I.A.U. Karaj Branch

Journal of Applied Chemical Research, 8, 3, 91-95 (2014)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

Synthesis of Ibuprofen with Modified and Economical Process as an NSAID Drug

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Received 06 Feb. 2014; Final version received 27 May. 2014

Abstract

Ibuprofen (**I**) is the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) has been synthesized in recent years. NSAIDs are the first choice of drugs that are normally used for the treatment of pain and inflammation. There are many methods for synthesizing of **I** but each one has some difficulties as raw materials preparation, reaction conditions and etc.

In an effort to establish modified method with improved and economical yield, **I** was synthesized by the mesylation of ethyl lactate in the presence of triethylamine or pyridine at 273 K to obtain the corresponding ethyl-2-(methylsulphonyloxy) propanoate (**II**). Then, Friedel-Crafts alkylation of **II** with isobutylbenzene for single step synthesis of ethyl-2-(4-isobutylphenyl) propanoate (**III**) was carried out by heating with $AlCl_3$ under neat reaction conditions. Finally, ethyl-2-(4-isobutylphenyl) propanoate (**I**) formed in 50 % yield was hydrolyzed with KOH in methanol and acidified with HCl to afford the desired product.

Keywords: *Non-steroidal anti-inflammatory drugs (NSAIDs), Ibuprofen, modified method with improved and economical yield.*

Introduction

Ibuprofen[(±)-2-(4-isobutylphenyl)]propionic acid (I) belongs to a class of non-steroidal anti-inflammatory drugs (NSAIDs), which are used to reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid by cyclooxygenase enzyme (COX) thereby the production of prostaglandin [1-8]. It is considered to be the prototype for the family of synthetic 2-arylpropionic acids, profens, a sub-class of the non-steroidal anti-inflammatory drugs (NSAIDS). In recent

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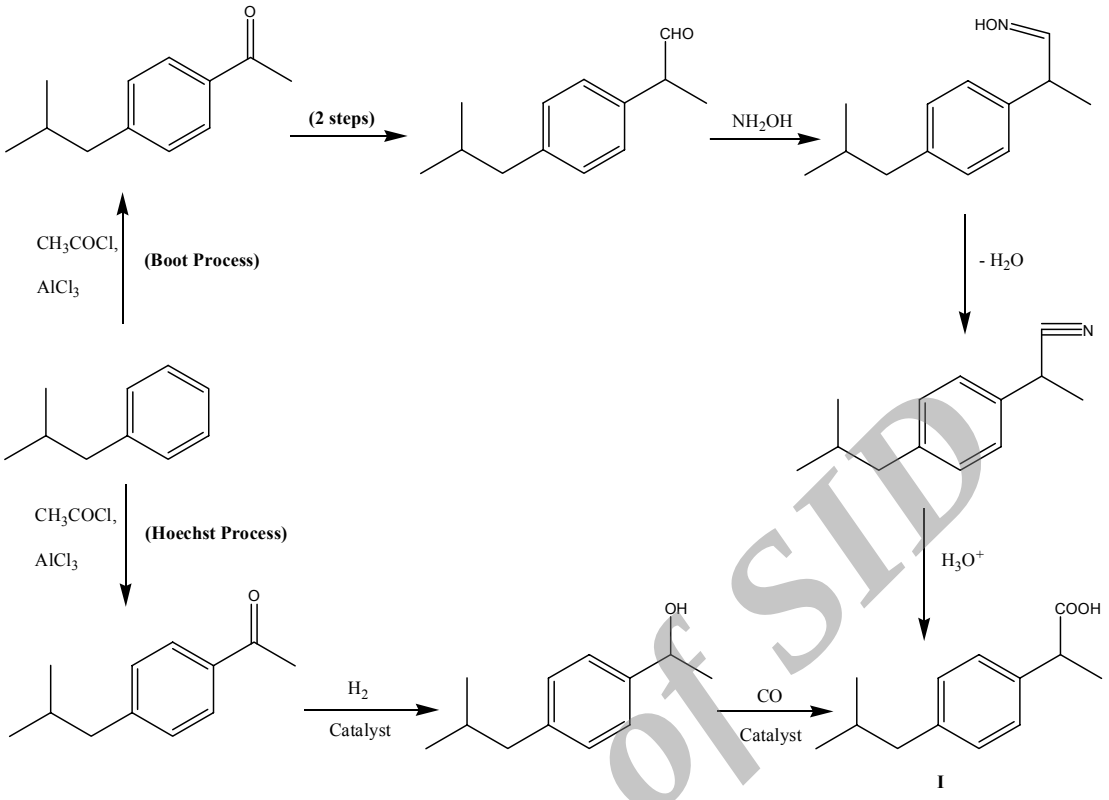
years, the profens have come to dominate this therapeutic class. It is used to treat arthritis, muscular strain, cephalalgia, and others. The profens have an asymmetric carbon centre attached to a carboxylic acid, a methyl, and an aryl group of varying structure. Some of the available profen drugs are ibuprofen, naproxen, ketoprofen, and flurbiprofen [9].

I is distributed over the counter and naproxen belongs to the top-ten of drugs marketed worldwide in 1989. It is used to relieve the symptoms of a wide range of illnesses such as headaches, backache, period pain, dental pain, neuralgia, rheumatic pain, muscular pain, migraine, cold and flu symptoms and arthritis. The two most popular ways to obtain ibuprofen are the Boot process and the Hoechst process (Scheme .1). The Boot process is an older commercial process developed by the Boot Pure Drug Company, and the Hoechst process is a newer process developed by the Hoechst Company. Boot's Company has developed the process for the synthesis of ibuprofen and patented in 1960s [10]. This synthesis consists of six steps and resulted in unwanted by-products.

Most of these routes to ibuprofen begin with isobutylbenzene and use Friedel-Crafts acylation. Hoechst process, with the assistance of catalysts, is completed in only three steps. Cheminor Drugs have developed a process for an improved version of production of ibuprofen based on chiral synthesis. This method is significant given that pure (S)- ibuprofen (the active form of ibuprofen) could near halve the regular ibuprofen dosage, besides improving the side-effect profile.

However, the human body can convert the inactive (R) form into the (S) form, so eventually 100 % of the ibuprofen taken becomes active. The process discovered by Cheminor is therefore unlikely to have commercial significance. It has three major types of effect which are all linked to its primary action, the inhibition of an enzyme known as arachidonate cyclooxygenase or COX of which there are two types COX-1 and COX-2 [11].

In this research, synthesis of ibuprofen by Friedel-Crafts alkylation of isobutylbenzene with lactic acid was done using solid acid catalyst like $AlCl_3$.



Scheme .1 Boot's and Hoechst synthesis of ibuprofen.

Experimental Section

General

All chemicals were purchased from Merck Chemical Company. Melting points (uncorrected) were determined with a digital Electro Thermal Melting Point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK).

Preparations (Scheme 2)

A.Preparation of ethyl-2-(methylsulphony loxy) propanoate (II)

To a solution of ethyl lactate (8.47 mmol) and triethylamine (1.77 ml, 12.71 mmol) in 15 ml of dry DCM was added portionwise MsCl (9.32 mmol) at 0°C. The resultant mixture was stirred at 273 K for an hour and then at room temperature for 2 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography over silica gel (100 – 200 mesh) afforded pure ethyl-2-(methylsulphonyloxy) propanoate **II** (1.25 g, 75 %).

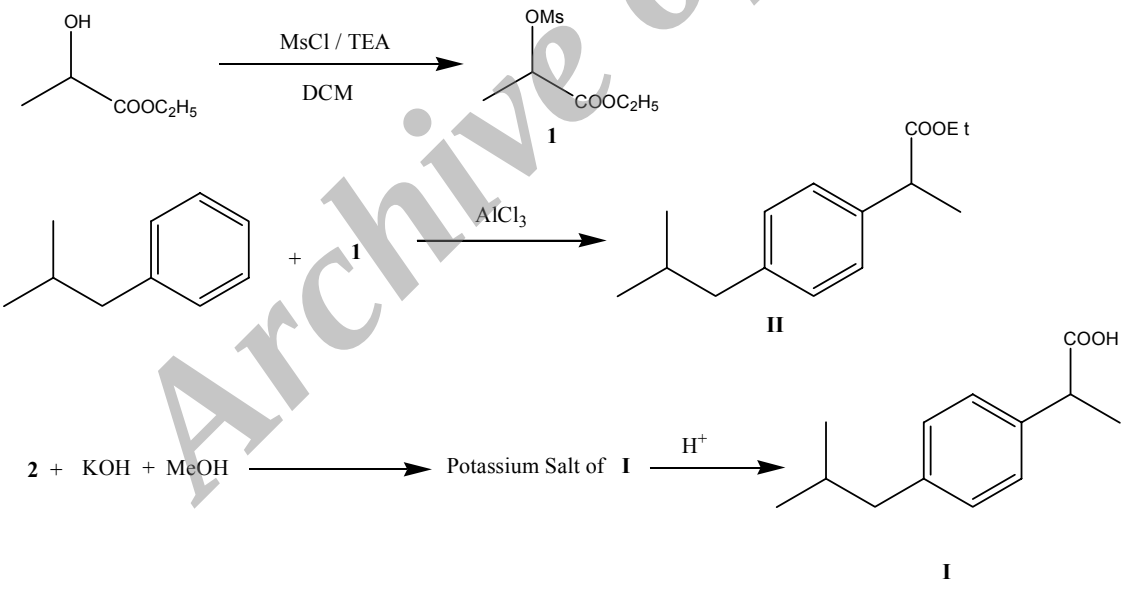
B. Preparation of ethyl-2-(4-isobutylphenyl) propanoate (III)

$AlCl_3$ (10.20 mmol) was added to

isobutylbenzene (20.41 mmol) at 273 K. Ethyl-2-(methylsulphonyloxy) propanoate (II) was added to the cold solution portionwise and the mixture was warmed to room temperature. It was then heated to 353 K for 8 h and then cooled to room temperature. The reaction mixture was quenched with dil. HCl at 273 K and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. Purification of the crude compound by column chromatography over silica gel using hexane as an eluent yielded the pure product **III** (2.38 g, 50 %).

C. Preparation of ibuprofen (I)

To a solution of ethyl-2-(4-isobutylphenyl) propanoate (4.27 mmol) in 6 ml of MeOH was added a solution of KOH (8.55 mmol) in 5 ml of water. The resultant solution was stirred at room temperature for 4 h. Methanol was removed under reduced pressure and the resulting solution was extracted with EtOAc and the organic mixture was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the potassium salt of compound I which converted to free acid (**I**) by acidification with HCl (750 mg, 85 %).



Scheme 2. Our modified method for synthesizing of ibuprofen.

Results and discussion

Different chemical structures of 2-arylpropionic acids (main family of NSAIDs) have been found to show different analgesic and anti-inflammatory activities. The main structural features of these compounds may be considered in terms of three basic units: (i) the acidic side chain; (ii) the central aryl moiety; and (iii) a hydrophobic terminal residue [12-15].

In this research, ibuprofen was synthesized by Friedel-Crafts type alkylation of isobutylbenzene with ethyl lactate instead of reaction with lactic acid itself. Also, AlCl3 was employed as a catalyst for this alkylation and mesylate of ethyl lactate was done by the reaction of ethyl lactate and mesyl chloride as a good leaving group.

Therefore by this method, ibuprofen was could be produced as improved and economical yield which was applied in industry as a workable method.

Acknowledgements

This article is a report made out a research project that enjoyed the financial supports of Karaj Branch, Islamic Azad University, Karaj, Iran. The authors thank appreciate S. Azami, N. Alizade, S. Kazemi and M. Daniali for their assistance in this research.

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