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Chapter- 4

Green Solvents in Organic Synthesis: A Futuristic Approach

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Abstract:

The field of Green or Sustainable Chemistry has gained recognition as a significant scientific topic, gathering immense interest from the scientific community. The research conducted in this field relies significantly on the "Twelve Principles of Green Chemistry," which serve as the fundamental framework for all chemical processes. Researchers are highly interested in developing chemical processes that might mitigate the environmental harm caused by toxic solvents, taking into consideration environmental concerns. Extended exposure to hazardous solvents has a detrimental impact on living beings, causing significant harm to the majority of human organs. Volatile organic molecules derived from petrochemicals, commonly referred to as conventional organic solvents, provide a significant peril to terrestrial, atmospheric, and aquatic organisms. The concept of utilizing water, ionic liquids, organic carbonates, supercritical carbon dioxide, deep eutectic solvents, and non-toxic liquid polymers as catalysts or reaction mediums has gathered significant interest due to their potential to remove environmental hazards. These diverse combinations of solvents fall under the category of green solvents, which are distinguished by their low toxicity, easy handling and reusability. However, the total substitution of traditional solvents with environmentally friendly solvents has a negative effect on industrial production and chemical synthesis. Despite this, some effective alternatives have demonstrated their chemical efficiency and widespread utilization. This chapter will provide a concise overview of ecologically friendly solvent alternatives to traditional solvents, focusing on their application in chemical processes with a green matrix.

Introduction:

The advancement of synthetic organic chemistry is closely linked to the progress towards a more sustainable and environmentally conscious society. This growth has prompted an ethical response aimed at fostering eco-friendly research opportunities. Green Chemistry (Anastas and Eghbali, 2010) is a significant approach with environmental concerns in Chemical sciences. Currently, Green chemistry is widely recognized as a promising direction for the chemical industry, as it aims to promote bio-sustainability and operate at the molecular level. The

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principles of Green Chemistry take into account a holistic approach to green technology, ensuring safety, efficiency, and biodegradability. Conventional chemical processes, whether used in academia or in industry, contribute to environmental and health hazards, including air, water, and soil pollution (Bhattacharya, 2015; Banerjee et al., 2021; Biswas & Saha, 2021; Mondal et al., 2022; Prasad et al., 2023). Given that the majority of organic reactions take place in a solution, selecting the appropriate solvent is a crucial requirement for any organic synthesis. In recent years, there has been a growing recognition of the necessity to decrease the utilization of traditional solvents in favour of less harmful alternatives, mostly due to concerns regarding toxicity and environmental implications. Therefore, from a synthetic perspective, it is imperative and very promising to explore environmentally friendly synthetic alternatives as substitutes for traditional ones.

Conventional Solvents Versus Green Solvents

Carbon-based chemicals, hydrocarbons, and halogenated hydrocarbons are the conventional organic solvents. The majority of them exhibit elevated vapor pressure and are incapable of mixing with water. Volatile organic molecules, which exhibit chemical diversity, are mostly derived by the petrochemical sources. Volatile organic solvents possess flammable, explosive, poisonous, narcotic, mutagenic, and carcinogenic properties, hence posing significant hazards during their use and storage. If they come into contact with the mucous linings, eyes, skin, etc., they can cause detrimental effects leading to health hazards. The intensity of the effects increases, leading to potential health risks when they are dispersed throughout the bloodstream or other vital organs of the body. From an environmental point of view, the majority of organic solvents are classified as volatile organic compounds. Their release into the environment contributes to environmental pollution by participating in the creation of photochemical smog and the halogenated solvents contribute to the depletion of the ozone layer. Organic solvents, such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), halogenated hydrocarbons, and aromatics like benzene, toluene, and xylenes, are commonly employed in large quantities in many industrial applications despite their severe toxicity. Given this context, there is a pronounced inclination to substitute the majority of traditional organic solvents with alternative options that have a reduced environmental footprint while still yielding comparable outcomes. The concept of non-conventional or green solvents in synthesis emerges as an acceptable result. Solvents and solvent classes that have been classified as environmentally friendly solvents include water, ionic liquids, organic carbonates, supercritical carbon dioxide, deep eutectic solvents, non-toxic liquid polymers, and many more. These organic compounds are eco-friendly, non-evaporating, biocompatible, reusable, relatively recent materials, and serve as good solvents, reaction media, or occasionally catalysts for reactions. The scientific concept of substituting a solvent that is considered 'non-green' with a solvent that is considered 'green' in a given process inherently enhances its environmental efficacy (Chakraborty et al., 2016). However, this has sparked arguments on the comparative environmental friendliness of various solvents (Clark and Tavener, 2007). However, during this era of development, there have been other synthetic procedures that have been classified as 'Green' based on certain green criteria. These criteria have clearly defined the distinction between green and non-green processes. This chapter will primarily focus on the utilization of water, ionic liquids, and deep eutectic solvents in the context of greener synthesis.

Water

Although water is often seen as a problem in modern organic synthesis for the laborious purification procedures and the need for final drying of the product, it can nevertheless be considered a more favourable solvent alternative. The use of water as a solvent has been observed to expedite certain reactions and exhibit notable selectivity, even for chemicals that possess limited solubility or insolubility. This phenomenon, commonly referred to as hydrophobic interaction, is widely recognized in biological science. Water is a superior choice over other green solvents due to its abundance, lack of toxicity, non-corrosiveness, and non-flammability. Furthermore, water possesses the ability to be confined due to its comparatively elevated vapor pressure in comparison to other organic solvents, rendering it an environmentally friendly and sustainable substitute (Zha et al., 2005; Kobayashi et al., 2002). Currently, there is a growing interest in organic reactions occurring in water, since it is a cost-effective, secure, and ecologically harmless solvent. The organic co-solvents and surfactants actively enhance the solubility in water when combined with water. The interaction between organic solutes and micelles is influenced by their polarity. Non-polar solutes tend to be confined within the micelle's interior, while moderately polar molecules tend to be located closer to the polar surface. On the other hand, distinctly polar solutes are found at the surface of the micelle and collectively contribute to the reaction in an aqueous medium. In 1980, Breslow(Rideout and Breslow, 1980) conducted a significant study that demonstrated the ability of water to accelerate the reaction rate of the Diels Alder reaction. Since then, water has gained recognition as a highly esteemed reaction medium, after the groundbreaking contributions of the Sharpless (Narayan et al., 2005) and Breslow (Breslow., 2004) groups. In recent times, water has emerged as a significant reaction medium in various chemical reactions. The activation of C-H bonds on water has emerged as an important field of study in recent times (Li and Dixneuf, 2013). Reactions such as Heck reaction (Fernandes et al., 2008) and Suzuki coupling (Liu et al., 2011) can now be conducted in aqueous environments with comparable or enhanced rates, yields, and selectivities when compared to their counterparts in organic solvents. The field of aqueous chemistry is mostly utilized in biological processes, and its advancement can contribute to our comprehension of the intricate mechanisms underlying the chemistry of life, which in turn are relevant to biotechnological applications.

Similarly, sustainable methods (Chakraborty et al., 2018; Chakraborty et al., 2019) were employed to synthesize pharmaceutically and morphologically significant pharmacophores utilizing water as a reaction medium, resulting in a higher yield of products. Due to the inherent difficulty of conducting organic reactions in water, the addition of surfactants as an additive has resulted in high product yields through micellar aggregation.

Ionic liquids

Ionic liquids are liquid electrolytes that consist exclusively of ions. The composition of ionic liquids can be altered by employing a specific strategy. Therefore, the term "designer solvents" has become widely employed. Typically, ionic liquids are composed of a salt in which one or both ions exhibit significant size, while the cation possesses a relatively low level of symmetry. Ionic liquids can be classified into two primary categories: simple salts, which consist of a single anion and cation, and binary ionic liquids, which involve an equilibrium. In the past decade, the scientific community has shown significant interest in ionic liquids (ILs) due to their unique features and their various applications in fields such as organic synthesis (Welton, 1999), catalysis(Zhao et al., 2002; Cole et al., 2002; Welton, 2004), biocatalysis (Sheldon et al., 2002) etc. Ionic liquids (ILs) are a highly suitable substitute for volatile organic solvents in environmentally friendly technologies, also known as "green technologies". This is due to their low vapor pressures, thermal and chemical stability, catalyst-like properties, non-flammability and non-corrosive nature. By adjusting the characteristics of their cations and anions, the physical qualities such as melting temperatures, viscosity, density, and hydrophobicity can be altered.

Ionic liquids can be categorized into three groups based on their acidic, basic and neutral nature namely acidic (Fig 4.1), basic (Fig 4.2), and neutral (Fig 4.3) ionic liquids. These classifications are determined by the presence of cations and anions in the liquid.

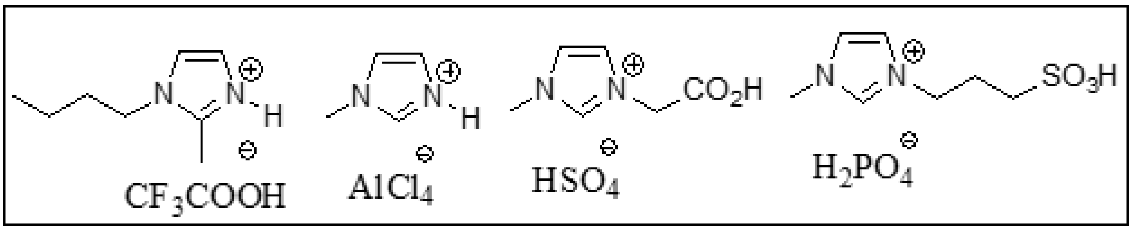

Figure.4.1. Acidic Ionic liquids

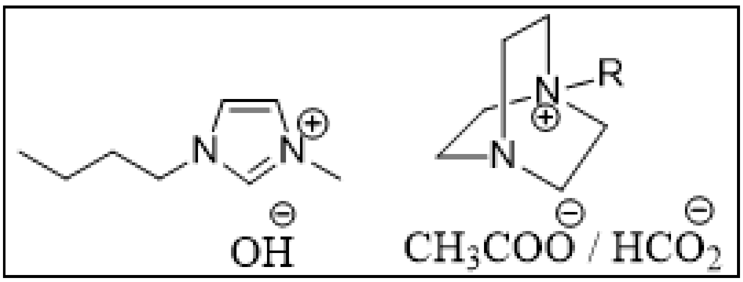

Figure.4.2. Basic Ionic liquids

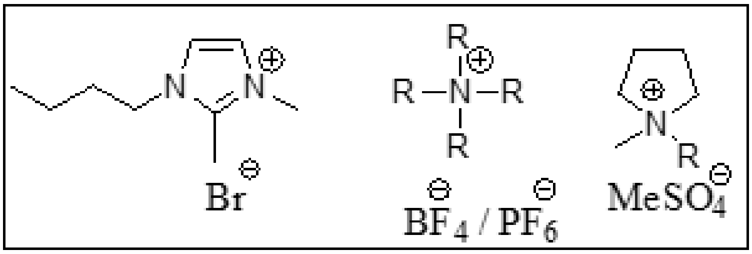

Figure.4.3. Neutral Ionic liquids

Ionic liquids have been documented to possess task-specific properties, as evidenced by several research articles that explore their utilization as solvents or catalysts to enhance reaction performance. Among the several reactions occurring in organic synthesis, the significance of protection and deprotection techniques in peptide synthesis has been underscored by the utilization of ionic liquids. Imidazolium-based ionic liquids (Chakraborty et al., 2016; Majumdar et al., 2014) have demonstrated significant efficacy in the protection of amine functionality, as well as in tolerating deprotection strategies (Majumdar et al., 2014). Additionally, they have played a role in carbon-carbon bond formation and cleavage (Chakraborty et al., 2016) resulting in substantial yield of products.

Deep eutectic solvents

Deep eutectic solvents (DESs) are a distinct category of ionic fluids that bear resemblance to ionic liquids at normal temperature. However, they are characterized by the presence of an organic molecule component as their primary constituent. The term "deep eutectic solvent" was initially introduced by Abbot (Abbot et al., 2003; Abbot et al., 2004) to describe ionic fluids that often consist of two substances capable of self-association, resulting in the formation of a eutectic mixture with a significantly lower melting point compared to the separate components. Various types of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) (Fig 5.1) with distinct physicochemical properties are commonly encountered, necessitating the use of diverse appropriate methodologies for the synthesis of deep eutectic solvents (DESs). DESs are a new type of solvent that are both sustainable and environmentally friendly. They were initially introduced as versatile alternatives to traditional RTILs. DESs are typically created by reacting a quaternary ammonium halide salt, such as choline chloride, with metal salts or a hydrogen-bond donor (HBD) such as urea, carboxylic acids, amides, or polyalcohols. This reaction allows the DESs to form a complex with the halide ion, resulting in a significant decrease in the freezing point. DESs can be seen as closely related to room temperature ionic liquids, yet there is a distinct ecological distinction between the two. Specifically, it should be noted that DESs do not qualify as RTILs due to their composition, which does not only consist of ions but rather includes a molecule component, which may be more prevalent in some cases. Furthermore, DESs are more convenient to produce as they involve straightforward blending of the two constituents, produce no by products during the procedure, and do not require any purification. These characteristics align with the concepts of Green Chemistry. In practical terms, DESs present themselves as appealing alternatives to RTILs due to their notable characteristics, such as minimal or low vapor pressure, humidity tolerance, thermal stability, tunability, and superiority in addressing various problems associated with RTILs. These substances possess cost-effectiveness, non-toxicity, synthetic availability, and biodegradability.

The utilization of deep eutectic solvents has been significantly increased in the synthesis of heterocyclic compounds. The Knoevenagel reaction (Liuet al., 2014), cyclization reaction (Sebest et al., 2020) andring opening reactions (Azizi and Gholibeglo, 2012) were facilitated by DES. The formation of carbon-sulfur bonds (Dilauro et al., 2017) is a subject of significant interest due to its presence in numerous biologically significant compounds and its relevance in the field of material sciences. The utilization of deep eutectic solvents presents an opportunity for the sustained advancement of nano material creation, in addition to organic synthesis. Deep eutectic solvents (DESs) play a crucial role in several manufacturing processes, facilitating the development and design of nano structures and nano composites (Mernissi Cherigui et al., 2017) with distinct morphology and properties. These methods can also be tailored to precise reaction conditions (Nam et al., 2023).

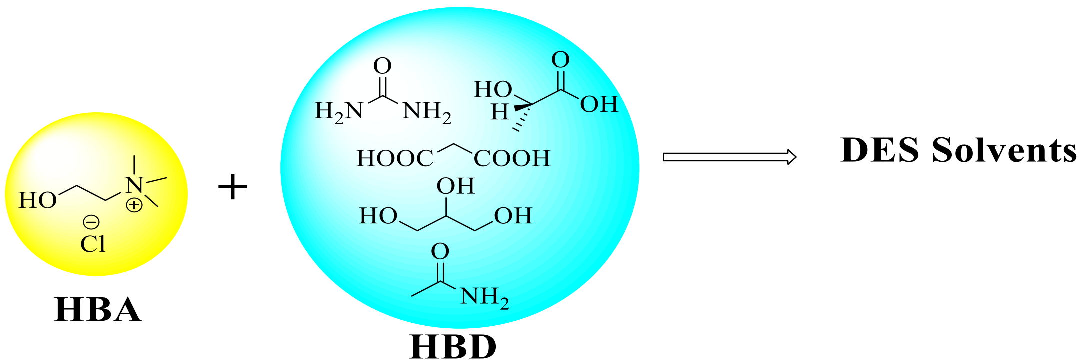

Figure.5.1. Hydrogen bond acceptors (HBA) and hydrogen bond donors (HBDs) constituting the deep eutectic solvents

Conclusion

This chapter provides a concise overview of various green solvents, including water, the universal solvent, ionic liquids, and deep eutectic solvents. It is important to note that there are numerous additional green solvents that can be included. In recent decades, these compounds have gained significant importance in the field of synthesis. The utilization of environmentally friendly solvents for the sensitive synthesis of heterocycles and asymmetric synthesis aligns closely with the concepts of green chemistry. The objective of Green Chemistry is to substitute frequently employed solvents with environmentally friendly alternatives in order to minimize environmental consequences. This chapter has the potential to shed light on the utilization of potential green alternatives in organic synthesis for the production of bioactive scaffolds. The solvents mentioned here demonstrate the superiority of environmentally friendly alternatives over traditional solvents. This could potentially facilitate the advancement of sustainable development and the subsequent implementation of Green Chemistry in near future.

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