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KO^{t}Bu Mediated Alcohol Dehydrogenation Strategy: Synthesis of 2-Aryl Quinazolinones

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Herein we report an atom-economical, transition metal-free method for synthesizing 2-aryl quinazolinones through a cascade annulation of 2-amino benzamide and benzyl alcohol. The reaction proceeds via KO^{t}Bu-mediated acceptorless alcohol dehydrogenation pathways. The procedure tolerates a wide variety of functional groups and provides a convenient method for the synthesis of 2-aryl quinazolinones. Mechanistic insights by experiments and DFT calculations lead to unveil the reaction mechanism.

Introduction

Quinazolinones are nitrogen-containing fused heterocycles that show a close resemblance to natural alkaloids, owning to these quinazolinone scaffolds have been employed extensively in synthetic drugs . Functionalized quinazolinone derivatives are largely used in pharmaceutical industries (see Figure 1),[1] particularly as anti-HIV,[2] antifungal,[3] anti-inflammatory,[4] anti-cancer,[5] antimutagenic agents,[6] etc. Several substituted quinazolinone also serve as ligands, as well as DNA binders.[7] In recent years, tremendous advancement has been made in developing efficient methods to synthesize quinazolinone derivatives.[8]

Lately, emphasis has been devoted to the development of catalytic coupling methods to increase the efficiency and selectivity in the construction of quinazolinone core structures.[9] Over the past few decades transition-metal-catalyzed direct coupling of aminobenzamides with carbonyl compounds have been successfully explored to synthesize quinazolinone derivatives.[10] Transition-metal-catalyzed three-component couplings of 2-aminobenzamides, aryl halides or equivalents, and isocyanides are important examples of catalytic synthesis of quinazolinones.[11]

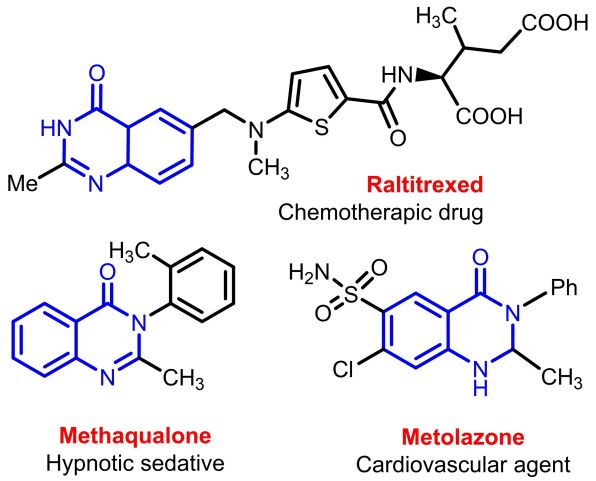

Figure 1. Selected examples of important quinazolinone containing pharmaceutical molecules.

Acceptorless dehydrogenative coupling (ADC) reactions[12,13] offer a direct approach for the synthesis of diverse heterocyclic compounds from relatively inexpensive and readily available starting materials.[14] The protocol is considered to be relatively more benign and atom economical synthetic route since the only by-products that are generated are hydrogen and water, which makes the strategy more environmentally benign. Moreover, considering alcohols as inexpensive and abundant starting materials, dehydrogenation of the alcohol followed by coupling with an appropriate partner to produce a variety of heterocycles is an extremely useful synthetic process.[15] This method is largely explored using transition metals like Fe,[16] Ni,[17] Co,[18] Ir,[19] Ag,[20] Rh,[21] Ru,[22] Os,[23] Pt,[24] Cu,[25] Mn[26] etc. We have found some recent literature, where the aforementioned strategy has been adopted for the synthesis of substituted quinazolinone derivatives.[27]

Zhou and Fang developed a $[Cp^*IrCl_2]_2$-catalyzed cyclization of primary alcohols with 2-aminobenzamides to quinazolinones (see Scheme 1).[28] In 2014 Siddiki *et al.* reported the synthesis of aryl quinazolinone via heterogenous platinum-catalyzed alcohol dehydrogenation followed by a condensation reaction with 2-aminobenzamide.[29] Srimani and coworkers used a Mn catalyst

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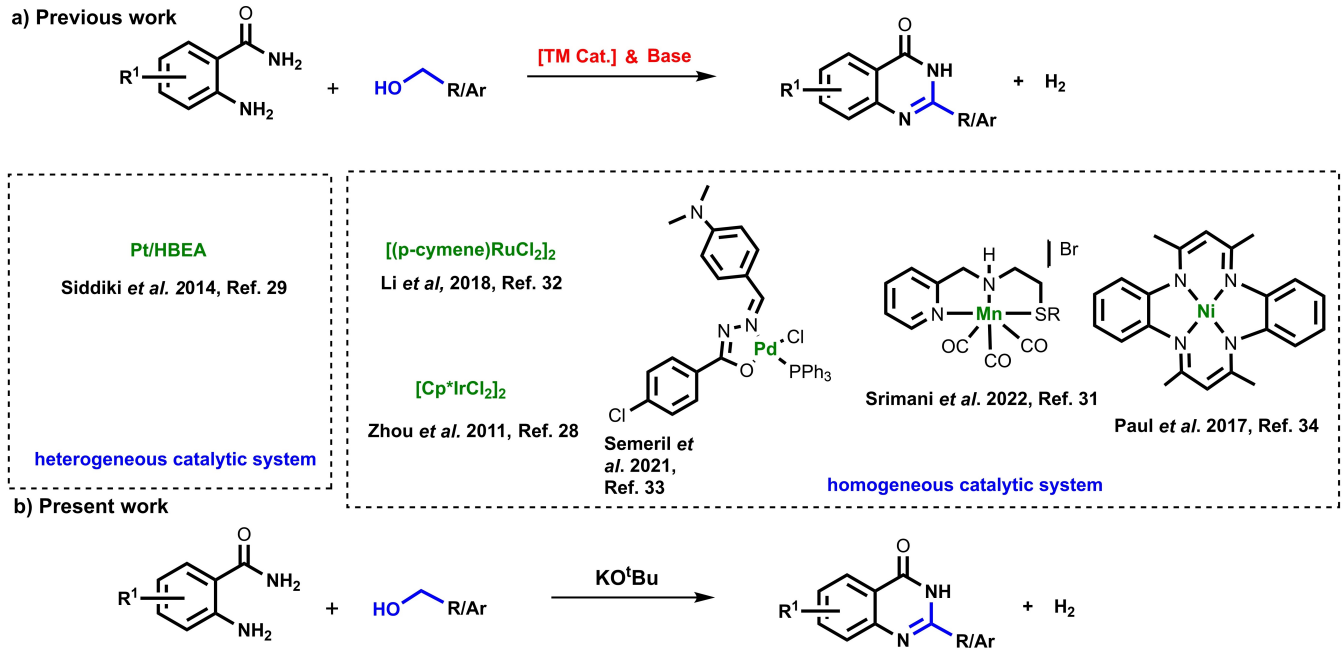

Scheme 1. Synthesis of quinazolinone using the alcohol dehydrogenation method using 2-amino benzamide.

for the synthesis.[30,31] Zang *et al.* used allylic alcohol for the construction of quinazoline via redox isomerization/acceptorless dehydrogenation.[32] Later, Semeril and coworkers reported a palladium-catalyzed synthesis for quinazolinone.[33] Similarly, Paul and his group used a nickel catalyst for the same synthesis.[34]

The use of transition metals in organic reactions has some serious limitations as heavy metals are environmentally toxic, expensive, and scarce in nature. Similarly, ligands are generally difficult to prepare, expensive, and hazardous to nature. Hence, to overcome these challenges, transition metal-free protocols are gaining tremendous importance. Transition metal-free, base-catalyzed alcohol dehydrogenation and subsequent transformations have attained popularity in recent times.[35,36] Inspired by these approaches, we decided to investigate the role of potassium tertiary butoxide in the mediated oxidation reaction,[37] and particularly, in the dehydrogenation of alcohol for the construction of the C–N bond. We previously reported a transition metal-free synthesis of quinazoline using 2-amino-benzyl alcohol and benzamide.[38] In continuation of our research on transition metal-free acceptorless dehydrogenative synthesis of heterocycles, we report the synthesis of 2-aryl quinazolinone using 2-amino benzamide and benzyl alcohol as coupling partners mediated by KO^{t}Bu. Density Functional Theory (DFT) calculations have been performed to gain better insights regarding the reaction mechanism and the particular role of the potassium ion.[39,40] This protocol provides an atom economical, ligand-free and transition metal-free route for the synthesis of 2-aryl quinazolinones.

Results and Discussion

The reaction protocol is simple and straightforward. A mixture of amino benzamide and benzyl alcohol in xylene was stirred at 130 °C in the presence of potassium tertiary butoxide for 24 h. Standard workup and purification by column chromatography afforded the product. We optimized the reaction condition using various solvents, bases, and temperatures for different time intervals (Table 1). For t-amyl alcohol at 130 °C for 16 h we obtained only 30% of the product (Table 1, entry 1). When we used toluene as a solvent, the product yield increased to 62% for the same time duration (Table 1, entry 2). For xylene the yield increased (Table 1, entry 5) and we obtained a maximum yield of 85% in 24 h (Table 1, entry 6).

However, in DMF and water, the reaction was failed to initiate(Table 1, entries 3 and 4). When the amount of KO^{t}Bu is reduced to half the reaction yields also reduced (Table 1, entry 7). Moreover, with decreasing the temperature the conversion was drastically affected (Table 1, entry 9) and at room temperature, the reaction was unable to proceed (Table 1, entry 8). The reaction progress was significantly reduced when KO^{t}Bu was replaced by a weaker base (Table 1, entries 12–14). With mild base e.g. cesium carbonate and potassium carbonate, the reaction did not proceed at all (Table 1, entries 12 and 13). Similarly, the organic base DABCO is also unable to carry out the reaction (Table 1, entry 15).

Several structurally varied substituted aryl and aliphatic alcohols underwent couplings with 2-amino benzamide to yield the corresponding quinazolinones as a product. The results are reported in Tables 2 and 3. Methyl substituted benzyl alcohol underwent the reaction smoothly (Table 2, entries 2 and 3). Similarly, halogen-functionalized alcohols also gave a moder-

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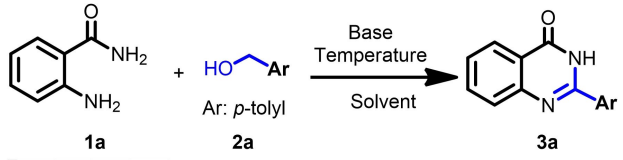
Table 1. Optimisation of reaction conditions.



1a 2a 3a

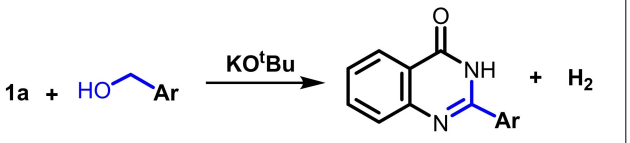
Entry	Solvent	Base	Temperature (°C)	Time (h)	Yield [b] (%)
1	t-amyl alcohol	^{t}BuOK	130	16	30
2	Toluene	^{t}BuOK	130	16	62
3	DMF	^{t}BuOK	130	16	No reaction
4	H_2O	^{t}BuOK	130	16	No reaction
5	Xylene	^{t}BuOK	130	16	75
6	**Xylene**	**^{t}BuOK**	**130**	**24**	**85**
7	Xylene	^{t}BuOK	130	24	55[c]
8	Xylene	^{t}BuOK	rt	24	No reaction
9	Xylene	^{t}BuOK	100	24	29
10	Xylene	KOH	130	24	34
11	Xylene	^{t}BuONa	130	24	<10
12	Xylene	Cs_2CO_3	130	24	<10
13	Xylene	K_2CO_3	130	24	No reaction
14	Xylene	NaOH	130	24	<10
15	Xylene	DABCO	130	24	No reaction

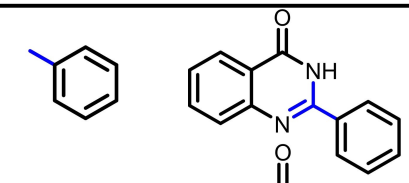
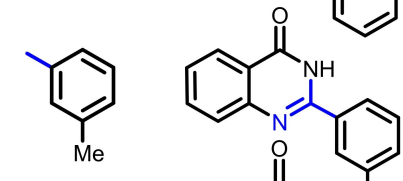
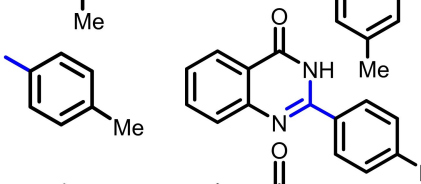
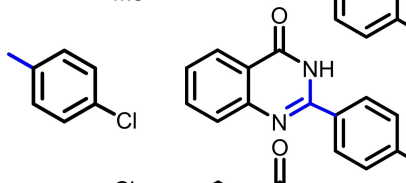
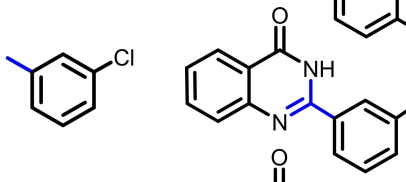
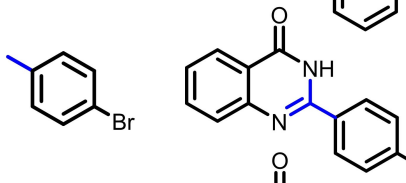
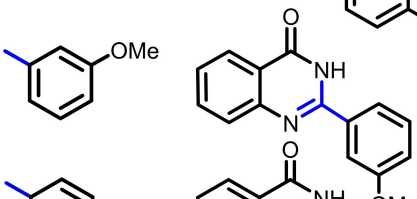
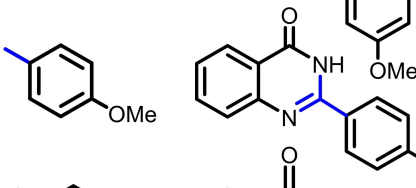
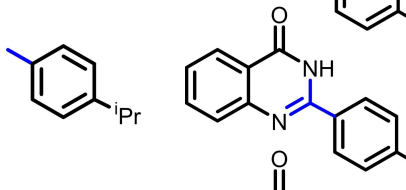
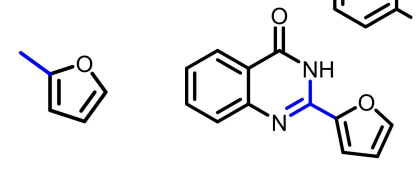
[a] 2-amino benzamide (0.5 mmol), and benzyl alcohol (0.75 mmol) stirred in the presence of a base (1 mmol) under an argon atmosphere using a preheated heating block for the required time. [b] Yields refer with ^{1}H NMR with respect to 1,4-dimethoxy benzene as internal standard. [c] 0.5 mmol KO^{t}Bu

ately good yield (Table 2, entries 4–6). Methoxy-substituted benzyl alcohol also gave good results for the reaction (Table 2, entries 7 and 8). Moreover, para-isopropyl benzyl alcohol also gave a good yield for the reaction (Table 2, entry 9). Surprisingly not only benzylic alcohol but furfural alcohol also gave good results (Table 2, entry 10). Notably, aliphatic alcohols (Table 3, entries 1–3) participate efficiently in this reaction to form 2-alkyl-quinazolinones.

Moreover, to check the gram scale utility of the present methodology, we carried out an experiment using 10 mmol starting benzamide and isolated the product in 65% yield (vs 80% for 0.5 mmol scale) (Scheme 2).

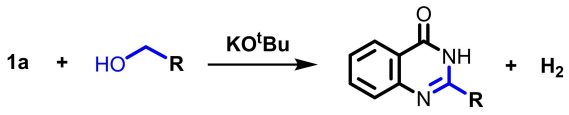
Table 2. Substrate scope for aromatic alcohols.[a]

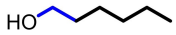
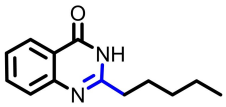
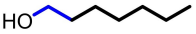
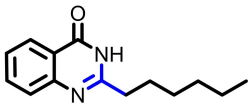
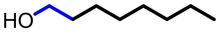
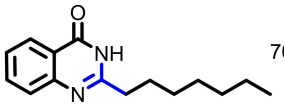
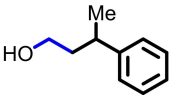
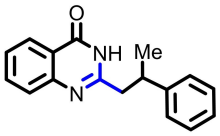


Entry	R_2	Product	Yield [b]
1			80 %
2			73 %
3			77 %
4			70 %
5			71 %
6			70 %
7			75 %
8			78 %
9			75 %
10			65 %

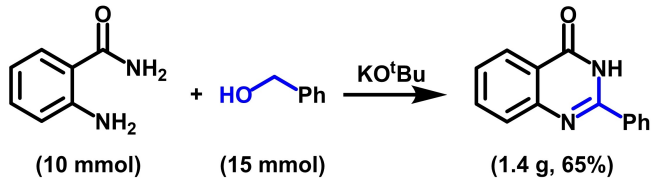
[a] 2-amino benzamide (0.5 mmol) and benzyl alcohol (0.75 mmol) stirred in the presence of KO^{t}Bu (1 mmol) in xylene at 130 °C under an argon atmosphere using a preheated heating block for 24 h. [b] isolated yield after column chromatography.

Table 3. Substrate scope for aliphatic alcohols.[a]



Entry	Alcohols	Product	Yield [b]
1			75 %
2			78%
3			70 %
4			70 %

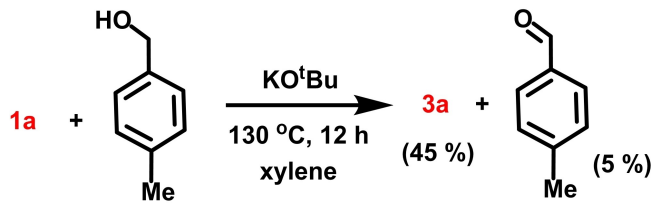
[a] 2-amino benzamide (0.5 mmol) and aliphatic alcohol (0.75 mmol) stirred in the presence of KO^{t}Bu (1 mmol) in xylene at 130 °C under an argon atmosphere using a preheated heating block for 24 h. [b] isolated yield after column chromatography.



Scheme 2. Gram scale synthesis.

After exploring the reactivity of various benzyl alcohols, we have studied the mechanism of the reaction. To identify the reaction mechanism and formation of the intermediate, we stopped the reaction after 12 h and carefully studied the crude ^{1}H NMR (Figure S1, ESI). It showed that benzaldehyde is the main reaction intermediate in the reaction (Scheme 3).

Alternatively, it was found that the reaction was completed within 12 hr while using benzaldehyde instead of benzyl alcohol as substrate. Indicating, the formation of aldehyde is a requisite step for the reaction (ESI, Table S1). Additionally, the evolved hydrogen gas has been qualitatively detected by Gas Chromatography (Figure S2, ESI).

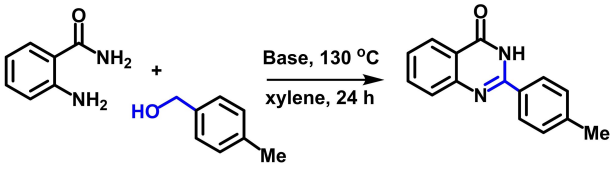


Scheme 3. Intermediate study.

Unexpectedly, it has been observed that NaO^{t}Bu was unable to form even the marginal yield of the product (Table 1, entry 11 and Table 4, entry 2) A similar trend was noted in the case of NaOH (Table 1, entry 14) in comparison to KOH (Table 1, entry 10). Therefore, to understand the role of potassium metal ions in the reaction, metal-ion trapping experiments with 18-crown-6 have been performed (Table 4, entry 3). In the presence of 18-crown-6, the progress of the reaction was hampered drastically which indicates the crucial role of potassium ions in the reaction mechanism.

For the sake of consistency, DFT calculations to unveil the reaction mechanism were performed (Figure 2). First, KO^{t}Bu oxidizes a molecule of benzyl alcohol.[41] This step initially involves the formation of complex **1** ($\Delta G = -12.0$ kcal/mol), followed by the benzaldehyde **2** formation at the kinetic cost of overcoming an activation energy barrier of 33.5 kcal/mol. At the same time, KO^{t}Bu can also act as a base and deprotonate an amino group of the *o*-aminobenzamide. Looking at the thermodynamics, the amide moiety protons result more acid with respect to amino ones ($\Delta G = -11.5$ kcal/mol for RC(=O)NH$_2$ proton vs $\Delta G = -5.5$ kcal/mol for Ar-NH$_2$ proton). Hence, once the amido group is deprotonated forming **3**, it reacts with the electrophilic carbon of benzaldehyde resulting in the formation of potassium 1-aminoalcoxide **5**, being 4.0 kcal/mol exergonic with respect to **1**. The formation of **5** is favoured by the potassium cation since it acts as a Lewis acid activating the benzaldehyde carboxylic oxygen in overall $\Delta G^{\neq} = 29.4$ kcal/mol. The resulting intermediate **8** is then deprotonated by KO^{t}Bu.[42] The deprotonation and the intermediate **4** and bringing the electrophilic carbon closer to the amide anion.

Table 4. Role of metal ion.[a]



Sl No.	Base/Additive	Conversion(%)[b]
1	KO^{t}Bu	85
2	NaO^{t}Bu	< 10
3	KO^{t}Bu,Crown ether[c]	< 5

[a] 2-amino benzamide (0.5 mmol) and benzyl alcohol (0.75 mmol) stirred in the presence of base (1 mmol) in xylene at 130 °C under an argon atmosphere using a preheated heating block for 24 h. [b] Calculated by ^{1}H NMR using 1,4-dimethoxy benzene as internal standard [c] Reaction in the presence of 18-crown-6 (2 mmol).

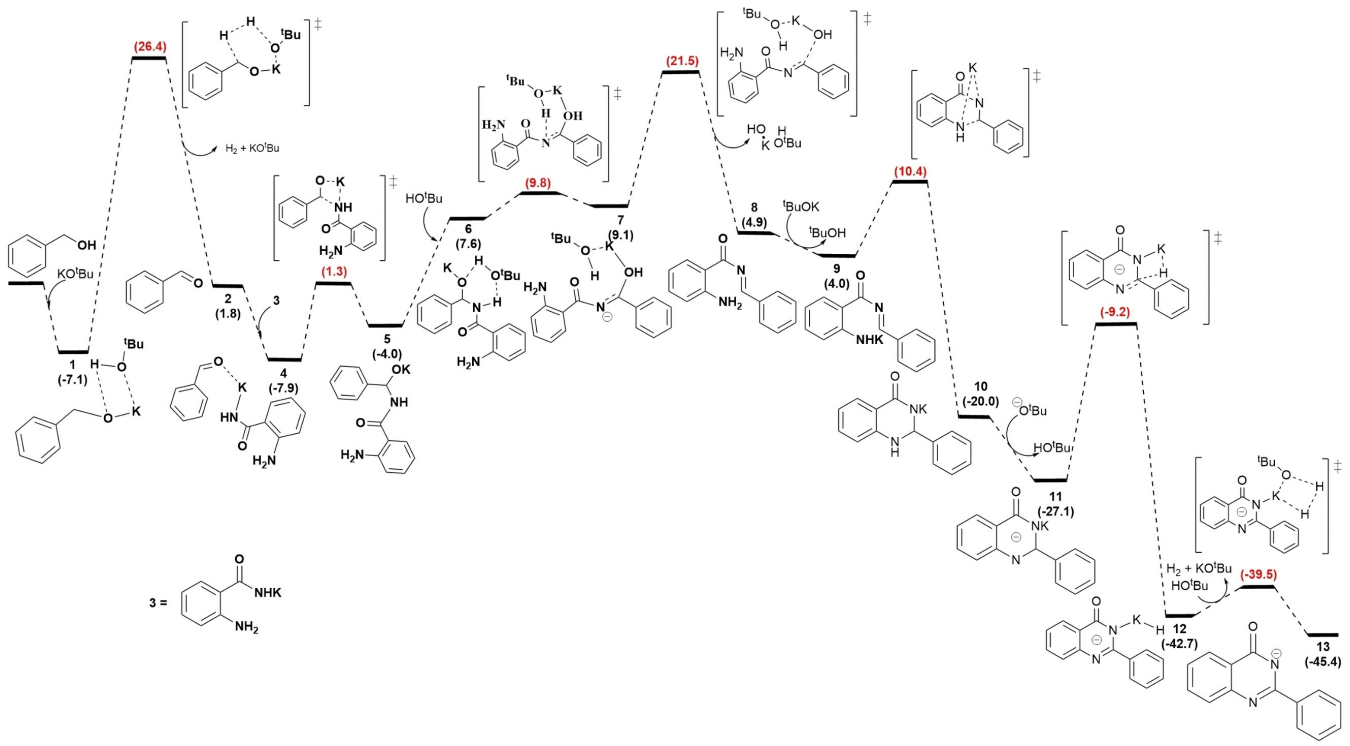


Figure 2. Reaction mechanism leading to quinazolinone starting from benzyl alcohol and 2-aminobenzamide via an alcohol dehydrogenation strategy promoted by potassium tertiary butoxide (relative Gibbs energies in kcal/mol) at the M06-D3/def2-TZVPP(smd)//BP86-D3/def2-SVP level of theory.

These two conditions also stabilize **TS 4→5** with a rather low energy barrier ($\Delta G^{\ddagger} = 9.2$ kcal/mol). Next, the formation of complex **6** by interactions of **5** with a ^{t}BuOH molecule favours the dehydration of **5** through an E1cb mechanism. Indeed, first a proton transfer from the nitrogen to alkoxide occurs through **TS 6→7** ($\Delta G^{\ddagger} = 2.2$ kcal/mol, thus 16.9 kcal/mol with respect to **1**) and, next intermediate **7** loses its alcohol moiety via **TS 7→8** with an following formation of **9** favours the nucleophilic attack of the amino group to imine ($\Delta G^{\ddagger}_{TS\ 9\rightarrow10} = 17.5$ kcal/mol) that leads to **10**, 20.0 kcal/mol below the initial reactants. From the latter intermediate, the reaction proceeds with the deprotonation of the amino functionality with the consequent formation of **11** with an energy release of 7.1 kcal/mol. At this point, a hydride can be easily abstracted by a potassium cation via **TS 11→12** ($\Delta G^{\ddagger} = 17.9$ kcal/mol) leading to the formation of intermediate **12**, with an exergonicity of 42.7 kcal/mol. Finally, the following addition of a ^{t}BuOH molecule to **12** leads to the formation of the quinazolinone anion **13** with an additional release of 2.7 kcal/mol via **TS 12→13** ($\Delta G^{\ddagger} = -3.2$ kcal/mol) and releasing into solution KO^{t}Bu and H_2. The calculations in Figure 2 help to understand why KO^{t}Bu is needed in stoichiometric amounts with respect to previous organocatalytic examples.[43] The desired product is then obtained by protonation of **13**. Overall, the rate-determining state (rds) corresponds to **TS 1→2**, *i.e.* to the hydrogen release. To see if there could be an additional predictive effort,[38,39] and above all, also to validate the nature of the rds, the alcohol was taken from Entry 10 of Table 2, which shows the worst yield, with a value of 65%. The kinetic cost reaches a value of 35.4 kcal/mol, therefore, significantly higher, specifically by 1.9 kcal/mol, than for benzyl alcohol, which reached an 80% yield.

Conclusions

In conclusion, we have carried out a potassium tertiary butoxide mediated synthesis of substituted quinazolinones *via* an alcohol dehydrogenation strategy. In addition to operational simplicity and excellent regio-selectivity, this methodology provides general applicability to the synthesis of a wide range of 2-substituted quinazolinones derivatives (including alkyl, aryl, and heterocyclic), with moderate to good yields. The role of K^{+} ions was established by trapping them with 18-crown-6-ether. DFT calculations allow us to disclose the mechanism and highlight the rate-determining step. Undoubtedly, the present protocol would represent an important addition to the existing methods for quinazolinone synthesis. To the best of our knowledge, we are not aware of any report for quinazolinone synthesis starting from benzyl alcohol and 2-amino benzamides as substrates without using a transition metal catalyst.

Experimental Section

Under an argon atmosphere, amine (0.5 mmol), alcohol (0.75 mmol), and 1 mmol of KO^{t}Bu were introduced into a reaction vessel previously dried in an oven and equipped with a magnetic stir bar. Subsequently, 2.0 mL of toluene was added to the mixture, and the reaction blend was stirred for 24 hours in a preheated

heating block set at 130 °C. Upon completion of the reaction, the reaction vessel was cooled to room temperature, and 5 mL of ethyl acetate was used for dilution. The resulting mixture underwent filtration with celite. Volatile impurities were eliminated under vacuum using a rotary vacuum evaporator, and the product underwent further purification through column chromatography with silica gel as the stationary phase and a hexane/ethyl acetate mixture as the eluent. The compounds were characterized through ^{1}H and ^{13}C NMR spectroscopy.

We employed the Gaussian16 program[44] to perform static calculations based on DFT. The BP86 functional, developed by Becke and Perdew,[45] was utilized along with corrections for dispersion using Grimme's method (GD3 keyword in Gaussian16).[46] The electronic configurations of the molecular systems were described using the double-ζ basis set with Ahlrichs' polarization scheme for main-group atoms (def2-SVP keyword in Gaussian).[47] Geometry optimizations were carried out without imposing symmetry constraints, and the identified stationary points were confirmed through analytical frequency calculations. Calculated frequencies were utilized to account for the zero-point energies (ZPEs). Additionally, single-point calculations were conducted at 130 °C using the M06-D3 functional[48] and the triple-ζ basis set def2-TZVPP. To incorporate solvent effects, we estimated the impact of amyl alcohol using the universal solvation model SMD developed by Cramer and Truhlar.[49] The reported Gibbs energies in our study encompass electronic energies obtained at the M06-D3/def2-TZVPP(smd)//BP86-D3/def2-SVP level of theory. These energies were corrected with zero-point energies, thermal corrections, and entropy effects computed at the BP86-D3/def2-SVP level.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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