Green chemistry trends toward sustainability*

M. Kidwai

Green Chemistry Research Laboratories, Department of Chemistry, University of Delhi, Delhi-110007, India

Abstract: Green chemistry is not an emerging trend, but is already a reality owing to its applications. A large number of case studies are presented here in addition to literature work. The case studies cover new approaches and new experiments, which will articulate the requirement for industrial application of sustainable chemistry.

Keywords: green chemistry; atom economy; biocatalysts; environmentally benign chemistry; biosynthesis.

INTRODUCTION

The term "green chemistry" is defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances" [1]. Green chemistry can diminish the need for other approaches to environmental protection. Ideally, the application of green chemistry principles and practice renders regulation, control, clean-up, and remediation unnecessary, and the resultant environmental benefit can be expressed in turns of economic impact [2].
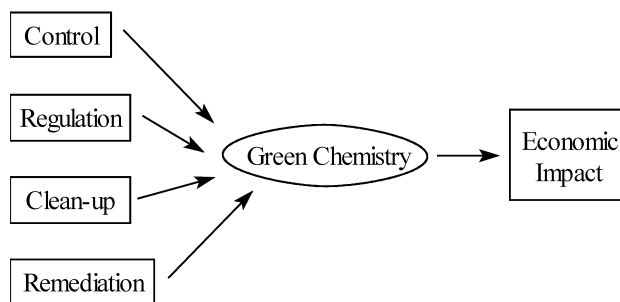
The goal of atom economy [3,4] is to create synthesis in which most of the atoms of the reactants become incorporated into the desired final product, thus leading to fewer waste by-products [5].

The concept of atom economy has also been employed by Shell Corporation to make methyl methacrylate, which employs palladium catalyst and enjoys 100 % atom economy [6].

There are also health concerns associated with the use of biocatalysts [7]. Draths and Frost have developed a biosynthetic method to produce adipic acid, catechol, and 3-deoxy-D-arabino-heptulo-

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sonates (DHS) from glucose using genetically altered *Escherichia coli* [8]. By using glucose in place of benzene, this biosynthetic pathway minimizes the use of certain reagents with significant toxicity.

Biocatalytic transformations represent an immense potential in organic synthesis. Enzymes occupy a prominent place among biocatalysts and have a wide spectrum of biotechnological applications [9]. The stability of enzymes in organic solvents has pushed them into the frontier areas of organic synthesis [10].

A useful bioconversion is the epoxidation of styrene to epoxystyrene. Two enzyme systems were used for this purpose, namely, xylene monoxygenase system of *P. putida* mt2. The reaction was carried out using *E. coli* recombinants carrying only the xylene monoxygenase system, encoded by XylMA, resulting in efficient formation of epoxystyrene with an enantiomeric excess of 92 % [11].

Deacylation of cephalosporin derivatives using lipase from Fusarium globulosum has also been carried out (Scheme 1) [12].
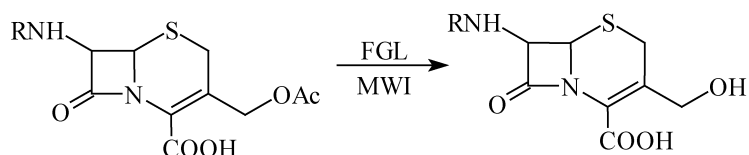
Scheme 1

The enzymes provide a methodology for transformations with high selectivity and specificity under mild conditions.
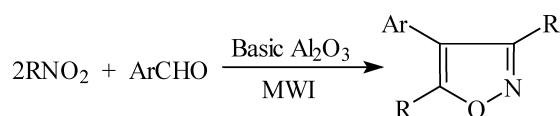
GREEN TECHNOLOGIES

Historically, chemists thought that compounds react only in the liquid state or if dissolved [13]. This has made solvents common in chemical syntheses, however, many compounds used as solvents were found to be environmentally unfriendly. The problem associated with waste disposal of solvents has been overcome by performing reactions without a solvent under microwave irradiation (MWI) [14]. Coupling of MWI with the use of mineral-supported catalyzed reactions, under solvent-free conditions, provides clean chemical processes with the advantage of enhanced reaction rates, higher yields, greater selectivity, and greater ease of manipulation.
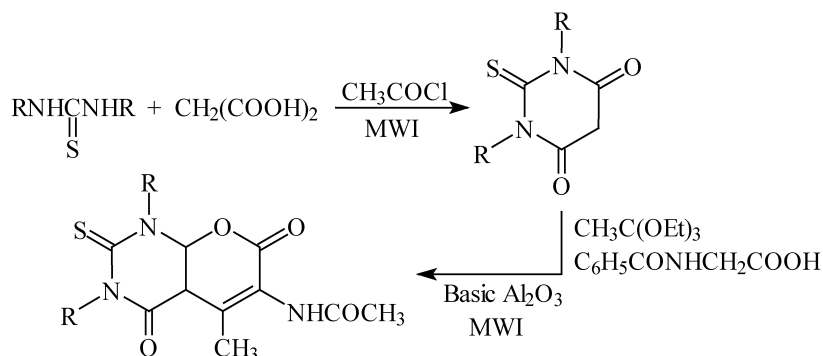
These expeditious and solvent-free approaches involve the exposure of neat reactants to MWI in conjunction with the use of supported reagents or catalysts [15].

Dry media reactions

Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient, and economical technology (green chemistry). There is an increasing interest in the use of environmentally benign reagents and procedures. Or, in other words, the absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for synthesis. In the present discussion, we describe the advantages of dry reaction techniques coupled with microwave activation and their applications to organic synthesis using solid supports. The practical dimension to the microwave heating protocols has been added by accomplishing reactions on solid supports under solvent-free conditions [16]. These solvent-free microwave-assisted reactions [17] provide an opportunity to work with open vessels, thus avoiding the risk of high-pressure development and increasing the potential of such reactions to upscale. The practical feasibility of microwave-assisted solvent-free synthesis has been demonstrated in various useful transformations [18,19] and in synthesis of heterocyclic systems (Schemes 2 and 3) [20,21].
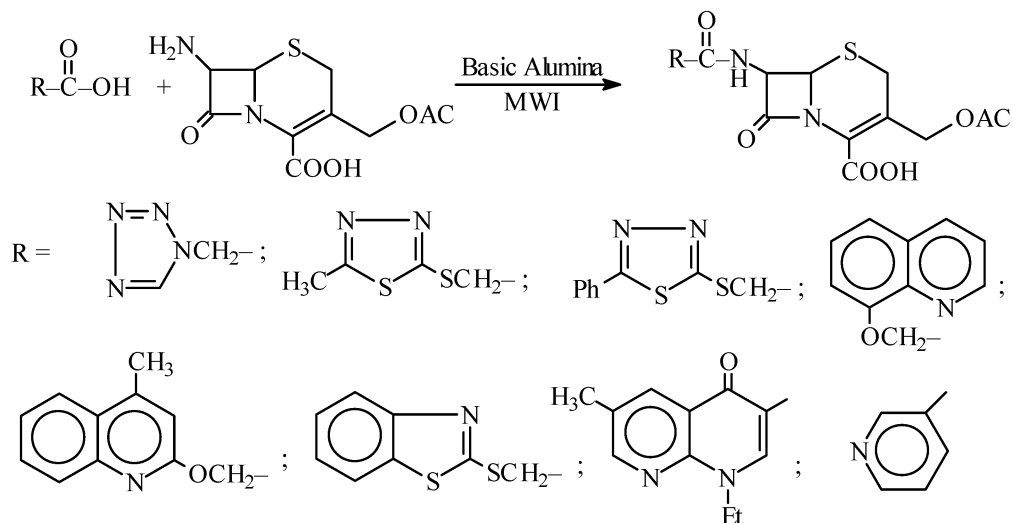
$$2RNO_2 \ + \ ArCHO \xrightarrow[\text{MWI}]{\text{Basic Al}_2O_3}$$

Scheme 2

$$RNHCNHR \ + \ CH_2(COOH)_2 \xrightarrow[\text{MWI}]{CH_3COCl}$$

$$\xleftarrow[\substack{\text{Basic Al}_2O_3 \\ \text{MWI}}]{\substack{CH_3C(OEt)_3 \\ C_6H_5CONHCH_2COOH}}$$

Scheme 3

Reaction of 7-ACA with carboxylic acids by adsorption on basic alumina under MWI for 90–120 s (Scheme 4) afforded the 7-substituted cephalosporanic acid derivatives with amidic bond [22].
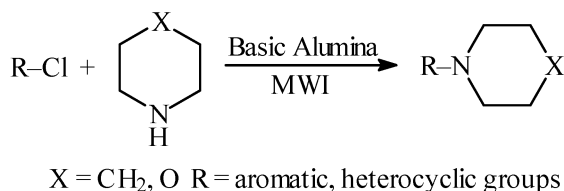
$$R-\overset{O}{\overset{\|}{C}}-OH \ + \quad \xrightarrow[\text{MWI}]{\text{Basic Alumina}}$$

R =

Scheme 4

5-Substituted-2-amino-1,3,4-thiadiazoles were synthesized within 40–80 s with improved yield using acidic alumina, which undergo insertion reaction with 5-alkyl-2-mercapto-1,3,4-oxadiazoles and yielded the thiadiazolyl-substituted triazoles within 40–80 s. A drastic reduction in reaction time and improved yield was observed due to the rapid heating capability of solid support under microwaves [23].

A series of novel bioactive organotin compounds has been synthesized on basic alumina in an open vessel under MWI. The reaction time has been brought down from hours to seconds as compared to the conventional heating [24].

A nonconventional synthetic procedure for nucleophilic aromatic substitution of cyclic amines using microwaves avoiding catalysts has been developed (Scheme 5) [25]. Results obtained show the drastic reduction in reaction time and improved yield in solid-phase reaction compared to other methods.
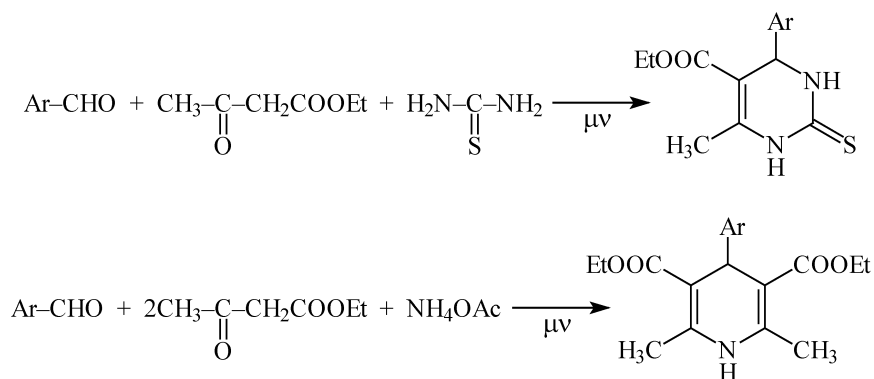
$$R–Cl + \underset{\underset{H}{N}}{\overset{X}{\bigcirc}} \xrightarrow[\text{MWI}]{\text{Basic Alumina}} R–N\overset{\frown}{\underset{\smile}{\bigcirc}}X$$

$$X = CH_2, O \quad R = \text{aromatic, heterocyclic groups}$$

Scheme 5

For example, the traditional catalyst hydrogen fluoride, an extremely corrosive, hazardous, and toxic chemical used in the production of linear alkylbenzenes (LABs), has been successfully replaced by a solid acid catalyst, viz. fluorided silica-alumina catalyst, which does not require special material of construction, involves lower operating costs, and obviates the need for an acid scrubbing system and waste disposal of calcium fluoride.

Neat reaction technology

Environmental concerns in research and industry are increasing the pressure to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by evermore strict laws. Hence, the challenge for a sustainable environment calls for clean procedures, which can avoid the use of harmful solvents. "Neat reaction technique" is an alternative environmentally benign solvent-free approach that eliminates the use of solvent from the reaction. These no-solvent reactions prove to be advantageous for environmental reasons and also offer benefits of shorter reaction times when coupled with MWI or ultrasound due to their uniform heating effect (Schemes 6–12) [26–32]. Reactions discussed below are based on neat reaction technology.
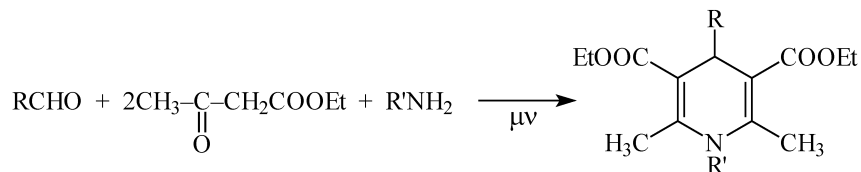
Synthesis of pyrimidine and pyridine derivatives

$$Ar–CHO + CH_3–\underset{O}{\overset{\|}{C}}–CH_2COOEt + H_2N–\underset{S}{\overset{\|}{C}}–NH_2 \xrightarrow{\mu v} \text{(4-Ar-5-EtOOC-6-H}_3\text{C-2-thioxo-tetrahydropyrimidine)}$$

$$Ar–CHO + 2CH_3–\underset{O}{\overset{\|}{C}}–CH_2COOEt + NH_4OAc \xrightarrow{\mu v} \text{(dihydropyridine product)}$$
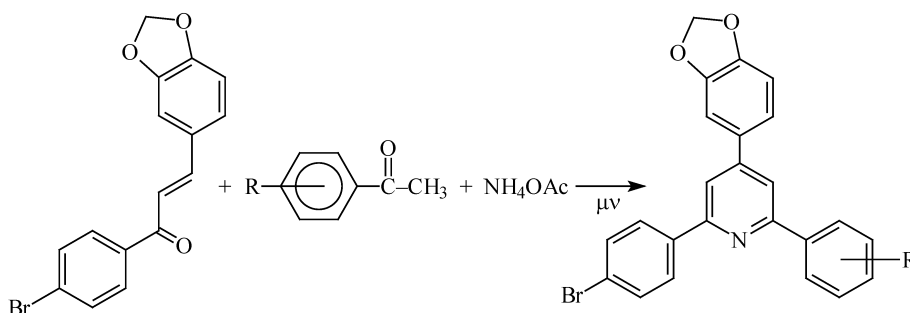
Scheme 6

Modified Biginelli and Hantzsch reactions were carried out using benign processes. Neat reactants viz. aromatic/heteroaromatic aldehydes, ethylacetoacetate, urea/thioureas, or ammonium acetate were subjected to MWI and gave the required products more quickly and in better yields in comparison to traditional methodologies. The observed yields and enhancement in the reaction rates are due to solvent-free conditions coupled with MWI.

Synthesis of N-substituted pyridine derivatives

RCHO + 2CH$_3$–C–CH$_2$COOEt + R'NH$_2$ $\xrightarrow{\mu\nu}$

Scheme 7

*Synthesis of 2,4,6-triaryl pyridine derivatives*

Scheme 8

This [3+2+1] pyridine ring synthesis utilizes the enone functionality as the three-carbon component, differently substituted α-methyl ketone as two-carbon component, and ammonium acetate as one-carbon component under solventless conditions. This microwave-assisted neat synthesis is environmentally benign as it includes a simple reaction set-up, remarkably enhanced product yield, short reaction time, and, above all, complete elimination of solvent [28].

*Synthesis of octahydroquinazoline-2-one/thione-5-one derivatives*
One pot solvent-free method for the synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one derivatives is described, which devoids the use of any organic solvents and auxiliaries. All the synthesized compounds were screened for their in vitro antibacterial activity against standard strains of *Staphylococcus aureus*, *E. coli,* and *Pseudomonas aeruginosa* and were found to be active [29].

R–CHO + ... + H$_2$N–C–NH$_2$ $\xrightarrow{\mu\nu}$
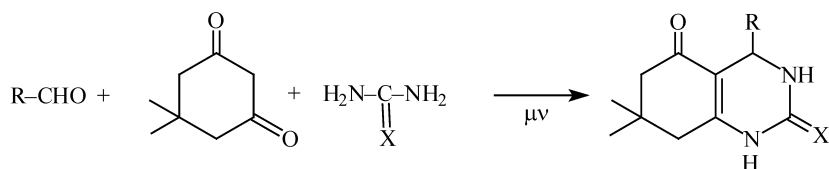
Scheme 9

*Synthesis of 1,2-dihydrotriazine derivatives*
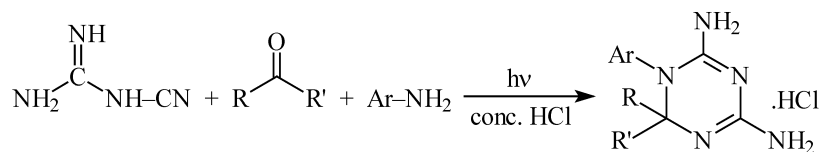
Scheme 10

Pharmacologically important 1,3,5-triazines were synthesized by neat technology. This condensation is effective under anhydrous conditions as formation of water led to incomplete condensation and resulted in arylbiguanidine as side product. Triethylorthoacetate or triethylorthoformate were used as dehydrating agent in the normal course that an agent was required. Microwave exposure induces equilibrium shift by evaporation of light polar molecules such as water, which strongly interact with electromagnetic radiations. This technology also accommodates formaldehyde directly as a substrate in contrast to literature where dimethoxy methane was used as formaldehyde equivalent [30].

Synthesis of tetrahydroacridinones
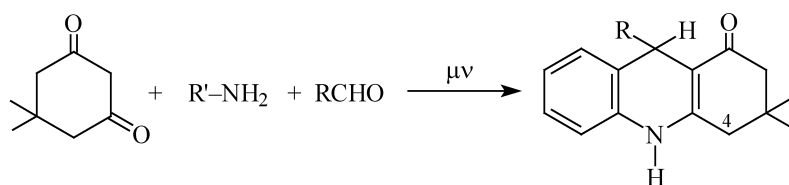
Scheme 11

Synthesis of tetraacridinones in neat reaction technology is described. The use of solvent during course of reaction is completely eliminated.

Synthesis of 1,5-benzodiazepines

Because of the pharmacological utility of benzodiazepines, several protocols have been reported for their synthesis, but most of these processes suffer limitations such as drastic reaction conditions, tedious work-up procedure, expensive and hazardous catalysts, stoichiometric amounts of catalyst and strong acidic conditions, thus rendering the procedure uneconomical and polluting. We synthesized a new series of 1,5-benzodiazepines, eradicating the use of any acid or catalyst under microwave-assisted neat
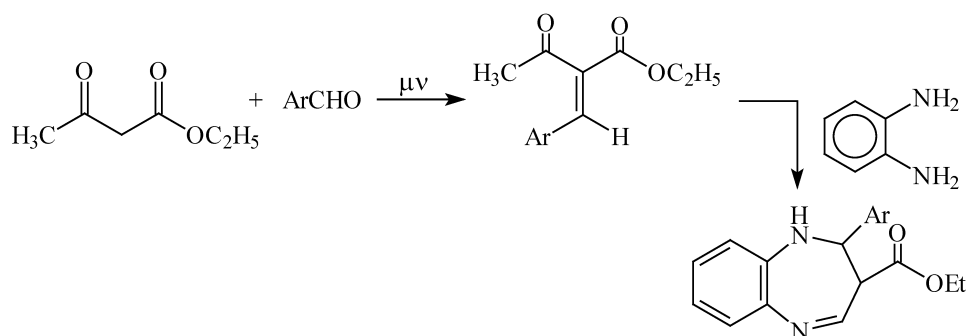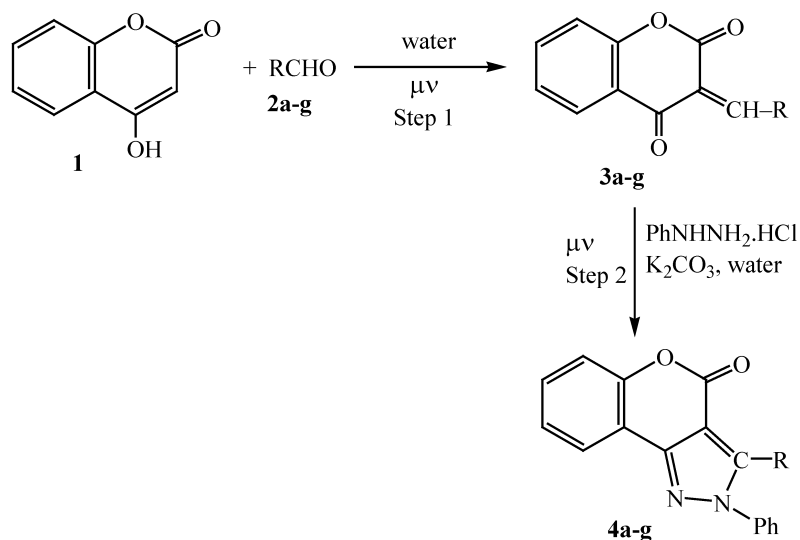

Scheme 12

reaction technology. Benzodiazepines were obtained in good yields within a few minutes of irradiation. The remarkable features of the new procedure are high conversion, shorter reaction times, elimination of hazardous reagents, cleaner reaction profile, solvent-free conditions, and simple experimental and work-up procedures [32].

Aqua-mediated reactions

The most important aspect of the reaction is that higher yields are achieved when the reaction is carried out in water as compared to organic solvents. Water is recognized as an attractive medium for many organic reactions as it is the cheapest abundantly available solvent. The use of aqueous K_2CO_3 under MWI [33,34] not only gives good yield in less reaction time, but also provides a procedure that devoids the use of corrosive organic bases viz. synthesis of diazines, thiohydantoins, amino-chromenes. The hydrophobic effect, by which nonpolar materials cluster to escape contact with water, can lead to advantages in rates and selectivity, when reactions are performed in water.

Water, being polar in nature, is used in the synthesis of benzopyrano[4,3-c]pyrazoles under MWI (Scheme 13). In this protocol, an active methylene reagent, 4-hydroxy coumarin, has been utilized with aromatic/heteroaromatic aldehydes and phenyl hydrazine hydrochloride taking K_2CO_3 as green base and water as green solvent to furnish a library of benzopyrano[4,3-c]pyrazoles [35]. Since water is used as solvent, this completely circumvents the use of other hazardous solvents to get improved yields with purity. The usage of K_2CO_3 also eliminates the requirement of solvent at work-up stages.
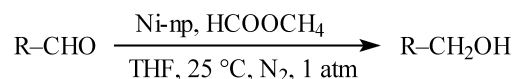

Scheme 13

CATALYTIC PROCESSES

Catalysis is a central part of industrial chemical synthesis: about 75 % of current chemical processes make use of catalysts in four main areas: environmental protection (36 %), chemicals (23 %), oil processing in refineries (22 %) and polymers (20 %). Efficient homogeneous and heterogeneous catalysts, biocatalysts, photocatalysts, electrocatalysts, etc. ensure that chemical reactions are high yielding and economical, but they avoid by-products and decrease energy inputs.

In recent years, there is growing interest in [36] catalytic properties of transition-metal nanoparticles as they show better results in comparison with traditional methods using metal compliers/metals.

The high surface area to volume ratio of solid supported metal nanoparticles is mainly responsible for their catalytic properties. This can be exploited in many industrial important reactions [37]. In this respect, it is expected that transition-metal nanoparticles of 1–10 nm in size will exhibit physical and chemical properties intermediate between those of the smallest element from which they can be composed and those of bulk material. Indeed, in many cases, this new generation of nanoparticles gives rise to unique catalytic activities and selectivities. For example, Ni nanoparticles act as a green catalyst for chemoselective reduction of aldehydic group in the presence of other functional groups, viz. $-NO_2$, $-CN$, and alkenes to give the corresponding alcohols in excellent yields [38]. This can be achieved by Raney–Nickel, etc. catalysts but the use of Ni nanoparticles leads to chemoselectivity with loading of the even less than 10^{-3} mg of catalyst at room temperature, thereby reducing the side products (Scheme 14).

$$R–CHO \xrightarrow[\text{THF, 25 °C, N}_2\text{, 1 atm}]{\text{Ni-np, HCOOCH}_4} R–CH_2OH$$
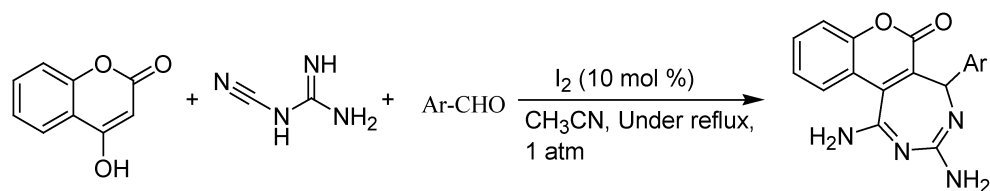
Scheme 14

As a result of the compelling need for industry to consider the reengineering of entire processes, ionic liquids have begun to receive worldwide academic and industrial attention. Ionic liquids provide a unique opportunity for science, engineering, and business of a field's development and thus lead more quickly to innovative environmentally and economically sustainable industrial processes [39]. The general advantages of ionic liquids are that they have no measurable vapor pressure, are thermally robust, will tolerate impurities such as water, and, if the extraction solvent is recycled, generate almost no waste product. Ionic liquids have been described as designer solvents, and this means that their properties can be adjusted to suit the requirement of a particular process. Properties such as melting point, viscosity, density, and hydrophobicity can be varied by simple changes in the structure of the ions.

An ecofriendly facile synthesis of imidazo[2,1-b]-1,3,4-thiadiazoles was conducted using ionic liquid, [bmim]PF_6(1-butyl-3methylimidazolium); significant increase in reactivity was observed, thus reducing the reaction time and improving the yields remarkably. The simple experimental and product isolation procedures, combined with the ease of recovery and reuse of this novel reaction media, are expected to enhance the development of green strategies for the preparation of imidazothiadiazoles [40]. This technique could prove to be a boon for chemists, especially natural chemists.

Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields. In the presence of the catalytic amount of I_2 (10 mol %), we were successful in obtaining 7-arylbenzopyrano[1,3]diazepines (Scheme 15) in protic solvents that avoid multistep and harsh reaction conditions. Surprisingly, results of this reaction cannot be obtained in protic solvents even after prolonged heating in the presence or absence of catalyst [41].

Scheme 15

MICROWAVE-ASSISTED PARALLEL LIBRARY SYNTHESIS ON THIN-LAYER CHROMATOGRAPHY PLATES

Thin-layer chromatography (TLC) has been reported as a tool for reaction optimization in microwave-assisted synthesis. This technique [42] has been used for the synthesis of acridine and quinazoline derivatives and is a valuable technique for computational chemistry.

CONCLUSION

It is clear that the challenge for the future chemical industry is based on production of safer products and processes designed by utilizing new ideas in fundamental research. On the other hand, it should be easy to foresee that the success of environment-friendly reactions, products, and processes will improve competitiveness among the chemical industry. If companies are able to meet the needs of society, people will influence their own governments to foster those industries attempting such environmental initiatives. In this context, chemical sciences will play a key role in the realization of the conditions for a sustainable development with green chemistry strategies.

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