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Green Synthesis of 2-Benzoyl-4-quinazolinones

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A catalyst-free synthesis of 2-benzoyl-4-quinazolinones is described here. Anthranilamides and α-haloacetophenones were used as the starting reagents. The effects of molar ratio of reactants, catalyst, solvent, base, temperature and time on the reaction were investigated and then the optimal reaction conditions were achieved. All of the substrates examined under the optimized conditions gave high yields. Compared to traditional synthesis method of 2-benzoyl-4-quinazolinones, this method has several advantages, such as no catalyst, cost saving and environmentally benign process.

Keywords: Catalyst-free, 2-Benzoyl-4-quinazolinones, Anthranilamides, α-Haloacetophenones.

INTRODUCTION

Quinazolinones is a kind of important nitrogen-containing heterocycle. They exist as alkaloids extensively in natural products[1]. It is known that the folium isatidis or the saxifrage plants also have similar core structure. Natural quinazolinone alkaloids have about 150 species, such as chrysogine[2], luotonin A[3] and tryptanthrin[4].

In addition, quinazolinones compounds have shown good activity in antibacterial[5], anti-inflammatory[6], anti-hypertensive[7], anti-cancer[8] and other aspects. They can reduce the peripheral vascular resistance. They can also decrease systolic and diastolic blood pressure. Recently, they have been rated as antagonist of many biological receptor. Such as the receptor of 5-HT5A[9] which associated with diseases and the receptor of antidiuretic hormone V3[10]. Besides the biological activities and the pharmacological activities, quinazolinones have also shown the good activities in pesticides[11,12].

Because of its important bioactivity and medicinal value, study of quinazolinones become a hot research field in recent years. According to the reported synthetic routes, quinazolinones are typically synthesized from four substrates, that is, *o*-nitrophenyl carboxamides[13-15], *o*-amino-benzamides[16-18], isatoic anhydrides[19-21] and *o*-halobenzoic acid[22-24].

As our on-going research on synthesis of heterocycles[25-28], we use anthranil amides and α-haloacetophenones as raw material to synthesize 2-benzoyl-4-quinazolinones.

EXPERIMENTAL

The chemicals and reagents were purchased from Aldrich, Acros, Alfa Aesar, Aladdin, or Kelong Chemicals Company and used without further purification.

General procedure: An oven-dried test tube with a stir bar was charged with anthranil amides (1 mmol), α-haloacetophenones (1 mmol) and $NaHCO_3$ (1 mmol). And then DMSO (5 mL) was added by a syringe. The tube was put into an oil bath preheated at 120 °C and the mixture was kept stirring at that temperature for 24 h. The reaction mixture was then cooled to room temperature, quenched with water and extracted with ethyl acetate (20 mL) for three times. The combined organic-layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography with a solution of petroleum ether and ethyl acetate (volume ratio from 1/5 to 2/1) to afford 2-benzoyl-4-quinazolinones.

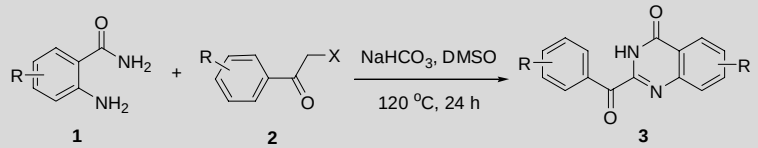
Detection method: The purities of all the synthesized compounds were checked by thin-layer chromatography (TLC) using suitable organic solvents. The IR spectra were recorded on a Bruker Tensor-27 FT-IR spectrophotometer in KBr discs. ^{1}H NMR spectra were recorded on a Bruker advance 300 MHz NMR or 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 containing tetramethylsilane (TMS) as an internal standard. Melting points were determined on an X-4 melting-point apparatus with microscope and are uncorrected.

RESULTS AND DISCUSSION

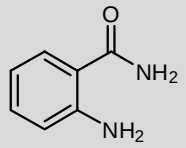
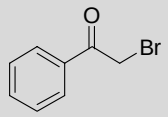
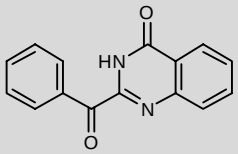
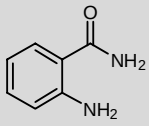
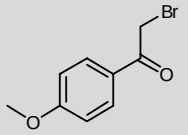
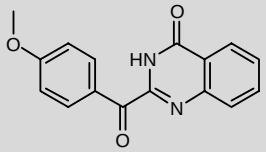
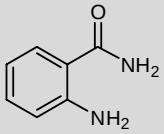
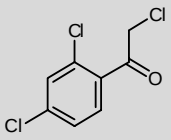
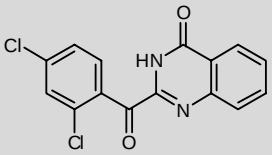
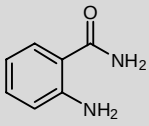
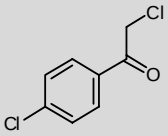
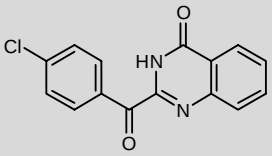
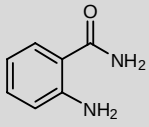
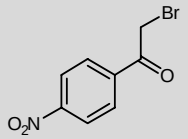
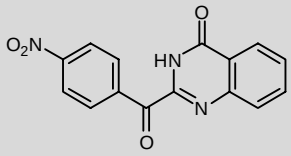
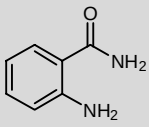
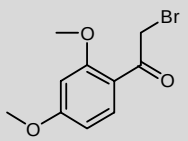
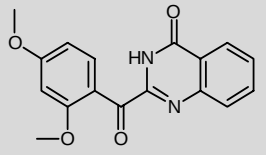
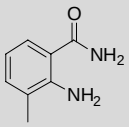
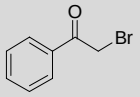
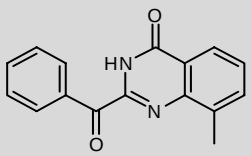
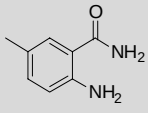
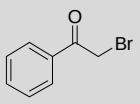
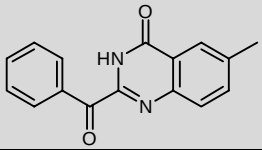
Firstly, we took anthranilamide and α-bromoacetophenone as the model substrates of synthesis of 2-benzoyl-4-quinazolinones to optimize the reaction conditions. After examining a series of molar ratio of reactants, catalyst, solvent, base, temperature and time. Finally, we achieved the optimized reaction conditions: catalyst-free, $NaHCO_3$ (1 equivalent), anthranilamide (1 mmol), α-bromoacetophenone (1 mmol) in DMSO (5 mL) at 120 °C for 24 h.

With the optimized conditions at hand, the reaction of various α-haloacetophenones and anthranilamides were investigated (Table-1 entry 1-6). The experimental results show that the reaction has a wide scope of the substrates. Most of the reactants afforded the corresponding desired products with high yields. The yield of other α-haloacetophenones have slightly lower than that of α-bromoacetophenones (entry 1-6). The α-haloacetophenones containing of electron-donating groups have higher yields than electron-withdrawing groups (entries 2,5,6).

TABLE-1
CATALYST-FREEREACTION OF ANTHRANILAMIDE AND α-HALOACETOPHENONES[a]



1 2 3

Entry	Anthranilamide	α-Haloacetophenone	2-Benzoyl-4-quinazolinones	Yield (%)
1				85.0
2				76.8
3				79.3
4				79.7
5				61.8
6				80.5
7				75.6
8				78.1

[a]Reaction conditions:anthranilamide (1 mmol), α-Haloacetophenone (1 mmol), $NaHCO_3$ (1 mmol), DMSO (5 mL), 120 °C, 24 h, air

In addition, under the optimized conditions, we also took α-bromoacetophenone to react with several anthranilamides to examine the scope of the reaction (Table-1, entries 1,7,8). The experimental results demonstrate substituted anthranilamides also achieved fairly good yields (entries 7,8).

A proposed mechanism is shown in Fig. 1. As a start, a nucleophilic substitution happens between anthranilamide and α-bromoacetophenone. Weak alkaline condition is good to promote this nucleophilic substitution. Then it is oxidized to generate an α-benzoylimine. The electronegativity of carbon is smaller than that of nitrogen of α-benzoylimine, it will be susceptible to be attacked by nitrogen of amide. And thus an intramolecular nucleophilic addition happens, which generates an intermediate of six-membered ring. This intermediate is oxidized by air to give the final product 2-benzoyl-4-quinazolinone.

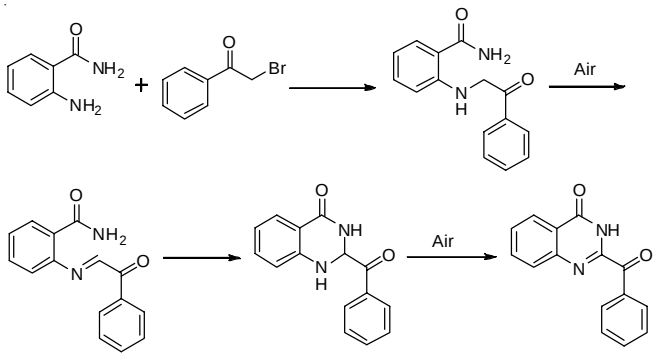


Fig. 1. A plausible mechanism for the reaction of anthranilamide and α-bromoacetophenone

Conclusion

The catalyst-free synthesis of 2-benzoyl-4-quinazolinones *via* the reaction of anthranilamides and α-haloacetophenones is feasible. All of the substrates gave good yields and under the optimized reaction conditions. The synthetic method of 2-benzoyl-4-quinazolinone compounds needs no catalyst and only needs one equivalent weak base, so this new process is greener, simple and practical.

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