International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

Experimental Evaluation of Green Approach in Organic Synthesis

Veenu Gupta[1], Sourabh Gupta[2]

M.Sc., M.Ed., M.Phil, CSIR NET (Chemistry)

M. Sc, B.Ed., M. Phil (Chemistry)

Abstract: ***Unlimited use of chemical and disposal of chemical waste makes the environment polluted. To avoid or minimize the damage of environment; green techniques are used in various organic synthesis. Green techniques have important environmental and economic advantages over traditional synthetic processes. Herein, some green techniques such as multi-component reactions, green solvents, green catalysis, microwave and ultra-sonications reactions are discussed. The development of the concepts for "Green Chemistry" and the main principles of this field are reviewed. Examples of the application of these principles in different areas of chemistry are included. The frequently used alternative solvents (green solvents – water, PEG, per fluorinated solvents, supercritical liquids) in preparative organic chemistry are described. The present and the future developments of green chemistry in education and organic chemical technology are considered. Green chemistry is one of the most important research topics and has attracted most of the researchers. The use of green chemistry in chemical synthesis can reduce the damage to the environment occurred by the use of hazardous chemicals. With the increasing demands in relation to environmental protection, the use of green chemistry approach in organic synthesis is desirable. The design of promising Lewis acid catalysts has attracted considerable interest inorganic synthesis because of their unique Catalytic performances in organics reactions. Cardiovascular diseases have been the principal cause of death in many developing countries and disability in industrialized nations and are among the syndromes most commonly encountered in clinical practice. The major diagnosis of heart failure carries a risk of mortality comparable to that of the major malignancies. Heart failure occurs when cardiac output is insufficient to meet the demands of tissue perfusion and may primarily be due to systolic or diastolic dysfunction. It is frequently, but not always, caused by a defect in myocardial contraction. Myocardial contractility is largely dependent upon the activity of the cardiac sympathetic nerves, but it can also be increased by circulating catecholamine, tachycardia and isotropic drugs. These drugs induce changes in myoplasmic calcium and this may be responsible for the cardio active properties. Cardiac glycosides and catecholamine have been used as the main therapeutic drugs in the treatment of congestive cardiac failure.***

Keywords: Green Chemistry, ***diastolic dysfunction,*** catecholamine, **Green Techniques, Nitractin, Monastrol,** phloroglucinol

1. Introduction

Green Chemistry is also called as sustainable chemistry which focuses on enhance production efficiency and minimize the use and generation of hazardous substances. In organic synthesis to avoid disadvantage of gray chemistry the best alternative is green chemistry. Dr. Paul Anastas and Dr. John Warner outlined Principles of Green chemistry which are as follow:

1) **Prevention:** It is better to prevent formation of waste rather than disposal of it after generation.
2) **Atom Economy:** Design the processes such that avoid or minimize the formation of by-products and increase the production of required product.
3) **Less Hazardous chemical synthesis:** Synthetic pathway should be designed by using less or no toxic chemical for protection of human health and environment.
4) **Designing safer chemicals:** Preference should be given to make chemicals which are not poisonous and not toxic.
5) **Safer Solvent and Auxiliaries:** Safer and greener solvent such as water, Ionic liquid, carbonic ester etc. used for chemical synthesis or best way avoid the use of solvent wherever possible that is go for solvent free synthesis.
6) **Design for energy efficiency:** Try to carry out synthesis at room temperature instead of harsh heating and cooling conditions wherever possible.
7) **Use of Renewable feedstock**: Raw Material required to carry out organic synthesis should be renewable in nature.
8) **Reduce Derivatives**: Unnecessary protection and de-protection of groups, blocking of groups should be minimized or avoided wherever possible, because it increases number of steps in organic synthesis which increases the waste.
9) **Catalyst:** Use a catalyst to bring out chemical transformation instead of stoichiometric reagents.
10) **Design for Degradation**: Chemical products should be designed in such a way that they are easily degradable without any harm to environment and human health after its use.
11) **Real Time Analysis:** Monitor reaction in such a way that there is no wastage of energy and avoid formation of hazardous substances.
12) **Inherently Safer Chemistry for Accident Prevention**:Avoid the use of explosive chemicals, chemicals which are poisonous or emit harmful gaseous.

1.1 Green Techniques

1) Multi-Component Reactions (MCR's): MCR is a process in which there are three or more reactant are reacted in single vessel to form a complex heterocyclic compound. Advantages of MCR's are simplicity of operation, no need toisolate the intermediate and its purification. Minimization of cost, time, energy and waste formation. In scientific literature survey there are large numbers of research paper

showing the one pot synthesis of most of the heterocyclic compounds.

2) Green Solvent in Organic synthesis: Green Solvents are easily biodegradable, having high boiling point, low miscibility in water and less or no toxicity.

a) **Ionic Liquid:** Ionic liquids are generally salt of organic cation having high boiling point above 100oC , chemical and thermal stability, non-flammability and electro-chemical potential. In most of the cases ionic liquid acts as recylable organic solvent as well as catalyst.
b) **Water:** Water as solvent increase reactivity and selectivity in some reactions. Advantages of water as solvent are simplification of work up procedure after reaction completion, recycling of metal catalyst as most of the metal catalyst are insoluble in water.
c) **Carbonic esters:** Dimethyl carbonate is green solvent used as replacement for hazardous solvent dimethylsulphate and dimethyl chloride.

3) Microwave Assistance in Organic Synthesis:
Microwaves are in form of electromagnetic energy which lie in frequency 30GHz to 300 MHz Advantages of microwave heating in organic synthesis over conventional heating are reduce the reaction time, uniform heating, reduction of formation of by-products and avoid environmental heat loss. So it is important technique in synthesis.

4) Sonication in Organic Synthesis: It brings out the chemical reaction by using sound energy. The ultrasound frequencies for chemical reaction ranges between 20 – 100 KHz. It accelerates the chemical reaction by acoustic cavitation phenomenon. It increases the reactivity of catalyst and reagent. Most of the chemical reaction done by sonication is at room temperature instead of conventional heating and time required under sonication to complete the reaction is very low as compared to classical processes. It is non-classical form of energy and eco-environmental technology in green synthesis.

5) Green Catalysis in Organic Synthesis: Use of catalyst in organic synthesis is a important part of green synthesis. Catalyst accelerate the reaction and lower the energy required to complete the reaction. Use of catalyst avoids the use of reagent in stoichiometric quantity. Green catalyst has high catalytic efficiency, environment friendly nature, Such catalysts are Zeolites, Clays and biodegradable acids which may replaces the hazardous catalyst which are in use. Enzyme catalysis is example of homogenous green catalysis.

1.2 General Procedure

To a stirred mixture freshly distilled benzaldehyde (2.5mmol), ethylacetoacetate (2.5 mmol) and urea (3.75 mmol) were mixed with [bmpy] HSO_4 (11 mmol) ionic liquid was added, and the reaction mixture was stirred for an appropriate time at room temperature. On complete conversion, monitored by TLC, the product was dissolved in methanol, followed by mere filtration to remove the catalyst. After evaporating methanol under vacuum, crushed ice wasadded to it and the slid product was scratched from ice-cold water, filtered and dried. The pure product for H and CNMR, and IR analysis was obtained by recrystallization from hot 95% ethanol.

Spectral Data of Nitractin: IR (KBr): 3340, 3214, 2922, 1653, 1585, 1264, 1132 cm1 . 1H NMR (CDCl3/DMSO-d6) δ: 9.32 (bs, 1H, -NH), 7.83 (bs, 1H,-NH), 7.37(d, J= 3.5 Hz, 1H,-Ar), 6.44 (d, 1H, J= 3.5 Hz, -Ar), 5.44 (d,1H, J= 3.18 Hz, -CH), 3.68 (s, 3H, -COOCH3), 2.39 (s, 3H, -CH3). 13C NMR (CDCl3/ DMSO-d6) δ: 164.50, 158:56, 152.07, 150.29, 150.01, 112.33, 112.20, 108.49, 50.11, 48.11, 17.33.

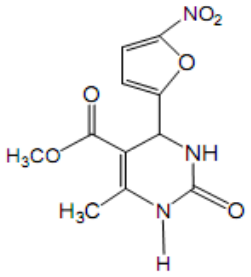


Fig. 2 Nitractin

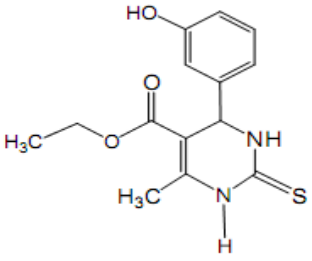


Figure 3: Monastrol

Spectral Data Of Monastrol: IR (KBr): 3465, 3301, 3182, 2902; 2600, 1678, 1650, 1622, 1570, 1216 cm-1 ; 1H NMR ($CDCl_3$/DMSO-d6) δ: 10.18, (bs, 1H, -NH), 9.51 (bs, 1H, -NH), 9.31 (bs, 1H, -OH), 6.68-6.98 (m, 3H, -Ar), 7.06-7.12 (m, 1H, -Ar), 5.13 (d, 1H, J=3.3Hz, -CH-) 4.03 (q, 2H, J= 6.8 Hz, -OH)-OCH2-), 2.31 (s, 3H, -CH3) 1.15 (t, 3H, J= 6.9Hz), -OCH_2-CH_3). 13C NMR ($CDCl_3$/DMSO)δ: 175.01, 165.09, 158.06, 143.11, 144.52, 129.13, 117.09, 114.52, 113.30, 100.88, 59.39, 54.05, 54.06, 17.14, 13.96.

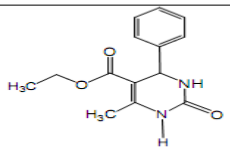
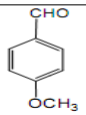
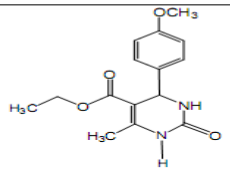
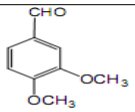
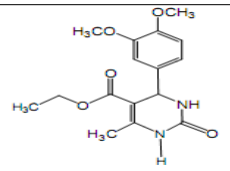
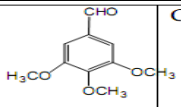
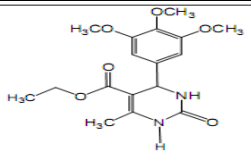
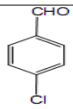
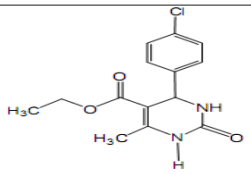
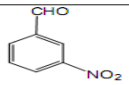
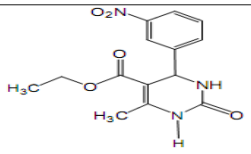
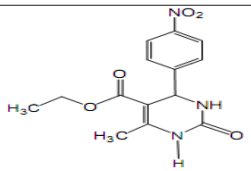
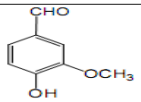
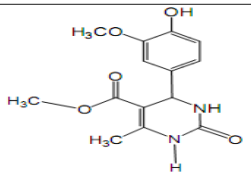
Table 1: One-pot Biginelli condensation of benzaldehyde, ethylacetoacetate and urea using [bmpy] HSO4 under different reaction conditions

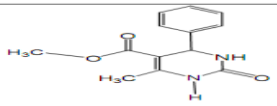
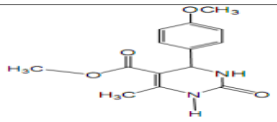
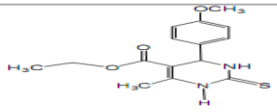
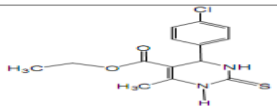
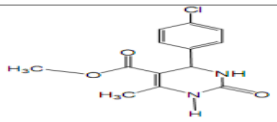
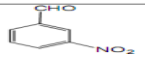
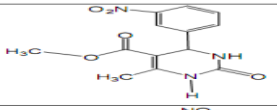
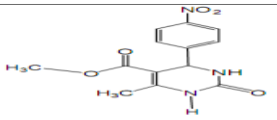
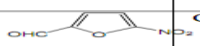
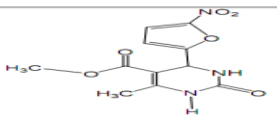
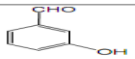
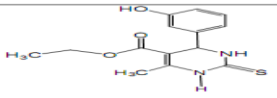
Entry	Mode of activation	Solvent	Time (min)	Conversion (%)
1	Δ (100 °C)	Methanol	60	91
2	Δ (100 °C)	No Solvent	30	93
3	)))))	Methanol	60	50
4	Stirring (r.t)	No Solvent	05	97

Table 2: Comparison of various catalysts for solventless, selective multicomponent one-pot Biginelli condensation

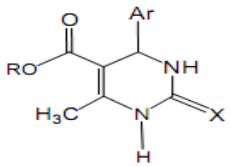
Entry	Catalyst	Yield (%)
1	Mont. K-10 clay	52
2	KSF	50
3	β- H Zeolite	55
4	Fe^{+3}-Mont. K-10 clay	70
5	[bmpy]HSO_4	97

Table 3: Synthesis of various dihydropyrimidiones catalyzed by [bmpy] HSO4 under stirring at room temperature in dry media

Entry	Reactant			Product	Stirring/ r.t		
	Aldehyde	R	X		Time (min)	Yield (%)	mp (°C)
1		C_2H_5			05	97	206-208
2		C_2H_5	O		06	95	202-204
3		C_2H_5	O		07	89	172-174
4		C_2H_5	O		07	86	210-212
5		C_2H_5	O		05	97	210-212
6		C_2H_5	O		05	91	224-226
7		C_2H_5	O		05	96	208-210
8		CH_3	O		05	93	230-232

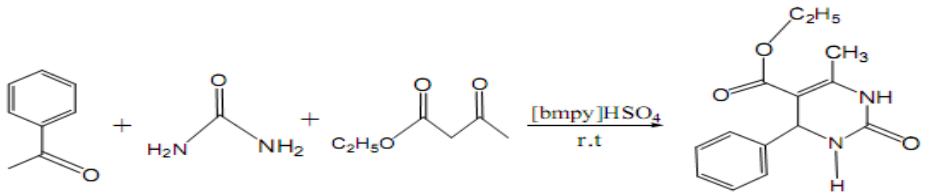
9		CH_3	O		05	95	210-212
10		CH_3	O		06	94	192-194
11		C_2H_5	S		05	93	150-152
12		C_2H_5	S		05	96	192-194
13		CH_3	O		05	97	204-206
14		CH_3	O		06	91	239-242
15		CH_3	O		06	95	228-230
16		CH_3	O		05	89	188-186
17		C_2H_5	S		05	91	180-182

In a similar fashion a variety of aromatic aldehydes underwent three-component condensation smoothly to give products with general formula as shown in fig.1 to afford a wide range of substituted dihydropyrimidinones and are given in Table 3. The catalyst was recycled three times after washing it with acetone.



R= CH_3, C_2H_5; X= O or S; Ar= Aromatic

Fig. 1 DHPM



Scheme 1

Synthesis of nitractin and monastrol

As early as the 1940s DHPMs (Fig.1) were known to possess antiviral activity. Eventually, the nitrofuryl-substituted analog nitractin (Fig.2) was developed, which displayed good activity against the viruses of the trachoma group56-59, in addition to showing modest antibacterial activity. Mayer et al. have recently identified the structurally rather simple DHPM monastrol (Fig.3) by screening a 16,320-member library of diverse small molecules as a novel cell-permeable molecule that blocks normal bipolar mitotic spindle assembly in mammalian cells and therefore causes cell cycle arrest 60,61. Monastrol is the only molecule currently known to inhibit mitotic KinesinEg 5 specifically and can therefore be considered as a lead for the development of new anticancer drugs. Using our developed methodology, we have synthesized the target molecules

nitractin and monastrol in high yield of 89% and 91% using [bmpy] HSO4 as ionic liquid catalyst using stirring at room temperature shown in Table 3 (entry number 16 and 17), respectively.

Plausible Mechanism: We propose a plausible mechanism as shown in Fig. 4. The overall reaction cycle has been divided into two halves. In the first half of the cycle. Bronsted acidity of the catalyst has been exploited for formation of an acylimine (IV) via intermediate (III) by the reaction between aldehyde and urea as the key rate-limiting step. In the second half on the cycle, it can be regarded as the addition of a π-nucleophile, ethyl acetoacetateenolate to the electrondeficient N-acyliminium ion intermediate (IV), which are stabilized by the Lewis acid site of [bmpy]HSO_4 as a catalyst. Interception of the iminium ion (IV) by ethylacetoacetate, possibly through its enoltautomer, produces an open chain ureide (VI), subsequently cyclizes to the desired 3, 4-dihydopyrimidinone (VII).

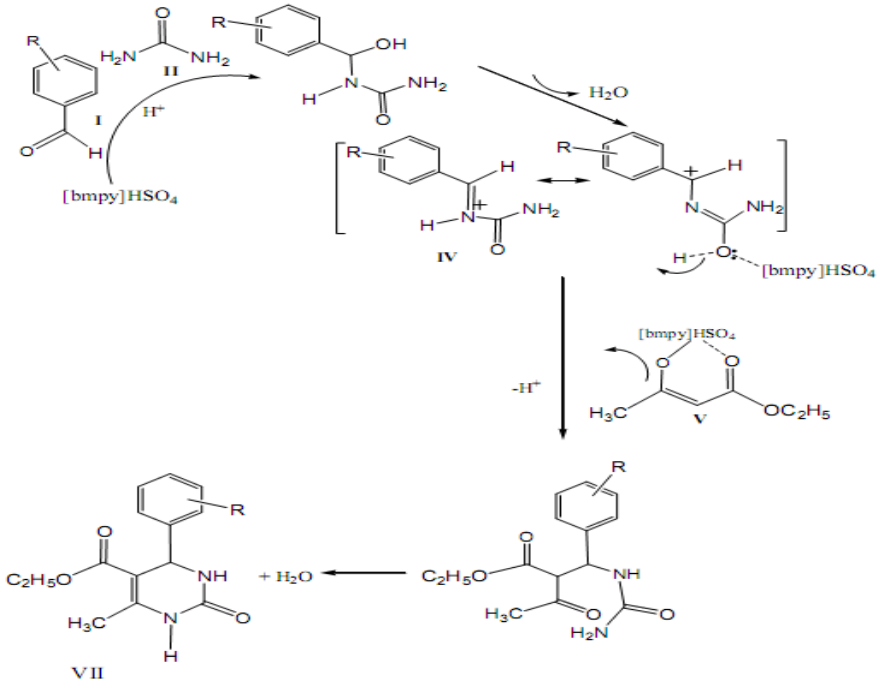


Figure 4: Plausible Mechanism

A comparative study with the literature reported methods and protocols for Biginelli reaction to synthesize various multifunctionalizeddihydropyrimidinones is compiled in Table 4 to show the efficacy and efficiency of the catalyst and is given in the supplementary information.

Table 4: Comparison of different catalysts reported in literature for multicomponent one-pot Biginelli condensation reaction

S.No.	Catalyst	Mode of activation	Solvent	Temperature /Power level	Time	Conversion (%)
1	Mont. KSF	Δ	$C_6H_5CH_3$ & H_2O	100 °C	10-48	70-88
2	NH_2SO_3H	)))))	C_2H_5OH	25-30 °C	40-60min	62-97
3	$Ag_3PW_{12}O_{40}$	Δ	H_2O	80 °C	3-4.5 h	95-100
4	Zn $(OTf)_2$	Δ	CH_3CN	Refluxing	4.5-6 h	71-92
5	$LaCl_3.7H_2O$	Δ	C_2H_5/H^+	Refluxing	5 h	56-97
6	IL: $BMImBF_4$ $BMImPF_4$	Δ	No Solvent	100 °C	0.5 h	56-97
7	$FeCl_3$ over Si-MCM-41	MW	No Solvent	---	3-5 min	90
8	Lanthanide triflates	Δ	H_2O CH_3CN H_2O-THF $C_6H_5CH_3$ THF CH_2Cl_2 No Solvent	100 °C	20-40min	24 83 28 95 56 22 95-99
9	$Mn(OAc)_3 2H_2O$	Δ	CH_3CN	Refluxing	2-4 h	75-96
10	Yb (III)-resin and polymer scavengers	Δ	No Solvent	120 °C	48 h	61-80

11	CAN	)))))	CH_3OH	r.t	3-9 h	84-92
12	HCl and piperidine	MW/Stirring	C_2H_5OH	MW(HCl)	5 min	50-60
13	$SnCl_2.2H_2O$	Δ	CH_3OH, CH_3CN	Refluxing	5-7 h	80
14	$[bmpy]HSO_4$	Stirring	No Solvent	r.t	5-7 min	86-97

Development of Organic Synthesis

The well - being of modern society is unimaginable without the myriad products of industrial organic synthesis. Our quality of life is strongly dependent on, inter alia, the products of the pharmaceutical industry, such as antibiotics for combating disease and analgesics or anti - inflammatory drugs for relieving pain. The origins of this industry date back to 1935, when Domagk discovered the antibacterial properties of the red dye, prontosil, the prototype of a range of sulfa drugs that quickly found their way into medical practice. The history of organic synthesis is generally traced back to W ö hler ' s synthesis of the natural product urea from ammonium isocyanate in 1828. This laid to rest the visvitalis (vital force) theory, which maintained that a substance produced by a living organism could not be produced synthetically. The discovery had monumental significance, because it showed that, in principle, all organic compounds are amenable to synthesis in the laboratory. The next landmark in the development of organic synthesis was the preparation of the first synthetic dye, mauveine (aniline purple) by Perkin in 1856, generally regarded as the first industrial organic synthesis. It is also a remarkable example of serendipity. Perkin was trying to synthesize the anti - malarial drug quinine by oxidation of N - allyltoluidine with potassium dichromate. This noble but na ï ve attempt, bearing in mind that only the molecular formula of quinine (C 20 H 24 N 2 O 2) was known at the time, was doomed to fail. In subsequent experiments with aniline, fortuitously contaminated with toluidines, Perkin obtained a low yield of a purple - colored product. Apparently, the young Perkin was not only a good chemist but also a good businessman, and he quickly recognized the commercial potential of his finding. The rapid development of the product, and the process to make it, culminated in the commercialization of mauveine, which replaced the natural dye, Tyrian purple. At the time of Perkin ' s discovery Tyrian purple, which was extracted from a species of Mediterranean snail, cost more per kg than gold.

This serendipitous discovery marked the advent of the synthetic dyestuffs industry based on coal tar, a waste product from steel manufacture. The development of mauveine was followed by the industrial synthesis of the natural dyes alizarin and indigo by Graebe and Liebermann in 1868 and Adolf Baeyer in 1870, respectively. The commercialization of these dyes marked the demise of their agricultural production and the birth of a science - based, predominantly German, chemical industry. By the turn of the 20th century the germ theory of disease had been developed by Pasteur and Koch, and for chemists seeking new uses for coal tar derivatives which were unsuitable as dyes, the burgeoning field of pharmaceuticals was an obvious one for exploitation. A leading light in this field was Paul Ehrlich, who coined the term chemotherapy. He envisaged that certain chemicals could act as ' magic bullets ' by being extremely toxic to an infecting microbe but harmless to the host. This led him to test dyes as chemotherapeutic agents and to the discovery of an effective treatment for syphilis. Because Ehrlich had studied dye molecules as ' magic bullets ' it became routine to test all dyes as chemotherapeutic agents, and this practice led to the above - mentioned discovery of prontosil as an antibacterial agent. Thus, the modern pharmaceutical industry was born as a spin - off of the manufacture of synthetic dyestuffs from coal tar. The introduction of the sulfa drugs was followed by the development of the penicillin antibiotics. Fleming ' s chance observation of the anti - bacterial action of the penicillin mold in 1928 and the subsequent isolation and identification of its active constituent by Florey and Chain in 1940 marked the beginning of the antibiotics era that still continues today. At roughly the same time, the steroid hormones found their way into medical practice. Cortisone was introduced by the pharmaceutical industry in 1944 as a drug for the treatment of arthritis and rheumatic fever. This was followed by the development of steroid hormones as the active constituents of the contraceptive pill. The penicillins, the related cephalosporins, and the steroid hormones represented considerably more complicated synthetic targets than the earlier mentioned sulfa drugs. Indeed, as the target molecules shifted from readily available natural compounds and relatively simple synthetic molecules to complex semi - synthetic structures, a key factor in their successful introduction into medical practice became the availability of a cost - effective synthesis. For example, the discovery [1] of the regio - and enantiospecifi c microbial hydroxylation of progesterone to 11 α - hydroxyprogesterone (Figure 1.1) by Peterson and Murray at the Upjohn Company led to a commercially viable synthesis of cortisone that replaced a 31 - step chemical synthesis from a bile acid and paved the way for the subsequent commercial success of the steroid hormones. According to Peterson [2] , when he proposed the microbial hydroxylation, many outstanding organic chemists were of the opinion that it couldn ' t be done. Peterson ' s response was that the microbes didn ' t know that. Although this chemistry was invented four decades before the term Green Chemistry was officially coined, it remains one of the outstanding applications of Green Chemistry within the pharmaceutical industry.

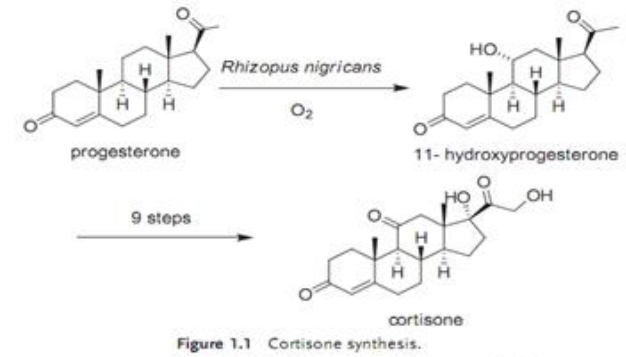


Figure 1.1 Cortisone synthesis.

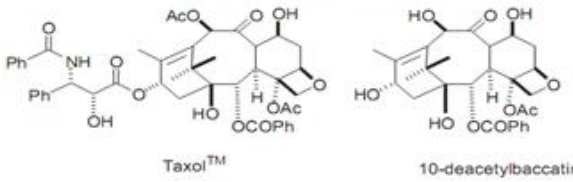


Figure 1.2: Structure of the anticancer drug Taxol ® and 10 - deacetylbaccatin III

This monumental discovery marked the beginning of the development, over the following decades, of drugs of ever - increasing molecular complexity. In order to meet this challenge, synthetic organic chemists aspired to increasing levels of sophistication. A case in point is the anticancer drug, Taxol ® [3] , derived from the bark of the Pacifi c yew tree, Taxusbrevifolia, and introduced into medical practice in the 1990s (see Figure 1.2). The breakthrough was made possible by Holton ' s invention [4] of a commercially viable and sustainable semi - synthesis from 10 - deacetylbaccatin III, a constituent of the needles of the English yew, TaxusbaccataIn short, the success of the modern pharmaceutical industry is firmly built on the remarkable achievements of organic synthesis over the last century. However, the down side is that many of these time - honored and trusted synthetic methodologies were developed in an era when the toxic properties of many reagents andsolvents were not known and the issues of waste minimization and sustainability were largely unheard of.

The Environmenal Factor

In the last two decades it has become increasingly clear that the chemical and allied industries, such as pharmaceuticals, are faced with serious environmental problems. Many of the classical synthetic methodologies have broad scope but generate copious amounts of waste, and the chemical industry has been subjected to increasing pressure to minimize or, preferably, eliminate this waste. An illustrative example is provided by the manufacture of phloroglucinol, a reprographic chemical and pharmaceutical intermediate. Up until the mid - 1980s it was produced mainly from 2,4,6 - trinitrotoluene (TNT) by the process shown in Figure 1.3 , a perfect example of vintage nineteenth - century organic chemistry. For every kg of phloroglucinol produced ca. 40 kg of solid waste, containing $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$, and $KHSO_4$, were generated. This process was eventually discontinued as the costs associated with the disposal of this chromium - containing waste approached or exceeded the selling price of the product. That such an enormous amount of waste is formed is easily understood by examining the stoichiometric equation (see Figure 1.3) of the overall process, something very rarely done by organic chemists. This predicts the formation of ca. 20 kg of waste per kg of phloroglucinol, assuming 100% chemical yield and exactly stoichiometric quantities of the various reagents. In practice, an excess of the oxidant and reductant and a large excess of sulfuric acid, which subsequently has to be neutralized with baseis used, and the isolated yield of phloroglucinol is less than 100%. This explains the observed 40 kg of waste per kg of desired product.

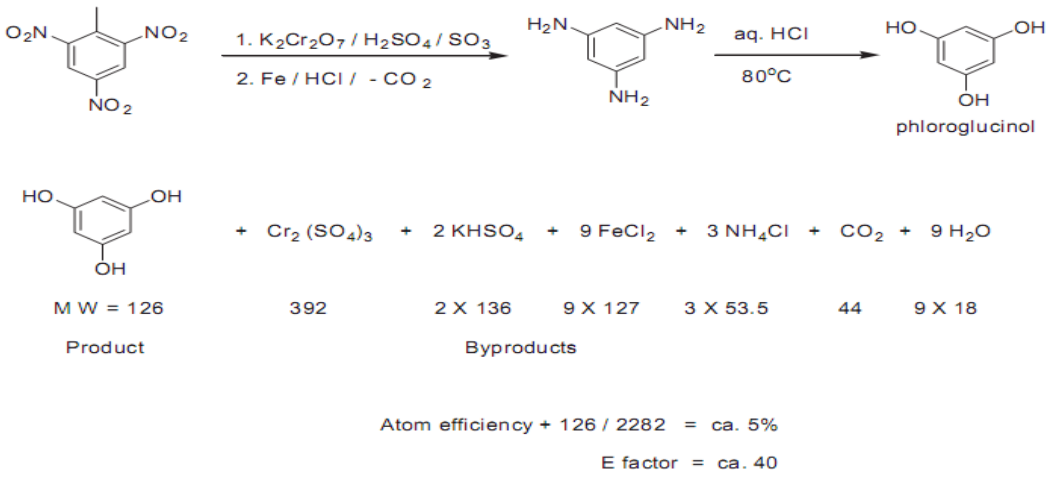


Figure 1.3: Manufacture of phloroglucinol from TNT

Table 1.1: E factors in the chemical industry

Industry segment	Volume ($t y^{-1}$)[a]	E factor (kg waste/ kg product)
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals industry	10^2–10^4	5– > 50
Pharmaceutical industry	10–10^3	25– > 100

a) Annual production of the product world - wide or at a single site

Indeed, an analysis of the amount of waste formed in processes for the manufacture of a range of fi ne chemicals and pharmaceuticals intermediates has revealed that the generation of tens of kilograms of waste per kilogram of desired product was not exceptional in the fi ne chemical industry. This led to the introduction of the E

(environmental) factor (kilograms of waste per kilogram of product) as a measure of the environmental footprint of manufacturing processes [5] in various segments of the chemical industry (Table 1.1). The E factor represents the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, process aids, and, in principle, even fuel. Water was generally excluded from the E factor as the inclusion of all process water could lead to exceptionally high E factors in many cases and make meaningful comparisons of processes difficult. A higher E factor means more waste and, consequently, a larger environmental footprint. The ideal E factor is zero. Put quite simply, it is the total mass of raw materials minus the total mass of product, all divided by the total mass of product. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, the calculation being for a particular product or a production site or even a whole company. It is clear from Table 1.1 that the E factor increases substantially on going from bulk chemicals to fi ne chemicals and then to pharmaceuticals. This is partly a reflection of the increasing complexity of the products, necessitating multistep syntheses, but is also a result of the widespread use of stoichiometric reagents (see below). A reduction in the number of steps of a synthesis will in most cases lead to a reduction in the amounts of reagents and solvents used and hence a reduction in the amount of waste generated. This led Wender to introduce the concepts of step economy [6] and function oriented synthesis (FOS) [7] of pharmaceuticals. The central tenet of FOS is that the structure of an active lead compound, which may be a natural product, can be reduced to simpler structures designed for ease of synthesis while retaining or enhancing the biological activity. This approach can provide practical access to new (designed) structures with novel activities while at the same time allowing for a relatively straightforward synthesis.

As noted above, a knowledge of the stoichiometric equation allows one to predict the theoretical minimum amount of waste that can be expected. This led to the concept of atom economy [8] or atom utilization [9] to quickly assess the environmental acceptability of alternatives to a particular product before any experiment is performed. It is a theoretical number, that is, it assumes a chemical yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation. In short, the key to minimizing waste is precision or selectivity in organic synthesis which is a measure of how efficiently a synthesis is performed. The standard definition of selectivity is the yield of product divided by the amount of substrate converted, expressed as a percentage. Organic chemists distinguish between different categories of selectivity:

- **Chemoselectivity** (competition between different functional groups)
- **Regioselectivity** (selective formation of one regioisomer, for example orthovspara substitution in aromatic rings)
- **Diastereoselectivity** (the selective formation of one diastereomer)
- **Enantioselectivity** (the selective formation of one of a pair of enantiomers)

However, one category of selectivity was, traditionally, largely ignored by organichemists: the atom selectivity or atom utilization or atom economy . The virtually complete disregard of this important parameter is the root cause of the waste problem in chemicals manufacture. As Lord Kelvin remarked, ‘ To measure is to know ’ . Quantification of the waste generated in chemicals manufacturing, by way of E factors, served to bring the message home and focus the attention of fi ne chemical and pharmaceutical companies on the need for a paradigm shift from a concept of process efficiency, which was exclusively based on chemical yield, to one that is motivated by elimination of waste and maximization of raw materials utilization. Indeed, the E factor has been widely adopted by the chemical industry and the pharmaceutical industry in particular. To quote from a recent article : ‘ Another aspect of process development mentioned by all pharmaceutical process chemists who spoke with Chemical and Engineering News is the need for determining an E factor. ’ The Green Chemistry Institute (GCI) Pharmaceutical Roundtable has used the Process Mass Intensity (PMI), defined as the total mass used in a process divided by the mass of product (i.e. PMI = E factor + 1) to benchmark the environmental acceptability of processes used by its members (see the GCI website). The latter include several leading pharmaceutical companies (Eli Lilly, GlaxoSmithKline, Pfizer, Merck, AstraZeneca, Schering - Plow, and Johnson & Johnson). The aim was to use this data to drive the greening of the pharmaceutical industry. We believe, however, that the E factor is to be preferred over the PMI since the ideal E factor of 0 is a better reflection of the goal of zero waste. The E factor, and derived metrics, takes only the mass of waste generated into account. However, the environmental impact of waste is determined not only by its amount but also by its nature. Hence, we introduced the term ‘environmental quotient’, EQ, obtained by multiplying the E factor by an arbitrarilyassigned unfriendliness quotient, Q. For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100 – 1000 to a heavy metal salt, such as chromium, depending on factors like its toxicity or ease of recycling. Although the magnitude of Q is debatable and difficult to quantify, ‘quantitative assessment’ of the environmental impact of waste is, in principle, possible. Q is dependent on, inter alia, the ease of disposal or recycling of waste and, generally speaking, organic waste is easier to dispose of or recycle than inorganic waste.

The Role of Catalysis

The main source of waste is inorganic salts such as sodium chloride, sodium sulfate, and ammonium sulfate that are formed in the reaction or in downstream processing. One of the reasons that the E factor increases dramatically on going from bulk to fi ne chemicals and pharmaceuticals is that the latter are more complicated molecules that involve multi - step syntheses. However, the larger E factors in the fi ne chemical and pharmaceutical industries are also a consequence of the widespread use of classical stoichiometric reagents rather than catalysts. Examples which readily come to mind are metal (Na, Mg, Zn, Fe) and metal hydride ($LiAlH_4$,$NaBH_4$) reducing agents and oxidants such as permanganate, manganese dioxide, and chromium(VI) reagents. For example, the phloroglucinol process (see above) combines an oxidation by stoichiometric chromium (VI) with a reduction with Fe/HCl. Similarly, a

plethora of organic reactions, such as sulfonations, nitrations, halogenations, diazotizations, and Friedel - Crafts acylations, employ stoichiometric amounts of mineral acids (H_2SO_4 , HF, H_3PO_4) or Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3) and are major sources of inorganic waste. Once the major cause of the waste has been recognized, the solution to the waste problem is evident: the general replacement of classical syntheses that use stoichiometric amounts of inorganic (or organic) reagents by cleaner, catalytic alternatives. If the solution is so simple, why are catalytic processes not as widely used in fi ne and specialty chemicals manufacture as they are in bulk chemicals? One reason is that the volumes involved are much smaller, and thus the need to minimize waste is less acute than in bulk chemicals manufacture. Secondly, the economics of bulk chemicals manufacture dictate the use of the least expensive reagent, which was generally the most atom economical, for example O_2 for oxidation H_2 for reduction, and CO for C – C bond formation. A third reason is the pressure of time. In pharmaceutical manufacture ' time to market ' is crucial, and an advantage of many time - honored classical technologies is that they are well tried and broadly applicable and, hence, can be implemented rather quickly. In contrast, the development of a cleaner, catalytic alternative could be more time consuming. Consequently, environmentally (and economically) inferior technologies are often used to meet stringent market deadlines, and subsequent process changes can be prohibitive owing to problems associated with FDA approval.

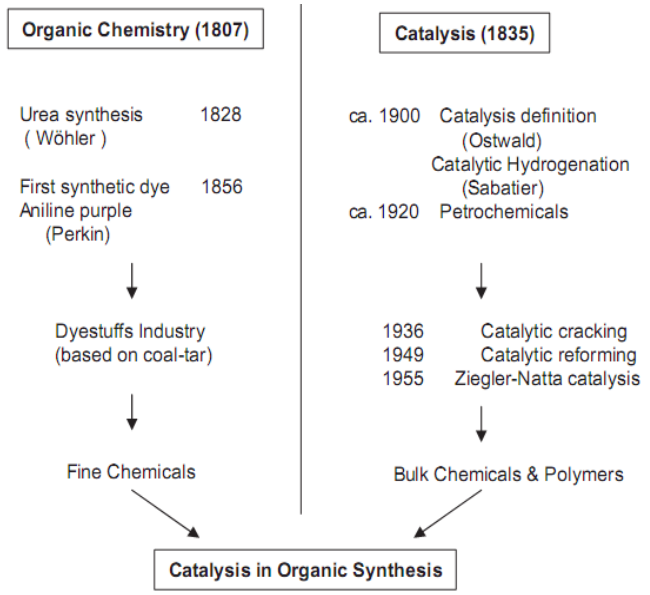


Figure 1.4: The development of organic synthesis and catalysis

Another reason, however, is the more or less separate paths of development of organic synthesis and catalysis (see Figure 1.4) since the time of Berzelius, who coined the terms ' organic chemistry ' and ' catalysis ' , in 1807 and 1835, respectively [14] . Subsequently, catalysis developed largely as a sub - discipline of physical chemistry. With the advent of petrochemicals in the 1930s, catalysis was widely applied in oil refining and bulk chemicals manufacture. However, the scientists responsible for these developments were, generally speaking, not organic chemists but were chemical engineers and surface scientists. Industrial organic synthesis, in contrast, followed a largely ' stoichiometric ' line of evolution that can be traced back to Perkin ' s synthesis of mauveine, the subsequent development of the dyestuffs industry based on coal tar, and the fi ne chemicals and pharmaceuticals industries, which can be regarded as spin - offs from the dyestuffs industry. Consequently, fi ne chemicals and pharmaceuticals manufacture, which is largely the domain of synthetic organic chemists, is rampant with classical 'stoichiometric' processes. Until fairly recently, catalytic methodologies were only sporadically applied, with the exception of catalytic hydrogenation which, incidentally, was invented by an organic chemist, Sabatier, in 1905.

The desperate need for more catalytic methodologies in industrial organic synthesis is nowhere more apparent than in oxidation chemistry. For example, as anyorganic chemistry textbook will tell you, the reagent of choice for the oxidation of secondary alcohols to the corresponding ketones, a pivotal reaction in organic synthesis, is the Jones reagent. The latter consists of chromium trioxide and sulfuric acid and is reminiscent of the phloroglucinol process referred to earlier. The introduction of the storage - stable pyridiniumchlorochromate (PCC) and pyridinium dichromate (PDC) in the 1970s, represented a practical improvement, but the stoichiometric amounts of carcinogenic chromium (VI) remain a serious problem. Other stoichiometric oxidants that are popular with synthetic organic chemists are the Swern reagent [15] and Dess - Martin Periodinane [16] (DMP). The former produces the evil smelling dimethylsulfi de as the by - product, the latter is shock sensitive, and oxidations with both reagents are abominably atom inefficient (see Figure 1.5).

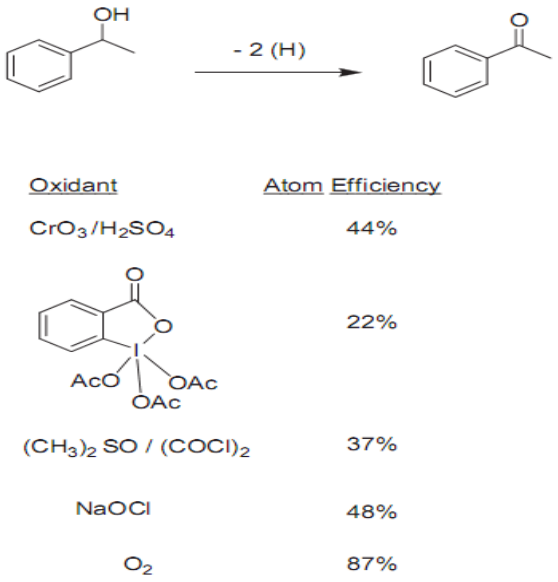


Figure 1.5: Atom efficiencies of alcohol oxidations

Obviously there is a definite need in the fi ne chemical and pharmaceutical industry for catalytic systems that are green and scalable and have broad utility [10]. More recently, oxidations with the inexpensive household bleach (NaOCl) catalyzed by stable nitroxyl radicals, such as TEMPO [17] and PIPO [18] , have emerged as more environmentally friendly methods. It is worth noting at this juncture that 'greenness' is a relative description and there are many

shades of green. Although the use of NaOCl as the terminal oxidant affords NaCl as the by - product and may lead to the formation of chlorinated impurities, it constitutes a dramatic improvement compared to the use of chromium (VI) and other reagents referred to above. Moreover, we note that, in the case of pharmaceutical intermediates, the volumes of NaCl produced as a by - product on an industrial scale are not likely to present a problem. Nonetheless, catalytic methodologies employing the green oxidants, molecular oxygen (air) and hydrogen peroxide, as the terminal oxidant would represent a further improvement in this respect. However, as Dunn and coworkers have pointed out, the use of molecular oxygen presents significant safety issues associated with the flammability of mixtures of oxygen with volatile organic solvents in the gas phase. Even when these concerns are reduced by using 10% oxygen diluted with nitrogen, these methods are on the edge of acceptability. An improved safety profile and more acceptable scalability are obtained by performing the oxidation in water as an inert solvent. For fine chemicals or large volume pharmaceuticals the environmental and cost benefits of using simple air or oxygen as the oxidant would justify the capital investment in the more specialized equipment required to use these oxidants on a large scale.

2. Conclusion

Green chemistry has grown from a small idea into a new approach to the scientifically based environmental protection. By using green chemistry principles we can change or modify the conventional methods which are not eco-friendly. Researchers and pharmaceutical companies need to be encouraged to consider the principles of green chemistry while designing and choosing reagents. Green Chemistry is not a new branch of science. It is a new philosophical approach that, through the introduction and expansion of its principles, could lead to a substantial development in chemistry, the chemical industry and environmental protection. - Future generations of chemists should be trained in the principles of Green Chemistry and should possess knowledge and habits that should be applied in practice. - At present, one can easily find in the literature quite interesting examples of the use of the rules of Green Chemistry. These principles could be applied not only to the synthesis, but to the processing and use of chemical substances. Numerous new analytical methodologies have been described and these are carried out according to the rules of Green Chemistry. These approaches are particularly important in conducting chemical processes and assessing their impact on the environment. - In the coming decades Green Chemistry will continue to be attractive and practical. It is expected that this approach will solve numerous ecological problems. The development of waste-free technologies as well as technologies that have a lesser impact on the environment at the research stage does not guarantee their adoption on an industrial scale. The implementation of such technologies in industry can be ensured by more flexible legislation, new programs for the acceleration of the technological transfer between academia and governments and, last but not least, tax advantages for companies for the industrial application of cleaner technologies. - All of us, by using the comforts of modern civilization, contribute to environmental pollution and are in debt to Mother Nature. The education in Green Chemistry of future generations of chemists will contribute to the solution of numerous ecological problems on the national, regional and global scale and will allow the specialists trained by us to be competitive within the global economy. - By starting education in Green Chemistry right now we should travel a long way along the path to fulfill our mission and to enjoy the results of our efforts for future generations of chemists and other specialists. Finally, let us cite Raveendran “The Nobel Prize for Green Chemistry will definitely boost the efforts for a sustainable chemistry” In our opinion this will inevitably happen in the very near future.

References

[1] Anastas, P.T.; Warner, J. Green Chemistry: Theory and Practice, Oxford University Press: Oxford, 1988.
[2] Wardencki, W.; Curylo, J.; Namiesnic, J. Green chemistry – current and future. Pol. J. Environ. Stud., 2005, 14(4), 389-395.
[3] Ahluwalia, V.K.; Kidwai, M. New Trends in Green Chemistry, Kluwer Academic Publishers: Dordrecht, 2004.
[4] Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y. F. ThreecomponentFriedel-Crafts Reaction of indoles, glyoxylate, and amine under solvent-free and catalyst-free conditions - synthesis of (3-indolyl)glycine derivatives. Synlett, 2006, 1, 96-101.
[5] Narashimulu, M.; Mahesh, K. C.; Reddy, T. S.; Rajesh, K.; Venkateswarlu, Y. Lanthanum(III) nitrate hexahydrate or p-toluenesulfonic acid catalyzed one-pot synthesis of 4(3H)-quinazolinones under solvent-free conditions. Tetrahedron Lett., 2006, 47, 4381-4383.
[6] Geng, L.-J.; Li, J.-T.; Wang, S.-X. Application of Grinding Method to solidstate organic synthesis. Chin. J. Org. Chem., 2005, 25(5), 608-613.
[7] Guzman-Lucero, D.; Guzman, J.; Likhatchev, D.; Martinez-Palou, R. Microwave-assisted synthesis of 4,4-diaminotriphenylmethanes. Tetrahedron Lett., 2005, 46(7), 1119-1122.
[8] Trost, B. M. The atom economy--a search for synthetic efficiency.Science, 1991, 254, 1471- 1477.
[9] Trost, B. M. On inventing reactions for atom economy. Acc. Chem. Res., 2002, 35, 695-705.
[10] Deng, Y.; Ma, Z.; Wang, K.; Chen, J. Clean synthesis of adipic acid by direct oxidation of cyclohexene with H2O2 over peroxytungstate–organic complex catalysts. Green Chem., 1999, 1, 275-276.
[11] http://en.wikipedia.org/wiki/Thalidomide