Tetrahedron Letters 59 (2018) 2099–2102

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Jinwei Sun [a,*], Tao Tao [a], Dan Xu [a], Hui Cao [a], Qinggang Kong [a], Xinyu Wang [a], Yun Liu [b], Jianglin Zhao [c,*], Yi Wang [d,*], Yi Pan [d]

[a] Jiangsu Collaborative Innovation Center of Atmospheric Environment and Equipment Technology, Jiangsu Key Laboratory of Atmospheric Environment Monitoring and Pollution Control, School of Environmental Science and Engineering, Nanjing University of Information Science & Technology, Nanjing 210044, PR China
[b] School of Chemistry & Chemical Engineering, Jiangsu Normal University, Xuzhou 221116, Jiangsu, PR China
[c] Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, 1068 Xueyuan Avenue, Shenzhen 518055, PR China
[d] School of Chemistry & Chemical Engineering, Nanjing University, Nanjing 210023, PR China

ARTICLE INFO

Article history:
Received 24 December 2017
Revised 19 April 2018
Accepted 21 April 2018
Available online 22 April 2018

Keywords:
Metal-free
Cyclization
Oxidation
Primary alcohols

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.

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.[23,8,24–45] Bharate[38], Yin[39] and Li[41] 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.[39]

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[27], platinum[40], iron[41], zinc[33], manganese[46] and palladium.[28,47] Besides, iodine/DMSO promoted oxidative cyclization for the synthesis of quinazolinones using alcohol as reactant has also been achieved[32], although the scope of alcohol was respectively limited (Fig. 1).

Based on our interest in selective sp^3 C—H bond functionalization[48,49] 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 °C 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

* Corresponding authors.
E-mail addresses: gysunjinwei@126.com (J. Sun), zhaojianglin1314@163.com (J. Zhao), yiwang@nju.edu.cn (Y. Wang).

https://doi.org/10.1016/j.tetlet.2018.04.054
0040-4039/

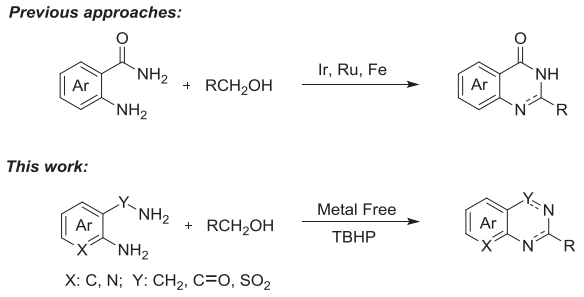
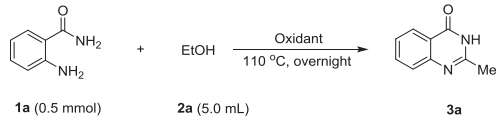


Fig. 1. Synthesis of quinazolinones approach.

Table 1
Optimization of the reaction conditions.



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.

delight, **3a** was obtained in high yield with TBHP as oxidant (89%, entry 7).

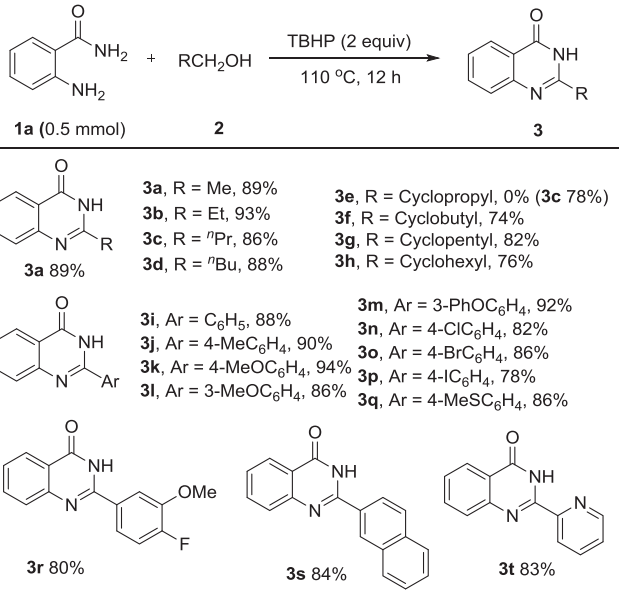
With the optimized conditions in hand, the scope of alcohol was investigated under this oxidative amination reaction and the results were present in Table 2. Both alkyl- and aryl-primary alcohols could be used to react with 2-aminobenzamide and gave the corresponding quinazolinone derivatives in good 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.

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.

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**).

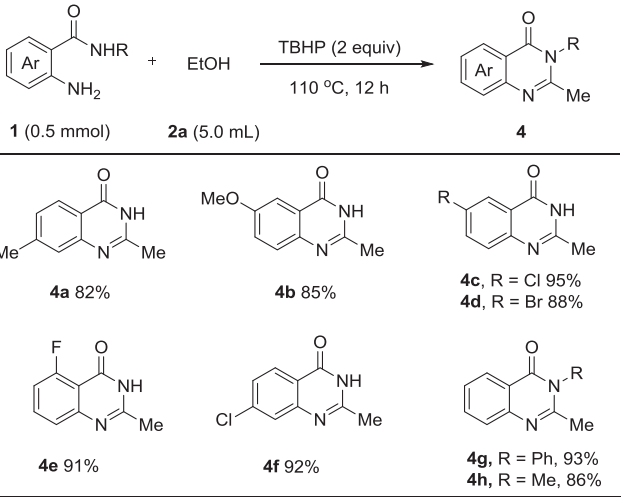
Benzothiadiazine and quinazoline derivatives were prepared by the condensation of *o*-amino-benzenesulfonamide and aldehydes promoted by stoichiometry amount of acids.[50–53] Yokoyama developed a palladium-catalyzed oxidative amination process for the synthesis of benzothiadiazines with primary alcohols and amides.[47] Under our metal-free approach, various of thiadiazines

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.

Table 3
Scope of 2-aminobenzamide derivatives.



(**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[54–57] was isolated in 80% yield under our reaction conditions. 5**d** as a high blood pressure regulator which is commercially available by Merck was obtained in 63% yield using of methanol as solvent.[58] Quinazoline compounds such as **5g** and **5h** were successfully obtained under the reaction conditions (Table 4).

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.

Based on the above control experiments, the reaction mechanism of this metal free oxidative process was proposed in