**Comparative Evaluation of Conventional and Sustainable Synthetic Approaches for Ibuprofen Production**

Author: Priyabrata Roy

Department of Chemistry, Victoria Institution (College), 78B, A.P.C. Road, Kolkata 700009, West Bengal, India

e-mail: priyo\_chem@yahoo.co.in

ABSTRACT

Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), has traditionally been synthesized via a six-step process involving stoichiometric use of toxic reagents such as hydrochloric acid and ammonia, resulting in multiple intermediates, low atom economy (40.04%), and significant generation of inorganic waste, including aluminum trichloride hydrate. In contrast, the green synthesis route, developed through a streamlined three-step process, demonstrates substantial improvements in environmental and process efficiency. This alternative method minimizes hazardous inputs, reduces waste production, and achieves a higher atom economy (77.44%), with acetic acid as the only major by-product—readily applicable in other chemical processes. The comparison underscores the green synthesis of Ibuprofen as a model for sustainable pharmaceutical manufacturing, highlighting its potential for reduced ecological impact, improved resource utilization, and alignment with the principles of green chemistry.

*Keywords****:*** Ibuprofen, Aspirin, Green Chemistry, Sustainable Synthesis, NSAIDs

**I. INTRODUCTION**

The development of non-steroidal anti-inflammatory drugs (NSAIDs) represents a major milestone in the history of medicinal chemistry1. One of the earliest and most iconic NSAIDs, aspirin (acetylsalicylic acid), was first synthesized in 1883 in Germany by chemists at Friedrich Bayer & Co2. Aspirin was designed as a derivative of salicylic acid, a natural compound originally isolated from willow bark and known for its analgesic and antipyretic properties3. However, salicylic acid in its native form caused severe gastric irritation and was poorly tolerated in long-term therapy4.

The introduction of aspirin marked a breakthrough, as it retained the anti-inflammatory, analgesic, and antipyretic effects of salicylic acid while being less irritating to the gastric mucosa. This was achieved through acetylation of the phenolic hydroxyl group, a modification that reduced the compound’s acidity and corrosiveness. Aspirin soon became a widely prescribed medication for conditions such as headaches, muscle pain, fever, and rheumatoid arthritis. Nonetheless, despite being a gentler alternative to salicylic acid, aspirin still retained some gastrointestinal toxicity, especially with frequent or prolonged use, often leading to gastritis, peptic ulcers, or even duodenal bleeding in susceptible individuals.

By the mid-20th century, the medical community had begun to recognize the need for safer and more effective alternatives to aspirin5. This led to a global research initiative to discover next-generation NSAIDs with improved therapeutic indices. In the 1960s, pharmaceutical chemists at the Boots Pure Drug Company in Nottingham, England, undertook a systematic exploration of arylpropionic acid derivatives, structurally related to salicylic acid. Among the series of synthesized analogues, one compound—later named ibuprofen—emerged as particularly promising due to its potent anti-inflammatory activity and significantly improved gastrointestinal tolerability profile.

Ibuprofen, chemically known as (±)-2-(4-isobutylphenyl)propionic acid, differs structurally from aspirin in both its mechanism of action and pharmacokinetics. While both drugs function primarily through cyclooxygenase (COX) inhibition, ibuprofen exerts a reversible inhibition of COX enzymes, whereas aspirin irreversibly acetylates the active site6. This reversible nature contributes to ibuprofen's better safety profile in many cases.



A key feature of the ibuprofen molecule is the presence of a chiral center at the α-carbon adjacent to the carboxylic acid group, rendering it capable of existing as two enantiomers: the (S)-(+)-enantiomer, which is pharmacologically active, and the (R)-(–)-enantiomer, which is significantly less active7. Interestingly, when racemic ibuprofen is administered, the human body is capable of unidirectional chiral inversion, enzymatically converting a substantial portion of the inactive R-enantiomer to the active S-form in vivo8. This stereochemical interconversion, mediated primarily by acyl-CoA synthetases and epimerases, ensures that even racemic mixtures of ibuprofen deliver a predominantly active pharmacological effect.

Despite this metabolic chiral inversion, modern pharmaceutical science has increasingly advocated for the use of enantiomerically pure drugs, where feasible, due to their enhanced potency, lower effective doses, and reduced side effects9. For many chiral drugs, only one enantiomer exerts the desired therapeutic activity, while the other may be inactive, less potent, or in some cases toxic. Examples of this phenomenon abound in medicinal chemistry, reinforcing the importance of chirality in drug design and development10.

In the case of ibuprofen, the racemic mixture remains in wide clinical use, primarily due to its cost-effectiveness, rapid onset of action, and proven safety in large populations11. The active S-enantiomer (known commercially as dexibuprofen) has been marketed in some regions as a potentially more efficient alternative, though the clinical advantages over the racemic drug have not been deemed sufficient to replace it in mainstream practice.

The evolution from aspirin to ibuprofen not only exemplifies the progressive refinement of NSAID pharmacology but also reflects broader advances in stereoselective synthesis, metabolic understanding, and rational drug design12. These innovations continue to shape the development of next-generation anti-inflammatory agents, aiming for improved selectivity, reduced side effects, and enhanced patient compliance.

**2. SYNTHESIS**

For aldehydes and most aliphatic ketones, the position of equilibrium favorscyanohydrin formation. For many aryl ketones (ketones in which the carbonyl carbonis bonded to a benzene ring) and sterically hindered aliphatic ketones, however,the position of equilibrium favors starting materials; cyanohydrin formation is not auseful reaction for these types of compounds13. The following synthesis of ibuprofen,for example, failed because the cyanohydrin was formed only in low yield.



Reducing an alcohol involves converting the alcohol to the tosylate ester, then using a hydride reducing agent to displace the tosylate leaving group. This reaction works with most primary and secondary alcohols. Wade, page: 479

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A major consideration in any industrial synthesis is atomefficiency; it is most efficient to use only reagents whoseatoms appear in the final product. An example of theevolution of syntheses with greater and greater atomefficiency is the industrial synthesis of ibuprofen14.

***Synthesis I***

One of the earliest industrially adopted synthetic routes for the manufacture of ibuprofen, a widely prescribed non-steroidal anti-inflammatory drug (NSAID), was a multi-step process centered on the strategic introduction of a methyl substituent adjacent to the carboxylic acid moiety of 4-isobutylphenylacetic acid. This classical method, developed in the 1960s by Boots Pure Drug Company, represented a significant advancement at the time in large-scale organic synthesis, enabling the commercial availability of ibuprofen15. However, it also embodied many of the limitations of early pharmaceutical manufacturing in terms of environmental sustainability and atom efficiency.

The synthesis commenced with the Fischer esterification of 4-isobutylphenylacetic acid. In this step, the carboxylic acid was converted into its ethyl ester derivative by refluxing with ethanol in the presence of a strong acid catalyst, typically concentrated sulfuric acid. The purpose of esterification was twofold: it served to activate the molecule for subsequent carbon–carbon bond-forming reactions and also protected the carboxylic acid group under the strongly basic conditions of the next step.

The resulting ethyl ester underwent a crossed Claisen condensation with diethyl carbonate, using sodium ethoxide as the base. This transformation led to the formation of a β-keto diester intermediate (commonly referred to as compound B) via generation of a resonance-stabilized enolate. This intermediate possessed a central active methylene group, which is flanked by two electron-withdrawing carbonyl groups, significantly enhancing its acidity and reactivity. The stabilized enolate of compound B is then well-suited for electrophilic alkylation.

Subsequently, methyl iodide was introduced as the electrophilic methylating agent, allowing for the installation of the desired methyl group on the methylene carbon. This alkylation resulted in the formation of a disubstituted malonic ester (compound C). The two ester groups in compound C were then subjected to acidic or basic hydrolysis, converting them into carboxylic acids and yielding the corresponding disubstituted malonic acid (compound D).

The final step involved thermal decarboxylation of compound D. Upon heating, one of the carboxylic acid groups was lost as carbon dioxide, and the remaining structure was rearranged to furnish racemic ibuprofen—the target molecule. While this synthesis was robust and reproducible on an industrial scale, it required multiple unit operations, careful pH control during hydrolysis, and elevated temperatures for decarboxylation, all of which contribute to increased energy consumption and process complexity.

From a green chemistry perspective, this route is not atom-economical. Out of the 18 carbon atoms present in intermediate C, only 13 carbon atoms are retained in the final ibuprofen structure. The remainder are lost as waste16, predominantly in the form of carbon dioxide and by-products generated during ester hydrolysis. Moreover, the use of stoichiometric quantities of toxic and corrosive reagents, such as methyl iodide and strong mineral acids, raises additional concerns regarding operator safety, waste management, and environmental impact.

This significant loss of carbon content and generation of inorganic and organic waste highlights one of the major drawbacks of early pharmaceutical synthetic methods. Though efficient in terms of yield and feasible for large-scale implementation, such processes lacked the sustainability and resource conservation considerations that are now central to modern chemical manufacturing. The inefficiencies of this traditional route have driven the development of newer, greener synthetic strategies that emphasize minimal step count, atom economy, waste reduction, and safer reagent profiles.



The transition from this early methodology to modern alternatives represents a paradigmatic shift in pharmaceutical chemistry—from maximizing yield alone to optimizing holistic process metrics, including E-factor, process mass intensity (PMI), and life-cycle assessment (LCA). The need for such improvement has been particularly acute in the context of active pharmaceutical ingredients (APIs) like ibuprofen, where global demand and high production volumes necessitate not just cost-effective, but also environmentally responsible synthetic technologies.

***Synthesis II***

An alternative synthetic route to ibuprofen that exhibits significantly improved atom economy and aligns better with the principles of green chemistry begins with 4-isobutylacetophenone as the starting material17. This method reduces the number of steps and minimizes waste by employing more direct transformations and avoiding stoichiometric use of hazardous reagents, making it more attractive for large-scale pharmaceutical manufacturing.

The first step in this sequence involves the reaction of 4-isobutylacetophenone with chloroacetonitrile in the presence of a strong base such as sodium ethoxide. This reaction results in the formation of an epoxynitrile intermediate (compound E) via nucleophilic addition and subsequent intramolecular epoxidation. The base facilitates the formation of the enolate of the ketone, which then undergoes alkylation with chloroacetonitrile, followed by cyclization to form the three-membered epoxide ring. The nitrile group introduced in this step serves as a latent carboxylic acid moiety that will later be unmasked during hydrolysis.

In the next step, compound E is treated with lithium perchlorate (LiClO3), a Lewis acid catalyst, which promotes the rearrangement of the epoxide ring. The electrophilic lithium ion activates the epoxide oxygen, facilitating ring opening and rearrangement to yield an α-cyanoketone intermediate (compound F). This transformation is a key step, converting a strained heterocycle into a more stable, functionally rich intermediate capable of undergoing facile hydrolysis.

The α-cyanoketone group in compound F is chemically analogous to an acid chloride in terms of its reactivity toward hydrolysis. The adjacent carbonyl and nitrile functionalities activate the methylene group, making it susceptible to nucleophilic attack by water under acidic or basic conditions. Upon hydrolysis, compound F is converted into ibuprofen, with the nitrile group transforming into a carboxylic acid and releasing cyanide ion (CN⁻) as a by-product. This step is particularly efficient, as it converts both functional groups into the desired carboxylic acid without requiring the use of harsh chlorinating agents or complex protecting group strategies18, 19.

This synthetic route stands out for several reasons. Firstly, it minimizes the number of reaction steps compared to the traditional synthesis. Secondly, the process utilizes carbon atoms more efficiently, resulting in a higher atom economy. In contrast to the original route, which involved significant loss of carbon content through decarboxylation and hydrolytic degradation, this pathway ensures that a greater proportion of the atoms from the starting materials are incorporated into the final ibuprofen molecule. The improved yield, reduced waste generation, and use of catalytic rather than stoichiometric reagents position this synthetic strategy as a more environmentally benign and economically favorable approach for ibuprofen production20.

Overall, this route illustrates the advantages of modern synthetic design in pharmaceutical chemistry—integrating atom economy, functional group interconversion, catalytic processes, and mild reaction conditions to create a cleaner, safer, and more sustainable manufacturing protocol. It serves as a compelling example of how advances in organic synthesis and reaction engineering can transform the production of widely used drugs, aligning with both regulatory expectations and environmental sustainability goals20, 21.



***Synthesis III***

The development of a more environmentally benign and industrially efficient synthesis of ibuprofen stands as a milestone in green chemical process innovation. This alternative, known as the “green route,” was engineered by Boots–Hoechst–Celanese (BHC) Company in the United States and garnered international recognition for its contributions to sustainable industrial practices. In acknowledgment of its technological and environmental significance, the process was awarded the Kirkpatrick Chemical Engineering Achievement Award in 1993 and subsequently honored with the prestigious Presidential Green Chemistry Challenge Award in 199722.

The first step of this three-step synthetic sequence involves the acid-catalyzed Friedel–Crafts acylation of isobutylbenzene using acetic acid in the presence of hydrogen fluoride (HF), which acts as both solvent and catalyst. Remarkably, hydrogen fluoride in this context is fully recoverable and reusable, thereby minimizing environmental hazards and waste production. When the acetic acid formed as a by-product in this step is valorized for alternative industrial applications, the effective atom economy approaches 100%, reflecting a zero-waste ideal in line with green chemistry principles.

The second step involves the reduction of the intermediate aryl ketone to its corresponding secondary alcohol. This transformation is achieved through catalytic hydrogenation using Raney nickel, a finely divided, highly porous form of nickel alloyed with aluminum. Raney nickel is widely respected for its stability, high surface area, and robust catalytic performance under mild conditions. Importantly, this reaction proceeds with complete incorporation of all atoms into the product, yielding an atom economy of 100%.In the final stage, the synthesized alcohol undergoes carbonylation to yield ibuprofen. This reaction is catalyzed by palladium (Pd) complexes, known for their excellent turnover efficiency and recyclability in carbon–carbon bond-forming reactions. Like the previous steps, this transformation is conducted under mild and controlled conditions and generates no stoichiometric waste, thereby achieving an ideal atom economy of 100%.Collectively, the BHC green route exemplifies the transformative impact of green chemistry in pharmaceutical manufacturing. The process not only reduces the number of synthetic steps—from six in the traditional route to three—but also minimizes waste, improves yield, and eliminates the need for hazardous reagents such as aluminum trichloride, hydrochloric acid, and stoichiometric bases. Additionally, the catalyst systems used in the green process (HF, Raney nickel, and Pd) are all recoverable, recyclable, and operate under environmentally benign conditions.This synthesis route has become a textbook example of green process design, illustrating how conventional multi-step procedures with poor atom economy can be re-engineered into streamlined, efficient, and environmentally responsible alternatives. It underscores the feasibility of scaling up green chemistry principles to meet the demands of large-volume drug production, without compromising cost, performance, or safety. The BHC ibuprofen process remains a benchmark for future developments in the design of sustainable pharmaceutical processes.



The ultimate in atom efficiency in the synthesis of ibuprofen is achieved in the following synthesis. Catalytic reduction of the carbonyl group of 4-isobutylacetophenone gives the alcohol G. Palladium-catalyzed carbonylation of G gives ibuprofen. The one carbon atom introduced in the synthesis appears in the final product!

**3. Conclusions**

When assessed through the principles of green chemistry, the traditional synthesis of ibuprofen—consisting of six steps—reveals several inefficiencies, including high energy consumption, significant waste generation, and the use of hazardous reagents. In contrast, the Boots–Hoechst–Celanese (BHC) green route offers a streamlined, three-step alternative that minimizes environmental impact. This modern approach employs recyclable catalysts and solvents, significantly reduces by-products, and operates under milder, energy-efficient conditions, making it a more sustainable and economically favorable process for large-scale pharmaceutical manufacturing.

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