Chapter 1

Introduction

1. Introduction

Heterocyclic compounds are cyclic organic compounds where other atoms, such as nitrogen, oxygen, or sulfur, replace one or more carbon atoms in the ring. These compounds are classified based on the number of atoms in the ring structure, ranging from three to eight members, and fused ring structures. Nitrogen, oxygen, and sulfur-containing five, six-membered, and fused heterocyclic compounds have particularly captivated researchers throughout the history of organic synthesis.

1.1. Five-Membered Heterocyclic Compounds: Key five-membered heterocyclic compounds containing a single heteroatom include pyrrole, furan, and thiophene. Compounds with multiple heteroatoms in the five-membered ring include isoxazole, pyrazole, imidazole, azole, thiazole, thiadiazole, oxadiazole, and triazene. Partially reduced heterocyclic compounds are often referred to as dihydro or tetrahydro derivatives of their parent compounds. (Figure 1.1)

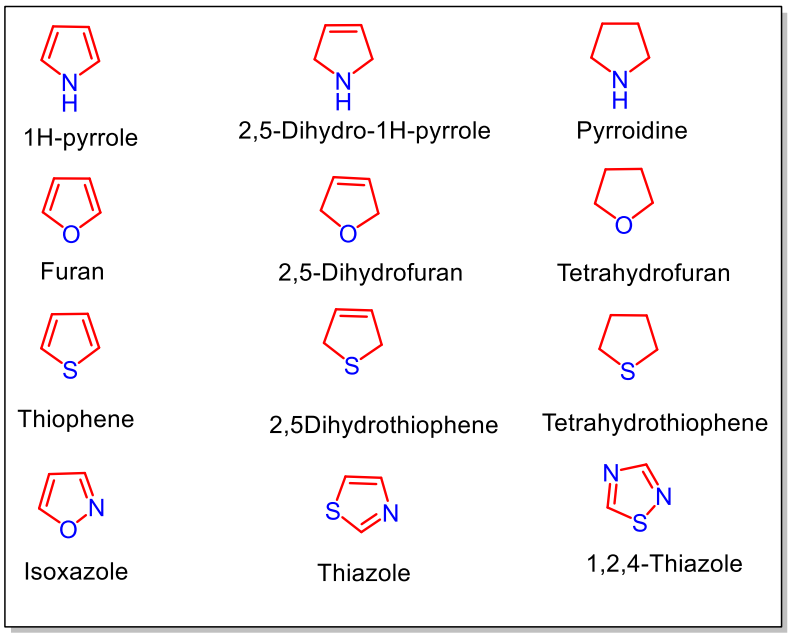


Figure 1.1: Examples of five membered heterocycles.

1.2 Six-Membered Heterocyclic Compounds: Examples of six-membered heterocyclic compounds with a single heteroatom include pyridine, pyran, and thiopyran. Six-membered heterocycles with more than one heteroatom include pyrazine, dioxane, dithiane, oxazine, and thiazine. (Figure 1.2)

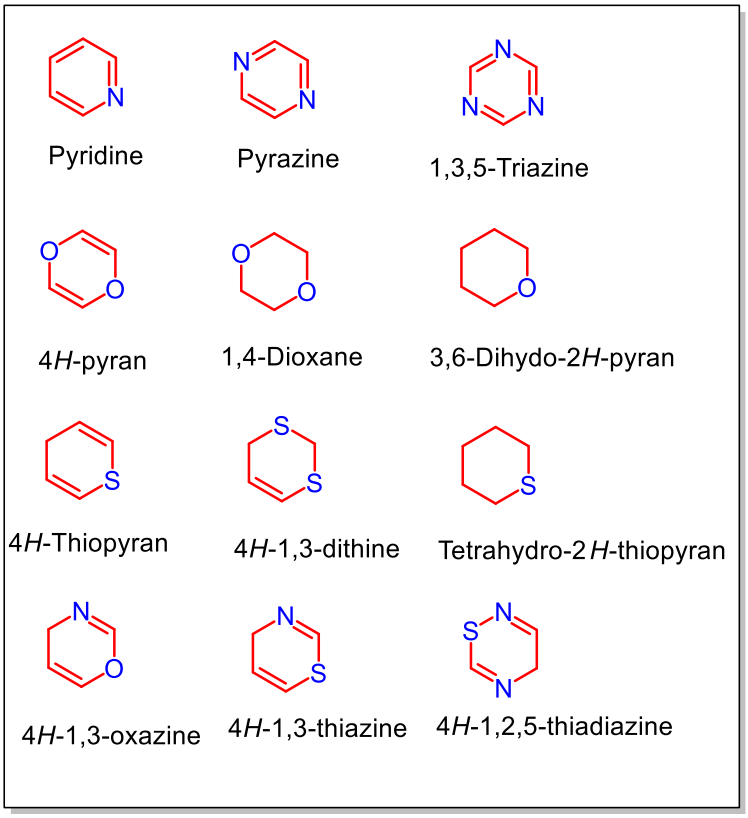


Figure 1.2: Examples of six-membered heterocycles.

1.3 Fused Heterocyclic Compounds: Fused heterocyclic compounds are formed by fusing two or more rings. Notable examples with a single heteroatom include quinoline, 1H-indole, coumarin, and benzothiophene. Fused heterocyclic compounds with multiple heteroatoms include imidazo[1,2-a]pyridine, benzothiazole, benzooxathiole, and furopyran. Pyrazolooxazole is a fused heterocyclic compound containing one oxygen and three nitrogen atoms. (Figure 1.3)

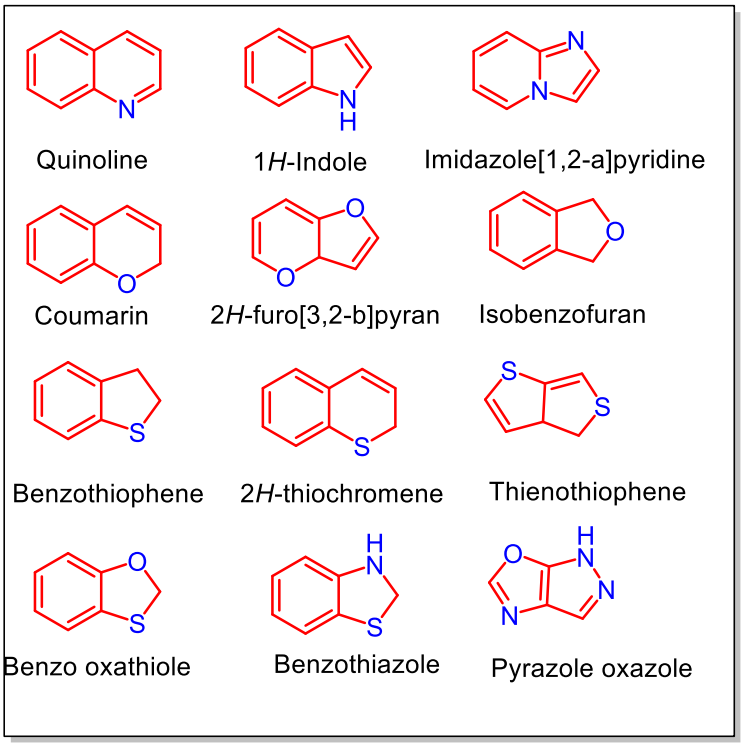


Figure 1.3: Examples of fused heterocycles.

Heterocyclic compounds are crucial in organic chemistry due to their natural prevalence and significance in human life. They are essential components in many natural products like vitamins, hormones, antibiotics, and pigments, making them pivotal in the design of biologically active molecules. Modern society relies on synthetic heterocycles for various applications, including pharmaceuticals, pesticides, dyes, plastics, cosmetics, solvents, antioxidants, and vulcanization accelerators.

1.4 3,3′-Diindolylmethane (DIM)

Glucobrassicin is a bioactive molecule predominantly found in cruciferous plants such as cabbage, broccoli, bok choy, kohlrabi, Brussels sprouts, and kale. This compound undergoes enzymatic degradation catalyzed by plant-derived enzyme myrosinase, leading to the formation of indole-3-carbinol (I3C). Upon ingestion, I3C is converted into its condensation product, 3,3′-Diindolylmethane (DIM), in the acidic environment of the stomach.[1-6]

Apart from cruciferous plants, DIM and its derivatives are also present in marine and terrestrial microorganisms. For example, Vibrio parahaemolyticus produces vibrindole A,[7] *Arcyria* denudate synthesizes bisindole sulfate[8] as a secondary metabolite, *Streptomyces staurosporeus* generates staurosporine,[9] and *Nocardia aerocoligenes* produces rebeccamycin.[10] DIMs are known for their diverse biological activities, including anticancer, antioxidant, antihyperlipidemic, antimicrobial, and anti-inflammatory properties.[11] These pharmacological attributes have sparked continuous interest in developing efficient synthetic routes for DIMs.

1.4.1 Synthesis of DIMs: Challenges and Advances

In the literature, the synthesis of DIM has been mediated through various catalytic systems[12], including Lewis acids,[13] protic acids,[14] rare earth metals,[15] and ion exchange resins.[16] However, these methods often suffer from several drawbacks, such as harsh reaction conditions, stoichiometric loading of catalysts, limited substrate scope, long reaction times, and the generation of harmful waste.

Alternative approaches, such as microwave[17] and ultrasound radiation,[18-19] have been explored to overcome these challenges. While these methods address some issues, they remain insufficient for large-scale production. Reusable and ionic liquids combined with metal triflates or Fe (III) salts have also been employed,[19-22] but these materials are costly, limiting their practical application. Solid acid catalysts like modified zirconia,[23] zeolites,[24] and clays[25] often require long reaction times and volatile organic solvents as reaction media. (Scheme 1.1)

1.4.2 Green Synthesis Approaches

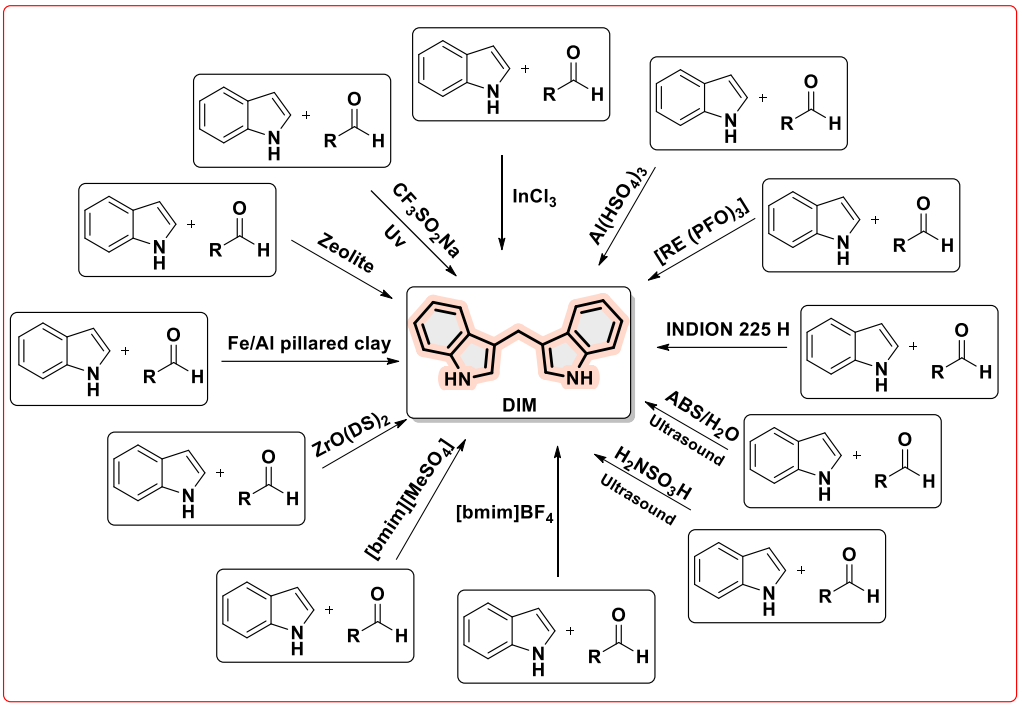
Efforts have been made to develop greener synthetic routes for DIMs. Mukherjee *et al.* utilized Fe/Al pillared heterogeneous clay catalysts under solvent-free conditions, offering a more environmentally friendly approach. Huo *et al.* used sodium triphenylphosphine-m-sulfonate (TPPMS) and carbon tetrabromide, which are recoverable and reusable.[26] Kim *et al.* developed hyper-cross-linked recyclable polyphenanthrene and polypyrene microspheres decorated with bromomethyl groups as catalysts for DIM synthesis.[27] (Scheme 1.1)

1.4.3 Light-Mediated Approaches

Light-mediated synthesis has emerged as a promising approach for DIM construction in recent years. Zhang *et al.* performed aerobic oxidative cross-coupling of indoles with glycine derivatives in the presence of Rh-6G under visible light,[30] demonstrating an efficient and eco-friendly method. Qiu *et al.* utilized CF_3SO_2Na reagent under oxygen and UV irradiation to synthesize DIM, further advancing the field.[31] (Scheme 1.1)

1.4.4 Ongoing Research and Future Directions

Significant research is ongoing to develop novel methodologies for the synthesis of DIMs. These efforts aim to enhance the efficiency, scalability, and environmental sustainability of the synthetic processes. As new catalytic systems and innovative approaches are explored, the potential for DIMs in various therapeutic applications continues to expand, promising exciting advancements in both organic synthesis and biomedical research.



Scheme 1.1: Synthesis of DIM using various catalysts.

1.5 Imidazo[1,2-a]pyridine

Imidazo[1,2-a]pyridines are significant building blocks composed of a five-membered imidazole ring fused with a six-membered pyridine ring. This unique structure results in a variety of imidazo[1,2-a]pyridine derivatives exhibiting diverse biological activities, including anti-tumor, antiviral, sedative, hypnotic, anti-inflammatory, and anti-ulcer properties. In recent years, many clinically approved drugs have been derived from imidazo[1,2-a]pyridines, such as Soraprazan (an anti-secretory drug), Zolimidine (an anti-ulcer drug) , Olprinone (used in the treatment of heart failure), Zolpidem (used for insomnia), Alpidem, Saripidem (anxiolytic drugs), Minodronic acid (used for osteoporosis), and GSK812397 (used in the treatment of HIV infection).[32]

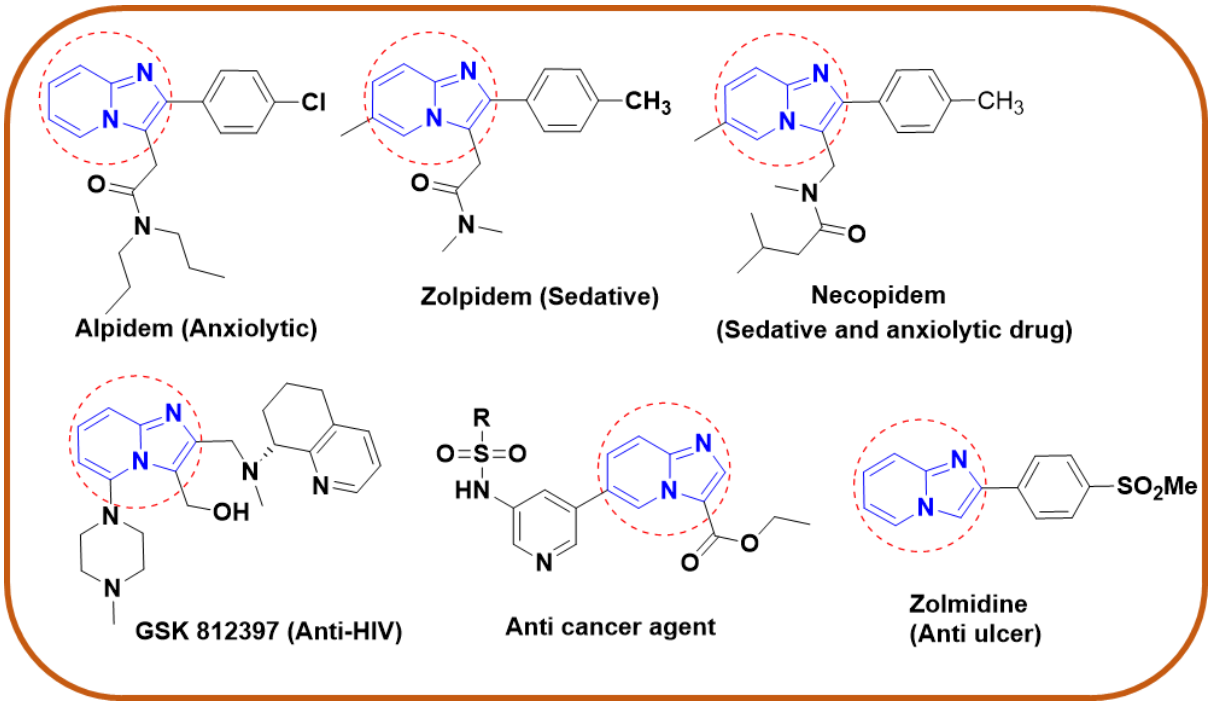


Figure 1.4: Examples of biologically active imidazo[1,2-a]pyridines.

As a result, continuous synthetic protocols have been developed to access a diverse range of imidazo[1,2-a]pyridines, including methods such as condensation reactions, tandem reactions, multicomponent reactions, oxidative coupling, intramolecular amination, and dehydrogenative aminooxygenation. Figure 1.5 illustrates different methods for synthesizing imidazo[1,2-a]pyridines utilizing different types of starting materials.

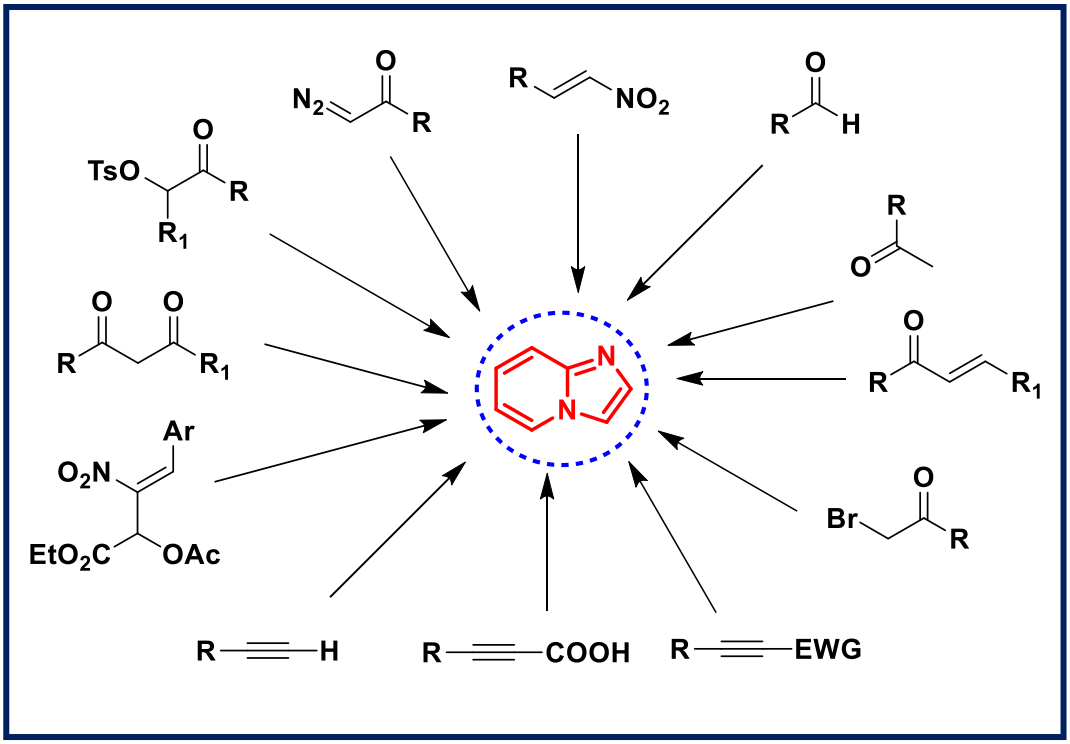


Figure 1.5: Examples of various starting material for synthesis of imidazo[1,2-a]pyridines.

The direct activation and functionalisation of inactive bonds, particularly C–H bonds, stand as forefront methodologies in synthetic chemistry, as demonstrated by numerous representative methodologies. These groundbreaking approaches, including arylation, carbonylation, thiolation, oxidative cycloaromatization, formylation, and dithiocarbamation, deviate from traditional strategies and eliminate the need for pre-functionalization of reagents and raw materials, aligning with modern synthetic ideals such as high efficiency, atom economy, and environmental protection. Additionally, direct C(sp^2)–H functionalization has unequivocally emerged as a pivotal strategy for synthesizing aromatic and heterocyclic compounds. This approach has been successfully utilized in the recent synthesis of various imidazo[1,2-a]pyridine compounds, showcasing the significant impact of direct C–H bond functionalization techniques.[33] (Figure 1.6)

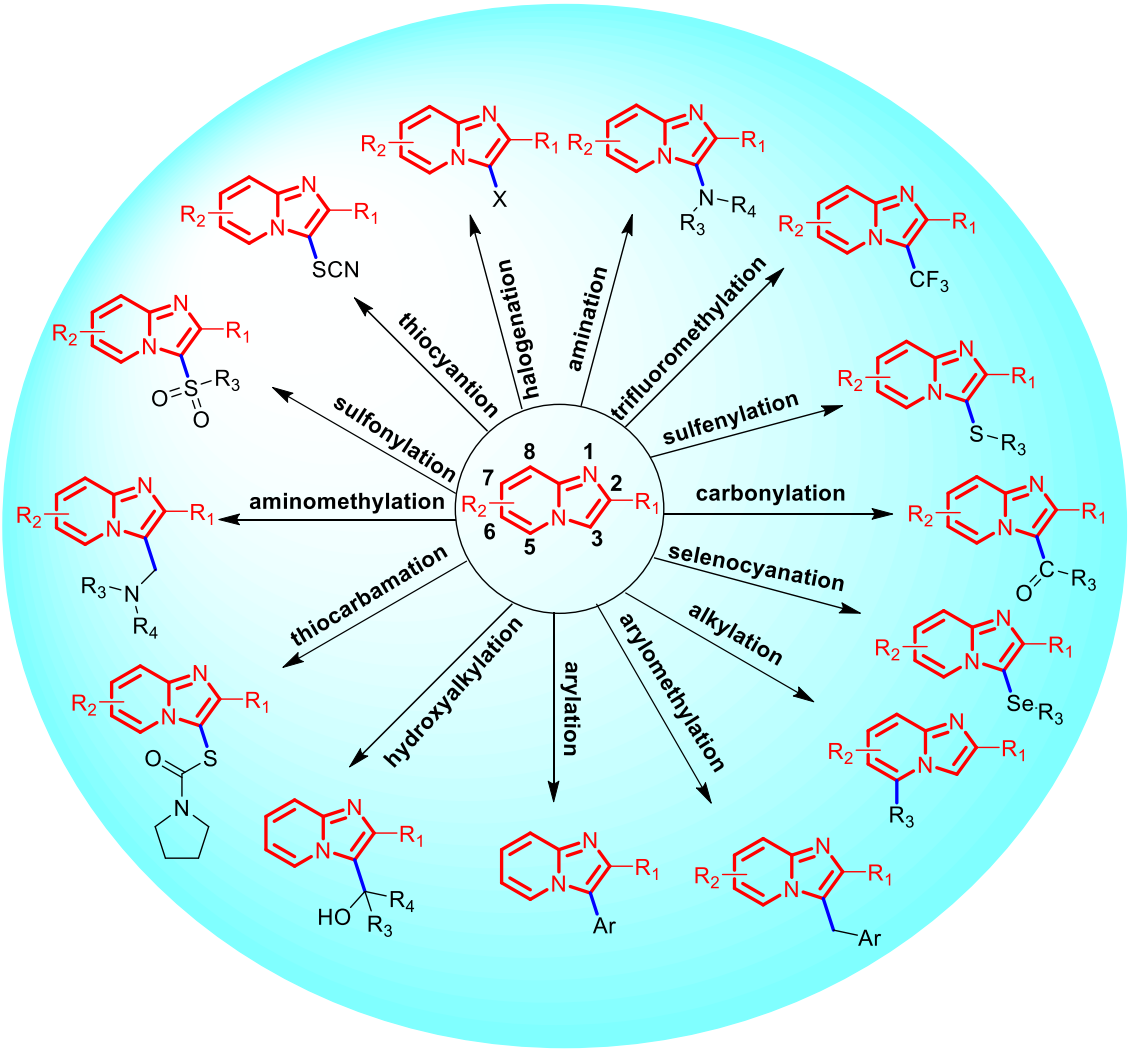
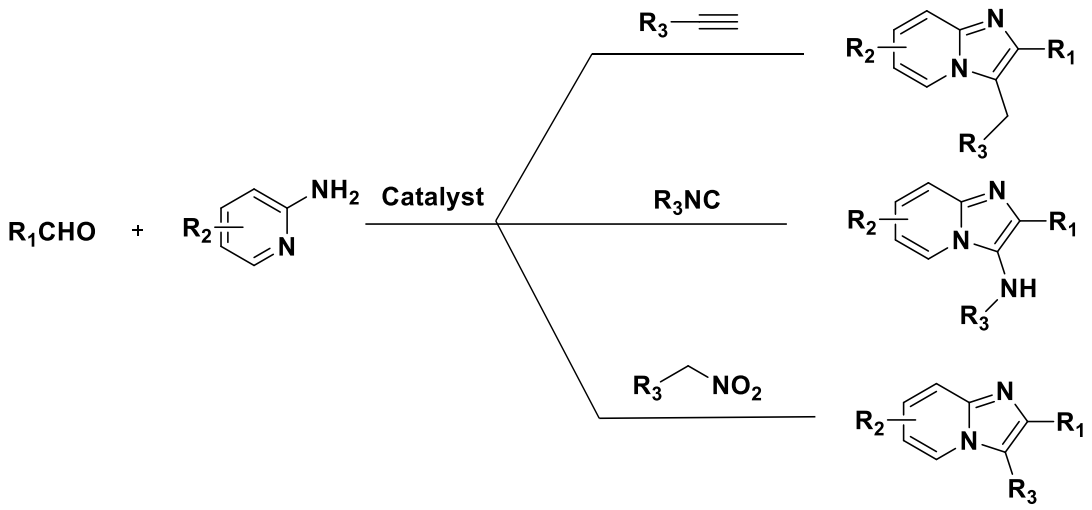


Figure 1.6: Examples of functionalised imidazo[1,2-a]pyridines.

1.5.1 Multicomponent Approach

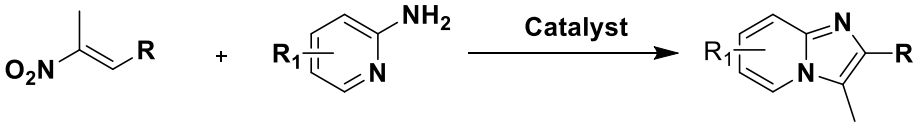
A multicomponent method that involves the reaction of 2-aminopyridine, aldehyde, and cyanide or isocyanide with the help of different catalysts has been used to synthesize imidazo[1,2-a]pyridines. These catalysts include scandium triflate,[34] copper,[35] K_2CO_3,[36] and bromodimethylsulfonium bromide (BDMS).[37] Furthermore, 2-aminopyridine, aldehyde, and terminal alkyne can be reacted to produce imidazo[1,2-a]pyridines using catalysts including $Cu(OTf)_3$,[38] $CuSO_4$, [39] and nano-Fe_3O_4–$KHSO_4{\cdot}SiO_2$.[40] The reaction of nitromethane, aldehyde, and 2-aminopyridine can also synthesize them.[41] (Scheme 1.2)



Scheme 1.2: Imidazo[1,2-a]pyridines synthesis using multicomponent reaction.

1.5.2 Cascade reaction

Imidazo[1,2-a]pyridines have been synthesized through a cascade reaction involving 2-aminopyridine and nitroalkenes. This process utilizes various catalysts to facilitate the reaction. For instance, iron(II)[42] catalysts have been employed, as well as iron(III) catalysts.[43] These catalytic methods have proven effective in producing imidazo[1,2-a]pyridines, showcasing the versatility and efficiency of iron-based catalysts in such tandem reactions. (Scheme 1.3)

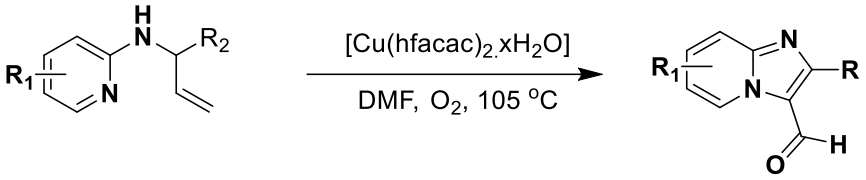


Scheme 1.3: Imidazo[1,2-a]pyridines synthesis using cascade reaction

1.5.3 Aminooxygenation

Imidazo[1,2-a]pyridines have also been derived via a copper-catalysed intramolecular dehydrogenative aminooxygenation reaction.[44] This catalytic process not only enhances the

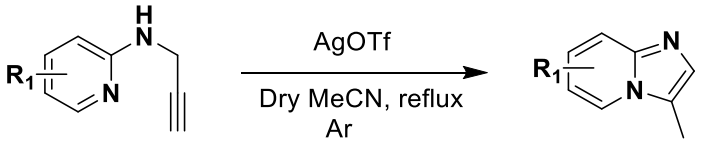
efficiency of the synthesis but also provides a streamlined approach to constructing the imidazo[1,2-a]pyridine framework. (Scheme 1.4)



Scheme 1.4: Imidazo[1,2-a]pyridines synthesis through aminoxygenation

1.5.4 Hydroamination

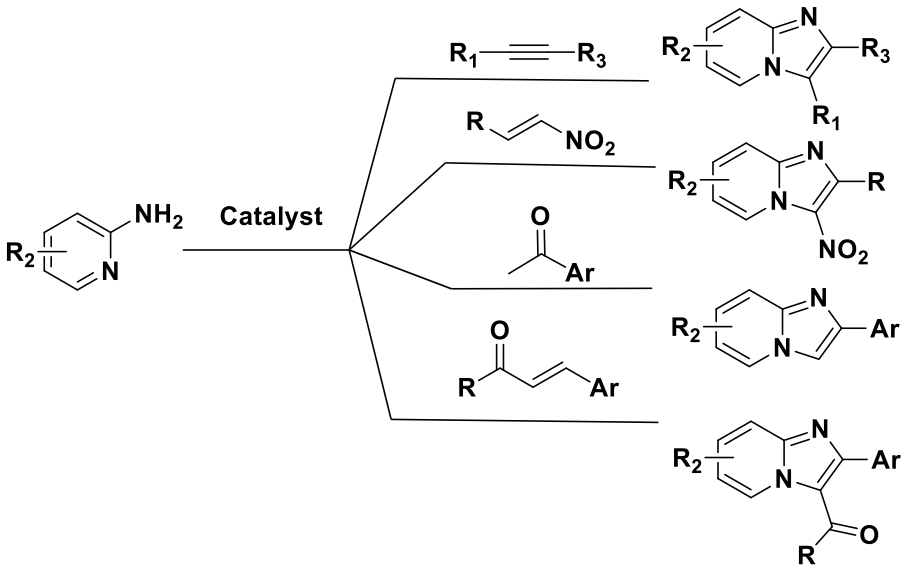
Chioua has pioneered a synthetic method that leverages silver (Ag) as a catalyst to expedite the cyclization of N-(prop-2-yn-1-yl)pyridine-2-*a*mines, yielding 3-methylimidazo[1,2-a]pyridines. This approach effectively generates a imidazo[1,2-a]pyridine ring structure, incorporating a methyl group on the third position.[45] (Scheme 1.5)



Scheme 1.5: Imidazo[1,2-a]pyridines synthesis through a hydroamination.

1.5.5 Oxidative Process

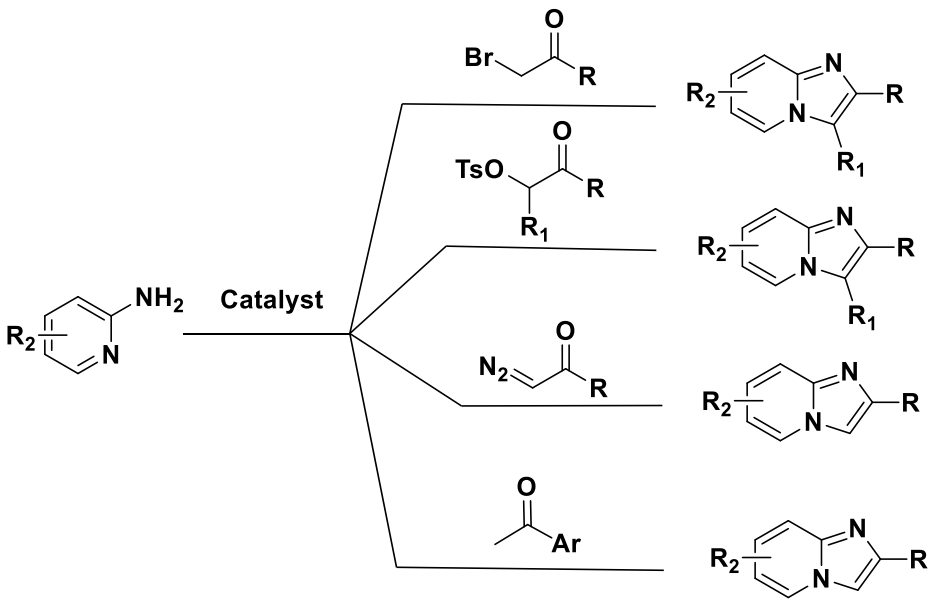
Imidazo[1,2-a]pyridines have been synthesized through the oxidative coupling of 2-aminopyridine with a range of reagents, including alkynes,[46-48] nitroolefins,[49] aryl methyl ketones,[50-52] and chalcones,[53] as reported in various studies between 2012 and 2018. Different metal catalysts have been used to facilitate these oxidative coupling reactions, highlighting the diverse catalytic systems capable of generating imidazo[1,2-a]pyridine structures. (**Scheme 1.6**)



Scheme 1.6: Imidazo[1,2-a]pyridines synthesis through a oxidative coupling.

1.5.6 Condensation Reaction

Imidazo[1,2-a]pyridines have been synthesized using various methods, including the condensation of α-haloketones and 2-aminopyridines with different catalysts like neutral Al_2O_3,[54] $NaHCO_3$,[55] MgO,[56] and even in catalyst-free conditions.[57-59] This synthesis has also been achieved through the reaction of 2-aminopyridine with substrates such as α-tosyloxyketones, catalyzed by various agents including $BPyBF_4$ with Na_2CO_3,[60] α-diazoketones catalyzed by copper,[61] and methyl aryl ketones in the presence of catalysts like iodobenzene,[62] I_2/NaOH, graphene oxide (GO)/NaI,[63] iodine ammonium acetate,[64] NBS,[65] I_2 in cyclohexane,[66] HI,[67] and $FeCl_3/I_2$.[68] These methods span from 2001 to 2019, demonstrating the evolution and diversity of catalysts employed in the synthesis of imidazo[1,2-a]pyridines. (Scheme 1.7)



Scheme 1.7: Imidazo[1,2-a]pyridines synthesis through a oxidative process.

1.6 Coumarin

Coumarin compounds are noteworthy commonly appearing and synthetic oxygen-containing heterocyclic compounds, characterized by their distinctive benzopyrone framework. This unique structure enables coumarin analogs to interact with an array of enzymes and receptors in organisms through weak bond interactions, making them extensively utilized in medicinal chemistry. The history of coumarin dates back to 1820 when Vogel successfully isolated it from tonka beans, also referred to as coumarou in French.[69]

The benzopyrone structure of coumarins underpins their versatility and efficacy in interacting with biological molecules, which has led to their widespread application in medicinal chemistry. These compounds play a pivotal role in diverse natural processes, particularly in plant biology. Coumarins are involved in the actions of plant growth hormones and growth regulators, as well as in controlling essential processes such as respiration and photosynthesis.[70]

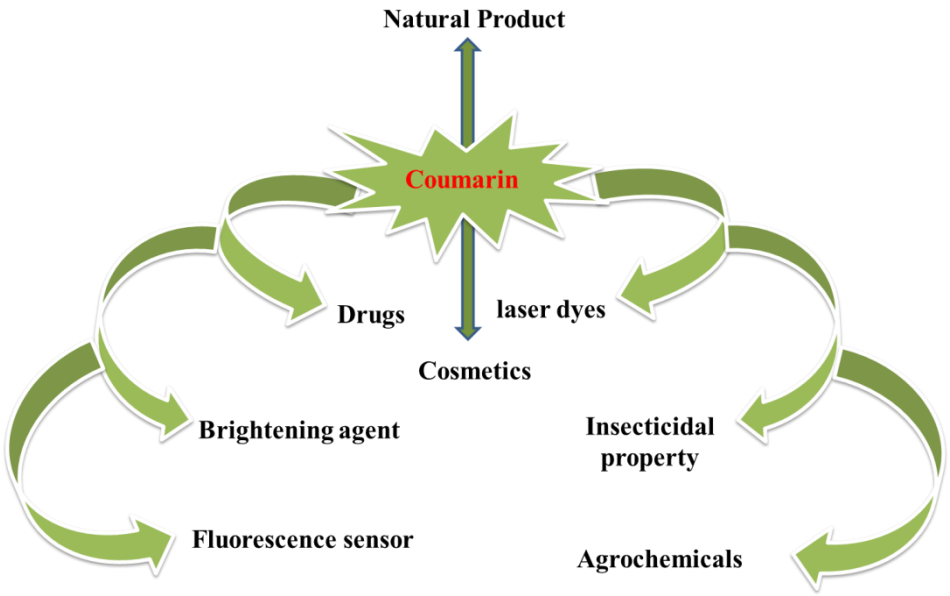


Figure 1.7: Importance of coumarin in various fields.

In recent years, the field of supramolecular chemistry, which holds significant importance in pharmaceutical science, has seen the emergence of coumarin-containing supramolecular medicines as a novel class of drugs. Beyond their medicinal applications, coumarins have been extensively investigated for their properties in various other fields. They are used in fragrance and perfume formulations, as additives in food and cosmetics, in laser dyes, agrochemicals, brightening agents, insecticides, fluorescence sensors, and in diverse drug formulations.[71]

Figure 1.8 illustrates several biologically active natural products and drugs containing coumarin. For instance, Umbelliferon is employed as a sunscreen agent, Dicoumarol is utilized as an anticoagulant drug, Seselin functions as a significant metabolite, Calanolide A exhibits anti-microbial activities, Chlorobiosin is used as an antimicrobial agent, and Lamellarin D shown cytotoxic different cancer cell lines. These examples underscore the wide-ranging applications of coumarins across different fields.

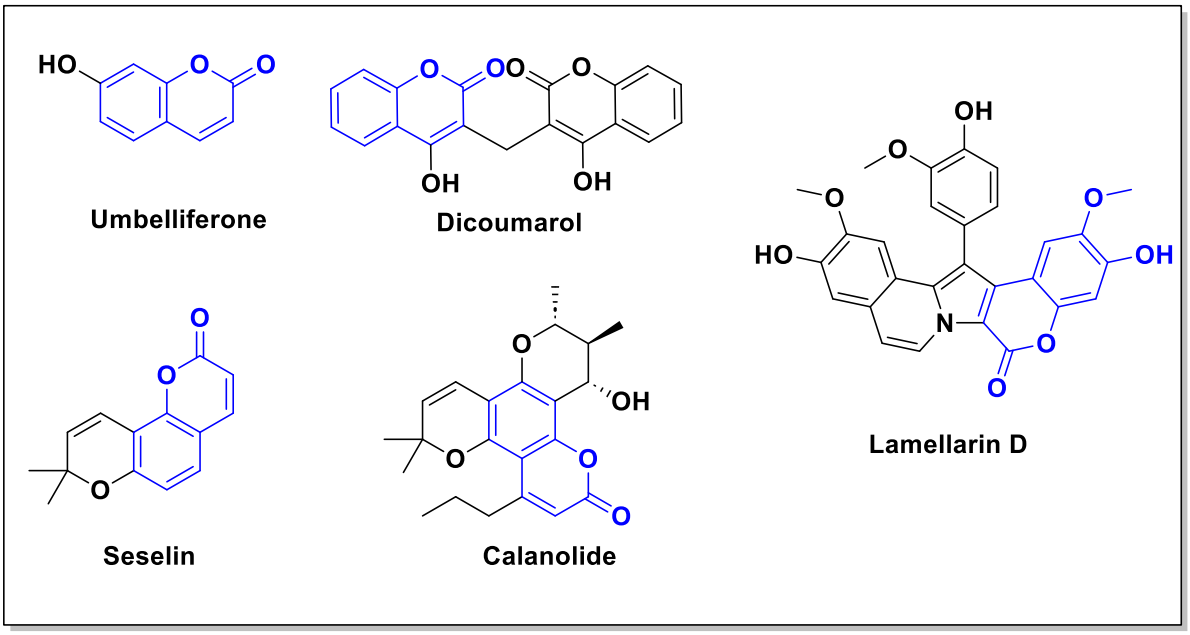


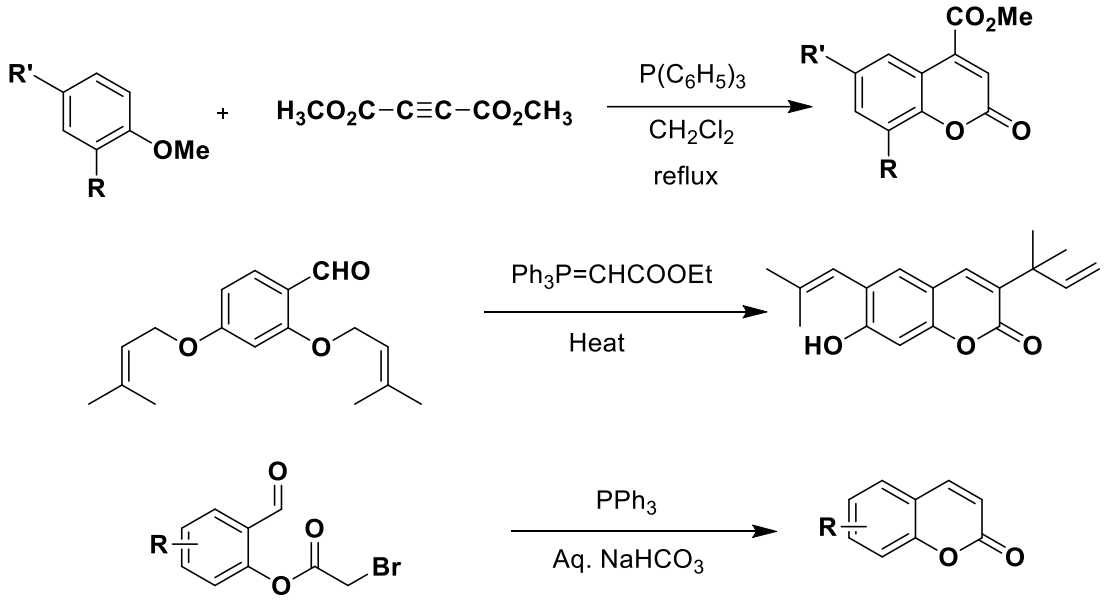
Figure 1.8: Some examples of biologically active coumarins.

Given the extensive utility and significance of coumarins, numerous natural coumarins have been isolated from sources such as fungi, bacteria, and plants. Additionally, coumarins can be synthesized through chemical methods.[72,73] The synthesis of coumarins has consistently been a subject of great interest for organic chemists, leading to the development of various methodologies for synthesizing this biologically important moiety.

The literature describes numerous methods for the synthesis of coumarins, employing various starting reagents and catalysts. Some of the notable synthetic approaches include the Wittig reaction, the Perkin reaction, the Baylis-Hilman reaction, Pechmann condensation, and Knoevenagel condensation. These diverse synthetic routes highlight the ingenuity and resourcefulness of organic chemists in creating efficient and effective methods for producing coumarins, thereby facilitating their application in a wide array of scientific and industrial domains.

1.6.1 Wittig Reaction

The utilization of the Wittig reaction in synthesizing natural compounds is a proven method for efficiently creating vital C-C bonds. This reaction has demonstrated its versatility and effectiveness through successfully synthesizing coumarins under diverse reaction conditions.[74-76] (Scheme 1.8)

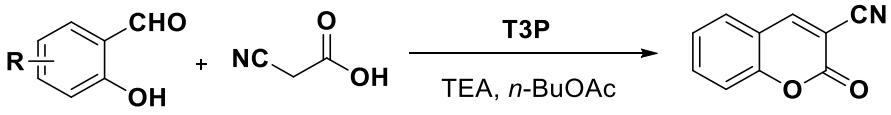


Scheme 1.8: Synthesis of coumarin through a Wittig reaction.

1.6.2 Perkin reaction

The Perkin reaction is another useful approach for the production of coumarins. This classical reaction is widely used in organic chemistry due to its effectiveness in forming carbon-carbon bonds. A notable example of its application in the synthesis of coumarins was described by Augustine and co-workers. They reported a detailed methodology for synthesizing coumarins from salicylaldehyde and cyanoacetic acid, mediated by propylphosphonic anhydride (T3P). In their procedure, salicylaldehyde, a key aromatic aldehyde, reacts with cyanoacetic acid in the presence of T3P, which serves as a dehydrating agent, facilitating the formation of the

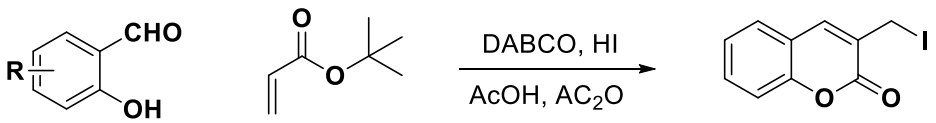
coumarin ring system. This approach under Perkin reaction conditions highlights the utility of T3P in promoting the cyclization process, leading to the efficient synthesis of coumarin derivatives. The use of T3P in this reaction offers several advantages. It not only acts as a strong dehydrating agent but also enhances the reaction efficiency by providing a mild and more environmentally friendly alternative compared to traditional methods. This makes the synthesis process more sustainable and aligns with green chemistry principles.[77] (Scheme 1.9)



Scheme 1.9: Synthesis of coumarin through Perkin reaction.

1.6.3 Baylis-Hilmann Reaction

When salicylaldehyde is combined with *t*-butyl acrylate, DABCO, hydroiodic acid, and acetic acid, it leads to the creation of coumarins through the Baylis-Hillman method. The existance of DABCO, HI, and acetic acid under catalytic and acidic conditions efficiently facilitates the formation of the crucial carbon-carbon bond and subsequent cyclization, resulting in the formation of valuable coumarin derivatives. This process holds great promise for the development of important coumarins.[78](Scheme 1.10)



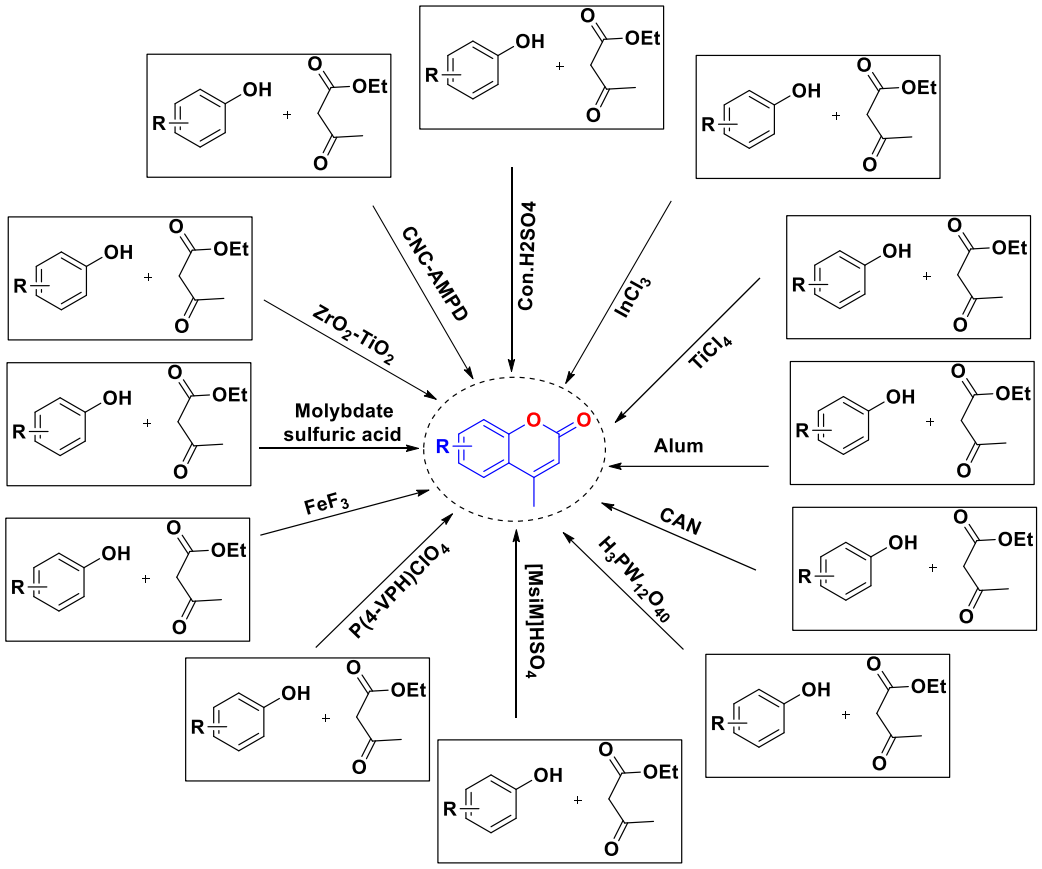
Scheme 1.10: Synthesis of coumarins through a Baylis-Hilmann reaction.

1.6.4 Pechmann Condensation

The synthesis of coumarins has traditionally been accomplished over the decades using Pechmann condensation. This approach involves the synthesis of coumarins by reacting phenol with maleic acid or β-keto esters while using different catalysts. Several catalysts have been employed to enhance the efficiency of the Pechmann reaction, including:

- Concentrated sulfuric acid
- Indium(III) chloride
- Titanium tetrachloride ($TiCl_4$)
- Alum
- Ceric ammonium nitrate (CAN)
- Phosphotungstic acid
- Acidic ionic liquid
- Poly(4-vinylpyridinium) perchlorate
- Ferric fluoride (FeF_3)
- Molybdate sulfuric acid
- Zirconia-based heterogeneous catalysts
- Cellulose nanocrystal-supported palladium nanoparticles

These catalysts have been shown to effectively facilitate the synthesis of coumarins by promoting the cyclization process, thus demonstrating the versatility and robustness of the Pechmann reaction in producing these valuable compounds.[79-90] (Scheme 1.11)



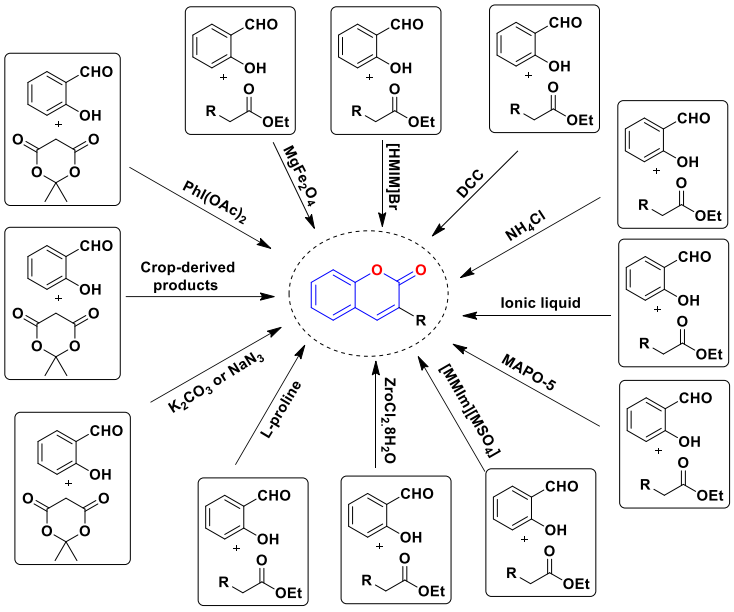
Scheme 1.11: Synthesis of coumarin using a various catalyst through Pechmann reaction.

1.6.5 Knoevenagel condensation

The Knoevenagel condensation is one of the popular processes for synthesizing coumarins. In this methodology, coumarins are synthesized by reacting o-hydroxybenzaldehydes, such as salicylaldehyde analogs, with active methylene compounds in the existence of various catalysts. Notable catalysts used in this reaction include:

- Dicyclohexylcarbodiimide (DCC)
- Ammonium chloride
- Ionic liquids
- Lewis acid metal ion-exchanged MAPO-5 molecular sieves

- [MMIm][MSO_4] containing proline
- Zirconyl chloride octahydrate ($ZrOCl_2.8H_2O$)
- L-proline
- Potassium carbonate (K_2CO_3) or sodium azide (NaN_3)
- Crop-derived products
- Iodobenzene diacetate ($PhI(OAc)_2$)
- Magnesium ferrite ($MgFe_2O_4$) nanocatalyst
- 1-Methyl-3-pentylimidazolium bromide ([HMIM]Br), piperidine, and acetic acid (AcOH) (Scheme 1.12) [90-99]



Scheme 1.12: Synthesis of coumarin using a various catalyst through a Knoevenagel condensation.

These catalysts have proven effective in facilitating the Knoevenagel condensation, making this method highly efficient for synthesising coumarins. The reaction conditions and choice of catalysts can significantly influence the yield and selectivity of the desired coumarin products, underscoring the versatility and practicality of this synthetic approach.

1.7 Objectives of Thesis Work

From this brief introduction, it's evident that heterocyclic compounds play a crucial role in a plethora of fields such as organic synthesis, biochemistry, medicinal chemistry, material sciences, and agriculture. Consequently, our goal is to devise efficient, eco-friendly approaches for synthesizing and functionalizing biologically relevant heterocyclic compounds through transition metal-free processes. This endeavour aims at propelling the progression of green and sustainable chemistry practices. The main focus of this thesis work includes:

1. **Synthesis of Diindolylmethanes**: To synthesize diindolylmethanes from alcohols and indoles using potassium persulfate as a green oxidizing agent.
2. **Investigation of Diindolylmethane Synthesi**s: To investigate the synthesis of diindolylmethanes from arylacetic acid and alcohols by utilizing potassium persulfate with glucose as an activator.
3. **C3 Functionalization of Imidazo[1,2-a]pyridines**: To develop a practical method for the synthesis of C3 functionalized imidazo[1,2-a]pyridines employing glyoxylic acid and potassium persulfate under metal-free conditions.
4. **Synthesis of Aminated Coumarins**: To investigate a new, simple, effective, and scalable path for synthesizing aminated coumarins using a multifunctional reagent, 2-4-dichloropyrazine in a greener and more sustainable approach.
5. **Amidation and Anti-*a*lzheimer Compounds**: To demonstrate the use of tert-butyl nitrite and N-hydroimides to generate N-hydroxyimide esters, which are subsequently converted into amides in one pot. Additionally, to apply this amidation method to the synthesis of anti-Alzheimer’s compounds.

By achieving these objectives, this work aims to make a significant contribution to the field of green chemistry, promoting more sustainable and environmentally friendly chemical processes.

References

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