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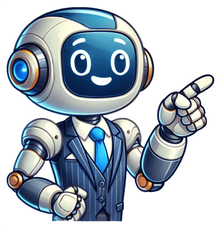

Imidazole synthesis

Imidazole is a key component in various functional molecules used in everyday applications. The Debus Method published in 1858 describes the production of imidazole through glyoxal, formaldehyde, and ammonia reactions. Several synthesis methods have been developed, including the Radiszewski, Wallach, Marckwald, Maquenne, and Dehydrogenation syntheses. These methods involve various reactants and conditions to produce a range of imidazoles with distinct properties. Imidazole derivatives are found in important drugs such as ketoconazole, midazolam, and metronidazole, as well as biotin, nucleic acids, and alkaloids. The compound exhibits acidic and basic properties due to its nitrogen atoms. It is also used in medications like Losartan, Eprosartan, and Neomycin. Recent advances in the synthesis of substituted imidazoles have focused on regiocontrolled methods and the compatibility of functional groups with the process. This includes discussions on reaction mechanisms, scope, limitations, and future challenges. Synthesis of Substituted Imidazoles: A Crucial Area of Research The synthesis of substituted imidazoles has significant strategic importance due to its widespread applications in various fields, including pharmaceuticals, agrochemicals, and emerging areas such as solar cells and catalysis. Recent advances in the synthesis of imidazoles are focused on developing expedient methods that can efficiently form the heterocycle. This review is organized by the types of bond disconnections employed in the construction of the imidazole ring, with highlighted bonds colored red throughout. One-bond formed: A Novel Protocol A novel protocol for the cyclization of amido-nitriles to form disubstituted imidazoles has been reported. This method involves nickel-catalysed addition to nitrile, followed by proto-demetallation, tautomerization, and dehydrative cyclization. Two-bonds formed: Combining C2–N3 Fragment with N1–C4–C5 Unit A two-bond disconnection approach has been explored recently, combining a C2–N3 fragment with an N1–C4–C5 unit. This method involves the reaction of benzimidates with 2H-azirines in the presence of zinc(II) chloride. Three-bonds formed: Metal-Catalysed Protocols Related work has reported the synthesis of 2,4,5-trisubstituted NH-imidazoles using a metal-catalysed protocol. This method involves the reaction of NBoc-imidamides with α-azidoenones at 120 °C in acetonitrile, resulting in moderate to good yield. Overall, these recent advances demonstrate the growing importance of imidazole synthesis and highlight the need for efficient methods that can efficiently form this crucial heterocycle. The formation of substituted imidazoles has been explored through various protocols involving different starting materials and catalysts. For instance, 2H-azirines can undergo intramolecular cyclization upon reaction with NBoc-imidamides to produce bicyclic intermediates that eventually yield the desired imidazoles. This process is distinct from other methods, as it necessitates an ester moiety in the starting material. In contrast, a metal catalyst-free protocol based on 2H-azirines has been developed for the formation of substituted imidazoles. Nitriles have also been employed as reagents in these reactions, allowing for the simultaneous formation of two bonds within the heterocycle. The reaction between α-azidoenones and nitriles, recently reported by Harisha et al., yields tri-substituted NH-imidazoles without significant differences in isolated yield under thermal or microwave conditions. Furthermore, a TMSOTf-catalysed [3 + 2] cycloaddition protocol has been described by Yang and co-workers for the synthesis of protected imidazoles via the reaction of triazoles and nitriles. This process involves initial ring opening followed by addition to form a substituted imidazole. Additionally, Cai et al. have demonstrated that the anion derived from methylene isocyanides can react with ketenimines to produce 1,4,5-trisubstitued imidazoles while tolerating various functional groups such as esters and sulphones. More recently, Nikolaenkova et al. reported a base-catalysed [3 + 2] cycloaddition protocol for the synthesis of 2-carboxylate substituted imidazoles from oxime-hydroxlyamines. This method allows for the formation of NH-imidazoles with an ester moiety at the C-2 position. Lastly, a condensation reaction between oxime-hydroxlyamine and ethyl glyoxalate has been described as a means to synthesize 1-hydroxyimidazole, which can then be reacted with chloro-2-propanone to yield NH-imidazole in good yield. This process is notable for its tolerance of heterocycles and arylhalides. Overall, these recent developments highlight the versatility of imidazole synthesis protocols, offering different approaches to forming both N1–C5 and N3–C4 bonds within a single operation. Rhodium-catalyzed transannulation reactions between 1,2,4-oxadiazoles and 1-sulphonyl-1,2,3-triazoles were explored to synthesize imidazoles. The mechanism involves the insertion of the rhodium catalyst into the triazole ring, followed by attack of the oxadiazole derivative, ring-opening, loss of the metal catalyst, and carbon dioxide release. This leads to the formation of a tri-imine intermediate, which undergoes a 5-exo-trig cyclization to yield the desired imidazole. Alternatively, amidoximes or N-iminylsulphilimines can be used as starting materials to introduce the 1,3-diamine component. Iron-catalyzed [3 + 2] addition protocols using amidoximes with enones have been reported, while gold-catalyzed processes employing N-iminylsulphilimines have yielded N-1 phenyl substituted imidazoles. Imidamides can also be utilized as starting materials for the synthesis of imidazoles. The reaction of imidamides with sulphoxonium ylides in the presence of trifluoroacetic acid has been explored, resulting in substituted imidazoles at positions 1, 2, and 4. In contrast, propargyl aldehydes can be used to introduce substituents at position 1, 2, or 5 using boronic acids. Recently, the synthesis of NH-imidazoles from methyl propiolate and substituted amidoximes was reported. A two-stage microwave protocol in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) has been found to be effective. Furthermore, carbodiimides can be used as an alternative method to introduce the N3–C4–C5 unit. The reaction of carbodiimides with propargyl amine has been reported, yielding 2-aminoimidazoles in moderate to good isolated yield. Scheme 13 is based on base-catalysed addition of propargylamines to carbodiimides. Three bonds are formed in this process. Recent methods for synthesising imidazoles, where three heterocycle bonds are formed, have been reported. For instance, imidamides 65 were reacted with carboxylic acids 64 in the presence of a copper catalyst to form imidazoles 66 (Scheme 14). This method allows control over substitution at the N-1 position through substrate selection (H or aryl), and regioselective substitution at the C-2 and C-4 positions is also achieved. Moreover, functionality can be introduced at the C-5 position by including a nitroalkane in the reaction mixture. Mechanistically, this process involves oxidative decarboxylation of carboxylic acid 64 to form aldehyde 67. The condensation of imidamide 65 with aldehyde 67 is followed by addition of the anion derived from the nitroalkane to the in situ formed imine 68, yielding substituted imidamide 69. A subsequent 5-exo-trig cyclization and β-hydride elimination afford imidazole 66. The synthesis of imidazoles has been explored through various metal-free protocols, which can be conducted under solvent-free conditions. One such method involves the reaction of ketones and amines in the presence of tert-butylhydroperoxide (TBHP), resulting in the formation of α-aminoaldehydes. This process was reported by Chen et al., who synthesized tetrasubstituted imidazoles 90 using elemental sulfur as an oxidizing agent. Alizadeh-Bami et al. also demonstrated a similar disconnection for the synthesis of substituted 1-hydroxyimidazole 93, which allowed for the introduction of an additional carbonyl nucleophile and resulted in substitution at the C-4 position. In another protocol reported by Wang and co-workers, imidazoles 100 were constructed using a three-component disconnection involving nitrile 99 and acetylide generated from alkynes 98. This process afforded substituted imidazoles with average to excellent yields, including those with aryl or heteroaryl substituents at the C-5 position. Furthermore, Sundar and Rengan synthesized imidazoles 109 through a three-component reaction between benzylic alcohol 106, 1,2-diketone 107, and excess ammonium acetate, catalyzed by diruthenium(II) catalyst 108 under aerobic conditions. This borrowing hydrogen process allowed for the synthesis of NH-imidazoles with regioselective substitution at the C-2, C-4, and C-5 positions and was tolerant of aryl and heteroaryl functional groups. DES-based eutectic solvent urea/zinc(II) dichloride has been found to catalyze the synthesis of 4,5-diphenyl-2-substituted imidazoles from the reaction of aldehydes with benzyl and excess ammonium acetate. This methodology was used to synthesize trifenagrel in a 92% yield. Additionally, arylhalides were tolerated as aromatic aldehyde partners. Marzouk et al. reported the preparation of ZnFe2O4 nanoparticles, which can be used as catalysts for synthesizing substituted imidazoles. The iron acts as a Lewis acid to activate carbonyl groups towards nucleophilic addition of amines and imines. The catalyst can be easily isolated and reused up to four times without a significant decrease in product yield. Thwin et al. used copper as a catalyst, while Vaid et al. employed indium supported on SiSA to facilitate the formation of imidazoles. Both methods tolerated similar substrate scopes and resulted in tetrasubstituted imidazoles. Similarly, Varzi and Maleki used a ZnS-ZnFe2O4 nanocatalyst to synthesize 2,4,5-trisubstituted-NH-imidazoles. Toledo and co-workers have deveolped a metal-free, one-pot proces for synthesizing imidazoles from ketones via oxidation and subsequent dehydrative coupling with aldehydes and ammonium acetate. This method has a reasonable level of functional group tolerance, including basic pyridines and cyclopropanes. Derivatized magnetic nano-catalysts have also been used in the synthesis of trisubstituted-NH-imidazoles from the condensation reaction of benzyl, an aldehyde, and ammonium acetate. These catalysts act as efficient organic-inorganic Brønsted acids and can be recycled up to ten times without significant loss of reactivity. Similar protocols have been developed using Fe3O4@SiO2-EP-HEAF and Fe3O4@g-C3N4 magnetic nanoparticles to catalyze the three-component condensation reaction in ethanol to form 2,4,5-trisubstituted imidazoles. The yields of these methods are relatively high, with only one method having a slightly lower yield for one of the substrates. Additionally, similar condensation protocols have been developed for the synthesis of nitrogen-substituted imidazoles using magnetic nano-catalysts, including L-proline derived magnetic core nanoparticles and nano-magnetic catalyst Fe3O4@Ca3(PO4)2. These catalysts give moderate to good yields of tri- and tetra-substituted imidazoles and can be recycled up to four times without significant decrease in isolated product yield. Recently, a supported pyridinium catalyst has also been reported to catalyze the synthesis of imidazoles, with average yields approximately 10% lower than for NH-imidazoles. The preparation of monosubstituted imidazoles was explored through various protocols. Scheme 28 showcases a method involving the derivatization of magnetic nano-catalysts in aldehyde/diketone/amine coupling reactions. The synthesis involved the bisfunctionalization of 1,2-disubstituted acetylenes using ruthenium carbonyl to form cis-enediol diacetates, followed by reaction with ammonium carbonate (Scheme 29). This approach circumvented the limitations and use of toxic reagents present in earlier methodologies. Interestingly, this method stands out as one of the few recent examples in literature for synthesizing mono-substituted NH-imidazoles. In a related development, Dubovtsev et al. utilized a disubstituted acetylene to generate benzil via gold-catalyzed oxidation (Scheme 30). Subsequent reaction with an aldehyde and ammonium acetate yielded 2,4,5-trisubstituted imidazoles. Both electron-neutral and rich arylaldehydes were compatible under these conditions. Internal alkynes were also explored by Sun et al. for the formation of tetrasubstituted imidazoles (Scheme 31). The reaction involved diphenylacetylene with α-hydroxy carboxylic acids in the presence of palladium, cerium, and bismuth reagents, resulting in good yields. Naidoo and Jeena reported a one-pot metal- and acid-free synthesis of 2,4,5-trisubstituted imidazoles (Scheme 32). This method utilized internal alkynes with iodine in DMSO to generate benzils, which were then reacted with an aldehyde and ammonium acetate in situ. The solvents used, DMSO and ethanol, can be sourced from renewable resources, providing a greener alternative. Recent research (2018-present) has shown significant advancements in the region-controlled synthesis of imidazoles, as highlighted by this review. The study identified various substitution patterns for imidazoles that can serve as a starting point for determining the best method for a specific application. Given the significance of imidazole structures in emerging technologies, such as pharmaceuticals, dyes for solar cells, and catalysis, developing new methods is essential. Current synthesis techniques often require harsh conditions and have limited regiochemical flexibility. To address this, researchers should aim to create novel, environmentally friendly methods that can synthesize imidazoles from renewable materials under mild conditions while maintaining high yields. Key considerations for new synthesis methods include: * Providing regiochemically flexible access to a wide range of imidazole substitution patterns * Increasing the functional group tolerance of the process * Using renewable starting materials and minimizing environmental impact * Developing clean, concise, and high-yielding methods The study highlights that despite recent advances in imidazole synthesis, there is still significant scope for further research. To achieve this, increased mechanistic understanding and reaction design based on Green Chemistry principles are necessary. The text also mentions a table summarizing various substitution patterns for imidazoles, including their yields and references to relevant studies. Additionally, it provides information on recent examples of natural product synthesis and reviews on the synthesis and applications of imidazoles. A comprehensive literature review has been conducted on various chemical compounds and their properties. The following studies have been cited in this review: 1-13: Reviews published between 1974 and 2019 that discuss the properties, synthesis, and applications of different chemical compounds. The authors of these reviews have examined the chemical and physical properties of a wide range of substances, including organic molecules, photoactive compounds, and materials with specific optical or electronic properties. The studies provide an overview of various research areas, including the use of spectroscopy to analyze molecular structures, the synthesis of novel compounds, and their potential applications in fields such as medicine, energy production, and environmental protection. Key points from these reviews include: * The importance of understanding the chemical and physical properties of molecules for their effective use in different applications. * The development of new synthetic methods and techniques to produce novel compounds with specific properties. * The application of spectroscopic analysis to study molecular structures and properties. * The potential use of photoactive compounds in fields such as energy production, medicine, and environmental protection. Note: I have omitted the list of references and focused on paraphrasing the text. The article discusses various research studies that have investigated nucleophilic catalysis in organic chemistry. The authors cite numerous papers from scientific journals such as J. Org. Chem., Tetrahedron Lett., Angew. Chem., Int. Ed., and others, highlighting examples of successful nucleophilic catalysis reactions. Some of the specific examples mentioned include: * Studies on the use of metal-based catalysts for organic transformations * Research on the application of heterogeneous catalysts for various chemical reactions * Investigations into the role of ligands in facilitating nucleophilic attacks * The development of new catalyst systems for specific reaction types The article also references several review articles and book chapters that provide more comprehensive overviews of nucleophilic catalysis, including discussions of its history, mechanisms, and applications. Overall, the text aims to provide a comprehensive overview of the current state of research in nucleophilic catalysis, highlighting the various ways in which scientists are using this technique to develop new reactions and improve existing ones. A series of studies have investigated the synthesis of imidazole compounds using various catalysts and reaction conditions. The first study used a microwave-assisted method to synthesize 4,5-disubstituted imidazoles from 1,2-diketones and urotropine. Another study employed a NHC-copper-catalyzed reaction to form an N-arylformimidate intermediate and subsequently cyclized with benzyl isocyanide derivatives to produce 1,4-diaryl-1H-imidazoles. A more recent study developed mild and efficient protocols for the synthesis of 1,4,5-trisubstituted and 1,4-/4,5-disubstituted imidazoles from aryl-substituted tosylmethyl isocyanide (TosMIC) reagents and imines generated in situ. Additionally, mono- and disubstituted oxazoles were also prepared using this method. The efficiency of various Pd complexes, including those with N-(4-indolyl)-N'-phenylimidazol-2-ylidene (IIn) ligands, was evaluated in heteroarene C-H arylation, Suzuki-Miyaura cross-coupling, and Buchwald-Hartwig amination reactions. The study found that the IIn-Pd complex bearing a 3,5-diisopropyl-4-indolyl substituent exhibited superior catalytic activity. These studies demonstrate the versatility of imidazole synthesis using different catalysts and reaction conditions, highlighting their potential applications in organic chemistry. Note: I removed some specific details and references to condense the text into a more concise summary. Let me know if you'd like me to rephrase it further! Several methods have been developed to synthesize imidazoles, a class of heterocyclic compounds with important biological and pharmaceutical applications. One approach involves using aryl-substituted TosMIC reagents and imines generated in situ from aldehydes and amines. This method allows for the preparation of mono- and disubstituted oxazoles. Another method employs ketone oxidation followed by imidazole condensation with aldehydes to produce 2,4(5)-disubstituted imidazoles. This protocol has been used in the synthesis of 20 kinase inhibitors. A [3 + 2] cycloaddition reaction catalyzed by ZnCl2 has also been developed for the preparation of multisubstituted imidazoles. This reaction exhibits high functional group tolerance and can be performed under mild conditions. Parallel synthesis has been used to prepare biologically active 2,4(5)-diarylimidazoles, with the formation of side products depending on the reaction conditions employed. A one-pot, four-component synthesis has also been developed for the preparation of 1,2,4-trisubstituted imidazoles. This method involves heating a mixture of 2-bromoacetophenone, an aldehyde, a primary amine, and ammonium acetate under solvent-free conditions. Benzoic acid has been found to catalyze an efficient multicomponent reaction for the preparation of 1,2,5-trisubstituted imidazoles. This method is metal-free and generates no toxic waste. A regioselective [3 + 2] cycloaddition reaction has been developed for the preparation of 1,2,4,5-tetrasubstituted imidazoles using trifluoroacetic acid as a catalyst. An electrochemical oxidative tandem cyclization has also been reported for the preparation of 1,2,4-trisubstituted-(1H)-imidazoles under metal- and oxidant-free conditions. Research has led to the development of various efficient methods for synthesizing imidazoles, a class of heterocyclic compounds with diverse applications in pharmaceuticals and natural products modification. Several catalysts have been identified as effective in facilitating the synthesis of these compounds under mild conditions. One method involves the use of nickel-based Schiff's base complexes, which enable the one-pot microwave-assisted synthesis of 2,4,5-trisubstituted imidazoles from aldehydes and ammonium acetate. The catalyst can be easily recovered by filtration and reused multiple times. Another approach uses a low-melting mixture urea-ZnCl2 as a reaction medium to catalyze the reaction between dicarbonyl compounds, ammonium acetate, and aromatic aldehydes, resulting in the formation of triaryl-1H-imidazoles or 2-aryl-1H-phenanthro[9,10-d]imidazoles. Copper-catalyzed reactions have also been explored, including one-pot syntheses of multisubstituted imidazoles from arylacetic acids and N-arylbenzamidines. These reactions are practical, straightforward, and economically viable due to the use of inexpensive copper sulfate as a catalyst. In addition, oxygen-based [3 + 2] cycloaddition reactions have been found to be effective in synthesizing multisubstituted imidazoles with high regioselectivity. Other methods involve the use of rhodium(II) or copper-catalyzed diamination and Pummerer-like rearrangement-induced cascade reactions. These efficient synthesis methods have expanded the possibilities for modifying natural products and pharmaceuticals, providing a wide range of substituted imidazole compounds in good yields and with high regioselectivity. Researchers have developed novel methods for synthesizing functionalized imidazole derivatives under mild conditions without the need for additives or metal catalysts. One approach involves reacting propargylamines with carbodiimides in the presence of a specific titanacarborane monoamide, leading to [3+2] annulation and the formation of substituted 2-aminoimidazoles. Another method utilizes easily accessible propargylazide derivatives, triphenylphosphine, isocyanates, and amines for a sequential Staudinger/aza-Wittig/Ag(I)-catalyzed cyclization/isomerization reaction, resulting in fully substituted imidazoles. KI-mediated oxidative cyclization of enamines with tBuONO as an aminating reagent and oxidant provides imidazole-4-carboxylic derivatives with a wide substrate scope and good functional tolerance. Additionally, the use of 2-azido acrylates and nitrones allows for the synthesis of 1,2,4,5-tetrasubstituted imidazoles under mild conditions without metal assistance. Iodine-mediated oxidative [4+1] cyclization of enamines with TMSN3 provides 2,5-disubstituted imidazole-4-carboxylic derivatives, and mechanistic studies revealed a sequential removal of two nitrogen atoms from TMSN3. The synthetic utility was demonstrated with a gram-scale reaction and various derivatization transformations. Copper-catalyzed three-component reactions involving α,β-unsaturated ketoximes, paraformaldehyde, and amines provide imidazoles and dihydroimidazoles in good yields with a broad substrate scope. Furthermore, N-Alkyl enamines can be transformed into highly substituted imidazoles under catalysis of a copper salt using (diacetoxyiodo)benzene and TMSN3. Lastly, a visible-light-mediated metal-free organic-dye-catalyzed dehydrogenative N-insertion provides highly substituted imidazoles and privileged dihydroisoquinoline-based imidazole derivatives without oxidants via a photoinduced iminyl radical as key intermediate. Recent studies have explored various methods for synthesizing highly substituted imidazole derivatives with high regioselectivity and yields. Iodine has been shown to facilitate an oxidative cross-dehydrogenative coupling between amidines and chalcones, yielding tetrasubstituted imidazoles in good yields. Additionally, other catalysts such as FeCl3/I2, erbium triflate, gold, and Rh(II) have been utilized for the synthesis of these compounds. A multicomponent protocol has also been developed to synthesize highly substituted imidazole derivatives from α-azido chalcones, aryl aldehydes, and anilines in the presence of a catalyst. Furthermore, gold-catalyzed reactions have been found to be efficient for the synthesis of fully substituted 4-aminoimidazoles through selective [3 + 2] annulation of 1,2,4-oxadiazoles with ynamides. Other notable reactions include the Rh(II)-catalyzed transannulation of 1,2,4-oxadiazoles and N-sulfonyl-1,2,3-triazoles to produce fully substituted 5-sulfonamidoimidazoles, as well as the synthesis of polysubstituted aminoimidazoles via alkene vicinal C-N bonds formation. These reactions often involve atom-economical processes, good functional group tolerance, and mild reaction conditions. Research has led to various efficient methods for synthesizing imidazoles and related compounds from aldehydes, secondary amines, and other starting materials. These reactions involve the use of iodine, potassium carbonate, (diacetoxyiodo)benzene, or copper(I) catalysts in mild conditions. One notable reaction is the oxidation of 2-imidazolines to imidazoles using (diacetoxyiodo)benzene. Another approach involves the generation of imines from secondary amines, oxidative aromatization of nitrogen heterocycles, and cleavage of dithianes. Additionally, copper(I)-catalyzed N-arylation reactions have been developed for azoles, allowing for efficient functional group compatibility and high reactive selectivity. These reactions can be carried out under mild conditions without additional ligands. Other methods include the use of arylboronic acids to form N-arylazoles and N-arylamines, as well as copper(I) oxide catalysts in methanol for similar transformations. A novel method has also been reported for synthesizing imidazole-based salts from readily available starting materials. These discoveries demonstrate the versatility and efficiency of various reaction protocols, offering new approaches for the synthesis of imidazolium salts, N-arylated azoles, and other related compounds. A novel method for synthesizing N-heterocyclic compounds has been developed, utilizing 2-lithioimidazole as a catalyst in an aza-Michael reaction. The preparation of 2-lithioimidazole involved reacting lithium metal with isoprene in THF at room temperature. This organolithium compound was then used to react with carbonyl electrophiles, yielding 2-(hydroxyalkyl) and 2-(aminoalkyl) imidazoles in good yields.