

## SYNTHESIS AND APPLICATION OF Cu-Fe HYDROTALCITE IN ALDOL REACTION

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### Abstract

The heterogeneous recyclable catalyst, Cu-Fe hydrotalcite, was synthesized by coprecipitation, activated at 200°C and then successfully applied in Aldol reaction. The Aldol products were obtained in moderate yield under mild conditions, simple and environmentally benign process, with the recovery of hydrotalcite catalyst up to 99%. This procedure also exhibited efficiency in the total synthesis of Abhexone, a flavor with high demand in the food and cosmetic industry.

**Keywords:** Aldol reaction; hydrotalcite; heterocatalyst; abhexone.

### 1. Introduction

The utilization of mineral or organic acids and bases as homogeneous catalysts in the syntheses of fine chemicals and drugs is always associated with environmental pollution as well as the requirement of a neutralization step at the end of the reaction. In contrast, heterogeneous catalysis has become the more efficient and environmentally benign process in recent years because of its advantages such as economic benefit, waste reduction, catalyst recovery and ease of operation. Among heterogeneous catalysts, hydrotalcite-like compounds (also briefly called hydrotalcites) have emerged as one of the leading candidates in sustainable chemistry.

Hydrotalcites are a class of ionic and basic compounds known as layered double hydroxides (LDH). This family is named after hydrotalcite, a mineral having formula  $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$  found in small quantities in the Snarum area of Norway and the Ural area of Russia [1]. Hydrotalcites consist of both divalent and trivalent metal cations with the general formula  $[M_{1-x}^{II}M_x^{III}(OH)_2][A^{n-}]_{x/n} \cdot yH_2O$  where M(II) is Mg, Zn, Cu(II) or Ni(II), and M(III) is Al, Ga, Fe(III) or Mn(III),  $A^{n-}$  may be carbonate, phosphate, sulphate, nitrate, halides or organic anions as well as complex anions, with x is between 0.2–0.4. They have a layer structure containing positively charged layers that are made up of metal cations locating in coplanar octahedral like brucite  $Mg(OH)_2$  skeleton. Anions and water molecules occupy the interlayer space to compensate the charge [1, 2]. The modification in metal ions and interlayer anions leads to a wide variety of hydrotalcites. The diversity in their composition makes hydrotalcites versatile

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materials. These compounds are used as CO<sub>2</sub> adsorbents [2], anion exchangers [3], flame retardants [4], polymer additives [5], and even drug delivery hosts [6]. Especially, hydrotalcites provide tremendous catalytic applications including alcohols synthesis; acylation of phenols, amines and thiols; selective oxidation of alcohols to aldehydes; reduction of aldehydes to alcohols; epoxide ring-opening; epoxidation; esterification. Furthermore, hydrotalcites are mild and efficient catalysts for Baylis-Hillman reaction [7], cyanoethylation, Claisen-Schmidt condensation [8], Knoevenagel condensation [9]. However, it is necessary to point out that up-to-date hydrotalcites utilized in Aldol reaction are original Mg-Al form (naturally appeared form) or slightly modified with other metals such as Ca-Al hydrotalcite, Ca-Mn-Al hydrotalcite [10]. They are solid bases with no significant difference compared to previous Aldol reaction catalysts. Whilst, transition elements such as copper and iron are known as valuable catalysts in organic transformations. Indeed, Cu hydrotalcite demonstrated its utility in the arylation of amines [11], benzoyl ether synthesis [12]. Hence, we, herein, wish to develop a novel hydrotalcite - like catalyst for Aldol reaction based on Cu (II) and Fe (III) to benefit from the dramatic catalytic characteristics of these metals.

## 2. Experiments

All reagents were purchased from Sigma - Aldrich and used without further purification. All reactions have been carried out under nitrogen atmosphere and anhydrous conditions. The solvents used were freshly distilled under anhydrous conditions unless otherwise specified. The reaction mixtures have been magnetically stirred with Teflon stirring bars. All the reactions have been monitored by thin-layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of *n*-hexane and ethyl acetate, with detection by UV light, or potassium permanganate staining solution. The infrared spectra have been recorded with Perkin Elmer spectrometer at Le Quy Don Technical University. The XRD has been recorded with D8 Advance Bruker spectrometer at Vietnam National University. The nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Advance 500 MHz spectrometer at Vietnam National University. <sup>1</sup>H-NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using [δ (CDCl<sub>3</sub>) = 7.26 ppm] as an internal reference. <sup>13</sup>C-NMR spectra: δ (C) are given in ppm relative to TMS, using [δ (CDCl<sub>3</sub>) = 77.0 ppm] as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (qt), multiplet (m) or br (broad).

### 2.1. Synthesis of Cu-Fe hydrotalcite

The Cu-Fe hydrotalcite (with the Cu<sup>2+</sup>:Fe<sup>3+</sup> ratio of 3:1) was prepared by adding two aqueous solutions simultaneously: one solution containing Cu(NO<sub>3</sub>)<sub>2</sub> (0.3 mol, 72.6 g Cu(NO<sub>3</sub>)<sub>2</sub>.3H<sub>2</sub>O) and Fe(NO<sub>3</sub>)<sub>3</sub> (0.1 mol, 40.4 g Fe(NO<sub>3</sub>)<sub>3</sub>.9H<sub>2</sub>O) in 175 ml

deionized water and the other containing KOH (0.5 mol, 28 g) and Na<sub>2</sub>CO<sub>3</sub> (0.25 mol, 26.5 g) in 25 ml deionized water. The second solution was dropwised into the first one under vigorous stirring at room temperature, while maintaining pH of 11-12 for 30 minutes. The resulting gel-like material was heated at 60°C for 24 hours. The precipitate was filtered, thoroughly washed with deionized water, dried at 80°C for 2 hours and then heated in the oven at 200°C for 3 hours. The catalyst was characterized by XRD.

## **2.2. Aldol reactions between substituted benzaldehydes and pentan-3-one**

The mixture of 1 mmol substituted benzaldehyde, 2 mmol pentan-3-one and Cu-Fe hydrotalcite (Cu<sup>2+</sup>/Fe<sup>3+</sup> = 3/1) (1% mass of benzaldehyde) in 5 ml DCM was heated to reflux at 40°C. After the reaction was completed, the catalyst was filtered, and the product was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford the desired product.

**1-hydroxy-2-methyl-1-phenylpentan-3-one:** 93.4 mg (48.64%). IR: 3187, 3071, 2927, 1691, 1204, 827, 706 cm<sup>-1</sup>.

**1-hydroxy-2-methyl-1-(4-nitrophenyl)pentan-3-one:** 148.8 mg (62.78%). IR: 3184, 3067, 2851, 1703, 1343, 813 cm<sup>-1</sup>.

**1-(4-bromophenyl)-1-hydroxy-2-methylpentan-3-one:** 134.4 mg (49.59%). IR: 3091 (br), 2858, 1672, 1202, 809 cm<sup>-1</sup>.

**1-(4-fluorophenyl)-1-hydroxy-2-methylpentan-3-one:** 112.0 mg (53.33%). IR: 3184, 3083, 2925, 1733, 1231, 844 cm<sup>-1</sup>.

**1-hydroxy-2-methyl-1-(*p*-tolyl)pentan-3-one:** 97.2 mg (47.18%). IR: 3211, 3054, 2922, 1711, 1221, 823 cm<sup>-1</sup>.

## **2.3. Aldol reaction between benzaldehyde and acetophenone**

The mixture of 1 mmol benzaldehyde, 2 mmol acetophenone and Cu-Fe hydrotalcite (Cu<sup>2+</sup>/Fe<sup>3+</sup> = 3/1) (1% mass of benzaldehyde) in 5 ml DCM was heated to reflux at 40°C. After the reaction was completed, the catalyst was filtered, the product was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford 95.1 mg 3-hydroxy-1,3-diphenylpropan-1-one (42.08%). IR: 3125, 3066, 1705, 1245, 809, 704 cm<sup>-1</sup>.

## **2.4. Aldol reaction between propionaldehyde and pentan-3-one**

The mixture of 1 mmol propionaldehyde, 2 mmol pentan-3-one and Cu-Fe hydrotalcite (Cu<sup>2+</sup>/Fe<sup>3+</sup> = 3/1) (1% mass of propionaldehyde) in 5 ml DCM was heated to reflux at 40°C. After the reaction was completed, the catalyst was filtered, the product was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford 62.7 mg 5-hydroxy-4-methylheptan-3-one (43.48%). IR: 3217, 2983, 2944, 1714, 1239 cm<sup>-1</sup>.

## 2.5. Application in the total synthesis of Abhexone

### 2.5.1. Aldol reaction between ethyl glyoxylate and pentan-3-one

The mixture of 1mmol ethyl glyoxylate, 2 mmol pentan-3-one and Cu-Fe hydrotalcite ( $\text{Cu}^{2+}/\text{Fe}^{3+} = 3/1$ ) (1% mass of ethyl glyoxylate) in 5 ml DCM was heated to reflux at 40°C. After the reaction was completed, the catalyst was filtered, the product was extracted with EtOAc and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford 156.9 mg ethyl 2-hydroxy-3-methyl-4-oxohexanoate (83.46%). IR: 3425, 2983, 1738, 1215, 1018  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.08 (s, 2H), 4.85 (s, 1H), 4.19 – 4.23 (m, 2H), 3.77 – 3.80 (m, 1H), 3.56 – 3.66 (m, 2H), 1.25 – 1.27 (m, 4H), 1.17 – 1.20 (m, 4H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.58, 166.83, 92.16, 63.98, 62.93, 62.24, 18.36, 15.09, 14.03.

### 2.5.2. Cyclization of ethyl 2-hydroxy-3-methyl-4-oxohexanoate

1 mmol ethyl 2-hydroxy-3-methyl-4-oxohexanoate and 0.5 ml benzyl bromide were dissolved in 5 ml  $\text{CH}_3\text{OH}$ . The mixture was cooled down to 0°C. Then 76 mg  $\text{NaBH}_4$  was partially added to the mixture. The reaction was stirred at 0°C for 1 hour. After the reaction was completed, the product was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford 89.8 mg 5-ethyl-3-hydroxy-4-methyldihydrofuran-2-one (62.35%). IR: 3455, 2923, 1737, 1211, 1093  $\text{cm}^{-1}$ .

### 2.5.3. Oxidation of 5-ethyl-3-hydroxy-4-methyldihydrofuran-2-one

0.17 ml oxalyl chloride and 0.28 ml DMSO were dissolved in 10 ml anhydrous DCM to form mixture A. Meanwhile, 1 mmol 5-ethyl-3-hydroxy-4-methyldihydrofuran-2-one and 7 ml  $\text{Et}_3\text{N}$  were dissolved in 5 ml anhydrous DCM to form mixture B. The two mixtures were cooled down to -78°C. Gradually add mixture A to mixture B and the reaction was stirred at -78°C for 2 hours, then warmed up to room temperature. After the reaction was completed, the product was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by column chromatography (eluent *n*-hexane/EtOAc) to afford 74.3 mg 5-ethyl-4-methyldihydrofuran-2,3-dione (Abhexone) (52.33%). IR: 2958, 2928, 1724, 1268  $\text{cm}^{-1}$ .

## 3. Results and discussion

### 3.1. Catalyst characterization

The structure pattern was shown in XRD (Fig. 1). The  $\text{Cu}^{2+}$  ratio was recorded in 66.67%. A well-crystallized hydrotalcite structure was presented in the sample, exhibiting sharp and symmetrical reflections. The peak  $2\theta$  at  $26^\circ$  (d spacing = 3.45 Å) was attributed to

the reflections from the (100) family of crystallographic planes. The XRD of the calcined sample (Fig. 2) indicated the presence of a cubic oxide phase which is obtained by the loss of water and CO<sub>2</sub> from the anionic interlayer of hydrotalcite. It showed the formation of the CuO phase only with Fe(III) inside.

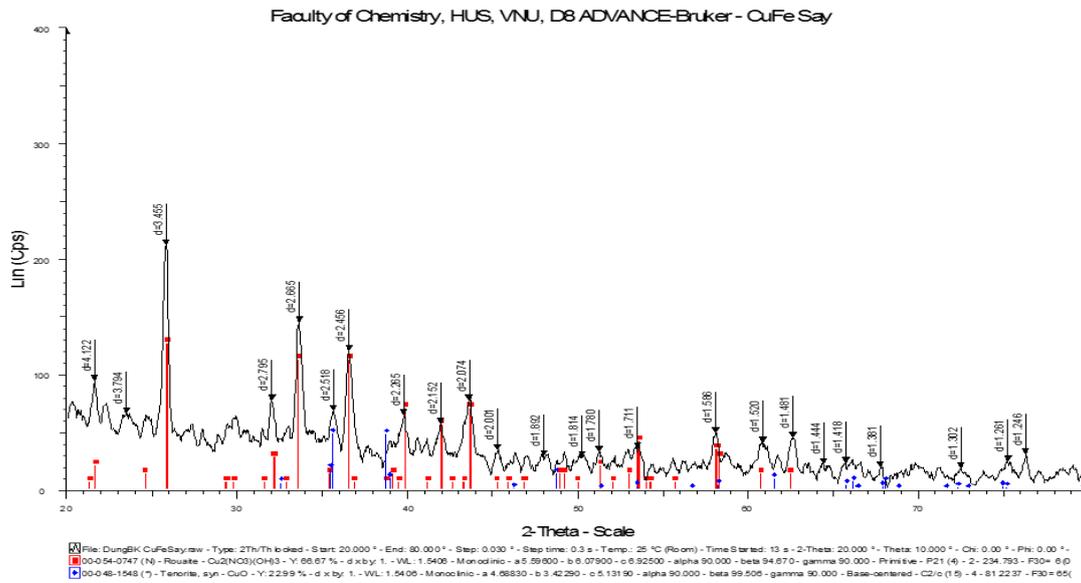


Fig. 1. XRD powder pattern of the catalyst

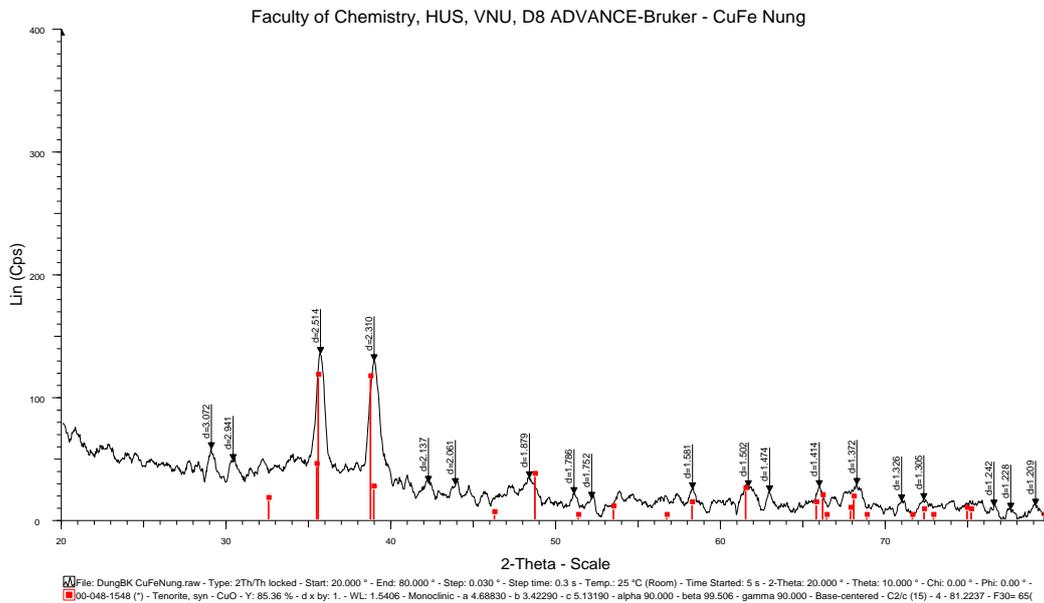
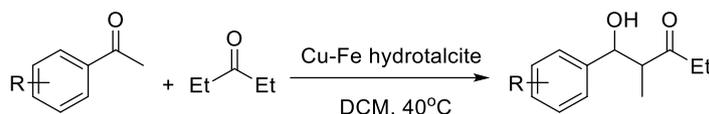


Fig. 2. XRD powder pattern of the calcined sample

### 3.2. Catalytic performance of Cu-Fe hydrotalcite on the Aldol reaction

The Cu-Fe hydrotalcite was applied in Aldol reaction between benzaldehydes and pentan-3-one to study its catalytic performance. The obtained results are summarized in Table 1.

Table 1. Aldol reaction between benzaldehydes and pentan-3-one

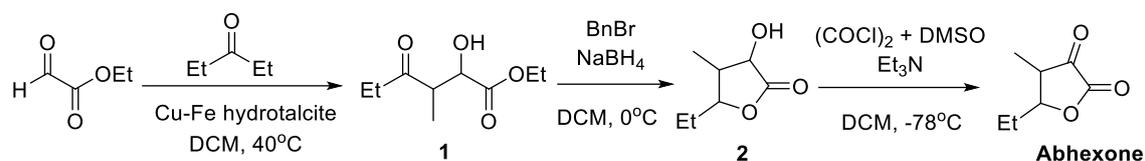


Entry	Benzaldehyde	Yield (%)
1		48.64
2		62.78
3		49.59
4		53.33
5		47.18

The reactions occurred with moderate yields. The nitro substituent in the benzene ring of benzaldehyde induced the aldolization while the electron-donating group such as methyl group reduced the reaction yield. Besides, we investigated the Aldol reaction of two aromatic carbonyl (benzaldehyde and acetophenone) or two aliphatic carbonyl compounds (propionaldehyde and pentan-3-one). Both reactions proceeded smoothly to deliver the desired products in considerable yields (42.08% and 43.48%).

### 3.3. Synthesis of Abhexone

The Cu-Fe hydrotalcite catalyzed Aldol transformation was applied in the total synthesis of Abhexone, a caramellic flavor used widely in the cosmetics and food industry. The synthesis of Abhexone was illustrated in Scheme 1. At first, ethyl glyoxylate reacted with pentan-3-one under Cu-Fe hydrotalcite catalysis to afford ethyl 2-hydroxy-3-methyl-4-oxohexanoate (**1**) in 83.46% yield. IR data, <sup>1</sup>H-NMR (Fig. 3) and <sup>13</sup>C-NMR spectra showed that **1** was prepared successfully.



In the second step, the cyclization of **1** led to the formation of 5-ethyl-3-hydroxy-4-methyltetrahydrofuran-2-one (**2**) with 62.35% yield. And finally, Abhexone was obtained in 52.3% yield and excellent selectivity when **2** was oxidized by the oxidizing agent generated in situ from oxalyl chloride and dimethyl sulfoxide at  $-78^{\circ}\text{C}$ . Spectral data revealed the formation of desired products and was in agreement with the data in the literature [13].

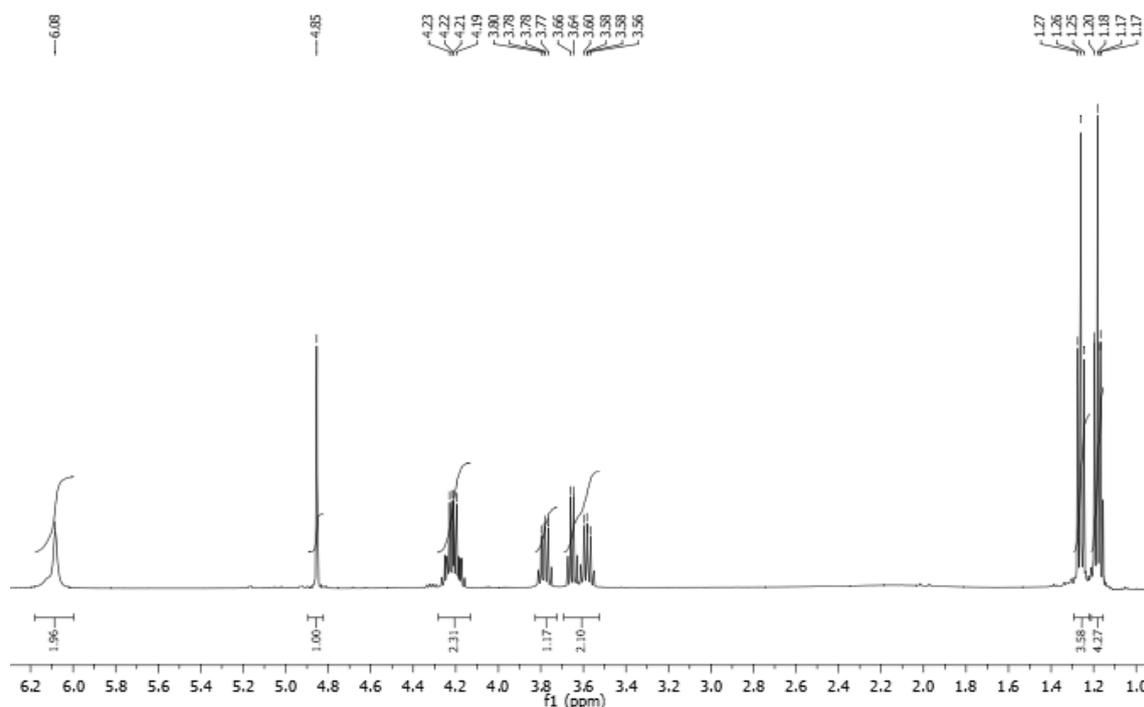


Fig. 3.  $^1\text{H-NMR}$  spectrum of **1**

#### 4. Conclusion

Cu-Fe hydrotalcite catalyst was successfully prepared by continual coprecipitation method. Its catalytic performance was investigated through the Aldol reaction between aromatic/aliphatic aldehydes or ketones. This reaction was also applied to the total synthesis of the desired product Abhexone in moderate yield and excellent selectivity.

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## NGHIÊN CỨU TỔNG HỢP XÚC TÁC Cu-Fe HYDROTALCITE VÀ ỨNG DỤNG TRONG PHẢN ỨNG ALDOL HÓA

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**Tóm tắt:** Nghiên cứu tổng hợp xúc tác dị thể Cu-Fe hydrotalcite bằng phản ứng đồng kết tủa, và hoạt hóa ở 200°C, xúc tác thu được đã ứng dụng thành công trong phản ứng Aldol hóa. Phản ứng diễn ra trong điều kiện êm dịu, dễ tiến hành và thân thiện với môi trường do xúc tác có thể thu hồi đến 99%, sản phẩm thu được với hiệu suất tương đối cao. Hệ xúc tác này còn thể hiện tính hiệu quả trong quy trình tổng hợp Abhexone, một hương liệu được sử dụng nhiều trong công nghiệp thực phẩm và mỹ phẩm.

**Từ khoá:** Phản ứng aldol hoá; hydrotalcite; xúc tác dị thể; abhexone.

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