

Green Chemistry

(By A. Bacher, UCLA, 9-16-2014)

While organic chemistry is a very important part of everybody's life, the production of drugs, fuels, polymers, pigments, insect repellants, etc. also generates many problems due to the magnitude of the production today. In the mid-19th century, organic dyes were produced and the waste products were vented into the atmosphere, dumped into rivers, lakes and landfills (W.H. Perkin accidentally discovered mauveine, the first synthetic organic dye, in 1856). Due to the heavy contamination of the environment, many people were exposed to many hazardous compounds giving rise to countless illnesses (i.e., cholera, typhoid fever, emphysema, infant mortality). However, as the awareness for health and environmental impact of chemical production has grown, these methods of waste management have become very much unacceptable. Today, waste management is heavily regulated on every level (local, state and federal). While the danger that certain compounds can pose to the health of humans, animals and plants has been recognized a long time ago, very little has been done in some cases to minimize or eliminate them.



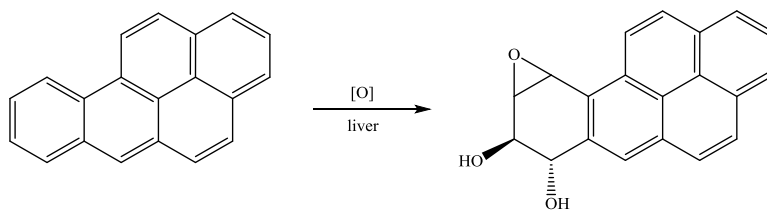
The famous Swiss-German scientist Paracelsus recognized in the early 16th century already that the same compound could be a remedy or a poison depending on the dose that was administered. While this even applies to ordinary compounds like water and sodium chloride, many drugs and even some vitamins are significantly more toxic compared to these compounds. Thus, the need for proper dosage of drugs arises. In general, each compound has to be assessed for its specific hazards (acute, chronic). The acute toxicity is often quantified by the LD₅₀ measure. The table below shows that the degree of toxicity can differ quite a lot

| Compound | LD ₅₀ (g/kg) |
|-------------------|-------------------------|
| Water | 180 |
| Ethanol | 7.06 |
| Sodium chloride | 3.75 |
| Ibuprofen | 0.636 |
| Vitamin D | 0.619 |
| Aspirin | 0.20 |
| Caffeine | 0.13 |
| Nicotine | 0.05 |
| Sodium cyanide | 0.015 |
| Sarin (nerve gas) | 4*10 ⁻⁴ |
| Botulinium toxin | 3*10 ⁻¹¹ |

Aside of the acute toxicity, there are various hazards that a compound can pose:

1. Carcinogens and Suspect Carcinogens

Carcinogen are compounds that are known to cause cancer in animals and/or humans. Compounds like benzo[a]pyrene, commonly found in cigarette smoke, charred meat and diesel exhausts, is well known to be a carcinogen. In the liver, this compound is converted to a diol epoxide which is highly carcinogenic because it binds strongly to the DNA. Aminonaphthalenes, benzidine and its derivatives as well as several chlorinated ethers are also recognized carcinogens according to OSHA General Industry Standards (full list of known carcinogens can be found on their website). Compounds like asbestos, formaldehyde, benzene and vinyl chloride are considered carcinogens as well.



Many other polycyclic aromatic hydrocarbons (PAH), their nitro (i.e., nitropyrene) and many nitroso compounds are considered suspect carcinogens because they possess chemical or structural similarities with known carcinogens. Many powerful alkylating agents i.e., methyl iodide, dimethyl sulfate, etc. are considered suspect carcinogens as well.

2. Mutagens and Teratogens

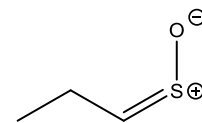
A reproductive toxin is defined as a chemical “which affects the reproductive capabilities including chromosomal damage (mutations) and effects on fetuses (teratogenesis)”. Many drugs have effects on the human reproductive system. Some may be desired effect like hormonal contraception, others have minor unwanted side effect (i.e., many antidepressants).

Mutagens are compounds that cause mutations in the DNA. The DNA damage can cause cancer in humans, animals and bacteria. Representative mutagens are 2-aminopurine, 5-bromouracil and hydroxylamine. X-rays, gamma rays and alpha particles are considered physical mutagens because they may cause DNA breakage and other damages due to their ionizing character.

Teratogens are substances that cause developmental malformations (birth defects). The list contains many compounds ranging from inorganic compounds (i.e., cadmium, thallium, beryllium), organic solvents (i.e., benzene, chloroform, toluene, DMF), biological compounds (i.e., testosterone) and drugs (i.e., (*R*)-thalidomide). Currently, this list contains already more than 3100 compounds, among them caffeine, cholesterol, corn oil, hexane and toluene (see also <http://www.purdue.edu/ehps/rem/ih/terat.htm>).

3. Lachrymators, Corrosives and Unstable Compounds

Lachrymators are compounds that irritate the mucous membrane. Exposure to the vapors of these compounds leads to severe eye watering. These compounds are used as tear gas used by the police in riot control or to incapacitate attackers. Compounds like bromoacetone, benzyl bromide, benzyl chloride, thionyl chloride and *syn*-propanethial *S*-oxide (released from onions) belong to this class.



Certain compounds are sensitive towards impact, heat or friction causing them to decompose explosively. Many peroxides and polynitrated compounds fall into this class (i.e., diethyl ether peroxide, acetone peroxide, benzoyl peroxide, nitroglycerin, trinitrotoluene, metal and organic azide, silver and mercury fulminate, nitrogen(III) halides).

Corrosives are compounds that cause severe skin irritation and tissue damage upon contact. Strong acids and strong bases (i.e., concentrated sulfuric acid, concentrated sodium hydroxide solution) as well as compound that can form them belong into this group.

What is Green Chemistry?

Anastas and Warner proposed “The Twelve Principles of Green Chemistry” in their book (“Green Chemistry: Theory and Practice”, Oxford University Press, Oxford, UK, 1998):

1. *Prevention*

It is better to prevent waste than to treat or clean up waste after it has been created.

2. *Atom Economy*

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. *Less Hazardous Chemical Syntheses*

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. *Designing Safer Chemicals*

Chemical products should be designed to affect their desired function while minimizing their toxicity.

5. *Safer Solvents and Auxiliaries*

The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. *Design for Energy Efficiency*

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. *Use of Renewable Feedstocks*

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. *Reduce Derivatives*

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or be avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

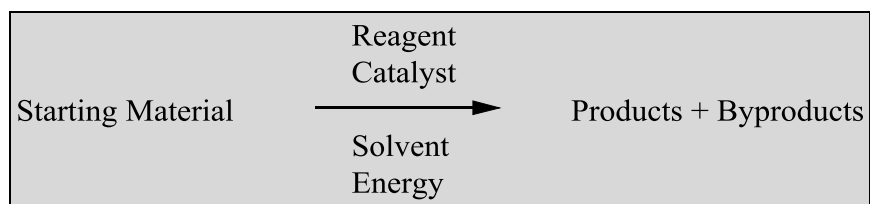
12. Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

What are the strategies used in Green Chemistry?

The risk that the synthesis of compound poses is a function of exposure and intrinsic hazards caused by all compounds used in the synthesis. Even a harmless compound can become dangerous upon excessive exposure. Therefore, the traditional approach has been focusing on the minimization of exposure (i.e., filter systems, proper waste disposal, etc.). However, the Pollution Prevention Act of 1990 emphasized the prevention of pollution at the source rather than the treatment of pollutants after they are formed and was more or less the start of the green chemistry initiative. Green chemistry aims to minimize risk by eliminating or reducing the use of hazardous substances. It involves inventing new methods to reduce chemical hazards while producing superior products in a more efficient and more economical way.

A chemical reaction can generally be written as



Thus, the hazards involving the starting materials, the reagents, the catalyst and the solvent have to be assessed. After identifying the hazards and inefficiencies, the process is modified. If the efficacy test for the new process is favorable, a greener alternative was developed for the synthesis of the target compound. If not, the process should be further improved.

1. Solvents

While solvents appear to be necessary for many reactions to occur, their presence also causes many problems i.e., they reduce the reactivity of many reagents and starting materials. They limit the lower and upper temperature at which the reaction can take place. Solvents are also used in the workup process (i.e., extraction, recrystallization, chromatography, etc.). In addition, many of the commonly used solvents are volatile (see the vapor pressure at 20 °C in the tables below). Thus, the experimenter and the environment can be exposed to them.

a. Hydrocarbons

Hydrocarbons (i.e., alkanes, aromatics) are volatile, which poses a substantial inhalation risk. They tend to affect primarily the central nervous system and can cause lung damage. They are also flammable and represent a significant fire risk as well.

| Name | Formula | mp (°C) | bp (°C) | Vapor Pressure at 20 °C (mm Hg) |
|----------|---|---------|---------|---------------------------------|
| Benzene | C ₆ H ₆ | 5 | 80 | 75 |
| Hexane | C ₆ H ₁₄ | -95 | 69 | 132 |
| Heptane | C ₇ H ₁₆ | -90 | 98 | 40 |
| Toluene | C ₆ H ₅ CH ₃ | -95 | 111 | 22 |
| o-Xylene | C ₆ H ₄ (CH ₃) ₂ | -24 | 144 | 5.2 |

b. Halogenated Hydrocarbons

Halogenated hydrocarbons (i.e., dichloromethane, chloroform) are highly effective solvents because they are able to dissolve a broad variety of compounds. Most of them display relatively low boiling points and are very volatile. Thus, the experimenter can be exposed to the liquid and the vapors potentially leading to problems with the central nervous system, kidneys, liver and heart. Many of them are considered suspect carcinogens, mutagens and/or teratogens. That is the main reasons why they are not very popular in industry and are not used in the lower division laboratory courses at UCLA (and elsewhere) anymore.

| Name | Formula | mp (°C) | bp (°C) | Vapor Pressure at 20 °C (mm Hg) |
|-----------------------|----------------------------------|---------|---------|---------------------------------|
| Dichloromethane | CH ₂ Cl ₂ | -95 | 40 | 349 |
| Chloroform | CHCl ₃ | -64 | 61 | 160 |
| 1,1,1-Trichloroethane | CH ₃ CCl ₃ | -33 | 74 | 100 |
| Carbon tetrachloride | CCl ₄ | -23 | 77 | 90 |

c. Alcohols

Many alcohols are commonly used in the lab (i.e., methanol, alcohol, *iso*-propanol). They are flammable and some of them are toxic (i.e., methanol). In addition, extended exposure to their vapors can also lead to health problems.

| Name | Formula | mp (°C) | bp (°C) | Vapor Pressure at 20 °C (mm Hg) |
|-------------|--------------------------------------|---------|---------|---------------------------------|
| Methanol | CH ₃ OH | -98 | 65 | 92.2 |
| Ethanol | CH ₃ CH ₂ OH | -114 | 78 | 44 |
| Isopropanol | (CH ₃) ₂ CHOH | -90 | 82 | 33 |

d. Ethers

Like alcohols, ethers (i.e., diethyl ether, tetrahydrofuran) are frequently used solvents in organic synthesis (i.e., Grignard reaction, Diels-Alder reaction). Their volatility makes them a fire hazard. In addition, they tend to form explosive peroxide upon extended exposure to air and light. The ether peroxides have higher boiling points than the ethers themselves.

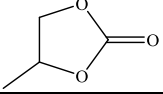
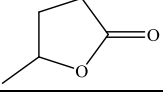
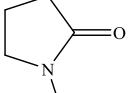
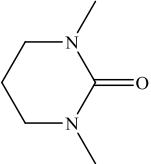
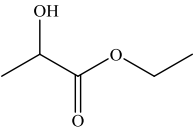
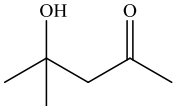
| Name | Formula | mp (°C) | bp (°C) | Vapor Pressure at 20 °C (mm Hg) |
|---------------------|--|---------|---------|---------------------------------|
| Diethyl ether | $(\text{CH}_3\text{CH}_2)_2\text{O}$ | -116 | 36 | 440 |
| Tetrahydrofuran | $\text{C}_4\text{H}_8\text{O}$ | -108 | 66 | 145 |
| Diisopropyl ether | $((\text{CH}_3)_2\text{CH})_2\text{O}$ | -60 | 69 | 119 |
| 1,2-Dimethoxyethane | $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_3$ | -58 | 84 | 48 |
| 1,4-Dioxane | $\text{C}_4\text{H}_8\text{O}_2$ | +12 | 101 | 27 |

e. Dipolar Solvents

Acetone, acetonitrile, *N,N*-dimethylformamide and dimethylsulfoxide belong into this group. Ketones are generally low in toxicity but they are volatile and pose a fire hazard. Acetonitrile is toxic in higher concentrations, while DMF can impair the liver and kidney function. Dimethylsulfoxide enhances skin absorption of solutes and can cause dermatitis and liver dysfunction on chronic exposure. Nitrobenzene is very toxic and is like DMSO readily absorbed through the skin. Hexamethylphosphoramide (HMPA) is a very toxic and a known carcinogen.

| Name | Formula | mp (°C) | bp (°C) | Vapor Pressure at 20 °C (mm Hg) |
|--------------|--|---------|---------|---------------------------------|
| Acetone | CH_3COCH_3 | -95 | 56 | 180 |
| Acetonitrile | CH_3CN | -48 | 80 | 72 |
| DMF | $\text{HCON}(\text{CH}_3)_2$ | -61 | 153 | 3.5 |
| DMSO | CH_3SOCH_3 | +18 | 189 | 0.45 |
| Nitrobenzene | $\text{C}_6\text{H}_5\text{NO}_2$ | +6 | 211 | 0.15 |
| HMPA | $((\text{CH}_3)_2\text{N})_3\text{PO}$ | +7 | 232 | 0.03 |

The combination of toxicity and volatility makes many of these solvents hazardous. Thus, in order to make a solvent safer, their intrinsic toxicity and their volatility has to be low. If possible, the amount of the solvent should be reduced and the recycling of the solvent should be pursued. While the best approach is to use no solvent in the reaction, this is unfortunately not possible in most reactions according to current knowledge. Ethanol and isopropanol are generally good choices because they are relatively nontoxic. Benzene is often replaced by toluene or xylene because they are less volatile and appear to be a little bit less hazardous. Chlorinated solvents are difficult to replace because of their unique ability to dissolve many compounds. In some cases, a solvent mixture of an ester and a hydrocarbon can be used (i.e., an equal volume mixture of ethyl acetate and hexane is used in the epoxidation to replace dichloromethane). Ethers sometimes can be replaced by esters (i.e., ethyl acetate, other acetates, phthalates), which are less volatile. The table below contains some of the suggested “green solvents”. In addition to these solvents, water, supercritical solvents (i.e., carbon dioxide) or ionic liquids (i.e., *N*-dodecylpyridinium chloride or 1-ethyl-3-methylimidazolium acetate) can be used in some reaction. Lately, solvents like 2-methyltetrahydrofuran (obtained by acid-catalyzed digestion of sugars followed by hydrogenation) and cyclopentylmethyl ether have gained a lot of interest as well.

| Name | Structure | mp (°C) | bp (°C) | Flash Point (°C) | Vapor Pressure at 20 °C (mmHg) |
|---|---|---------|-------------------|------------------|--------------------------------|
| Propylene carbonate |  | -55 | 242 | 135 | 0.03 |
| γ -Valerolactone |  | -31 | 207 | 81 | |
| N-methyl-2-pyrrolidinone (NMP) |  | -24 | 202 | 91 | 0.29 |
| 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) |  | -20 | 146 ⁴⁶ | 120 | low |
| Ethyl lactate |  | -25 | 154 | 46 | 1.7 |
| Diacetone alcohol |  | -44 | 172 | 58 | 0.95 |

2. Reagents

Alternative reagents have to be milder than the old reagents but reactive enough to perform the chemical transformation with comparable or superior efficiency. The formation of byproducts should be minimized reducing the need for separation and purification steps. The need for protective groups has to be reduced as well to minimize waste and increase atom economy, which is defined as the ratio of the mass of the product over the mass of all reactants. If all atoms from the reactants are incorporated in the product, the atom economy is 100 % (i.e., addition of bromine to double bonds, hydrogenation reactions). However, most common reactions (i.e., Fischer esterification, elimination, oxidation, Wittig reactions) are far from close this ideal case. The atom economy will decrease significantly if protective groups or chiral auxiliaries are used in the reaction. The alternative reagent should display a low volatility, a low flammability and low toxicity. The environmental impact of the alternative reagent should be low. In some cases, electrosynthesis, photochemistry, biological reagents, biocatalysis (enzymes or coenzymes) or catalysis in general can serve as alternative methods as well.

Generally, parameters like recovery, reuse (recycling) and regeneration have to be considered when designing a new reaction (“Three R’s of green chemistry”). Recovery refers to the isolation of solvents and spent reagents after the reaction was completed. A more effective the recovery simplifies the recycling and the regeneration process (i.e., catalyst). Ultimately, the atom economy of the reaction should be as high as possible to reduce the need for recovery, recycling and regeneration. The perfect chemical reaction is completely selective, highly efficient, safe, and does not require solvent or energy input.

3. Starting materials

Traditionally, many starting materials are derived from coal or petroleum. Unfortunately, these are nonrenewable resources and their extraction brings its own set of problems (i.e., environmental, health problems, dependability from OPEC). As a result, the trend has been going towards a biomass-based feedstock. For instance, ethanol and biodiesel are obtained from corn and soybeans. Glycerol is a byproduct in the biodiesel production, which is converted to propylene glycol by catalytic hydrogenation. Many compounds in the “chiral pool” can be isolated from the biomass as well (i.e., amino acids, hydroxy acids (tartaric acid), carbohydrates, terpenes (α -pinene), alkaloids). The hydrolysis of six-carbon sugars leads to the formation of hydroxymethylfurfural, which can be further hydrolyzed to form levulinic acid.

4. Energy sources

While the ideal reaction does require any energy input, this is not the case with most reactions in the lab. Heat is frequently needed to increase the rate of the reaction or the solubility of the reagents in the reaction medium. The cheapest source of energy is the sun but it is often challenging to harvest this energy efficiently. However, the sunlight is sometimes used in photochemical reactions (i.e., benzopinacol, formation of $\text{Fe}_2(\text{CO})_9$ from $\text{Fe}(\text{CO})_5$). Other than using the conventional heating methods (i.e., hotplate with Al-block, heating mantles, water bath, oil baths), the reaction mixture can also be heated using a microwave. Microwave reactions are often solvent-free or employ a high-boiling solvent (i.e., DMSO, propylene glycol, etc.). In rare cases, grinding the reaction mixture produces enough heat to promote the reaction (see below).

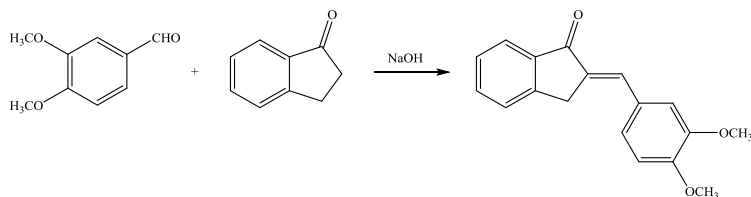
5. Examples

a. Elimination reaction

The dehydration of cyclohexanol is traditionally carried out with concentrated sulfuric acid or acid mixtures containing concentrated sulfuric acid. Unfortunately, the reaction medium is very corrosive that causes a lot of charring of the organic material. The use of concentrated phosphoric acid, which is a milder reagent, reduces the decomposition and potentially increases the yield. Other alternatives include clay-catalyzed or acidic resin based dehydrations reactions. These solid-state catalysts can often be recycled several times.

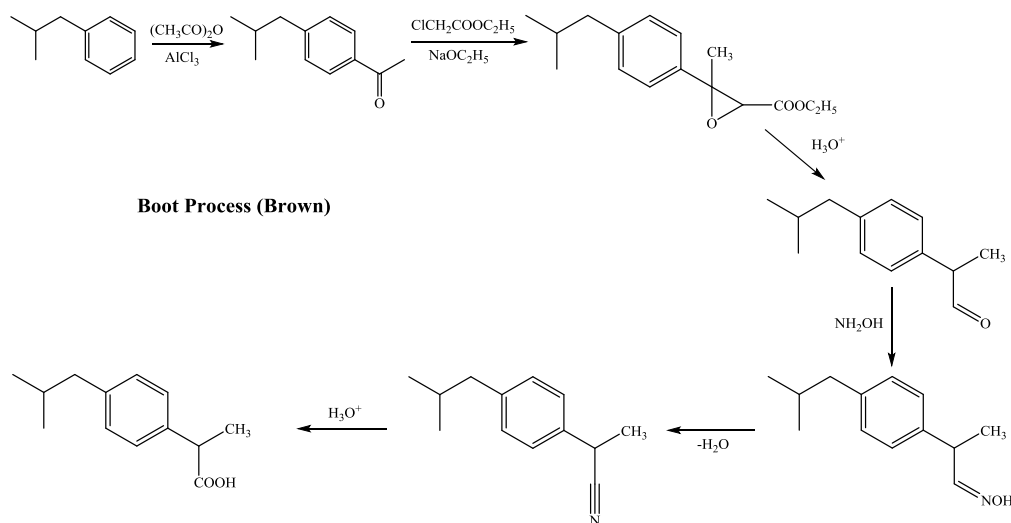
b. Aldol condensation

Traditionally, aldol or Claisen-Schmidt condensations are carried out in ethanol using elevated temperatures (i.e., tetraphenylcyclopentadienone). However, more recently it was found that these condensations could also be carried out solvent-free. The aldehyde and ketone are ground together in the presence of the catalyst. Many α,β -unsaturated ketones (=chalcones) can be obtained this way.

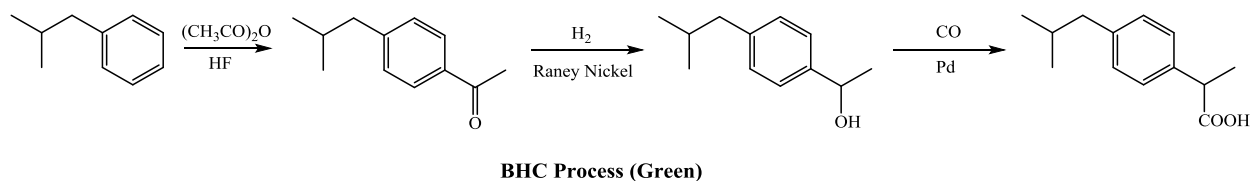


c. *Synthesis of Ibuprofen (industrial, 1997 Presidential Green Chemistry Challenge Winners)*

The Boots Company of England (now BASF) developed the original synthesis of ibuprofen in the 1960's. It involved a six-step process that generated millions of pounds of unwanted waste. This process became known as the Brown process because many of the reactants in the process are not incorporated into the product resulting in poor atom utilization (~40 %).

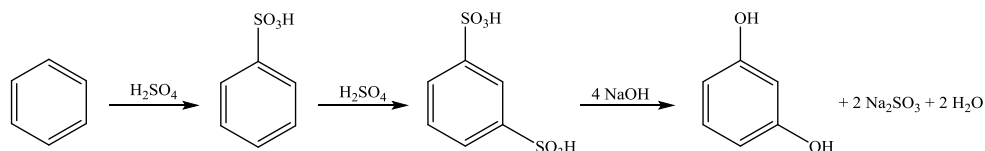


In 1991, BHC Company (Boots-Hoechst-Celanese, now part of BASF) developed a greener synthesis, which only required three steps. This process incorporated most of the reactants (77 % without recycling, 99 % with recycling) into the final product, reducing or eliminating most of the waste byproducts. Hydrofluoric acid, Raney nickel and palladium metal can be recovered and can be reused.

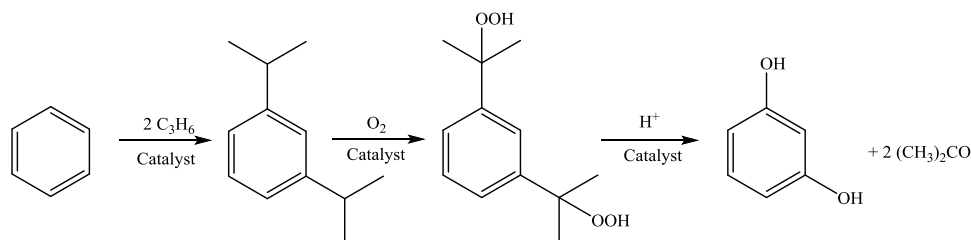


d. *Resorcinol (industrial)*

Resorcinol is used in polymer synthesis and can be included as an anti-dandruff agent in shampoo or in sunscreen cosmetics. The traditional synthesis of resorcinol that uses sulfonation reactions leads to a large amount of sodium sulfite, a compound that does not have a commercial outlet, which means it is considered waste.



The greener alternative that is similar to the phenol synthesis uses fewer reagents, milder conditions and produces a useful byproduct, acetone.



6. Green chemistry in undergraduate education

Many of the ideas and procedures have already been incorporated in Chem 30BL and Chem 30CL (i.e., reuse of products in multi-step synthesis, use of less hazardous reagents, use of rotary evaporator to remove solvents, lack of use of chlorinated solvents). However, some processes are not feasible for undergraduate education because many reactions require too much time or the reagents and techniques are too expensive. In some case, the techniques and equipment needed is not appropriate for undergraduates to handle.

7. Outlook

Ultimately, green chemistry is chiefly about sustainability. Scientists need to find ways of reducing the negative human impact on the environment by developing more environmentally friendly chemical engineering, by using a more responsible management of environmental resources and by considering environmental protection in any process more while maintaining the quality of life that we are accustomed to today. While in many cases there are already alternatives, they are economically not always feasible because they are too expensive (i.e., solar energy, biodiesel). Thus, there is still plenty of work to do for further generations of scientists. This holds particularly true because the environmental impact (I) will increase because of the world population (P) keeps growing together with the level of the individual consumption (A=affluence) and the impact per unit of resource use (T).

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