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# Facile and efficient synthesis of quinazoline-2,4(1*H*,3*H*)-diones through sequential hydrogenation condensation

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#### ABSTRACT

The heterocyclizations from various methyl (2-nitrobenzoyl) carbamates to substituted quinazoline-2,4(1*H*,3*H*)-diones under hydrogenation conditions were investigated in this study. In the presence of *p*-toluenesulfonic acid monohydrate in methanol, various quinazoline-2,4(1*H*, 3*H*)-diones were obtained in good to excellent yields within 12 h. The reaction was proposed to proceed through the cascade reactions of nitro reduction and condensation.

#### **GRAPHICAL ABSTRACT**



#### ARTICLE HISTORY

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#### **KEYWORDS**

Cascade reaction; heterocyclization; hydrogenation condensation; quinazoline-2,4(1*H*,3*H*)-dione

#### Introduction

Heterocycles are of special interest and significant importance in the search for new biologically active scaffolds in the pharmaceutical industries. Among different types of the nitrogen containing heterocycles, quinazolinones and quinazolinediones have attracted great attention due to their diverse pharmacological activities, such as anticancer, anticonvulsive, anti-inflammatory, and antihypertensive activities, etc.<sup>[1-7]</sup> Owing to the widespread applications of the quinazolinedione skeleton, substantial efforts have been made to the chemical derivatization on the scaffold. Thus, various synthetic methods have been developed to construct substituted quinazolinediones, with the most common method as the heterocyclization of 2-aminobenzoic acid with urea above 150 °C (method A, Scheme 1)<sup>[8]</sup> or metal-catalyzed condensation (methods B–E, Scheme 1),<sup>[9–12]</sup> and several other conditions (methods F–H, Scheme 1).<sup>[13–15]</sup> Among these methods, it is obviously that the introduction of 2-position carbonyl group was crucial to the

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<sup>()</sup> Supplemental data (full experimental detail, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HR-MS spectra) can be accessed on the publisher's website.

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**Scheme 1.** Representative strategies for the construction of quinazolinediones. *Note*: DMF, dimethylformamide; THF, tetrahydrofuran.

construction of quinazolinedione with the key precursor reagents such as urea, DMF, CO, and KOCN (Scheme 1).

Although above synthesis methods are very useful, many of them have drawbacks such as involving harsh reaction condition, long reaction time, use of toxic and expensive chemicals and low reaction yields. Herein, we wish to design a facile and efficient protocol for the preparation of quinazoline-2,4(1H,3H)-diones through sequential hydrogenation condensation under mild reaction conditions with a novel and simple method for the introduction of 2-position carbonyl group. To our knowledge, this is the first time that methyl (2-nitrobenzoyl)carbamates are used as the starting materials to construct quinazolinediones under hydrogenation/condensation conditions.

#### **Results and discussion**

Initially, ethyl (2-nitrobenzoyl)carbamate (**A**) as an important substrate was conveniently synthesized from 2-nitrobenzamide by the use of oxalyl chloride and  $C_2H_5OH$ , in which the 2-position carbonyl was formed in advance. Then, Pd/C hydrogenation was proceeded to reduce the nitro group. Finally, after 3 h hydrogenation at room temperature, removal of Pd/C and evaporation of the solvent at 30 °C, we found that a mixture of nitro reduction product (**B**) and trace quinazolinedione (**1a**) was formed according to the <sup>1</sup>H NMR spectra (Scheme 2). Interestingly, when a drop of DCl was added to the mixture of **1a** and **B** in the NMR tube and laid overnight, the compound **B** could completely convert to the target



Scheme 2. Exploration of the synthesis of quinazolinedione 1a.

compound **1a**. This result indicated that the acid could promote the cyclization process. It is anticipated that quinazolinedione **1a** could be directly prepared with a combination of Pd/C and acid through hydrogenation from substrate A. Herein we report the development of heterocyclization toward quinazolinediones through a cascade of nitro reduction and condensation.

First, we screened the leaving group OR, solvent and acid that might affect the heterocyclization (Table 1). The results displayed that the leaving group (OR) was crucial for the reaction due to the steric hindrance effect. The use of methoxy group resulted in a much higher yield (entry 1) compared to the ethoxy or phenoxy group (entries 2, 3), but *tert*-butoxy group did not proceed cyclization (entry 4). When  $PTSA \cdot H_2O$  was used as the catalyst, the reaction yields were increased from 61.8 to 82.4% (OR=OC<sub>2</sub>H<sub>5</sub>, entry 2 vs entry 6), and 60.1 to 76.7% (OR=OPh, entry 3 vs entry 7), respectively. The results revealed that PTSA · H<sub>2</sub>O could be favorable to the cyclization reaction. However, for the bulky tert-butoxy group, the heterocyclization still did not occur even in the presence of PTSA  $\cdot$  H<sub>2</sub>O (entry 8). Second, with optimized leaving group OCH<sub>3</sub> and PTSA  $\cdot$  H<sub>2</sub>O in

		R Pd/C, H <sub>2</sub>	0 NH NH H 1a	NH <sub>2</sub>	
				Yield	(%)
Entry	R	Acid <sup>b</sup>	Solvent	1a	С
1	CH₃	-	CH₃OH	87.0	-
2	CH <sub>2</sub> CH <sub>3</sub>	-	CH₃OH	61.8	_
3	Ph	-	CH₃OH	60.1 <sup>c</sup>	_
4	CH(CH <sub>3</sub> ) <sub>3</sub>	-	CH₃OH	-	90.4
5	CH <sub>3</sub>	PTSA · H₂O	CH₃OH	88.1	_
6	CH <sub>2</sub> CH <sub>3</sub>	$PTSA \cdot H_2O$	CH₃OH	82.4	_
7	Ph	$PTSA \cdot H_2O$	CH₃OH	76.7 <sup>c</sup>	-
8	CH(CH <sub>3</sub> ) <sub>3</sub>	$PTSA \cdot H_2O$	CH <sub>3</sub> OH	-	88.7
9	CH₃	$PTSA \cdot H_2O$	C₂H <sub>5</sub> OH	83.3	-

0

Table 1.	Optimization	of reaction	conditions. <sup>a</sup>

<sup>a</sup>Reaction was run at room temperature with  $H_2$  balloon for 3 h, evaporation of the solvent at 45 °C after removal of Pd/C. The concentrate was washed with water to afford the product.

THF

DME

\_

NR<sup>d</sup>

NR

PTSA · H<sub>2</sub>O

PTSA · H<sub>2</sub>O

<sup>b</sup>Using 5% of PTSA  $\cdot$  H<sub>2</sub>O.

 $CH_3$ 

CH<sub>3</sub>

<sup>c1</sup>H NMR yield.

10

11

<sup>d</sup>No reaction.

DME, dimethylether; PTSA, p-toluenesulfonic acid; THF, tetrahydrofuran.

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hand, the solvents were screened. We found that the use of  $C_2H_5OH$  resulted in a slight lower yield than  $CH_3OH$  (entry 9 vs entry 5), but no reaction in tetrahydrofuran (THF) and dimethylether (DME) (entries 10, 11). The possible reason was that the hydrogenation reaction was prone to occur in alcoholic solvents and  $CH_3OH$  was proved to be the best solvent for this tandem reaction.

Encouraged by this promising result, the scope of the method for substituted quinazoline-2,4(1H,3H)-diones was then investigated. To our delight, various substrates 2 could smoothly undergo heterocyclization to afford substituted quinazolinediones 1 in good to excellent yields. It was noticed that the substrates containing electron-donating groups or halogen substituents generally gave higher yields (1a-j in Table 2) under the optimal reaction conditions, while the substrates containing electron-deficient group like trifluoromethyl gave very low yield (1k, entry 11). The disubstituted electron-donating substituents provided a higher yield than the single substituents (1d vs 1e). Interestingly, when the substrate 2i with fluoro group in the ortho position of nitro displayed the lowest yield compared to its isomers with fluoro group attached to the different position on phenyl ring. The possible reason is that the intramolecular hydrogen bond between fluoro and amino reduced the nucleophilicity of amino group. To improve the yield of 1k, the reaction temperature was raised from room temperature to 40 °C. The yield of 1k was increased from 12.4 to 37.4% but the intermediate amine D still left (entry 12). With the continuous efforts, the amount of PTSA  $\cdot$  H<sub>2</sub>O was increased from 5 to 20% and also the reaction time was prolonged from 3 to 12 h, the yield was raised to 67.0% without remaining of the intermediate amine D (1k, entry 13).

To clarify the proposed reaction mechanism, we focused on the transformation of the reaction intermediate D inspired by the result of 1k. When substrate 2k was treated with

$R_{3}$ $NO_{2}$ $Pd/C, H_{2}$ $R_{3}$ $NO_{2}$ $PtSA, CH_{3}OH$ $R_{3}$ $R_{4}$ $NH$							
		2a-k	1a-k				
Entry	No.	R <sub>1,2,3,4</sub>	Time	Yield (%)			
1 <sup><i>a</i></sup>	1a	$R_{1,2,3,4} = H$	3 h	89.9			
2 <sup><i>a</i></sup>	1b	$R_{1,2,3} = H; R_4 = CH_3$	3 h	90.5			
3 <sup>a</sup>	1c	$R_{1,3,4} = H; R_2 = CH_3$	3 h	86.4			
4 <sup><i>a</i></sup>	1d	$R_{1,4} = H; R_{2,3} = OCH_3$	3 h	94.2			
5 <sup>a</sup>	1e	$R_{1,3,4} = H; R_2 = OCH_3$	3 h	81.5			
6 <sup><i>a</i></sup>	1f	$R_{2,3,4} = H; R_1 = F$	3 h	75.3			
7 <sup>a</sup>	1g	$R_{1,3,4} = H; R_2 = F$	3 h	86.7			
8 <sup><i>a</i></sup>	1ĥ	$R_{1,2,4} = H; R_3 = F$	3 h	90.3			
9 <sup><i>a</i></sup>	1i	$R_{1,2,3} = H; R_4 = F$	3 h	67.8			
10 <sup><i>a</i></sup>	1j	$R_{1,3,4} = H; R_2 = OCOCH_3$	3 h	95.5			
11 <sup>a</sup>	1k	$R_{1,2,4} = H; R_3 = CF_3$	3 h	12.4 <sup>d</sup>			
12 <sup>b</sup>	1k	$R_{1,2,4} = H; R_3 = CF_3$	3 h	37.4 <sup>d</sup>			
13 <sup>c</sup>	1k	$R_{1,2,4} = H; R_3 = CF_3$	12 h	67.0			

Table 2. Heterocyclizations from methyl (2-nitrobenzoyl)carbamates 2a-k.

0 0

<sup>*a*</sup>Reaction was run at room temperature with  $H_2$  balloon using 5% of PTSA  $\cdot$   $H_2O$ .

<sup>b</sup>Reaction was run at 40 °C with  $H_2$  balloon using 5% of PTSA  $\cdot$   $H_2O$ .

<sup>c</sup>Reaction was run at 40 °C with  $H_2$  balloon using 20% of PTSA  $\cdot$   $H_2O$ .

 $^{d1}$ H NMR yield; a mixture of **1k** and intermediate amine **D**.

PTSA, p-toluenesulfonic acid.



Scheme 3. Exploration of the possible mechanism of 1k production.



Scheme 4. Proposed mechanism for the synthesis of quinazoline-2,4(1H,3H)-dione 1a.

Pd/C hydrogenation without catalyst  $PTSA \cdot H_2O$  at room temperature, the intermediate **D** was formed exclusively (Scheme 3). With the assistance of  $PTSA \cdot H_2O$  at 40 °C, the intermediate **D** smoothly underwent intramolecular cyclization to afford quinazolinedione 1k.

A plausible mechanism based on our experiments is proposed in Scheme 4. First, the ethyl (2-nitrobenzoyl)carbamate **A** is reduced to the intermediate **E** by Pd/C hydrogenation. Then intramolecular cyclization of **E** generates the intermediate **F** in the presence of PTSA  $\cdot$  H<sub>2</sub>O. At last, removal of C<sub>2</sub>H<sub>5</sub>OH and hydrogen ion affords the desired product **1a** by ammonolysis of ester process. The nucleophilicity of amino group in the intermediate **E** plays a key role in the intramolecular ammonolysis reaction. This could be the possible reason why substrates with electron-donating groups generally gave higher yields.

#### Conclusion

In summary, we have described a novel and efficient method for a PTSA-catalyzed reaction to prepare various quinazoline-2,4(1H,3H)-diones from substituted methyl (2-nitrobenzoyl)carbamates through sequential hydrogenation condensation. The crucial 2-position carbonyl group of quinazoline-2,4(1H,3H)-diones is constructed using oxalyl chloride as the key precursor reagent to avoid harsh reaction condition and expensive chemicals. This approach has several advantages, such as no-column separation, mild reaction conditions and high yields. Further explorations to broaden the scope and synthetic applications of this efficient approach are currently underway in our group. This useful method could potentially be complementary to the existing methods for the synthesis of quinazoline-2,4(1H,3H)-diones.

#### Experimental

Melting points were determined on Yanaco MP-J3 microscope melting point apparatus. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Varian 400 or 500 MHz NMR spectrometer with  $CDCl_3$  or DMSO- $d_6$  as a solvent. ESI-HRMS data were measured on Thermo Exactive

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Orbitrap plus spectrometer. All solvents and reagents were obtained from commercial suppliers and used without further purification.

#### General procedure for the preparation of methyl (2-nitrobenzoyl)carbamate (2a)

To a magnetically stirred solution of 2-nitrobenzamide (2 g, 12.04 mmol) in 1,2dichloroethane (15 mL) was added oxalyl chloride (1.8 mL, 20.47 mmol). The reaction mixture was heated to reflux for 3 h under an atmosphere of argon. The solvent was evaporated under reduced pressure. The residue was dissolved in anhydrous acetonitrile (30 mL). The mixture of CH<sub>3</sub>OH (10 mL) and anhydrous acetonitrile (10 mL) was slowly added to the reaction mixture keeping the reaction under -10 °C. The reaction mixture was stirred for 2 h keeping the reaction under -10 °C. The solvent was evaporated under reduced pressure. The residue was washed with water, filtrated and dried to give a white solid (2.27 g, 84.0%). mp 119–120 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.25 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.2$  Hz, 1H), 8.11 (brs, 1H), 7.75 (td,  $J_1 = 7.6$  Hz,  $J_2 = 1.2$  Hz, 1H), 7.66-7.62 (m, 1H), 7.45 (dd,  $J_1 = 7.6$  Hz,  $J_2 = 1.2$  Hz, 1H), 3.69 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta$ 167.2, 152.5, 145.1, 134.9, 132.6, 130.8, 128.5, 124.1, 52.7; ESI-HRMS m/z calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>Na (M+Na<sup>+</sup>): 247.0325, found: 247.0325.

#### General procedure for the preparation of quinazoline-2,4(1H,3H)-dione (1a)

To a magnetically stirred solution of **2a** (200 mg, 0.892 mmol) in CH<sub>3</sub>OH (50 mL) was added 10% Pd/C (10% Pd loaded on Carbon wetted with ca. 55% water, 20 mg) and PTSA · H<sub>2</sub>O (8.6 mg, 0.045 mmol). The reaction mixture was stirred under an atmosphere of hydrogen at room temperature for 3 h. After filtration of Pd/C and concentration under reduced pressure at 45 °C, 20 mL H<sub>2</sub>O was added to the residue and the mixture was stirred at 0 °C for 1 h. After filtration, the product was dried to give a white solid (130 mg, 89.9%). mp >250 °C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 11.26 (brs, 1H), 11.12 (brs, 1H), 7.89–7.87 (m, 1H), 7.64–7.61 (m, 1H), 7.17–7.15 (m, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  163.0, 150.5, 141.0, 135.1, 127.1, 122.4, 115.5, 114.5; ESI-HRMS *m*/*z* calcd for C<sub>8</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub> (M+H<sup>+</sup>): 163.0502, found: 163.0501.<sup>[8]</sup>

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