Can Tho Journal of Medicine and Pharmacy 6(2) (2020)

SYNTHESIS OF IBUPROFEN IMPURITY C

Nguyen Thanh Duy[1*], Nguyen Nhat Thong[1], Phung Thi Anh Thu[1], Hoang Minh Dang[2], Nguyen Thi Thu Tram[2], Nguyen Thi Ngoc Van[1],
[1]Pharmacy Faculty, Can Tho University of Medicine and Pharmacy
[2]Basic Sciences Faculty, Can Tho University of Medicine and Pharmacy
**Corresponding author: nguyenthanhduy8@gmail.com*

ABSTRACT

***Background**: Synthesis ibuprofen impurity C (α-methyl-4-(2-methylpropyl) benzeneacetamide) which offers material in controlling and monitoring impurities in medications containing Ibuprofen in the ingredients. **Objectives**: Constructing Ibuprofen impurity C synthesis, purifying, identifying structure with the help of IR, HPLC, NMR. **Subjects and method**: Ibuprofen impurity C, chlorinate Ibuprofen with Oxalyl chloride, amidate acyl chloride with ammoniac. **Results**: Efficient, high-yielding procedure to synthesis Ibuprofen-related impurity C. Examination some conditions impact to the synthesis procedure. **Conclusion**: This method is facile and allows us to get the pure impurity C of Ibuprofen from simple starting materials.*

***Keywords:** Ibuprofen impurity C; Amide bond formation; N, N-imethylformamide.*

I. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have been one of the most popular drugs chosen in the treatment of pain, degenerative joint diseases and rheumatic disorders for years. The clinical effects of NSAIDs are based on the inhibition of the enzyme cyclooxygenase (COX), which catalyzes the formation of prostaglandins (PGs). Production of PGs is induced at sites of inflammation, where they are involved in the propagation of inflammation, pain, and fever. Inhibition of PGs production alleviates these pathologic effects, but it also interferes with the normal physiologic role of these molecules, that is, cytoprotection of gastric mucosa, hemostasis, renal function, gestation, and parturition [1]. As a result, long-term therapy with NSAIDs is frequently limited by their adverse effects, particularly those caused by gastrointestinal bleeding, ulceration and perforation [2]. Ibuprofen, chemically 2-(4-isobutylphenyl)propionic acid, is a well-known NSAID widely prescribed for the treatment of musculoskeletal disorders, inflammation, fever, primary dysmenorrhea and also in the management of mild pain [1], [2]. Similar to other prototypical NSAIDs (aspirin, indomethacin, etc.), ibuprofen suffers from the limitation of gastrointestinal toxicity caused by the presence of a carboxylic acid moiety in its structure [3].

Ibuprofen is one of the most common NSAIDs drugs that is indicated in many therapies. But over the times, ibuprofen may decompose into some related impurity of it. They are 2-(3-Isobutylphenyl) propanoic acid (A), 2-(4-butylphenyl) propanoic acid (B), 2-(4-isobutylphenyl) propanamide (C), 2-(4-methylphenyl) propanoic acid (D), 1-(4-isobutylphenyl) ethanol (E) that were reported. There are different quality control restrictions of ibuprofen impurities published worldwide accepted pharmacopoeias. In US Pharmacopoeia, impurity C is controlled by using HPLC method, (no more than 0.25% for each tablet). Impurity C is decomposed by ibuprofen over the times, so it is important to control impurity C concentration during expiry date. Especially, British pharmacopoeia 2016 and The United State pharmacopoeia 40 require that impurity C be included to compare when controlling the quality of materials and medicines containing ibuprofen [3].

There are several methods to synthesis impurity C of ibuprofen but most of them are carried out with a complex route and expensive materials. Herein, we are going to describe our method to synthesis impurity C easily by using simple chemical which can be proceeded in the laboratory with a rather quantitative yield.

Moreover, the impurity C of ibuprofen (4-isobutylacetophenone) appears via radical-induced decarboxylation followed by benzylic oxidation, and it has adverse effects on the central nervous system. Therefore, controlling and monitoring it from the ibuprofen products is an essential work. A reverse phase HPLC is a suitable method to follow the concentration as well as the impurity's appearance in ibuprofen products [4].

II. MATERIALS AND METHODS

2.1. Study contents

The materials used in this study are mentioned as follow ibuprofen, oxalyl chloride, dimethylformamide, concentrated ammonia solution and some organic solvents, such as methanol, dichloromethane, petroleum ether, diethyl ether were produced by Merck, Xilong Scientific or SigmaAldrich. The melting range of compounds was recorded on a Melting Point Apparatus, Stuart SMP3 based on the instruction of Vietnam Pharmacopoeia V. TLC Analysis was carried out using GF254 (Merck Millipore, Darmstadt, Germany) under UV Lamp 254/366nm (Camag TM, Camag Chemie-Erzeugnisse and Adsorptionstechnik AG, Muttenz, Switzerland). The infrared spectroscopy data of ibuprofenamide were recorded on a Bruker FTIR Spectrometer Alpha over the range of 4000 – 500 cm−1 by pressed pellet method using KBr. The spectrum was acquired by the accumulation of 3 scans with 4 cm−1 resolutions. The absorption values were represented in cm−1 [5]. HPLC was carried out by the Agilent LC 1100 (Agilent Technologies, Mississauga, ON, Canada), the acquisition of chromatogram and integration used MassLynx SCN 85 software. The chromatographic separation was achieved using an HPLC BEH C18 column (2.1 x 100 mm, 1.7 µm). The detection wavelength of 230 nm for paracetamol and ibuprofen (from 0 min to 7.20 min); 254nm for impurity C at room temperature (from 7.21 min to 10 min) was selected, with an injection volume of 2 µL and flow rates of 0.2 mL/min. The mobile phase was a three-step linear solvent gradient system consisting of (A) 0.01% aqueous triethylamine (pH = 7) and (B) methanol. The elution profile was: 2.5 min 98% A; then the solvent B was increased first to 50% in 2 min and subsequently to 98% in 2.5 min. The mobile phases were prepared fresh each day, vacuum-filtered through a 0.22 µm and degassed for 15 min [4]. ^{1}D NMR (^{1}H, ^{13}C Spectroscopy) experiments were performed on an Ascend™ Bruker 500 MHz NMR spectrometer (Bruker, Fallanden, Switzerland) using deuterated chloroform (CDC_{l3}) as a solvent and tetramethylsilane (TMS) as an internal standard. The ^{1}H chemical shift values were reported on δ scale in parts per million (ppm), relative to TMS (δ=0.00 ppm) and ^{13}C chemical shift values were reported relative to $CDCl_3$ (δ=49.3 ppm).

2.2. Synthesis of 2-[4-(2-methylpropyl)phenyl]propanamide

In a round bottom flask, we have 1.9 mL oxalyl chloride (22 mmol) slowly added to 5g ibuprofen (22 mmol) and 0.02 mL DMF (0.258 mmol) in 100 mL CH_2CI_2 at 5 °C. The mixture was stirred at room temperature with a magnetic stirrer (900 rpm) for 10 h and then cooled in an ice bath (1). In the next step of the route, we slowly added 10 mL concentrated NH_4OH to the mixture (1) at 5°C. After stirring for 1 hour at room temperature, the volatile organics were removed in vacuum and then we added 200 mL H_2O to the mixture. After

that, the residue resulting in a precipitated solid was collected by filtering in vacuo, washing by cool water and recrystallized from CH_2Cl_2: MeOH (5:5) to afford the corresponding amide [6]. Subsequence purification is proceeding by solid-phase extraction (SPE), which offered analytically pure Ibuprofenamide. The impurity is then identified by the help of TLC and IR, NMR spectrum.

2.3. Optimization of the synthesis

In 12 screw cap test tubes, we have 0.19 mL oxalyl chloride (0.22 mmol) slowly added to 0.225g ibuprofen (1 mmol) and 1 drop of DMF (0.258 mmol) in 10 mL CH_2CI_2 at 5 °C. The mixtures in these test tubes were stirred at room temperature with a magnetic stirrer (900 rpm) for 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24 hours, respectively. Then 1ml concentrated NH_4OH was slowly added to the mixture (1) at 5°C. After stirring for 1 hour at room temperature, the volatile organics were removed in vacuum and then we added 10 mL MeOH to the mixture. These mixtures were analyzed by TLC and HPLC. Semi-quantification results of TLC and quantification results of HPLC will identify the optimal time of synthesis.

III. RESULTS

The FT-IR spectra showed the absorption bands (cm^{-1}) at 3359. This absorption was due to the presence of N-H in amide functional group, while the absorption bands at 2951, 2867, 3185 was respectively due to the presence of asymmetrical C-H, symmetrical C-H and C=C vibration in the aromatic phenyl ring of compound 2 (2). The absorption band at 1658 indicated the presence of the conjugated carbonyl group.

The ^1H and ^{13}C NMR spectra also showed the appropriate chemical environment for protons and carbons of compound 2.

3.1. Characterization of new compounds

Melting point: m.p. = 113^0C - 114^0C.

3.2. 2-[4-(2-methylpropyl)phenyl]propanamide

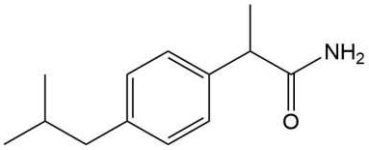

Figure 1. Structure of 2-[4-(2-methylpropyl)phenyl]propanamide.

The title compound was prepared from oxalyl chloride (1.9 mL, 22 mmol), ibuprofen (5g, 22 mmol) and DMF (0.02 mL, 0.26mmol) in CH_2CI_2 (100mL) according to General procedure 1. Purification by solid phase extraction gave the product as a white solid (2.28g, 46,29% yield). **^1H NMR** (500MHz, $CDCl_3$): δ = 7.21 (dd, J = 6.5, 1.5 Hz, 2H), 7,12 (d, J = 8Hz, 2H), 5.72 and 5.47 (b, 2H, NH_2), 3.58 (q, J = 7.5Hz, 1H), 2.46 (d, J = 7Hz, 2H), 1.84 (sept, J = 7 Hz, 1H), 1.52 (d, J = 7 Hz, 3H), 0.9 (d, J = 6.5 Hz, 6H), **^{13}C NMR** (125MHz, $CDCl_3$): δ 177.26, 140.95, 138.29, 129.70, 127.31, 46.20, 45.01, 30.15, 22.36, 18.22, **IR (film)** 3359 (br s), 3185 (br s), 2951 (s), 2867 (s), 1907 (w), 1657 (br s) 1514 (m) 1460 (s) 1405 (s), 1266 (m), 1114 (m), 998 (w), 842 (m), 690 (m).

3.3. HPLC

The representative chromatograms of the sample of impurity C was shown that the purity of the impurity was 79,45% (Table 1).

$$Purity = \frac{\textbf{C Area}}{\textbf{SumofArea}}.100\ (\%)$$

Table 1. Purity of C impurity.

SumofArea	C Area	Purity (%)
2682.31184	2130.972	79.45

IV. DISCUSSION

4.1 Reaction design and optimization

Based on the precedents above, we were attracted to the idea of preparing amide via chloride acylation. In terms of the proposed mechanism, this following sequence of events was envisioned. First, chlorination of the carboxyl group would form the corresponding acyl chloride, which would be attacked easily by the nucleophilic concentrated ammonia.

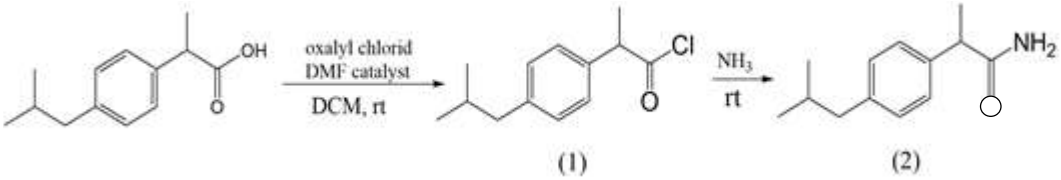

Figure 2. Reaction design.

The first step is chlorination of the carboxyl group in nonaqueous conditions via an oxalyl chloride agent. With the help of DMF (dimethylformamide) catalyst, acyl chloride derivative would be formed easily through Friedel-Craft acylation mechanism in dichloromethane solvent. As expected, ibuprofen was able to provide an unstable acyl chloride (compound 1) at room temperature after 6 hours of magnetic stirring in a round bottom flask. The reaction can perform at room temperature to provide an unstable acyl chloride. These agents and catalysts could give near quantitative yields for most carboxylic acid in general.

This step was carried out in several conditions and the results were provided in Figure 3 and Table 2.

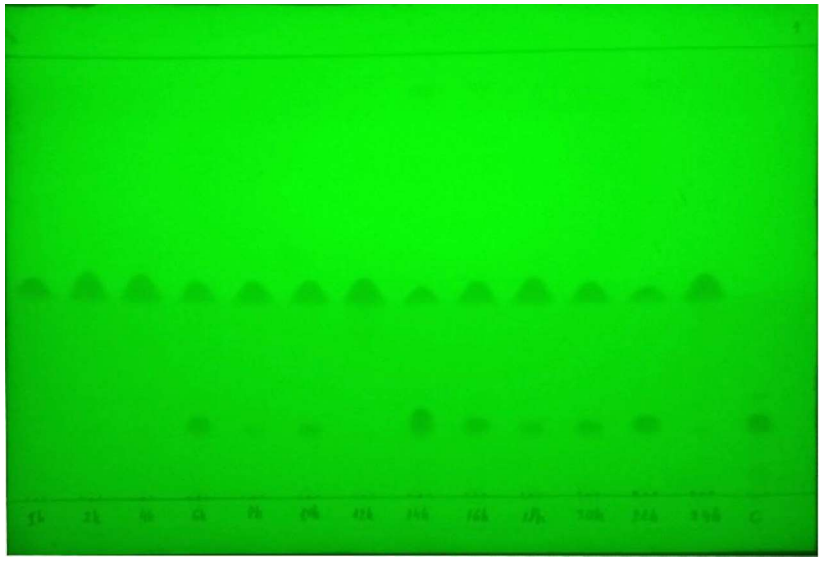

Figure 3. result of TLC.

Table 2. Yields of the total synthesis with the corresponding time.

Entry	Time (hours)	T (^{0}C)	Yield (%)
1	2	RT	3.84
2	4		3.3
3	6		67.83
4	8		12.3

The reaction in the first step would offer the most quantitative yield when it is carried out for 6 hours at room temperature.The second step is proceeding by an amidation between the product from the previous step (acyl chloride) and the ammonia solution in a round bottom flask. The reaction was conducted at room temperature for an hour to form the Ibuprofenamide (impurity C) finally.The method that we studied with the conditions above gave an efficient, high-yield, and convenient way to form an amide.

4.2. Proposal mechanism

The mechanism of these events follows a similar pathway to what has previously been described in this passage. The reaction of a carboxylic acid with oxalyl chloride started with a carboxyl substitution using the oxalyl chloride as an electrophilic and carboxylic acid as a nucleophile. The liberated chloride ion then acted as a nucleophile in a cascade reaction that released CO_2 and CO as an acid chloride form [7]. These events were promoted by the addition of a drop of DMF. The catalytic role of DMF was described in Figure 4. However, one of the major disadvantages of the previously cited chlorination agents is the HCl byproduct. The ammonia agents in the second step were acid sensitive and as a result, the acidifying ammonium chloride was formed, which decreased the pH of the reaction system and the amount of the ammonia substance. In terms of the second step, the amide bond was formed by reacting the acyl chloride with ammonia solution (Figure 5). The first stage involves a nucleophilic attack on the fairly positive carbon atom by the lone pair on the nitrogen atom in the ammonia [7] (Figure 5). The second stage happens in two steps. In the first, the carbon-oxygen double bond reforms and a chloride ion is pushed off (Figure 4). That is followed by the removal of a hydrogen ion from the nitrogen. This event might produce HCl as a byproduct.

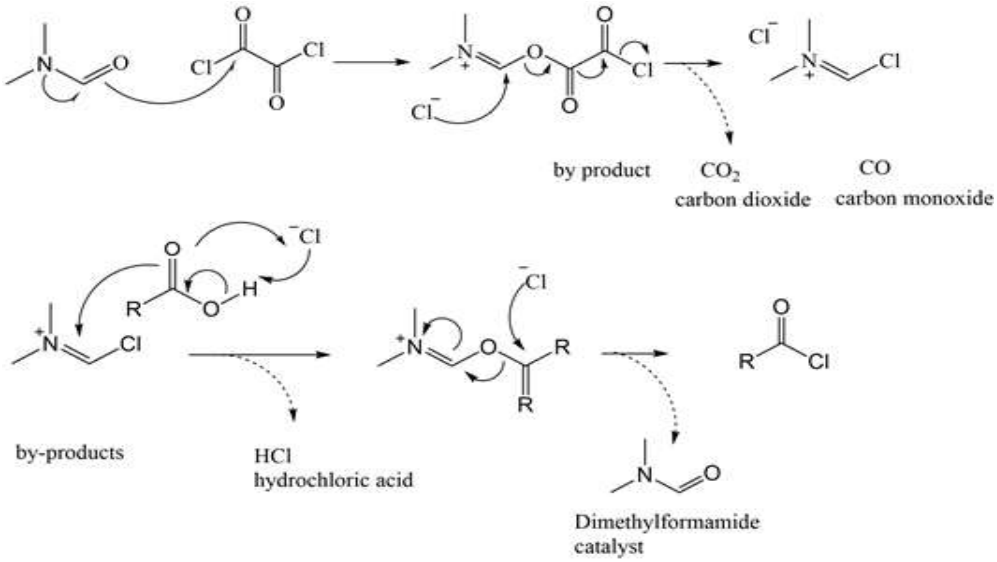

Figure 4

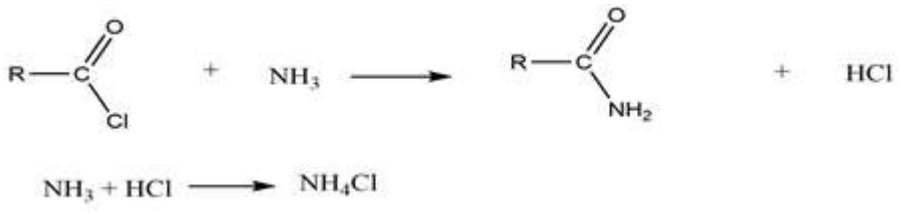

Figure 5

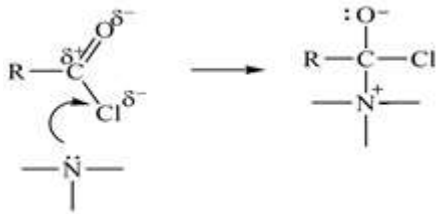

Figure 6

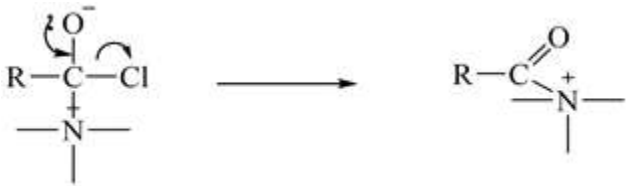

Figure 7

V. CONCLUSION

A two-step reaction has been conducted for the formation of an impurity C of ibuprofen. All the spectroscopic data agreed with the structure of the product that was expected. Besides, we have described an efficient, high-yielding, and two-stepped route to access an amide via the reactions between ibuprofen, oxalyl chloride, and ammonia solution. This method was facile and allowed us to get the pure impurity C of ibuprofen from simple starting materials. Ibuprofenamide (impurity C of Ibuprofen) formed from the reaction offers material in controlling and monitoring impurities in medications having Ibuprofen in the ingredients.

Acknowledgements: This research was supported by Can Tho University of Medicine and Pharmacy, Viet Nam. The authors thank Warenteck Company for the use of analytical instruments.

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Wolfram Ziegler, Matt Lindstrom, and Ruth McTavish (1971), "Nature Publishing Group", *Nature*, 26(138), pp. 584–585, 1971.

2. Carel IJsselmuiden and Ruth Faden (1992), "The New England Journal of Medicine Downloaded from nejm.org on January 31 2011,. Copyright © 1992 Massachusetts Medical Society. All rights reserved…" , 326,

3. Rocío García-álvarez, Javier Francos, Pascale Crochet, and Victorio Cadierno (2011), "Ibuprofenamide : a convenient method of synthesis by catalytic hydration of 2- (4-isobutylphenyl) propionitrile in pure aqueous medium", 52, pp. 4218–4220.

4. Nguyen Thi Ngoc Van, Tran Thi Tiet Nghia, Nguyen Manh Quan, and Nguyen Trung Kien (2018), "Rapid and simultaneous determination of paracetamol, ibuprofen and related impurity of ibuprofen by UPLC/DAD", *Pharm. Sci. Asia*, 45(4), pp. 213–220.
5. Neeraj Kumar, Subba Rao Devineni, Prasad Reddy Gajjala, Shailendra Kumar Dubey, and Pramod Kumar (2017), "Synthesis, isolation, identification and characterization of new process-related impurity in isoproterenol hydrochloride by HPLC, LC/ESI-MS and NMR", *J. Pharm. Anal.*, 7(6), pp. 394–400,.
6. Francis Kerdesky, Clint Brooks, Keren Hulkower, Jennifer Bouska, and Randy Bell (1997), "Conversion of Cyclooxygenase Inhibitors into Hydroxythiazole 5-lipoxygenase Inhibitors", 5(2), pp. 393–396,.
7. "Reaction between acyl chlorides and amines - addition / elimination." [Online]. Available: https://www.chemguide.co.uk/mechanisms/addelim/amines.html. [Accessed: 13-Oct-2019].

(Received: 08/11/2019 - Accepted: 13/12/2019)

STUDY ON PHYTOCHEMICAL OF THE STEMS OF *MORINDA PERSICAEFOLIA* COLLECTED IN AN GIANG PROVINCE

Nguyen Thi Thu Nguyet, Ly Tieu Hanh, Nguyen Ngoc Phuong Thao, Lam Tuan Nghia, Nguyen Xuan An, Tran Cong Duyen, Le Thanh Vinh Tuyen*
Can Tho University of Medicine and Pharmacy
**Corresponding author: ltvtuyen@ctump.edu.vn*

ABSTRACT

Objectives: *To determine the phytochemical of the stems of Morinda persicaefolia collected in Tan Phu, An Giang Province, Vietnam; to fractionate and isolate pure compounds from the anthranoid-enriched fractions.* ***Methods:*** *stems powder was extracted with ethanol 70% by percolation and liquid-liquid partition. The chloroform fraction was further isolated by vacuum liquid chromatography (VLC), fractional partition with different pH solution and column chromatography (CC) to obtain pure compound(s). The isolated compound(s) were structurally identified on the basis of UV-Vis spectra.* ***Results:*** *the pure compound isolated from anthranoid-enriched fractions was identified as an alizarin derivative.* ***Conclusion:*** *the results provide informative references to conduct research on biological effects afterward.*

Keywords: *Morinda persicaefolia, Anthranoid, An Giang.*

I. INTRODUCTION

Morinda persicaefolia Ham., locally known as Nhau nuoc or Nhau nho, was traditionally used as a laxative or antihypertensive therapies. Contemporary, studies on phytochemical of *Morinda persicaefolia* were still limited. In order to contribute information in phytochemical, biological effects and to take the advantages of Vietnamese botanical drugs in treatment, the study on *Morinda persicaefolia,* which was collected in Tan Phu, An Giang Province, was carried out with a main focus on:

- Investigating the qualitative phytochemical of the stems of *Morinda persicaefolia*
- Fractionating and isolating pure compound(s) from the anthranoid-enriched fractions.