JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Ecofriendly Solvents used in the Chemistry

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Abstract

Solvents have many uses, both commercial and domestic. In the chemicals industry, solvents are used in the production of chemicals as media for chemical reactions and for chemicals separation/purification. Here, I attempt to demonstrate how appropriate selection of solvents for chemicals processing has been used to improve the sustainability of these processes using examples that have been, to the best of my knowledge using publicly available information, in commercial use at some time. These have been selected for illustrative purposes and are not an exhaustive collection of all the available examples in the literature.

Keywords – Solvents, Chemistry, Sustainable.

Introduction

In 1987, the United Nations defined sustainable development as development that enabled the current generation to meet its own needs, without compromising the ability of future generations to meet their needs. Sustainable Chemistry is the implementation of the concept of sustainability in the production and use of chemicals and chemical products and the application of chemistry and chemical products to enable sustainable development.

The first part of this overlaps significantly with green chemistry—the reduction or elimination of the use or generation of hazardous substances in the design, manufacture and application of chemical products.

The second part makes it clear that the benefits of modern chemistry and chemical products should be made available to all communities. Horváth and co-workers have described sustainable chemistry as: resources including energy should be used at a rate at which they can be replaced naturally and the generation of wastes cannot be faster than the rate of their remediation.

Green metrics

The sustainability of a chemical product or process is necessarily the result of a complex interaction of environmental, technological and economic factors and is difficult to predict. Guides are required to provide means to select probably useful avenues for further research and development. Early stage techno-economic modelling techniques are relatively well established. Measures of environmental sustainability are less well developed. Life cycle assessment (LCA) is considered the gold-standard environmental impact assessment for any product or process. LCA is a collection of techniques designed to assess the environmental impacts associated with all stages of a product's creation, use and disposal, including any reuse or recycling, from 'cradle to grave'. While LCA attempts to be comprehensive, it is sensitive to the amount and quality of data available and to choices made about precisely what is included, and how, in the analysis. Consequently, different analyses of the same product or process can come to different conclusions. LCA can also be prohibitively expensive. LCA approaches can be relevant to products and processes either already in commercial application or those at high technology readiness levels. However, LCA is not a useful tool for those engaged earlier in the innovation pipeline. For these, simpler metrics are required.

The simplest green metric is Atom Economy. This was introduced to focus chemists' attention away from yield as the only measure of reaction efficiency and on to the inherent efficiencies of different types of reactions.

'Green' solvents

Many commonly used solvents have been recognized as being of environmental concern. These concerns arise in three areas: the source and synthesis of the solvent itself; its properties in use, including accidental discharge; and finally disposal. A great deal of the literature of solvent use advocates that one solvent or class of solvents should be regarded as inherently 'green'. Solvents and solvent classes that have been suggested as 'green' solvents include water supercritical fluids, gas expanded liquids, ionic liquids, liquid polymers and solvents derived from biomass. This is based on the idea that replacing a 'non-green' solvent in a process with a 'green' solvent necessarily improves its environmental performance. This, in turn, has led to debates in the literature about which of these solvents is greener. Ionic liquids have, with their often complex syntheses and toxicities, been particularly criticized in this respect, although so has water.

The selection of the solvent for a reaction can dramatically affect the reaction outcome. Hence, it is possible that a replacement of a 'non-green' solvent by a 'green' solvent could lead, for example, to a lower yield of the product and greater waste, or the need for harsher operating conditions that require more energy. In these cases, the process could become less environmentally sustainable overall. In order to thoroughly understand how a solvent change can affect the sustainability of a process, it is necessary to consider all its impacts on the overall process. Hence, the idea that a liquid can be regarded as inherently 'green' is somewhat naive, even irrelevant. What matters is whether the use of one solvent or solvent system rather than another can give a more sustainable process and/or product Notwithstanding the above, it is possible to make some points about the general acceptability of different solvents. A number of solvent selection guides have emerged from the pharmaceutical industry, i.e. ACS GCI-PR (http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf), GSK, Pfizer and Sanofi. While different in detail, these all share the aim of distilling a great deal of information into an easily used form. There is good general agreement between the guides, but they do not all come to precisely the same conclusions as to how desirable every solvent might be. This is not a problem if these are treated as general guides that can be applied quickly and easily and not as definitive statements as to the applicability of any particular solvent in any particular process.

recommended	recommended or problematic	problematic	problematic or hazardous	hazardous	highly hazardous
water	methanol	2-methyltetrahydrofuran	2-methoxy-2-methylpropane	diisopropylether	diethylether
ethanol	*tert*-butyl alcohol	heptane	tetrahydrofuran	1,4-dioxane	benzene
2-propanol	benzyl alcohol	methylcyclohexane	cyclohexane	dimethyl ether	chloroform
1-butanol	ethylene glycol	toluene	dichloromethane	pentane	carbon tetrachloride
ethyl acetate	acetone	xylenes	formic acid	hexane	dichloroethane
2-propyl acetate	butanone	chlorobenzene	pyridine	dimethylformamide	nitromethane
1,1-dimethylethyl acetate	4-methyl-2-pentanone	acetonitrile		*N,N*-dimethylacetamide	
anisole	cyclohexanone	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one		1-methyl-2-pyrrolidone	
sulfolane	methyl acetate	dimethyl sulfoxide		methoxy ethanol	
	acetic acid			triethanolamine	
	acetic anhydride				

Sustainable solvent use

As green chemistry spread some tension between those working in the field, largely in academia, and those working in process chemistry, largely in industry, began to emerge. The target of creating low-waste, efficient chemistry that delivers products in an economically viable way is not new and both endeavours are equally capable of contributing to sustainable chemical solutions. Indeed, the sustainability of any chemical synthesis process equally depends upon finding chemical engineering solutions.

Reports of direct replacement in industry of a solvent by an alternative in an existing commercial process just for the purpose of creating a greener process are rare in the literature. In pharmaceuticals production, the need for renewed regulatory approval of the product, particularly in multiple jurisdictions, after a significant change in the synthesis process can create a barrier to such replacements. In bulk chemicals production, the cost of replacing large-scale production plant equipment can generate a commercial barrier to such replacements. Consequently, any changes must be accompanied by economic improvements in the process to be able to compensate for these expenses.

Biocatalysts in water

Biocatalysis has become a standard synthetic technique across a wide range of the chemicals and pharmaceutical industries While enzyme catalysis in non-aqueous solvents has been known for a long time, water is the solvent of choice for biocatalytic processes. Hence, the use of enzyme-catalysed reactions is often accompanied by a replacement of non-aqueous solvents with water and so is included here. The use of enzymes in water has also enabled improvements in other environmental impacts of many processes.

Pfizer's chemoenzymatic synthesis of pregabalin

Pregabalin, (S)-3-(aminomethyl)-5-methylhexanoic acid, is a treatment for central nervous system disorders. Its original commercial synthesis (scheme 3) began with a Knoevenagel condensation,

followed by cyanation, introducing a chiral centre as a racemic mixture, then hydrolysis, decarboxylation and hydrogenation in methanol to yield a γ-aminoacid. (S)-(+)-Mandelic acid was then added in aqueous iso-propyl alcohol (i-PrOH) to give a classic chiral resolution and the resulting diastereomeric salt was split by recrystallization from aqueous THF, followed by recrystallization from i-PrOH to yield pure pregabalin. This malonate route was compared all the way to pilot plant scale with another that used γ-isobutylglutaric acid. Costs, throughput and the amount of waste generated were largely comparable, but the γ-isobutylglutaric acid route used chloroform and so was rejected because the necessary control measures would have led to greater capital outlay. This demonstrates how the avoidance of hazardous solvents can reduce the cost of chemicals production.

The generation of the γ-aminoacid as a racemic mixture and the need to obtain theenantiomerically pure pregabalin led to both waste of the compound itself and the use of large amounts of solvents. Reports can be found in the literature from both Pfizer and Dowpharma of the development of asymmetric hydrogenation-based routes to avoid this problem. However, Pfizer's eventual solution was an enzyme-catalysed process

An enzyme-catalysed kinetic resolution hydrolyses one of the esters of the β-cyano diester to yield the sodium salt of the carboxylic acid. The unreacted diester is then recycled and racemized in toluene to be reused, while the carboxylic acid is thermally decarboxylated in the aqueous solution. This yields the β-cyano ester as a water-insoluble oil, which separates leaving the majority of the impurities in the aqueous layer. Hydrogenation in aqueous i-PrOH completes the synthesis. The authors report that this led to a reduction of the E-factor from 86 for the original commercial route to 17 for the new route and a reduction in solvent use from 50 kg kg^{-1} product to 6.2 kg kg^{-1}. Perhaps some concern remains at the use of toluene in the racemization process, but the environmental performance of the synthesis has been significantly improved.

Mitsubishi Rayon's synthesis of acrylamide

Acrylamide is a commodity chemical used as the monomer for the polymer polyacrylamide. It is prepared by the hydration of acrylonitrile.

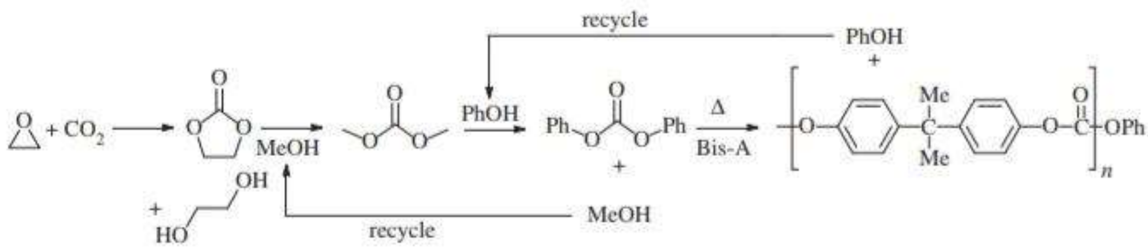
Whole-cell biocatalysis

Biocatalysis can also be performed using whole microorganisms. Three such commercial routes to vitamin B2, riboflavin, use Ashbya gossypii, a filamentous fungus (BASF), Candida famata, a yeast (ADM USA), or Bacillus subtilis, a Gram-positive bacterium (Roche) [119]. The earlier synthetic chemistry route required multiple steps, several solvent replacements and gave a maximum yield of 60%. The biocatalytic methods use less energy, reduce waste and use renewable resources, such as sugar or plant oil, as the starting materials and produce the riboflavin at approximately half the cost of the synthetic chemistry route.

The solvent is one of the reacting species

Asahi Kasei's polycarbonate synthesis

The polymer most often referred to simply as polycarbonate (PC) is an aromatic carbonate polymer based on the monomer bisphenol-A (Bis-A). It has increased in use and importance



with the spread of modern electronic devices. Asahi Kasei introduced a new process for the

production of PC (scheme 5) that is acclaimed for replacing phosgene (COCl2) as the source of the carbonate link in the polymer with CO2 [120–122]. However, this process also led to the removal of dichloromethane (DCM) as a solvent. The new process is conducted in a 'melt' of the reaction mixture. While one might not choose one of the components to be the solvent for the others, this is undoubtedly a solution process.

In the original production of PC Bis-A dissolved in water reacts with phosgene dissolved in DCM. The reaction occurs at the interface of these two immiscible solutions. The DCM is a solvent. for the PC product, thus maintaining a homogeneous solution throughout the process. However, the DCM is used in very large amounts (10× the amount of PC by mass). A similar mass of contaminated waste water is produced in this process (or 100× for optical grade PC). DCM also contaminated the product, leading to the release of this toxic solvent to the environment and a lower quality product. Also, although forming two layers, DCM has some solubility in water and water has some solubility in DCM, leading to energy-intensive and expensive separations.

The solvent enables product separation

BASF's BASIL (biphasic acid scavenging utilizing ionic liquids) process

BASF produces alkoxyphenylphosphanes as the raw materials for a range of UV-photoinitiators. Originally, Et3N was used as a proton scavenger, leading to the formation of [Et3NH]Cl. The alkoxyphenylphosphanes are liquid and the [Et3NH]Cl solid, resulting in a thick slurry that required separation using filter presses that regularly blocked. The BASIL process (scheme 12) solved this by replacing the Et3N with 1-methylimidazole, which gives 1-methylimidazolium chloride ([HC1im]Cl, mp = 75◦C) with the HCl formed, which separates spontaneously as a second liquid phase under the reaction conditions [157,158]. This eliminated the costly and unreliable filtration step. The by-product [HC1im]Cl is deprotonated to recycle the 1-methylimidazole, again reducing costs. 1-Methylimidazole is also a nucleophilic catalyst [159]. This enabled the development of a new jet stream design for the new all-liquid BASILTM reactor, which gave an increased productivity of a factor of 8 × 104 to 690.000 kg m−3 h−1, giving significant cost savings. A recent ecoefficiency analysis has shown that the BASIL technology is far more environmentally sustainable than the process using tertiary amines.

Conclusion

The environmental concerns that surround the use of solvents for chemicals processing will ensure that this remains an active area for research for some time to come. The examples that I have shown above demonstrate that it is possible to make considerable advances in the reduction of the amounts of solvents used in chemicals processing. They also go beyond this to demonstrate the potential of appropriate solvent selection to improve other areas of a process's performance and hence its overall sustainability. These examples also demonstrate that the implementation of the concept of sustainability in the production and use of chemicals and chemical products requires that chemicals processing must be both environmentally and commercially sustainable.

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