# ADVANCES IN ORGANIC COMPOUND SYNTHESIS

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## 1.1 Introduction

The chemistry of carbon compounds is the contemporary definition of organic chemistry. Entire branch of chemistry is so committed to its compounds that means what makes carbon so special? Carbon setup a bond with broad range of elements and to other carbon atoms, which is distinct trait of carbon.

Heterogeneity of carbon compounds is what gives cornerstone for life on earth. Majority of living things are constituted mainly of complex organic compounds that have ask of structural, chemical or genetic.

The expression organic exactly means "derived from living organism". At first the phenomenon of organic chemistry was simply research of substances taken from living things and from their derivatives. Sugar, urea, wax, starch and plant oil were all seen as organic substances and people agreed to Vitalism, the idea that natural compounds need an essential strength to exist (Wade, 2008).

Due to the time constraints and textbooks rarely include much information on it, the instructors of chemistry cannot simply cover the history of organic chemistry in all depths, keeping in mind the vastness of the subject it is not common. For that reason, the students may perhaps not come to have a sound comprehension of why this is called "Organic Chemistry" and of those who teach it as organic chemists (Wentrup, 2022). Organic synthesis is unique branch of chemical synthesis and is linked with the calculated establishment of organic compounds. Organic molecules' synthesis has evolved into one of the most prime

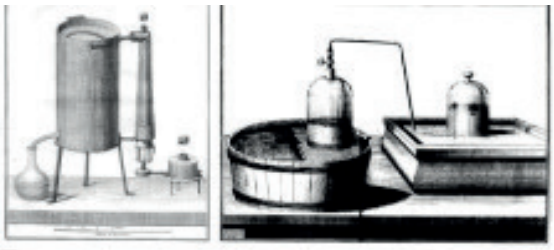


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branches of organic chemistry and are frequently more complex than inorganic compounds. The principle chemical process is Organic synthesis that also is fundamental to many scientific disciplines. Medical industry, pharmaceutical industry and many others are some specimens of fields that be in need of organic synthesis but are beyond chemistry. Industrial-level production of pharmaceutical products are allowed by organic processes (Tejeda, 2017).

## 1.2 Historical overview

The expressions Organic and Synthesis arises from Aristotle; denotes ('instrumental' and 'put together' respectively) but had distinctives meanings from time to time. In 1600s, Iatrochemists put together innumerable pharmaceutical medicines, but had no idea or organic chemistry. Definition of organic bodies as living things was given by Buffon, Bergman and Gren in the 1700s, but discrete organic compounds continue to exist unknown. Scheele and Chevereuil, both isolated organic natural products in the late 1700s and early 1800s, they separated carboxylic acids from saponification of fats. That resulted in Organic chemistry. For organic characterization Lavoisier invented and Berzelius improved combustion analysis. Descartes'



Lavoisier's apparatuses for combustion analysis, 1784.

dictum that Synthesis is needed to show an analysis was validated by Bergman and others. When Wohler and Kolbe prepared organic compounds from element the idea of organic chemistry changed completely. In 1853, modern synthetic organic chemistry came into being as chemistry of carbon compounds when Berthelot's did synthesis of non-natural fats, regardless whether it occurs in nature or not. In the middle ages, the organic chemistry and organic synthesis began way before the concept of molecular compositions were understood. Lavoisier, Chevreuil, Wohler, Liebig, Kolbe and Berthelot caused Paradigm shifts are highlighted.



From left to right: Lavoisier, Chevreuil, and Berthelot.

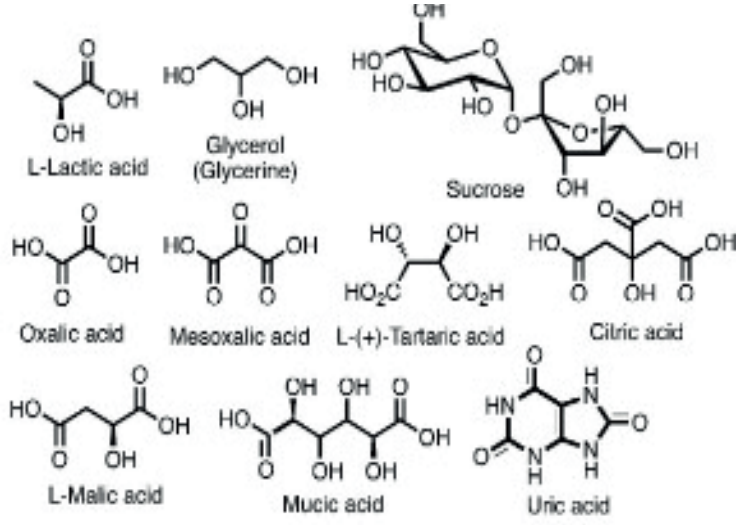
The graphic illustrates early key organic molecules. However, despite the fact that synthesis and analysis had become well established sciences by the 1840s, the chemical structures of these molecules remained largely unknown (Wentrup, 2022). Scarcely any discrete organic substances were known to Bergman in 1777. Since the 12th century, Ethanol by the distillation of wine had been acquired. Some vegetable acids and salts, such as tartaric acid and tartar (potassium hydrogen tartrate and calcium tartrate), sugar (an "essential salt"), "sugar acid" (oxalic acid, prepared by Bergman and Johan Afzelius by oxidation of sugar with nitric acid), acetocella salt (potassium hydrogen oxalate) from sorrel, citric acid, and acetic acid were known. Bergman classified organic and inorganic bodies as follows:

1. The most advanced natural substances found on the Earth's surface can be categorized into organic and inorganic.

2. Organic bodies contain numerous internal systems that extracts, processes, and distribute nourishment, facilitating their growth, maintenance and reproduction.

3. Organic bodies, are also known as living organisms, are classified into two main groups, animals and plants (based on their sensory capabilities) which are commonly regarded as two distinct Kingdoms of Nature.

4. Inorganic bodies are those which lack organic structure and can only grow by external addition of parts" (for the original Swedish and German texts, see Supporting Information, Section S3). The major thanks in large part to Lavoisier and Berzelius for the considerable advancement in organic chemistry that occurred in the late 1700s and early 1800s, so that elemental composition of organic materials could now be established. Other than Bergman and Gren, Berzelius could therefore start talking about organic and inorganic chemistry. Organic nature encompassed living things, but the chemical constituents of the organic bodies were still largely unexplored. Initially, contested by Berzelius, the isolation of discrete organic compounds from organic materials were becoming increasingly common. While the concept of structure was not yet developed, chemical compositions could at least be identified (Wentrup, 2022).




Some organic compounds known by the late 1700s (but structures unknown at the time).

### 1.3 Modern concept of organic synthesis

By combining few advancements in chemical techniques and methodologies, the contemporary notion of organic chemistry has progressed notably. The branch of chemical synthesis that mainly focuses on constructing organic compounds is Organic Synthesis, compounds that are essentially composed of carbon, hydrogen, oxygen and nitrogen atoms. Many methodologies, applications, and advancements changed the contemporary outlook of organic synthesis and helped in shaping the field.

#### 1.3.1 Green Chemistry

The definition of Green Chemistry is "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances". Green chemistry is generally a new concept of organic chemistry that attempts to function at molecular level in order to obtain sustainability. In order to meet environmental and economic objectives all at once, green chemistry has gained extensive interest in the past decade due to its ability to harness chemical innovations. Framework of Green Chemistry

The three main points about the Green Chemistry framework can be summed up as:

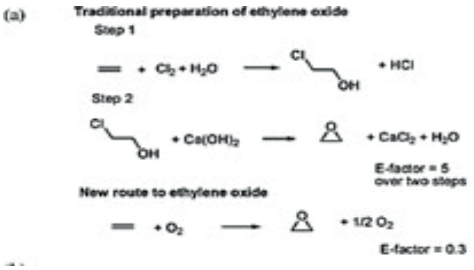
1. Green Chemistry designs across all stages of the chemical life-cycle.

2. Green Chemistry seeks to design the inherent nature of the chemical products and processes to reduce their intrinsic hazard.

3. Green Chemistry serves as a cohesive system of principles or design criteria.

The Twelve Principles: In 1998 Paul Anastas and John Warner introduced The Twelve Principles of Green Chemistry (Clark, 2006).

**1. Prevention:** Preventing waste is more effective than dealing with it after it has been produced example Traditional preparation of ethylene oxide and the new route relying on molecular oxygen.



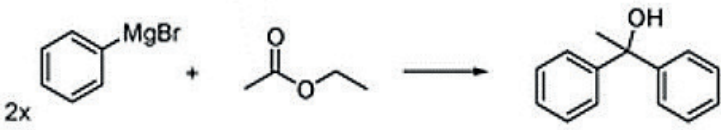

**2. Atom Economy:** Barry Trost presented the concept of synthetic efficiency in 1990: Atom Economy (AE) also known as Atom Efficiency, refers to the principle that an ideal reaction should utilize all of the atoms of the reactants.

**The Atom Economy AE**

$$AE = \frac{\text{MW Product}}{\text{MW of reagents}}$$

Synthetic methods should aim to maximize the inclusion of all materials used in the process into the final product, thereby minimizing waste. To exemplify this idea, consider the Grignard reaction. Although highly regarded in organic synthesis, The Grignard reaction is relatively inefficient in terms of atom economy. This is because the need for stoichiometric amount of metal reactant and the requirement to put together the Grignard reagent separately. As a result, the atom economy values are 44% and 56% indicating a significant loss of the raw materials. In contrast, the one-step multicomponent coupling reaction, such as the A3 coupling (Alkyne, Aldehyde and Amine), demonstrates greater efficiency and atom conservation, with 92% of original atoms being retained in the final product. Similarly, the Diels–Alder reaction is an excellent example of an atom-economical process, reflecting high atom economy and minimal

**Example of a Grignard reaction**




**AE = 44.2 %**

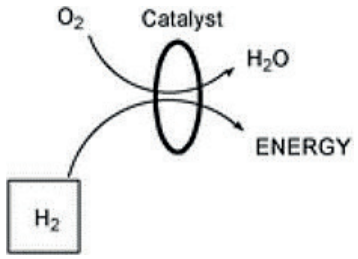
material waste.

**3. Less hazardous chemical synthesis:** Wherever feasible, synthetic methods should use and produce substances that have minimal or zero toxicity to human health and the environment.

**4. Designing safer chemicals:** Chemical products should be engineered to achieve their intended purpose while minimizing toxicity.

**5. Safer solvent and Auxiliary:** When necessary, the use of auxiliary substances (like solvents) should be reduced or made non-poisonous. Solvents are arguably the most active focus of Green Chemistry research. Wherever possible, the ideal scenario would involve avoiding the use of any solvent, as incorporating an auxiliary necessitates additional effort and energy to remove it from the systems. Consequently, significant efforts have been made towards developing solvent-free systems.

**6. Design for energy efficiency:** Energy demands should be kept down, ideally by conducting reactions at ambient temperature and pressure. Growing concerns about the depletion of petroleum resources and the rise in energy consumption has accelerated the development of more energy efficient processes and for the pursuit of renewable energies sources; sustainable resources in a time frame relevant to human scale. Chemists can address these challenges by lowering the energy barrier of a chemical reaction or selecting suitable reactants that facilitate the transformation at room temperature, thus acquiring all the direct and indirect benefits associated with it. Furthermore, Proton Exchange Membrane (PEM) fuel cells, which utilize hydrogen and oxygen gases, offer a promising solution to the anticipated surge in energy demand, embodying the core principle of hydrogen fuel cell technology (Ahluwalia et al., 2004).




**7. Use of renewable feed stocks:** Whenever possible, raw materials should be drawn/sourced from renewable rather than from depleting ones.

**8. Catalysis:** Catalytic reagents are favored over stoichiometric reagents, as they are effective in smaller quantities and offer great efficiency.

**9. Design for degradation:** Chemical products should be engineered to decompose into non- harmful substances after their intended use.

**10. Real-time analysis for pollution prevention:** Processes should integrate real-time monitoring to reduce or prevent the creation of hazardous substances.

**11. Minimize the potential for accidents:** Chemicals and their physical forms should be engineered to mitigate the risks of accidents, such as explosions or releases into the environment.

**12. Reduce derivatives:** Minimize unnecessary derivatization that demands extra reagents and contribute to waste generation (Anastas & Warner, 2000).

### 1.3.2 Automation and Robotics

Organic synthesis is one the influential tool for generating and crafting complex molecules, and its automation has dramatically transformed the field, facilitating faster and more efficient creation of organic compounds. Some advantages of automated organic synthesis include increased productivity, lower costs, and improved safety. However, it's not that straightforward, where there is automation of organic synthesis there is a requirement of knowledge to operate and specialized tools, where specialized software playing a crucial role in binding the gap between the chemist and the machine.

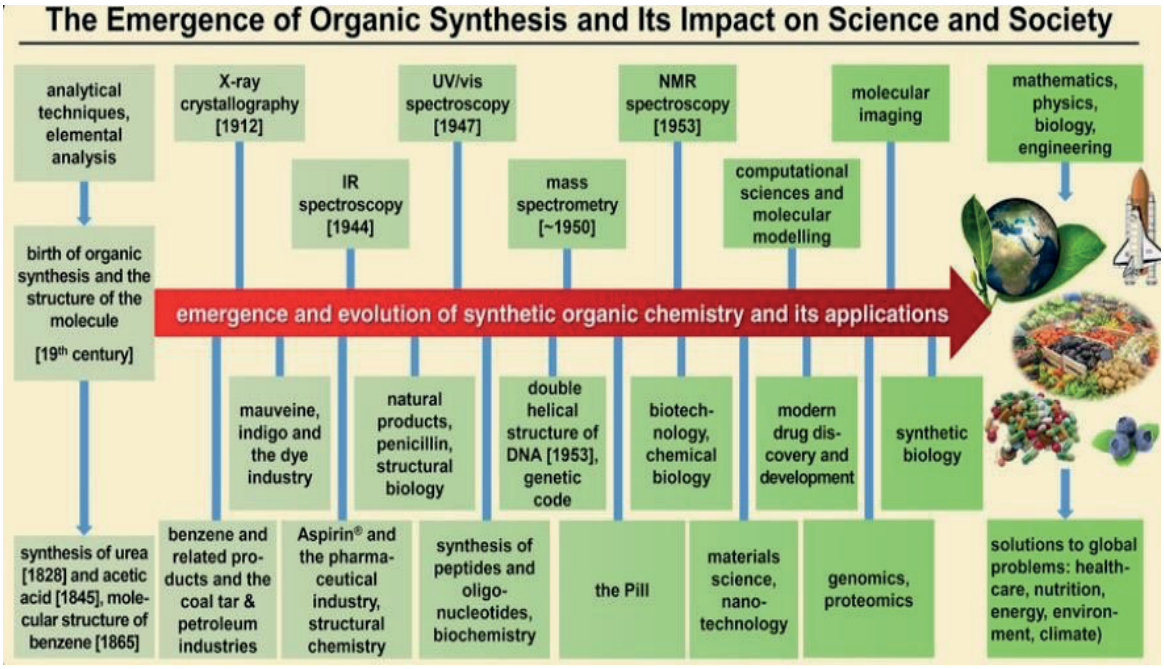
However, many people see software as merely a reaction input system. In reality, the capabilities of software surpass that significantly. Such software can serve to optimize and design synthetic pathways, forecast reaction outcomes and lead to comprehensive reports on the results. It can also serve to simulate reaction conditions, examine reaction data, and maximize process efficiency. Eventually, it can enhance data-driven decision-making by optimizing the organic synthesis process ultimately saving time and reducing cost.

The software should have the following modules to construct an ideal automated organic synthesis management platform (Gangwal & Lavecchia, 2024):

- Computer assisted synthesis planning (CASP)
- Reaction submission system
- Inventory management
- Integration with external databases and ability to interface with ELNs
- Instrument Control Software
- Data Acquisition and Analysis Software
- Database Management Software
- Visualisation Software
- Additional Specialised Software Packages

### 1.3.3 Computational Chemistry

A career in computational chemistry not only demands a keen interest in computer modeling and statistical analysis but also requires patience, logical thinking, and careful attention to detail. Additionally, strong "People skills" are crucial for this field. Computational chemists must collaborate effectively with other scientists and clearly communicate their findings to clients. Success in this field is greatly supported by excellent communication abilities, an outgoing personality, and a tendency for offering expert advice (Barbiric et al., 2015).



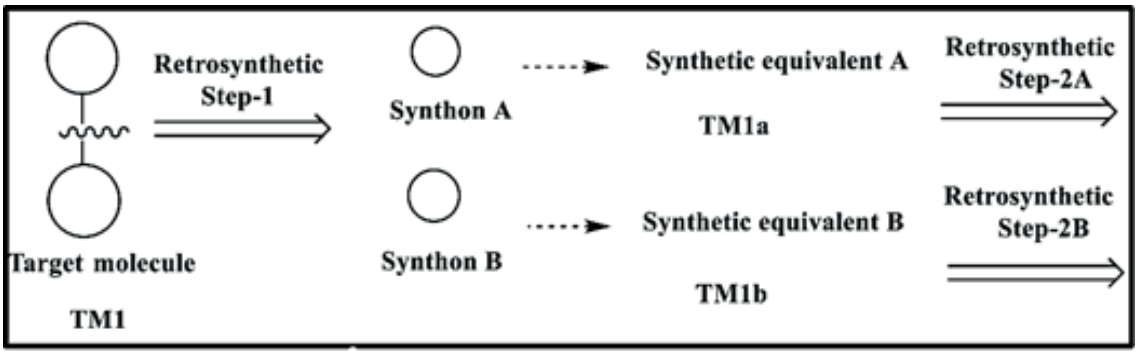
## 1.4 Applications of Organic Synthesis

► **Pharmaceutical development:** Organic synthesis is essential for developing of pharmaceutical compounds. For example, synthesizing ibuprofen demands multiple steps, such as reduction and carboxylation, to efficiently produce this commonly used pain reliever. Organic synthesis is also pivotal in rational drug design, where chemists use structure-activity relationship (SAR) studies to refine the biological activity of lead compounds. By systematically altering molecular structure, functional groups and stereochemistry, chemists can investigate the structure-activity landscape and pinpoint crucial molecular features responsible for activity.

Organic synthesis enables medicinal chemists to create drug like molecules with optimal pharmacokinetic and pharmacodynamic characteristics. Through rational design and structure-activity relationship (SAR) studies, chemists can adjust the molecular structure, optimize key pharmacophores and improve drug-likeness.

► **The importance of organic synthesis in drug discovery:** Organic synthesis is fundamental to drug discovery, offering a way to create diverse chemical libraries and identify potential lead compounds. It involves designing and constructing target molecules through various chemical transformations, allowing for the efficient and selective synthesis of complex structures. Effective collaboration between synthetic chemists and medicinal chemists is crucial for optimizing synthetic methods, addressing synthetic challenges, and refining the production of drug candidates (Zhang & Cue, 2018).

► **Retrosynthesis:** In Organic chemistry, synthesis involves creating more complex organic molecules from simpler starting compounds. A chemist begins with a basic compound and devises reaction pathways to build upon it. Synthesis and retrosynthesis differ in their approach to designing a sequence of reactions for the creating an organic compound. Synthesis starts with the initial compounds and progress towards the final product, while Retrosynthesis begins with the target compound and work backwards to identify the starting compounds. Both methods that are synthesis and retrosynthesis usually involve three types of transformations (Jabbar & Al-Hamashi, 2024).




General scheme of retrosynthetic analysis.

**Retrosynthesis Strategies (Vosburg, 2008)**

How to form a carbon-carbon bond

- Reaction of an aldehyde or ketone with a Grignard or organolithium reagent
- Reaction of an alkyl halide with a Gilman reagent
- Reaction of an organometallic reagent with an epoxide How to synthesize particular functional groups

Alcohols:

- Nucleophilic substitution of an alkyl halide with HO- or H2O
- Reduction of an aldehyde with NaBH4
- Reduction of a ketone with LiAlH4
- Reaction of an aldehyde or ketone with a Grignard or organo-lithium reagent
- Reaction of an organometallic reagent with an epoxide

Aldehydes:

- Oxidation of a primary alcohol with PCC

Alkenes:

- β Elimination of an alkyl halide or an alkyl tosylate with base
- Dehydration of an alcohol with acid
- Dehydration of an alcohol using POCl3 and pyridine

Alkyl halides:

- Radical halogenation of an alkane with X2
- Reaction of an alcohol with SOCl2 or PBr3
- Reaction of an alcohol with HX

Carboxylic acids:

- Oxidation of a primary alcohol with Na2Cr2O7

Epoxides:

- Intramolecular SN2 reaction of a haloalcohol using base

Ethers:

- Williamson ether synthesis: SN2 reaction of an alkyl halide with an alkoxide
- Reaction of an alkyl tosylate with an alkoxide

Ketones:

- Oxidation of a secondary alcohol with PCC or Na2Cr2O7

► **Industrial applications:** The European Journal of Organic Chemistry is presenting a special collection on "Industrial Organic Synthesis" which will highlight the impact of organic synthesis within the field of Life Sciences. The collection will cover industrial synthetic organic chemistry projects across various fields of Life Science, including process research, technology application for small molecules, and emerging modalities like PROTACs.

**Summary**

Organic chemistry, the study of Carbon compounds, explores the unique properties of carbon that enables it to create a diverse range of substances. The key to wide variety of molecules is carbon's ability to bond with variety of other carbon atoms and elements, which are crucial for life on earth. It is documented that, Organic chemistry originated from the isolation of and examination of substances found in living organisms, originally guided by the concept of Vitalism. Important breakthrough in its development includes the synthesis of organic compounds from inorganic materials by Kolbe and Wohler, which challenged the vitalism and paved the way for contemporary Organic chemistry. Organic synthesis, vital part of Organic chemistry, is essential in various fields, including medicine and industry by focusing on the intentional formation of Organic compounds. Applications extends from pharmaceutical development, where organic chemistry facilitate the production of drugs such as ibuprofen, to industrial processes that promote sustainability via Green Chemistry Principles. Automation and computational instrument have transformed organic synthesis by enhancing efficiency and enabling the design of intricate molecules. These advancements are continuously shaping the field, frosting innovation and expanding practical applications across diverse scientific area.

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