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Metal-Free Oxidative Cyclization of 2-Amino- benzamides, 2-Aminobenzenesulfonamide or 2-(aminomethyl)anilines with Primary Alcohols for the Synthesis of Quinazolinones and their Analogues

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ABSTRACT

A general metal-free oxidative cyclization process has been developed for the synthesis of quinazolinones, benzothiadiazines and quinazolines. By this protocol, a range of substituted 2-aminobenzamides, 2-aminobenzenesulfonamide and 2-(aminomethyl)anilines react with various alcohols, leading to the desired annulated products smoothly. This protocol features many advantages as broad substrate scope, mild reaction conditions, low environmental pollution, high atom-economy and good to excellent yields.

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Introduction

Among numerous bioactive *N*-heterocycles[1-7], quinazolinones are useful compounds which have a broad range of pharmacological activities[8-9] in many hypolipidemic[10], anti-inflammatory[11], anti-convulsant[12], antiulcer[13], anti-cancer[14] and anti-tuberculosis[15] drugs. Because of their important applications, many synthetic efforts have been made for quinazolinone and its derivatives[16-19]. For examples, Tang[20], Long[21] and Wang[22] have used oxidative annulation strategies of arylamidines to access quinazolines. Despite these contributions, many of them require special prefunctionalized reagents which increases preparative difficulties.

The condensation reaction of 2-aminobenzamide is one of the most popular methods for the approach of quinazolinones[23-46]. Bharate[39], Yin[40] and Li[42] have developed similar strategies for quinazolinones *via* oxidative amination of unactivated sp^3 carbons. Zhou's group developed a way through selective C−C bond cleavage to synthesize quinazolinones[40].

Recently, the direct oxidative cyclization of primary alcohol with 2-aminobenzamide for the formation of *N*-heterocyclic rings has attracted much attention. Many oxidative coupling approaches have been reported using metal catalysts including iridium[28], platinum[41], iron[42], zinc[34], manganese[47] and palladium [29, 48]. Besides, iodine/DMSO promoted oxidative cyclization for the synthesis of quinazolinones using alcohol as reactant has also been achieved[33], although the scope of alcohol was respectively limited (**Figure 1**).

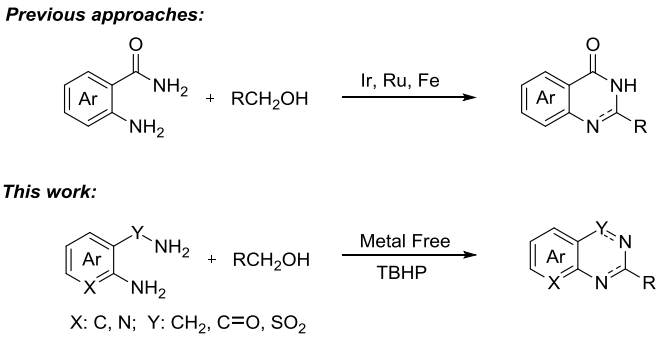


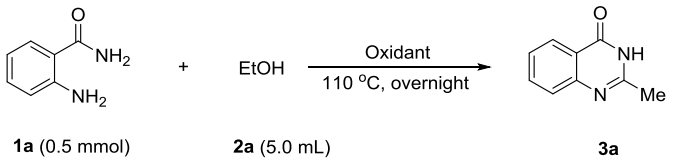
Figure 1. Synthesis of quinazolinones approach.

Based on our interest in selective sp^3 C−H bond functionalization[49, 50] and recent findings, we herein report a general metal-free methodology for the preparation of quinazolinone derivatives using 2-aminobenzamides and various primary alcohols.

Results and discussion

Our study began with a model reaction of 2-aminobenzamide and ethanol in the presence of oxidants (Table 1). The heating of 1, 4-benzoquinone and 2-aminobenzamide under ethanol solvent at 110 ℃ for 12 h, trace product was observed (entry 1). Other oxidants such as DDQ and $K_2S_2O_8$ afforded trace amount of product quinazolinone **3a** (entry 2-3). Peroxide including DCP and TBP lead to **3a** generation in moderate yields (entry 4-5). To our great delight, **3a** was obtained in high yield with TBHP as oxidant (89%, entry 7).

Table 1. Optimization of the reaction conditions.



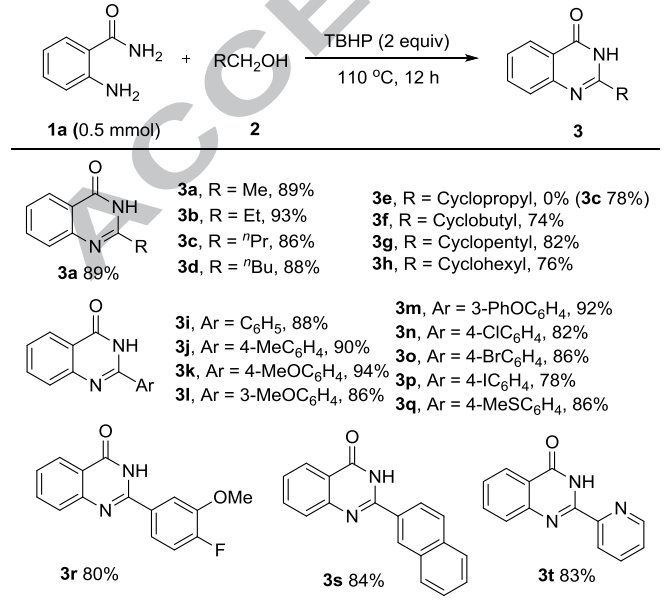
1a (0.5 mmol) **2a** (5.0 mL) **3a**

Entry	Oxidant (2 equiv)	yield (%)
1	BQ	trace
2	DDQ	trace
3	$K_2S_2O_8$	3
4	DCP	50
5	TBP	68
6	DTBP	18
7	TBHP	89

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-Benzoquinone. BQ: 1,4-Benzoquinone, DCP: Dicumyl peroxide, DTBP: Di-*tert*-butyl peroxide, TBP: *tert*-Butyl peroxybenzoate. TBHP: *tert*-Butyl hydroperoxide.

With the optimized conditions in hand, the scope of alcohol was investigated under this oxidative amination reaction and the results were present in Table 2. Both alkyl- and aryl- primary alcohols could be used to react with 2-aminobenzamide and gave the corresponding quinazolinone derivatives in good yields. The reaction of 2-aminobenzamide with methanol could not proceed under the reaction conditions. It was presumably due to that formaldehyde derived from methanol was difficult to react with 2-aminobenzamide under the optimal conditions.

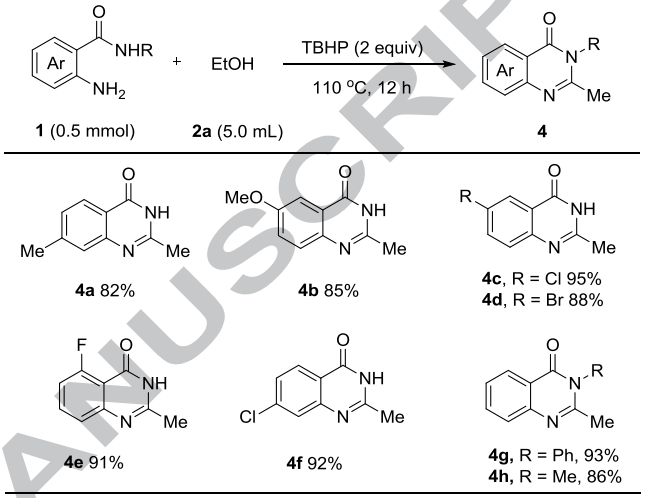
Table 2. Scope of primary alcohol[a]



[a]The reaction using 5 mL alcohol for **3a**-**3h** synthesis and the reaction with 5 mL DMSO as solvent for **3i**-**3t** synthesis.

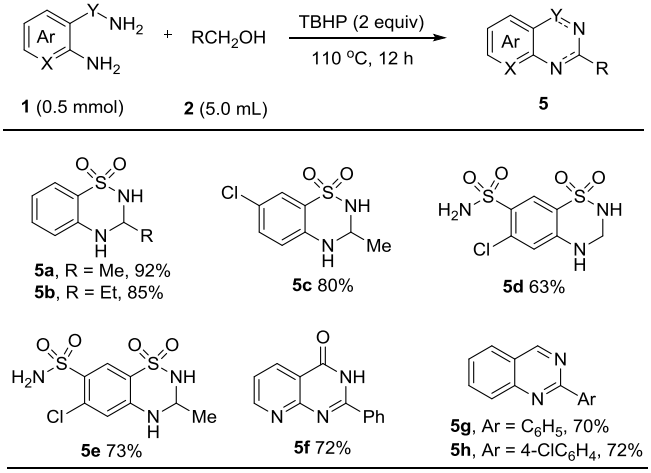
Various alkyl-substituted derived alcohols all gave the products in satisfied yields (**3a**-**3d**). Interestingly, when cyclopropylmethanol was used as the reactant, the desired product **3e** was not observed, and an oxidative ring-opening product formation was isolated in 78% yield. Other cyclic alkyl-group contained alcohols gave desired product successfully (**3f**-**3h**). Aryl- group contained alcohols all gave desired products in high yields (**3i**-**3s**). Pyridin-2-ylmethanol could be used as well giving **3t** in 83% yield.

Table 3. Scope of 2-aminobenzamide derivatives



To explore the generality of this protocol, different aminobenzamide derivatives were tested and the results were summarized in Table 3. Alkyl-substituted and halogenated aminobenzamide gave corresponding quinazolinones in good yields (**4a**-**4f**). Secondary amides also could furnish the desired products in high yields (**4g** and **4h**).

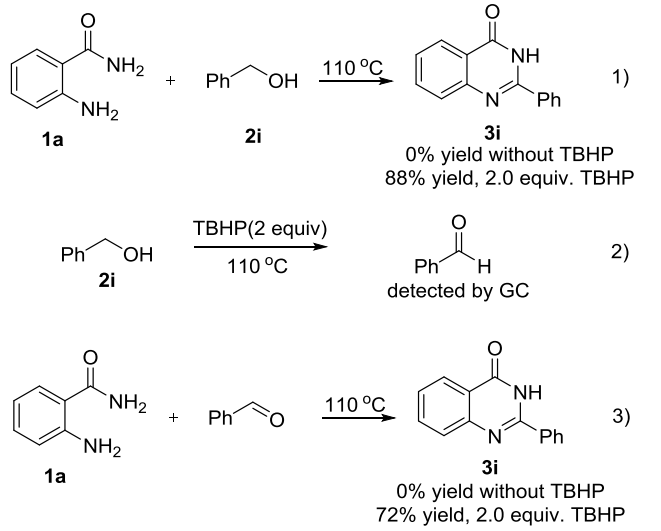
Table 4. Synthesis of benzothiadiazines and quinazolines



[a]The reaction using 5 mL alcohol for **5a**-**5e** synthesis and the reaction with 5 mL DMSO as solvent for **5f**-**5h** synthesis.

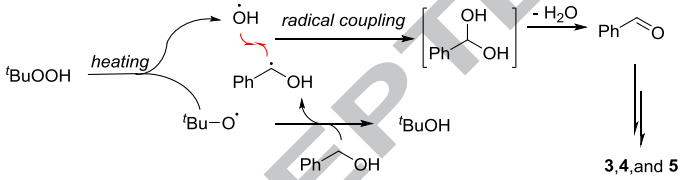
Benzothiadiazine and quinazoline derivatives were prepared by the condensation of *o*-amino-benzenesulfonamide and aldehydes promoted by stoichiometry amount of acids.[51-54] Yokoyama developed a palladium-catalyzed oxidative amination process for the synthesis of benzothiadiazines with primary alcohols and amides[48]. Under our metal-free approach, various of thiadiazines (**5a**-**5e**) were obtained in good yields. Notably, 7-Chloro-3-methyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (IDRA-21) **5c** as a modulator of AMPA receptor

desensitization[55-58] was isolated in 80% yield under our reaction conditions. **5d** as a high blood pressure regulator which is commercially available by Merck was obtained in 63% yield using of methanol as solvent[59]. Quinazoline compounds such as **5g** and **5h** were successfully obtained under the reaction conditions (Table 4).



Scheme 1. Control experiments

To understand the reaction pathway, the listed control experiments were tested (Scheme 1). No reactions were observed when the reaction of phenylmethanol and 2-aminobenzamide under the oxidant free conditions. The treatment of the benzyl alcohol under 110 °C for overnight led to benzaldehyde formation. The replacement of phenylmethanol by benzaldehyde under above oxidant free conditions also led to **3i** formation unsuccessfully.



Scheme 2. Proposal mechanism for the oxidative process

Based on the above control experiments, the reaction mechanism of this metal free oxidative process was proposed in Scheme 2. The heating of tert-butyl hydroperoxide resulted in the formation of hydroxyl radicals and tert-butanol radicals. Hydrogen atom transfer between tert-butanol radical and phenylmethanol gave α-hydroxyl- carbon radical, then the radical cross coupling of hydroxyl radical and carbon radical gave an unstable phenylmethanediol intermediate then gave the benzaldehyde by an elimination reaction of water, which underwent the unknown reaction pathway leading to the quinazolinones, benzothiadiazines and quinazolines formation.

Conclusion

In summary, we have developed a metal-free oxidative amination protocol for N-heterocycles synthesis providing a feasible access to bioactive quinazolinones, quinazolines and benzothiadiazine derivatives. Good functional group compatibility, metal free conditions and various primary alcohols all tolerant enable the present method to be great valuable in organic synthesis.

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