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Recent Advances in the Green Synthesis of Poly Functionalized Pyrroles

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ABSTRACT

Pyrroles are five-membered heterocyclic organic compounds with a broad and attractive chemistry. Functionalized pyrroles have a diverse structural variation, and they are important scaffolds in modern technological advancement. Pyrrole derivatives have been widely used as drugs, dyes, catalysts, pesticides etc*.* Therefore, the synthesis of these heterocyclic skeletons using robust and green methodologies is a great challenge in modern synthetic organic chemistry. In the present literature review, the currently developed green methodologies have been summarized in the synthesis of pyrrole derivatives. The reported methods, which are environmentally benign synthetic procedures as well as highly efficient techniques for the production of pyrrole derivatives, have been scrutinized. So, the present review article will be attractive for synthetic organic chemists who are interested in the application of Green Chemistry principles in the synthesis of pyrrole derivatives.

***Keywords**: Pyrroles; Heterocyclic Compounds; Biological Activity; Green Chemistry; Green Synthesis; Paal-Knorr Synthesis*

Introduction

Pyrrole is a nitrogen containing five membered- aromatic, heterocyclic organic compound. Pyrrole is a weak base due to the contribution of lone pair of electrons on the nitrogen to the aromaticity in the ring structure (Figure-1).

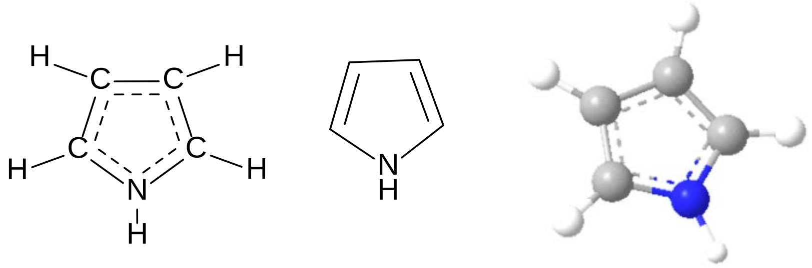
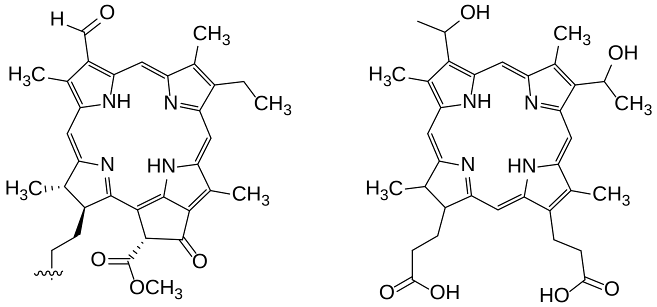


Figure 1: Structure of Pyrrole

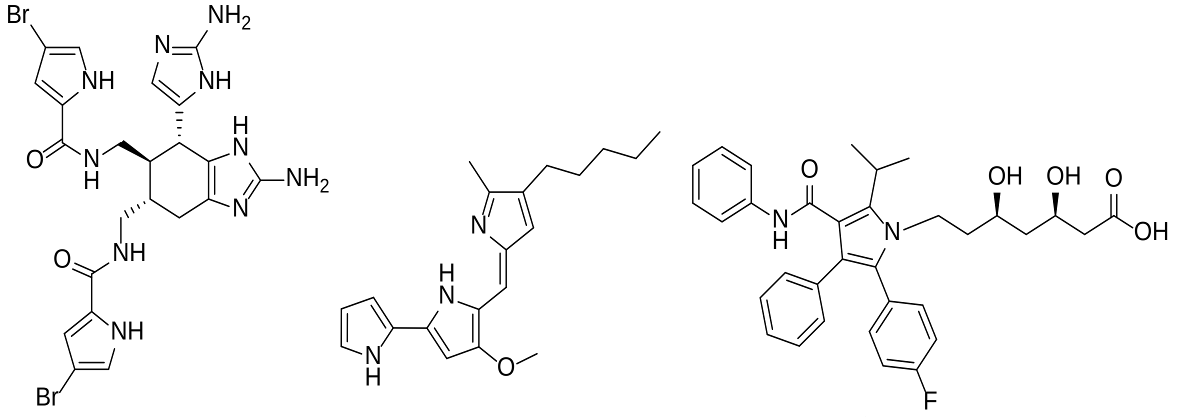
Pyrrole was first detected by F.F. Runge in 1834 from coal tar and subsequently, the structure was determined by Baeyer and Emmerling in 1870. Although the Pyrrole molecules are not as such naturally abundant, the various derivatives of these scaffolds are observed in a series of natural products and cofactors. Here are some examples of naturally occurring molecules that contain pyrrole scaffold as one of their main constituents: vitamin B_{12}, bile pigments *e.g* bilirubin, biliverdin and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorin, porphyrinogens etc. It is also found in the secondary metabolites (Young, Thornton & Thompson 2010) (Figure-2).



Chlorophyll Hematoporphyrin

Figure 2: Structure of Some Important Natural Molecule Containing Pyrrole Ring

The derivatives of pyrrole are considered an important class of biologically active molecules with diverse types of activities and they also act as different pharmacophores (Jacobi *et al*., 2000). These types of compounds exhibit anti-bacterial activities that have been extensively investigated during the last few decades, particularly tested on drug-resistant Gram-positive and Gram-negative pathogens (Yamada *et al*., 2017). Another important application of pyrrole derivatives is that they can be used for the production of anti-tumour agents that can act on gene modulation or suppression and conjugate antibodies. They are also employed as coating agents for medical implants (Dadas *et al.,* 2015).



Ageliferin Prodigiosin Atorvastatin

Figure 3: Structure of Few Important Synthetic Molecules that Contain Pyrrole Scaffold

Literature Review

Due to their huge importance, pyrrole scaffolds have attracted the great attention of synthetic organic chemists and it has been an important research area to develop newer methodologies for the synthesis of these compounds. So, several classic named reactions have been developed by various organic chemists to produce these moieties (Ferreira *et al.,* 2001). Here are some classic examples of synthetic procedures that are developed for the synthesis of pyrroles-

(i) Hantzsch synthesis (Trautwein, Süßmuth & Jung, 1998), which furnishes pyrroles through the reaction of α-halo ketones with β–ketoesters and ammonia or primary amines.

(ii) Knorr synthesis (Alberola *et al.*, 1999), which is used to construct the pyrroles scaffold by reacting α–amino-ketones derived from α–haloketones, ammonia and β–ketoesters.

(iii) Paal-Knorr condensation reaction (Pak-Kan & Sannes, 1990), it is one of the most common approaches which uses the primary amines or ammonia and various promoting agents (Figure 4 and Figure 5).

(iv) Buchwald-Hartwig coupling reaction (Bonnaterre, Bois-Choussy & Zhu, 2006).

Several other methods were also demonstrated for the production of specific pyrrole skeletons, such as multi-component reactions (Balme, 2004), addition reaction, Wittig reaction etc. arylglyoxal, which is actually an organic compound with carbonyl functionality adjacent to the aldehydes group, is a quite reactive precursor for the synthesis of different heterocyclic compounds (Eftekhari-Sis, Zirak & Akbari, 2013). Multi-component reactions of arylglyoxals have been utilized for the synthesis of a variety of poly-functionalized pyrrole derivatives (Wang *et al.,* 2013, Ambethkar, Padmini & Bhuvanesh, 2016 & Mishra *et al.,* 2017).

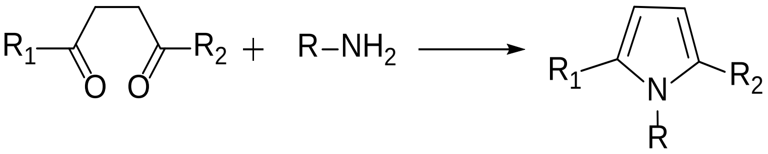


Figure 4: General Paal-Knorr Synthesis of Pyrrole

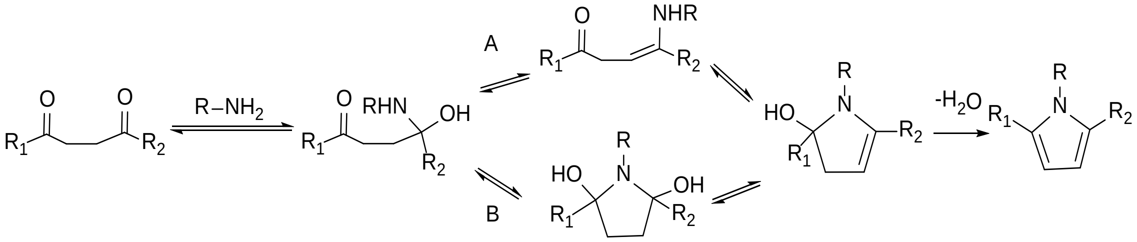


Figure 5: Proposed Pathway for the Paal-Knorr Synthesis of Pyrroles-(A) the Enamine Pathway and (B) the Hemi-aminal Pathway

However, in the above-mentioned methods, some sort of problems are encountered that are not environment friendly, such as extended reaction times, the use of toxic and low boiling solvents, diminished yields, tedious purification methods, the need for high reaction temperature etc.

Discussion

To resolve these eco-unfriendly problems, chemists are in search of novel technologies that follow the principles of Green Chemistry. One of the most important goals of green chemistry is the replacement of hazardous/toxic organic solvents with environmentally benign green solvents. On the other hand, synthetic and industrial chemists are always trying to design suitable solvents or solvent systems as reaction media to improve the efficiency of an organic transformation (Reinhardt *et al.,* 2008). In this context, a wide range of synthetic methodologies have been discovered such as –(i) use of microwave, ultrasound and visible light techniques, (ii) use of Green Solvents (water, ethanol) over conventional solvents, (iii) reaction by mechanical activation (ball milling), (iv) reaction using Nano and Green Catalyst.

This review article summarizes the latest developments in pyrrole synthesis and gives an emphasis on designing the targeted reactions more eco-friendly using green methodologies for the production of functionalised pyrrole compounds.

Use of Ball Milling Method

Mechanochemistry is the process where grinding the solid reactants increases the surface area, which helps intimate mixing and increases contact among different reactants. The grinding process generates heat, which sometimes melts the reactants and reactions can proceed in a molten state. It is also believed that mechanical energy is directly absorbed by the molecule and undergoes bond rupture to produce reactive species like radicals, which help propagate the reaction. There are a few typical methods, such as shearing, stretching and grinding, that are followed to create reactive species. Mechano-chemical reactors are used for those reactions where high energy and longer reaction times are required.

Prof. Akelis *et al.* (2016) demonstrated the synthesis of *N*-substituted pyrrole derivatives through mechano-chemical activation (ball milling). Bio sourced organic green acids such as citric acid, pyroglutamic acid, succinic acid, ascorbic acid, camphor-sulfonic acid, and oxalic acid have been used as catalysts for this transformation (Figure 6).

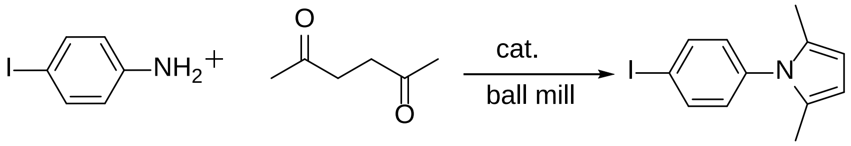


Figure 6: Paal-Knorr Pyrrole Synthesis with 4-Iodoaniline and 2,5-Hexanedione under Ball Milling

After investigating various solid organic acids as catalyst, it is found out that citric acid gives the best result. It was observed that good conversion was seen by using 1 mol (catalyst amount) citric acid at 30 Hz (frequency of ball milling) (Figure 7).

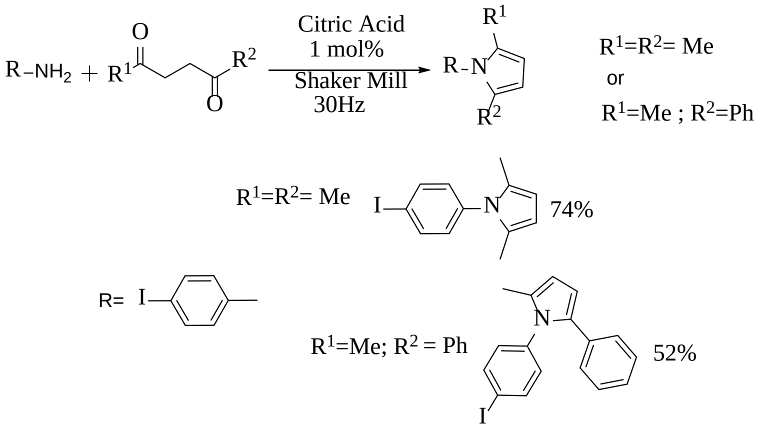


Figure 7: Citric acid Catalysed Pyrrole Synthesis in a Ball Milling

This method is efficient for preparing N-substituted pyrroles in very short times at room temperature rather than the traditional Paal-Knorr method. The main advantages of the present procedure are –(1) it is a solventless methodology (2) use of a “green” organic acid that is non-toxic and generated from biomass.

Use of Ultrasound

Sonochemistry is a branch of chemistry that deals with the effects of ultrasound on chemical reactions. Ultrasonic sound (US) acts as a non-conventional energy source. Generally, ultrasounds with frequencies 20KHz to 1 MHz are used in sonochemistry. Electromagnetic waves travel in a vacuum, but mechanical waves require an elastic medium to propagate. Ultra sound (US) can be focused, reflected or refracted in an elastic medium. It propagates in a medium like sound waves. Ultrasound also causes compression and rarefaction which create alternative zones of high pressure and low pressure. The low-pressure zones create cavities or bubbles, which suddenly collapse in the compression zone and generate a shock wave. This phenomenon of bubble or cavity formation and collapse is referred to as 'cavitation'. Direct interaction between waves and reactants to induce a chemical reaction is not possible, an indirect phenomenon known as cavitation acts as a relay to induce a chemical reaction. Sonochemical reactions are beneficial to conventional heating because of the following reasons: (1) Ultrasonic sound can conduct a reaction at an ambient temperature without warming the air in close vicinity of the reaction systems. (2) Most of the heat energy is lost to the environment. A small part of the total heat produced is utilized for the actual purpose for which it is generated. (3) It has been observed that in many cases, the use of ultrasound reduces the reaction time and temperature and increases efficiency and selectivity.

Dr. Eftekhari-Sis research group has demonstrated a novel synthesis of pyrrole *via* three component reaction of aryl glyoxal hydrates, β-di carbonyl compound and ammonium acetate in aqueous medium under ultrasonic irradiation (Eftekhari-Sis & Vahdati-Khajeh, 2013) (Figure 8).

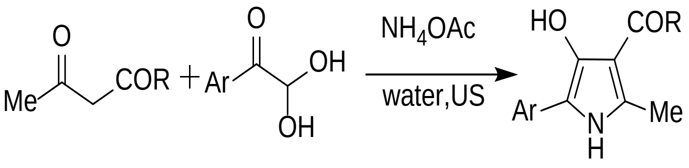


Figure 8: Ultra-sound Promoted Synthesis of Pyrroles

The main advantages of the present methodology are high yield, short reaction time, mild reaction condition. This reaction is the simplest and useful process (according to environmental and economical points) which is the most important advantage (Figure 9).

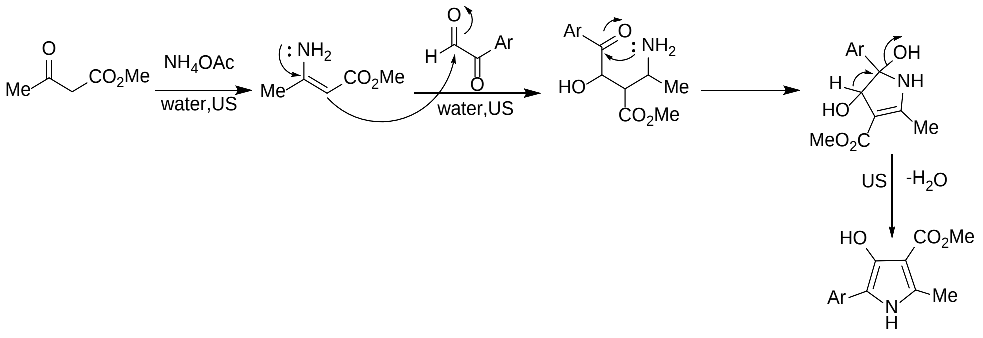


Figure 9: The Plausible Reaction Mechanism of Pyrrole Synthesis

Using Green Solvents

Solvent is the major constituent of a reaction mixture and becomes the prime source of waste mass in the synthetic process. Most organic solvents suffer from their toxicities, hazards, flammability and explosive nature. Nowadays, solvent-free reactions are promoted to overcome this problem. Still, the choice of solvent has a great role in controlling the rate, selectivity and equilibrium position of a chemical reaction. Among all the environmentally benign solvents, water is the most innocuous solvent and it has environmental and economic benefits. Sometimes, the solvent mixture, such as water and ethanol, possesses many interesting inherent properties that make it a unique reaction medium.

In a recent report, the research group of Anary-Abbasinejada disclosed the synthesis of tetrone derivatives through a three-component reaction between arylglyoxal, acetylacetone and enaminoketone. These poly-functionalized intermediates are easily converted to poly-functionalized pyrrole derivatives (Anary-Abbasinejada, Nezhad-Shshrokhabadi & Mohammadi, 2020) (Figure 10).

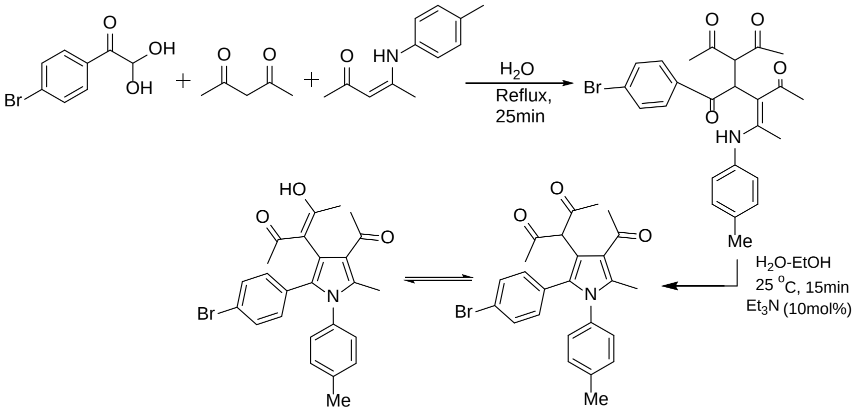


Figure 10: Synthesis of 3-acetayl-4-(4-bromobenzoyl)-5-(p-tolylamino)ethylidene)heptan-2, 6-dione

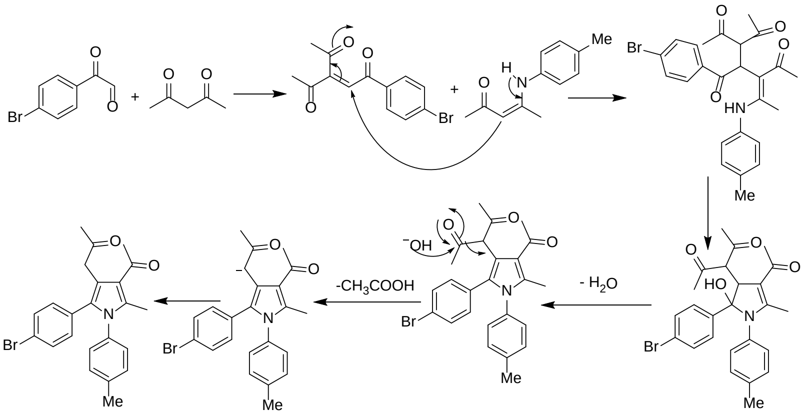


Figure 11: Proposed Mechanism for Formation of Pyrroles Derivatives

The attractive improvements of this method are the convenient workup method and the use of water or a water-ethanol mixture as an environmentally benign solvent. The authors have reported that all the desired products are easily separated and purified by a simple filtration method, followed by washing with diethyl ether. So, they have avoided the tedious chromatographic purification techniques.

Using Nano-catalyst

Prof. Yousif research group has disclosed a facile and effective methodology for the environmentally benign and speedy production of biologically active poly-substituted pyrroles through Cu@imine/Fe_3O_4 MNPs catalysed reaction under solventless conditions. This catalytic system has been proven to be excellent in terms of high reactivity for the generation of poly-substituted pyrroles in short reaction times. The reactivity of this catalyst greatly depends on the catalyst loading factor and reaction temperature. The most interesting fact is that the catalyst is recyclable and it was reused six times without significant loss of reactivity. The other advantages of this methodology are short reaction times, easy workup procedure (Thwin *et al*., 2019) (Figure 13).

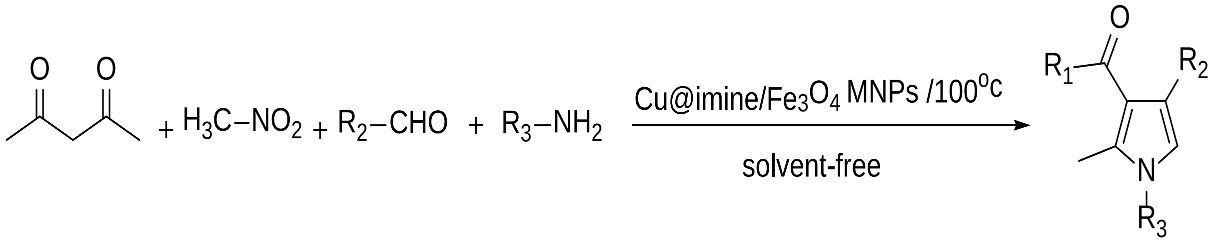


Figure 12: Preparation of Poly-substituted Pyrroles Derivative using Nano catalyst

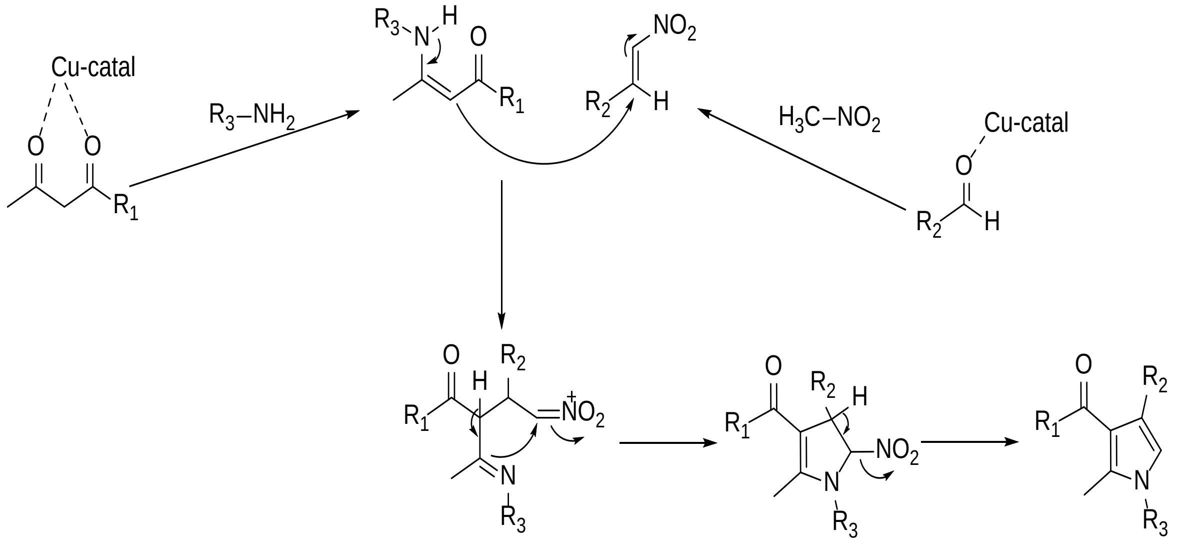


Figure 13: Plausible Mechanism for the Synthesis of Poly-substituted Pyrrole Derivative 3.5

Use of Visible Light

Prof. Wen-Jing Xiao *et al.* have reported an organic dye photocatalyst mediated synthesis of tetra substituted pyrrole derivatives through the formal [3+2] cycloaddition reaction of 2H azirines with alkynes under irradiation by visible light (Figure 14, 15). This synthetic method furnishes efficient access to highly functionalized pyrroles in good yields (Xuan *et al*., 2014).

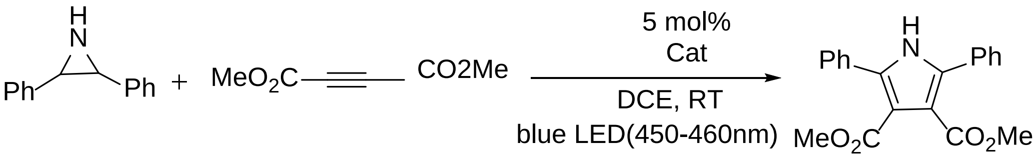


Figure 14: Preparation of Pyrroles Derivative using Visible Light

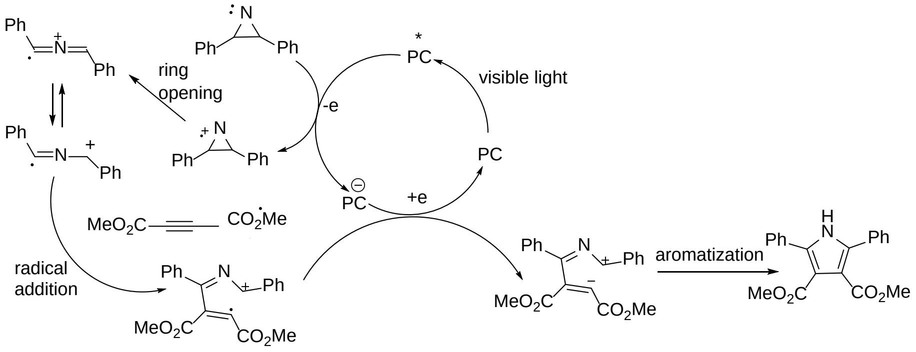


Figure 15: Plausible Reaction Mechanism of Pyrroles Derivative using Photocatalyst

Use of Green Catalyst

A green method for the synthesis of poly-substituted pyrroles in good yield has been achieved very recently (Louroubi *et al.,* 2021). It is a four component reaction of 1,3-dicarbonyl compound, amines, aldehydes, and nitro-alkanes (Figure 16). The natural **hydroxyapatite (HAP**) has been used as an efficient green catalyst in a *one-pot* methodology (Figure 17).

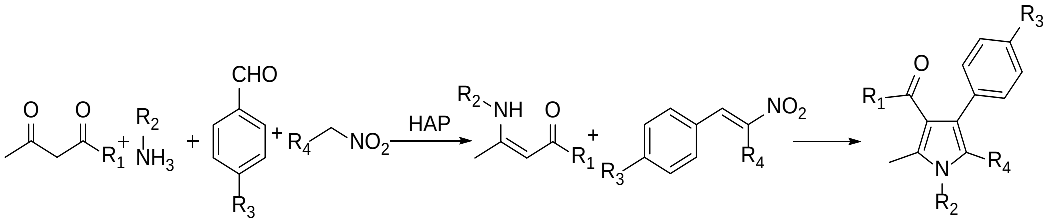


Figure 16: Synthesis of Pyrrole Using Green Catalyst

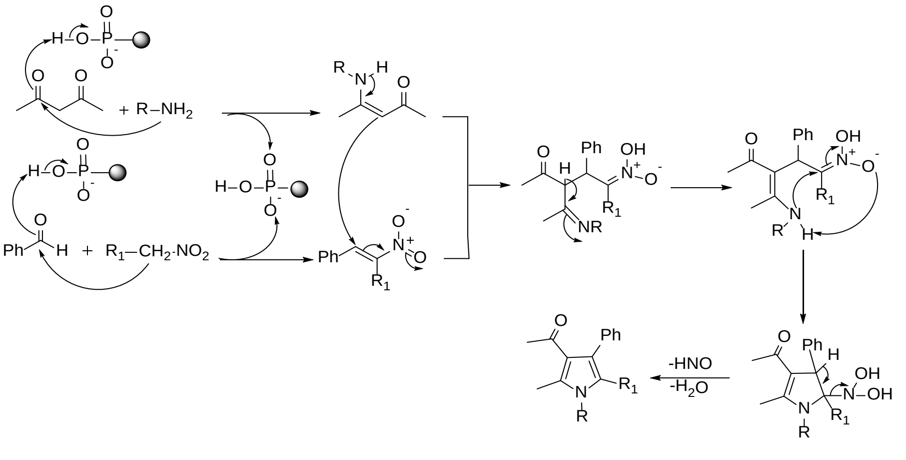


Figure 17: Plausible Mechanism for the Formation of Pyrrole Derivative

The above developed method is an environment friendly, operationally simple, cost-effective and efficient pathway for the synthesis of pyrroles derivative through the four component domino reaction strategy in *one-pot*. This green protocol leads to the generation of densely functionalized pyrroles. The most interesting benefit of this methodology is the use of hydroxyapatite as a cost-effective, natural and safe catalyst.

Use of Microwave

Microwave (MW) is an electromagnetic radiation with wave length ranging from 1mm to 1m. The frequencies and energies of the microwave region are 300 GHz to 300 MHz and 1.24×10^{-3} to 1.24×10^{-6} Ev respectively. In the electromagnetic spectrum, the microwave region is placed between the infrared and radio wave frequencies. Microwave radiation is not as energetic, so it cannot ionize an atom or molecule or break a chemical bond to initiate a chemical transformation. But surprisingly, MW-irradiated chemical reactions are often faster than those operated by conventional heating. Microwave radiations have been used as a non-conventional energy source in the field of synthetic organic chemistry for the following reasons- (a) reaction time is dramatically shortened compared to classical procedure, (b) reaction efficiency is increased, (c) improved yield with less side product, (d) sometimes organic solvents can be replaced by innocuous solvent water, (e) solvent-free reactions can be performed, (f) reactions under MW-irradiations are cleaner with easy workup. Originally, domestic MW ovens were used to carry out organic reactions in an open pot or in a sealed tube, but later MW reactors were modified to carry out reactions in solution under refluxing conditions. Now, microwave reactors are available to carry out a reaction at a particular pressure or temperature in the presence or absence of a solvent.

Microwave assisted Paal-Knorr reactions have been demonstrated by Prof Taddei Research Group (Minetto *et al.,* 2005). They were successful in reacting various well accessible β-keto esters with Et_2Zn/CH_2Cl_2 and aldehydes. The resultant reaction mixture on subsequent oxidation with pyridinium chlorochromate (PCC) furnishes poly-substituted 1,4-dicarbonyl compounds in two steps. In the final step, the authors have demonstrated that microwave irradiation is an excellent energy source for Paal-Knorr cyclisation to afford the pyrroles in good yield (Figure 18).

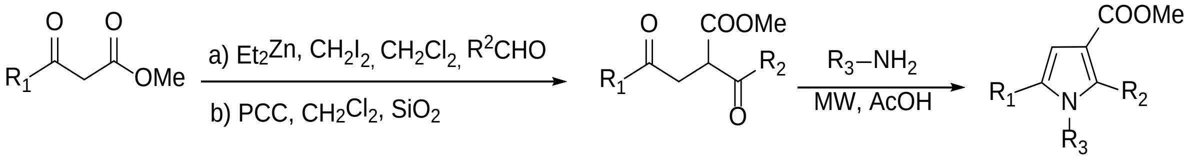


Figure 18: Microwave-assisted Synthesis of Pyrroles

In this transformation, the optimized result was obtained, when the reaction mixture was placed in an open vessel at 120-150ºC only for 2-10 min under MW.

Conclusion

One of the main targets of Green Chemistry is to wisely eliminate the production of hazardous or harmful materials or replace them with less harmful and safer ones. Pyrroles derivatives are important materials due to their diverse biological activities and huge demand in the pharmaceutical industry. So, the application of Green Chemistry principles in the synthesis of these heterocyclic compounds involves multiple economic and social developments. That is why the chemists have developed newer and novel methodologies of green activation, such as microwaves, ultrasound, and continuous flow processes at room temperature, which have resulted in cost and waste reduction and greater efficiency for the production of pyrrole derivatives. In the present review article, the green synthetic techniques that have been used to synthesize pyrrole derivatives in recent years have been documented. The future direction of this study should result in many newer Green protocols for the synthesis of functionalized pyrroles and related heterocycles such as furans and thiophenes in a cost effective way to meet industrial demand.

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