseases and lipid metabolism disorders [7], while balaglitazone is developed for the treatment of type 2 diabetes [8]. Recently, RVX-208 was found effective to reactivate HIV-1 in latent reservoirs [9], which stimulated our interest to synthesize the compounds bearing a quinazolione core.

Figure 1. Structures of RVX-208 and balaglitazone.
A variety of convenient methodologies have been developed for the synthesis of quinazolinones [10–13]. α-Aminobenzamides [14–22] and α-bromobenzamides [12,23–31] are the most frequently used starting materials by far, and α-Aminobenzoic acid [32], α-haloaniline [26,33], and isatoic anhydride [34] were also introduced. Alternatively, α-aminobenzonitrile [35–37] was applied to prepare quinazolinones by Wu and co-workers [35], considering that the variation of α-aminobenzonitriles is much more available than α-aminobenzamides. Similarly, α-bromobenzonitriles can also be transformed into α-bromobenzamides in situ, and as mentioned above, α-bromobenzamide is one of the most studied starting materials (Scheme 1) to synthesize quinazolinones. From a synthetic point of view, we strived to explore α-bromobenzonitriles as an alternative substrate to access quinazolinones for following reasons: (1) with α-bromobenzonitrile as an alternative starting material, the scope of substrates could be substantially extended, and thus increase the variety of quinazolinones; (2) in our methodology, transforming α-bromobenzonitrile into quinazolinones in one pot can save an extra step (benzonitrile into benzamide [38,39] thus the cost can be reduced; and (3) to the best of our knowledge, the substituted α-bromobenzonitriles were usually cheaper than the corresponding α-bromobenzamides.

![Scheme 1](https://example.com/scheme1.png)

Scheme 1. In situ transformation from α-bromobenzamide to α-bromobenzonitrile.

Meanwhile, most of these reactions using DMSO or DMA as solvent, suffered from unpleasant smells in high temperature. In addition, it is hard to remove solvent after the reaction. Langer and co-workers [36] provided a green protocol so that dihydroquinazolinons can be prepared in H₂O with good yields, whereas quinazolinones can only be obtained by adding oxidant TBHP(tert-butyl hydroperoxide). In the context of green chemistry, water was widely explored as a solvent in various reactions [40–43], not only due to its low cost, non-toxicity, easy availability, and eco-benign features, but also because the theoretical and practical advantages of water substantially improved the “on-water” reaction [44–46]. To date, water has never been used as media to synthesize quinazolinones directly without adding any oxidant. Cognizant of these challenges, we tried to introduce water as reaction media into the synthesis of quinazolinones. To our delight, we finally explored a versatile and practical “on-water” protocol for the quinazolinone preparation from α-bromobenzonitriles with comparable yields. Surprisingly, with this protocol, a dihydroquinazolinone skeleton could also be built just under the protection of N₂. Finally, we successfully synthesized 31 compounds including quinazolinones and dihydroquinazolinons, and 10 (4aa, 4ee, 4eq, 4ff, 5aa, 5ea, 5eb, 5ee, 5eq, 5fe) of them were novel compounds. Herein, we would like to present our research towards quinazolinones synthesis in detail.

2. Discussion and Results

Preliminary investigation started with the reaction of α-bromobenzonitrile 1a (instead of α-bromobenzamide) [27], benzaldehyde 2 and ammonia 3 under 100 °C in the present of CuBr, L-proline, and Cs₂CO₃ for 24 h. The expected product 2-phenylquinazolin-4(3H)-one 4aa was obtained (Entry 1, Table 1). The reaction conditions could further be optimized. The results collected in Table 1 showed that the reaction performed under 100 °C using Cs₂CO₃ as a base provided the highest yield (Entries 1–8, Table 1). The further screening of the catalyst (Entries 9–15, Table 1) showed that copper (Cu (II)) salts gave higher yields of product 4aa (Entries 12 and 14, Table 1) than Cu (I) in this case, being totally different from the reported results [11,12,25,29,31].

With the catalyst CuCl₂, solvent effects were examined (Entries 16–21, Table 1) and H₂O was successfully introduced. Without any oxidant, the “on-water” reaction provided compound 4aa with yield of 75% (Entry 18, Table 1), much higher than using DMF and DMA media. Further attempts to
increase the yield by adding DMSO or PEG (polyethylene glycol) in water as a co-solvent failed (Entries 19–20, Table 1). Additionally, air was found to be important for the fusion of quinazolinone core, as only traces of the product formed when the transformation was conducted under the protection of N₂ (Entry 22, Table 1). Based on these results, we can conclude that air and H₂O are vital to promote the formation of quinazolinone. Therefore, we obtained the optimal reaction conditions (CuCl₂ (0.1 mmol), Cs₂CO₃ (2 mmol), L-proline (0.2 mmol), H₂O (2 mL)) for the condensation of o-bromobenzonitriles, aldehydes, and aqueous ammonia toward quinazolinones, which are highlighted in Table 1 (Entry 18).

![Diagram](image)

Table 1. Conditional optimization for the condensation of o-bromobenzonitrile 1a with benzaldehyde 2a.

| Entry | Catal. (10 mol %) | Base (2 eqv.) | Solvent          | Temp (°C) | Yield (%)<sup>b</sup> |
|-------|------------------|---------------|------------------|-----------|-----------------------|
| 1     | CuBr             | Cs₂CO₃       | DMSO             | 100       | 54                    |
| 2     | CuBr             | Cs₂CO₃       | DMSO             | 80        | 49                    |
| 3     | CuBr             | Cs₂CO₃       | DMSO             | 120       | 42                    |
| 4     | CuBr             | -             | DMSO             | 100       | 38                    |
| 5     | CuBr             | K₂CO₃        | DMSO             | 100       | 47                    |
| 6     | CuBr             | K₃PO₄       | DMSO             | 100       | 51                    |
| 7     | CuBr             | NaOH         | DMSO             | 100       | 37                    |
| 8     | CuBr             | Et₃N         | DMSO             | 100       | 21                    |
| 9     | CuCl             | Cs₂CO₃       | DMSO             | 100       | 54                    |
| 10    | -                | Cs₂CO₃       | DMSO             | 100       | 16                    |
| 11    | CuI              | Cs₂CO₃       | DMSO             | 100       | 33                    |
| 12    | CuCl₂            | Cs₂CO₃       | DMSO             | 100       | 62                    |
| 13    | FeCl₃            | Cs₂CO₃       | DMSO             | 100       | 28                    |
| 14    | CuO              | Cs₂CO₃       | DMSO             | 100       | 63                    |
| 15    | ZnCl₂            | Cs₂CO₃       | DMSO             | 100       | 45                    |
| 16    | CuCl₃            | Cs₂CO₃       | DMA              | 100       | 24                    |
| 17    | CuCl₂            | Cs₂CO₃       | DMA              | 100       | 41                    |
| 18    | CuCl₂            | Cs₂CO₃       | H₂O              | 100       | 75                    |
| 19    | CuCl₂            | Cs₂CO₃       | H₂O/DMSO (4:1)   | 100       | 47                    |
| 20    | CuCl₂            | Cs₂CO₃       | H₂O/PEG400 (4:1) | 100       | 55                    |
| 21    | CuCl₂            | Cs₂CO₃       | DMSO             | 100       | 67                    |
| 22    | CuCl₂            | Cs₂CO₃       | H₂O              | 100       | Trace<sup>c</sup>      |

<sup>a</sup> Reaction conditions: o-bromobenzonitrile 1a (1 mmol), benzaldehyde 2a (2 mmol), aqueous ammonia 3 (27%, 1 mL), catalyst (0.1 mmol), base (2 mmol), l-proline (0.2 mmol), and solvent (2 mL), heated, sealed, and stirred for 12 h, then refluxed under air for 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction was conducted under protection of N₂.

With such an eco-friendly protocol in hand, the workup procedure was simple on account of water. Thereupon, it is necessary to investigate the scope and limitation to explore the versatility of this protocol. Before that, other o-halobenzonitriles (Entries 2–4, Table 2) were tested and the results collected in Table 2 showed that o-bromobenzonitrile is the most active substrate for this reaction. Various aryl aldehydes 2 were firstly evaluated under standard reaction conditions (Table 2). Generally, most of them were well tolerated and successfully transformed into the corresponding products with moderate to good yields. The electro-donating groups (-Me, -OMe) made a positive influence for the reaction and resulted in higher yields (4af, 4ae, 4af, Table 2) than electro-withdrawing counterparts (4ab, 4ac, 4ai, Table 2). It is noteworthy that almost no steric effect was observed for benzaldehyde, and o-methoxybenzaldehyde 2f even gave a higher yield up to 83% (4af, Table 2) than p-methoxyone (4ae, Table 2). Then we extended this protocol to substituted o-bromobenzonitriles.
The electro-withdrawing group on o-bromobenzonitrile (Entries 20–23, Table 2) was beneficial to the transformation and gave higher yields of corresponding products than those electro-donating group on o-bromobenzonitrile (Entries 24–28, Table 2). Therefore, we got an excellent yield of 92% (4ef, Table 2) when 2-bromo-5-fluorobenzonitrile reacted with 2-methoxylbenzaldehyde, which further proved that electro-donating benzaldehydes, especially 2-methoxylbenzaldehyde, were more active than electro-withdrawing benzaldehydes.

**Table 2.** The scope and limitation for the synthesis of 2-aryl quinazolin-4(3H)-one 4.

| Entry | R^1 | R^2 | Product | Yield b |
|-------|-----|-----|---------|---------|
| 1     | Br  | -   | C_6H_5  | 4aa     | 75%     |
| 2     | F   | -   | C_6H_5  | 4aa     | 0%      |
| 3     | Cl  | -   | C_6H_5  | 4aa     | 21%     |
| 4     | I   | -   | C_6H_5  | 4aa     | 17%     |
| 5     | Br  | -   | 4-ClC_6H_5 | 4ab | 44%     |
| 6     | Br  | -   | 2-ClC_6H_5 | 4ac | 41%     |
| 7     | Br  | -   | 4-CH_3C_6H_5 | 4ad | 71%     |
| 8     | Br  | -   | 4-MeOC_6H_5 | 4ae | 73%     |
| 9     | Br  | -   | 2-MeOC_6H_5 | 4af | 83%     |
| 10    | Br  | -   | 4-HOC_6H_5 | 4ag | 42%     |
| 11    | Br  | -   | 2-HOC_6H_5 | 4ah | 0%      |
| 12    | Br  | -   | 4-CF_3C_6H_5 | 4ai | 27%     |
| 13    | Br  | -   | 4-N(CH_3)_2C_6H_5 | 4aj | 30%     |
| 14    | Br  | -   | naphthalene | 4ak | 66%     |
| 15    | Br  | -   | 4-Pyridine | 4al | 48%     |
| 16    | Br  | -   | 2-Pyridine | 4am | 0%      |
| 17    | Br  | -   | 2-furan | 4an | 0%      |
| 18    | Br  | -   | 2-thiophene | 4ao | 0%      |
| 19    | Br  | -   | 2-pyrrole | 4ap | 27%     |
| 20    | Br  | 5-F | C_6H_5  | 4ea     | 60%     |
| 21    | Br  | 5-F | 4-MeOC_6H_5 | 4ee | 73%     |
| 22    | Br  | 5-F | 2-MeOC_6H_5 | 4ef | 92%     |
| 23    | Br  | 5-F | 3-MeO-4-HOC_6H_5 | 4eq | 60%     |
| 24    | Br  | 5-CH_3 | C_6H_5  | 4fa     | 63%     |
| 25    | Br  | 5-CH_3 | 4-ClC_6H_5 | 4fb | 47%     |
| 26    | Br  | 5-CH_3 | 4-MeOC_6H_5 | 4fe | 51%     |
| 27    | Br  | 5-CH_3 | 2-MeOC_6H_5 | 4ff | 62%     |
| 28    | Br  | 5-MeO | 4-MeOC_6H_5 | 4ge | 67%     |

^a Reaction conditions: substituted o-halobenzonitrile 1 (1 mmol), aryl aldehyde 2 (2 mmol), aqueous ammonia 3 (27%, 1 mL), CuCl_2 (0.1 mmol), Cs_2CO_3 (2 mmol), L-proline (0.2 mmol), and H_2O (2 mL), heated, sealed, and stirred for 12 h, then refluxed under air for 12 h. ^b Isolated yield.

Meanwhile, dihydroquinazolinones 5 were isolated as the side products in these reactions. We then repeated the model reaction under the protection of N_2 (Entry 22, Table 1), after which it failed to produce the compound 4aa. 2,3-Dihydro-2-phenylquinazolin-4(1H)-one 5aa was obtained and yielded 74%. This discovery suggested that 2-arylquinazolin-4(3H)-one 4 and 2,3-dihydro-2-arylquinazolin-4(1H)-one 5 can be selectively prepared from o-bromobenzonitrile by controlling the air.

With this result, other substituted benzaldehydes were subsequently employed to prepare 2,3-dihydro-2-arylquinazolin-4(1H)-ones 5. The selected substituted benzaldehydes were smoothly transformed into corresponding expected products with good to excellent yields.
Unexpectedly, an opposite result was observed compared to the synthesis of 2-arylquinazolin-4(3H)-ones 4. The electro-withdrawing group (4-Cl) helped to improve the yield up to 96% (5ab), while the electro-donated group substituted benzaldehyde gave relatively lower yields (5ae, 5af, Table 3). Especially, o-methoxybenzaldehyde 2f, which have provided 2-(2-methoxyphenyl)quinazolin-4(3H)-one 4af in high yield up to 83%, resulted in the lowest yield of 2,3-dihydro-2-(2-methoxyphenyl)-quinazolin-4(1H)-one 5af (54%) under N2 in this case. This interesting observation partially manifested that the electron-rich benzaldehyde is good to form 2-arylquinazolin-4(3H)-ones 4, while electron-deficient benzaldehyde tends to produce 2,3-dihydro-2-aryl quinazolin-4(1H)-ones 5.

Therefore, 2-bromo-5-fluorobenzonitrile as well as 2-bromo-5-methylbenzonitrile was treated with benzaldehydes and aqueous ammonia under the the protection of N2 with standard reaction conditions (5ea–5fe, Table 3). Most of them were smoothly transformed into the expected dihydroxy-products in good yields.

Table 3. The scope and limitation for the synthesis of 2,3-dihydro-2-aryl quinazolin-4(1H)-one 5 a.

| Entry | R1  | R2     | Product | Yield b |
|-------|-----|--------|---------|---------|
| 1     | -   | C6H5   | 5aa     | 74%     |
| 2     | -   | 4-ClC6H5 | 5ab   | 96%     |
| 3     | -   | 4-MeOC6H5 | 5ae   | 71%     |
| 4     | -   | 2-MeOC6H5 | 5af   | 54%     |
| 5     | 5-F | C6H5   | 5ea     | 39%     |
| 6     | 5-F | 4-ClC6H5 | 5eb   | 27%     |
| 7     | 5-F | 4-MeOC6H5 | 5ee   | 53%     |
| 8     | 5-F | 2-MeOC6H5 | 5eq   | 53%     |
| 9     | 5-CH3 | C6H5 | 5fa     | 77%     |
| 10    | 5-CH3 | 4-ClC6H5 | 5fb   | 0       |
| 11    | 5-CH3 | 4-MeOC6H5 | 5fe   | 50%     |

a Reaction conditions: substituted o-bromobenzonitrile 1a (1 mmol), aryl aldehyde 2 (2 mmol), aqueous ammonia 3 (27%, 1 mL), CuCl2 (0.1 mmol), Cs2CO3 (2 mmol), L-proline (0.2 mmol), and H2O (2 mL), heated, sealed, and stirred under protection of N2 for 24 h. b Isolated yield.

According to the results and similar reactions [12,13,24,32], a possible mechanism was proposed and outlined in Scheme 2. In the presence of Cs2CO3, the coordination of L-proline with CuCl2 helped to promote the subsequent Ullmann-type reaction to form 2-amino, while oxidation from -CN to -CONH2 occurred simultaneously in the presence of CuCl2, base, and H2O, so that intermediate 2-aminobenzamide was generated. Actually, 2-aminobenzamide was detected as intermediate during the reaction, and then condensation and addition occurred on 2-aminobenzamide and benzaldehyde. 2,3-Dihydro-2-aryl quinazolin-4(1H)-one 5 was produced under the protection of N2, and when the reaction was exposed to air after the starting materials were stirred in sealed tubes at 100 °C for 12 h, oxidation occurred further to afford products 2-aryl quinazolin-4(3H)-one 4.
Although at the outset of this work we only expected to develop an “on-water” protocol towards quinazolinones from o-bromobenzonitrile 1a, the explicit outcome above proved the versatility of this protocol. Then other commonly used substrates were evaluated for this protocol. o-Bromobenzamide 1h was first reacted with p-methoxybenzaldehyde and ammonia under the standard conditions. As outlined in Scheme 3, 2-(4-methoxyphenyl)-quinazolin-4(3H)-one 4ae and 2,3-dihydro-2-phenylquinazolin-4(1H)-one 5ae were produced smoothly at 74% and 68%, respectively, almost having the same yields with o-bromobenzonitrile (73% for 4ae in Table 2, and 71% for 5ae in Table 3).

Subsequently, o-aminobenzonitrile 1i was tested and the results in Scheme 4 showed that the yield of 2-phenylquinazolin-4(3H)-one 4aa was only 43%, while o-bromobenzonitrile 1a yielded in 75% (4aa, Table 2). But, when under the protection of N₂, 76% of the yield of 2,3-dihydro-2-phenylquinazolin-4(1H)-one 5aa was obtained, almost the same with the result
from o-bromobenzonitrile 1a (5aa, Table 3). Obviously, o-aminobenzenitrile 1i was less active than o-bromobenzonitrile 1a for the synthesis of quinazolin-4(3H)-one, which explained why 2,3-dihydro-quinazolin-4(1H)-ones were the only products listed in the literature reported by Langer and co-workers [36], wherein oxidant TBHP had to be added in addition to help the formation of quinazolin-4(3H)-one.

Scheme 4. The “on-water” reaction starting from o-aminobenzanitrile.

This interesting finding prompted us to undertake the reaction starting from o-aminobenzamide 1j immediately, as shown in Scheme 5. Unexpectedly, oxidized product 2-phenylquinazolin-4(3H)-one 4aa failed to produce, while 2,3-dihydro-2-phenylquinazolin-4(1H)-one 5aa yielded up to 95% without the protection of N2. It implies that o-aminobenzamide 1j tends to be transformed into 2,3-dihydro-quinazolin-4(1H)-ones 5 with this protocol.

Scheme 5. “On-water” reaction starting from o-aminobenzamide.

With these results from the extended substrates, we found the newly developed “on-water” protocol was much more flexible for the construction of 2,3-dihydro-quinazolin-4(1H)-ones 5 than its oxidized products quinazolin-4(3H)-ones 4. In addition, for the preparation of quinazolin-4(3H)-ones 4, the priority of the commonly used substrates is: o-bromobenzenitrile 1a or o-bromobenzamide 1h > o-amino- benzonitrile 1i > o-aminobenzamide 1j.
3. Conclusions

In summary, we have newly developed a versatile and practical “on-water” protocol towards compounds containing a quinazolinone core, and o-bromobenzonitrile was explored as an alternative starting material. Water and air were found to be of importance for the formation of oxidized products quinazolin-4(3H)-ones 4, and various aryl aldehydes as well as several substituted o-bromobenzonitriles were successfully applied to this protocol and provided the expected quinazolin-4(3H)-ones 4. Moreover, we found that 2,3-dihydro-quinazolin-4(1H)-ones 5 could also be obtained when the reaction was carried out under the protection of N₂, and the subsequent scope investigation resulted in the successful synthesis of various 2,3-dihydro-quinazolin-4(1H)-ones 5. Therefore, we can selectively produce the compounds 2,3-dihydro-quinazolin-4(1H)-ones 5 or their oxidized products 4 from o-bromobenzonitrile by controlling air. In addition, o-bromobenzonitrile, o-aminobenzonitrile, and o-aminobenzamide were evaluated and all of them could be transformed into 2,3-dihydro-quinazolin-4(1H)-ones 5 with good to excellent yields, but o-bromobenzonitrile or o-bromobenzamide was proved to be the best substrate for the synthesis of the oxidized products quinazolin-4(3H)-ones compared with o-aminobenzonitrile and o-aminobenzamide. With these new findings in mind, further work involving the synthesis of RVX-208 and related structural modifications are ongoing in our group.

4. Materials and Methods

4.1. General

All chemicals were purchased from commercial suppliers Shanghai Energy Chemical Co., Ltd. (Shanghai, China), Adamas Reagent, Ltd. (Shanghai, China), TCI Industry Co., Ltd. (Shanghai, China), without further purification. All reactions were monitored by TLC (thin-layer chromatography) which was performed on GF254 silica gel glass plates (Qingdao Haiyang Chemical Co. Ltd., Qingdao, Shandong, China). Column chromatography was performed with silica gel (200–300 mesh). All unknown compounds were structurally verified by ¹H-NMR, ¹³C-NMR and MS, and ¹H-, and ¹³C-NMR spectra were recorded on a Bruker Advance drx 400 spectrometer (Bruker Bioscience, Billerica, MA, USA) operating at 400 MHz and 100 MHz, respectively. The chemical shifts were reported in ppm and the coupling constant in Hz. Mass Spectrometry analysed for the known compounds by Waters HPLC/ZQ 4000 Thermo Fisher Scientific (Waltham, MA, USA).

4.2. General Procedure for the Synthesis of 2-Phenylquinazolin-4(3H)-one (4aa)

To a mixture of 2-Bromobenzonitrile (183.4 mg, 1 mmol), benzaldehyde (210.5 mg, 2 mmol), CuCl₂ (17.2 mg, 0.1 mmol), Cs₂CO₃ (652.2 mg, 2 mmol), and L-proline (23.2 mg, 0.2 mmol) in H₂O (2 mL) was added 27% aqueous ammonia (1 mL) in a tube under air atmosphere. Then the tube was sealed, and the mixture was stirred at 100 °C for 12 h. Next, the tube was opened to air and the mixture was stirred at 100 °C for another 12 h. After being cooled to room temperature, the resulting mixture was quenched with NH₄Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, and then dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenylquinazolin-4(3H)-one (4aa) in 75% isolated yield. ¹H-NMR (400 MHz, Chloroform-d) δ 11.24 (s, 1H, -NH-), 8.27 (d, J = 7.8 Hz, 1H, Ar-H), 8.16 (dd, J = 6.6, 3.0 Hz, 2H, Ar-H), 7.82–7.71 (m, 2H, Ar-H), 7.57–7.49 (m, 3H, Ar-H), 7.48–7.41 (m, 1H, Ar-H). ¹³C-NMR (100 MHz, Chloroform-d) δ 151.60, 134.87, 132.77, 131.64, 129.05, 127.97, 127.25, 126.79, 126.34, 120.84. HRMS (ESI) calcd for C₁₄H₁₁N₂O [M + H]+: 223.0866. Found: 223.0865.

4.3. General Procedure for the Synthesis of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa)

2-bromobenzonitrile (182.3 mg, 1 mmol), benzaldehyde (213.6 mg, 2 mmol), CuCl₂ (17.1 mg, 0.1 mmol), Cs₂CO₃ (651.3 mg, 2 mmol) and L-proline 23.4 mg, 0.2 mmol) in H₂O (2 mL) were added
into a tube and stirred. Remove the air inside the tube under the reduced pressure and flush with N$_2$, and protected the starting materials under N$_2$. 27 % aqueous ammonia (1 mL) was added into the reaction mixture. The tube was then sealed and the mixture stirred at 100 °C for 24 h. After cooling to room temperature, the resulting mixture was quenched with NH$_4$Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa) in 74% isolated yield.

$^1$H-NMR (400 MHz, Chloroform-d) $\delta$ 7.97 (d, $J$ = 7.8 Hz, 1H, Ar-H), 7.67–7.56 (m, 2H, Ar-H), 7.55–7.41 (m, 3H, Ar-H), 7.36 (t, $J$ = 7.7 Hz, 1H, Ar-H), 6.93 (t, $J$ = 7.5 Hz, 1H, Ar-H), 6.70 (d, $J$ = 8.0 Hz, 1H, Ar-H), 5.93 (s, 1H, -CH-), 5.80 (s, 1H, -NH-), 4.42 (s, 1H, -NH-).

$^{13}$C-NMR (101 MHz, DMSO) $\delta$ 163.98, 148.27, 142.04, 133.70, 128.85, 128.72, 127.75, 127.26, 117.51, 115.36, 114.80, 66.96. HRMS (ESI) calcd for C$_{14}$H$_{13}$N$_2$O [M + H]$^+$: 225.1022. Found: 225.1021.

4.4. General Procedure for the Synthesis of 2-Phenylquinazolin-4(3H)-one (4aa) with Scheme 3

o-Aminobenzanitrile (119.8 mg, 1 mmol), benzaldehyde (217.8 mg, 2 mmol), CuCl$_2$ (17.6 mg, 0.1 mmol), Cs$_2$CO$_3$ (652.3 mg, 2 mmol), and L-proline 23.6 mg, 0.2 mmol) in H$_2$O (2 mL) was added in a 5 mL reaction bottle. Then the mixture was stirred at 100 °C for 48 h. After cooling to room temperature, the resulting mixture was quenched with NH$_4$Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenylquinazolin-4(3H)-one (4aa) in 43% isolated yield.

4.5. General Procedure for the Synthesis of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa) with Scheme 3

o-Aminobenzanitrile (120.8 mg, 1 mmol), benzaldehyde (216.7 mg, 2 mmol), CuCl$_2$ (17.3 mg, 0.1 mmol), Cs$_2$CO$_3$ (653.7 mg, 2 mmol), and L-proline 23.3 mg, 0.2 mmol) in H$_2$O (2 mL) was added in a 5 mL reaction bottle under nitrogen. Then the mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the resulting mixture was quenched with NH$_4$Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa) in 76% isolated yield.

4.6. General Procedure for the Synthesis of 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa) with Scheme 4

o-Aminobenzamide (139.1 mg, 1 mmol), benzaldehyde (209.9 mg, 2 mmol), CuCl$_2$ (17.6 mg, 0.1 mmol), Cs$_2$CO$_3$ (657.0 mg, 2 mmol) and L-proline 23.6 mg, 0.2 mmol) in H$_2$O (2 mL) was added in a 5 mL reaction bottle. Then the mixture was stirred at 100 °C for 14 h. After cooling to room temperature, the resulting mixture was quenched with NH$_4$Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5aa) in 95% isolated yield.

Experimental procedures and analytical data of all compounds ($^1$H NMR and $^{13}$C NMR), copy of the $^1$H NMR and $^{13}$C NMR and data are available in the Supplementary Materials.

Supplementary Materials: The experiment procedure, spectral and analytical data, characterization data including $^1$H-, $^{13}$C-, and $^{19}$F-NMR spectra of compounds 1-31 are available online.

Author Contributions: B.X. and S.L. conceived and designed the study; Z.L., L.-Y.Z., C.L., F.Y. and F.Q. performed the experiments; all author analyzed the data; all authors contributed to writing and editing the paper.

Funding: This research was funded Guangdong Science and Technology Department of China [2013B051000056].
Acknowledgments: We thank the Guangdong Science and Technology Department of China (2013B051000056) for financial support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Safavi, M.; Ashtari, A.; Khalili, F.; Mirfazli, S.S.; Saeedi, M.; Ardestani, S.K.; Rashidi, R.P.; Barazandeh, T.M.; Larjani, B.; Madhavi, M. Novel quinazolin-4(3H)-one linked to 1,2,3-triazoles: Synthesis and anticancer activity. *Chem. Biol. Drug Des.* 2018, 92, 1373–1381. [CrossRef] [PubMed]

2. Logé, C.; Testard, A.; Thiéry, V.; Lozach, O.; Blairvacq, M.; Robert, J.-M.; Meijer, L.; Besson, T. Novel 9-oxo-thiazolo [5, 4-f] quinazoline-2-carbonitrile derivatives as dual cyclin-dependent kinase 1 (CDK1)/glycogen synthase kinase-3 (GSK-3) inhibitors: Synthesis, biological evaluation and molecular modeling studies. *Eur. J. Med. Chem.* 2008, 43, 1469–1477. [CrossRef] [PubMed]

3. Moussa, G.; Alaeddine, R.; Alaeddine, L.M.; Nassra, R.; Belal, A.S.F.; Ismail, A.; El-Yazbi, A.F.; Abdel-Ghany, Y.S.; Hazzaa, A. Novel click modifiable thioquinazolinones as anti-inflammatory agents: Design, synthesis, biological evaluation and docking study. *Eur. J. Med. Chem.* 2018, 144, 635–650. [CrossRef] [PubMed]

4. Zhan, X.; Xu, Y.; Qi, Q.; Wang, Y.; Shi, H.; Mao, Z. Synthesis, cytotoxic, and antibacterial evaluation of quinazolinone derivatives with substituted amino moiety. *Chem. Biodivers.* 2018, 15, e1700513. [CrossRef] [PubMed]

5. Liao, B.-L.; Pan, L.W.; Pan, Y.-J.; Zhang, W. Four natural compounds were separated from folium isatidis: Crystal structures and antibacterial activity. *Chem. Biodivers.* 2018, e1800152. [CrossRef] [PubMed]

6. Wolfe, J.F.; Rathman, T.L.; Sleevi, M.C.; Campbell, J.A.; Greenwood, T.D. Synthesis and anticonvulsant activity of some new 2-substituted 3-aryl-4(3H)-quinazolinones. *J. Med. Chem.* 1990, 33, 161–166. [CrossRef] [PubMed]

7. Ghosh, G.C.; Bhadra, R.; Ghosh, R.K.; Banerjee, K.; Gupta, A. RVX 208: A novel BET protein inhibitor, role as an inducer of apo A-I/HDL and beyond. *Cardiovasc. Ther.* 2017, 35, e12265. [CrossRef] [PubMed]

8. Larsen, P.J.; Lykkegaard, K.; Larsen, L.K.; Fleckner, J.; Sauerberg, P.; Wassermann, K.; Wulff, E.M. Dissociation of antihyperglycaemic and adverse effects of partial peroxisome proliferator-activated receptor (PPAR-γ) agonist balaglitazone. *Eur. J. Pharmacol.* 2008, 596, 173–179. [CrossRef] [PubMed]

9. Zhang, X.-X.; Lin, J.; Liang, T.; Duan, H.; Tan, X.-H.; Xi, B.-M.; Li, L.; Liu, S.-W. The BET bromodomain inhibitor apabetalone induces apoptosis of latent HIV-1 reservoir cells following viral reactivation. *Acta Pharmacol. Sin.* 2018. [CrossRef] [PubMed]

10. Connolly, D.J.; Cusack, D.; O’Sullivan, T.P.; Guiry, P.J. Synthesis of quinazolinones and quinazolines. *Tetrahedron* 2005, 61, 10153–10202. [CrossRef]

11. He, L.; Li, H.; Chen, J.; Wu, X.-F. Recent advances in 4(3H)-quinazolinone syntheses. *RSC Adv.* 2014, 4, 12065–12077. [CrossRef]

12. Upadhyaya, K.; Thakur, R.K.; Shukla, S.K.; Tripathi, R.P. One-pot copper(i)-catalyzed ligand/base-free tandem cyclooxidative synthesis of quinazolinones. *J. Org. Chem.* 2016, 81, 5046–5055. [CrossRef]

13. Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. Ligand-free Pd-catalyzed and copper-assisted C–H arylation of quinazolin-4-ones with aryl iodides under microwave heating. *Org. Lett.* 2015, 17, 1700–1703. [CrossRef] [PubMed]

14. Ge, W.; Zhu, X.; Wei, Y. Iodine-catalyzed oxidative system for cyclization of primary alcohols with o-aminobenzamides to quinazolinones using DMSO as the oxidant in dimethyl carbonate. *RSC Adv.* 2013, 3, 10817–10822. [CrossRef]

15. Jiang, X.; Tang, T.; Wang, J.-M.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed One-Pot Synthesis of Quinazolinones via tert-Butyl Isocyanide Insertion. *J. Org. Chem.* 2014, 79, 5082–5087. [CrossRef] [PubMed]

16. Kim, N.Y.; Cheon, C.-H. Synthesis of quinazolinones from anthranilamides and aldehydes via meta-toluenesulfonic acid catalyzed cyclocondensation and phenylodine diacetate mediated oxidative dehydrogenation. *Synthesis* 2013, 45, 2998–3006. [CrossRef] [PubMed]
18. Sharif, M.; Opalach, J.; Langer, P.; Beller, M.; Wu, X.-F. Oxidative synthesis of quinazolinones and benzothiadiazine 1,1-dioxides from 2-aminobenzamidine and 2-aminobenzenesulfonamide with benzyl alcohols and aldehydes. RSC Adv. 2014, 4, 8–17. [CrossRef]
19. Wu, X.-F.; He, L.; Neumann, H.; Beller, M. Palladium-catalyzed carbonylative synthesis of quinazolinones from 2-aminobenzamide and aryl bromides. Chem.-Eur. J. 2013, 19, 12635–12638. [CrossRef] [PubMed]
20. Xu, W.; Zhu, X.-R.; Qian, P.-C.; Zhang, X.-G.; Deng, C.-L. Copper-catalyzed tandem reaction of 2-aminobenzenes with tertiary amines for the synthesis of quinazoline derivatives. Synlett 2016, 27, 2851–2857. [CrossRef]
21. Zhan, D.; Li, T.; Wei, H.; Weng, W.; Ghandi, K.; Zeng, Q. A recyclable CuO-catalyzed synthesis of 2,3-disubstituted quinazolinone derivatives through copper catalyzed C–H amidation reactions. Eur. J. Org. Chem. 2016, 1182–1193. [CrossRef]
22. Li, F.; Lu, L.; Liu, P. Acceptorless dehydrogenative coupling of o-aminobenzamides with the activation of methyl as a C1 source for the construction of quinazolinones. Org. Lett. 2016, 18, 2580–2583. [CrossRef] [PubMed]
23. Hu, B.-Q.; Wang, L.-X.; Xiang, J.-F.; Yang, L.; Tang, Y.-L. Cu(II)-catalyzed domino reaction of 2-halobenzamide and arylmethanamine to construct 2-aryl quinazolinone. Chin. Chem. Lett. 2015, 26, 369–372. [CrossRef]
24. Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. Highly efficient copper-catalyzed cascade synthesis of quinazoline and quinazolinone derivatives. Chem. Commun. 2008, 6333–6335. [CrossRef] [PubMed]
25. Kotipalli, T.; Kavala, V.; Janreddy, D.; Bandi, V.; Kuo, C.-W.; Yao, C.-F. Synthesis of 2,3-disubstituted quinazolinone derivatives through copper catalyzed C–H amidation reactions. Eur. J. Org. Chem. 2016, 2016, 1182–1193. [CrossRef]
26. Larksarp, C.; Alper, H. Palladium-catalyzed cyclocarbonylation of o-idoanilines with heterocumulenes: Regioselective preparation of 4(3H)-quinazolinone derivatives. J. Org. Chem. 2000, 65, 2773–2777. [CrossRef] [PubMed]
27. Xu, L.; Jiang, Y.; Ma, D. Synthesis of 3-substituted and 2,3-disubstituted quinazolinones via Cu-catalyzed aryl amidation. Org. Lett. 2012, 14, 1150–1153. [CrossRef] [PubMed]
28. Xu, W.; Fu, H. Amino acids as the nitrogen-containing motifs in copper-catalyzed domino synthesis of n-heterocycles. J. Org. Chem. 2011, 76, 3846–3852. [CrossRef] [PubMed]
29. Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. Copper-catalyzed domino synthesis of quinazolinones via uillmann-type coupling and aerobic oxidative C.–H. amidation. Org. Lett. 2011, 13, 1274–1277. [CrossRef] [PubMed]
30. Yu, L.; Wang, M.; Li, P.; Wang, L. Fe3O4 nanoparticle-supported copper(I): Magnetically recoverable and reusable catalyst for the synthesis of quinazolinones and bicyclic pyrimidinones. Appl. Organomet. Chem. 2012, 26, 576–582. [CrossRef]
31. Guo, S.; Li, Y.; Tao, L.; Zhang, W.; Fan, X. Rapid assembly of quinazolinone scaffold via copper-catalyzed tandem reaction of 2-bromobenzenamides with aldehydes and aqueous ammonia: Application to the synthesis of the alkaloid tryptanthrin. RSC Adv. 2014, 4, 59289–59296. [CrossRef]
32. Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. A simple and efficient approach to quinazolinones under mild copper-catalyzed conditions. Angew. Chem. Int. Ed. 2009, 48, 348–351. [CrossRef] [PubMed]
33. He, L.; Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. Highly efficient four-component synthesis of 4(3 H)-quinazolinones: Palladium-catalyzed carbonylative coupling reactions. Angew. Chem. Int. Ed. 2014, 53, 1420–1424. [CrossRef] [PubMed]
34. Zeng, L.-Y.; Cai, C. Iodine: Selectively promote the synthesis of mono substituted quinazolin-4(3H)-ones and 2,3-dihydroquinazolin-4(1H)-ones in one-pot. J. Heterocycl. Chem. 2010, 47, 1035–1039. [CrossRef]
35. Li, H.; He, L.; Neumann, H.; Beller, M.; Wu, X.-F. Cascade synthesis of quinazolinones from 2-aminobenzenitriles and aryl bromides via palladium-catalyzed carbonylation reaction. Green Chem. 2014, 16, 1336–1343. [CrossRef]
36. Wu, X.-F.; Oschatz, S.; Block, A.; Spannenberg, A.; Langer, P. Base mediated synthesis of 2-aryl-2,3-dihydroquinazolin-4(1H)-ones from 2-aminobenzenitriles and aromatic aldehydes in water. Org. Biomol. Chem. 2014, 12, 1865–1870. [CrossRef] [PubMed]
37. Wu, X.-F.; Oschatz, S.; Sharif, M.; Beller, M.; Langer, P. Palladium-catalyzed carbonylative synthesis of N-(2-cyanoaryl)benzamides and sequential synthesis of quinazolinones. Tetrahedron 2014, 70, 23–29. [CrossRef]
38. Schmid, T.E.; Gómez-Herrera, A.; Songis, O.; Sneddon, D.; Révolte, A.; Nahra, F.; Cazin, C.S. Selective NaOH-catalysed hydration of aromatic nitriles to amides. *Catal. Sci. Technol.* **2015**, *5*, 2865–2868. [CrossRef]

39. Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. Cs2CO3 in pyrrolidinone promoted hydration of functionalized (hetero)aryl nitriles under metal-free conditions. *Tetrahedron Lett.* **2012**, *53*, 2860–2863. [CrossRef]

40. Zeng, L.-Y.; Liu, T.; Yang, J.; Yang, Y.; Cai, C.; Liu, S. “On-Water” facile synthesis of novel pyrazolo[3,4-b]pyridinones possessing anti-influenza virus activity. *ACS Comb. Sci.* **2017**, *19*, 437–446. [CrossRef]

41. Yadong, F.; Yudong, L.; Guolin, C.; Lianhui, W.; Xiuling, C. Copper-catalyzed synthesis of 2-arylquinazolinones from 2-arylindoles with amines or ammoniums. *J. Org. Chem.* **2015**, *80*, 7099–7107. [CrossRef] [PubMed]

42. Mitsuaki, Y.; Yukari, N.; Seiya, H.; Akira, I. One-pot synthesis of polyhydropyrido [1, 2-a] indoles and tetracyclic quinazolinones from 2-arylindoles using copper-mediated oxidative tandem reactions. *Tetrahedron* **2016**, *72*, 4123–4131. [CrossRef]

43. Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification. *Bioorg. Med. Chem.* **2016**, *24*, 2361–2381. [CrossRef] [PubMed]

44. Butler, R.N.; Coyne, A.G. Water: Nature’s reaction enforcer—Comparative effects for organic synthesis “in-water” and “on-water”. *Chem. Rev.* **2010**, *110*, 6302–6337. [CrossRef] [PubMed]

45. Dam, B.; Nandi, S.; Pal, A.K. An efficient ‘on-water’ synthesis of 1,4-dihydropyridines using Fe3O4@SiO2 nanoparticles as a reusable catalyst. *Tetrahedron Lett.* **2014**, *55*, 5236–5240. [CrossRef]

46. Saikia, B.; Boruah, P.R.; Ali, A.A.; Sarma, D. ‘On-water’ organic synthesis: A green, highly efficient, low cost and reusable catalyst system for biaryl synthesis under aerobic conditions at room temperature. *RSC Adv.* **2015**, *5*, 50655–50659. [CrossRef]

**Sample Availability:** Samples of the compounds are not available from the authors.

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