

# Application of Beckmann Rearrangement in the Green Synthesis of Amide Compounds

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## Abstract

Four factors (temperature, catalyst (PPA, H<sub>3</sub>PO<sub>4</sub>-Ac<sub>2</sub>O and ionic liquid), time and solvent) and three levels orthogonal test L<sub>9</sub>(3<sup>4</sup>) was applied, to explore the optimal condition for Beckmann rearrangement of benzophenone oxime, p-chloroacetophenone oxime and p-nitrobenzophenone oxime as substrate, to explore the adaptability of the optimal conditions to different substrates and substituents, <sup>1</sup>H NMR and <sup>13</sup>C-NMR spectroscopy, infrared spectroscopy and high performance liquid chromatography (HPLC) were used to analyze the structure of benzanilide. The result showed that the optimal condition for Beckmann rearrangement of benzophenone oxime was at temperature of 60°C, with reaction of 120 min, and under addition of 10mL PPA in ultrasonic environment, with yield up to 56.65%. In addition, the yield catalyzed by ionic liquid was relatively low, ranged from 22.60 to 36.65%. The products were further confirmed by HPLC, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and FT-IR to be benzanilide in high purity. Therefore, it is feasible to synthesize benzanilide in a greener way combining ultrasonic and PPA catalyst at low temperature (60°C).

**Keywords:** Benzophenone oxime, Beckmann rearrangement, orthogonal test, green synthesis.

## 1. Introduction

Amide is one of the important functional groups in organic chemistry and biochemistry [1]. Such functional group is widely used in pharmaceuticals, natural products and a large number of industrial materials such as polymers, detergents and lubricants. The most popular and versatile methods for the preparation of amides include the reaction of carboxylic acid derivatives such as acyl chlorides, anhydrides and esters with amines, or the carboxylic acid reacts directly with the amine under certain amount of dehydrating agent [2]. However, these methods are associated with defects of low atom economy and by-products. Therefore, it is of vital realistic significance to develop efficient and sustainable methods to prepare amide compounds. Recently, based on the principle of atom economy and low cost, synthesis of amide compounds catalyzed by metals has been rapid developed [3]. A large number of compounds such as nitriles, aldehydes, ketones, oximes, primary alcohols or amines can be used as starting materials for the construction of amide bonds under the promotion of metal catalysts.

Among them, Beckmann rearrangement reaction with oxime as the starting material for the synthesis of amide already has a long history. The reaction was first discovered by the German chemist Beckman in 1886. This classical reaction has an incalculable value in organic synthesis, such as the synthesis of ε-caprolactam, which is precursor substance of nylon-6, is synthesized by Beckmann rearrangement of cyclohexanone oxime [4].

The Beckmann rearrangement of the oxime involves the rearrangement of the group at the trans-position of hydroxyl from the carbon atom to the nitrogen atom under the catalysis of the Lewis acid or the Bronst acid. The aryl and alkyl groups are prone to such rearrangements and therefore particularly suitable for the preparation of the corresponding N-substituted amides from ketoxime.

The traditional Beckmann rearrangement method requires harsh conditions and strong acid as catalyst [5], to proceed successfully, and the requirements for equipment and cost are high, meanwhile accompanied by heavy water pollution. As the emerging green catalyst, ionic liquid is recyclable and has little environmental pollution, therefore has many applications in Beckmann rearrangement reaction [6-8]. Solvents, reaction temperatures and reaction time have great influence on the reaction rate, equilibrium and conversion rate of chemical reactions, and rearrangement reactions are also affected accordingly [9-10].

In this paper, for the purpose of green synthesis, four factors (temperature, catalyst (PPA, H<sub>3</sub>PO<sub>4</sub>-Ac<sub>2</sub>O and ionic liquid), time and solvent) and three levels orthogonal test L<sub>9</sub> (3<sup>4</sup>) was applied, to explore the optimal condition for Beckmann rearrangement of benzophenone oxime, the effects of factors such as ultrasonic, ionic liquid, solvent, reaction time and reaction temperature on the rearrangement reaction were studied. p-chloroacetophenone oxime and p-nitrobenzophenone oxime as substrate, to explore the adaptability of the optimal conditions to different substrates and substituents, <sup>1</sup>H NMR and <sup>13</sup>C-NMR spectroscopy, infrared spectroscopy and high performance liquid chromatography (HPLC) were used to analyze the structure of Benzanilide.

## 2. Experimental Details

### 2.1. Experimental Apparatus and Reagents

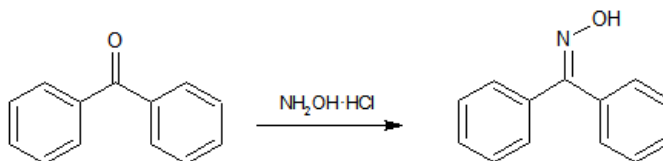
*Experimental apparatus.* Infrared spectrometer (Thermo Nicolet IS10, USA), High Performance Liquid Chromatography (LC-2130, Japan), <sup>1</sup>H NMR and <sup>13</sup>C NMR Spectrometer (Bruker, Advance III HD 500MHz, USA).

*Reagents.* n-BPyBF<sub>4</sub>(ark Pharm, Inc, 97% in purity), acetic anhydride (Shanghai Ling Feng Chemical Reagent Co., Ltd), tetrahydrofuran (Tianjin Yongda Chemical Reagent Company limited), hydroxylamine hydrochloride (Shanghai Ling Feng Chemical Reagent Co., Ltd.), p-chloroacetophenone (Shanghai Shao far reagent limited), 4-nitrobenzophenone (Shanghai Jiuding chemical Technology Co., Ltd), polyphosphoric acid (Jiangsu Yonghua Fine Chemical Co., Ltd), Phosphate (Wuxi prospect Chemical Reagent Co., Ltd.), phosphorus pentachloride(Shanghai Macklin Biochemical Co., Ltd.) ,ethyl acetate (Shanghai Macklin Biochemical Co., Ltd.), all chemicals above are analytical pure; benzophenone (China Shanghai NO.1 chemical reagent factory, chemical pure), polyphosphoric acid (Jiangsu Yonghua Fine Chemical Co. Ltd., chemical pure).

### 2.2. Synthesis of Benzophenone Oxime

In the 250 mL three-neck flask, 5.0 g of benzophenone and 5.72 g of hydroxylamine hydrochloride dissolved in ethanol (50.0 mL 1 g benzophenone dissolved in 7.5 mL ethanol), add 1 mL of water, then add 3.29 g of sodium hydroxide and stirred vigorously with a magnetic stirrer, after a few minutes, place the three neck flask on the steam bath temperature boil 3 h-3.5 h, control the temperature at 70 °C. Cold to room temperature before transfer into a beaker in which contain 20 mL of hydrochloric acid and 100 mL of water, next benzophenone oxime is precipitated in a white powdery crystal. After cooling, filtration,

wash crystals with a little cold water, drying, for the next reaction products directly. The synthesis process is as follows:

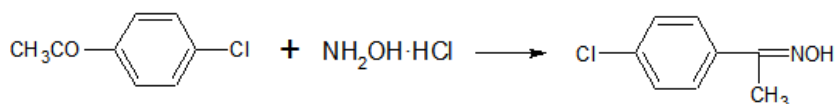


### 2.3. Preparation of Benzoyl Aniline

In a 100ml beaker, add a certain amount of catalyst, 1.000 g oxime, mix evenly and place in the sink of the ultrasonic cleaner, at a certain temperature (60, 70 and 80°C), under ultrasonic action after a certain time, place for 10 min, pour the reactants into 150mL of ice water. Stir constantly, a large number of white solids appear immediately, filtering, wash in a small amount of cold water, the crude product was recrystallized from the mixed solvent of ethanol and water, and the silver white crystalline of aniline was obtained, air drying, calculating the yield.

### 2.4. Preparation of Different Substrates

Preparation of acetophenone oxime: add 2.5g of hydroxylamine hydrochloride, 2.5mL of p-chloroacetophenone, 8 mL of 95% ethanol and 2mL of water in 100mL round bottom flask, 1.5 g flake of sodium hydroxide was added separately under vibration, the reaction is severe, cool the round bottomed flask with cold water, installed the reflux condenser after the sodium hydroxide is completely dissolved, heating and refluxing for 5 minutes then cooling, pour the reactants into a beaker containing 12.5 mL of concentrated hydrochloric acid and 100 mL of distilled water, filtration, washed thoroughly with cold water solid, dry the product in the dry tube, finally get the white solid. The synthesis process is as follows:



The nitro two benzophenone oxime preparation: add 0.5g benzophenone and 0.5g hydroxylamine hydrochloride in 250 mL three neck flask, dissolved in 20 mL ethanol, and add 1 mL of water, then add 0.3 g sodium hydroxide and stirred with a magnetic stirrer, after a few minutes, place the three necked flask in a steam bath, gently boil 3h-3.5h, and control the temperature at about 70 degrees. After slightly cold, transfer into a beaker with 2 mL of concentrated hydrochloric acid and 10 mL of water, lay overnight. Get orange crystal, filtered, Wash crystals with a little cold water, recrystallization, air drying, the products are used for the next reaction, and the synthesis process refers to benzophenone oxime.

### 2.5. Synthesis of Amides

The optimum conditions of Beckmann rearrangement were obtained by orthogonal test, and the different substrates were rearranged under the optimum conditions. Experiments were carried out in accordance with the steps of the preparation of amides with two phenyl oxime. When the amide prepared by different substrates is dissolved in water, chloroform can be used to extract the liquid, to lower the liquid, distillation, crystallization, filtration and air drying, carried out to calculate the yield.

## 2.6. Characterization of Products

In accordance with the relevant steps, diphenyl-ketoxime, p-chloroacetophenone oxime and p-nitrobenzophenone oximes and corresponding amides thereof are synthesized. The products are characterized by melting point analysis,  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  (nuclear magnetic resonance spectroscopy), infrared spectroscopy and high performance liquid chromatography (HPLC).

**Table 1.** Four factors and three levels orthogonal test  $L_9$  ( $3^4$ )

Entry	catalyst	T/ $^{\circ}\text{C}$	solvent	reaction time/min
1	ionic liquid	60	THF	30
2	ionic liquid	70	alcohol	120
3	ionic liquid	80	blank	60
4	$\text{H}_3\text{PO}_4\text{-Ac}_2\text{O}$	60	alcohol	60
5	$\text{H}_3\text{PO}_4\text{-Ac}_2\text{O}$	70	blank	30
6	$\text{H}_3\text{PO}_4\text{-Ac}_2\text{O}$	80	THF	120
7	PPA	60	blank	120
8	PPA	70	THF	60
9	PPA	80	alcohol	30

*Fourier-transform infrared spectroscopy (FT-IR).* In essence, infrared spectroscopy is a method of determining the structure of molecular substances and identifying compounds according to the relative vibration and molecular rotation of atoms in molecules. When a beam of infrared light by continuous wavelength material, molecular vibration in a certain group or the rotation frequency of the infrared and the same frequency, can absorb energy from the molecular level of the original ground state transition to a higher energy, the molecular absorption of infrared light to record information, get the infrared spectra. Infrared spectrum usually uses wavelength or wave number as abscissa to indicate the position of absorption peak, and uses transmittance or absorbance as ordinate to indicate absorption intensity. In this experiment, the sample preparation method is to mix the sample with the pure KBr in the proportion of 1:100 and then press it, then test.

*High performance liquid chromatography (HPLC).* Products by HPLC analysis using 60% methanol as the mobile phase, the flow rate is 1 mL/min, the column temperature was 30 degrees, according to the maximum absorption peak wavelength is set to 254nm, the retention time qualitative and quantitative analysis method of peak area.

*$^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra.*  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  were analyzed using 30 mg corresponding products, using the instrument as Bruker NMR (AVANCE III 500MHz), and the solvent is dimethyl sulfoxide-d.

## 3. Results and Discussion

### 3.1. Orthogonal Test Results

In this paper, benzophenone oxime was selected as the research object, using the four-factor three-level "orthogonal design" method, to investigate the effects of four main factors, such as reaction temperature, reaction time, catalyst type and solvent type on the rearrangement reaction. The results of

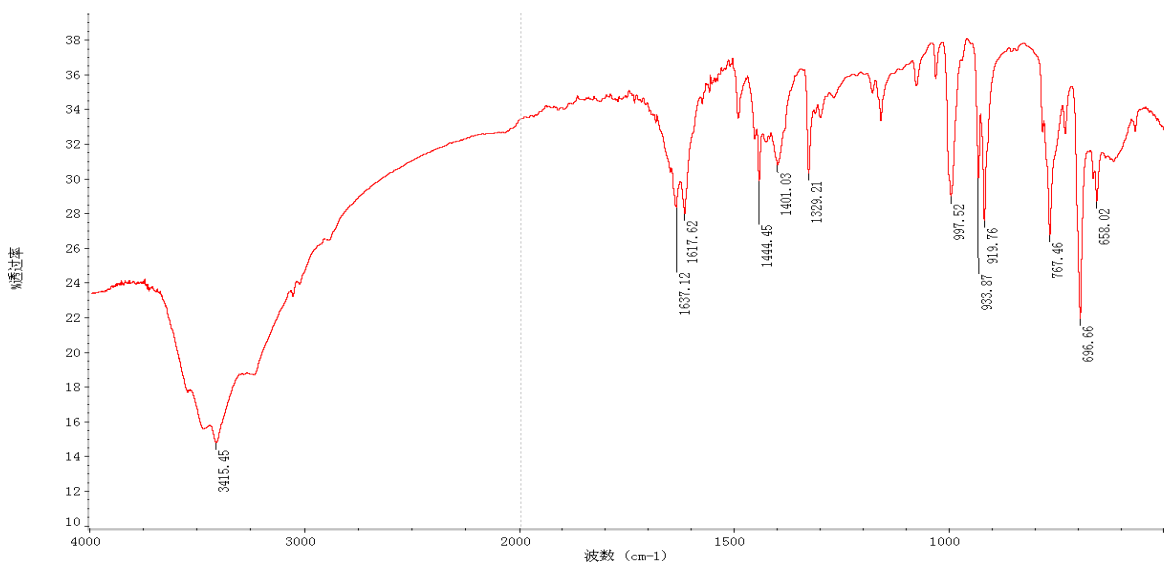
orthogonal test and analysis are shown in Table 2. From the results of orthogonal test, the reaction was carried out at 70°C for 30 min with H<sub>3</sub>PO<sub>4</sub>-Ac<sub>2</sub>O as catalyst; the reaction was carried out at 60°C for 120 min to obtain the amide with good yield.

**Table 2.** Orthogonal test for Beckmann rearrangement

	catalyst	temperature/°C	solvents	Reaction time/min	Yield/%
1	Ionic liquid	60	THF	30	36.65
2	Ionic liquid	70	Anhydrous ethanol	120	33.65
3	Ionic liquid	80		60	22.60
4	H <sub>3</sub> PO <sub>4</sub> -Ac <sub>2</sub> O	60	Anhydrous ethanol	60	51.98
5	H <sub>3</sub> PO <sub>4</sub> -Ac <sub>2</sub> O	70		30	52.60
6	H <sub>3</sub> PO <sub>4</sub> -Ac <sub>2</sub> O	80	THF	120	26.00
7	PPA	60		120	56.65
8	PPA	70	THF	60	44.54
9	PPA	80	Anhydrous ethanol	30	34.29

### 3.2. Analysis of Synthesis of Ketoxime by Different Substrates

The product of the orthogonal test was first measured by a melting point apparatus, the melting range is 139.3-142.0°C, and the theoretical melting point of benzophenone oxime 141-144°C coincide, and then further characterized by infrared spectroscopy (Fig. 1). The peak of the product at 1500-1550 cm<sup>-1</sup> is the absorption peak of the benzene ring, at 3650-3500 cm<sup>-1</sup> is the characteristic absorption peak of the oxime, indicating that the product is benzophenone oxime.



**Fig.1.** FT-IR spectrum of Benzophenone oxime

Among the products of the different substrate experiments, the yield of p-nitrobenzophenone oxime was 42.5%, the melting point was 101.5-103.0°C, the infrared spectrum is shown in Fig.2. The peak of the product at 1500-1550 cm<sup>-1</sup> is the absorption peak of the benzene ring, the characteristic absorption peak

of oxime at  $3650-3500\text{ cm}^{-1}$ , and the peak at  $1380-1340\text{ cm}^{-1}$  is the absorption peak of nitro, indicating that the product is p-nitrobenzophenone oxime.

The yield of p-chlorocyclohexanone oxime was 43.9%, the melting point was  $85.6-86.9^{\circ}\text{C}$ , the infrared spectrum is shown in Fig.3. The peak of the product at  $1500-1550\text{ cm}^{-1}$  is the absorption peak of the benzene ring. At  $3650-3500\text{ cm}^{-1}$  is the characteristic absorption peak of oxime, and there is a strong absorption peak at  $750-700\text{ cm}^{-1}$ , which is the absorption peak of chlorine, indicating that the product is p-chlorocyclohexanone oxime.

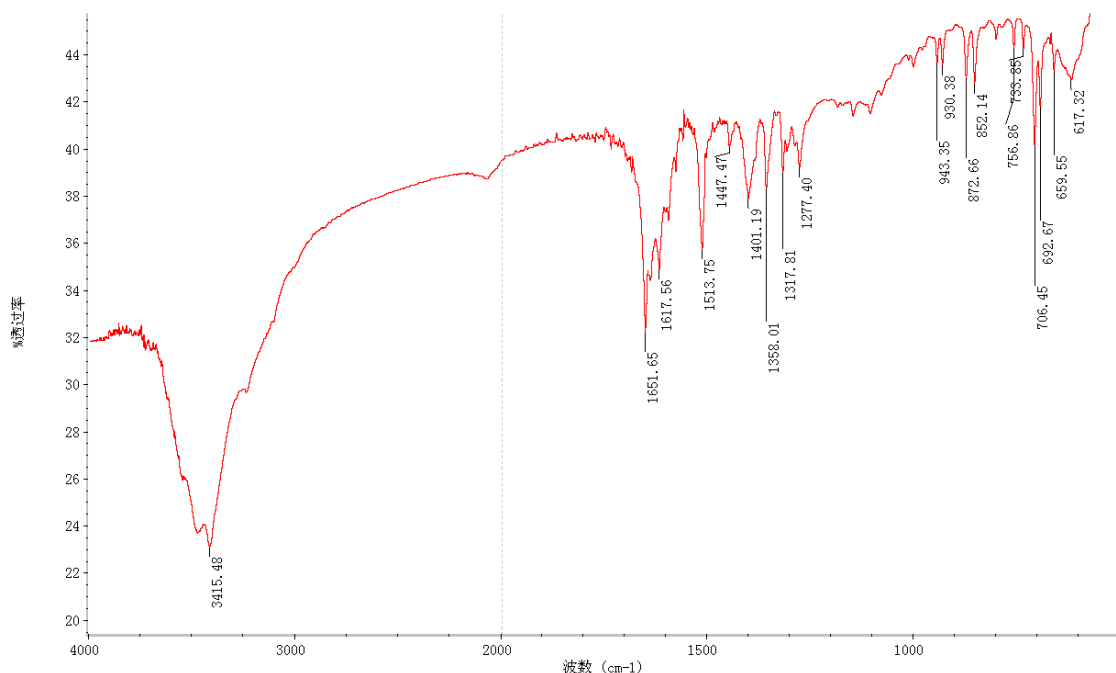


Fig.2. FT-IR spectrum of Nitrodiphenylketone oxime

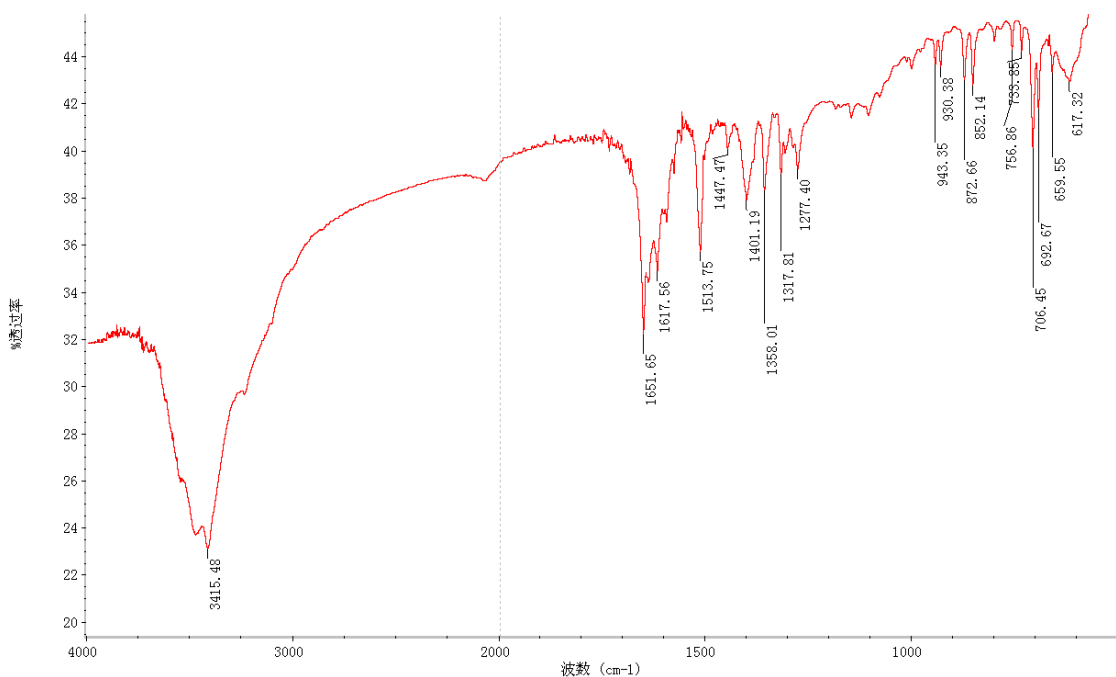


Fig.3. FT-IR spectrum of Chlorcyclohexanone oxime

### 3.3. Analysis of Beckmann Rearrangement Reaction Products

In this paper, benzoanilide was synthesized by orthogonal experiments. The product was first measured by a melting point apparatus, the results are shown in Table 3. Experiment 5, experiment 7 and experiment 9 gave a melting range of 154.9-162.5°C, coincide with benzoyl aniline with the theoretical melting point of 161-165°C. Then the products were further characterized by IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR nuclear and HPLC.

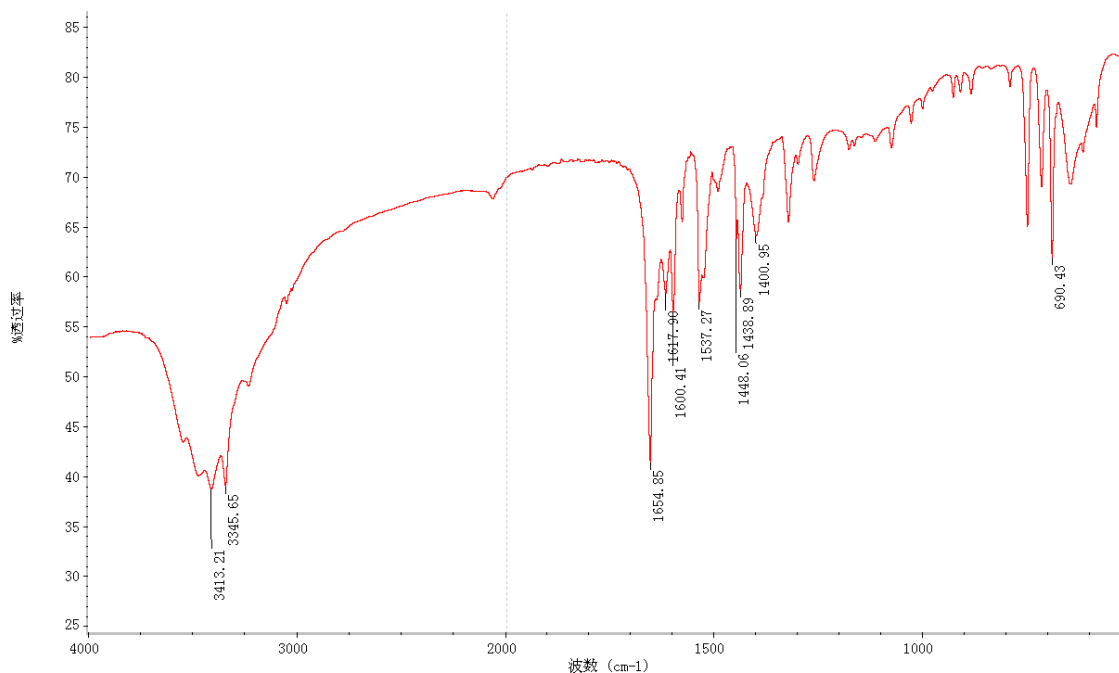


Fig.4. FT-IR spectrum of Product for Experiment 7

Table 3 Melting point analysis of products

Entry	Initial melting/°C	Final melting/°C	Melting range /°C
1	133.9	140.0	6.1
2	134.5	142.5	7.0
3	129.5	135.5	4.0
4	137.8	141.8	4.0
5	161.5	162.5	1.0
6	135.7	141.6	5.9
7	161.9	162.6	0.7
8	156.1	159.4	3.3
9	159.3	161.0	1.7

### 3.4. Qualitative Analysis of Infrared Spectroscopy

Through the analysis of infrared spectra of No.5, No.7 and No.9, product No.7 is more consistent with standard spectra. The infrared characterization of benzamide aniline for No.7 is shown in Fig.4. The peak at 1420-1400 cm<sup>-1</sup> is the absorption peak of C-N bond. The peak at 1500-1550 cm<sup>-1</sup> is the absorption peak of the benzene ring, and the peak at 3500-3100 cm<sup>-1</sup> is the absorption peak of NH stretching vibration, 1655-1590 cm<sup>-1</sup> is the absorption peak of N-H bending vibration, 1420-1400cm<sup>-1</sup> is the

absorption peak of C-N stretching vibration,  $1680\text{-}1630\text{cm}^{-1}$  is the absorption peak of C=O stretching vibration, indicating that the product is benzoylaniline.

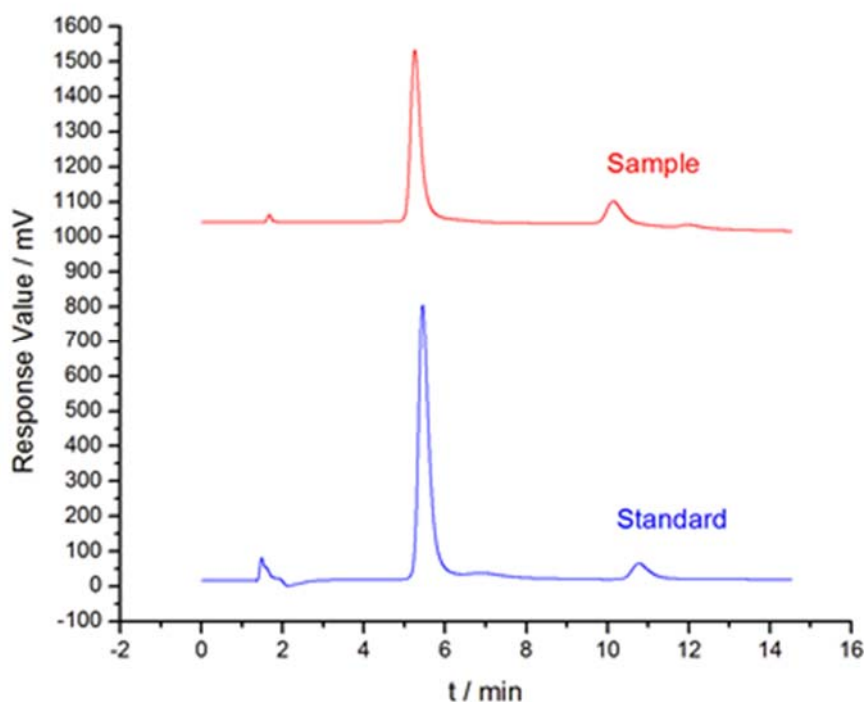
### 3.5. Qualitative and Quantitative Analysis of HPLC

The results of the liquid chromatographic analysis of the product are shown in Fig.5. According to the figure, the retention time ( $t_R = 4.977$ ) and peak area  $A = 9788497$  were obtained, therefore the product contains 85.0% benzophenone oxime.

### 3.6. Nuclear magnetic resonance spectroscopy Analysis of benzophenone oxime and rearrangement products

The synthesized benzophenone oximes were determined by melting point, and coincide with the theoretical melting point of benzophenone oxime. The obtained benzophenone oxime was characterized by  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ . As shown in Fig.6 and 7, according to the spectral data, there were nine kinds of carbon on the benzophenone oxime, and the proportion of different hydrogens was close to 1:10, which confirmed the product to be benzophenone oxime.

The product after rearrangement was characterized by  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ , as shown in Fig.8 and 9, according to the spectral data, there are 9 kinds of carbon on the product, and the ratio of various hydrogen is 1: 1: 2: 2: 2: 2, which confirmed the product to be benzanilide.



**Fig.5.** HPLC spectrum for Benzanilide of  $10^{-4}\text{ mol}\cdot\text{L}^{-1}$  (standard) and product (sample) of experiment 7



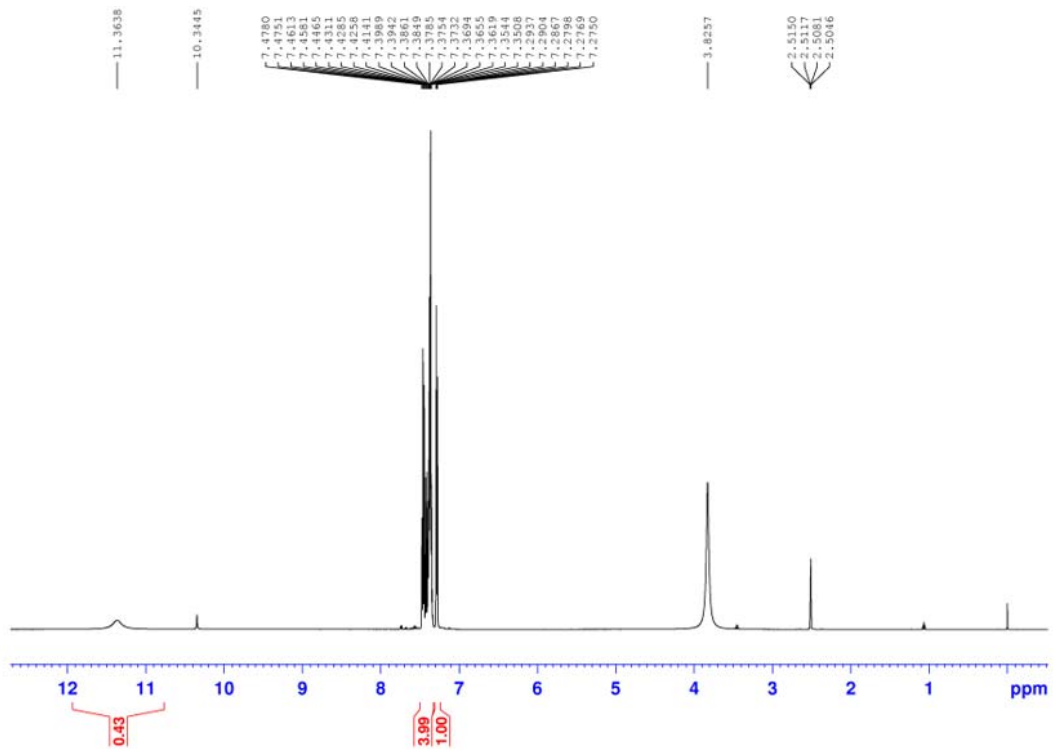


Fig.6. <sup>1</sup>H NMR spectrum for Benzophenone oxime

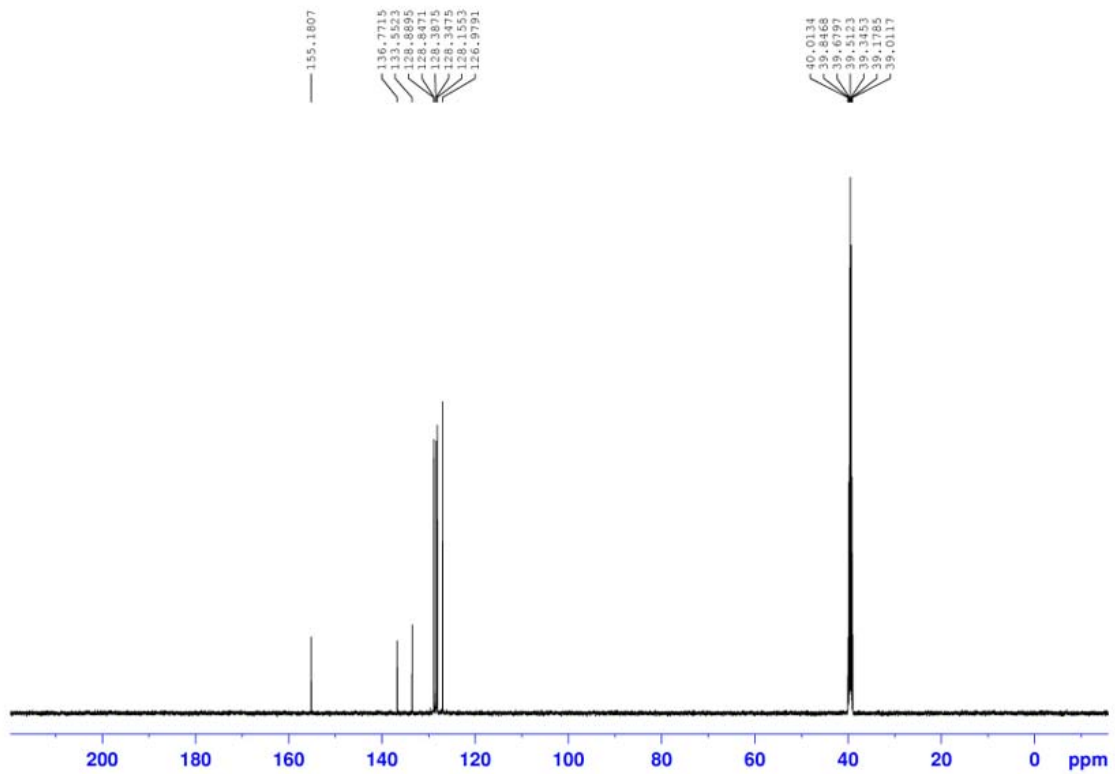


Fig.7. <sup>13</sup>C NMR spectrum for Benzophenone oxime

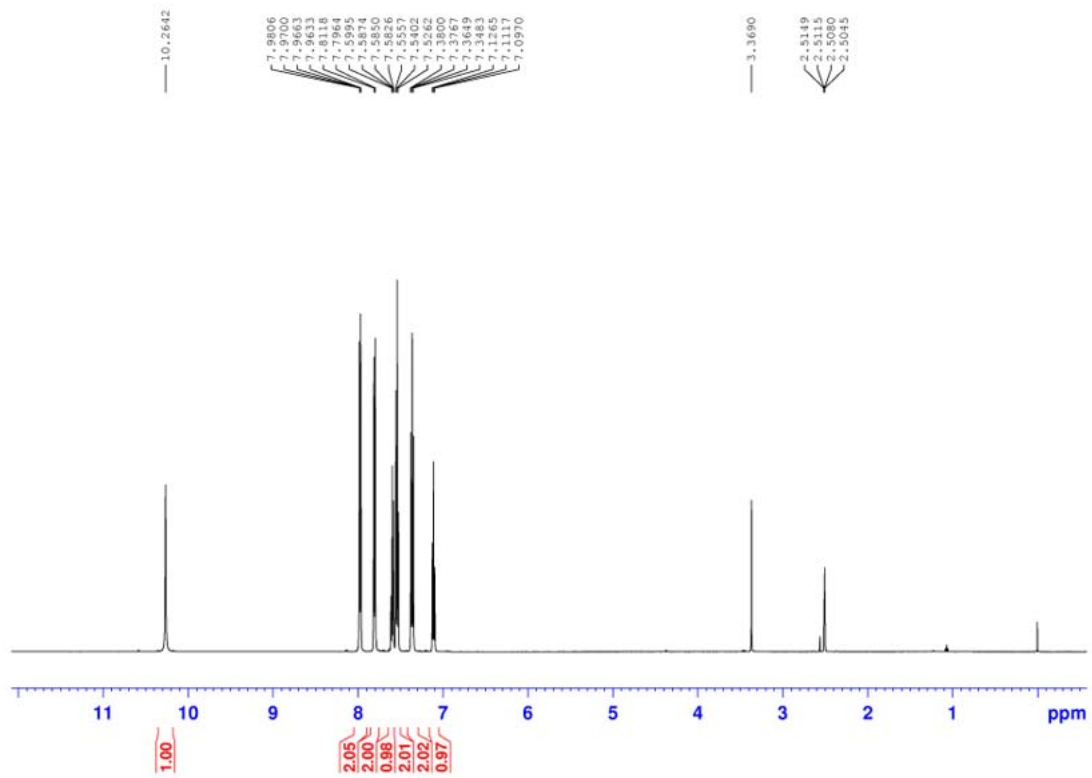


Fig.8. <sup>1</sup>H NMR spectrum for Benzanilide

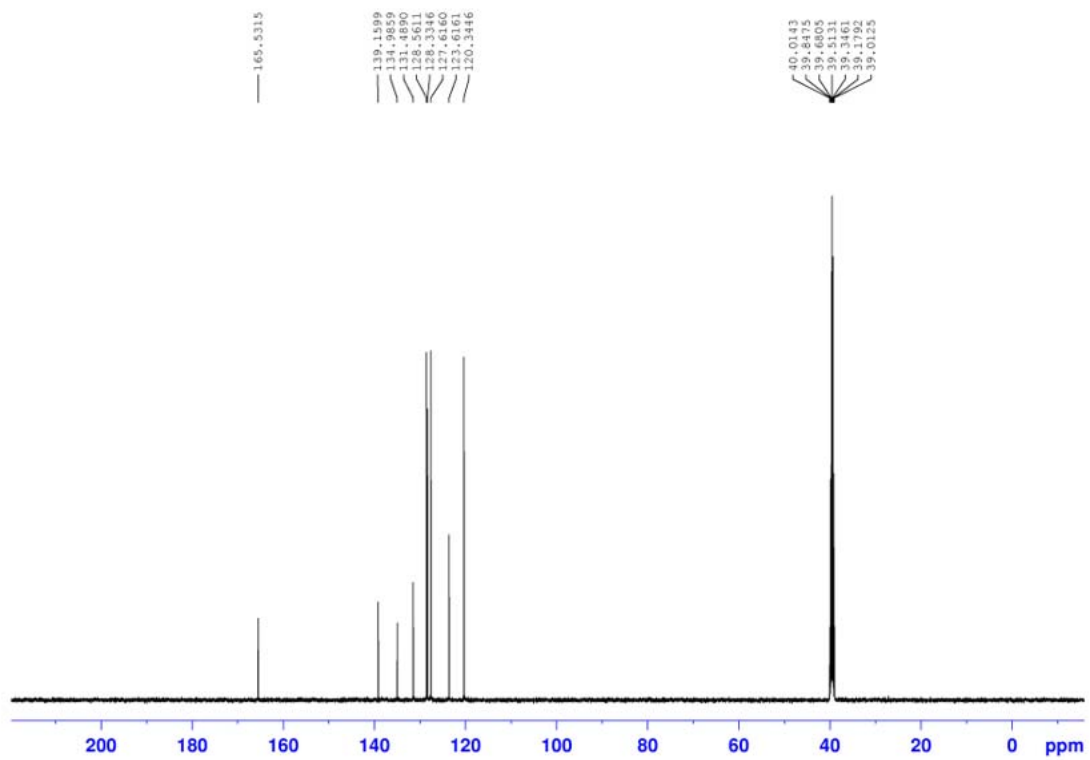


Fig.9. <sup>13</sup>C NMR spectrum for Benzanilide

#### 4. Conclusions

The products were characterized by HPLC, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR spectroscopy and FT-IR, which is benzoylanilide with a high purity. It was confirmed that the pathway of PPA as a catalyst to catalyze the synthesis of benzanilazide with benzophenone oxime at the low temperature (60 °C) is green and feasible.

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