

Research Article

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An efficient and green synthesis of 2-phenylquinazolin-4(3*H*)-ones via *t*-BuONa-mediated oxidative condensation of 2-aminobenzamides and benzyl alcohols under solvent- and transition metal-free conditions

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Abstract: Quinazolinone synthesis usually requires employing sensitive substrates, hazardous solvents, large excess oxidants, and expensive catalysts. In this study, an efficient and environmentally benign pathway was developed to synthesize 2-phenylquinazolin-4(3*H*)-one via oxidative coupling between commercially available and stable chemicals, including 2-aminobenzamide and benzyl alcohol without toxic oxidizing agents and transition-metal catalysts. A high yield of the desired product (up to 84%) was obtained at 120°C for 24 h in the presence of oxygen as a green oxidant and *t*-BuONa as a base. Importantly, the study scope was expanded toward successfully producing various 2-phenylquinazolin-4(3*H*)-one derivatives in moderate-to-good yields. Furthermore, control experiments proposed that the conversion involved the initial partial oxidation of benzyl alcohol to the benzaldehyde intermediate under basic conditions, followed by the condensation, intramolecular

nucleophilic addition, and oxidative dehydrogenation to 2-phenylquinazolin-4(3*H*)-one.

Keywords: 2-phenylquinazolin-4(3*H*)-one, benzyl alcohol, green conditions, oxidative coupling

1 Introduction

Quinazolinone derivatives, one of the important classes of six-membered nitrogen-containing heterocyclic skeletons, have attracted much attention due to their broad application scope in chemistry and pharmaceuticals [1–7]. Biologically crucial molecules involving the quinazolinone core occurred naturally in various classes of plants, microorganisms, and animals [8–15]. In particular, numerous 4(3*H*)-quinazolinone-based compounds have been commonly explored in medicinal chemistry with noteworthy pharmacological activities such as anticonvulsant, anticancer, anti-inflammatory, antimicrobial, anti-HIV, antiviral, and antidiabetic properties and inhibitory effects on poly-(ADP-ribose) polymerase, thymidylate synthase, and tyrosine kinase (Figure 1) [16–33]. Therefore, many efforts have been made to investigate new efficient and facile approaches toward constructing 4(3*H*)-quinazolinones. The traditional route to obtain 4(3*H*)-quinazolinones could be based on three-component condensation involving carboxylic acid, amine, and 2-aminobenzoic acid or the cascade condensation/oxidation sequence of aldehydes with 2-aminobenzonitrile, promoted by acid or base [34–38]. These approaches are indeed highly efficient but limited by major drawbacks such as difficult-to-prepare starting materials, use of hazardous solvents, large excess oxidants, and harsh reaction conditions [2,39–41]. Thus, the development of more simple and milder methods to synthesize 4(3*H*)-quinazolinone derivatives remains an attractive task for organic chemists [6,42,43].

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without further purification unless otherwise noted. Silica gel 60 F254 plates (20 cm × 20 cm) with a layer thickness of 0.25 mm for thin-layer chromatography (TLC) were purchased from Merck.

Gas chromatography (GC) was performed on a Shimadzu GC 2010-Plus equipped with a flame ionization detector and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). For GC analysis, the sample was initially held at 100°C for 1 min, then heated from 100°C to 280°C with a ramp rate of 40°C·min⁻¹, and further held at 280°C for another 4.5 min before being cooled down to 100°C. The inlet and detector temperatures were maintained at 280°C during the analysis course.

Gas chromatography–mass spectrometry (GC–MS) was conducted on a Shimadzu GC-MS-QP2010 Ultra equipped with a ZB-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). For GC–MS analysis, the sample was kept at 50°C for 2 min, then heated from 50°C to 280°C with a ramp rate of 10°C·min⁻¹, and finally kept at 280°C for 10 min. The inlet temperature was maintained at 280°C. The obtained mass spectra were compared with references from the NIST library.

Nuclear magnetic resonance (¹H NMR and ¹³C NMR) spectra were recorded in DMSO-*d*₆ using the residual solvent peak or tetramethylsilane as a reference on a Bruker AV 500 spectrometer.

The melting points of the isolated products were determined using a Stuart SMP30 device.

2.2 Procedure for the synthesis of 2-phenylquinazolin-4(3H)-one

In a typical experiment, 2-aminobenzamide (40.8 mg, 0.3 mmol), benzyl alcohol (1 mL), and sodium *tert*-butoxide (43.2 mg, 1.5 equivalents) were sequentially added to an 8-mL vial. The reaction mixture was purged with oxygen 2 min before being tightly sealed. Subsequently, the reaction was performed under vigorous stirring at 120°C. After a predetermined time period, the vial was cooled down to room temperature, and diphenyl ether

(51.1 mg, 0.3 mmol) as an internal standard was added. Ethyl acetate (3 mL) was then added to dilute the reaction mixture. An aliquot withdrawn from the resulting mixture was quenched with brine (2 mL), extracted with ethyl acetate (2 mL), dried over anhydrous sodium sulfate, and filtered through a cotton layer. The final organic sample was analyzed by GC using the diphenyl ether internal standard to determine the product yield. To determine the completion of this transformation, the reaction experiments were performed for different time intervals from 0.5 to 30 h.

For the isolation and purification of 2-phenylquinazolin-4(3H)-one, after the reaction described above, the resulting mixture was cooled to room temperature, then diluted with ethyl acetate (20 mL), and quenched with brine (10 mL). The obtained organic phase was dried over anhydrous Na₂SO₄, filtered through a thin cotton layer, and evaporated under reduced pressure, yielding a solid product. The raw product was further purified by washing with *n*-hexane (3 × 15 mL), affording 2-phenylquinazolin-4(3H)-one as a white solid. During the isolation and purification steps, TLC was performed using a mixture of ethyl acetate and *n*-hexane (volume ratio = 1:3). Visualization of the TLC plates was performed under ultraviolet light (254 and 365 nm). The product structure was identified by GC–MS, ¹H NMR, and ¹³C NMR.

3 Results and discussion

According to the previous studies on the synthesis of 2-phenylquinazolin-4(3H)-one via oxidative condensation of 2-aminobenzamide with benzyl alcohol (Figure 3), it was found that the base should be applied to promote the formation of the desired product under the transition-metal-based catalysis [2,48,54]. Initial studies therefore focused on the effect of bases on metal-free transformation. As shown in Table 1, the weak bases including DABCO and Na₂CO₃ were found to be unsuitable for this reaction, giving only trace amounts of the desired product (Entries 1 and 2). This result is consistent with the

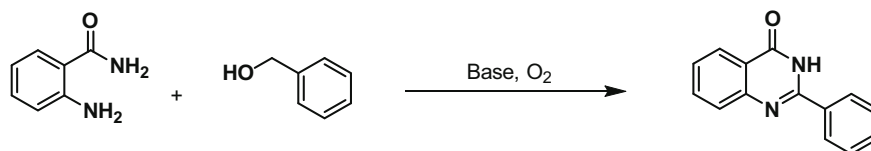


Figure 3: Model reaction of 2-aminobenzamide and benzyl alcohol toward 2-phenylquinazolin-4(3H)-one for screening of the reaction conditions.

Table 1: Screening of the reaction conditions^a

Entry	Temperature (°C)	Time (h)	Base	Base amount (equivalents)	Oxidant	GC yield (%)
1	140	24	DABCO	1.5	O ₂	Trace
2	140	24	Na ₂ CO ₃	1.5	O ₂	Trace
3	140	24	<i>t</i> -BuOLi	1.5	O ₂	34
4	140	24	NaOH	1.5	O ₂	60
5	140	24	<i>t</i> -BuOK	1.5	O ₂	62
6	140	24	KOH	1.5	O ₂	63
7	140	24	<i>t</i> -BuONa	1.5	O ₂	82
8	140	24	<i>t</i> -BuONa	0	O ₂	Trace
9	140	24	<i>t</i> -BuONa	0.25	O ₂	9
10	140	24	<i>t</i> -BuONa	0.5	O ₂	48
11	140	24	<i>t</i> -BuONa	1	O ₂	65
12	140	24	<i>t</i> -BuONa	2	O ₂	83
13	RT	24	<i>t</i> -BuONa	1.5	O ₂	Trace
14	60	24	<i>t</i> -BuONa	1.5	O ₂	45
15	80	24	<i>t</i> -BuONa	1.5	O ₂	57
16	100	24	<i>t</i> -BuONa	1.5	O ₂	68
17	120	24	<i>t</i> -BuONa	1.5	O ₂	84
18	120	24	<i>t</i> -BuONa	1.5	None (Ar)	Trace
19	120	24	<i>t</i> -BuONa	1.5	Air	21
20	120	24	<i>t</i> -BuONa	1.5	DTBP	10
21	120	24	<i>t</i> -BuONa	1.5	H ₂ O ₂	29 ^b , 46 ^c , 39 ^d
22	120	0.5	<i>t</i> -BuONa	1.5	O ₂	16
23	120	2.5	<i>t</i> -BuONa	1.5	O ₂	54
24	120	5	<i>t</i> -BuONa	1.5	O ₂	58
25	120	15	<i>t</i> -BuONa	1.5	O ₂	68
26	120	20	<i>t</i> -BuONa	1.5	O ₂	75
27	120	30	<i>t</i> -BuONa	1.5	O ₂	84

^aGeneral conditions: 2-aminobenzamide (0.3 mmol), benzyl alcohol (1 mL), and a base. ^bH₂O₂ (1 equivalent), ^cH₂O₂ (2 equivalents), ^dH₂O₂ (3 equivalents). DABCO: 1,4-diazabicyclo[2.2.2]octane; *t*-BuOLi: lithium *tert*-butoxide; *t*-BuOK: potassium *tert*-butoxide; *t*-BuONa: sodium *tert*-butoxide.

previous work of Qiu *et al.*, in which it was suggested that carbonate salts were not strong enough to promote the last dehydrogenation toward 2-phenylquinazolin-4(3*H*)-one [55]. As can be expected, using stronger bases such as alkali hydroxides and alkali *t*-butoxide resulted in significantly improved production of quinazolinone. It should be noted that no transition-metal catalysts were present in this protocol. Indeed, a quinazoline yield of 34% could be obtained in the reaction mediated by *t*-BuOLi, while NaOH, *t*-BuOK, and KOH, respectively, gave higher yields of the desired product (>60%) (Entries 3–6). Among the tested bases, *t*-BuONa exhibited the best performance, producing 2-phenylquinazolin-4(3*H*)-ones with the highest yield of 82%.

Furthermore, the impact of the *t*-BuONa amount on quinazoline production was explored (Entries 7–12). No major product was detected after 24 h in the absence of *t*-BuONa, verifying the importance of the base for this transformation. The desired product was obtained in a low yield of 9% as 0.25 equivalents of *t*-BuONa was used. Using more base amounts led to considerable increases in

the formation of 2-phenylquinazolin-4(3*H*)-one. However, using 2 equivalents of *t*-BuONa was found to be unnecessary, with no further yield improvement obtained.

Next, the reaction of 2-aminobenzamide with benzyl alcohol was investigated at different temperatures ranging from room temperature to 140°C. It was observed that the reaction temperature greatly impacted on the production of 2-phenylquinazolin-4(3*H*)-one (Entries 13–17). No reaction toward quinazolinone was observed at room temperature. As expected, conducting the reactions at elevated temperatures, namely, 60°C, 80°C, 100°C, and 120°C, gave higher product yields of 45%, 57%, 68%, and 84%, respectively. No further enhancement in the formation of the desired product was observed when the reaction temperature was increased to 140°C. In general, under transition-metal-free conditions, a higher temperature was required to obtain 2-phenylquinazolin-4(3*H*)-one compared to the previous studies, in which the metal catalysts allowed the reaction to take place under milder conditions. Indeed, using α -MnO₂ as the solid catalyst for this reaction was reported

by Zhang and co-workers, giving the desired product in a good yield of 79% at 80°C [45]. Furthermore, the coupling of 2-aminobenzamide with alcohol catalyzed by iron(III) nitrate readily produced 2-phenylquinazolin-4(3H)-one at 100°C [48].

In this study, benzyl alcohol could play a dual role in the reactant and the reaction medium. Therefore, the amount of benzyl alcohol was also an important factor that should be concerned to afford the desired product in high yields (Entries 1–6, Table S1 in Supplementary material). It was observed that the reaction using 0.25 mL of benzyl alcohol produced 2-phenylquinazolin-4(3H)-one in a moderate yield of 57%, probably due to the hindered interaction of solid substrates, namely, 2-aminobenzamide and *t*-BuONa, with benzyl alcohol in a limited amount (Entry 1). Therefore, adding more 0.5 and 0.75 mL of benzyl alcohol significantly accelerated the transformation, increasing the yield of 2-phenylquinazolin-4(3H)-one to 70% and 76%, respectively (Entries 2–3). As expected, the reaction proceeded more readily in the presence of 1 mL of benzyl alcohol, affording a yield of 84% (Entry 4). However, no notable differences in the reaction performance were observed in the benzyl alcohol amount range of 1.0–1.5 mL with product yields of around 80% recorded (Entries 4–6).

As previously reported, an oxidant was required to convert benzyl alcohol to benzaldehyde, which was proposed as an important intermediate in the formation of 2-phenylquinazolin-4(3H)-ones [7,55]. In this study, various oxidative conditions were therefore tested for the reaction. The results in Table 1 (Entries 17–21) indicated that the transformation toward 2-phenylquinazolin-4(3H)-one strongly depended on the oxidant nature. As predicted, no desired product was obtained under an argon atmosphere, while the reaction could proceed slowly in air, finally giving a poor yield of 21% after 24 h, probably due to a shortage of oxygen for the oxidation of benzyl alcohol. Indeed, 2-phenylquinazolin-4(3H)-one was favorably generated under an O₂ atmosphere in 84% yield. Furthermore, other liquid oxidants, including DTBP and H₂O₂, with different amounts exhibited poor performances with low yields of 2-phenylquinazolin-4(3H)-ones (10–50%). These results could be rationalized by the fact that using such strong oxidants could lead to unwanted oxidation of the amine group in 2-aminobenzamide at an elevated temperature. O₂ emerges as a green, cheap, and efficient oxidant for this annulation.

To emphasize the efficiency of the pathway under solvent-free conditions, various polar and non-polar solvents were added to the reaction, and the yield results are presented in Table S1. The presence of water, a protic

solvent, completely shut down the reaction, while low yields of 2-phenylquinazolin-4(3H)-one (15–39%) were obtained in the reactions containing polar aprotic solvents, namely, DMF and DMSO (Entries 7–9). The earlier studies indeed reported that such polar solvents were incompatible with converting benzyl alcohol and 2-aminobenzamide into 2-phenylquinazolin-4(3H)-one [55,56]. Interestingly, better performances were obtained when less polar and non-polar solvents, including 1,2-dichlorobenzene and toluene, respectively, were added (Entries 10 and 11). In a similar work on the oxidative synthesis of 2-phenylquinazolin-4(3H)-one from benzyl alcohol and 2-aminobenzamide, a large amount of toluene solvent was also required [55]. However, organic solvents usually cause serious problems related to human health, ecosystem, and safety due to their high toxicity and flammability. In addition, the work-up procedure would be more complicated for the removal and disposal of the organic solvents. Solvent-free conditions are therefore highly desired. Notably, it was found that the solvent-free reaction produced 2-phenylquinazolin-4(3H)-one with the best yield of 84%, highlighting the undeniable benefits of this annulation.

Finally, the reaction of 2-aminobenzamide and benzyl alcohol was carried out in the time range from 0.5 to 30 h (Entries 22–27, Table 1). The kinetic investigation of the reaction revealed that conversion to 2-phenylquinazolin-4(3H)-one promptly proceeded in the first 2.5 h, affording a 54% yield. Prolonging the reaction to 24 h led to an additional yield of approx. 30%; however, this yield value was maintained in the 30-h reaction. Notably, a large-scale reaction involving 2.0 mmol of 2-aminobenzamide and 32 equivalents of benzyl alcohols was also performed under identical conditions investigated. After a simple purification procedure without column chromatography, the major product, 2-phenylquinazolin-4(3H)-one, could be successfully obtained in a well-isolated yield of 70%, showing the great potential of this transition-metal catalyst-free pathway.

To investigate the transformation mechanism, a series of control experiments were carried out. As mentioned previously, no 2-phenylquinazolin-4(3H)-one was obtained in the absence of either oxygen or *t*-BuONa (Figure 4a and b). On the other hand, the treatment of benzyl alcohol under the established conditions without adding 2-aminobenzamide resulted in the observation of benzaldehyde, implying that benzaldehyde could be formed via the oxidation of benzyl alcohol in the presence of *t*-BuONa and oxygen (Figure 4c). Notably, benzaldehyde and dihydrogenated quinazolinone were also detected as the intermediates when the standard reaction was performed within 5 h (Figure 4d). To investigate the role of *t*-BuONa in this

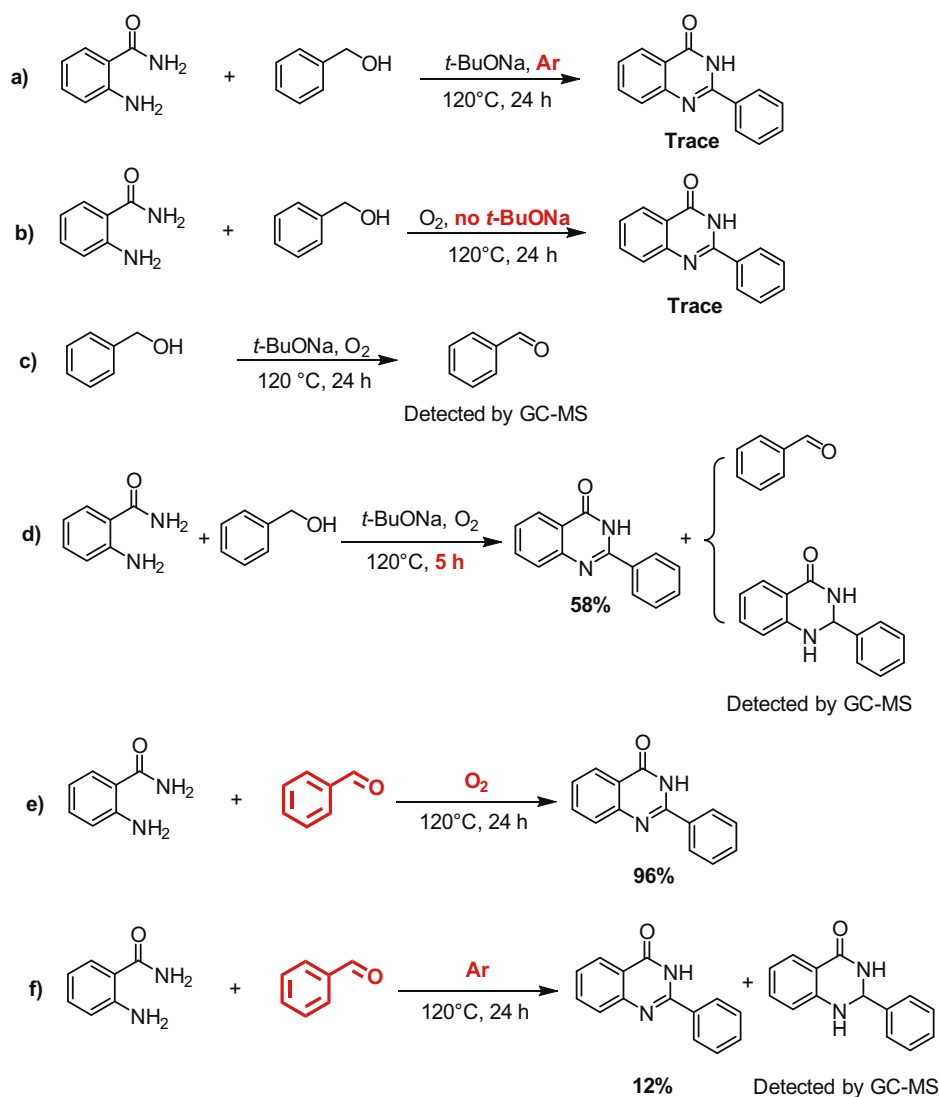


Figure 4: Control experiments.

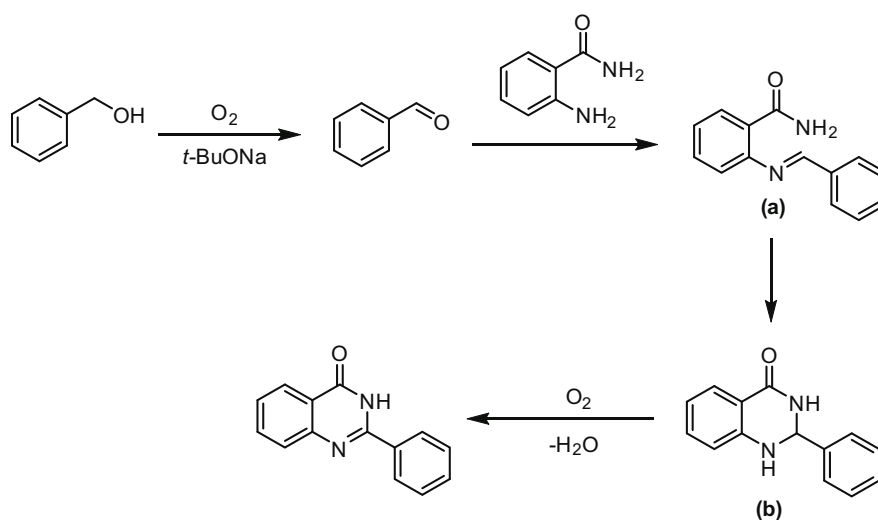
Figure 5: Plausible mechanism for forming 2-phenylquinazolin-4(3H)-one from 2-aminobenzamide and benzyl alcohol in the presence of O_2 and t -BuONa.

Table 2: Oxidative coupling between *o*-aminobenzamides and benzyl alcohols to 2-phenylquinazolin-4(3*H*)-ones in the presence of *t*-BuONa and O₂^a

Entry	Reactant 1	Reactant 2	Product	Isolated yield (%)	Melting point (°C)
1				75	230–232
2				67	208–210
3				69	230–232
4				66	242–244
5				31	198–200
6				29	298–300
7				Trace	—
8				Trace	—
9				57	236–238
10				51	291 (decomposed)
11				63	254 (decomposed)

^aReaction conditions: reactant 1 (0.3 mmol), reactant 2 (32 equivalents), *t*-BuONa (1.5 equivalents), 120°C, under an O₂ atmosphere for 24 h.

pathway, the reaction of 2-aminobenzamide and benzaldehyde was carried out under identical conditions in the absence of *t*-BuONa, giving quinazolinone in an excellent yield (96%) (Figure 4e). It was therefore suggested that *t*-BuONa could accelerate the oxidation of benzyl alcohol to benzaldehyde, which would participate in the next condensation reaction with 2-aminobenzamide. Note that benzaldehyde and its derivatives are organic compounds highly sensitive to air, light, and moisture. Benzaldehyde spontaneously undergoes unexpected oxidation to yield benzoic acid upon exposure to air under ambient conditions, while the presence of such an impurity can significantly affect the reaction involving benzaldehyde [57]. Therefore, preservation of benzaldehyde under an inert atmosphere or purification of benzaldehyde prior to use is usually required with high consumption of cost and energy. From the viewpoint of green chemistry, benzyl alcohol has emerged as a more stable, more available, and less costly starting material alternative to benzaldehyde in numerous organic transformation reactions [58–61]. In this study, the use of benzyl alcohols with the assistance of a base indeed offered an environmentally benign and efficient pathway for synthesizing 2-phenylquinazolin-4(3*H*)-ones.

Interestingly, in the reaction of 2-aminobenzamide with benzaldehyde under *t*-BuONa- and O₂-free conditions, only a 12% yield for the major product was obtained, while a large amount of dihydrogenated quinazolinone was produced (Figure 4f), implying the essential role of O₂ in the dehydrogenative step of dihydrogenated quinazolinone to quinazolinone [2,51]. Based on the obtained results, the pathway for *t*-BuONa-promoted oxidative coupling of 2-aminobenzamide with benzyl alcohol toward 2-phenylquinazolin-4(3*H*)-one was proposed (Figure 5). With the assistance of *t*-BuONa, benzyl alcohol was first oxidized by O₂ at a high temperature to benzaldehyde, which underwent condensation with 2-aminobenzamide to produce imine **a**. Subsequently, an intramolecular nucleophilic addition allowed the conversion of **a** into dihydrogenated quinazolinone **b**, which was dehydrogenated by oxygen to finally yield the desired product.

With the optimal conditions in hand, the substrate scope was expanded to the synthesis of 2-phenylquinazolin-4(3*H*)-one derivatives from substituted 2-aminobenzamides and benzyl alcohols (Table 2). The standard reaction of 2-aminobenzamide with benzyl alcohol produced 2-phenylquinazolin-4(3*H*)-one in an isolated yield of 75% (Entry 1). Good yields of quinazolin-4(3*H*)-ones also remained in the reactions using benzyl alcohols containing an electron-donating group, in good agreement with the study on the Ni-catalyzed synthesis of quinazolin-4(3*H*)-one derivatives from 2-aminobenzamide and benzyl

alcohols [51]. Indeed, 3-methylbenzyl alcohol and 4-methylbenzyl alcohol (Entries 2 and 3) afforded the corresponding quinazolin-4(3*H*)-ones in 67% and 69% isolated yields, respectively. A similar result was also obtained for the case of 4-methoxybenzyl alcohol (66%, Entry 4). By contrast, electron-withdrawing groups in benzyl alcohol significantly inhibited the production of 2-phenylquinazolin-4(3*H*)-one. The reaction of 2-aminobenzamide with 2-chlorobenzyl alcohol or 3-chlorobenzyl alcohol gave low quinazolinone yields of 31% and 29%, respectively (Entries 5 and 6). These results indicated negligible steric hindrance of the substituent at the *ortho* position of benzyl alcohol. Besides, no desired products were observed in the reaction involving 2-nitro or 4-nitrobenzyl alcohols (Entries 7 and 8). Next, several substituted 2-aminobenzamides were also used to react with benzyl alcohol under identical conditions. This annulation showed good tolerance to both the electron-donating (methyl-) and electron-withdrawing (fluoro-, chloro-) groups in 2-aminobenzamide, affording the corresponding products in good yields of 51–63% (Entries 9–11).

4 Conclusions

In this study, 2-phenylquinazolin-4(3*H*)-one was successfully synthesized from more stable and available substrates, namely, 2-aminobenzamide and benzyl alcohol, in the presence of a strong base and oxygen as a green and cheap oxidant without further use of any additional solvent and transition-metal catalyst. The mechanistic experiments provided reliable evidence for the *in situ* formation of benzaldehyde via *t*-BuONa-assisted oxidation of benzyl alcohol followed by coupling with 2-aminobenzamide and oxidative dehydrogenation to the desired products. The oxidative annulation demonstrated remarkable tolerance with different functional groups in 2-aminobenzamide and benzyl alcohol. The corresponding quinazolin-4(3*H*)-one derivatives could be obtained in the isolated yields of 29–75%. The significant results of this study are expected to guide a simple, efficient, and environmentally friendly approach to form the quinazolin-4(3*H*)-one moiety in biologically active molecules.

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Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

- [1] Abdel-Jalil RJ, Voelter W, Saeed. M. A novel method for the synthesis of 4 (3H)-quinazolinones. *Tetrahedron Lett.* 2004;45(17):3475–6. doi: 10.1016/j.tetlet.2004.03.003.
- [2] Balaji S, Balamurugan G, Ramesh R, Semeril D. Palladium(II) N[^]O chelating complexes catalyzed one-pot approach for synthesis of quinazolin-4(3H)-ones via acceptorless dehydrogenative coupling of benzyl alcohols and 2-Aminobenzamide. *Organometallics.* 2021;40(6):725–34. doi: 10.1021/acs.organomet.0c00814.
- [3] Demeunynck M, Baussanne I. Survey of recent literature related to the biologically active 4 (3H)-quinazolinones containing fused heterocycles. *Curr Med Chem.* 2013;20(6):794–814. doi: 10.2174/092986713805076711.
- [4] Huang X, Yang H, Fu H, Qiao R, Zhao Y. Efficient copper-catalyzed synthesis of 2-amino-4 (3H)-quinazolinone and 2-aminoquinazoline derivatives. *Synthesis.* 2009;2009(16):2679–88. doi: 10.1055/s-0029-1216871.
- [5] Mishra S. Quinazolinone and quinazoline derivatives: synthesis and biological application. London, UK: Intechopen; 2020. p. 75–90.
- [6] Reddy MM, Sivaramakrishna A. Remarkably flexible quinazolinones-synthesis and biological applications. *J Heterocycl Chem.* 2020;57(3):942–54. doi: 10.1002/jhet.3844.
- [7] Wang ZZ, Tang. Y. Mechanistic insights into a catalyst-free method to construct quinazolinones through multiple oxidative cyclization. *Tetrahedron.* 2016;72(10):1330–6. doi: 10.1016/j.tet.2016.01.027.
- [8] Chen AL, Chen K. The constituents of Wu Chü Yü (Evodia rutaecarpa). *J Am Pharm Assoc.* 1933;22(8):716–9. doi: 10.1002/jps.3080220804.
- [9] Liang JL, Cha HC, Jahng Y. Recent advances in the studies on luotonins. *Molecules.* 2011;16(6):4861–83. doi: 10.3390/molecules16064861.
- [10] Mhaske SB, Argade NP. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. *Tetrahedron.* 2006;62(42):9787–826. doi: 10.1016/j.tet.2006.07.098.
- [11] Michael JP. Quinoline, quinazoline and acridone alkaloids. *Nat Prod Rep.* 2008;25(1):166–87. doi: 10.1039/B612168N.
- [12] Mohanta PK, Kim K. A short synthesis of quinazolinocarboline alkaloids rutaecarpine, hortiacine, euxylophoricine A and euxylophoricine D from methyl N-(4-chloro-5H-1, 2, 3-dithiazol-5-ylidene) anthranilates. *Tetrahedron Lett.* 2002;43(22):3993–6. doi: 10.1016/S0040-4039(02)00711-6.
- [13] Qiu D, Wang Y, Lu D, Zhou L, Zeng Q. Potassium hydroxide-promoted transition-metal-free synthesis of 4(3H)-quinazolinones. *Monatsh Chem.* 2015;146(8):1343–7. doi: 10.1007/s00706-015-1434-7.
- [14] Wang J, Zhang MM, Wang XS. Structurally diversified synthesis of 2,3-dihydroquinazolin-4-(1H)-ones from 2-aminobenzamides and 1,2-dicarbonyl compounds in ionic liquids catalyzed by iodine. *Res Chem Intermed.* 2017;43(5):2985–3005. doi: 10.1007/s11164-016-2807-1.
- [15] Wattanapiromsakul C, Forster PI, Waterman PG. Alkaloids and limonoids from *Bouchardatia neurococca*: systematic significance. *Phytochemistry.* 2003;64(2):609–15. doi: 10.1016/S0031-9422(03)00205-x.
- [16] Al-Amiery AA, Kadhun AAH, Shamel M, Satar M, Khalid Y, Mohamad AB. Antioxidant and antimicrobial activities of novel quinazolinones. *Med Chem Res.* 2014;23(1):236–42. doi: 10.1007/s00044-013-0625-1.
- [17] Deep A, Narasimhan B, Ramasamy K, Mani V, Kumar Mishra R, Bakar Abdul Majeed A. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-ones clubbed with quinazolinone. *Curr Top Med Chem.* 2013;13(16):2034–46. doi: 10.2174/15680266113139990130.
- [18] Deetz MJ, Malerich JP, Beatty AM, Smith BD. One-step synthesis of 4 (3H)-quinazolinones. *Tetrahedron Lett.* 2001;42(10):1851–4. doi: 10.1016/S0040-4039(01)00096-X.
- [19] Ghorab MM, Ismail ZH, Radwan AA, Abdalla M. Synthesis and pharmacophore modeling of novel quinazolines bearing a biologically active sulfonamide moiety. *Acta Pharmaceutica.* 2013;63(1):1–18. doi: 10.2478/acph-2013-0006.
- [20] Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudersanam V, et al. Design, synthesis and characterization of novel 2-(2, 4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazolin-4-one derivatives as inhibitors of NF- κ B and AP-1 mediated transcription activation and as potential anti-inflammatory agents. *Eur J Med Chem.* 2009;44(5):2184–9. doi: 10.1016/j.ejmech.2008.10.031Get.
- [21] Guiles J, Sun X, Critchley IA, Ochsner U, Tregay M, Stone K, et al. Quinazolin-2-ylamino-quinazolin-4-ols as novel non-nucleoside inhibitors of bacterial DNA polymerase III. *Bioorg Med Chem Lett.* 2009;19(3):800–2. doi: 10.1016/j.bmcl.2008.12.038.
- [22] Hattori K, Kido Y, Yamamoto H, Ishida J, Iwashita A, Mihara K. Rational design of conformationally restricted quinazolinone inhibitors of poly (ADP-ribose) polymerase. *Bioorg Med Chem Lett.* 2007;17(20):5577–81. doi: 10.1016/j.bmcl.2007.07.091.
- [23] Jiang S, Zeng Q, Gettayacamin M, Tungtaeng A, Wannaying S, Lim A, et al. Antimalarial activities and therapeutic properties of febrifugine analogs. *Antimicrob Agents Chemother.* 2005;49(3):1169–76. doi: 10.1128/AAC.49.3.1169-1176.2005.
- [24] Khalil AA, Hamide SGA, Al-Obaid AM, El-Subbagh HI. Substituted quinazolines, part 2. synthesis and In-vitro anticancer evaluation of new 2-substituted Mercapto-3H-

- quinazoline Analogs. *Arch Pharm Pharm Med Chem.* 2003;336(2):95–103. doi: 10.1002/ardp.200390011.
- [25] Khosropour AR, Mohammadpoor-Baltork I, Ghorbankhani H. Bi (TFA) 3-[nbp] FeCl₄: a new, efficient and reusable promoter system for the synthesis of 4 (3*H*)-quinazolinone derivatives. *Tetrahedron Lett.* 2006;47(21):3561–4. doi: 10.1016/j.tetlet.2006.03.079.
- [26] Krishnan S, Ganguly S, Veerasamy R, Jan B. Synthesis, anti-viral and cytotoxic investigation of 2-phenyl-3-substituted quinazolin-4 (3*H*)-ones. *Eur Rev Med Pharmacol Sci.* 2011;15(6):673–81. doi: 10.4103/1735-5362.217425.
- [27] Laddha SS, Wadodkar SG, Meghal SK. Studies on some biologically active substituted 4 (3*H*)-quinazolinones. Part 1. Synthesis, characterization and anti-inflammatory-antimicrobial activity of 6, 8-disubstituted 2-phenyl-3-[substituted-benzothiazol-2-yl]-4 (3*H*)-quinazolinones. *Arkivoc.* 2006;11:1–20. doi: 10.3998/ark.5550190.0007.b01.
- [28] Liu S, Liu F, Yu X, Ding G, Xu P, Cao J, et al. The 3D-QSAR analysis of 4 (3*H*)-quinazolinone derivatives with dithiocarbamate side chains on thymidylate synthase. *Biorg. Med Chem.* 2006;14(5):1425–30. doi: 10.1016/j.bmc.2005.09.064.
- [29] Nagar AA, Rathil L, Chugh N, Pise VJ, Bendale A. Microwave assisted one pot synthesis of 2, 3-di-substituted quinazolin-4-(3*H*)-ones and their potential biological activity. *Der Pharm Chem.* 2010;2(3):37–43. doi: 10.1016/j.tetlet.2005.01.008.
- [30] Orvieto F, Branca D, Giomini C, Jones P, Koch U, Ontoria JM, et al. Identification of substituted pyrazolo [1, 5-*a*] quinazolin-5 (4*H*)-one as potent poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors. *Bioorg Med Chem Lett.* 2009;19(15):4196–200. doi: 10.1016/j.bmcl.2009.05.113.
- [31] Samira I, Patel S, Hasmin M, Patel S. Biological profile of quinazoline. *Int J Pharm Chem Sci.* 2012;1(4):1519–28. doi: 10.1186/1752-153X-7-95.
- [32] Singh V, Singh S, Gangwar L. Synthesis and antimicrobial activity of nove fused 4-(3*H*) quinazolinone derivatives. *Chemistry.* 2013;20(50):50. doi: 10.1016/j.jscs.2017.07.008.
- [33] Vijayakumar K, Ahamed AJ, Thiruneelakandan G. Synthesis, antimicrobial, and anti-HIV1 activity of quinazoline-4 (3*H*)-one derivatives. *J Appl Chem.* 2013;2013:387191. doi: 10.1155/2013/387191.
- [34] Balakumar C, Lamba P, Kishore DP, Narayana BL, Rao KV, Rajwinder K, et al. Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. *Eur J Med Chem.* 2010;45(11):4904–13. doi: 10.1016/j.ejmech.2010.07.063.
- [35] Connolly DJ, Cusack D, O'Sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. *Tetrahedron.* 2005;43(61):10153–202. doi: 10.1016/j.tet.2005.07.010.
- [36] He L, Li H, Chen J, Wu XF. Recent advances in 4 (3*H*)-quinazolinone syntheses. *RSC Adv.* 2014;4(24):12065–77. doi: 10.1039/C4RA00351A.
- [37] Wu XF, Oschatz S, Block A, Spannenberg A, Langer P. Base mediated synthesis of 2-aryl-2, 3-dihydroquinazolin-4 (1*H*)-ones from 2-aminobenzonitriles and aromatic aldehydes in water. *Org Biomol Chem.* 2014;12(12):1865–70. doi: 10.1039/C3OB42434K.
- [38] Zhan D, Li T, Wei H, Weng W, Ghandi K, Zeng Q. A recyclable CuO-catalyzed synthesis of 4 (3*H*)-quinazolinones. *RSC Adv.* 2013;3(24):9325–9. doi: 10.1039/C3RA41370E.
- [39] 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(27):10817–22. doi: 10.1039/c3ra40872h.
- [40] Wang C, Li S, Liu H, Jiang Y, Fu H. Copper-catalyzed synthesis of quinazoline derivatives via ullmann-type coupling and aerobic oxidation. *J Org Chem.* 2010;75(22):7936–8. doi: 10.1021/jo101685d.
- [41] Zhang ZH, Zhang XN, Mo LP, Li YX, Ma FP. Catalyst-free synthesis of quinazoline derivatives using low melting sugar-urea-salt mixture as a solvent. *Green Chem.* 2012;14(5):1502–6. doi: 10.1039/C2GC35258C.
- [42] Akbari A, Zahedifar M. Synthesis of Quinazolin-4(3*H*)-ones via a novel approach. *J Saudi Chem Soc.* 2023;27(2):101597. doi: 10.1016/j.jscs.2023.101597.
- [43] Dutta N, Dutta B, Dutta A, Sarma B, Sarma D. Room temperature ligand-free Cu₂O–H₂O₂ catalyzed tandem oxidative synthesis of quinazoline-4(3*H*)-one and quinazoline derivatives. *Org Biomol Chem.* 2023;21(4):748–53. doi: 10.1039/D2OB02085H.
- [44] Nguyen VT, Ngo HQ, Le DT, Truong T, Phan NTS. Iron-catalyzed domino sequences: One-pot oxidative synthesis of quinazolinones using metal-organic framework Fe₃O(BPDC)₃ as an efficient heterogeneous catalyst. *Chem Eng J.* 2016;284:778–85. doi: 10.1016/j.cej.2015.09.036.
- [45] Zhang Z, Wang M, Zhang C, Zhang Z, Lu J, Wang F. The cascade synthesis of quinazolinones and quinazolines using an α-MnO₂ catalyst and tert-butyl hydroperoxide (TBHP) as an oxidant. *Chem Commun.* 2015;51(44):9205–7. doi: 10.1039/C5CC02785C.
- [46] Li H, He L, Neumann H, Beller M, Wu XF. Cascade synthesis of quinazolinones from 2-aminobenzonitriles and aryl bromides via palladium-catalyzed carbonylation reaction. *Green Chem.* 2014;16(3):1336–43. doi: 10.1039/C3GC42089B.
- [47] Chen L, Zhang SF, Chen Z, Zhen Q, Xiong W, Shao Y, et al. Ni-catalyzed cascade coupling reactions: synthesis and thermally-activated delayed fluorescence characterization of quinazolinone derivatives. *N J Chem.* 2021;45(44):20624–8. doi: 10.1039/D1NJ02871E.
- [48] Hu Y, Chen L, Li B. Iron nitrate/TEMPO-catalyzed aerobic oxidative synthesis of quinazolinones from alcohols and 2-aminobenzamides with air as the oxidant. *RSC Adv.* 2016;6(69):65196–204. doi: 10.1039/C6RA12164K.
- [49] Hu Y, Li S, Li H, Li Y, Li J, Duanmu C, et al. Copper-catalyzed tandem oxidative synthesis of quinazolinones from 2-aminobenzonitriles and benzyl alcohols. *Org Chem Front.* 2019;6(15):2744–8. doi: 10.1039/C9QO00657E.
- [50] Das S, Sinha S, Samanta D, Mondal R, Chakraborty G, Brandaõ P, et al. Metal-ligand cooperative approach to achieve dehydrogenative functionalization of alcohols to quinolines and quinazolin-4(3*H*)-ones under mild aerobic conditions. *J Org Chem.* 2019;84(16):10160–71. doi: 10.1021/acs.joc.9b01343.
- [51] Parua S, Das S, Sikari R, Sinha S, Paul ND. One-pot cascade synthesis of quinazolin-4(3*H*)-ones via nickel-catalyzed dehydrogenative coupling of o-aminobenzamides with alcohols. *J Org Chem.* 2017;82(14):7165–75. doi: 10.1021/acs.joc.7b00643.
- [52] Dalko PI, Moisan L. Enantioselective organocatalysis. *Angew Chem Int Ed.* 2001;40(20):3726–48. doi: 10.1016/j.drudis.2006.11.004.

- [53] Schreiner PR. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem Soc Rev.* 2003;32(5):289–96. doi: 10.1039/B107298F.
- [54] Sardar B, Jamatia R, Samanta A, Srimani D. Ru doped hydro-talcite catalyzed borrowing hydrogen-mediated N-alkylation of benzamides, sulfonamides, and dehydrogenative synthesis of quinazolinones. *J Org Chem.* 2022;87(9):5556–67. doi: 10.1021/acs.joc.1c02913.
- [55] Qiu D, Wang Y, Lu D, Zhou L, Zeng Q. Potassium hydroxide-promoted transition-metal-free synthesis of 4 (3*H*)-quinazolinones. *Monatsh Chem.* 2015;146(8):1343–7. doi: 10.1007/s00706-015-1434-7.
- [56] Das S, Mondal R, Chakraborty G, Guin AK, Das A, Paul ND, et al. Zinc stabilized Azo-anion radical in dehydrogenative synthesis of N-heterocycles. An exclusively ligand centered redox controlled approach. *ACS Catal.* 2021;11(12):7498–512. doi: 10.1021/acscatal.1c00275.
- [57] Sankar M, Nowicka E, Carter E, Murphy DM, Knight DW, Bethell D. The benzaldehyde oxidation paradox explained by the interception of peroxy radical by benzyl alcohol. *Nat Commun.* 2014;5(1):3332. doi: 10.1038/ncomms4332.
- [58] Bakavoli M, Shiri A, Ebrahimpour Z, Rahimizadeh M. Clean heterocyclic synthesis in water: I₂/KI catalyzed one-pot synthesis of quinazolin-4 (3*H*)-ones. *Chin Chem Lett.* 2008;19(12):1403–6. doi: 10.1016/j.cclet.2008.07.016.
- [59] 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(27):10817–22. doi: 10.1039/C3RA40872H.
- [60] Roy BC, Samim SA, Panja D, Kundu S. Tandem synthesis of quinazolinone scaffolds from 2-aminobenzonitriles using aliphatic alcohol–water system. *Catal Sci Technol.* 2019;9(21):6002–6. doi: 10.1039/C9CY01094G.
- [61] Siddiki SH, Kon K, Touchy AS, Shimizu KI. Direct synthesis of quinazolinones by acceptorless dehydrogenative coupling of o-aminobenzamide and alcohols by heterogeneous Pt catalysts. *Catal Sci Technol.* 2014;4(6):1716–9. doi: 10.1039/C4CY00092G.