**Sustainable Approaches for Synthesizing Paracetamol Using Renewable Phenolic Resources**

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ABSTRACT

This chapter discusses three renewable phenol-based synthetic routes to paracetamol reported in the literature: acetamidation of hydroquinone, imination and reduction of benzoquinone, and hydrogenation of 4-nitrophenol. These pathways were evaluated using Green Chemistry metrics and industrial applicability. While the hydroquinone and benzoquinone methods exhibited low conversion rates and limited selectivity, the 4-nitrophenol route demonstrated superior performance, offering high yields, efficient conversion, and favorable environmental metrics. When benchmarked against conventional industrial processes, the 4-nitrophenol route proved comparable or advantageous in terms of sustainability, feedstock cost, and process efficiency, highlighting its potential for greener pharmaceutical manufacturing.

*Keywords****:*** Paracetamol, Renewable, Green Chemistry, Sustainable Synthesis, Phenolic Resources

**I. INTRODUCTION**

Paracetamol (also known as 4-hydroxyacetanilide) was first synthesized in 1878 by the American chemist Harmon Northrop Morse, and later introduced into clinical use by von Mering in 18871,2. Despite this early recognition, it was soon overshadowed by phenacetin, which became the preferred analgesic for decades3. The crucial role of paracetamol as the active metabolite of both acetanilide and phenacetin was identified by Brodie and Axelrod in 1948, who also linked phenylhydroxylamine—a metabolite of acetanilide—to methemoglobinemia4.

Paracetamol was reintroduced to the pharmaceutical market in the mid-20th century, gaining wide acceptance by the 1980s as concerns over phenacetin's toxicity, including nephrotoxicity and psychotropic effects, led to its decline5,6. Although initially slow to gain global popularity due to doubts about its safety profile, paracetamol has since become one of the most widely used drugs for the treatment of pain and fever7. Beyond its therapeutic uses, it also finds application in chemical industries—as a stabilizer, intermediate, and even in ecological control8.

Despite its widespread use, the production of paracetamol remains geographically concentrated, causing supply vulnerabilities in many regions. These challenges are further exacerbated in developed countries where strict environmental regulations increase production costs9. Consequently, there is growing interest in developing alternative synthetic routes based on the principles of green chemistry. Such routes aim to reduce environmental hazards, diversify production, and improve access to this essential medicine across the globe10,11.

**2. SYNTHETIC ROUTES OF PARACETAMOL**

Paracetamolis an amide that can be disconnected either to amine + acyl chloride or to amine + anhydride.





**Fig. 1:** The hypothetical fragments of the disconnection of 1-butyne are an ethyl cation and an ethynide anion.

 In general, we call the fragments of a hypothetical retrosynthetic disconnection synthons. Seeing the synthons above may help us to reason that we could, in theory, synthesize a molecule of 1-butyne by combining an ethyl cation with an ethynide anion. We know, however, that bottles of carbocations and carbanions are not to be found on our laboratory shelves and that even as a reaction intermediate, it is not reasonable to consider an ethyl carbocation. What we need are the synthetic equivalents of these synthons. The synthetic equivalent of an ethynide ion is sodium ethynide, because sodium ethynide contains an ethynide ion (and a sodium cation). The synthetic equivalent of an ethyl cation is ethyl bromide.

Which reagent is best can often only be determined by experimentation—commercially, paracetamol is made from *para-*aminophenol and acetic anhydride largely because the byproduct, acetic acid, is easier to handle than HCl.

***Synthesis I***

An illustrative example of the environmental and operational limitations associated with traditional paracetamol synthesis is seen in the Hoechst-Celanese process, a widely cited industrial route. This method utilizes highly corrosive and toxic reagents, notably hydrofluoric acid (HF) and thionyl chloride (SOCl₂), both of which pose serious safety hazards to workers and require specialized equipment for containment and handling. Beyond the inherent risks of the chemicals involved, the process also demonstrates problems with chemical selectivity, leading to reduced yields and the need for additional purification steps. Moreover, the reaction relies on a homogeneous acid catalyst, which after use must be neutralized—typically with a base—thereby generating stoichiometric quantities of inorganic salt waste. This not only contributes to environmental burden but also increases the overall cost and complexity of waste management12,13. These drawbacks underscore the urgency of developing more sustainable and environmentally friendly synthetic alternatives, particularly those that minimize hazardous reagents, reduce waste output, and are compatible with modern green chemistry practices.



**Fig. 2:** Beckman rearrangement of 4-hydroxy acetophenone.

***Synthesis II***

One of the older methods employed for the synthesis of paracetamol involves the Bamberger rearrangement of phenylhydroxylamine, which is itself obtained through the nitration of benzene followed by reduction. This classical route, however, poses significant environmental and operational concerns. Notably, the reduction step demands the use of stoichiometric quantities of iron and strong acids, which results in the generation of substantial quantities of non-recoverable iron sludge and iron oxide waste. The management of such inorganic waste presents a major challenge, particularly in regions with strict environmental disposal regulations. Furthermore, the reaction pathway suffers from low selectivity, as the reduction of nitrobenzene often leads to aniline formation as a major by-product, thus reducing the overall efficiency and purity of the desired intermediate14,15. These limitations highlight the need for alternative synthetic approaches that begin with renewable, bio-derived raw materials and avoid the use of harsh reagents and environmentally burdensome processes.



**Fig. 3:** Bamberger rearrangement of phenylhydroxylamine.

Modern synthetic strategies should be designed to align with the principles of green chemistry, minimizing hazardous waste, improving atom economy, and ensuring compliance with environmental norms, especially in countries where pharmaceutical manufacturing is closely regulated.

***Synthesis III***

In pursuit of more sustainable alternatives to conventional paracetamol synthesis, Andreas S. Bommarius and colleagues explored the feasibility of employing three phenol-derived compounds—hydroquinone, 1,4-benzoquinone, and 4-nitrophenol—as starting materials for the development of greener synthetic pathways. These compounds offer potential advantages due to their structural relevance and accessibility from renewable resources. Additionally, pathways traditionally involving phenol derived from benzene, such as those incorporating the Beckmann rearrangement, were also evaluated under the lens of renewability, particularly when the phenol feedstock is derived from biomass or other non-fossil sources16.

A critical requirement for any new synthesis pathway is that it must be industrially feasible, demonstrating performance that meets or surpasses current methodologies in terms of Green Chemistry principles, such as atom economy, energy efficiency, and waste minimization17. Given the enormous global demand for paracetamol, priority was given to processes that are amenable to continuous flow systems, which are better suited to large-scale production18. Moreover, due to the drug's pharmaceutical application, high selectivity and product purity are of utmost importance, necessitating routes that minimize by-product formation19.



**Fig. 4:** Sustainable pathways for paracetamol synthesis

The three proposed renewable-based pathways were systematically evaluated and compared not only with one another but also against four existing synthetic approaches—namely the Bamberger rearrangement, the Beckmann route, and two emerging bio-based strategies derived from β-pinene and p-hydroxybenzamide20. Each method was assessed on the basis of environmental impact, efficiency, scalability, and overall process viability. This comparative analysis aimed to identify the most promising routes that could potentially replace or supplement traditional production processes in a commercially sustainable and environmentally responsible manner21.

**3. Conclusions**

The synthesis of paracetamol has undergone significant evolution, from early methods involving hazardous reagents and low selectivity to modern strategies aligned with green chemistry principles. Traditional industrial routes, such as the Hoechst-Celanese and Bamberger processes, pose serious environmental and operational challenges, including the use of corrosive chemicals and the generation of substantial inorganic waste. These concerns have intensified the need for alternative pathways that are both environmentally benign and industrially scalable. Recent advances focus on utilizing renewable phenol-based feedstocks such as hydroquinone, benzoquinone, and 4-nitrophenol—offering promising avenues for sustainable production. Among these, the 4-nitrophenol route stands out for its efficiency, selectivity, and compatibility with continuous processing. Comparative analyses indicate that renewable-based approaches can match or surpass conventional methods in terms of atom economy, process safety, and waste reduction. Continued innovation in this area is essential to decentralize production, meet growing global demand, and ensure pharmaceutical sustainability in an increasingly regulated world.

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