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Review Article

Solvent Role in Organic Chemistry in Comparison with Organic Synthesis under Solvent-Free Condition (Green Chemistry): A Mini Literature Review

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Abstract

Solvents are important components in the pharmaceutical and chemical industries, and they are increasingly being used in catalytic reactions. It is having a significant influence on the kinetics and thermodynamics of reactions, and it can significantly change product selectivity. Solvents can influence product selectivity, conversion rates, and reaction rates. However, solvents have received a lot of attention in the field of green chemistry. This is due to the large amount of solvent that is frequently used in a process or formulation, particularly during the purification steps. However, neither the solvent nor the active ingredient in a formulation is directly responsible for the reaction product's composition. Because these characteristics have little bearing on how well or quickly the system in which the solvent is applied works, it appears unnecessary to use toxic, combustible, or environmentally hazardous solvents. However, the beneficial properties of the solvent required for the application are strongly linked to these unfortunate side effects of solvent use. Distillation can be used to recover and purify solvents because they are volatile. However, this process can produce unwanted air pollutants and be hazardous to workers during exposure.

Keywords: Organic synthesis, Green chemistry, Purification, Solvent-free reaction.

التخليق العضوي في أوساط خالية من المذيبات (الكيمياء الخضراء): مراجعة مصغرة للنشريات

الخلاصة

المذيبات هي مكونات مهمة في الصناعات الدوائية والكيميائية، ويتم استخدامها بشكل متزايد في التفاعلات الحفازة. المذيبات لها تأثير كبير على الحركية والديناميكا الحرارية للتفاعلات، ويمكن أن تغير بشكل كبير انتقائية المنتج. ويمكن أن تؤثر على انتقائية المنتج ومعدلات التحويل ومعدلات التفاعل. ومع ذلك، فقد حظيت المذيبات بالكثير من الاهتمام في مجال الكيمياء الخضراء. ويرجع ذلك إلى الكمية الكبيرة من المذيبات التي يتم استخدامها بشكل متكرر في التفاعلات الكيمياوية، خاصة أثناء خطوات التنقية. ومع ذلك، لا يكون المذيب ولا المكون النشط في التركيبة مسؤولا بشكل مباشر عن تكوين منتج التفاعل. نظرا لأن هذه الخصائص لها تأثير ضئيل على مدى جودة أو سرعة عمل النظام الذي يتم فيه تطبيق المذيب، يبدو أنه من غير الضروري استخدام مذيبات سامة أو قابلة للاحتراق أو خطرة بيئيا. ومع ذلك، فإن الخصائص المفيدة للمذيب المطلوب للتطبيق ترتبط ارتباطا وثيقا بهذه الآثار الجانبية المؤسفة لاستخدام المذيبات. يمكن استخدام التقطير لاستعادة وتنقية المذيبات لأنها متطايرة. ومع ذلك، يمكن أن تنتج هذه العملية ملوثات هواء غير مرغوب فيها وتكون خطرة على العمال أثناء التعرض.

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INTRODUCTION

Because it operates on the premise that "like dissolves like," the one solvent method is the best choice for chemical synthesis. However, most, if not all, reactions can occur in mixed-solvent systems. The mixed solvent system has been widely used for a long time. Despite the fact that mixed solvents have been used in synthesis chemistry, there has been little research into how we can choose mixed solvents. Because water and ethanol are both effective solvents, the ethanol-water system has been widely used. According to numerous studies in this area over the last decade and recently published monographs, the effects of solvents on chemical processes and the physical and chemical properties of compounds continue to pique the interest of researchers. However, most, if not all, reactions can occur in mixed-solvent systems. The mixed solvent system has been used widely for a long time. Despite the fact that mixed solvents have been used in synthesis chemistry, there has been little research into how we can choose mixed solvents. Because ethanol and water are both effective solvents, the ethanol-water system has been widely used. According to numerous studies in this area over the last decade and recently published monographs, the effects of solvents on chemical processes and the physicochemical properties of compounds continue to pique the interest of researchers. The effect of the solvent on the protonation-deprotonation equilibrium or the change in basicity and acidity constants when switching solvents is one of the most important aspects of this issue [3,5]. Professors frequently discuss and rationalize the types of solvents used for various transformations when introducing new chemistry students to the concepts of organic reactivity. For operations involving Grignard reactions and the SN2 mechanism, examples include the commonly used solvents acetonitrile and dry ether. Students quickly wonder, "Which solvent should I select?" when developing conditions for their own chemistry experiments, having quickly realized that solvents are an important part of organic processes [6,7].

The Role of Solvents in Chemical Processes

Organic reactions are thought to take place in a solvent solution medium in general. The rationale for this concept is straightforward. That is, if the reactant compounds are in a homogeneous solution that can be shaken, stirred, or agitated in any way, the molecules of the reactant can interact efficiently and quickly. Furthermore, if necessary, it is extremely simple to uniformly heat or cool the combination in a solution. However, a solvent's role in the organic reaction entails much more than simply providing a homogeneous environment for numerous interactions between the reactants. A solvent can sometimes significantly increase or decrease the rate of a reaction [8]. A change in the solvent of a reaction can affect how quickly it proceeds and even change its direction. This could manifest as varying product yields and ratios. As a result, a solvent can be intimately and irreversibly linked to the processes of many organic reactions by preserving reactants, products, transition states, or other intervening species. Due to a variety of factors, including electrostatic, static, and conformational effects, the solvent and reaction partners have such direct contacts. Any liquid can be used as a solvent, but only a few are commonly used solvents—hydrocarbons, chlorinated hydrocarbons, alcohols, esters, ethers, ammonia, H_2O, and so on. With the exception of solvolysis reactions, the reactants can be used alone or in combination with silica, clays, zeolites, alumina, or many other matrices to conduct a solid reaction that produces a solvent-free product and is collected without change at the end of the reaction process. Even so, without a solvent, it may be impossible to imagine or plan a reaction [9].

Toxicity of Common Organic Solvents

Any product containing solvents, including fruits, meats, and vegetables, spoils quickly when left out at room temperature. This means that the use of solvents facilitates a variety of processes, such as chemical reactions that change the form of an object. Dry fish, meat, grains, vegetables, and so on will remain stable and in normal steps if the drying process is properly maintained. This fundamental understanding explains how chemical reactions occur in the liquid state. The general classifications for organic solvents are aliphatic hydrocarbons, aromatic hydrocarbons, cyclic hydrocarbons, halogenated hydrocarbons, amines, ketones, esters, ethers, aldehydes, alcohols, and so on (Table 1) [10].

Table 1: The general classes of the organic solvents [10]

Hydrocarbons	Alcohols	Ethers	Chlorinated solvents
n-Pentane	Methanol	Diethyl ether	Methylene chloride
n-Hexane	Ethanol	Diisopropyl ether	Chloroform
n-Heptane	n-Propanol	Dibutyl ether	Carbon tetrachloride
n-Octane	*i*- Propanol	Methyl *tert* butyl ether	1,2-dichloroethane
n-Nonane	*n*-Butanol	1,4-Dioxane	1, l,1 -Trichloroethane
n-Decane	*i*-Butanol	Tetrahydrofuran	Trichloroethylene
Benzene	2-Butanol	Esters	Perchloroethylene
Toluene	n-Amyl alcohol	Methyl acetate	Monochlorobenzene
2,2,4-Trimethyl pentane	*i*-Amyl alcohol	Ethyl acetate	Miscellaneous solvents
Cyclohexane	Cyclohexanol	Isopropyl acetate	Dimethylformamide
2,2,4-Trimethylpentane	*n*-Octanol	*n*-Butyl acetate	Dimethylacetamide
Cyclohexane	Ethanediol	Cellosolve acetate	Dimethylsulphoxide
Ethylbenzene	Diethylene glycol	Glycol Ethers	Sulfolane
Ketones	1,2-Propanediol	Propylene glycol methyl ether	Carbon disulphide
Acetone		Ethylene glycol methyl ether	Acetic acid
Methyl ethyl ketone		Ethylene glycol ethyl ether	Aniline
Methyl isobutyl ketone		Ethylene glycol monobutyl ether	Nitrobenzene
Cyclohexanone			Morpholine
n-Methyl-2-pyrrolidone			Pyridine
Acetophenone			2-Nitropropane
			Acetonitrile
			Furfuraldehyde
			Phenol

Organic synthesis is difficult to perform without organic solvents. Although many organic solvents are chemical compounds used to dissolve other chemical compounds, understanding the reactivity of each individual solvent under specific reaction conditions is critical. As a result, it is critical to always consider the appropriate solvents for a reaction. Solvents are typically chosen based on prior experience with specific solvents and their chemical structures or on similar patterns discovered in the literature and demonstrated in a laboratory setting [10]. However, due to some strict guidelines and regulations that we must follow, such as those regarding solvent power and volatility, which can be toxic to the researcher as well as our society and the environment as a whole, the situation has recently changed. This drives the search for ever-better alternatives, which is why solvent-free organic synthesis is booming right now [11,12] (Figure 2).

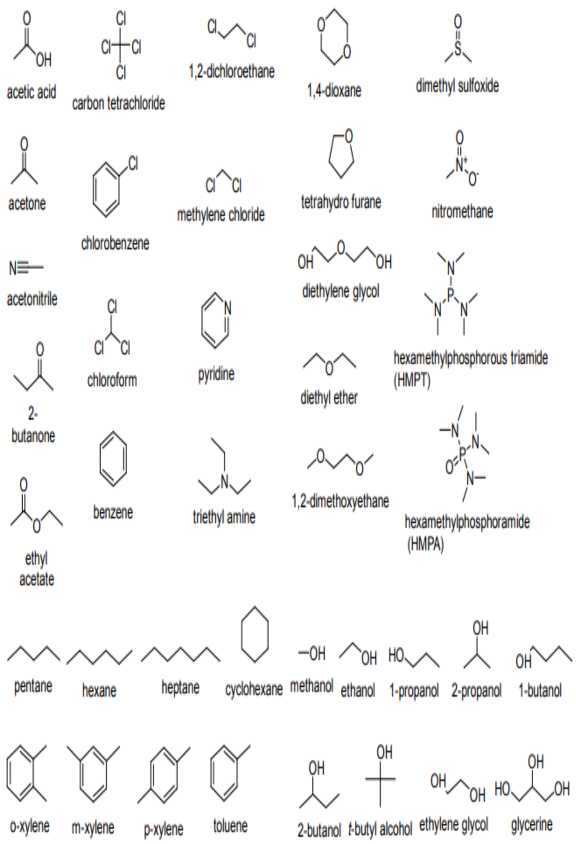

Figure 1: Common organic solvents' structures [11].

Numerous studies on the toxic effects of solvents have revealed the molecular mechanism as well as the likely main organs that may be affected [13-15]. Because researchers are becoming more aware of the dangers of organic solvents faster than the general public, there is a call for our safety, strict rules, and regulation, all of which reduce the danger and associated health effects. There are more laboratories with well-equipped setups, good ventilation to draw reagent and solvent fumes into very diluted atmospheres, and proper disposal systems; however, the yield of synthesis and the number of researchers are numerously growing, resulting in a higher volume of organic solvent consumption that still poses a risk. Many organizations are attempting to address this issue. Organic solvents have high lipophilicity and volatility because their skeletons are primarily composed of carbon and hydrogen atoms, with the occasional heteroatom. Lipophilicity effects the distribution of solvents to many body organs from the standpoint of toxicity. To improve renal elimination, the lipophilic compounds must be converted into a water-soluble form via a series of metabolic processes. The metabolite that forms is sometimes even more toxic than the original compound [12]. Organic solvents can cross the blood-brain barrier and have very negative effects because of their high lipophilicity. Some chemicals have anesthetic (Trichloroethylene, for example) [16], anxiolytic (Toluene, for example) [17], convulsive (Fluorothyl, for example) [18], anticonvulsant (Toluene, for example) [19], narcotic (Trichloroethylene), and antidepressant (Benzyl Chloride) effects at high doses. Organic solvents affect a large portion of the population as a result of the rapidly expanding plastic and chemical industries. Organic solvents are easily exposed to the air due to their high volatility. Because the majority of these solvents are inhaled through respiration, the lungs are the first to be affected, alerting employers to the need for adequate ventilation in the workplace. As a synthetic chemist, the researcher must spend a significant amount of time in a lab on a daily and ongoing basis, handling a variety of toxic reagents and organic solvents [14].

Guidelines for using Chemicals and Solvents

Always wear appropriate protective clothing when handling chemicals and read the Material Safety Data Sheet (MSDS) to learn more about specific chemicals, which will provide information about safety precautions, potential hazards, other handling techniques, and so on. When working with chemicals or solvents, always use fully operational chemical fume hoods, remove any contact lenses you may be wearing, and immediately wash your eyes with running water for at least 15-20 minutes. If you suspect chemical eye contact, keep the eyelid open to allow solvents to quickly evaporate from the eye and reduce your risk of further injury. Similarly, if skin contacts chemicals, properly rinse the area with water, apply an emollient to soothe the area, remove any contaminated shoes or clothing, and seek medical attention if necessary. If at all possible, avoid working alone in the lab [20].

Organic Reactions in the Solvent-free Conditions

Although any chemical reaction can occur in a gaseous, solid, or liquid state, many chemical changes in solutions typically occur in the liquid state. It is an ideal medium for transferring heat between endothermic and exothermic reactions. Solvents dissolve liquid or gaseous reactants; the solid reactants' crystal structure should be broken, which significantly affects reaction rates and chemical equilibrium positions. Furthermore, the reactant molecules can combine quickly if the reactants are in a homogeneous solution that allows for shaking, stirring, or other types of mixing [21,22]. Furthermore, it is simple to uniformly heat or cool the solution mixture as needed. However, the function of a solvent in an organic reaction entails much more than simply creating a homogeneous environment in which many reactants can collide. A solvent can sometimes significantly increase or decrease the rate of a reaction. If the solvent is changed, it can affect the rate of the reaction and even change its overall course. This could manifest as different product yields and ratios. As a result of reactant solvation, a solvent can become inextricably and irreversibly linked to the operation of an organic reaction, products, a transition state, or another species that came before. Although the solvent remains unchanged and is recovered after the reaction, electrostatic, steric, and conformational effects are the main causes of such close interactions between the reaction partners and the solvent. A reaction without a solvent has not yet been imagined or planned. However, another adage states that the best solvent is none at all [23]. Despite the strength of this assertion, the use and comprehension of solvent-free conditions have not advanced as much as solvent-based techniques. Because different names are frequently used, it can be difficult to define the idea of solvent-free synthesis. Scott *et al*. [24] make the following distinctions to make their points clear: solid-phase reaction, which is the reaction of molecules from the liquid phase with a solid substrate, such as polymer-supported synthetic peptide; ii) solvent-free reaction, which is any system in which reagents react with one another without the use of a solvent; and iii) solid-state reaction, or solid-solid reaction, which is when two macroscopic solids interact directly without the help of a liquid or vaporous phase to create a third, solid product. Despite the presence of macroscopic organic solids in many solvent-free reactions, the majority of them occur in a liquid or melt phase. This fascinating fact has served as the basis for extensive research on a variety of organic reactions [25,26]. These organic reactions reported as "in the solid phase" involve the formation of a liquid phase. This melting implies the presence of a eutectic mixture with a melting point lower than the melting points of the reactants. When heating is required, it is sometimes obvious that a phase change (from solid to liquid) occurs. Solvent-free reactions may provide access to many simple and complex reactions, as well as all classes of compounds. Among the most typical and significant reactions are carbonyl compound condensation, cycloadditions, alkylation, aromatic substitution, amine, water, and alcohol additions, cyclization, eliminations, rearrangements, carbon-carbon coupling, cascade reactions, and catalyzed reactions [27,28], compared to reactions in molecular solvents.

Green Technique and its Advantages

"Green chemistry" is the environmentally friendly synthesis of chemicals. The synthetic schemes are designed to cause the least amount of environmental damage possible (Figure 2). The majority of environmental pollution is currently caused by a variety of chemical industries. The cost of waste disposal is also extremely high. The 12 guiding principles of green chemistry can be applied to almost any aspect of chemistry, such as the design of molecules with desirable properties and structures, process catalysis, the use of less polluting reaction conditions, and so on [29,30].

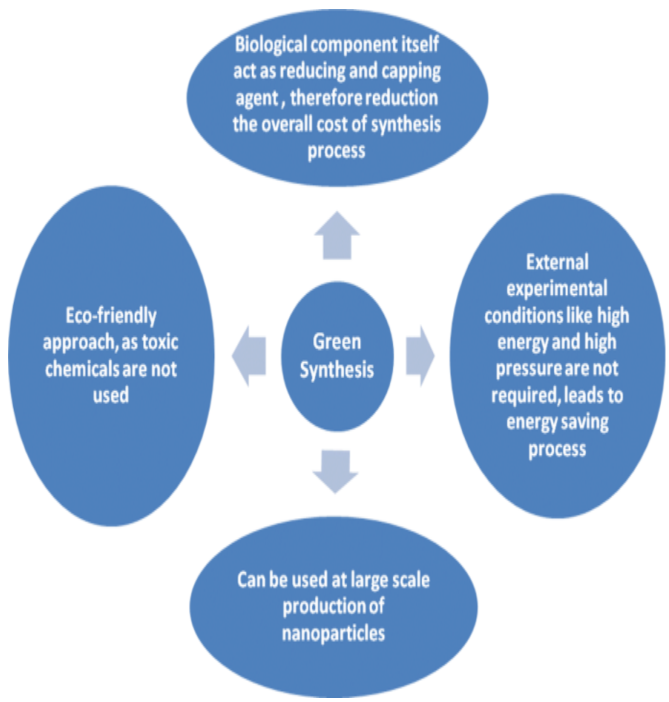

Figure 2: Key merits of the green synthesis methods [30].

These guidelines are summarized below:

1. Before they can be carried out, processes must be designed. Chemical products should be made with the least amount of toxicity possible while still performing the required function.

2. As a preventive measure, avoiding waste altogether is preferable to cleaning up or treating garbage that has already been generated.

3. The use of less hazardous solvents and auxiliaries. Auxiliary chemicals and processes (separation, solvents, reagents, etc.) should be rendered harmless and used as little as possible [31].

4. Energy-efficient design. The energy required to perform chemical reactions should be understood in many terms, including their effects on the economy and the environment, and it should be kept to a minimum. Synthetic procedures are to be carried out at room temperature and pressure whenever we can.

5. Lower-risk chemical synthesis. The synthetic pathways should always be designed to utilize and produce chemicals wherever possible that are healthy for both the environment and humans.

6. Atomic economy. The inclusion of all components utilized throughout the process into the finished product should be kept to a minimum when developing synthetic procedures. In this instance, Ibuprofen's synthesis by the BHC firm, which generates less waste and byproducts, is a very good example. In comparison to the 6-step brown synthesis (BOOTS approach), the 3-step catalytic green synthesis (BHC approach) is more economical by 77% and 40%, respectively. The percentage of atom economy increases to 99% from 77% when taking into account the recovered acetic acid produced in step 1 of green synthesis.

7. Utilizing catalysts Catalytic reagents, which are preferable to stoichiometric reagents, should be as selective as possible. By utilizing the catalytic reagents, one can increase selectivity, raise yield, and produce reactions that weren't previously achievable.

8. Minimize derivative use. Wherever possible, derivatization that is not necessary (such as the use of blocking groups, protection or deprotection, and temporary changes of chemical and physical processes) ought to be avoided as it might lead to waste and demand more reagents.

9. Planning for deterioration. When a chemical product has served its purpose, it should be designed to degrade into non-polluting degradation products [32].

10. Make use of sustainable feedstock. When it is technically and financially viable, renewable raw resources, or "feedstock," are preferable to finite ones.

11. Immediate analysis to prevent contamination. The analytic techniques must be strengthened much more. Prior to the production of dangerous compounds, real-time process monitoring and control are made possible.

12. Chemistry that is inherently safer for preventing accidents. To lessen the risk of chemical accidents like explosions, leaks, and fires, compounds and the forms of substances utilized in chemical processes should be carefully chosen [33].

Green chemistry has various benefits, including waste avoidance, non-toxicity, safety, economic viability, and environmental friendliness [34]. Synthesis manufacturing processes have been created to generate little waste, have no adverse effects on the environment, and be simple to discard [35]. To carry out reactions, starting materials, solvents, and catalysts must be carefully selected. For instance, benzene must never be used as a solvent because it is carcinogenic. Whenever possible, it is preferable to carry out reactions in the aqueous phase. Given this perspective, synthetic methods should be developed such that the starting materials are utilized as fully as is practical in the final product. The reaction must also not result in any negative byproducts [36]. It is no longer true, as once believed, that no reaction can take place without the presence of a solvent. Such reactions are essential for industry because they are easy to operate [37], emit few pollutants, are relatively inexpensive to run, and limit pollution. The many features of solid-state organic synthesis have been covered in the literature. It is thought that solvent-free organic synthesis and transformations have industrial value and are primarily environmentally favorable.

Conclusion

We have examined both historical and present general solvent selection guidelines in order to comprehend the advantages and disadvantages of each. More research is needed in the areas of application-specific techniques and life cycle studies in order to choose solvents in the future with more sophistication based on a sustainable supply chain. To do this, more knowledge will be required, especially about the physical properties and environmental effects of innovative solvents. Even though the synthesis of organic molecules without the use of solvents has become very widespread, it remains one of the most effective techniques in green chemistry for quickly and sustainably producing a wide range of important substances. Because of the numerous advantages of solvent-free reactions, new solvent-free procedures are being developed for the ecologically friendly synthesis of various compounds.

Conflict of interests

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