"Overview of Synthetic Approaches to Commercially Successful Drugs with Small-Ring Heterocyclic"

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ABSTRACT

Small-ring heterocycles are essential building blocks in pharmaceutical chemistry, widely found in approved drugs due to their unique reactivity and biological activity. This review summarizes recent synthetic strategies for constructing three- and four-membered rings such as aziridines, β-lactams, and azetidines. These rings exhibit high ring strain, enabling versatile transformations like cycloaddition and nucleophilic substitution. Chalcones are helpful building blocks for making various nitrogen-containing compounds, like pyrroles and triazoles, and eco-friendly methods like microwave and ultrasound treatment often improve this process. Oxygen-containing rings such as tetrahydropyrans and isoxazolines are synthesized via organocatalytic oxa-Michael reactions. Additionally, ring-closing metathesis and copper-catalyzed 1,3-dipolar cycloaddition offer efficient access to five- and six-membered heterocycles under mild, eco-friendly conditions. Thiosemicarbazides are known for synthesizing N-, O-, and S-containing heterocycles but remain underutilized in small-ring construction and biological evaluation. Ternary condensation strategies also yield bioactive fused heterocycles. Future efforts should focus on expanding structural diversity and understanding structure–activity relationships.

Keywords: small-ring heterocycles, cycloaddition, ring-closing metathesis, pharmaceutical chemistry, green chemistry.

INTRODUCTION

The synthesis of 5- and 6-membered heterocyclic compounds has garnered significant attention in recent literature due to their importance in pharmaceutical applications. Various synthetic methodologies have been developed to create these compounds, utilizing different reaction conditions and catalysts.

Aziridines, as three-membered nitrogen-containing heterocycles, have attracted significant attention in organic synthesis due to their unique ring strain and electrophilic nature, which render them highly reactive toward nucleophilic species. Recent advances highlight their participation in formal [3+2] cycloaddition reactions, providing an efficient strategy for the construction of a broad range of five-membered heterocycles with diverse functional groups, underlining their utility as synthetic intermediates in the development of complex molecular architectures.[1]

Similarly, β-lactams and azetidines have emerged as pivotal substrates in the pharmaceutical and agrochemical industries. Their potential for chemical modifications enables the synthesis of a variety of biologically active derivatives. These scaffolds, owing to their strained ring systems and reactive functionalities, serve as core structures in the development of compounds with promising pharmacological profiles.[14]

Chalcones, characterized by their conjugated α,β-unsaturated carbonyl system, are versatile precursors in the synthesis of nitrogen-containing heterocycles such as pyrroles, indoles, and triazoles. Their ease of synthesis, structural diversity, and reactivity under mild conditions make them attractive candidates in sustainable synthetic strategies. The literature emphasizes the incorporation of green chemistry principles and alternative activation techniques, including microwave and ultrasound-assisted reactions, to improve yield and reaction efficiency.[26]

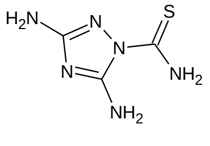
In the context of oxygen-containing heterocycles, the synthesis of structures like tetrahydropyrans and isoxazolines has benefited from organocatalytic asymmetric oxa-Michael reactions (OMR). These methodologies enable the generation of enantioenriched heterocyclic frameworks with high selectivity and functional group tolerance, expanding the toolkit for complex molecule construction.[27]

Other notable synthetic approaches include the application of ring-closing metathesis, particularly involving diene and enyne systems. This strategy provides a powerful and modular method for the formation of both five- and six-membered rings, with applications in natural product synthesis and drug discovery [28].

Furthermore, the synthesis of triazole derivatives via 1,3-dipolar cycloaddition reactions has seen significant advancements with the use of heterogeneous copper-based catalysts. These solvent-free systems offer operational simplicity, enhanced efficiency, and environmental benefits, aligning well with the goals of green and sustainable chemistry [29].

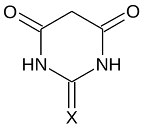
The ring-closing metathesis (RCM) of dienes and enynes has emerged as a versatile strategy for the synthesis of five- and six-membered heterocycles, offering significant utility in modern organic synthesis [2]. While the methodology is widely recognized for its structural efficiency, current literature often lacks specific quantitative outcomes, such as reaction yields across substrate scopes or statistical measures (e.g., p-values), to rigorously substantiate the observed reactivity trends. Conclusions regarding the success and synthetic value of these metathesis reactions are frequently inferred rather than explicitly demonstrated through comparative data or mechanistic clarity. Moreover, despite the widespread application of RCM in heterocycle formation, the mechanistic understanding, particularly for enyne systems, remains incomplete. This gap highlights the need for further exploration into the reaction pathways and intermediates. Additionally, there is growing interest in the development of new catalytic systems especially those that could offer improved efficiency, regioselectivity, and stereoselectivity under milder or more sustainable conditions. Advancing catalyst design and understanding could significantly broaden the application of these reactions, particularly in the total synthesis of structurally complex natural products and bioactive compounds.[2]

Thiosemicarbazides have served as versatile precursors in the synthesis of a wide range of heterocyclic compounds, predominantly targeting five- and six-membered ring systems incorporating two or three heteroatoms such as nitrogen, oxygen, and sulfur [3]. The reviewed literature presents a systematic account of the chemical transformations of thiosemicarbazides, offering valuable insight into their synthetic versatility. However, despite the breadth of the discussion and a comprehensive bibliography citing 190 references, there is a notable absence of detailed methodologies for the construction of three-membered heterocycles from thiosemicarbazides. This gap underscores the limited exploration of smaller ring systems within this chemical class. Additionally, while the transformation strategies are well outlined, there is minimal investigation into the structural diversity and distinct physicochemical properties of specific thiosemicarbazide derivatives. Moreover, the biological evaluation of heterocycles derived from thiosemicarbazides remains underexplored, indicating a need for more in-depth studies to establish clear structure–activity relationships. Future research should focus on expanding the scope of these transformations, investigating the reactivity of thiosemicarbazides under varied conditions, and elucidating the pharmacological potential of the resulting heterocycles.[3]



Ternary condensation of aromatic aldehydes with malononitrile and 3-acetylpyridine in the presence of ammonium acetate yields 2,3'-bipyridinyl derivatives. The reaction of 3-acetylpyridine, malononitrile, and nucleophilic reagents results in the formation of fused pyran, thiopyran, and pyrimidine derivatives. The synthesis of bipyridinyl derivatives was confirmed through elemental and spectral data from various aromatic aldehydes under similar reaction conditions. Ternary condensation of aromatic aldehydes with malononitrile and 3-acetylpyridine produced 2,3'-bipyridinyl derivatives. - The reaction utilized a 1:1:1 molar ratio of benzaldehyde, malononitrile, and 3-acetylpyridine in the presence of ammonium acetate. Structural confirmation of the derivatives was achieved through elemental and spectral data analysis.

Exploration of additional nucleophilic reagents for ternary condensation reactions to enhance the diversity of fused pyran, thiopyran, and pyrimidine derivatives. - Investigation of the biological activities of newly synthesized bipyridinyl derivatives to assess their potential applications. - Development of optimized reaction conditions to improve yields and efficiency in the synthesis of pyridine-containing heterocycles.[4]



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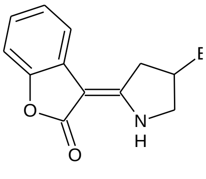
Compounds 4a and 4b are synthetic equivalents of heterocyclic alkylidene-azomethine ylides. - Reactions with aldehydes, ketones, and reactive alkenes produced 1,3-dipolar cycloadducts (8a-j, 9a-h) and derivatives (12-15, 17, 18). - The process involved 1,3-elimination of (methylthio)trimethylsilane.[5]

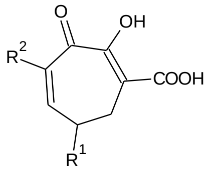


The haloform reaction of 3-acetyltropolone produces 3-carboxytropolone, which can be further transformed into various derivatives through reactions with diazomethane and hydrazine. - The reaction of 3-

carboxytropolone with hydrazine yields different products based on reaction time, resulting in either 2-hydrazino-3-hydrazinocarbonyltropone or 2-hydrazinotropone. - Treatment of 2-methoxy-3-methoxycarbonyltropone with hydrazine or phenylhydrazine leads to cyclization products, indicating potential pathways for synthesizing 3-membered heterocyclic compounds.

Exploration of the mechanisms behind the reactions involving 3-acetyltropolone and its derivatives. - Investigation of the potential biological activities of the synthesized tropolone compounds. - Development of more efficient synthetic routes for the production of tropolone derivatives.

The haloform reaction of 3-acetyltropolone produced 3-carboxytropolone, which led to various derivatives through reactions with diazomethane and hydrazine. - Reaction time influenced the formation of either 2-hydrazino-3-hydrazinocarbonyltropone or 2-hydrazinotropone. - Treatment of 2-methoxy derivatives with hydrazine or phenylhydrazine yielded cyclization products.[6]



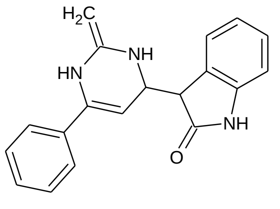
A review of the literature indicates that certain heterocycles can be synthesized with significant yields. The synthesis methods for these heterocycles can be modified for use in organic laboratories. The focus on heterocycles in the literature suggests their importance in organic synthesis and potential applications.

Identification of specific heterocycles with high yields that require further exploration. - Development of methods to modify these heterocycles for enhanced application in organic synthesis. - Investigation of the underlying mechanisms that lead to the observed significant yields in heterocycle synthesis.

Several heterocycles were identified that produced significant yields in synthesis. - These heterocycles can be modified for use in organic laboratory settings. - No specific quantitative results or p-values were provided in the context.[7]

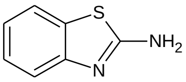
The reaction of isatin with acetophenone derivatives produces 3-hydroxy-3-phenacyl oxindole derivatives, which can be dehydrated to yield 3-phenacylidene-2-indolinone derivatives. - Condensation of the 3-phenacylidene-2-indolinone derivatives with hydrazine hydrate, phenylhydrazine, and phenylthiourea leads to the formation of new spiropyrazolines and spiropyrimidinethione. - The structures of the synthesized 3-membered heterocyclic compounds were confirmed through physical and spectral analysis.

Isatin reacted with acetophenone derivatives to produce 3-hydroxy-3-phenacyl oxindole derivatives (II). - Dehydration of (II) yielded 3-phenacylidene-2-indolinone derivatives (III). - Condensation of (III) with hydrazine hydrate and others resulted in new spiropyrazolines (IV & V) and spiropyrimidinethione (VI).[8]



The synthesis of N-, O-, and S-containing heterocycles has gained attention due to their diverse biological activities. The investigation of chemical synthesis methods is increasingly important because of environmental concerns. The use of metal and nonmetal catalysts, including nickel, is becoming a preferred alternative to traditional methods in modern synthetic chemistry. The review highlights the increasing interest in synthesizing N-, O-, and S-containing heterocycles due to their biological activity. - It emphasizes the role of catalysts, particularly nickel, as improved alternatives to traditional methods in organic reactions. - The focus is on the applications of nickel in synthesizing five-membered heterocycles.

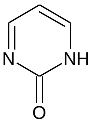
Need for more research on the environmental impact of synthetic methods for heterocycles. - Exploration of alternative catalysts beyond nickel in the synthesis of five-membered heterocycles. - Investigation into the biological activities of newly synthesized N-, O-, and S-containing heterocycles is essential to fully understand their potential applications in pharmaceuticals. By expanding the range of catalysts and methods used, researchers can enhance the efficiency and sustainability of these synthetic processes, ultimately leading to more effective and environmentally friendly drug development.[9]



New procedures for synthesizing heterocyclic compounds that include the sulfamide fragment have been developed. The analysis includes a comparative study of the structures and physicochemical properties of sulfamides and ureas, which may inform the synthesis of related heterocyclic compounds. The properties of the synthesized heterocyclic compounds containing sulfamide fragments are described in detail, providing insights into their potential applications.

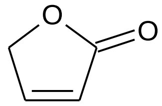
Need for further exploration of the physicochemical properties of sulfamides and ureas. Development of more efficient synthesis methods for heterocyclic compounds with sulfamide fragments.Investigation into the potential applications of the synthesized compounds in various fields.

A comparative analysis of sulfamides and ureas was conducted, focusing on their structures and physicochemical properties.New synthesis procedures for heterocyclic compounds with sulfamide fragments were explored. - The study includes a bibliography of 112 references, indicating extensive research.[10]



Heterocycles, including O-heterocycles like coumarin, pyran, oxazole, and thiazole, are significant in pharmaceuticals and have been extensively studied for their synthesis. - Dicarbonyl compounds, such as β-diketones and 1,3-diketones, are crucial in the synthesis of core heterocyclic compounds. - The review article specifically focuses on the synthesis of O-heterocycles derived from dicarbonyl compounds. Need for more comprehensive studies on the synthesis of O-heterocycles from various diketones. - Exploration of the pharmacological activities of newly synthesized heterocycles. - Investigation into the potential applications of dicarbonyl compounds in developing novel drugs.

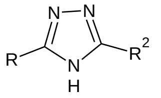
Heterocycles are crucial in pharmaceuticals, with compounds like coumarin, pyran, oxazole, and thiazole being significant for drug development. - O-heterocycles are found in medications such as ranitidine, doxepin, and paclitaxel. - Dicarbonyl compounds are essential for synthesizing core heterocyclic structures.[11]



The synthesis of seven-membered heterocyclic compounds, such as azepine and its derivatives, often involves ring expansion from five- or six-membered compounds using methods like thermal, photochemical, and microwave irradiation. - Various researchers have systematically designed schemes to synthesize different derivatives of azepine, azepinone, and azepane using similar chemical building blocks. - There is a significant gap in the biological exploration of N-containing seven-membered heterocycles, indicating potential opportunities for future research in this area.

Limited exploration of the biological properties of seven-membered heterocyclic compounds, particularly azepine derivatives. - Need for more systematic studies on the synthesis of various azepine derivatives and their therapeutic applications. - Potential for further research on N-containing seven-membered heterocycles to uncover new pharmacological uses.

Azepine and its derivatives have significant pharmacological and therapeutic potential, as highlighted in a review of the last fifty years of literature. - Synthesis methods include ring expansion of five- or six-membered compounds using thermal, photochemical, and microwave irradiation techniques. - There is a noted lack of exploration in the biological properties of N-containing seven-membered heterocycles, indicating further research opportunities.[12]



Various diketones, including 1,2-diketones and β-diketones, are utilized in the synthesis of three-membered heterocyclic compounds such as pyrazoles and isoxazoles. - Dicarbonyl compounds serve as important chelating ligands for lanthanides and transition metals, which can be relevant in the synthesis of heterocyclic compounds. - The synthesis of nitrogen-containing heterocyclic compounds is a significant focus in organic chemistry, with 50% of drugs containing these types of compounds.

Need for more efficient synthesis methods for nitrogen-containing heterocyclic compounds. - Exploration of diketones and dicarbonyl compounds as chelating ligands for additional transition metals. - Investigation of the biological activities of synthesized heterocyclic compounds to enhance drug development.

Diketones and dicarbonyl compounds are essential in synthesizing nitrogen-containing heterocyclic compounds like pyrazoles and quinolones. - 50% of drugs include nitrogen heterocyclic compounds, highlighting their significance in pharmaceuticals. - The review compiles various methodologies for synthesizing five- and six-membered nitrogen-containing heterocycles.[13]

4-membered nitrogen-containing heterocycles, like β-lactams and azetidines, are important in organic chemistry for creating biologically active compounds through the functionalization of their ring positions. see compounds serve as versatile building blocks for synthesizing other nitrogen-containing compounds that may have biological properties. cent data highlights the preparation methods and biological activities of 4-membered nitrogen-containing heterocyclic rings.

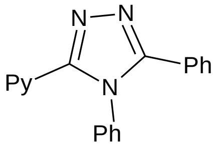
4-membered nitrogen-containing heterocycles, like β-lactams and azetidines, are valuable in organic chemistry for creating biologically active compounds. These compounds serve as versatile building blocks for synthesizing other nitrogen-containing compounds with potential biological properties. The review highlights recent findings on the preparation, properties, and biological activities of these heterocycles.

Exploration of the functionalization potential of different positions on 4-membered nitrogen-containing heterocycles. - Investigation of the biological properties of synthesized compounds derived from these heterocycles. - Development of new synthetic methods for creating diverse nitrogen-containing compounds using 4-membered rings.

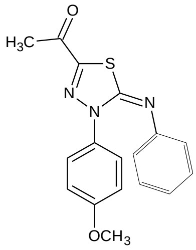
This review summarizes recent findings on the preparation, properties, and biological activities of 4-membered nitrogen-containing heterocycles, such as β-lactams and azetidines, highlighting their utility in designing biologically active compounds.[14]

The reaction of thioamides with hydrazides leads to the formation of 1,2,4-triazoles, which are four-membered heterocyclic compounds. - S-alkylation of piperidides or morpholides derived from carbothioic acids with iodomethane followed by reaction with the aforementioned compounds results in the synthesis of 1,3,4-oxadiazoles, another class of four-membered heterocycles. - Both triazoles and oxadiazoles are synthesized through specific reactions involving thioamides and hydrazides, highlighting their relevance in the context of four-membered heterocyclic compound synthesis.

Thioamides reacted with hydrazides to yield 1,2,4-triazoles. - S-alkylation of piperidides or morpholides with iodomethane produced carbothioic acid derivatives. - These derivatives then reacted with compound A to form 1,3,4-oxadiazoles.[15]



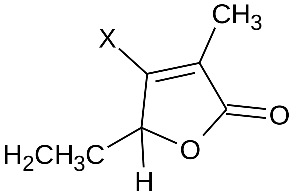
New C-acetyl and C-ethoxycarbonyl derivatives of hydrazonyl bromides have been synthesized and reacted with various unsaturated carbonyl compounds to produce novel pyrazoline, thiadiazoline, and pyrazole derivatives.The synthesis process yielded these compounds in excellent yields, indicating effective reaction conditions. The structural elucidation of the final products was achieved through spectral and analytical studies, confirming their identities. New C-acetyl and C-ethoxycarbonyl derivatives of hydrazonyl bromides were synthesized and reacted with various compounds, yielding novel pyrazoline, thiazolidine, and pyrazole derivatives.The reactions resulted in excellent yields, although specific quantitative results are not provided. - Structural elucidation of the final products was confirmed through spectral and analytical studies.[16]



Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans can be synthesized in yields up to 99% by reacting specific diol derivatives with electrophiles like I_2, IBr, and ICl at room temperature. The reaction requires the presence of trace amounts of water to facilitate the electrophilic cyclization process. The halides produced from this reaction can be further utilized in palladium-catalyzed coupling reactions for additional synthetic applications.

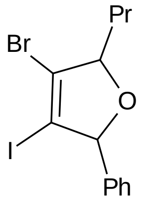
Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans were synthesized with yields up to 99%.Reactions involved 1,4-butyne-diol, 4-aminobut-2-yn-1-ol, and pent-2-yne-1,5-diol derivatives with electrophiles (I(2), IBr, ICl) at room temperature. - Trace amounts of water are crucial for the electrophilic cyclization process.

Investigate the impact of varying electrophiles on the yield and selectivity of the reactions. Explore the role of trace water in the electrophilic cyclization process. Assess the potential of the resulting halides in diverse palladium-catalyzed coupling reactions. Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans can be synthesized in yields up to 99% through the reaction of specific diols with electrophiles at room temperature, with trace water being crucial for the process.[17]



A variety of dihalogenated dihydrofurans, dihydropyrans, and dihydropyrroles can be synthesized effectively. These compounds are produced in good to high yields, indicating efficient synthesis methods. The focus on dihalogenated versions suggests a specific interest in modifying these heterocyclic compounds for potential applications.

A variety of dihalogenated dihydrofurans, dihydropyrans, and dihydropyrroles were synthesized. The yields of these compounds ranged from good to high. No specific quantitative results or statistical significance (p-values) were provided. A variety of dihalogenated dihydrofurans, dihydropyrans, and dihydropyrroles were successfully synthesized with good to high yields.[18]

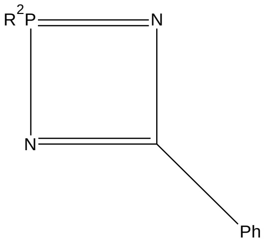


The review discusses the formation of five- and six-membered heterocyclic rings through ring-closing diene and enyne metathesis. - Specific quantitative results and statistical significance (p-values) are not provided in the context. - Conclusions regarding the effectiveness of these metathesis methods in synthesizing heterocycles are implied but not explicitly stated.

Limited understanding of the mechanisms involved in ring-closing diene and enyne metathesis. Need for exploration of new catalysts to improve reaction efficiency and selectivity. Insufficient studies on the application of these heterocyclic compounds in pharmaceuticals and materials science. This review discusses the synthesis of five- and six-membered heterocyclic rings in different compounds through the processes of ring-closing diene and enyne metathesis.[19]

The study focuses on the synthesis and reactivity of 4-membered heterocycles that contain a phosphazene group, which is a type of chemical structure. - Quantitative results and specific statistical significance (p-values) are not provided in the context. - Conclusions regarding the implications of these findings are not detailed in the provided information.

The discussion focuses on the synthesis and reactivity of 4-membered heterocycles with a phosphazene group.[20]



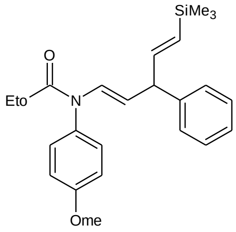
Heterogeneous copper catalysts enable the synthesis of triazoles via 1,3-dipolar cycloaddition of alkynes and azides, including solvent-free methods. - The Pd/C-catalyzed Yamanaka–Larock method produces 2- or 2,3-substituted indoles from 2-iodoaniline derivatives. - Hydrogenation with 10% Pd/C, Rh/C, or Ru/C facilitates the synthesis of indoles and saturated heterocycles under mild conditions. Heterogeneously catalyzed methods for synthesizing 1,2,3-triazoles involve a 1,3-dipolar cycloaddition of alkynes with azides using copper catalysts. - The Yamanaka–Larock method, utilizing palladium on carbon (Pd/C), allows for the synthesis of 2- or 2,3-substituted indoles from 2-iodoaniline derivatives and alkynes. - Intramolecular hydrogenative N-alkylation of 2-cyanomethylaniline can produce indole, while arene hydrogenation can yield piperidine and pyrrolidine derivatives under mild conditions. The discussion summarizes various heterogeneously catalyzed synthetic methods for preparing 1,2,3-triazoles, indolines, indoles, and saturated heterocycles, highlighting specific catalytic reactions and conditions used in these syntheses.[21]

Tetrodotoxin and its analogues present unique challenges for developing synthetic methodologies for 4-membered heterocyclic compounds. - Dynemicin A is a significant compound in the enediyne class of antitumor antibiotics, indicating a need for new synthetic methods for such 4-membered heterocycles. -

Simplified enediyne compounds were designed for examination, suggesting ongoing research into the synthesis of related 4-membered heterocyclic structures.

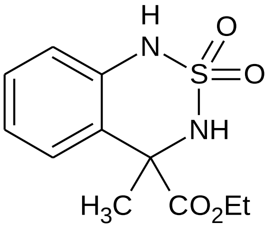
Tetrodotoxin and its analogues present challenges for developing synthetic methodologies targeting their unique heterocyclic ring systems. - Dynemicin A is a prominent enediyne class antitumor antibiotic, prompting the need for new synthesis methods. - Simplified enediyne compounds were designed for evaluation related to the bicyclo[7.3.1]-tridecenediyne ring system.

Development of synthetic methodologies for tetrodotoxin and its analogues. - New synthesis methods for Dynemicin A, an enediyne class antitumor antibiotic. - Examination of simplified enediyne compounds targeting the bicyclo[7.3.1]-tridecenediyne ring system.[22]



New procedures for synthesizing heterocyclic compounds that include the sulfamide fragment have been surveyed, indicating advancements in this area.The comparative analysis of sulfamides and ureas provides insights into the structures and physicochemical properties relevant to the synthesis of 4-membered heterocyclic compounds. The properties of the resulting compounds from these synthesis methods are described, suggesting their potential applications or characteristics.

A comparative analysis of sulfamides and ureas was conducted, focusing on their structures and physicochemical properties. New synthesis procedures for heterocyclic compounds containing sulfamide fragments were surveyed. The study includes a bibliography with 112 references, indicating extensive research. Need for further exploration of the synthesis procedures for heterocyclic compounds with sulfamide fragments. - Investigation into the specific physicochemical properties of sulfamides compared to ureas. Identification of potential applications for the newly synthesized compounds. The discussion summarizes a comparative analysis of sulfamides and ureas, detailing new synthesis procedures for heterocyclic compounds with sulfamide fragments and describing their properties, supported by 112 references.[23]



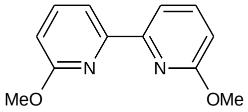
A review of the literature indicates that certain 4-membered heterocyclic compounds can be synthesized with significant yields. The synthesis methods for these heterocycles can be modified for use in organic laboratories. The review highlights the potential for further exploration and optimization of these synthesis techniques in practical applications.

Several heterocycles were identified that produced significant yields in synthesis. These heterocycles can be modified for use in organic laboratory settings. No specific quantitative results or p-values were provided in the context.

Identification of specific heterocycles with high yields that require further exploration. Development of modified synthesis methods for improved efficiency in organic laboratories. Investigation into the practical applications of synthesized heterocycles in various fields.[24]

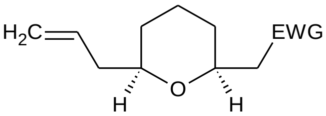
The synthesis of diverse six-membered heterocycles, such as tetrahydropyridines and dihydropyrans, can be achieved using diazo compounds and alkyne-substituted malonates as substrates. - This process yields polyfunctionalized cyclohexenes and other compounds in moderate to high yields under mild reaction conditions. The presence of a ligand is crucial in enhancing the efficiency of this copper-catalyzed synthesis method.

A new method for creating diverse six-membered carbo-/heterocycles using diazo compounds and alkyne-substituted malonates has been established. - Polyfunctionalized cyclohexenes, tetrahydropyridines, and dihydropyrans were produced in moderate to high yields. - The choice of ligand is crucial in this copper-catalyzed reaction. Further exploration of different ligands to optimize the copper-catalyzed reactions. - Investigation of additional diazo compounds and alkyne-substituted malonates for broader applicability. - Study of the mechanism behind the formation of polyfunctionalized products to enhance understanding and efficiency.[25]



Chalcones can be utilized to synthesize biologically active 5- and 6-membered nitrogen heterocycles, including pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, tetrazoles, pyridines, and pyrimidines. - The synthesis process involves two types of addition reactions: 1,2-addition to the carbonyl group and 1,4-conjugate addition to the β-carbon. - The review emphasizes the use of efficient, easy-to-handle, and inexpensive reagents along with greener protocols for the synthesis of these heterocyclic compounds.[26]

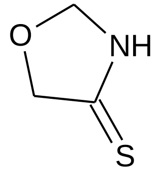
The oxa-Michael reaction (OMR) is a highly effective method for synthesizing a variety of 5- and 6-membered oxygen-containing heterocycles, such as tetrahydropyrans and isoxazolines. Recent advancements in organocatalytic asymmetric OMR have enabled the synthesis of diverse oxygen-containing heterocycles with high enantioselectivity (specific arrangement of molecules) and/or diastereoselectivity (specific arrangement of stereoisomers). - The review highlights significant progress in the application of OMR for synthesizing monocyclic oxo-heterocycles since 2013.[27]



The review focuses on the synthesis of five- and six-membered heterocyclic rings through the processes of ring-closing diene and enyne metathesis. - Ring-closing diene metathesis involves the formation of cyclic compounds from diene molecules, while enyne metathesis combines alkynes and alkenes to create rings. - Both metathesis methods are highlighted as effective strategies for constructing heterocyclic compounds with diverse applications in chemistry.[28]

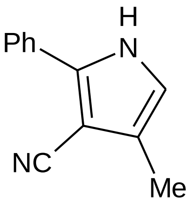
Heterogeneously catalyzed methods for synthesizing 1,2,3-triazoles involve the 1,3-dipolar cycloaddition of alkynes with azides using copper catalysts. - The Yamanaka–Larock method, catalyzed by palladium on carbon (Pd/C), produces 2- or 2,3-substituted indoles from 2-iodoaniline derivatives and alkynes. - Intramolecular hydrogenative N-alkylation using Pd/C can synthesize indoles from 2-cyanomethylaniline and piperidine, while arene hydrogenation can produce piperidine, pyrrolidine, and tetrahydrofuran derivatives from pyridine, pyrrole, and furan.[29]

Various 1,3-oxazolidine-2-thiones and tetrahydro-1,3-oxazine-2-thiones can be synthesized by reacting hydrogen peroxide with amino alcohols, carbon disulfide, and a base in a water-miscible organic solvent. - The yields of these heterocyclic compounds are reported to be between 80 and 100%, which is significantly higher than previously documented yields in the literature. - The synthesis method utilizes a combination of specific reactants and conditions to achieve high efficiency in producing these 5- and 6-membered heterocyclic compounds.[30]



The organocatalytic synthesis of 5- and 6-membered heterocycles has gained significant attention due to its advantages, such as being metal-free and environmentally friendly. - Research groups have focused on developing new organocatalytic methodologies that achieve excellent yields and stereoselectivities in the synthesis of these heterocycles. - Various organocatalytic methodologies have been described in recent reviews, highlighting their effectiveness in the synthesis of 5- and 6-membered heterocycles.

The review surveys synthetic strategies for 5-membered heterocycles, including pyrroles, furans, and thiophenes, from 1985 to the present. - It categorizes reactions based on synthetic methods using benzoylacetonitriles as starting precursors. - No quantitative results or statistical significance (p-values) are provided in the context. This review article surveys synthetic strategies for 5-membered heterocycles, categorizing reactions by methods used since 1985, focusing on compounds like pyrroles, furans, and thiophenes derived from benzoylacetonitriles.[31]

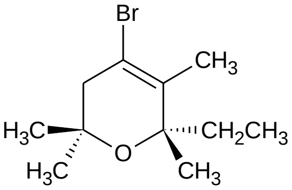


Novel phosphorus heterocycles, specifically 2,3-dihydro-1,3-oxaphospholes and 1,4,2-oxazaphosphinanes, can be synthesized with reactive parts that allow for various structural modifications. - Structural modifications for 2,3-dihydro-1,3-oxaphospholes can include the introduction of amino substituents, while 1,4,2-oxazaphosphinanes can undergo hydroxy- or aminoalkylation, Michael addition, or P-arylation. The reactions involved in these syntheses generally exhibit good to excellent kinetic diastereoselectivity, which can often be predicted using molecular models of the transition states.

Novel phosphorus heterocycles with α-amino or α-hydroxy motifs were synthesized, specifically 2,3-dihydro-1,3-oxaphospholes and 1,4,2-oxazaphosphinanes. - Structural modifications were achieved through various reactions, showing good to excellent kinetic diastereoselectivity. - The diastereoselectivity can often be predicted using molecular models of transition states.

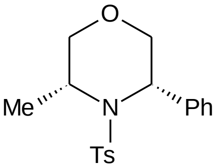
Novel phosphorus heterocycles with α-amino or α-hydroxy motifs were synthesized, showing reactive components that allow for various structural modifications, resulting in good to excellent kinetic diastereoselectivity predictable by transition state molecular models.[32]

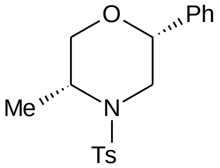
Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans can be synthesized in good to excellent yields (up to 99%) through the reaction of specific diol derivatives with electrophiles like I(2), IBr, and ICl at room temperature. - The synthesis process effectively utilizes both halogen atoms generated from the electrophiles, which can be further utilized in palladium-catalyzed coupling reactions. - The presence of a trace amount of water is essential for the electrophilic cyclization involved in the synthesis of these heterocyclic compounds. Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans were synthesized with yields up to 99%. - Reactions involved 1,4-butyne-diol, 4-aminobut-2-yn-1-ol, and pent-2-yne-1,5-diol derivatives with electrophiles (I(2), IBr, ICl) at room temperature. - Trace amounts of water were essential for the electrophilic cyclization process. Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2H-pyrans can be synthesized in good to excellent yields (up to 99%) through the reaction of specific diols with electrophiles at room temperature, with trace water being crucial for the process.[33]



A synthesis method for C-substituted morpholines, piperazines, azepines, and oxazepines is achieved through the reaction of amino alcohols or diamines with an α-phenylvinylsulfonium salt, yielding moderate to excellent results (27% to 75%). - The synthesis demonstrates high regio- and diastereoselectivity, with selectivity ratios ranging from 2:1 to greater than 20:1, influenced by the choice of base (Cs_2CO_3) and solvent (CH_2Cl_2). - The reactions are conducted at ambient temperature and in open air without the need for anhydrous solvents, and the deprotection of N-sulfonamide groups is also shown.

Stereodefined C-substituted morpholines, piperazines, azepines, and oxazepines were synthesized with yields ranging from 27% to 75%. - Regio- and diastereoselectivity levels varied from 2:1 to over 20:1, influenced by the choice of base (Cs2CO3) and solvent (CH2Cl2). - Reactions occurred at ambient temperature, open to air, without the need for anhydrous solvents. The discussion summarizes the successful synthesis of stereodefined C-substituted morpholines, piperazines, azepines, and oxazepines with high regio- and diastereoselectivity, achieved using specific bases and solvents under mild conditions, while also addressing factors influencing selectivity.[34]





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