2024 تشرين2 العدد 15
No.15 Nov 2024
المجلة العراقية للبحوث الإنسانية والإجتماعية والعلمية
Iraqi Journal of Humanitarian, Social and Scientific Research
Print ISSN 2710-0952 Electronic ISSN 2790-1254

The Most Important Recent Achievements in Organic Chemistry in the Preparation, Properties, and Applications of Pyrrole Chemistry

Nagham Mohammed Atiyah
Thi-Qar Education Directorate, Thi-Qar, Iraq
naghammohammed3478@gmail.com

ABSTRACT:

Industrial activities have had significant detrimental impacts on both the environment and human health, driving chemists to explore innovative strategies for minimizing the negative effects of chemical reactions and limiting the release of harmful by-products. This article provides an overview of the methods for synthesizing pyrrole compounds, which are crucial acyclic compounds in organic chemistry. Pyrrole derivatives hold a prominent place in medicinal chemistry and are essential for synthesizing various organic compounds, playing key roles in biological systems.Numerous methods have been developed for the synthesis of pyrroles, with the Powell-Nour method, which utilizes a range of catalysts, being the most widely used. Recently, there has been increased attention on the development of pyrrole-based biomolecules and pyrrole-containing polymers. Research has focused on refining and optimizing the preparation of pyrroles, aiming to achieve efficient, sustainable methods, a challenge that has intrigued scientists for over a century.

Keywords: Organic chemistry, pyrrole preparation, pyrrole derivatives, medicinal chemistry, biological systems, Powell-Nour method, sustainable strategies.

أهم الإنجازات الحديثة في الكيمياء العضوية في تحضير، خصائص، وتطبيقات كيمياء البيرول

نغم محمد عطية
مديرية تربية ذي قار، ذي قار، العراق.
naghammohammed3478@gmail.com

الملخص:

لقد أثرت الأنشطة الصناعية بشكل كبير وسلبي على كل من البيئة وصحة الإنسان، مما دفع الكيميائيين لاستكشاف استراتيجيات مبتكرة لتقليل التأثيرات السلبية للتفاعلات الكيميائية والحد من إطلاق المنتجات الجانبية الضارة. يقدم هذا المقال لمحة عامة عن طرق تحضير مركبات البيرول، التي تعتبر مركبات حلقية غير متجانسة هامة في الكيمياء العضوية. تحظى مشتقات البيرول بمكانة بارزة في الكيمياء الطبية وتعد أساسية في تخليق العديد من المركبات العضوية، حيث تلعب أدوارًا رئيسية في الأنظمة البيولوجية. تم تطوير العديد من الطرق لتحضير البيرولات، ومن أكثرها استخدامًا طريقة باول-نور التي تعتمد على مجموعة متنوعة من المحفزات. مؤخرًا، تم توجيه اهتمام متزايد نحو تطوير الجزيئات البيولوجية القائمة على البيرول والبوليمرات التي تحتوي على البيرول. وتركزت الأبحاث على تحسين طرق تحضير البيرولات بهدف تحقيق طرق فعالة ومستدامة، وهو تحدٍ شغل العلماء لأكثر من قرن.

الكلمات المفتاحية: الكيمياء العضوية، تحضير البيرول، مشتقات البيرول، الكيمياء الطبية، الأنظمة البيولوجية، طريقة باول-نور، استراتيجيات مستدامة.

Introduction

With the emergence of green chemistry and the increasing focus on environmental issues in chemical science, significant efforts have been made to reduce hazardous and polluting factors. These efforts have led to the development of new methods for preparing various chemical compounds. One of the key achievements within the green chemistry movement has been the advancement of multicomponent reactions. These reactions have gained significant attention due to their efficiency and sustainability. Some of the notable examples of these multicomponent reactions include. The preparation of 4-aryl-6-phenyl-3-proline [1].The synthesis of 4,3-L cyano-2-pyridone using 1)-one and thione in a glycerin-based environment for dihydropyridine-2 [2].The preparation of 8,1-dioxodecahydroacridine in a glycerin medium [3].The synthesis of 2-amino-10,5-dioxo-4-aryl-105 chromene-3-carbonitrile and benzo-H-10,5-dihydro-4-proline [4].The preparation of L-imidazoles [5].The preparation of Bmim-tetrasubstituted HSO_4 using Fe_3O_4 imidazoles [6].The use of ferric perchlorate for the preparation of 4,3,2,1 NPs@GO@$C_4H_8SO_3H$ tetrahydro-2-pyridinone and thiones [7].In addition, solvent-free reactions have also gained prominence. These include.The preparation of 3,1-oxazine [3] and 2,1-dihydro-1-arylnaphtho[2,1-8].The synthesis of 13-aryl-pyran-12 using iron phosphate [3] and pyran-12 [9].The preparation of benzimidazoles using $Fe(ClO_4)_3/SiO_2$ [10].The substitution of $Fe(ClO_4)_3/SiO_2$ for the acetylation of amines and thiols without additives [11]. Furthermore, heterogeneous catalysts have been applied in several other reactions, such as. The preparation of alpha-aminonitriles using H_2SO_4/silicagels with Fe/CeO_2-ZrO_2 [12].The synthesis of benzimidazoles using $Fe(ClO_4)_3/SiO_2$ nanoparticles and chromium-based compounds [13,14].

2-Pyrrol and its properties

The name pyrrole is derived from the Greek word for the color red, as pine wood shavings turn bright red when exposed to hydrochloric acid (HCl) containing pyrrole. Simple pyrroles and alkyl pyrroles are colorless liquids with a slightly unpleasant odor, similar to aniline, and they darken over time due to auto-oxidation. Pyrrole can be easily produced commercially through the reaction of furan with ammonia in the gas phase, in the presence of an alumina catalyst. Pyrrole was first isolated from coal tar in 1834 and later from bone breakdown products in 1857 [16].These five-membered ring compounds are planar, with a molecular mass of 78 g/mol. Their orbitals are similar to those of double-bonded

benzene, with the major atomic orbitals overlapping to form π donut-shaped molecular orbitals above and below the ring structure. The resonance stability value of pyrrole is measured at 31 kcal/mol. Pyrrole is more acidic than benzene and shows similarities to phenolic-type resonating benzenoid systems. However, pyrrole salts formed by reacting with strong acids are unstable.The deficiency of pyrrole lies in the partial positive charge on the nitrogen atom, which reduces its tendency to accept a proton. When pyrrole interacts with very strong acids, it forms salts, but the unshared electron pair on nitrogen is not free to move to other positions on the ring, resulting in the loss of the compound's aromaticity.Pyrrole's high reactivity in acidic solutions is comparable to that of dienes. Several resonance structures of pyrrole have been proposed by Pauling, Sherman, and Ingold (Figure 1).

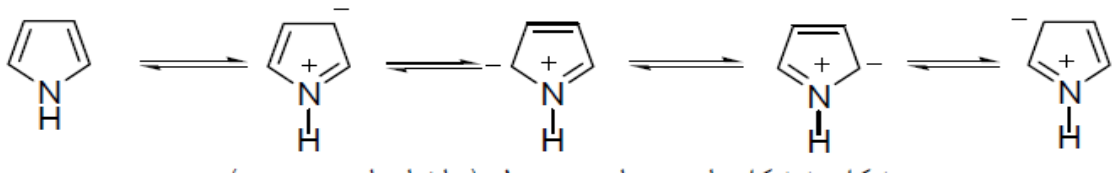

Figure 1. Resonance shapes of pyrrole (marble structures)

Applications of pyrrole derivatives

Pyrrole derivatives have found extensive use in pharmaceutical development due to their wide range of biological activities. They have been employed as antibacterial agents [17], antitumor agents [18], antioxidants [19], and anti-inflammatory compounds [20]. Pyrrole and many of its derivatives, particularly methylated pyrroles, are present in natural structures such as bitumen and bone fat. The biological importance of pyrrole is further highlighted by its presence in natural pigments like hemoglobin, vitamin B12, yellow bile pigments, and enzymes such as cytochromes, all of which contain a pyrrole core. Several alkaloids and at least two amino acids, proline and hydroxyproline, also contain a pyrrole ring. Natural molecules containing pyrrole have medicinal value, while synthetic pyrrole derivatives possess unique photochemical properties. For instance, Lamellarin D (Figure 2) [21], a pyrrole derivative, has shown strong cytotoxicity against tumor cells and acts as a potent topoisomerase inhibitor. Similarly, Ningalin B has been identified as a P-glycoprotein inhibitor, which helps to overcome drug resistance in cancer cells.

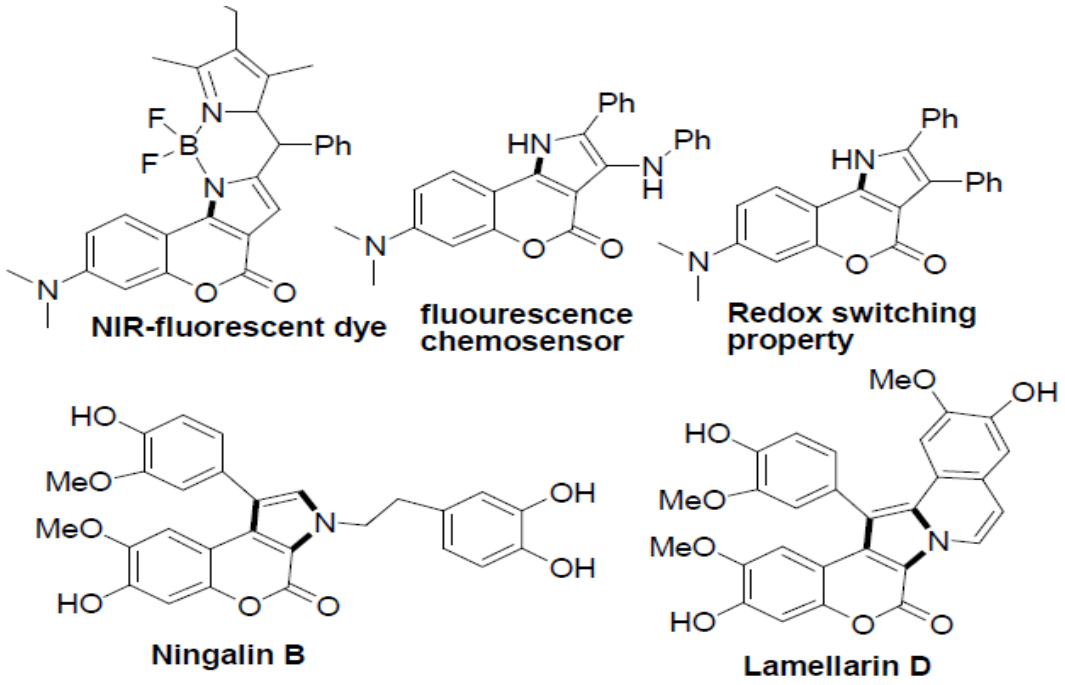

Figure 2. Natural and prepared pyrrole derivatives

Pyrrole structures are also found in other natural substances, such as hematoporphyrin, and in synthetic drugs like tolmetin, atorvastatin, and dictopyrrolopyrrole [22-24]. For example, Figure 4 illustrates several medicinal compounds containing pyrrole, where compound 1 acts as an antitumor agent, compound 2 is a potent potassium channel inhibitor, and compound 3 is a cholesterol-lowering drug [25]. Pyrrole derivatives also form the core skeleton of many natural substances, including chlorophyll (Figure 5) [26].

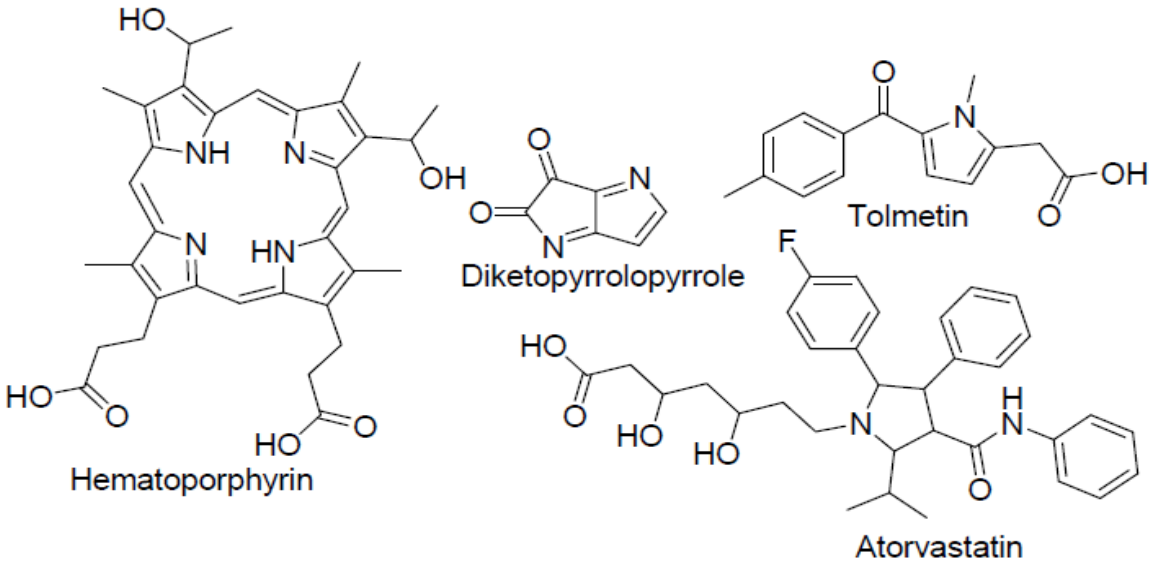

Figure 3. Structure of natural materials and unnatural structures containing pyrrole

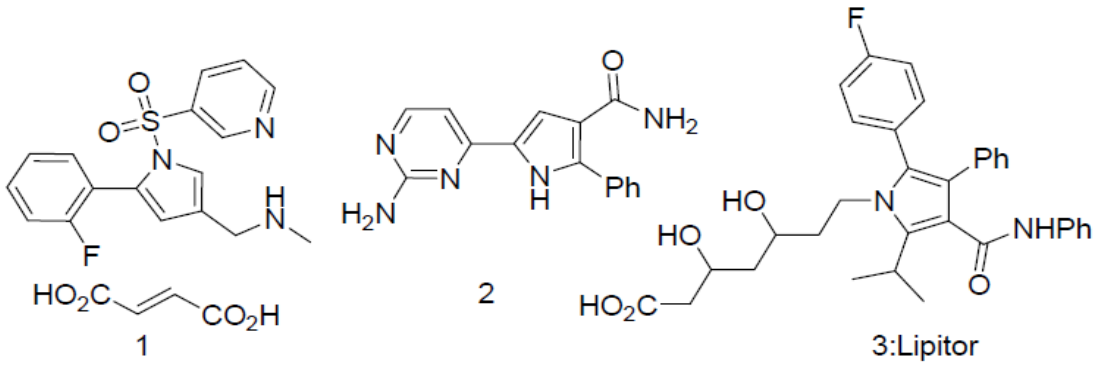

Figure 4. Pharmaceutical compounds containing pyrrole

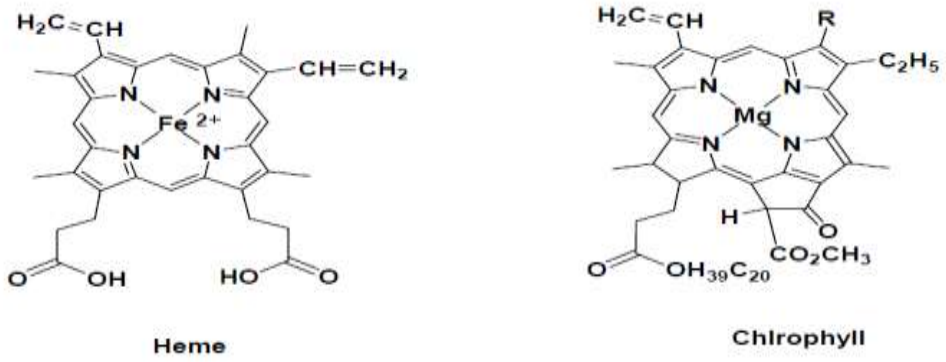

Figure 5. The structure of chlorophyll and heme

Several important pyrrole derivatives, such as pyrolonitrin, pyrrolomycins B and A, and antibacterial pylotovins, have undergone structural modifications to enhance their antifungal properties. For instance, efforts have been made to improve the antifungal strength of parent antibiotics (Figure 6). Additionally, a new series of 2-acetyl-3-cyano-4-phenylpyrrole derivatives containing sulfathiazole or sulfapyridine rings were developed and tested for cytotoxic activity in liver and breast cancer cells. These pyrrole derivatives showed significant medicinal activity, surpassing the effectiveness of the reference drug, doxorubicin. Some were identified as tyrosine kinase inhibitors (Figure 7) [27]. Various diarylpyrrole derivatives have also been evaluated for their antibacterial activity through in vitro and in vivo tests. One of the most effective compounds identified was a dimethylamine derivative that acted as a major inhibitor of Eimeria tenella. Further studies on these derivatives revealed stronger ω-inhibitors in comparison to their alkyl analogs (Figure 8) [28].

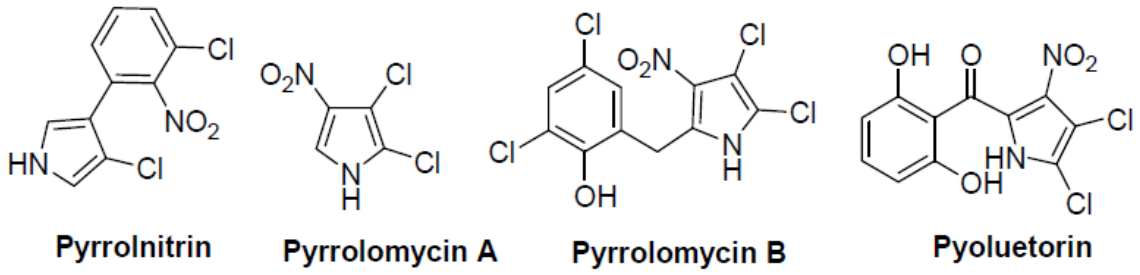

Figure 6. Different types of pyro derivatives with anti-bacterial and anti-fungal properties

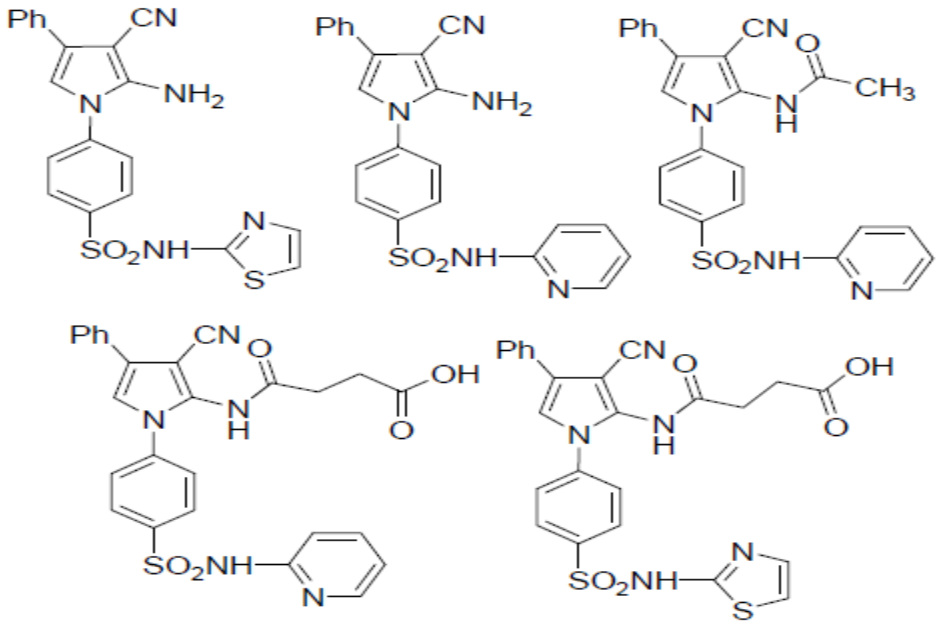

Fig. 7. Pyroantibody derivatives of liver and breast cancer cells

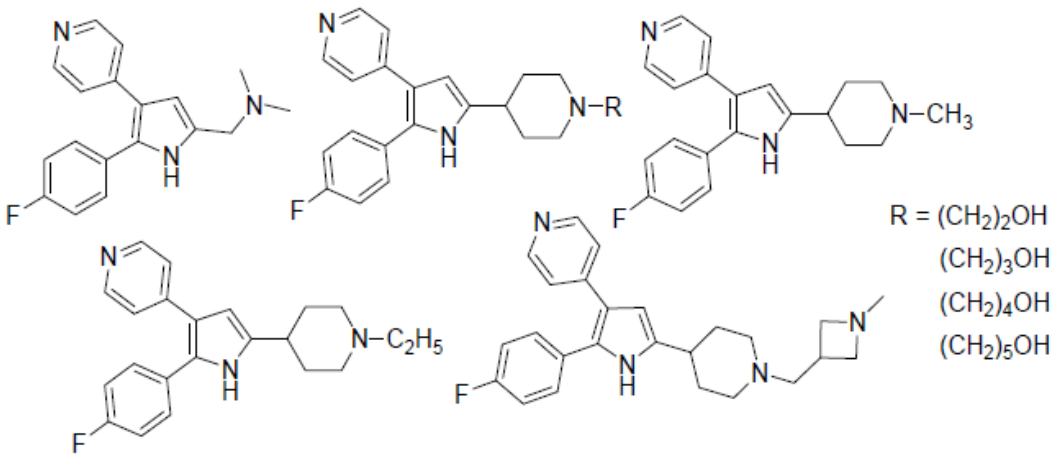

Figure 8. Pyro derivatives with antibacterial properties

3-Preparation methods of pyrrole and N-substituted pyrrole derivatives

One of the simplest methods for synthesizing pyrrole involves the use of furan, a process that was first reported by Harios in 2000 in the "Encyclopedia of Industrial Chemistry." In this method, pyrrole is synthesized through a substitution reaction between furan and ammonia in the gas phase, utilizing an alumina catalyst to facilitate the reaction (Figure 9).

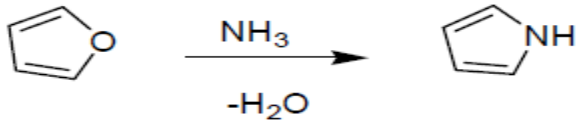

Figure 9. Preparation of pyrrole from furan

3-2 Preparation method of polysubstituted pyrroles

The preparation of polysubstituted pyrroles can be accomplished using several methods. Below are some notable techniques. The Hanes method is a widely recognized approach for the preparation of polysubstituted pyrroles. This method was reported by Stouz and his colleagues in 2013, as well as by Wang, Park, and Matichuk in their studies conducted in 2005 and 2004 [29-33] (Figure 10).

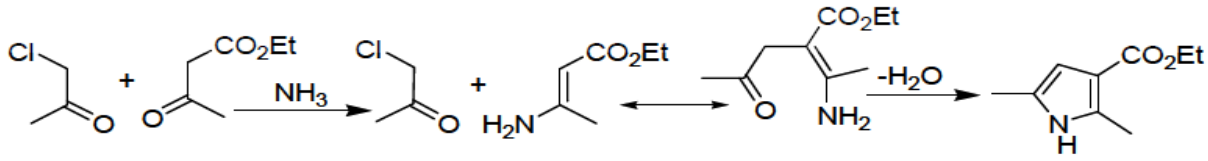

Figure 10. Preparation of pyrrole by Hanes method

The Piloti-Ribinson reaction is another effective method for synthesizing pyrrole derivatives. It involves using two equivalents of aldehyde and hydrazine in the presence of benzoyl chloride. This method was reported by Milgram and his colleagues in 2007 [34] (Figure 11).

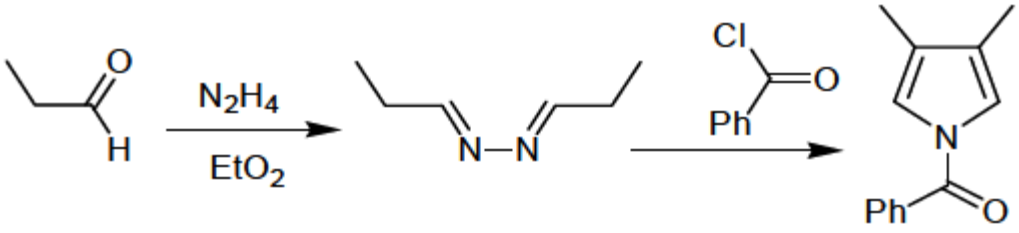

Figure 11. Preparation of pyrrole with aldehyde and hydrazine

The Clazon-Kas method, introduced by Clazon-Kas Division, employs a new catalytic N-substitution approach for preparing pyrrole derivatives. This method utilizes an acid solution of 1-hexyl-3-methylimidazolium and microwave irradiation (Hmim H_2SO_4) [35]. It is effective for creating acid-sensitive multistructures without producing acid-side products (Figure 12).

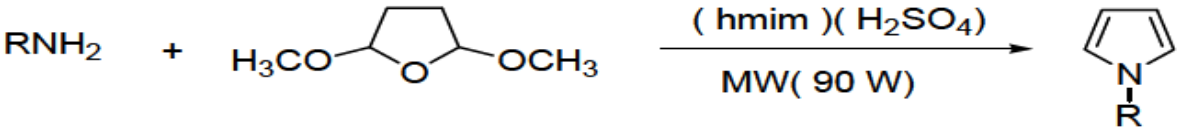

Figure 12. Clason-Kass reaction

In another reaction, N-assisted substitution allows for the preparation of pyrrole derivatives using type 1 amines and 5,2-dialkyltetrahydrofuran under microwave conditions. This process is conducted for 10 to 30 minutes under reflux conditions in acetic acid or water without adding a catalyst [37-36] (Figure 13).

Figure 13. Preparation of pyrroles with the help of first-type amines and 5,2-dimethoxytetrahydrofuran

The domino preparation method, introduced by Lee and his colleagues, involves the reaction between 2,2-dihydroxy-1-arylethanone and aromatic enamines. This reaction is carried out in the presence of Bronsted acid, using ethanol as a solvent and toluene sulfonic acid as a catalyst. This method selectively forms pyrrole derivatives with phenylhydrazine and acetylene dicarboxylate by controlling the mechanisms involved in producing pyrrole and pyrazole (Figure 14).

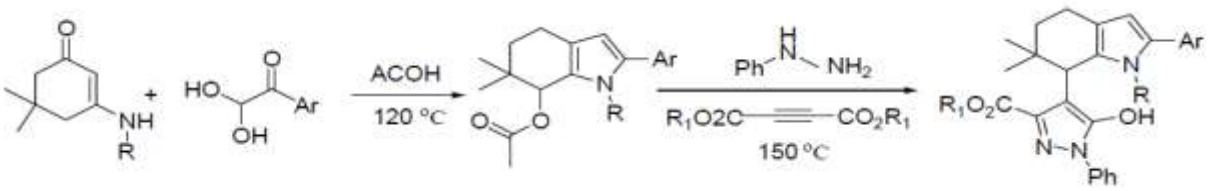

Figure 14. Preparation of domino derivatives of polysubstituted pyrrole

An easy preparation of pyrrole derivatives can be achieved through a mononuclear reaction of (E)-4,1-diaryl-2-butene-4,1-dione with methylammonium acetate salt in the presence of a palladium catalyst on carbon, based on the Powell-Noor method (Figure 15) [38].

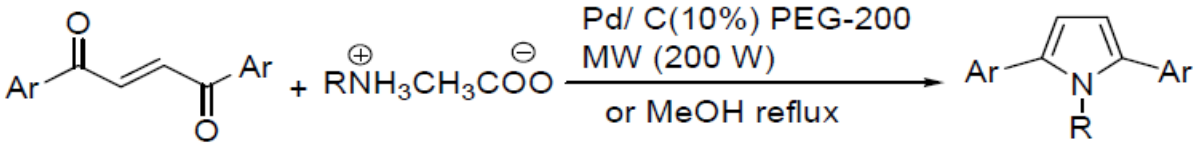

Figure 15. Preparation of pyrrole derivatives in the presence of palladium catalyst

Pyrrole derivatives are also prepared from the reaction between 2-butene-1,4-diyl and amines at 150°C in dioxane, using primary aliphatic catalysts and a ruthenium complex [39] (Figure 16).

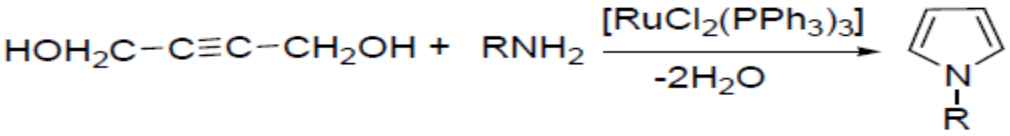

Figure 16. Preparation of pyrrole derivatives from 2-butene, 4,1-diyl and amines

The reaction of oxime with tosylaminoethylglyoxylate at 90°C for 16 hours, assisted by complex C catalyst, leads to the formation of dichloroethane, rhodium, and pyrrole [40] (Figure 17).

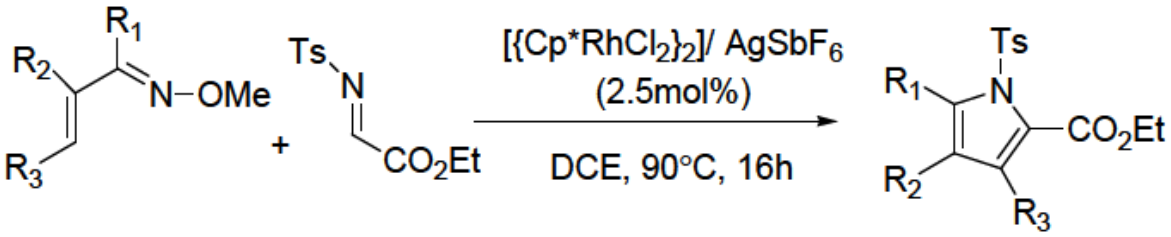

Figure 17. Generation of pyrrole by CMC Catalyst Rodim as a derivative of high acetylene with acetamidoacrylate in the blood of 70 BCMC Catalyst Complex Rodim Composition at °C (Figure 18).

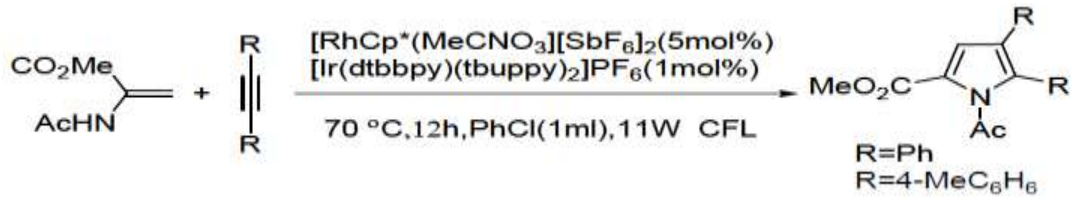

Figure 18. Preparation of pyrrole in the presence of rhodium catalyst

The reaction of aniline derivatives with diarylalkynes in the presence of copper and palladium catalysts leads to the formation of pyrroles (II) [41- 42]. In the research conducted by Stewart and his colleagues in 2010, a complex catalyst was introduced to facilitate the reaction with enamides and cationic rhodium compounds (Figure 19).

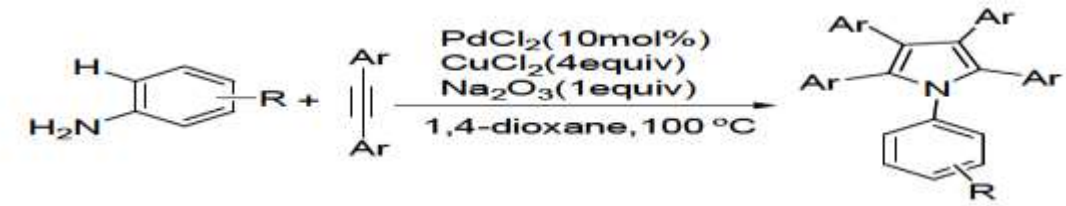

Figure 19. Preparation of pyrrole compounds in the presence of palladium and copper catalyst

Different alkyne polysubstituted pyrroles were prepared, with the reaction carried out in a controlled oxygen atmosphere (Figure 20) using copper enamino ester-β [43].

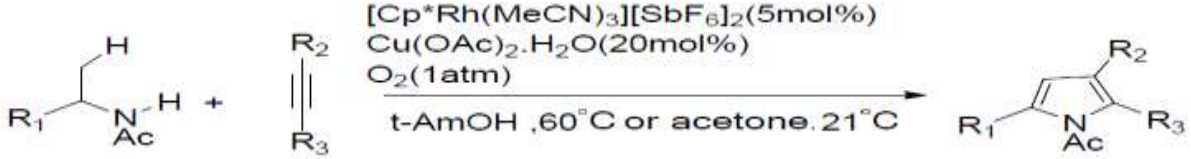

Figure 20. Preparation of pyrrole from enamides and alkynes

In another method, pyrrole was synthesized from the reaction of sulfonium ylide in the presence of an iridium catalyst, conducted in toluene under microwave conditions (Figure 21).

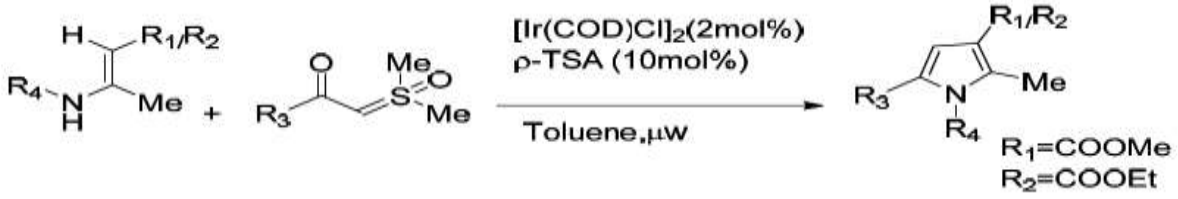

Figure 21. Preparation of pyrrole in the presence of iridium catalyst

Additionally, pyrrole derivatives can be prepared from the reaction of 2-amino-1-butanol with secondary alcohols in the presence of a ruthenium complex catalyst under reflux conditions in a toluene solvent (Figure 22). The mechanism of this reaction is depicted in Figure 23. Initially, the alcohol is oxidized to a ketone, which then reacts with the ethanol amine derivative. This reaction increases the nucleophilicity toward the ketone, leading to the formation of an imine intermediate. Subsequently, in the presence of potassium tert-butoxide, the acidic proton of the imine is removed, allowing the generated anion to intramolecularly attack the aldehyde, resulting in ring closure. After the removal of a water molecule, the desired pyrrole compound is obtained. The four-component reaction involving aldehyde derivatives, aniline, nitromethane, and acetoacetate in the presence of a copper complex catalyst also leads to the formation of tetrasubstituted pyrrole derivatives, accompanied by the production of magnetic iron nanoparticles, Fe_3O_4 (Figure 24).

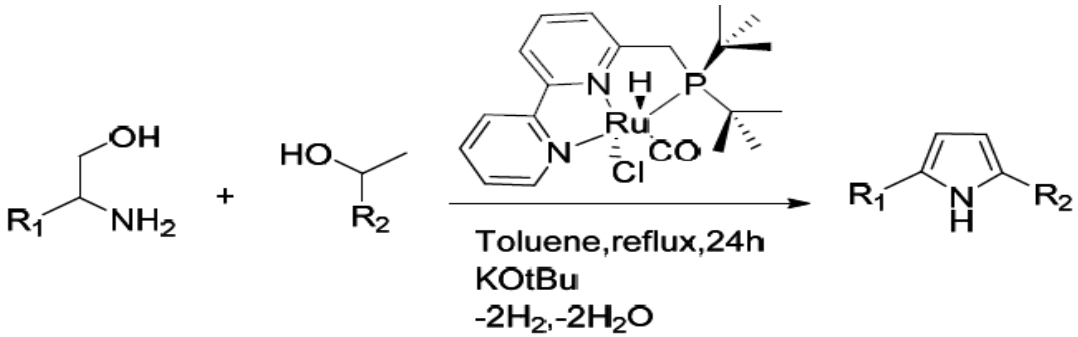

Figure 22. Preparation of pyrrole in the presence of ruthenium complex catalyst

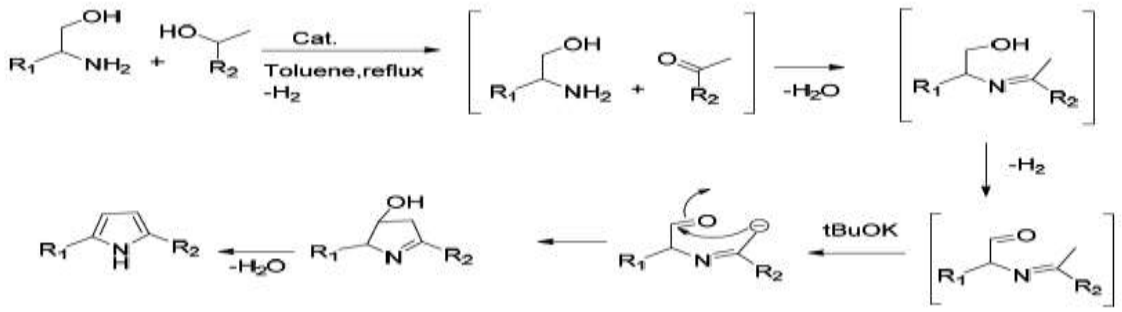

Figure 23. The mechanism of pyrrole preparation in the presence of ruthenium complex catalyst

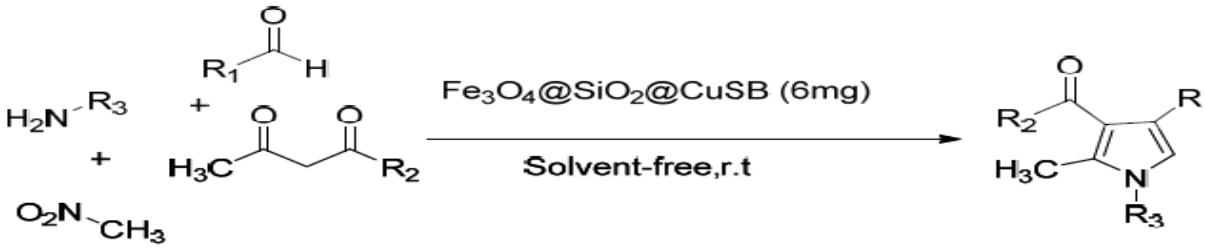

Figure 24. Preparation of four-component pyrrole derivatives using nanocatalyst 4

The following methods are employed for the preparation of pyrrole derivatives:

The reaction of 5,2-hexanedione with type 1 amines in the presence of a zirconium catalyst under solvent-free conditions leads to the formation of pyrrole derivatives. The highest reaction efficiency was reported to be achieved within 40 to 50 minutes (Figure 25).

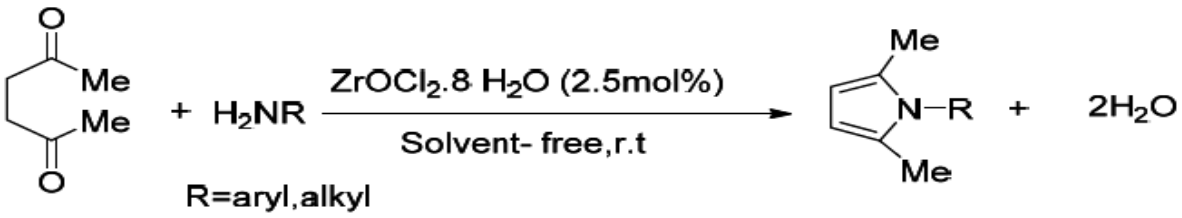

Figure 25. Preparation of pyrroles with the help of zirconium catalyst

3-pyrrolines can be synthesized through an allenylation reaction, facilitated by a catalyst. In this method, the presence of [Cu(IPr)Cl] and 3,2-dichloro-6,5-dicyano-4,1-benzoquinone converts the 3-pyrrolines into pyrrole (Figure 26).

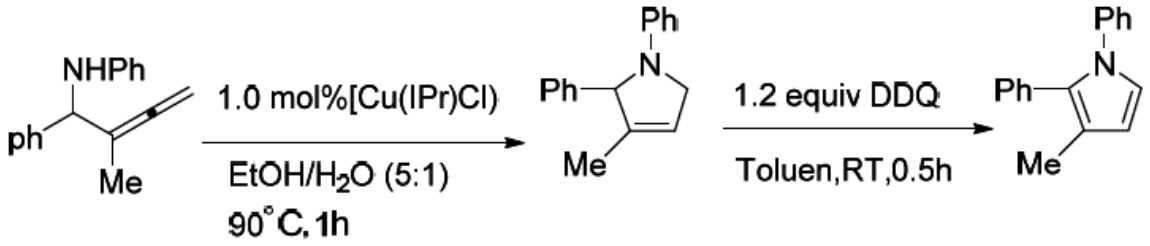

Figure 26. Preparation of pyrrole with the help of copper catalyst

The reaction of 3,1-diketones with aldehydes and amines in the presence of a titanium chloride catalyst has been used for the preparation of polyesterified pyrroles. The best reaction efficiency reported ranges from 75% to 98% (Figure 27).

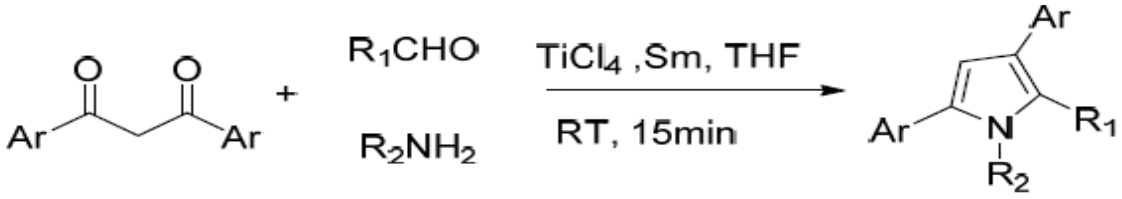

Figure 27. Preparation of pyrrole with the help of titanium chloride catalyst

In another study, the preparation of 5,4,3,2-substituted and PPh derivatives of pyrroles with oximes and alkynes was reported. Initially, vinyl DABCO oximes are prepared, which are then transformed into tetrasubstituted pyrrole derivatives during the cyclization reaction (Figure 28).

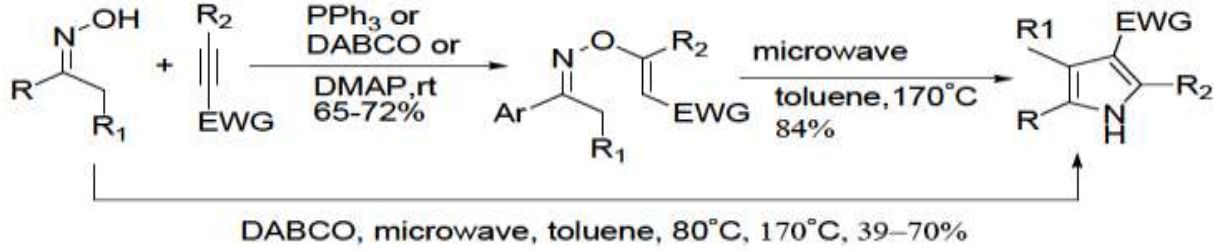

Figure 28. Preparation of pyrrole with the help of DABCO and PPh catalyst

Pyrrole derivatives can also be obtained from the reaction between an amine and 2-phenylacetaldehyde. This reaction is conducted under conditions of intense vibration at 60 Hz, with a rotation speed of 1800 revolutions per minute, without the presence of Mn(OAc). The products are achieved with high efficiency within 3 minutes in the presence of a solvent oxidant (Figure 29).

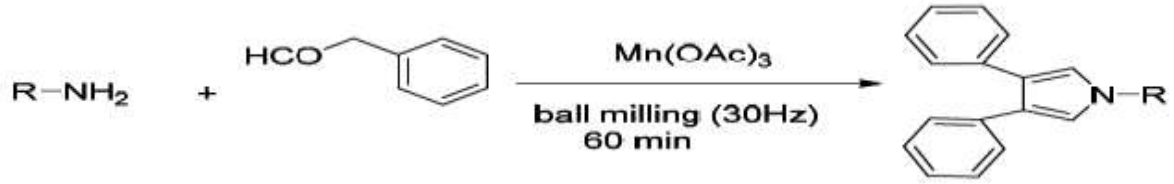

Figure 29. Preparation of pyrrole with the help of Mn(OAc) oxidant

The direct preparation of pyrroles from the reaction between aromatic and aliphatic type 1 amines can be performed without the presence of a solvent under microwave irradiation. This method demonstrates very good efficiency and can be completed in a short period of time (Figure 52). Additionally, pyrroles can be prepared from the reaction of 4,1-diketones with amines under microwave conditions without solvent in just 2 minutes (Figure 31).

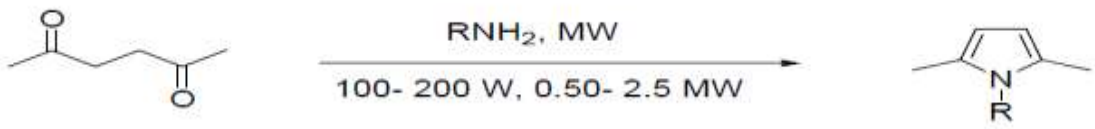

Figure 30. Preparation of pyrrole by Robinson's method

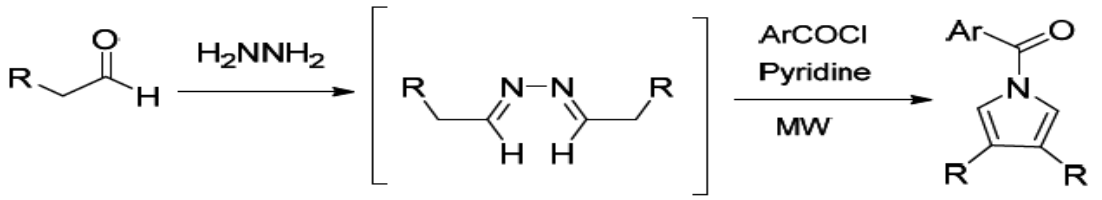

Figure 31. Piloti-Robinson preparation

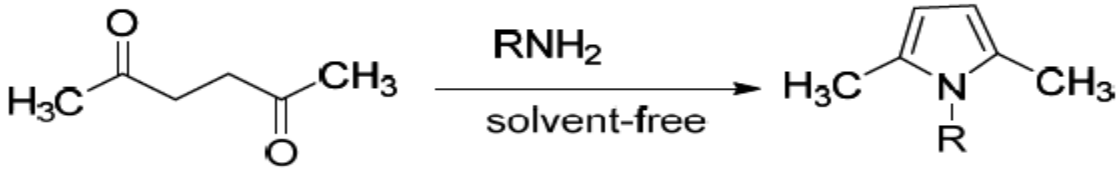

Figure 32. Preparation of pyrrole using 4,1-diketones

Aryl pyrroles are synthesized from the reaction between N-amines and aromatic derivatives, along with 5,2-dimethoxy tetrahydrofuran, in the presence of a polystyrene sulfonate catalyst. This reaction is carried out using water and ethanol solvents under microwave irradiation, achieving high efficiency (Figure 33).

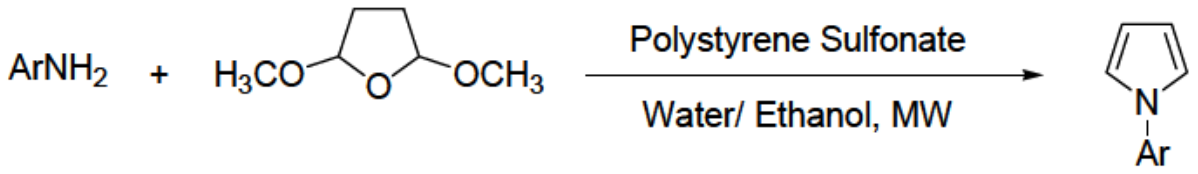

Figure 33. Preparation of pyrrole in the presence of polystyrene sulfonate catalyst

A TosMIC system can be prepared from the reaction of benzylbutenoate with Michael adducts of pyrrole compounds. This reaction occurs in the presence of sodium hydride and diethyl ether, as well as dimethylsulfoxide solvents at ambient temperature (Figure 34).

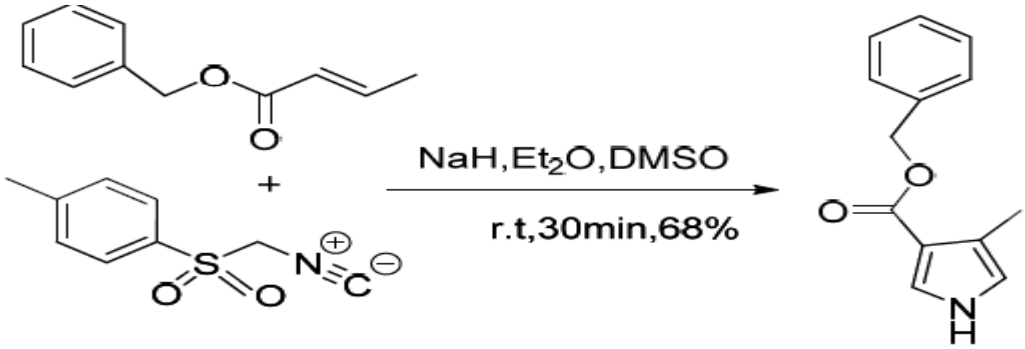

Figure 34. Using para-toluenesulfonylmethylisocyanide in the preparation of pyrrole derivatives (TosMIC)

A three-component reaction involving first-type amines and terminal acetylenes with 2,2-dihydroxyindene-3,1-dione is conducted as a nucleophilic substitution reaction. This reaction is performed under solvent-free conditions and exhibits high efficiency (Figure 35).

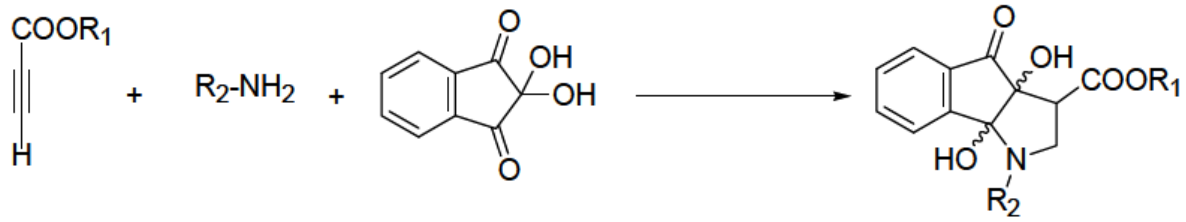

Figure 35. Three-component reactions in the preparation of reduced pyrroles

Pyrroles can also be synthesized from a three-component reaction utilizing sulfonium keto ester in β-enamine ester, which is produced from an amine and β-ylide, in the presence of an iridium complex catalyst (Figure 36).

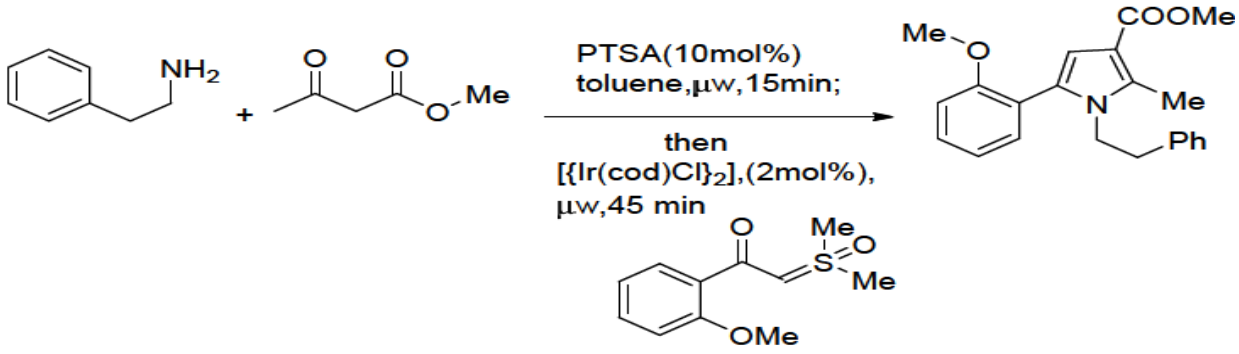

Figure 36 Preparation of pyrroles using iridium complex catalyst

The three-component reaction of 2,1-diphenylethanone, 2-phenyamine, and ethylene glycol, conducted in the presence of a complex catalyst at 130°C for 16 hours, leads to the formation of pyrrole derivatives. This method uses ruthenium and tert-amyl alcohol at the specified temperature (Figure 37). The reaction involving aryl and alkyl ketones and amines in the presence of the ruthenium catalyst also produces pyrrole derivatives (Figure 38).

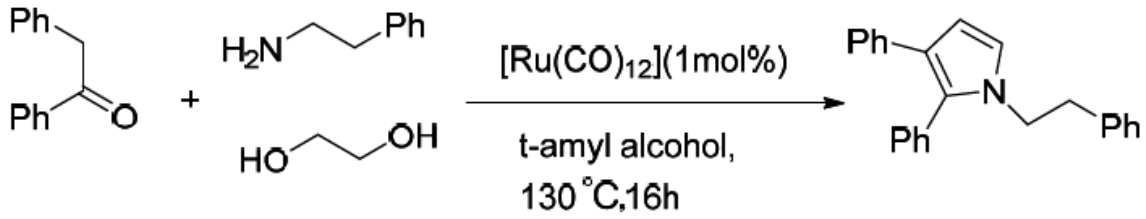

Figure 37: Preparation of pyrrole in a three-component reaction with the help of a ruthenium monoxide catalyst.

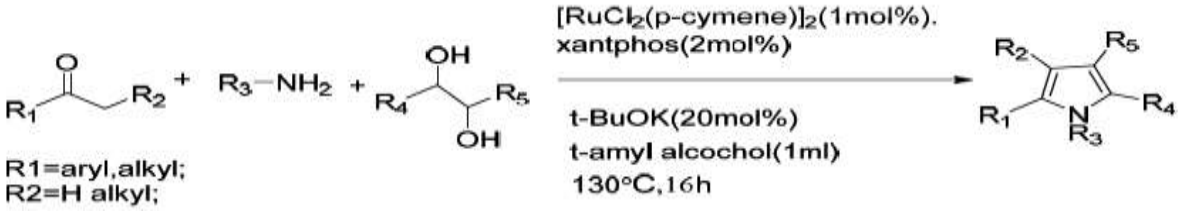

Figure 38. Preparation of pyrrole with aryl and alkyl ketones

Nitro compounds can be converted to amines in the presence of In/HCl. For instance, in the reaction with dialkyl acetylene dicarboxylate and phenacyl

bromide, an intermediate is formed, which subsequently undergoes cyclization to produce aromatic pyrrole (Figure 39).

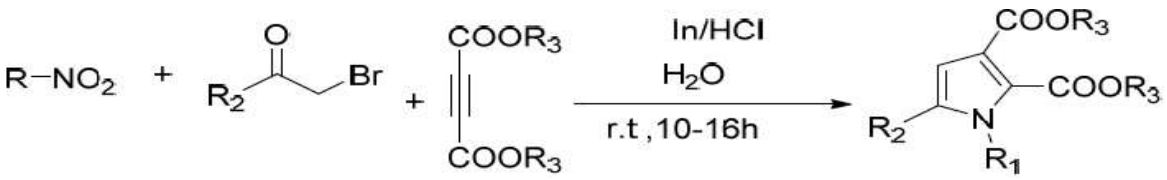

Figure 39. Preparation of three components of pyrrole using indium.

A rapid catalytic reaction for the preparation of pyrroles from cyanopyrrolines is conducted in dichloromethane solvent under microwave irradiation at 180 mW for 30 minutes (Figure 40). This method results in the formation of pyrrole derivatives, with the reaction mechanism following the neorearrangement pathway (Aza-Claisen) (Figure 41).

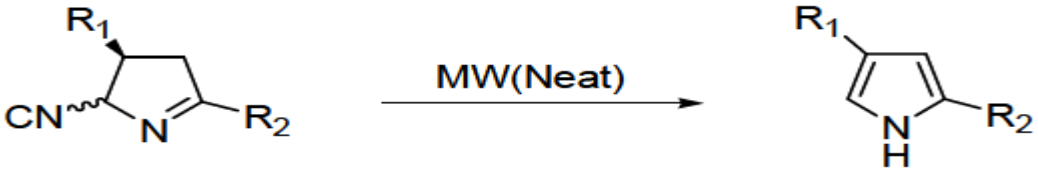

Figure 40 Using microwave radiation to prepare pyrroles.

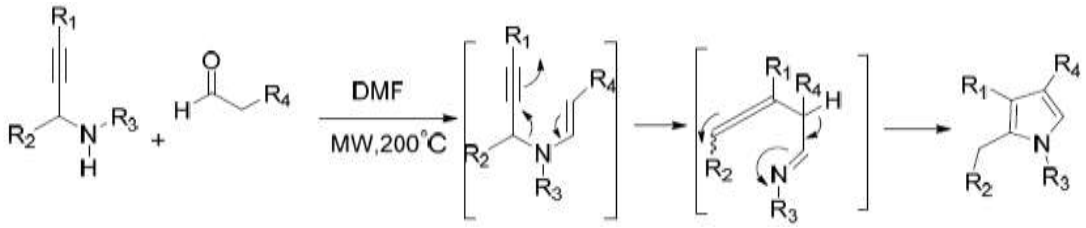

Figure 41. Preparation of pyrrole derivatives in microwave conditions

The four-component compression reaction, intramolecular cyclization, and crystallization of aldehydes, amines, beta-keto esters, and nitroalkanes with the aid of microwaves result in the preparation of polysubstituted pyrroles (Figure 42).

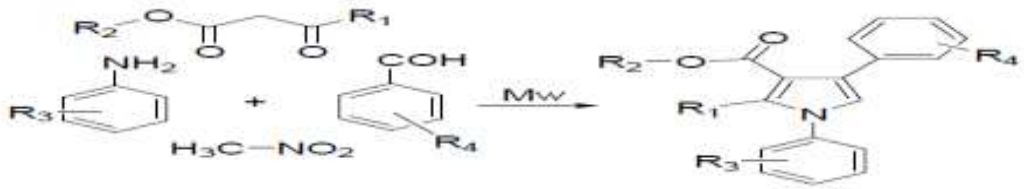

Figure 42. Preparation of highly volatile pyrroles

The ring formation between cis-1,4-dichloro-2-butene and various amines is facilitated by silicon dioxide (SiO_2) as a catalyst. In this method, an ether solvent is used for washing, and N-pyrroles are extracted. For purification, a Swangari column and a mixture of ethyl acetate and normal hexane in ratios of 2:1 and 6:1 are utilized (Figure 43).

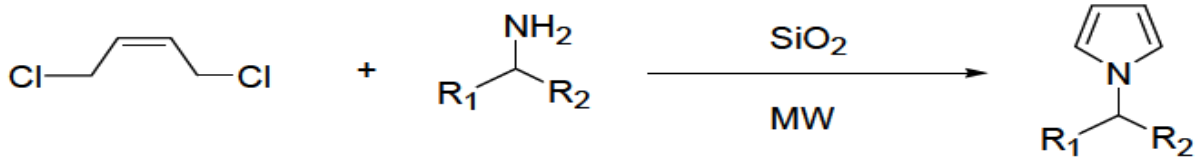

Figure 43: Ring-closing reaction.

This method is also employed to prepare many acyclic compounds from diyans. An effective ring-closing reaction is achieved in the presence of a ruthenium catalyst, introduced by Yang, using dichloromethane as a solvent and microwave irradiation. ZnI_2 can effectively denitrogenize dienyl azides, converting them into pyrrole (Figure 44).

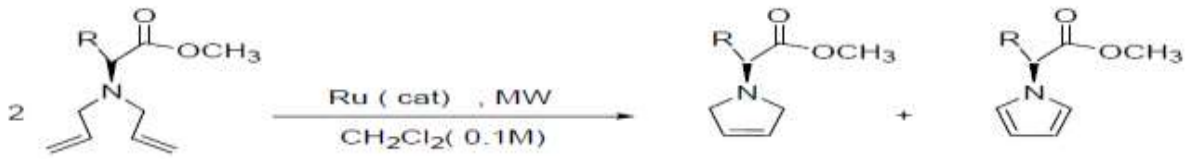

Figure 44. Ring-closing reaction from the center

Pyrrole can also be synthesized from vinyl azides using visible light, with metal catalysts employed in the process (Figure 45). Additionally, in the presence of glycerol, tosylpyrroles are prepared (Figure 47).

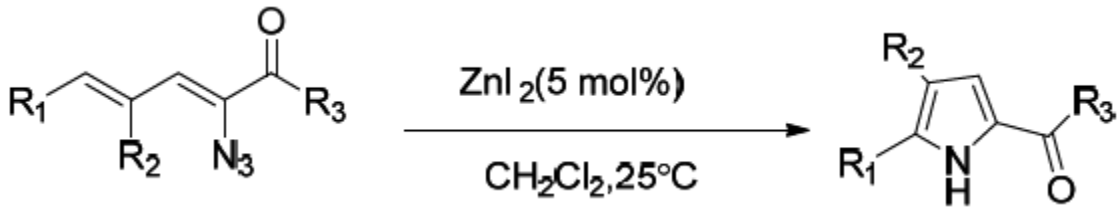

Figure 45. Preparation of pyrrole from dienyl azides

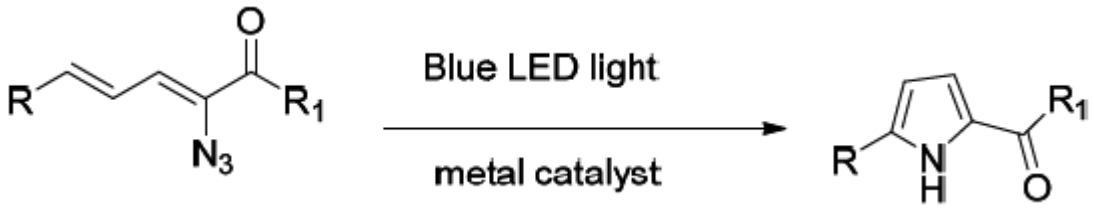

Figure 46. Preparation of pyrroles using-Catovinyl azide under visible light α

Figure 47. Preparation of pyrroles

Aromatic nitro compounds react with ethylisocyanoacetate in the presence of a DBU catalyst (8,1-diazabicyclo[4,4,0]undec-7-ene) in tetrahydrofuran at a temperature of 60°C (Figure 48).

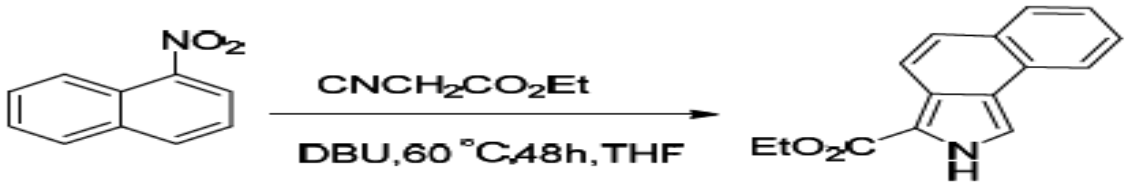

Figure 48. Preparation of pyrroles with aromatic rings

The preparation of 4,3,2-substituted pyrrole derivatives via the cyclization reaction of methyl isocyanide and acetylene was reported by Larinov and his colleagues in 2005 (Figure 49).

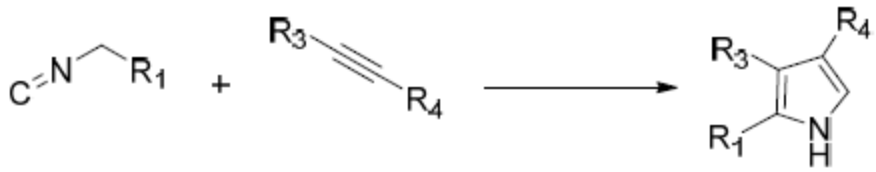

Figure 49: Preparation of esterified pyrroles with methyl isocyanide and acetylenes.

Preparation of pyrrole derivatives by Powell-Noor method

The Powell-Noor method involves the reaction of 4,1-dicarbonyls with ammonia or substituted amines to prepare the first type of pyrroles. The reaction of various types of amines and diamines with 5,2-hexanedione in the presence of an iron catalyst at room temperature and without solvent yields a high amount of the first pyrroles (Figure 50).

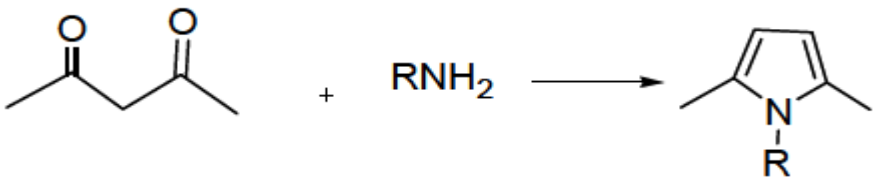

Figure 50. Powell-light reaction

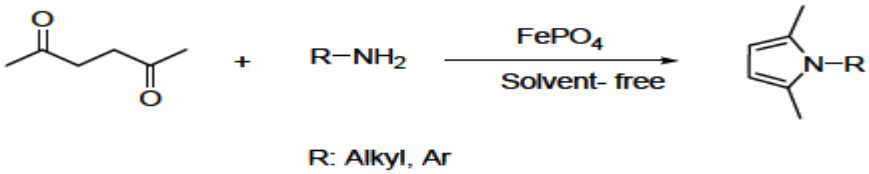

Figure 51. Preparation by Powell-Noor method

Two-component reactions between aliphatic and aromatic amines with 5,2-dione hexane were performed at room temperature under solvent-free conditions and using varying ratios of $Fe(ClO_4)_3/SiO_2$ catalyst. This study found that the reaction proceeds quickly in the presence of $Fe(ClO_4)_3/SiO_2$, yielding good product results. Advantages of this method include rapid speed, high efficiency, no side products, and environmentally friendly conditions (Figure 52).

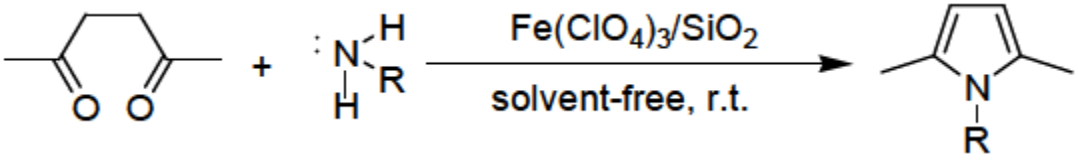

Figure 52. reaction for the preparation of pyrrole derivatives

The Powell-light reaction is a useful method for making ring structures and has wide applications for the preparation of irregular rings. Microwave is used to increase efficiency and reduce reaction time and millimeter conditions. The prepared dictons are exposed to microwaves. The reaction is carried out in acetic acid and the presence of different amines. The best results were obtained at 150 °C for 10 minutes, the temperature is 120 °C (Figure 53).

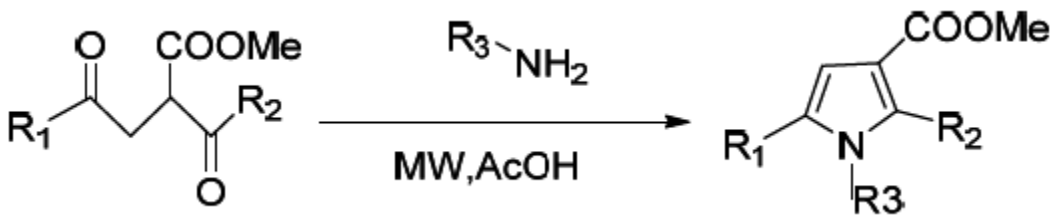

Figure 53. Powell-light reaction using microwaves

Pyrrole has been prepared with the help of H-nanocatalyst. To improve the separation of heterogeneous catalysts from the reaction mixture, some changes have been made in the catalyst. The main feature of magnetic nanoparticles is that by using an external magnetic field, they can be dispersed or aggregated, which will improve the separation and recovery of the catalyst (Figure 54).

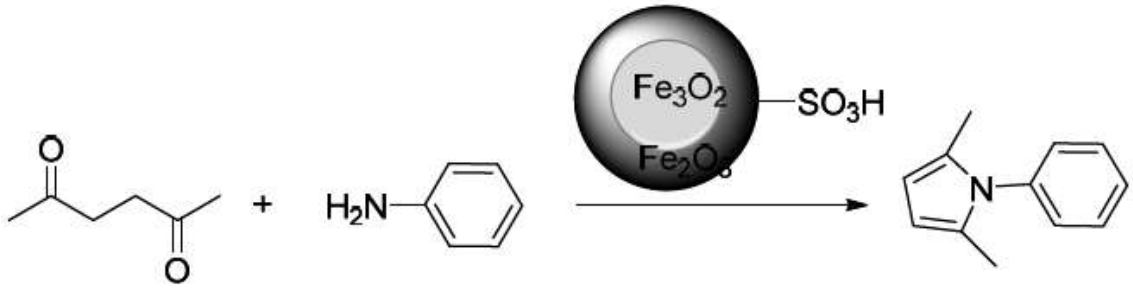

Figure 54. Powell-light reaction with the help of sulfonated iron magnetic nanocatalyst

The catalyst of iron oxide nanoparticles has been used for the preparation of ketones and amines of the first type in γ-pyrroles from liquid-phase N-isolation at room temperature (Figure 55). The reaction rate is very high and in the conversion of aniline, the best reported liquid (I[BMIm]) was 1-butyl-1-imidazolium iodide. Butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium chloride also had good results and The reaction was done in less time (Figure 56)

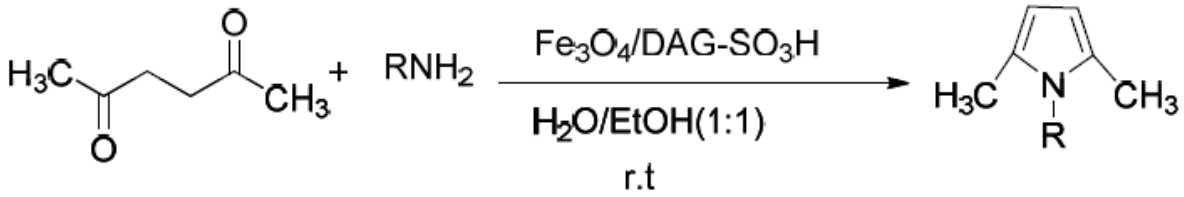

Figure 55. Powell-light reaction with the help of Fe_3O_4 nanomagnet catalyst

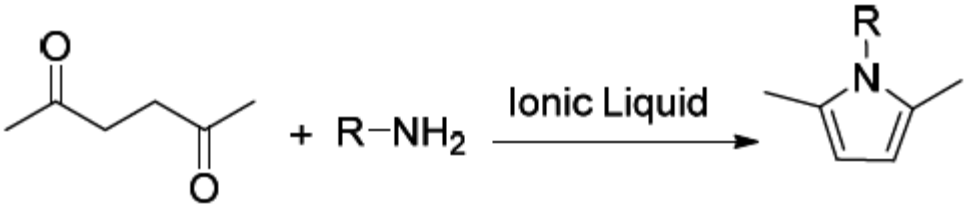

Figure 56. Preparation of pyrrole by Powell-light reaction in ionic liquids

Due to its powerful properties and properties (I) of molecular iodine (2), its heterogeneity as a Lewis acid plays an important role in the preparation of organic compounds. Iodine has been used in the preparation of Powell-Noor. This reaction was performed in a shorter time with exceptional efficiency and without solvent and at room temperature (Figure 57).

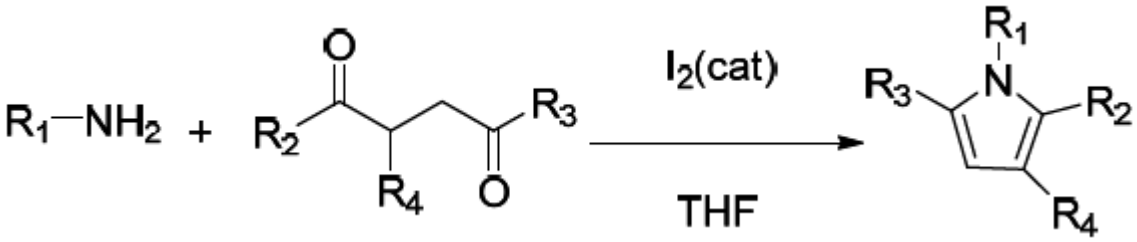

Figure 57. Preparation of pyrrole using molecular iodine

Natural sugars and unnatural sweeteners are used as reagents and catalysts in the transfer of functional groups. It is 1 and 1-dioxide of one (H 2)-saccharin 2,1-benzothiazole 3 Bronsted acid with moderate acidity. It is used as a catalyst for the Powell-Noor reaction (Figure 58).

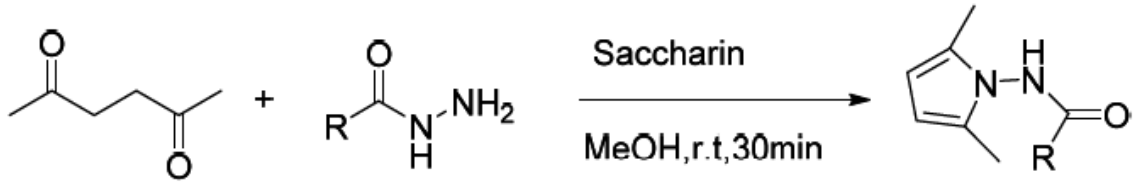

Figure 58. Preparation of pyrrole derivatives using saccharin as a catalyst

The preparation of tetrasubstituted pyrrole derivatives using H-2-azirines as a gold catalyst for the direct transfer of nitrogen from enamides to enamides in simple ways is introduced in very good performance. In this method, pyrroles are prepared (Fig. 59). Gold catalysts are prepared with high speed and high efficiency with a small amount of catalyst, and mainly pure aromatic rings are prepared within a few minutes (Fig.60)

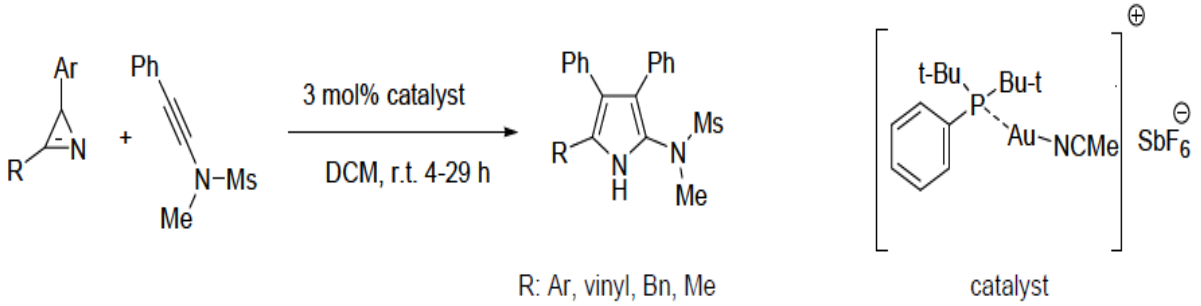

Figure 59. The direct transfer of nitrogen from H-2 of azirines to enamides in the presence of the gold catalyst

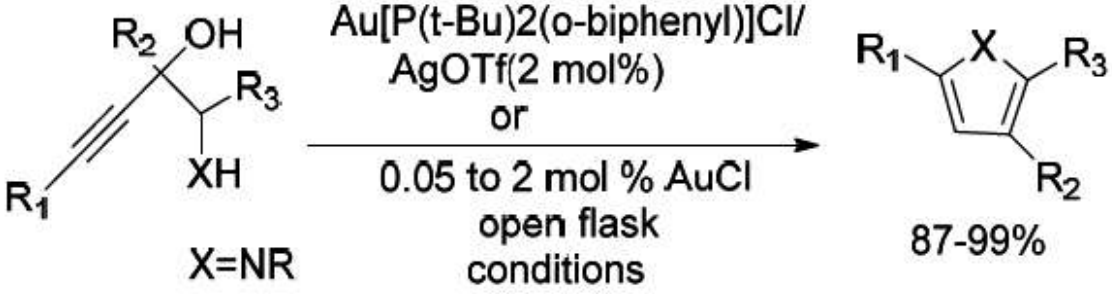

Figure 60. Preparation of pyrroles with the help of gold catalyst

By using an N-cationic catalyst, pyrrole derivatives are prepared from Claisen condensation of derivatives (I) of tala-enamino-β-allenyl-α-propargyl-enamino and intermediate cyclization (Figure 61).

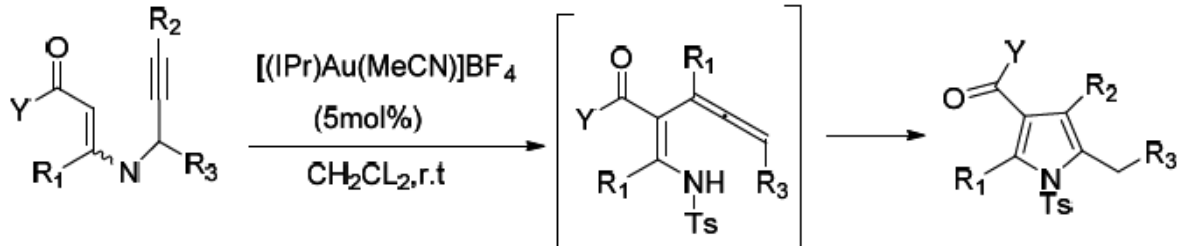

Figure 61. Preparation of pyrrole derivatives with the help of gold catalyst

Rousseau and his colleagues showed that mechanical activity can be used to prepare pyrroles from different ketones. In this substitution of pyrrole using the N-method, the preparation of mechanical activity derivatives of ball milling and solid green acids such as citric acid, pyroglutamic acid, succinic acid, ascorbic acid, camphorsulfonic acid and oxalic acid was introduced, but it was not as efficient as other methods and with A low efficiency was obtained. The most important advantage of this method is the absence of solvent and the use of a solid green organic acid (Fig 62)

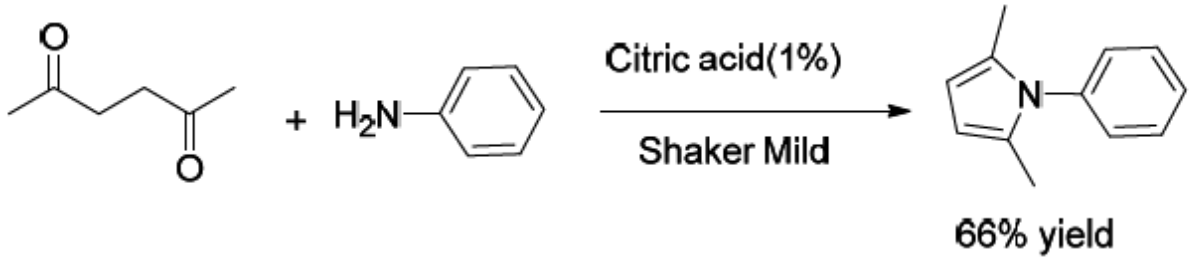

Figure 62. Preparation of pyrrole with the help of citric acid catalyst

Preparation of 2-amino pyrroles with gold catalyst from the intermolecular reaction of vinyl azides with enamides with efficiency in a two-step preparation method with very good performance. (Figure 63) using rhodium, palladium and iron catalysts, pyrroles are produced. In the first step, rhodium creates a ring. Chloride forms the aromatic compound (III) in the next step, iron gives pyrrole with good to high efficiency. The only side product of this method of preparation is water and ethane (Fig. 64).

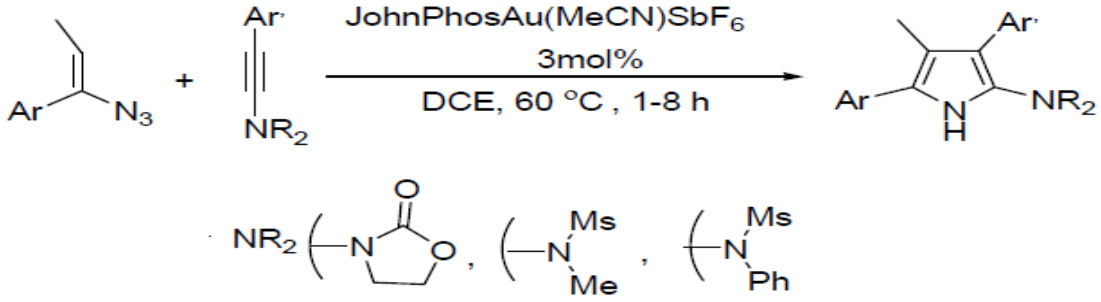

Figure 63. Preparation of 2-amino pyrroles

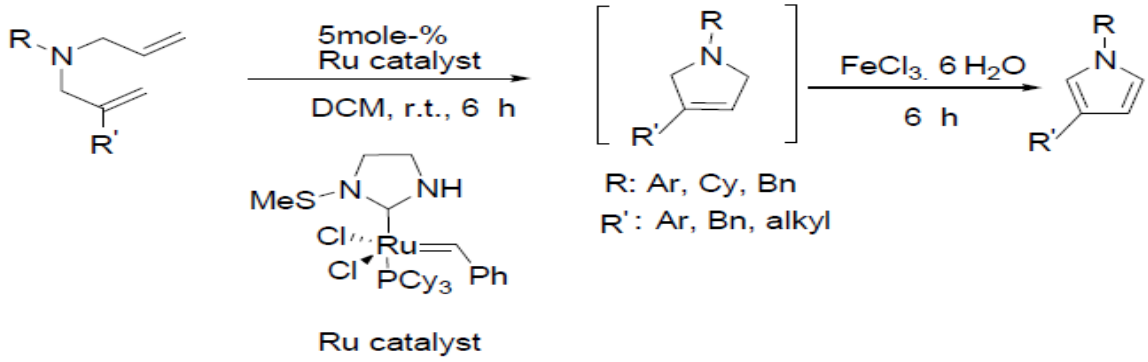

Figure 64. Two-step preparation of pyrroles

Using an iminyl radical, a compound such as TEMPO (tetramethylpiperidine-1-yloxyl) can be produced with additional functional groups, without generating toxic byproducts. Employing alkyne as a radical acceptor enables the synthesis of a

wide range of acylpyrroles with good yields 65).

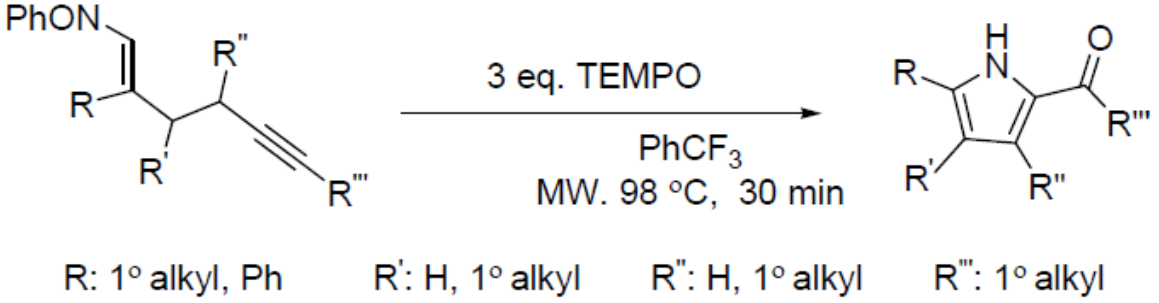

Figure 65. Method of preparation of acyl pyrroles

2-formyl pyrroles or 5-hydroxymethylpyrrole-2-carbaldehydes can be naturally derived from the reaction of sugars and amines. Kato and Fujimaki successfully prepared a mixture of 2-formylpyrrole from glucose reacted with methylamine, ethylamine, or butylamine (Figure 66).

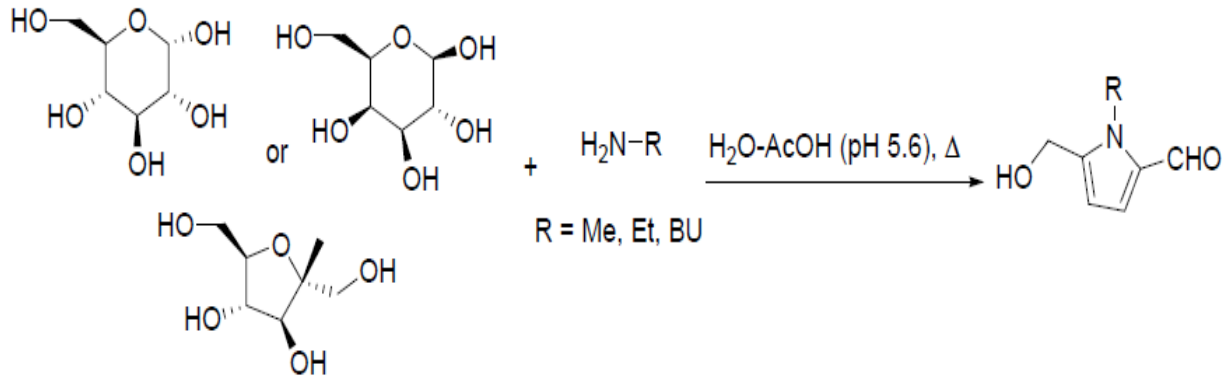

Figure 66. The method of preparing 2-formylpyrroles from reactions without Maillard enzyme

Chlorosulfonyl isocyanate reacts with pyrrole as well as pyrroles containing strong electron-donating groups at position 2. This careful selection of electron-acceptor groups allows for the targeted substitution at position 4 in the pyrrole ring. The resulting chlorosulfonylamides can be easily converted to their corresponding nitriles (Figure 67).

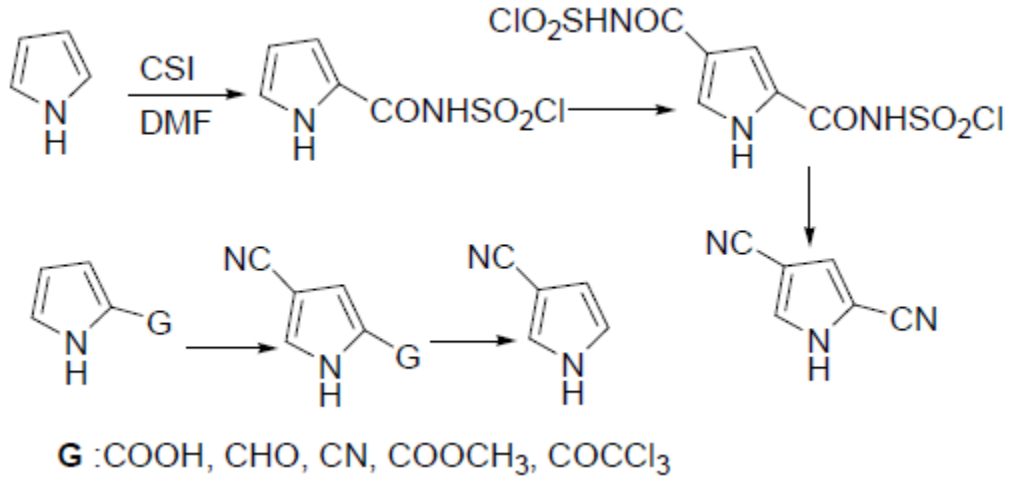

Figure 67. Reaction of pyrrole with chlorosulfonyl isocyanate

Aryl pyrroles are prepared through the reaction of nitroaryls with 3,1-dianyl and boronic esters using a monocyclic reaction facilitated by the Diels-Alder method. This reaction forms arylpyrrole rings with good yields, and the outcome depends on the electronic properties, orientation, or substitution of the boron and dienes (Figure 68).

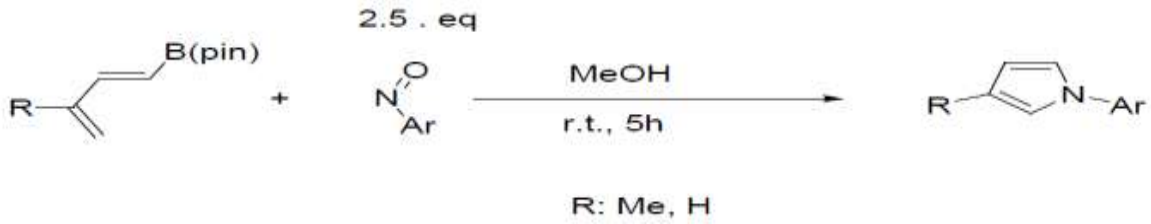

Figure 68. Preparation by Diels-Alder method

A method involving butyl-3-methylimidazolium hydrogen sulfate ([bmim]HSO_4), an ionic liquid, along with graphene oxide ([bmim]HSO_4/GO), is used as a reusable solid nanocatalyst in the presence of amines (e.g., benzene-N-pyrroles, purine-6-H amines, 2-amino-4-methylthiazole, and adenine). The reaction takes place at 95°C using 1,3-dicarbonyl and nitromethane at 90°C. This method results in the formation of new substituted pyrroles, including those with fluorine atoms, thiazole, and adenine nuclei, which are important for pharmaceutical research (Figure 69).

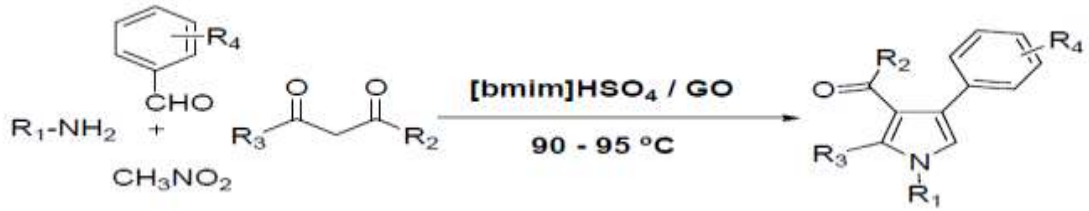

Figure 69. Preparation of tetrasubstituted pyrrole derivatives using Bmim[HSO4].

In 2017, Behbahani and colleagues reported a simple method for preparing 4,3,2,1-tetrasubstituted pyrroles from the reaction of dicarbonyl, amines, and β-aromatic aldehydes, phosphate compounds, and nitromethane under nitrogen. The use of iron phosphate as a green activator under mild reaction conditions is a key aspect of this method (Figure 70).

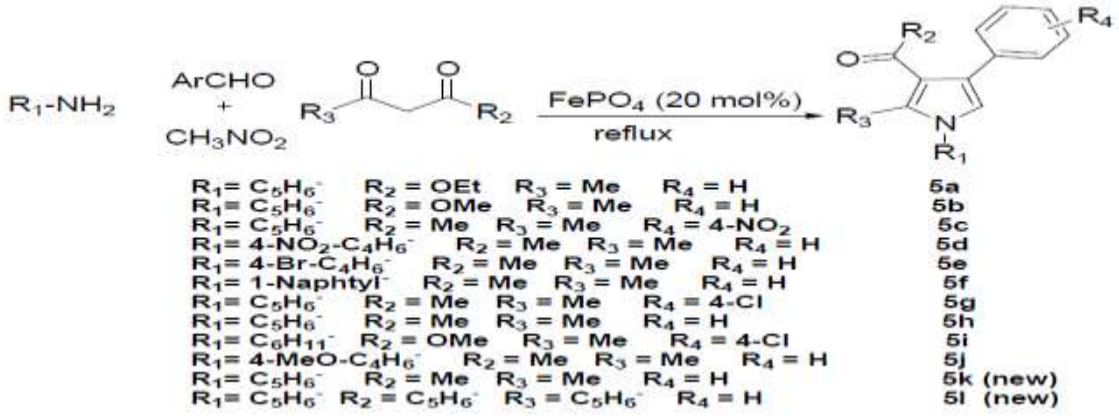

Figure 70. Preparation of tetrasubstituted pyrrole derivatives in the presence of FePO4

A novel method for the preparation of pyrroles using electrochemical oxidation via enamines has been introduced. In this method, polysubstituted pyrroles are produced easily in a simple undivided cell facilitated by sodium acetate, without the use of external oxidants. This approach offers a broad and practical application, utilizing C-C enolization and an oxidative cross-linking process (Figure 71).

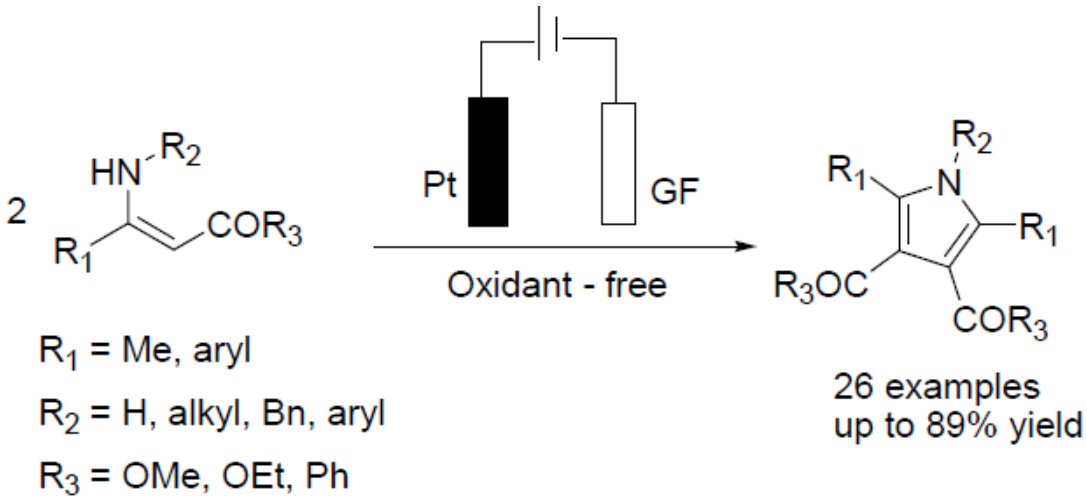

Figure 71. Electrochemical preparation of pyrrole derivatives

Another method for preparing trisubstituted pyrroles involves the cyclization of methylene isocyanides with ketones. This method, performed without transition metals, provides moderate to good yields and selectivity. The resulting compounds are expected to have potential as drug agents or prodrugs following further modification (Figure 72).

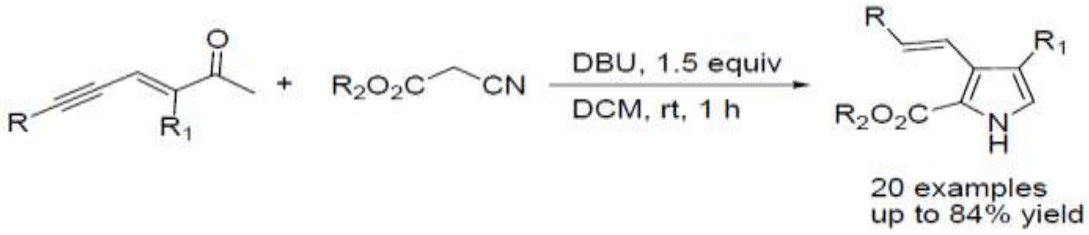

Figure 72. Preparation of tricyclic pyrroles.

Polysubstituted pyrroles were also synthesized via a four-component reaction using 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes with natural hydroxyapatite (HAp) as an efficient green catalyst. This method offers several advantages, such as simplicity, moderate conditions, high selectivity, and low cost, and is environmentally friendly (Figure 73). Additionally, the behavior of the compounds in 1 M hydrochloric acid was studied for corrosion inhibition of steel, with promising results.

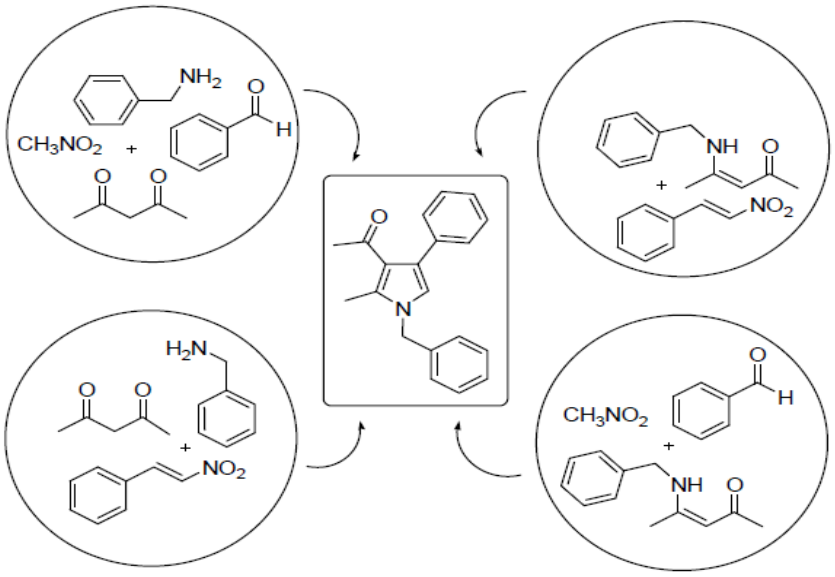

Figure 73. Method of preparation of polysubstituted pyrrole derivatives using hydroxyapatite.

A simple, fast, and eco-friendly method for preparing pentasubstituted pyrroles has been introduced, involving the reaction between 3-oxoanilides and carboxylic acid hydrazides in the presence of $VOSO_4 \cdot H_2O$ as a catalyst. The reactions were carried out in ethanol, and exposed to air as an oxidant. Nineteen pyrrole derivatives were produced, which were typically crystalline and did not require further purification (Figure 74).

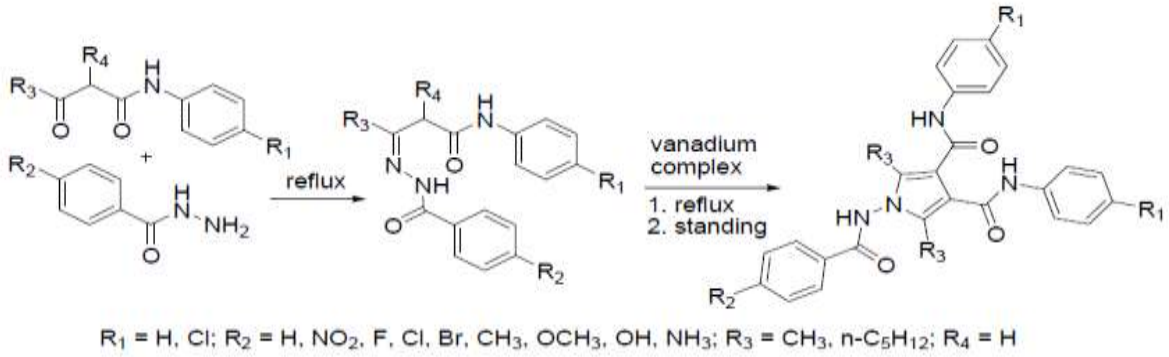

Figure 74. Preparation of pentasubstituted pyrrole derivatives with $VOSO_4 \cdot H_2O$

Conclusion

In this review, we have attempted to provide comprehensive information on the preparation, properties, and applications of pyrroles. Various methods for the synthesis of polysubstituted pyrrole compounds were discussed, including the use of solid acid catalysts like Lewis acids and nanocatalysts, fine waves, ultrasound, and ionic liquids. These methods were explored both under solvent and solvent-free conditions and at various temperatures, each with its advantages and disadvantages. Researchers have continuously worked to modify and improve traditional methods. The importance of the pyrrole core in many medicinal and natural compounds has also been highlighted. Pyrrole derivatives exhibit significant biological activities, including antibacterial, antiviral, and anticancer properties. In particular, some derivatives have been proven to possess anticancer activity, specifically against breast and liver cancers. Furthermore, the pyrrole nucleus is found in the structure of several natural pigments, including vitamin B12, hemoglobin, chlorophyll, and yellow bile pigment, as well as in enzymes such as cytochromes, emphasizing its biological importance. In addition, certain tetrasubstituted pyrrole derivatives have been identified as effective agents in preventing steel corrosion, demonstrating the diverse applications of these compounds across different fields.

REFERENCE

[1] Keshavarz, N.; Beibahani, F.K.; Chemistry Africa 1, 113-117, 2018.

[2] Anwar, S.G.; Beibahani, F.K.; Euro. Chemical. bull. 8, 301-306, 2019.

[3] Karimilad, F.; Beibahani, F.K.; Polycyclic. aromatic. Compounds, in press, 2020.

[4] Daloy, T.S.; Bebahani, F.K.; Polycyclic. aromatic. Compounds, in press, 2020.

[5] Shekach, M.; Beibahani, F.K.; Lars, J. Organization. Chemical. 56, 894-900, 2020.

[6] Hassanzadeh, F.; Beibahani, F.K.; Ras J. organize. Chemical. 56, 1070-1076, 2020.

[7] Hraoui, M.M.; Beibahani, F.K.; Oskoy, ha. jaw. J.Chemistry. 26, 2203-2206, 2008.

[8] Rahmani, P.; Beibakhani, F.K.; Inorganic nano- Met. Chemical. 47, 713-716, 2017.

[9] Nasseri, M.; Beibahani, F.K.; Jebari. 247- 253, 2015.

[10] Bebahani, F.K.; Lotfi, A.; Euro. Chemistry bull. 2, 694-697, 2013.

[11] Mojitahdi, M.M.; Abhay, M.A.; Hrawi, mm. Beibahani, F.K.; Monash. Chemistry 138, 95-99, 2007.

[12] Oskoy, H.A.; Hraoui, M.M.; Sardeniya, A.; Giannati, F.; Beibahani, F.K.; Monash. Chemical. 39, 27-29, 2008.

[13] Bebahani, F.K.; Ziei, P.; Fakhroueian, Z.; Doraj, N.; Monash. Chemistry 142, 901-906, 2011.

[14] Bebahani, F.K.; Naderi, M.; Lars. J.Gen. Chemical. 86, 2804-2806, 2016.

[15] Najafi, E.; Beibahani, F.K.; Ras. J. Organization. Chemical. 53, 454-458, 2017.

[16] Joule, J.A.; Mills, B.K.; Heterocyclic Chemistry. 5, 355, 2009.

[17] Idhayadhulla, A.; Kumar, R.S.; Nasser, A.J.A.; Manilal, A.; Bull. Chemical. Sooke. Ethiopia. 26, 429-435, 2012.

[18] Padron, J.M.; Tejedor, D.; Santos-Exposito, A.; Garcia-Terrado, F.; Martin, V.S.; J.Bioorg. medicine. Chemical. Letters 15, 2487-2490, 2005.

[19] Leverde, J.; Faucono, B.; Barrier, L.; Ulakov, M.; Piriou, A.; Villefond, J.M.; Euro. J. Med. Chemical. 34, 991-996, 1999.

[20] Forstner, A.; Anjiu. Chemical. internationality. Ed. 42, 3582-3603, 2003.

[21] Kumar, V.; Awasthi, A.; Salam, A.; Khan, T.J.; Organization. Chemical. 84, 11596-11603, 2019.

[22] Golap, S.S.; Euro. J. Med. Chemical. 110, 13-31, 2016.

[23] Estevez, V.; Villacampa, M.; Menendez, J.C.; Chem. Sooke. Rev. 43, 4633–4657, 2014.

[24] Battersby, A.R.; Nutt. product. Reports 17, 507–526, 2000.

[25] Arikawa, Y.; Nishida, H.; Kurasawa, O.; Renoka, A.; Hirase, K.; Inado, N.; Hori, Y. Matsukawa, J.; Imanishi, A.; Kondo, M.; Taii, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M.; J. Med. Chemical. 55. 4446 – 4456, 2012

[26] Attar, A.B.; Zheng, Y.T.; Tetrahedron Wright. 54, 5624, 2013.

[27] Gorab, M.M.; Ragab, F.A.; Blackfield, H.I.; Yusuf, H.A.; El-Ghazal, M.G.; Biological Tissue. medicine. Chemical. Wright. 20, 6316-20, 2010.

[28] Kaul, R.; Rani, V.; Abbott, V.; Kapoor, Y.; Konal, D.; Kumar, K.J. Pharm. Chemical. Chemical. science. January 17-32, 2017.

[29] Halles, A.L; Ellmans Encyclopedia of Industrial Chemistry, 2000

[30] Estevez, V; Villacampa, M.; Menendez, J.C.; Chem. Sooke. Rev. 43, 4633-4657, 2014.

[31] Wang X; Lane, Bachelor; same. D.J.; Yes. Chemical. Sooke. 127, 4996–4997, 2005.

[32] Matiychuk, V.S.; Matiyak, R.L.; Obshak, N.D.; Ostapik, Y.V.

Pidlypnyi N.I.; Chem. Heterocycle. compound. 40, 1218–1219, 2004.

[33] Parker, S; Chun, M; Song Jie; Jin, H. Korean Chemical Society, 26, 575-578, 2005.

[34] Milgram, BC; Eskilson. K; Richter, S.M; Scheit, W.R; Scheidt, K.A. J.; Organization. Chemistry, 72, 3941-3944, 2007.

[35] Myers, K.C.; Mays, S.M.; Sutherland, UK; Orville, T.J.; Kecha, D.M.; Alkovo. 14, 181-190, 2009.

[36] Sutherland, UK; Orville, T.J.; Kecha, D.M.; Arkivoc XIV, 181-190, 2009.

[37] Tu Xinchang; Fan, W.; Jiang, B.; Wang, S.L.; Tu, S.J. Tetrahedron 69, 6100-6107, 2013.

[38] Rao, H.S.P.; Jyotilingam, S.; Tetrahedron Wright. 42, 6595-6597, 2001.

[39] Tsuji, Y.; Yokoyama, Y.; Ha, K.-T.; Watanabe, Y.; J. Organomet. Chemical. 334, 157-167, 1987.

[40] Lien, Y.; Huber, T.; Hesp, K.D.; Bergman, Ellman, R.G.; Angieu. Chemical. internationality. Ed. 52, 629–633, 2013.

[41] Gao, C.; Xu, H. Bear, Y. Chemical. Sooke. Rev., 46, 2799-2823, 2017.

[42] Liu Jie; Zhu, J. Jiang, H. Wang, W. Lee, J. Asian Journal of Chemistry, 4, 1712-1716, 2009.

[43] Stewart, D.R.; Alsabe, P.; Kuhn, M.; Fagnu, K.; J. Am. Chem. Sooke. 132, 18326-18339, 2010.