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"On-Water" Synthesis of Quinazolinones and Dihydroquinazolinones Starting from *o*-Bromobenzonitrile

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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 N_2. 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 dihydroquinazolinons are important classes of nitrogen-containing heterocycles with an array of biological activities such an antitumor [1,2], anti-inflammatory [3], antibacterial [4,5], anticonvulsant [6], etc. As explicit examples, RVX-208 and balaglitazone, structurally based on quinazolin-4(3*H*)-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.

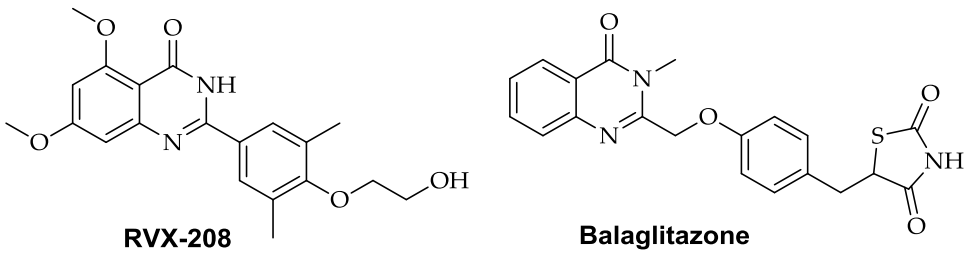
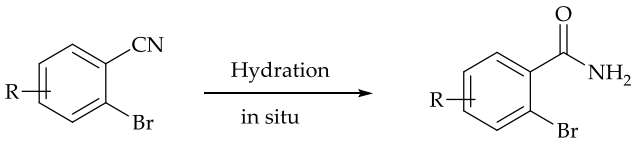


Figure 1. Structures of RVX-208 and balaglitazone.

A variety of convenient methodologies have been developed for the synthesis of quinazolinones [10–13]. *o*-Aminobenzamides [14–22] and *o*-bromobenzamides [12,23–31] are the most frequently used starting materials by far, and *o*-Aminobenzoic acid [32], *o*-haloaniline [26,33], and isatoic anhydride [34] were also introduced. Alternatively, *o*-aminobenzonitrile [35–37] was applied to prepare quinazolinones by Wu and co-workers [35], considering that the variation of *o*-aminobenzonitriles is much more available than *o*-aminobenzamides. Similarly, *o*-bromobenzonitriles can also be transformed into *o*-bromobenzamides in situ, and as mentioned above, *o*-bromobenzamide is one of the most studied starting materials (Scheme 1) to synthesize quinazolinones. From a synthetic point of view, we strived to explore *o*-bromobenzonitriles as an alternative substrate to access quinazolinones for following reasons: (1) with *o*-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 *o*-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 *o*-bromobenzonitriles were usually cheaper than the corresponding *o*-bromobenzamides.



Scheme 1. In situ transformation from *o*-bromobenzamide to *o*-bromobenzamide.

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 H_2O 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 *o*-bromobenzonitriles with comparable yields. Surprisingly, with this protocol, a dihydroquinazolinone skeleton could also be built just under the protection of N_2. 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.

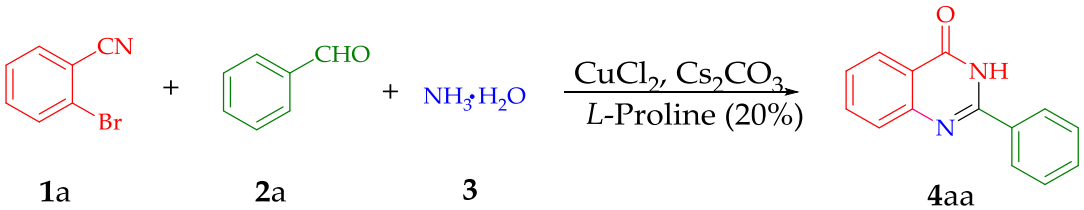
2. Discussion and Results

Preliminary investigation started with the reaction of *o*-bromobenzonitrile **1a** (instead of *o*-bromobenzamide) [27], benzaldehyde **2** and ammonia **3** under 100 °C in the present of CuBr, L-proline, and Cs_2CO_3 for 24 h. The expected product 2-phenylquinazolin-4(3*H*)-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 Cs_2CO_3 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 $CuCl_2$, solvent effects were examined (Entries 16–21, Table 1) and H_2O 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 N_2 (Entry 22, Table 1). Based on these results, we can conclude that air and H_2O are vital to promote the formation of quinazolinone. Therefore, we obtained the optimal reaction conditions ($CuCl_2$ (0.1 mmol), Cs_2CO_3 (2 mmol), L-proline (0.2 mmol), H_2O (2 mL)) for the condensation of *o*-bromobenzonitriles, aldehydes, and aqueous ammonia toward quinazolinones, which are highlighted in Table 1 (Entry 18).

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



1a **2a** **3** **4aa**

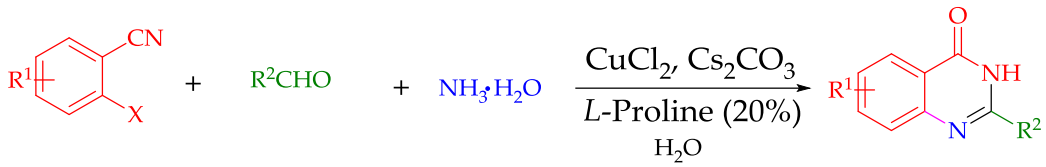
Entry	Catal. (10 mol %)	Base (2 eqv.)	Solvent	Temp (°C)	Yield (%) [b]
1	CuBr	Cs_2CO_3	DMSO	100	54
2	CuBr	Cs_2CO_3	DMSO	80	49
3	CuBr	Cs_2CO_3	DMSO	120	42
4	CuBr	-	DMSO	100	38
5	CuBr	K_2CO_3	DMSO	100	47
6	CuBr	K_3PO_4	DMSO	100	51
7	CuBr	NaOH	DMSO	100	37
8	CuBr	Et_3N	DMSO	100	21
9	CuCl	Cs_2CO_3	DMSO	100	54
10	-	Cs_2CO_3	DMSO	100	16
11	CuI	Cs_2CO_3	DMSO	100	33
12	$CuCl_2$	Cs_2CO_3	DMSO	100	62
13	$FeCl_3$	Cs_2CO_3	DMSO	100	28
14	CuO	Cs_2CO_3	DMSO	100	63
15	$ZnCl_2$	Cs_2CO_3	DMSO	100	45
16	$CuCl_2$	Cs_2CO_3	DMF	100	24
17	$CuCl_2$	Cs_2CO_3	DMA	100	41
18	$CuCl_2$	Cs_2CO_3	H_2O	100	75
19	$CuCl_2$	Cs_2CO_3	H_2O/DMSO (4:1)	100	47
20	$CuCl_2$	Cs_2CO_3	H_2O/PEG400 (4:1)	100	55
21	$CuCl_2$	Cs_2CO_3	DMSO	100	67
22	$CuCl_2$	Cs_2CO_3	H_2O	100	Trace [c]

[a] 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. [b] Isolated yield. [c] Reaction was conducted under protection of N_2.

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 (**4ad**, **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(3*H*)-one **4** [a].



1 **2** **3** **4**

Entry	X	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.

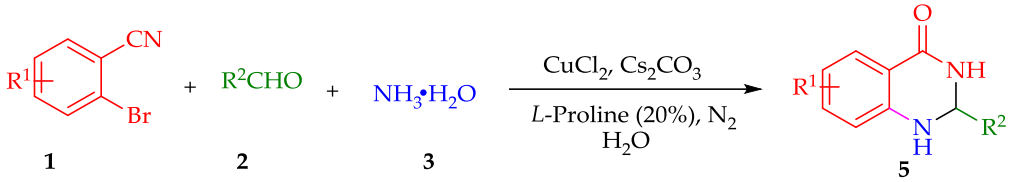
Meanwhile, dihydroquinazolinones **5** were isolated as the side products in these reactions. We then repeated the model reaction under the protection of N_2 (Entry 22, Table 1), after which it failed to produce the compound **4aa**. 2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one **5aa** was obtained and yielded 74%. This discovery suggested that 2-arylquinazolin-4(3*H*)-one **4** and 2,3-dihydro-2-arylquinazolin-4(1*H*)-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(1*H*)-ones **5**. The selected substituted benzaldehydes were smoothly transformed into corresponding expected products with good to excellent yields

(Table 3). Unexpectedly, an opposite result was observed compared to the synthesis of 2-arylquinazolin-4(3*H*)-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*-methoxylbenzaldehyde **2f**, which have provided 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one 4af in high yield up to 83%, resulted in the lowest yield of 2,3-dihydro-2-(2-methoxyphenyl)-quinazolin-4(1*H*)-one 5af (54%) under N_2 in this case. This interesting observation partially manifested that the electron-rich benzaldehyde is good to form 2-arylquinazolin-4(3*H*)-ones **4**, while electron-deficient benzaldehyde tends to produce 2,3-dihydro-2-aryl quinazolin-4(1*H*)-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 N_2 with standard reaction conditions (**5ea**–**5fe**, Table 3). Most of them were smoothly transformed into the expected dihydroxyl-products in good yields.

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

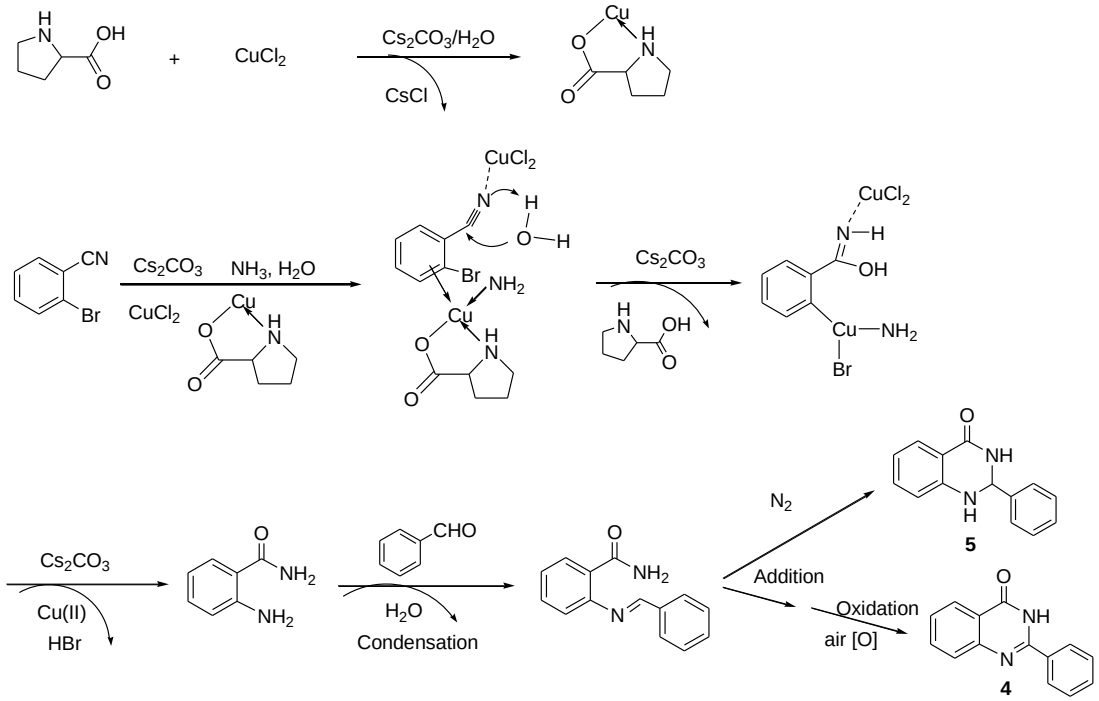


1 **2** **3** **5**

Entry	R^1	R^2	Product	Yield [b]
1	-	C_6H_5	**5aa**	74%
2	-	4-ClC_6H_5	**5ab**	96%
3	-	4-MeOC_6H_5	**5ae**	71%
4	-	2-MeOC_6H_5	**5af**	54%
5	5-F	C_6H_5	**5ea**	39%
6	5-F	4-ClC_6H_5	**5eb**	27%
7	5-F	4-MeOC_6H_5	**5ee**	53%
8	5-F	2-MeOC_6H_5	**5eq**	53%
9	5-CH_3	C_6H_5	**5fa**	77%
10	5-CH_3	4-ClC_6H_5	**5fb**	0
11	5-CH_3	4-MeOC_6H_5	**5fe**	50%

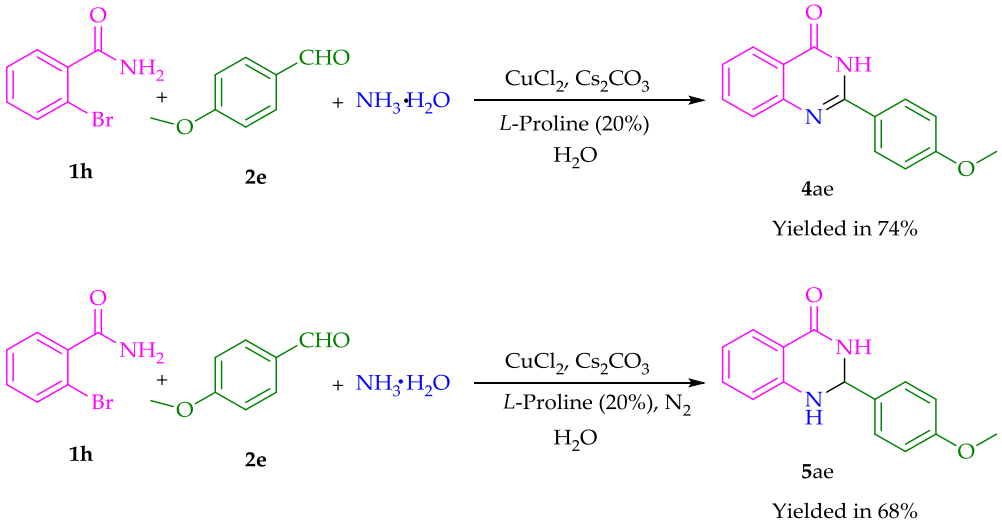
[a] Reaction conditions: substituted *o*-bromobenzonitrile **1a** (1 mmol), aryl aldehyde **2** (2 mmol), aqueous ammonia **3** (27%, 1 mL), $CuCl_2$ (0.1 mmol), Cs_2CO_3 (2 mmol), L-proline (0.2 mmol), and H_2O (2 mL), heated, sealed, and stirred under protection of N_2 for 24 h. [b] Isolated yield.

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 Cs_2CO_3, the coordination of L-proline with $CuCl_2$ helped to promote the subsequent Ullmann-type reaction to form 2-amino, while oxidation from -CN to -$CONH_2$ occurred simultaneously in the presence of $CuCl_2$, base, and H_2O, so that intermediate 2-aminobenzamide was generated. Actually, 2-aminobenzamide was detected as intermediate during the reaction, andthen condensation and addition occurred on 2-aminobenzamide and benzaldehyde. 2,3-Dihydro-2-aryl quinazolin-4(1*H*)-one 5 was produced under the protection of N_2, 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(3*H*)-one 4.



Scheme 2. Proposed mechanism.

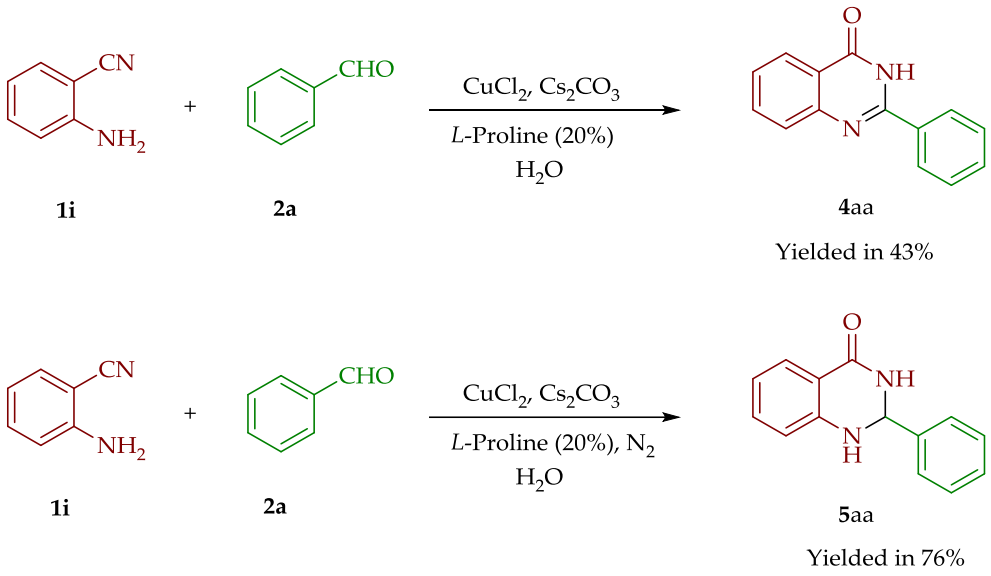
Although at the outset of this work we only expected to develop an "on-water" protocol towards quinazolinones from *o*-bromobenzonitrile **1a**, the explicit outcome above proved the versatility of this protocol. Then other commonly used substrates were evaluated for this protocol. *o*-Bromobenzamide **1h** was first reacted with *p*-methoxylbenzaldehyde and ammonia under the standard conditions. As outlined in Scheme 3, 2-(4-methoxyphenyl)-quinazolin-4(3*H*)-one **4ae** and 2,3-dihydro-2-phenylquinazolin-4(1*H*)-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).



Scheme 3. The "on-water" reaction starting from *o*-bromobenzamide.

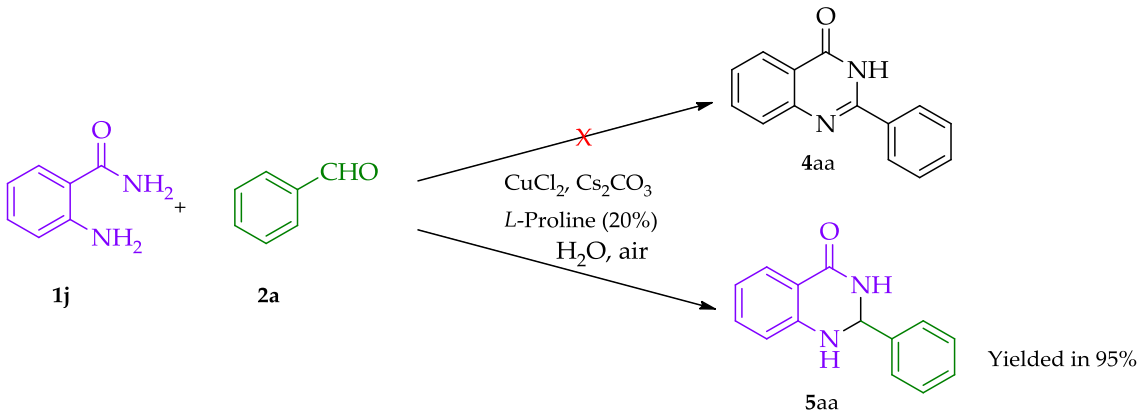
Subsequently, *o*-aminobenzonitrile **1i** was tested and the results in Scheme 4 showed that the yield of 2-phenylquinazolin-4(3*H*)-one **4aa** was only 43%, while *o*-bromobenzonitrile **1a** yielded in 75% (**4aa**, Table 2). But, when under the protection of N_2, 76% of the yield of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one **5aa** was obtained, almost the same with the result

from *o*-bromobenzonitrile **1a** (**5aa**, Table 3). Obviously, *o*-aminobenzonitrile **1i** was less active than o-bromobenzonitrile **1a** for the synthesis of quinazolin-4(3*H*)-one, which explained why 2,3-dihydro-quinazolin-4(1*H*)-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(3*H*)-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(3*H*)-one **4aa** failed to produce, while 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one **5aa** yielded up to 95% without the protection of N_2. It implies that *o*-aminobenzamide **1j** tends to be transformed into 2,3-dihydro-quinazolin-4(1*H*)-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(1*H*)-ones **5** than its oxidized products quinazolin-4(3*H*)-ones **4**. In addition, for the preparation of quinazolin-4(3*H*)-ones **4**, the priority of the commonly used substrates is: *o*-bromobenzonitrile **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(3*H*)-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(3*H*)-ones **4**. Moreover, we found that 2,3-dihydro-quinazolin-4(1*H*)-ones **5** could also be obtained when the reaction was carried out under the protection of N_2, and the subsequent scope investigation resulted in the successful synthesis of various 2,3-dihydro-quinazolin-4(1*H*)-ones **5**. Therefore, we can selectively produce the compounds 2,3-dihydro-quinazolin-4(1*H*)-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(1*H*)-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(3*H*)-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 ^{1}H-NMR, ^{13}C-NMR and MS, and ^{1}H-, and ^{13}C-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), $CuCl_2$ (17.2 mg, 0.1 mmol), Cs_2CO_3 (652.2 mg, 2 mmol), and L-proline (23.2 mg, 0.2 mmol) in H_2O (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 NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenylquinazolin-4(3*H*)-one (**4aa**) in 75% isolated yield. ^{1}H-NMR (400 MHz, Chloroform-d) δ11.24 (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). ^{13}C-NMR (100 MHz, Chloroform-d) δ151.60, 134.87, 132.77, 131.64, 129.05, 127.97, 127.25, 126.79, 126.34, 120.84. HRMS (ESI) calcd for $C_{14}H_{11}N_2O$ $[M + H]^+$: 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), $CuCl_2$ (17.1 mg, 0.1 mmol), Cs_2CO_3 (651.3 mg, 2 mmol) and L-proline 23.4 mg, 0.2 mmol) in H_2O (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_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_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(1*H*)-one(5aa) in 74% isolated yield. ^{1}H-NMR (400 MHz, Chloroform-d) δ 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) δ 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 $C_{14}H_{13}N_2O$ $[M + H]^+$: 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_2CO_3 (652.3 mg, 2 mmol), and L-proline 23.6 mg, 0.2 mmol) in H_2O (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_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford 2-phenylquinazolin-4(3*H*)-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_2CO_3 (653.7 mg, 2 mmol), and L-proline 23.3 mg, 0.2 mmol) in H_2O (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_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_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(1*H*)-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_2CO_3 (657.0 mg, 2 mmol) and L-proline 23.6 mg, 0.2 mmol) in H_2O (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_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_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(1*H*)-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.

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