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Green Solvents for Sustainable Organic Synthesis

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Abstract: ***One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. Generally, chloroform, dichloromethane, benzene, carbon tetra chloride etc are used as a solvent in organic synthesis which is not only costly but is very harmful for those who are handling them also. Thus, the development of solvent-free alternative processes is, of course, the best solution. In cases where the solvent is needed, less hazardous replacements should be employed. The application of alternative solvents such as water, fluorous and ionic liquids, supercritical media like supercritical CO_2 and their various combinations is rapidly increasing. Purification steps also generate large sums of solvent and other waste (chromatography supports, e.g.). This Review aims to describe an overview of chemical processes employing such green solvents which are proposed as sustainable alternatives.***

Keywords: Green solvents, Green chemistry, Aqueous medium, Ionic liquids, Fluorous solvents, Supercritical carbon dioxide, Sustainability

1. Introduction

Green chemistry can be defined as a chemistry that designs chemical products and processes that are harmless to the environment, thus preventing the formation of pollution.[1-3] In 1998, two US chemists, Dr. Paul Anastas and Dr John Warner outlined Twelve Principles of Green Chemistry to demonstrate how chemical production could respect human health and the environment while also being efficient and profitable. Out of these twelve principles, the most important aspect is the selection of the appropriate solvent. Solvents are used on a daily basis in numerous synthetic processes, and it is estimated that they comprise almost 60% of all industrial emissions and 30% of all volatile organic compound emission worldwide.[4]

In attempts to eliminate undesirable solvents, replacement strategies of solvents are good alternative. Thus benzene, since its formal recognition as a carcinogen in the mid-twentieth century, is generally replaced by toluene[5]. Nevertheless, toluene is in fact suspected of damaging the unborn child and of organ damage through prolonged exposure[6]. Similarly, the Montreal protocol has restricted the use of carbon tetrachloride since 1989 because of its role in depleting the ozone layer.[7] Typically, the halogenated solvents chloroform and dichloromethane (DCM) are now used instead. However, chloroform and DCM are likely to be carcinogenic to humans according to the World Health Organization IARC evaluations.[8] Accordingly, a growing area of research in the development of green technologies is devoted to designing new, environmentally-friendly and tunable solvents the use of which would meet both technological and economic demands. Among proposed solvents, room temperature ionic liquids, water, supercritical CO_2 and Fluorous biphasic solvents stand out as the most promising approaches for current solvent innovation. A brief overview of up-to-date knowledge regarding these solvents is presented herein, with special emphasis on their properties and applications as truly green solvents.

2. Ionic Liquids in Organic Synthesis

The development of a non-volatile and recyclable alternative solvent is a major emphasis in Green Chemistry. In this aspect, over the past 20 years, ionic liquids (ILs) have been receiving increasing attention in the scientific and industrial community due to their above-mentioned unique properties and abilities.[9]Generally ionic liquids are composed of discrete anions and cations (**Figure 1**) and have extremely high enthalpies of cations and have extremely high enthalpies of vaporization (ΔH_{vap}), making them effectively nonvolatile and a desirable substitute for volatile organic compounds.

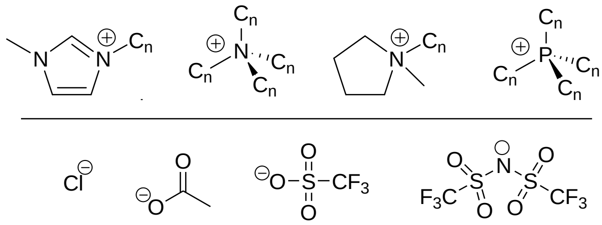


Figure 1: Common aprotic cations (top) and some anions (bottom), which may be paired in any combination.

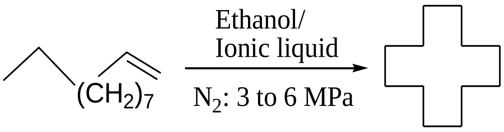
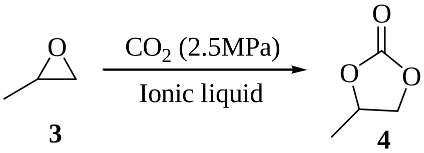
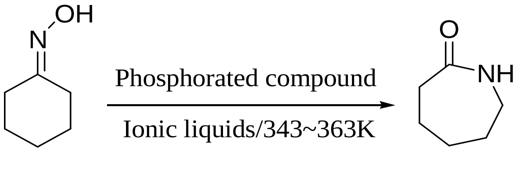
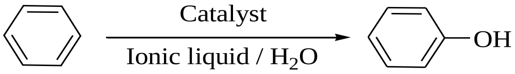
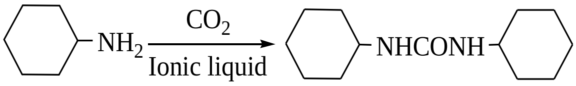
Moreover, ionic liquids are non-flammable and have high chemical and thermal stabilities (they usually exist as liquids well below room temperature up to a temperature as high as 200°C) and remarkable solvating power; hence, they were popularized as green solvents. Therefore, the room temperature ionic liquids were extensively used in electronic absorption spectroscopy, liquid–liquid extraction processes, [10] organic and organometallic syntheses, [11] catalytic cracking of polyethylene, radical polymerization, [12] analytical and physical chemistry, lubricant, [13] etc. Some of the remarkable uses of ionic liquid as green alternatives are summarized in the following **Table 1**.

3. Water as solvent in Organic Synthesis

Among all environmentally begin solvents, the most important solvents in green chemistry is water. It is non-flammable, nontoxic, inexpensive and it is amply available

As a protic and polar solvent, it plays an important role in view of green chemistry.[20] The use of water as solvent features many benefits such as improving reactivities and selectivities, simplifying the workup procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis in addition to being benign itself.

Table 1

Sl. no	Reaction with ionic liquids
1	 **1** **2** Cyclization of 1-dodecene to cyclo-dodecane[14]
2	 **3** **4** Cyclo-addition of carbon dioxide to propylene oxide[15]
3	$Ph-NH_2 \xrightarrow[\text{Ionic liquid}]{\text{MeOH / CO, Palladium complex}} Ph-NHCO_2Me$ **5** **6** Oxidative carbonylation of aniline in ionic liquid mediated palladium complex[16]
4	 **7** **8** Catalytic Beckmann rearrangement[17]
5	 **9** **10** Selective oxidation of benzene to phenol in ionic liquid–water biphasic system[18]
6	 **11** **12** Synthesis of symmetric ureas with carbon dioxide[19]

In addition, exploring organic chemistry in water can lead to uncommon reactivities and selectivities complementing the organic chemists' synthetic toolbox inorganic solvents. Studying chemistry in water also allows insight to be gained into Nature's way of chemical synthesis. The first organic reaction in aqueous medium was the preparation of urea from ammonium cyanate by Wohler's method in 1828. Another pioneering example is the synthesis of indigo in aqueous medium by heating a suspension of O-nitro benzaldehyde in aqueous acetone with NaOH solution. The most widely studied reaction in aqueous medium is Diels-Alder cycloaddition reaction. In 2005, Sharpless made another interesting study for the reaction of between quadricyclane and dimethylazo dicarboxylate in different solvent[22], where he found most promising result in water. In 2007, Marcus and Jun proposed a mechanism to understand the on-water reaction[23]. It is observed that water molecule in the bulk are all hydrogen bonded in a tetrahedral fashion but on the surface layer all hydrogen atoms water molecules are not H bonded and was calculated that one OH group remains free from H bonding in each four water molecules. Organic liquids poor solubility in water forms a clear organic phase with water. In the interface some of the unbounded hydrogens which are dangling outwards may enter into the hydrophobic oil layer due to the vigorous stirring (**Fig. 1**).

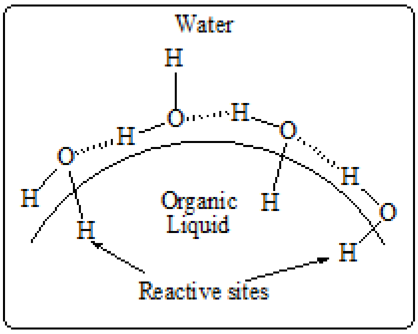
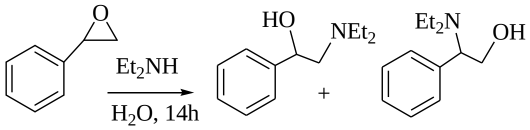
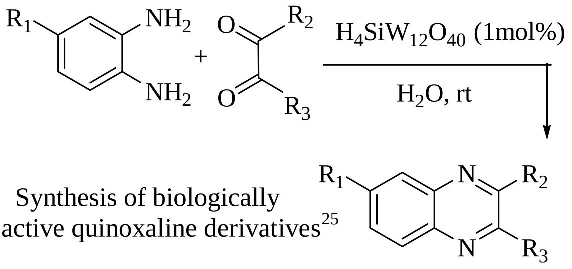
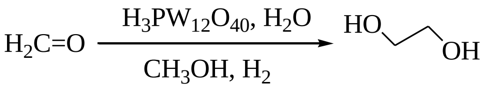
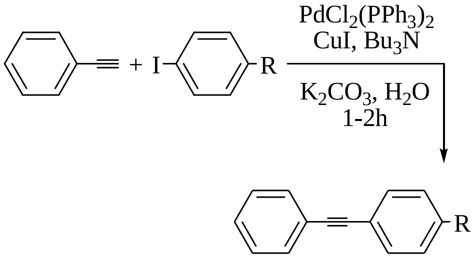


Fig. 1: A schematic presentation of Marcus *trans*-phase H-bonding of water[23]

These protons in the hydrophobic environment from highly reactive centers in comparison to a proton in aqueous phase. Such proton in hydrophobic environment behaves like a unsolvated free proton and reacts as a reactive catalytic site. A few examples in organic reaction in aqueous medium is given in the following **Table 2.**

Table 2

Sl no	Reactions in water
1	 **13** **14** **15** (**14: 15**= 55:45, 92%) Epoxide ring opening[24]
2	 Synthesis of biologically active quinoxaline derivatives[25]

3	 Synthesis of methyl glycolate[26]
4	$2PhCHO \xrightarrow{CN^-, H_2O} PhCHOHCOPh$ Benzoin condensation[27]
5	 Sonogarshira coupling[28]

4. Fluorous bi-phasic solvent in organic synthesis

Flourous solvent is one of the most promising solvent in the field of green chemistry. Highly fluorinated compounds are known as flourous solvents. Fully fluorinated solvents like C_6F_{14} are non-polar and immiscible with organic solvents and water. Some organic solvents although immiscible with flourous solvents at room temperature but forms a homogenous at elevated temperature. This property has been utilized in many catalytic reactions. Such flourous possesses almost similar boiling point with the corresponding hydrocarbons. These are incombustible and are capable of solubilizing many gases. These solvents are ideal for reaction involved in non-polar reactants and products. Use of flourous solvent and an organic solvent in a reaction is called a flourous a biphasic solvent and similarly multi-phasic system are known as flourous multiphase system.

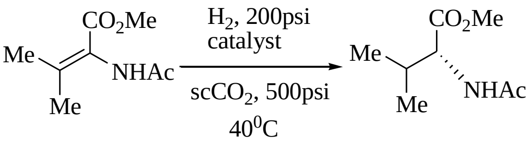
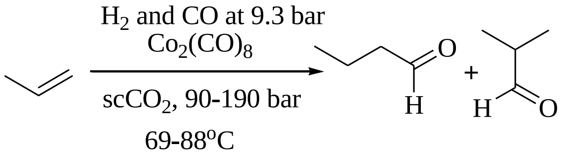
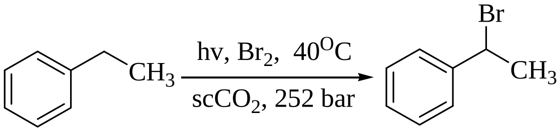
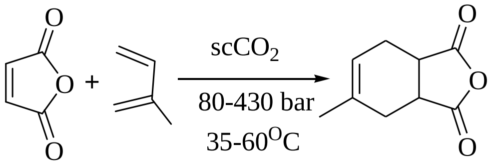
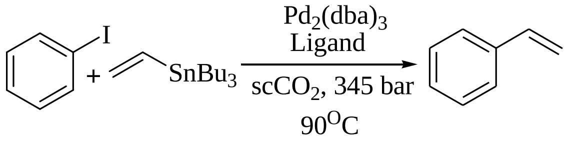
Another approach to solvent replacement is to switch from neat solvent to aqueous blends. These semi-aqueous solutions contain organic additives such as terpenes, alcohols, and aliphatic hydrocarbons. Terpenes are very effective n dilute aqueous solutions for removing grease, resin, and adhesives. On the other hand, the high polarity of common water also has a lot of advantages in regard to reactivity and selectivity, like in organometallic catalysis. It is possible to recover and recycle the catalyst in an aqueous biphasic system via phase extraction whereas the product stays dissolved in the organic phase. This simple and smooth separation overcomes the tedious recycling of the catalyst.

5. Supercritical Carbon Dioxide

Above a critical temperature (T_c) and pressure (P_c), fluids exist as one phase having densities and viscosities between those of a liquid and a gas and can have significantly different solvating capabilities than the liquid compounds below the critical point. Carbon dioxide (CO_2) is the most commonly used compound at supercritical conditions due to its accessible critical point (T_c= 304.2K, P_c= 78 atm). Super-critical CO_2 ($scCO_2$) is a nonpolar solvent and thus is capable of effectively solvating nonpolar oils. Comparative to other supercritical liquids, Super-critical CO_2 ($scCO_2$) is cheap and can readily be obtained as a by-product from different sources.

$scCO_2$ possesses properties in between a gas and a liquid. It exhibits diffusibility like a gas and has a solvent power like nonpolar light petroleum ether (a mixture of pentanes and hexanes). Due to such dual properties of $scCO_2$ it is used in organic synthesis as a green replacement of organic solvents, the extracted material can be recovered by releasing the pressure of CO_2. Decaffeination of coffee beans using $scCO_2$ is a popular decaffeination process as caffeine can be removed from the $scCO_2$by extraction with water rather than releasing the pressure. A few examples of organic reactions using $scCO_2$ are given in the following **Table 3.**

Table 3

Sl no	Reaction in $scCO_2$
1	 Asymmetric hydrogenation[29]
2	 Hydroformylation reaction[30]
3	 Free radical halogenation reactions[31]
4	 Diels–Alder cycloaddition reactions[32]
5	 Palladium mediated coupling reactions[33]

6. Conclusion

From the discussion of the selected four solvent alternatives (ionic liquids, water, supercritical carbon dioxide and fluorous solvents) in this review, it is obvious that the obtained results are similar and sometimes even better than these, resulting from conventional syntheses in organic solvents. Water, as a cheap, abundantly available, nontoxic and nonflammable solvent represents an ideal reaction medium for many processes. Fluorous solvents and ionic liquids are attractive alternatives for performing reactions. Supercritical carbon dioxide also exhibits outstanding characteristics for the utilization in Green Chemistry due to its intermediate properties between gas and liquid state. Taken together, the green approach, where solvent alternatives complement one another, provide the ideal basis for a sustainable chemical industry and will lead to fundamental innovations in chemical science. However, it leads to discussions about supremacy of one green solvent over another. In the future, scientists will have to focus more on the solvent selection, basing on sustainable development and environmental protection.

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