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Environmentally Benign and Efficient Approaches to Organic Synthesis of Drugs: A Review

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ABSTRACT

With the increasing number of development of new chemical entities, the harmful and unexpected environmental side effects are also increasing. These are the consequences of harsh methods used for processing of new chemicals. These effects ultimately result in the need of green chemistry. Green chemistry is one of the major upcoming areas of organic and medicinal chemistry which assists in sustainable development and hence also known as sustainable chemistry. The approaches for green synthesis vary in source of energy, amount of total energy required, renewability of source, feasibility of use. These methods aim at efficient and environment friendly synthesis which minimizes waste and production of by-products. A brief review of all the green methods available is discussed here with the pros and cons of each of them.

1. INTRODUCTION TO GREEN SYNTHESIS

1.1 Green chemistry

Green chemistry, also known as 'sustainable chemistry' is a design of chemical products and processes that reduce or eliminate the production and use of hazardous substances. [1]

"Sustainability" is a concept used to distinguish methods and processes that can ensure the long-term productivity of the environment, so that even subsequent generations of humans can live on this planet. [2]

"Sustainable development" has been defined as 'Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs'. It is the goal and Green Chemistry is the means to achieve it.

Green chemistry prioritizes safety, improving energy efficiency and minimizing or eliminating toxic waste from the very beginning. Processes should be efficient in both energy and raw materials consumption and produce minimal waste. This can be achieved by the widespread application of efficient catalytic technologies.

1.2 Twelve principles of green chemistry

Paul Anastas, Father of Green Chemistry set 12 principles to help designing a green method for synthesis.

Table 1: Twelve Principles of Green Chemistry [3]

1.Prevent waste	7.Use renewable feedstocks
2.Maximize atom economy	8.Avoid chemical derivatives
3.Design less hazardous chemical syntheses	9.Use catalysts, not stoichiometric reagents
4.Design safer chemicals and products	10.Design chemicals and products to degrade after use
5.Use safer solvents and reaction conditions	11.Analyze in real time to prevent pollution
6.Increase energy efficiency	12.Minimize the potential for accident

1.3 Green solvents

Solvent selection is the major criteria deciding the greenness of the method. Solvent removal process represents the largest part of total energy consumption. The organic pollution caused by release of harmful solvents into environment contributes to greenhouse effect. Water is always the first choice of solvent for green synthesis due to its nontoxicity, inertness, and availability. [4]

1.4 Green catalysts

In green reactions, catalytic reagents are superior to stoichiometric reagent, by focusing on one of the twelve principles of green chemistry.

In catalyzed reactions less energy is required for production. Also, higher efficiency is observed in the generation of fewer by-products, co-products and other waste substances.

Examples of green catalysts are zeolites, natural clays, and water soluble salts.

The ideal properties of green catalyst must include:

- It must be inert, nontoxic to environment.
- It should be recyclable.
- It must be water soluble. So that, easy separation of it is achieved.
- Naturally occurring catalysts are pollution free and costless. [5]

2. VARIOUS APPROACHES TO GREEN SYNTHESIS

From the literature, various methods to effective green synthesis are found out. They are as follows

2.1 Solvent free synthesis

Using 'neat' conditions save the solvent and energy consumption as solvent removal process is avoided. The product obtained is often pure and doesn't require the separation or purification step. No specialized equipment; so cost-effective process is achievable.

Besides the ease of process and purity of product, some drawbacks of this method are to be considered. The agitation is not proper in case of solid reactants; separate means are to be managed for mixing. Low heat and mass transfer is another major disadvantage. [6]

Depending on the initial state of the reactants, the solvent-free reactions are broadly classified into three categories:

- Liquid–liquid
- Liquid–solid
- Solid–solid

Undoubtedly the liquid-liquid and liquid-solid reactions are well processed with high yield and less energy consumption. Examples are solvent free aldol condensation reactions. [7]

A solvent free synthesis or solid state (in case of the entire reactants solid) may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina etc. That is eventually termed as solid support organic synthesis.

Example is silica gel supported synthesis of oligoribonucleotides.[8]

Sometimes silica acts as a catalyst. Example is silica-$ZnCl_2$ catalyzed synthesis of 4-methylcoumarins where silica acts as a catalyst as well provides solid support in the neat conditions. [9]

2.2 Mechano-chemical synthesis

The term mechanochemistry itself indicates that the mechanical energy is applied for completion of reaction.

It can be just a simple grinding of two reactants in a pestle and mortar or can be more complex, as with the use of ball mills. Ball mills, however, have the advantages of requiring no physical effort, supplying greater power, being programmable and allowing more systematic studies of the process.

Two types of commercially available ball milling equipment appropriate for laboratory scale syntheses are the shaker and planetary mills. [10]

Lesser energy consumption, less complicated instruments are the advantages. The less consumption due to the reduced particle size of reactants is one of the major advantages of this green method. The basic mechanism is increased molecular interactions of reduced particle size of reactants due to mechanical energy applied. This mechanism makes the process green and efficient.

Room temperature stirring using mechanical stirrers or shakers is the convenient ways to proceed for such reactions which can be carried out at room temperatures.

For examples, reactions of aldehydes (mostly liquid at room temperature) are very reactive and complete the reactions like condensation in certain minutes. Room temperature synthesis of 2-aryl benzimidazole synthesis using different aldehydes with o-phenylene diamine is method for green and efficient synthesis of benzimidazole derivatives. [11]

2.3 Microwave assisted organic synthesis

The reaction conditions which require higher temperature and consume more time for its completion are ideal for microwave. Microwaves are electromagnetic radiation which in polar media and reactants form polar intermediates and accelerate the rate of reaction. Polar solvents are the most suitable solvents for microwave synthesis. Most commonly used solvent is water. [12]

Microwave chemistry is based on the efficient heating of materials (in most cases solvents) by dielectric heating effects. Dielectric heating works by two major mechanisms:

- Dipolar polarization:

For a substance to be heated when irradiated with microwaves it must be a dipole. Since the microwave field is oscillating, the dipoles in the field align to the oscillating field. This alignment causes rotation, which results in friction and ultimately in heat energy.

- Ionic conduction:

During ionic conduction, dissolved (completely) charged particles (usually ions) oscillate back and forth under the influence of microwave irradiation. This oscillation causes collisions of the charged particles with neighboring molecules or atoms, which are ultimately responsible for creating heat energy. For example, if equal amount of distilled water and tap water are heated by microwave, tap water will be heated more due to its ionic content.

Microwave irradiation conditions are dependent on the ability of a specific substance to convert electromagnetic energy into heat. This ability is determined by the so-called loss tangent, tan δ. A solvent with a high tan δ is required for rapid heating in the microwave field. However, this does not mean that solvents with low tan δ values cannot be used for microwave synthesis.

Microwave transparency is another criterion for microwave heating. Interaction of different materials with microwaves is shown in fig 1.

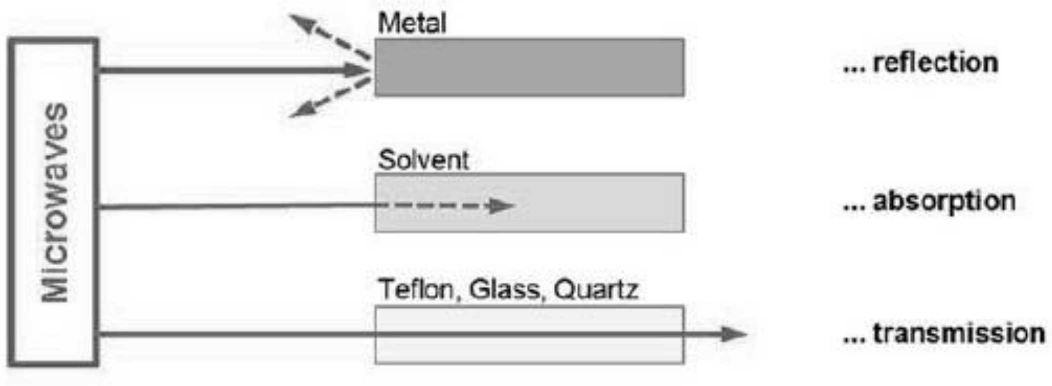

Fig 1: Microwave transparency of materials explaining reflection, absorption, transmission.

Microwave irradiation results in energy efficient internal heating by direct coupling of microwave energy with dipoles and/or ions that are present in the reaction mixture.

The main difference between conventional heating (burner/oil bath /sand bath) and microwave heating is microwave irradiation causes direct 'in-core' heating i.e. there is no initial heating of vessel surface. The conversion of electromagnetic radiation into heat energy results in extremely fast heating rates which are not possible in case of conventional heating.

One more important advantage is suppression of production of by-products due to raid heating to target temperature. Hence, microwave irradiation is proven to be green and cleaner process of synthesis. [13]

Temperature up to 300 ^{o} C is obtained with commercial microwave synthesis. As the temperature increases, the time required to complete the reaction decreases. In microwave heating, time is drastically reduced to from several hours to few minutes than in conventional heating.

Solvent free conditions are also possible under microwave irradiation. For example solvent free synthesis of tri-alkyl phosphates by reaction of alcohols with different phosphorous substances. [14]

2.4 Sonochemical synthesis

The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic cavitation (Fig 2). Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse.

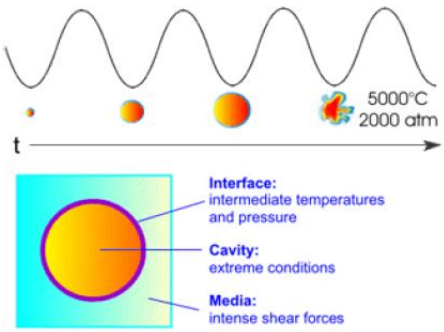

Fig 2: Cavitation in sonochemistry

Many reactions can be conducted even in a simple ultrasonic cleaning bath, although the amount of energy that reaches the reaction is only between 1 and 5 W cm^{-2}, and temperature control is normally poor. Large-scale reactions can be better conducted using immersible ultrasonic probes that circumvent the transfer of the energy through water and the reaction vessel. The applied energies in this case can be several hundred times higher. Laboratory equipment uses frequencies between 20 kHz to 40 kHz, but cavitation can be generated well above these frequencies and recent research uses a much broader range.

Various nanomaterials are synthesized by using sound waves as a source of energy. [15]

2.5 Solar energy as a source of thermal energy

Renewable sources of energy are the best source of energy which is inexhaustible and green. Solar photons are ideal green catalysts that leave no residue in reaction mixture. They are costless and a form of renewable source of energy. [16]

Photovoltaic (PV) devices are one of the most attractive solutions to clean and renewable source of energy with conversion of inexhaustible source of energy into electrical energy.

For example, the polymer synthesized from its monomer using a palladium-catalyzed coupling procedure. [17]

2.6 UV Visible light promoted synthesis

The reaction is accelerated because of breaking bonds that are sensitive towards UV. The process is also called as photo catalysis.

For example, ecofriendly visible light promote synthesis of dibenzofuran derivatives. The transformation requires a diazotizing agent and is promoted by the use of an organic photosensitizer under visible-light irradiation. [18]

3. SUMMARY

Every approach to green synthesis has its pros and cons. The green as well as efficient ways of organic synthesis are discussed here. Time and energy efficiency are the main benefits of all the described methods.

Microwave assisted organic synthesis is the most commonly used method for synthesis of molecules which require higher temperatures for processing; while sonochemistry aids the conventional method of mechanical stirring by increasing activation of molecules and decreasing the time for reaction. The ultimate green sources used for energy are solar and UV-visible light.

Contribution to greenness of the environment with the development of new molecules will be the prime advantage of these approaches.

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