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GREEN TECHNIQUE-SOLVENT FREE SYNTHESIS AND ITS ADVANTAGES

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ABSTRACT
Green Chemistry, the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances is an overarching approach that is applicable to all aspects of chemistry. All synthetic processes involve the use of different solvents. Unfortunately many of the solvents are used in industry and retail are volatile organic compounds (VOCs) which lead to environmental damage, through pollution, risks to human health and to resource depletion, we need to develop and apply more environmentally friendly approaches. So, all traditional and old synthetic routes obviously give adverse effects to the mankind and all living beings. Green chemistry provides "Green" paths for different synthetic routes using non-hazardous solvents and environmental- friendly chemicals. Solvent free synthesis has several advantages over the classical method of synthesis. Due to enormous advantages of solvent free reactions, new solvent-free approaches are being discovered for eco-friendly synthesis of many compounds.

KEY WORDS: Green chemistry, solvent free synthesis, microwave irradiation, ultrasonic processor.

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INTRODUCTION

Green chemistry is defined as environmentally benign chemical synthesis. The synthetic schemes are designed in such a way that there is least pollution to the environment. As on today, maximum pollution to the environment is caused by numerous chemical industries. The cost involved in disposal of the waste products is also enormous.

The twelve principles of Green Chemistry can be applied to almost every part of chemistry, which includes synthesis of molecules with a desired structure and property, catalysis of a process, less polluting reaction conditions etc[1].

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

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

3. Designing before Chemicals: Chemicals products should be designed to affect their desired function while minimizing their toxicity.

4. Atom economy: Synthetic methods should be designed to minimize the incorporation of all materials used in the process into the final product. A very good example is the BHC company synthesis of Ibuprofen, which creates less waste and fewer by products. The % economy for the three step catalytic green synthesis (BHC) Vs the six step brown synthesis (BOOTS) in 77% and 40% respectively. Considering the fact that acetic acid generated in steps 1 of green synthesis is recovered the % atom economy climbs to 99% from 77%.

5. Safer solvents and auxiliaries: The use of auxiliary substances (solvents, separation, agents, etc.) should be minimized whenever possible and should be made 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 renewable feed stocks: 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 and temporary modification of physical / chemical processes)

should be minimized or 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. Using catalytic reagents creates opportunities for increased selectivity, better yield, and feasibility of non feasible reaction.

10. Design for degradation: Chemical products should be designed so that at the end of the function they break down into innocuous degradation products and do not persists 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 chemical process should be chosen to minimize the potential for chemical accidents including releases, explosions and fires.

Green chemistry has many advantages like

- Non toxic
- Environment Friendly
- Simple
- Sustainable
- Economical
- Safe
- Avoid Waste

Attempts have been made to design synthesis for manufacturing processes in such a way that the waste products are minimum, they have no effect on the environment & their disposal is convenient. For carring out reactions it is necessary that the starting materials, solvents & catalysts should be carefully chosen. For example, use of benzene as a solvent must be avoided at any cost since it is carcinogenic in nature. If possible, it is best to carry out reactions in the aqueous phase. With this view in mind, synthetic methods should be designed in such a way that the starting materials are consumed to the maximum extent in the final product. The reaction should also not generate any toxic by-products.

The earlier belief that no reaction is possible without the use of a solvent is no more valid. It has been found that a large number of reactions occur in solid state without the solvent. In fact in a number of cases, such reactions occur more efficiently & with more selectivity compared to reactions carried out in solvents. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate & are especially important in industry. There is some literature available on different aspects of organic syn thesis in solid state. It is believed that solvent-free organic synthesis & transformations are industrially useful & largely green.

Numerous organic reactions can be successfully carried out under solvent free conditions. Some reactions also show higher yields and greater selectivity[2]. In many reactions enzymes have also been used to carry out reactions without solvents. Such reactions are environment friendly, for eg- synthesis of polyglycerol polyricinoleate can be synthesized using Rhizopus arrhizus lipase as a catalyst[3]. Multicomponent reactions including many reagents which give a single product, draws much attention of the chemists[4]. Many classical reactions have been modified using green methods, for eg- diketene is used as an alternative substrate for a new Biginelli-like multicomponent reaction[5].

Many natural substances having numerous advantages in industrial applications cannot be used because of some limitations. Such molecules can be modified by solvent free synthesis to facilitate its widespread use, for eg- solvent free acetylation of bacterial cellulose makes it suitable for industrial usage[6]. Allylation of carbonyl compounds have gained importance for designing various biologically active molecules. Allylation reactions can be carried out under mild and efficient solvent free conditions using magnesium powder as a catalyst[7]. Alumina can also be used as an effective environment friendly catalyst for the synthesis of quinoxaline and its derivatives which show a wide range of biological activities. Alumina is cheap, reusable and environment friendly catalyst[8].

Organic esters can be efficiently used in the synthesis of chemicals, drugs, food preservatives, plasticizers etc. Sulphated zirconia can be used as a catalyst for the acylation of alcohols, phenols, amines etc under solvent free conditions[9]. Cellulose sulphuric acid is a biodegradable solid acid catalyst which can be efficiently used for the synthesis of substituted pyrroles at room temperature under solvent free conditions. Pyrroles and its derivatives have a wide range of medicinal properties such as antimalarial, antibacterial, antiviral etc[10].

Another compound with different biological activities is α-aminophosphonates. It has many applications like antibiotics, herbicides etc. it can be synthesized under solvent free conditions using ytterbium perfluorooctanoate[11]. Amidoalkyl naphthols can be prepared under thermal solvent free conditions using bronsted acidic ionic liquid ([TEBSA] [HSO_4]). This catalyst is reusable, produces high yield, has a short reaction time and a easy work up[12].

Acetylation of alcohols, phenols and thiols can be easily carried out at room temperature in a short time using solid $TiCl_3$(OTf). The catalyst eliminates the use of harmful solvents[13]. Microwave irradiation is a modern green technique to carry out solvent free synthesis. It

reduces the reaction time, prevents the use of harmful solvents and in some reactions, it increases the yield. This technique can be efficiently used for the one-pot synthesis of tetra substituted imidazoles[14].

GREEN METHOD VS CLASSICAL METHOD

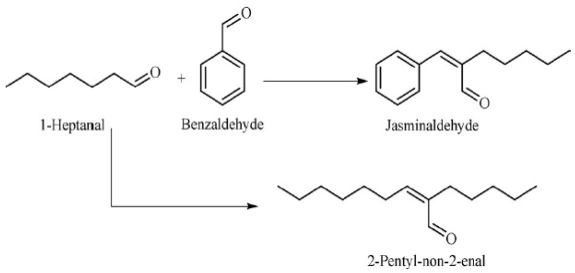
Synthesis of jasminaldehyde

Classical method

Jasminaldehyde can be synthesized commercially by the condensation of 1-heptanal with benzaldehyde in the presence of liquid alkali like NaOH or KOH. But this process has many disadvantages like lack of reusability of catalyst, hazardous liquid alkali waste & post reaction treatment of spent liquid bases.

Solvent free method

N.Sudheesh et al. proposed the synthesis of jasminaldehyde by also condensation reaction which involves the reaction between 1-heptanal & benzaldehyde in 1:5 ratio in the presence of chitosan as a catalyst in nitrogen atmosphere in order to prevent the formation of acids from aldehyde[15]. The temperature was maintained at 140`. This method has advantages like less reaction time, no hazardous waste production & greater selectivity.



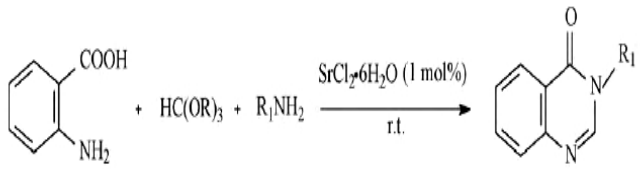
Synthesis of 4(3H)-quinazolinones

Classical method

4(3H)-quinazolinones can be prepared by different reactions. One of the reaction include the cyclocondensation of 2-fluorobenzoyl chlorides with 2-amino-N-heterocycles. But such reactions have drawbacks such as refluxed temperature, long reaction time, harmful organic solvent etc.

Solvent free method

In this procedure a mixture of anthranilic acid, an ortho ester, an amine & SrCl2.6H2O was stirred at room temperature for an appropriate time. It has advantages such as reaction can be carried out at room temperature, less reaction time & excellent yields. This method was proposed by M. Wang et.al[16].



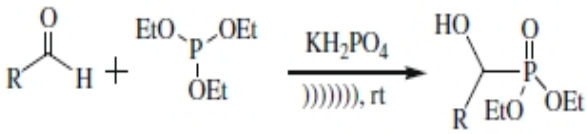
Synthesis of α-hydroxyphosphonates

Classical method

The classical synthesis of α-hydroxyphosphonates involves the reaction between dialkyl phosphite & substituted aldehyde in presence of a base such as ethyl magnesium bromide, quinine etc. but this has the disadvantages such as harsh reaction condition, high temperature, long reaction time, use of strong bases, mixture of products & poor yields.

Solvent free method

α-hydroxyphosphonates was synthesized in high yields (84-90%) by a reaction between aryl or hetero aryl aldehydes & tri-ethyl phosphate using potassium dihydrogen phosphate as a catalyst under ultrasonic waves for 5mins. This process was proposed by Charansingh H. Gill et al[17]. Its advantages are no involvement of organic solvents, less time, improved yields, mild conditions & ready operations.



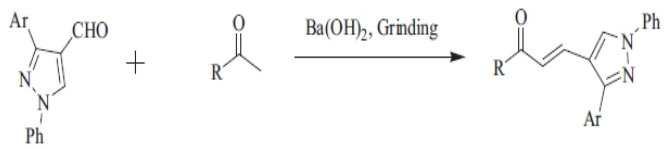
Synthesis of Pyrazole chalcones

Classical method

Generally, chalcones can be synthesized by Claisen Schmidt condensation between ketones & aryl halides using catalysts like alkali metal hydroxide or sodium ethoxide. It has disadvantages include use of harmful organic solvents & difficult extraction process.

Solvent free method

This process involves the grinding of a mixture of pyrazole aldehydes, acetophenones & activated barium hydroxide(C-200) in a mortar & pestle for 5-10mins in the absence of any solvent. It was proposed by P.Kumar et al. the advantages are less reaction time, high yield, reaction is carried out at room temperature & mild reaction conditions[18].



Synthesis of isobenzofuran

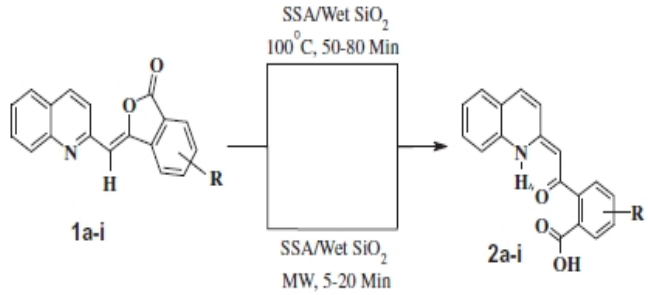
Classical method

Majority of the common esters can be hydrolysed using strong liquid protic acids such as HCl, TFA, H_2SO_4 & HNO_3 as catalysts dissolved in organic solvents. But this type of reaction has disadvantages like corrosive nature of the catalysts, difficulty in separation of the products, long reaction time & unsatisfactory yields.

Solvent free synthesis

Silica sulphuric acid can be used as a catalyst for hydrolysis of isobenzofuranone under solvent free

conditions using microwave irradiation. This reaction was proposed by J. Safari et al[19]. In this process a mixture of isobenzofuran & silica sulphuric acid was irradiated in a microwave oven for 5-20mins. The advantage of this reaction is that the catalyst is reusable & environment friendly, fast reaction, high yield.



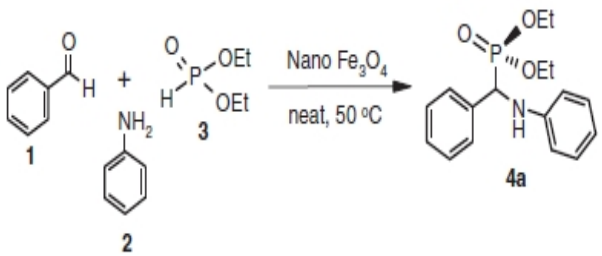
Synthesis of α-aminophosphonates

Classical method

α-aminophosphonates can be synthesized using catalysts like bronsted acids, lewis acids, heteropoly acids, heterogenous catalysts etc. but there are disadvantages like expensive catalysts, highly corrosive, involve tedious separation process & longer reaction time.

Solvent free synthesis

α-aminophosphonates are synthesized by a three component one pot reaction involving an aldehyde, an amine & diethyl phosphate using super magnetic nano iron oxide as a catalyst at 50`C, under solvent free conditions. The use of iron oxide nano particles make this reaction simple, convenient & practical for large scale synthesis. Also super magnetic nano iron oxide is recyclable, highly efficient & economically viable. This reaction was proposed by B.V.Subba Reddy et al[20].



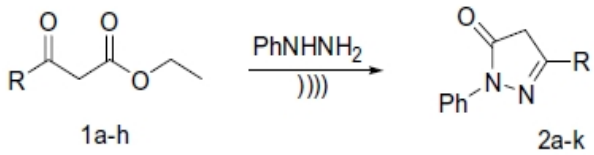
Synthesis of pyrazolones

Classical method

Pyrazolones can be traditionally synthesized by treating β-keto esters with hydrazine substrates at high temperature under acidic conditions. This methods have disadvantages like high temperature, less yield, use of harmful solvents etc.

Solvent free synthesis

Substituted pyrazolones can be obtained under solvent free condition by ultrasound mediated process. In this process a mixture containing phenyl hydrazine or hydrazine & β-keto ester was sonicated in a 10ml test tube for an appropriate length of time till TLC showed complete disappearance of starting material. The reaction was performed in a water bath at 25±1´C. this method was proposed by M.M.Mojtahedi et al[21].



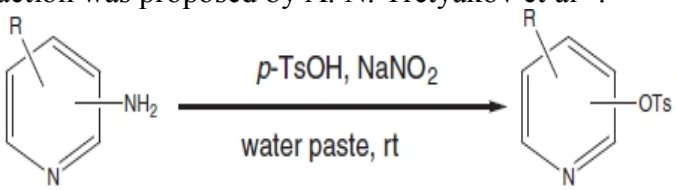
Synthesis of tosylates

Classical method

Aryl & heteroaryl tosylates are prepared in organic solvents by tosylation of the corresponding hydroxyl derivatives with p-toluenesulfonyl chloride. The main disadvantages of this reaction are longer reaction time, less yield, use of harmful solvents etc.

Solvent free method

Pyridinyl tosylates can be obtained by a one-pot solvent free synthesis via diazotisation. Typically an aminopyridine, p-toluene sulfonic acid(PTSA) monohydrate & water were ground in a mortar for 3-5 mins to give a homogenous mixture. Next NaNO2 was added & grinding was continued for another 5mins. The so formed slurry was left for 1-2 hours with grinding every 15-20 mins. Pure products were isolated simply by sequential washing of the reaction mixture with aqueous sodium carbonate & water. It has advantages operating simplicity, room temperature & high yields. This reaction was proposed by A. N. Tretyakov et al[22].



Synthesis of N-substituted pyrroles

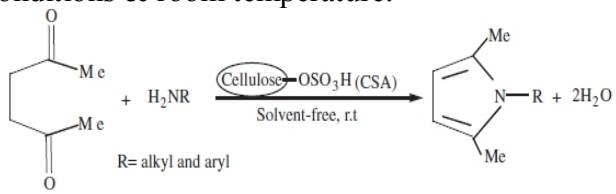
Classical method

N-substituted pyrroles can be prepared classically from many reactions like Hantzsch reaction, aza-wittig reaction etc using catalysts such as HCl, p-TSA, H_2SO_4 etc. but these processes have disadvantages like low yields, prolonged reaction time, harsh reaction conditions, requirement of excess catalysts, use of expensive reagents, high temperature, tedious work-up & generation of large amounts of toxic metal containing wastes.

Solvent free method

N-substituted pyrroles can be synthesized from the one pot condensation reaction of 2,5-hexandione with amines and diamines using cellulose sufuric acid as a catalyst under solvent free conditions at room temperature. In this procedure CSA was added to a solution of amine and 2,5-hexandione. The mixture was stirred at room

temperature, concentrated, diluted, filtered and purified and the pure product was obtained[23]. This reaction has advantages like reusable catalysts, environment friendly reaction, sustainable resources, inexpensive, solvent free conditions & room temperature.



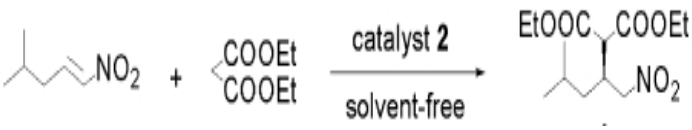
Synthesis of pregabalin

Classical method

Initially pregabalin was synthesized industrially by a racemic synthesis followed by resolution. Then a number of asymmetric processes were proposed like the routes proposed by sammian & Jacobsen , shibnahi's group, Amstrong et al, poe et al. Although such reactions gave excellent yields it had drawbacks such as harsh reaction conditions, high toxicity & expensive catalysts.

Solvent free synthesis

Michael addition is one of the best effective routes for construction a chiral center of pregablin. In recent years , the syn of pregablin has seen investigated by Michael addition of malonates with nitroalkene was added to stirred solution of diethyl malonate using thio urea as a catalyst in a solid carrier in a solvent free condition the mixture is stirred for 24 hours. Organo catalysed reaction is always environment friendly & easy to operate, readily available & uses low toxic catalysts. This reaction was proposed by Jin-ming Liu et al[24].



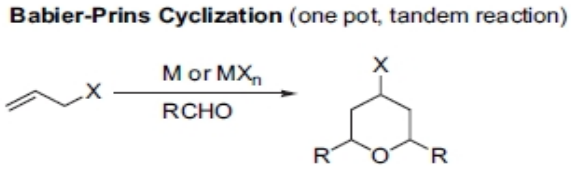
Synthesis of Tetrahydropyrans

Classical method

Tetrahydropyrans can be effectively synthesized by Prins cyclization involving the condensation of homoallylic alcohol & carbonyl compounds in presence of protic acids or lewis acids. Babier reaction can also be used which involves reaction between organolithium reagents with aldehyde. But such reactions have disadvantages like use of harmful bases, longer reaction time etc.

Solvent free method

Tetrahydropyrans can be directly synthesized via one-pot babier-prins cyclization which includes reaction of allylbromide with carbonyl compounds. This reaction is promoted by RTILs BPyX/SnX'_2. Interestingly babier reaction in combination with prins cyclisation for direct formation of tetrahydropyran. In a typical reaction mixture of cyclohexanone allylbromide and complex derived from BBIM Br and SnBn2 was stirred for 6 hours at ambient temperature. It has advantages like room temperature, less reaction time, reusable catalyst etc. it was proposed by Xian-Liang Zhao et al[25].



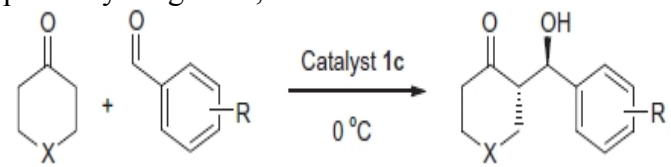
Aldol condensation reaction

Classical method

Intermolecular Aldol reaction was carried out between 3-nitrobenzaldehyde & cyclohexanone using an appropriate catalyst. But this had disadvantages like high temperature, low yields, use of organic solvents etc.

Solvent free method

Glucosamide derived prolinamide is used as efficient catalyst for the direct solvent free aldol reaction between ketones and aryl aldehydes. In recent years, prolinamide has been proved as an efficient oranocatalyst for the direct asymmetrical aldol reaction, such reaction are mild for catalytic enantioselective added reaction between ketones & aromatic aldehydes. In a typical procedure an aldehyde solution, organocatalyst (prolinamide) and cycloalkanone was stirred for 5-48hrs at 0°c. This reaction has advantages like high yields, avoidance of organic solvents, easy extraction etc. this method was proposed by J.Agarwal, R.K.Peddinti[26].



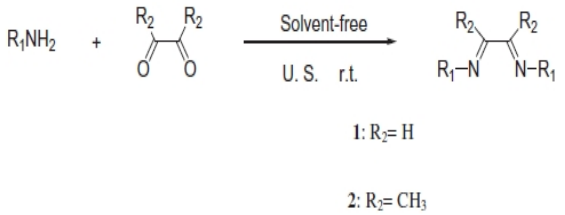
Synthesis of 1,4-diazabutadienes

Classical method

Classically 1,4-diazabutadienes can be synthesized by the condensation of an α-diketone & an amine in organic or aqueous solvents. But this reaction has disadvantages like harsh reaction condition, long reaction time, use of organic solvents & high temperature.

Solvent free method

Ultrasound irradiation method can be used to prepare 1,4-diaza butadiene's. The mixture, glyconal trimer dehydrate or 2,3 butanedione was irradiated under an ultrasonic processor. The solids were washed or recrystallized by ethanol when the indicated time was over. This process has advantages like less reaction time, environment friendly conditions, low temperature, high yields etc. this was proposed by J.Y He et al[27].



1: R_2= H

2: R_2= CH_3

R_1= a: 4-$CH_3OC_6H_4$; b: 4-$CH_3C_6H_4$; c: 2-$CH_3C_6H_4$; d: C_6H_5; e: 4-ClC_6H_4; f: 3,5-$(CF_3)_2C_6H_3$; g: 2,6-$(CH_3)_2C_6H_3$; h: 2,4,6-$(CH_3)_3C_6H_2$; i: 2,5-$F_2C_6H_3$; j: *i*-C_3H_7; k: *n*-C_4H_9; l: cyclohexyl.

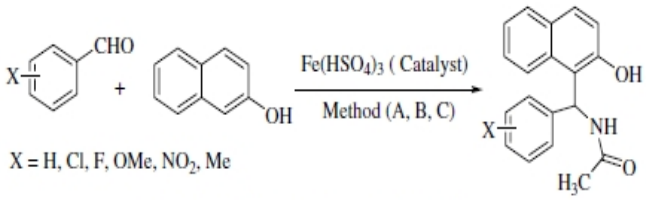
Synthesis of 1-amidoalkyl-2-naphthols

Classical method

1-amidoalkyl-2-naphthols can be synthesized by multicomponent condensation of aryl aldehydes, 2-naphthol and acetonitrile in the presence of lewis or bronsted acid catalysts $Ce(SO_4)$, iodine etc. Such catalysts prolong reaction time, induce toxicity,give low yields and has several other disadvantages.

Solvent free method

In the solvent free method amidoalkyl naphthols can be synthesized by a multicomponent, one-pot condensation reaction of β-naphthols, aromatic aldehydes and acetamide in the presence of ferric hydrogen sulphate in microwave conditions. It has advantages like shorter reaction time, simple work up process, high yields etc. this method was proposed by Hamid Reza Shaterian et.al[28].



Method A: CH_3CN (Ritter type reaction)
Method B: CH_3CONH_2 (Thermal Solvent-Free conditions)
Method C: CH_3CONH_2 (Microvawe Solvent-Free conditions)

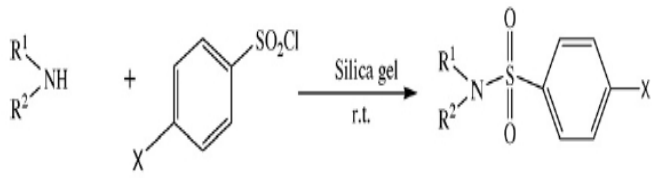
Synthesis of sulphonamides

Classical method

Classicaly sulphonamides can be synthesized by the condensation of 4-toluenesulphonyl chloride with aniline. This reaction is carried out at high temperature, it requires long reaction time with low yields.

Solvent free method

When 4-toluenesulphonyl chloride is reacted with aniline under the influence of silica gel under solvent free conditions, the yield is increased to 95% and the reaction time is reduced to 40mins.this was proposed by Maasoumeh Jafarpour et.al[29].



R^1, R^2= H, Alkyl, Aryl X= H, Me, NO_2, Br

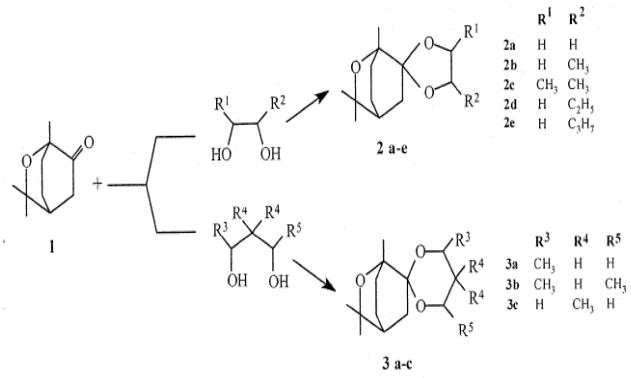
Synthesis of cyclic ketals

Classical method

Cyclic ketals can be synthesized classicaly by the reaction between carbonyl group and diols in the presence of acidic catalysts using benzene or toluene as solvents. Such solvents harmful to the environment.

Solvent free method

In this technique the reaction between carbonyl group and diols is carried out under microwave and dry conditions using PTSA in toluene. It increases the yield to a great extent and also reduces the reaction time. This was proposed by M.T.Genta et.al[30].



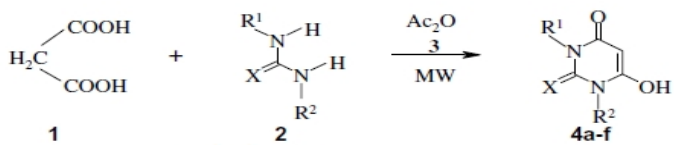
Synthesis of 6-aminouracils

Classical method

6-aminouracils were synthesized by the condensation of cyanoacetic acid and N,N-dialkylurea/N-monoalkylurea/urea in the presence of phosphorus oxychloride. It is then followed by cyclisation using sodium hydroxide. This reaction took several hours and gave poor yields.

Solvent free synthesis

In this reaction malonic ester, urea and acetic anhydride were allowed to react under microwave conditions for 7mins at 60ºC, at 40% power. This gave excellent yields of barbituric acid. This was proposed by Pulak J. Bhuyan et.al[31].



a R^1=R^2=CH_3, X=O
b R^1=CH_3, R^2=H, X=O
c R^1=R^2=H, X=O
d R^1=*n*-C_3H_7, R^2=H, X=O
e R^1=*n*-C_4H_9, R^2=H, X=O
f R^1=R^2=H, X=S

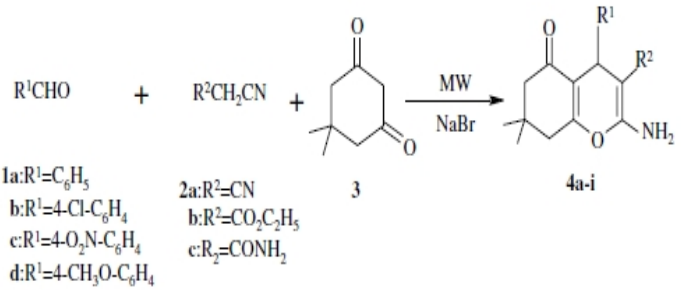
Synthesis of tetrahydrobenzopyrans

Classical method

Classical synthesis of 4Hbenzo(b)pyrans includes the use of harmful solvents like DMF which complicates the work up process.

Solvent free synthesis

4Hbenzo(b)pyrans can be synthesized by a 3 component cyclocondensation reaction of benzaldehyde, alkyl nitrile and dimedone using sodium bromide as a catalyst under microwave conditions. Thi s was proposed by P.J. Bhuyan[32].



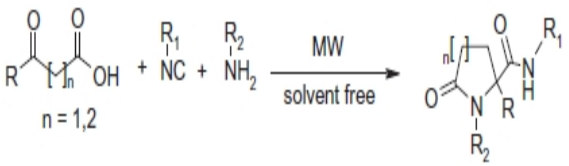
Synthesis of five and six membered lactams

Classical method

The classical synthesis of five and six membered lactams was carried out at room temperature using methanol and the reaction time was 48hrs.

Solvent free synthesis

Solvent free reactions was carried out under microwave conditions using levulinic acid, benzylisocyanide and benzylamine as precursors for five membered lactums. This reduced the reaction time and an excellent yield was obtained when the temperature was decreased to 80ºC. This reaction was proposed by Mouhamad Jida et.al[33].



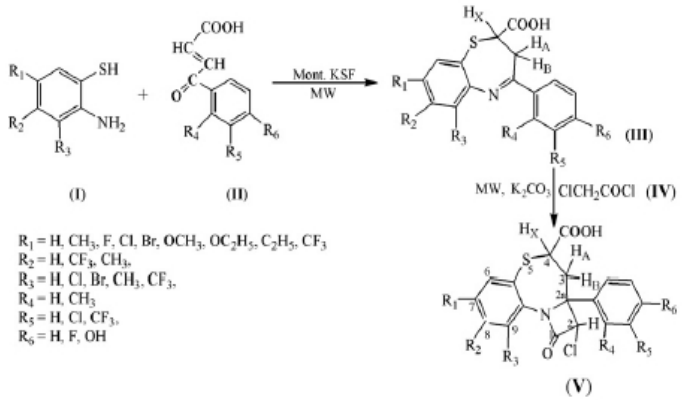
Synthesis of fluorinated benzothiazepine fused β-lactam derivatives

Classical method

Azeto[2,1-d][1,5]benzothiazepine can be synthesized by dissolving 2-carboxy-2,3-dihydro-1,5-benzothiazepine(iii) and chloroacetyl chloride(iv) in anhydrous benzene. Then dried triethylamine in anhydrous benzene was added drop wise for 20mins. The reaction mixture is then stirred for 3 days. The product obtained was dried and purified. This gives a yield of just 20% in 90hrs.

Solvent free synthesis

In this method the substituted -1,5-benzothiazepine(iii) was adsorbed on activated potassium carbonate using methanol. Then the solvent was removed using a rotator evaporator. Chloroacetyl chloride was added and mixed properly. This reaction mixture was then irradiated under microwave condition[34]. This method gave 78% yield in 4mins.



CONCLUSION

Solvent free synthesis of organic compounds has gained much popularity. It is one of the best techniques in green chemistry by which many important compounds can be synthesized in an efficient & environment friendly manner. Solvent free synthesis has several advantages over the classical method of synthesis. Some of the important advantages are as follows -

1. Prevention of waste/by-products.
2. Designing of safer reactions.
3. Maximum incorporation of the reactant (starting material & reagents) into the final products.
4. Prevention or minimization of hazardous products.
5. Products obtained are mostly biodegradable.
6. Energy requirement for such synthesis is minimum.
7. Prevention of harsh reaction conditions.
8. High yields of products.
9. Shorter reaction time.
10. High selectivity in many of the reactions.
11. Prevention of the use of harmful solvents.
12. Easy extraction process.

Due to enormous advantages of solvent free reactions, new solvent-free approaches are being discovered for eco-friendly synthesis of many compounds.

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