https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(6s) (December 2024); 783-792
Research Article

A Review On Various Synthetic Routes Of Pyrano[3,2-C]Pyridine Derivatives

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Abstract:
The exploration of pyrano[3,2-c]pyridine derivatives has garnered significant attention due to their diverse pharmacological properties and versatile applications in organic synthesis[1] Ramesh et al. This literature review aims to provide a comprehensive overview of the various synthetic strategies employed in the preparation of these complex molecular structures. By examining the existing methodologies.

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Received - 8/12/2024 Acceptance- 18/12/2024

DOI: https://doi.org/10.53555/AJBR.v27i6S.7435

Introduction:
The heterocyclic compounds, characterized by the fusion of pyran and pyridine rings, exhibit a range of pharmacological properties that make them valuable in drug development. Research into pyrano[3,2-c]pyridine derivatives has revealed their efficacy as antibacterial, antifungal, and anticancer agents Alam et al.[2] and Mandal et al.[3] The structural versatility afforded by their unique ring system allows for modifications that can enhance biological activity and optimize pharmacokinetic profiles.[4] Sharma et al.
The exploration of pyrano[3,2-c]pyridine derivatives is a fertile area of research within medicinal chemistry. Their diverse biological activities, coupled with ongoing advancements in synthetic methodologies, hold great promise for the development of new pharmaceutical agents capable of addressing various health challenges. Future investigations will undoubtedly enhance our understanding and utilization of these intriguing compounds.

These pyrano[3,2 C]pyridine derivatives have been recognized for their structural complexity, which poses challenges in the synthetic pathways employed. The synthesis of pyrano[3,2 C]pyridine derivatives has been approached through various methodologies that can be categorized into traditional reactions, microwave-assisted methods, green chemistry approaches, multicomponent reactions (MCRs) and the other emphasizing the advantages of utilizing microwave-assisted synthesis. The literature presents various synthetic methodologies, each with its unique advantages and limitations. This review highlights distinct results derived from different synthesis methods employed for the construction of these pyrano[3,2 C]pyridine derivatives.

Review
Synthesis Methods
1. Traditional Cyclization Approaches
Notable methodology explored in the synthesis of pyrano[3,2-c]pyridine derivatives involves cyclization

reactions, particularly involving pre-formed substrates. Cyclization techniques have revealed that the choice of solvents, temperatures, and catalysts significantly influence the formation of desired pyrano[3,2-c]pyridine structures.

Traditional cyclization methods remain a cornerstone of pyrano[3,2-c]pyridine synthesis. A notable technique involves the condensation of 2-aminomethyl-3-pyridinecarboxylic acids with various electrophiles.[1] Ramesh et al. describe a reaction sequence where 2-aminomethylpyridine derivatives are reacted with β-ketoesters under acidic conditions to yield the target pyrano derivatives. This method demonstrates high yields and selectivity, but it often requires prolonged reaction times, which can result in by-product formation.

Another method detailed by Saha and Talukdar employs the use of isocyanides in a Ugi reaction[5] system followed by cyclization under mild conditions. This multi-component reaction showcases versatility, producing a variety of substituted pyrano[3,2-c]pyridines in good to excellent yields. Nonetheless, the requirement for careful optimization of reaction parameters often poses challenges in scaling up the process for industrial applications.

The reaction between arylidenemalononitriles and acetoacetanilide yielded new tricyclic pyrano[3,2-c]pyridine derivatives of the undecane-1,3-dicarbonitrile family, confirmed by X-ray crystallography and NMR spectroscopy prepared by Ibrahim G et al[6].

A.S. Girgis et al.[7] developed a QSAR model to characterize the bioactivity of bronchodilatory active 4H-pyrano[3,2-c]pyridine-3-carbonitriles using CODESSA-Pro software. A straightforward reaction between 1-alkyl-4-piperidones and ylidenemalononitriles in methanol was used to create these chemicals. Using isolated guinea pig tracheal rings that had been precontracted with histamine and contrasted with theophylline, the in vitro bronchodilation capabilities were examined. The majority of the produced compounds exhibited encouraging bronchodilation characteristics.

B. P. Nikama et al.[8] synthesized acetyl and iodo derivatives of 4-hydroxy-6-phenyl-6H-pyrano[3,2-c]pyridine-2,5-diones (1) and 4-hydroxy-1-phenylpyridin-2(1H)-ones (5). Compounds (1) can be easily acetylated by refluxing in acetic acid and polyphosphoric acid, while compounds (1) and (5) can be iodinated with iodine and sodium carbonate in boiling dioxane, yielding 4-hydroxy-3-iodo-6-phenyl-6H-pyrano[3,2-c]pyridine-2,5-diones and 4-hydroxy-3-iodo-1-phenylpyridin-2(1H)-ones respectively.

A synthetic approach to 6-alkyl-2-amino-4-aryl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitriles was reported by Adel S. Girgis et al.[9] involving the reaction of 1-alkyl-4-piperidones with ylidenemalononitriles in methanol. The structure of was recognized through various spectroscopic techniques and confirmed by single crystal X-ray studies. In vitro vasodilation activities were investigated using isolated thoracic aortic rings of Wister rats. All the prepared analogues showed considerable vasodilation properties, with 2 derivatives showing the best potency. Molecular modelling studies showed high docking scores and fit values, confirming the experimental vasodilation activities of different compounds.

The synthesis of 3,5-bis(arylidene)piperidin-4-ones with a 2azidoethyl or propargyl group at the nitrogen atom was described by O. V. Bykhovskaya et al.[10] The compounds showed high activity against human tumor cells and embryonic kidney cells. The reaction of compounds with malononitrile produced 4H-pyrano[3,2c]pyridines without cytotoxicity. This highlights the importance of preserving the 1,5-diaryl-1,4-pentadiene moiety in drug design for new antitumor agents.

Dao-Cai Wang et al.[11] investigated a three-component Michael/cyclization process for the production of physiologically active 3-(sulfonyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridines under moderate reaction conditions. The process provides a wide range of derivatives (up to 97%), and the chemical structure of freshly synthesized pyridines is determined using 1H-NMR, 13C-NMR, and mass spectrometry. The process provides a simple setup, convenient access to starting ingredients, high atom use efficiency, high end product yields, and substrate flexibility.

Ivo C. Ivanova et al.[12] discovered that methyl esters (Y = COOCH3) produced high yields of the relevant compounds using the same basic approach as mono nitriles. The products' structure was identified by their spectral characteristics, with the main amino group exhibiting two IR absorption bands and a sharp 2H-singlet in their 1H-NMR spectra. For the ester carbonyl group, the methyl 3-carboxylates displayed bands ranging from 1657 to 1696 cm-1. Mass spectra validated the molecular masses. The stability of the compounds in relation to opening the 2-aminopyran ring was investigated using the product as a model compound. It was discovered that it is more stable in hydrolytic conditions than in other solvent. Chemical transformations of failed, contradicting the reported statement that ethyl α-cyanoacrylic esters react only in refluxing pyridine.

Andreas Marc Palmer et al.[13] synthesized spiro(imidazo[1,2-a]pyrano[2,3-c]pyridine-9-indenes) by a cross-metathesis process and acid-catalyzed cyclo isomerisation. These compounds are strong inhibitors of the stomach proton pump enzyme, similar to potassium-competitive acid blockers (P-CABs) from the 9-aryl-7H-8,9-dihydropyrano[2,3-c]imidazo[1,2-a]pyridine family. They are the first P-CABs with a changed distance between the heterocyclic scaffold and the aryl residue.

Hanan A. Soliman et al.[14] proposed the synthesis of diarylidenes occurs when 2,2,6,6-tetramethylpiperidin-4-one (1) reacts with different aromatic aldehydes. Compound 1 interacts with aromatic aldehydes and malononitrile in ammonium acetate to form 1,6-naphthyridine-3-carbonitriles, which are then acetylated

with acetic anhydride to make mono- and tri-acetylated derivatives. Furthermore, compound 1 reacts with cyanoacetamide and aromatic aldehydes in ammonium acetate or ethyl cyanoacetate to produce 1,6-naphthyridine-3-carboxamides. When triethylamine interacts with aromatic aldehydes and malononitrile, it produces pyrano[3,2-c]pyridine-3-carbonitriles and a tri-acetylated product. Compound 1 also generates pyrido[4,3-d]pyrimidine-2-thione derivatives, which react with chloroacetic acid to form 9-arylidene-pyrido[4,3-d]thiazolidino[3,2-a]pyrimidin-3-one derivatives. These are subsequently reacted with aromatic aldehydes to form 2,9-diarylidenes. Finally, compound 1 reacts with 4-chlorobenzaldehyde and 6-amino-S-methylthiouracil in DMF to produce pyrimido[4,5-b][1,6]naphthyridine derivatives and a 2-hydrazinyl derivative.

R. Ranjith Kumar et al.[15] investigated the 1,3-dipolar cycloaddition of nitrile oxides produced from benzohydroximinoyl chloride and triethylamine with 2-aminopyranopyridine-3-carbonitriles and 2-aminochromene-3-carbonitriles, yielding new 1,2,4-oxadiazole-pyranopyridine/chromene hybrid heterocycles. In vitro testing against Mycobacterium tuberculosis H37Rv (MTB) found that these hybrids were more effective than 1,2,4-oxadiazole-chromene hybrids. Specifically, 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl-4-(2,4-dichlorophenyl)-8-[(E)-(2,4-dichlorophenyl)-methylidene]-6-methyl-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]Pyridin-2-amine was more effective than typical antitubercular medicines.

Sonja Strah et al.[16] reviewed the synthesis of 5-substituted 3-benzoylamino-6-(2-substituted amino-1-ethenyl)-2H-pyran-2-ones and their conversion into 2H-pyrano[3,2-c]pyridine derivatives, indicating an increasing interest in these bicyclic systems. The article describes several synthesis techniques for substituted pyridine derivatives, as well as particular reaction schemes. It also looks at how substituents influence the structure and yield of produced molecules.

Francesca Clerici et al.[17] presented their findings on the synthesis and intramolecular cyclization of functionalized 6-pyronylacetamides, which resulted in the formation of novel 2,5,7-trioxo-pyrano[3,2-c]pyridines. The study focuses on two types of pyronylacetamides generated from reactions combining arylisocyanates and methyl 2-oxo-2H-pyran-6-acetate, stressing how structural influences impact the cyclization process. The discoveries add to our understanding of highly functionalized N-heterocycles and their prospective uses.

N. B. Marchenko et al.[18] studied the synthesis and transformation of various pyrano compounds using valerolactone derivatives and their interactions with primary aromatic amines. They effectively synthesized pyrano[2,3-b]quinoline and pyrano[3,2-c]pyridine derivatives employing innovative reaction techniques and reagents like triethyloxonium tetrafluoroborate. The research also explores processes for producing chemicals with potential applications in dye chemistry.

Kirill Tchabanenko et al.[19] aimed to synthesize these compounds using a reverse electron demand rearomatizing Diels-Alder reaction between 3-methylenepyridine-4-one and alkenes. They anticipated that thermally treating a 4-hydroxy-pyridine derivative with a suitable leaving group would yield the reactive intermediate. The cyclization precursor was synthesized from commercially available 4-methoxypyridine. The researchers adapted a previously published method to enhance the yield of the crude aldehyde, reduced it without column chromatography, and performed demethylation using an established method for 4-methoxypyridine at a lower temperature..

A pivotal study by Kaur et al.[20] expanded upon traditional cyclization methods by utilizing a copper-catalyzed approach for the construction of pyrano(3,2-c)pyridine derivatives from 2-aminobenzyl alcohols and 1,3-dicarbonyl compounds. The introduction of copper catalysts notably enhanced the yields and reaction rates compared to previous studies, which primarily employed conventional base-driven cyclization. The research indicated that the reaction conditions could significantly impact not only the yield but also the selectivity of the products, thereby demonstrating a tailored approach to synthesizing specific pyrano(3,2-c)pyridine derivatives.

Moreover, the work of Kaur et al.[20] also delved into the scope of substrate variation, suggesting that the incorporation of various functional groups on the starting materials allowed access to diverse pyrano(3,2-c)pyridine derivatives formed through cyclization. This strategy aligns with prior findings by Vasudevan et al.[21] emphasized that the manipulation of reaction parameters fosters compound diversity, thus underscoring significant implications in medicinal chemistry.

On the other hand, a comparative review by Singh et al.[22] noted that while cyclization methods heralded advancements in forming such heterocycles, they often required optimization concerning reaction times and temperatures. It was suggested that extensive experimentation is essential to tailor the conditions adequately and achieve reproducible results, highlighting the challenges faced when employing cyclization strategies.

2. Traditional Synthesis Methods

Traditional synthesis methods for Pyrano(3,2-c)pyridine derivatives predominantly involve multi-step reactions that often require stringent conditions and significant reaction times. One classical approach includes the condensation of 2-Pyridinecarboxaldehyde with malononitrile followed by cyclization and cyclodehydration Ishikawa et al.[23] Reporting on the efficiency of this method, the authors indicated a yield of approximately 70% for this multi-step synthesis, which underscores both the interest and the challenges associated with traditional methods of synthesis.

Furthermore, a notable report by Sinha et al.[24] utilized a one-pot three-component reaction where 2-pyridinecarboxaldehyde, activated methylene compounds, and various solvents yielded Pyrano(3,2-c)pyridine derivatives. The authors pointed out that optimizing reaction conditions (i.e., temperature, catalyst) could lead to improved yields of up to 85%.

The versatility of this method offers promising avenues for further explorations, particularly given its straightforward execution.

Despite the effective yields achieved in traditional methods, limitations such as lengthy procedures, hazardous waste production, and energy consumption pose significant drawbacks. The requirement for specialized equipment and reagents further complicates their viability in industrial settings Mandal et al.[25] Consequently, researchers have sought alternative methodologies to mitigate these issues.

The reaction of 4-hydroxy-6-methyl-2(1H)-pyridones with diethyl malonates forms pyrano[3,2-c]pyridines, which are degraded to ketones and condensed with hydroxyl amine or phenyl hydrazine hydrochloride this reaction was studied and proposed by El-Essawy et al.[26]

c].Irina O. Zhuravel et al.27 produced pyridine-3-(N-aryl) carboxamides by reacting pyridoxal hydrochloride with N-arylcyanoacetamides and aromatic amines. Synthesized compounds were tested for antibacterial and antifungal properties, and they shown strong action against bacterial and fungal strains, with efficacy equivalent to or better than current medications.

A series of unique 2-imino-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c].Irina O. Zhuravel et al.[27] produced pyridine-3-(N-aryl) carboxamides by reacting pyridoxal hydrochloride with N-arylcyanoacetamides and aromatic amines. Synthesized compounds were tested for antibacterial and antifungal properties, and they shown strong action against bacterial and fungal strains, with efficacy equivalent to or better than current medications.

Irina O. Zhuravel and colleagues synthesized unique 2-imino-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c] compounds, specifically pyridine-3-(N-aryl) carboxamides, by reacting pyridoxal hydrochloride with N-arylcyanoacetamides and aromatic amines. The resulting compounds exhibited strong antibacterial and antifungal activity, matching or surpassing the efficacy of existing medications.The mechanistic pathways of these traditional cyclization reactions have been explored to understand the formation of pyrano[3,2-c]pyridines. For instance, the proposed mechanism includes the nucleophilic attack of the amino group on the electrophile, which subsequently leads to intramolecular cyclization Saha & Talukdar[28]. Understanding these mechanisms allows chemists to fine-tune reaction conditions and improve yields.

3. Modern Green Chemistry Techniques

Recent advancements in green chemistry have introduced more sustainable and environmentally friendly methods for synthesizing these compounds. Microwave-assisted synthesis is one such technique that has gained traction due to its efficiency and speed. Solanki et al.[29] demonstrated a microwave-assisted synthesis of pyrano[3,2-c]pyridine derivatives, where the reaction times were significantly reduced from several hours to only a few minutes. The method accounted for high energy efficiency and reduction of solvent waste, thus aligning with green chemistry principles.

In addition, the utilization of ionic liquids as solvents in the synthesis of pyrano[3,2-c]pyridine derivatives has been proposed as an innovative approach. Mishra et al.[30] reported that the use of ionic liquids not only improved the solubility of reactants but also contributed to higher reaction yields and cleaner product profiles. Specifically, the hydrophobic nature of some ionic liquids facilitates phase separation, which further aids in the purification of the final products, thus addressing common challenges associated with traditional organic solvents.

Dao-Cai Wang et al.[31] developed an efficient cyclization method to synthesize (E)-8-arylidene-5,6,7,8-tetrahydrospiro[oxindole-3,4-pyrano[3,2-c]pyridin] derivatives, utilizing piperidine as a catalyst and ethanol as a green solvent, and assessed their antitumor activity in human cancer cell lines.

Rostamizadeh S. et al.[32] developed a magnetic amine-functionalized graphene oxide (Fe3O4-GO-NH2) nanocatalyst by reacting 3-aminopropyltriethoxysilane with magnetic graphene oxide. This catalyst proved to be an efficient, acid-base, and magnetically recyclable option for the solvent-free synthesis of pyrano[3,2-c]pyridine derivatives, demonstrating superior activity compared to conventional catalysts and allowing for easy recovery and reuse.

Raju Ranjith Kumar et al.[33] developed a green method was to manufacture fifteen 2-amino-6-methyl-4-aryl-8-[(E)-arylmethylidene]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitriles. These compounds were tested in vitro against Mycobacterium tuberculosis H37Rv (MTB), multidrug-resistant tuberculosis (MDR-TB), and Mycobacterium smegmatis. The most potent compound, 2-amino-4-[4-(dimethylamino)phenyl]-8-(E)-[4-(dimethylamino)phenyl] methylidene-6-methyl-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile, was found to be 100 times more effective than standard isoniazid in treating MDR-TB.

Twelve medicinally significant pyrano[3,2-c]pyridine derivatives were precipitated from ethanol solutions of malononitrile and (E)-3,5-bis(benzylidene)-4-piperidones at room temperature with very minimal work-up. Natural bond order simulations revealed that electron-drawing groups on phenyl rings reduce electron density on the b-atoms of piperidones, resulting in greater yields and shorter reaction durations. Shahnaz Rostamizadeh et al.[34] investigated and suggested this green approach, which offers simplicity, a fast reaction time, solvent non-toxicity, and economic feasibility.

Saeed Balalaie et al.[35] devised a novel, efficient, and atom-economic process for synthesizing 2-amino-6-methyl-4-aryl-8-[(E)-arylmethylidene].-5, 6, 7, 8-4H-pyrano [3,2-c]pyridine-3-carbonitriles by interacting with 3,5-bis[(E)-arylmethylidene].-tetrahydro-4(1H)-pyridinones with malononitrile in green medium containing diammonium hydrogen phosphate or piperidine.

Zhengbing Pan et al.[36] employed an ionic liquid medium ([BMIM]BF4) to perform a three-component synthesis

combining aromatic aldehydes, tert-butyl 2,4-dioxopiperidine-1-carboxylate, and N-methyl-1-(methylthio)-2-nitroethylen-1-amine. This process has simple conditions, readily available starting ingredients, and produces adequate yields, making it superior to other traditional methods. The synthetic compounds have considerable biological activity, including possible cardiovascular advantages from antiallergic, anti-inflammatory, and estrogenic characteristics. The essay stresses the use of ionic liquids to improve reaction yields and provide environmental advantages, which supports the emerging trend of green chemistry in drug production.

Michail N. Elinson et al.[37] devised a green, efficient synthesis technique for these medicinally significant chemicals by employing a PASE ('pot, atom, step economy') strategy to catalyze a multicomponent reaction combining aldehydes and C-H acids with ammonium acetate. This technique produces the target scaffolds fast (3-15 minutes) and selectively, with a high yield (88-97%). The synthesised derivatives have potential uses in a variety of medical fields, including antiviral, anticancer, and anti-HIV therapy. The publication emphasized the method's ecological benefits, simplicity, and absence of additional purification requirements, making it an important green chemistry contribution to drug development.

Asmaa M. Fahim et al.[38] investigated and concentrated on a green chemistry strategy that involved a multicomponent synthesis of aromatic aldehydes, ethyl cyanoacetate or malononitrile, and 3-hydroxy picolinic acid, with a tiny quantity of 4-dimethylaminopyridine (DMAP) catalyst. The microwave irradiation approach produced large volumes of product in a short period of time and was more efficient than traditional heating.

The synthetic chemicals were evaluated for antibacterial efficacy against a variety of bacteria and fungi. Furthermore, the antioxidant activity was assessed using the DPPH test, with several compounds demonstrating potential free radical scavenging properties. Notably, two compounds demonstrated high antioxidant activity with low IC50 values. Overall, the work provides an efficient and environmentally friendly synthesis approach that has potential uses in the development of bioactive molecules.

Shahnaz Rostamizadeh et al.[39] studied and presented the use of MCM-41-SO_3H, a novel acidic nanocatalyst, for the solvent-free synthesis of pyrano[3,2-c]pyridine derivatives, which are important compounds with various medicinal properties. This method showcases advantages such as high yields, short reaction times, and reusability of the catalyst, offering a significant improvement over traditional synthetic methods that often involve toxic solvents and non-reusable catalysts. The effectiveness of the MCM-41-SO_3H catalyst in facilitating reactions demonstrates its potential for greener synthetic processes in organic chemistry.

In highlighting the advantages of green methods, Rathi et al.[40] emphasized their scalability and eco-friendliness as substantial benefits over traditional methods. The integration of renewable resources and reducing harmful byproducts has sparked interest in these sustainable approaches within the chemical community, promising not only efficient synthesis processes but also a more responsible scientific practice.

The shift toward greener methodologies has been influenced by the necessity of minimizing the environmental impact of chemical processes. As documented by Solanki et al.[29] the application of microwave-assisted synthesis in pharmaceutical research not only expedites the production of bioactive compounds but also enhances the overall efficiency of drug discovery processes. However, challenges such as the scalability of these techniques in industrial settings remain a concern. Mishra et al.[30]

4. Multicomponent Reactions

One of the prevailing approaches in the synthesis of pyrano(3,2-c)pyridine derivatives is through multicomponent reactions (MCRs), which typically allow the one-pot assembly of multiple precursors. MCRs are known to simplify synthetic routes and improve yield while minimizing the need for extensive purification steps Doherty et al.[41]

A seminal study by Nair et al.[42] established a robust method for synthesizing pyrano(3,2-c)pyridines using a three-component reaction involving isocyanides, aldehydes, and 3-hydroxy-pyridine derivatives. The reaction demonstrated excellent regioselectivity and could be performed under mild conditions, providing an array of pyrano(3,2-c)pyridine derivatives in high yields. The procurement of starting materials—especially commercially available aldehydes and isocyanides—further streamlined the process, as noted.

Additionally, the study suggested that varying the substituents on the aldehyde could influence the biological activity of the resultant pyrano(3,2-c)pyridine derivatives, thus providing a pathway for the synthesis of targeted compounds with specific therapeutic properties. This finding aligns with earlier works, such as that of Liu et al.[43] who explored MCRs in the context of drug discovery and reported that structural diversity often correlates with enhanced bioactivity.

In contrast, other authors, such as Cheng et al.[44] highlighted the limitations of MCRs, such as substrate compatibility and the potential for side reactions that could complicate purification. This illustrates the need for methodical optimization to maximize yield and minimize unwanted by-products while achieving the desired molecular framework.

Multicomponent reactions have emerged as a prominent synthetic strategy for the synthesis of Pyrano(3,2-c)pyridine derivatives. MCRs involve the simultaneous reaction of three or more reactants, often resulting in the formation of complex products in a single step Drechsel & Voss,[45]. This efficiency not only simplifies the synthetic route but also reduces the amount of reagents and solvents required, making the process more environmentally friendly Figueiredo et al.[46]

One notable example in the literature highlights the use of a three-component reaction involving β-naphthol, isocyanides, and ethyl acetoacetate catalyzed by a Brønsted acid. This reaction has been found to produce Pyrano(3,2-c)pyridine derivatives in high yields under mild reaction conditions Kumar et al.[47] The mechanistic insight provided in this study suggests that the formation

of the pyridine ring occurs via a sequence of nucleophilic attacks followed by cyclization, showcasing the versatility of MCRs in constructing complex heterocycles.

Moreover, the introduction of isocyanides has been widely studied, as they facilitate the formation of isocyanide-derived products, which can subsequently react with other components to yield Pyrano(3,2-c)pyridine structures Islami et al.[48] The integration of such isocyanide-based MCRs has proven effective in creating diverse libraries of substituted Pyrano(3,2-c)pyridines, showcasing their potential in drug discovery and medicinal chemistry.

In addition to isocyanides, the incorporation of 1,3-dicarbonyl compounds has been explored in several studies. For instance, Zheng et al.[49] reported a robust method where a combination of 1,3-dicarbonyl compounds, aldehydes, and ammonium acetate was employed to achieve a one-pot synthesis of these derivatives. This method is particularly noteworthy for its simplicity, where all components can react in a single step, yielding the desired products in high yields and selectivity. The process is also beneficial as it minimizes the isolation of intermediates, further enhancing its operational efficiency.

While MCRs have made substantial advancements in the field, there are challenges to address, such as regioselectivity and the formation of byproducts that can complicate the purification process. Nevertheless, ongoing efforts aimed at optimizing reaction conditions and exploring new catalytic systems continue to advance this field Gupta & Sharma.,[50]

A four-component strategy for the synthesis of poly-substituted pyrano[3,2-c]pyridones and spiro[indoline-3,4′-pyrano[3,2-c]pyridine].Zhenhang Xu et al. have created -2,5′(6′H)-diones in water.[51] The reaction employed solid acid as a catalyst, which provided benefits such as atom and step economy, recyclability, ease of setup, and a wide range of substrates, making it an important tool in chemical and medicinal applications.

A novel 'on-solvent' multicomponent synthesis, utilizing sodium acetate as a catalyst in ethanol, produces modified 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitriles are produced in good yields of 92-99%. Fedor V. Ryzhkov et al.[52] synthesized promising chemicals for a variety of biological uses using this one-pot technique.

Sonja Strah et al.[53] described the 2H-pyrano[3,2-c]pyridine system as a novel technique. The process entails converting 5-benzoyl- amino-2H-pyran-2-ones into 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2H-pyran-2-one and 5-acetyl derivatives. The dimethylamino group is swapped with aromatic, heteroaromatic, and benzylamines to get 5-ethoxycarbonyl-3-benzoylamino-6-(2-arylamino-, heteroarylamino-, or benzylamino-1-ethenyl)-2H-pyran-2-ones and their 5-acetyl analog.

5.Microwave-Assisted Synthesis

The application of microwave-assisted synthesis has revolutionized the preparation of Pyrano(3,2-c)pyridine derivatives, providing an innovative approach that offers significant advantages over traditional heating methods. Microwave irradiation generates uniform heating and accelerates reaction rates, resulting in shorter reaction times and higher yields Bai et al.[54] This technique has been applied in various studies seeking to synthesize Pyrano(3,2-c)pyridine scaffolds efficiently.

For example, Kumar et al.[55] reported on a microwave-mediated synthesis of Pyrano(3,2-c)pyridine derivatives employing 4-hydroxycoumarin, an aldehyde, and ammonium acetate. The method showcased remarkable efficiency, allowing the synthesis of multiple derivatives within minutes as opposed to hours using conventional heating methods. This highlighted the potential of microwave-assisted techniques not just in increasing yields, but also in enhancing the diversity of the synthesized products due to quicker reaction times, which can limit the formation of side products.

Further studies have investigated the optimization of parameters such as time, temperature, and solvent choice to maximize product yields while minimizing unwanted reactions. A study conducted by Siddiqui et al.[56] explored the use of solvent-free conditions for microwave-assisted synthesis, yielding Pyrano(3,2-c)pyridines in excellent yields. The reduction or elimination of solvents not only made the method more sustainable but also simplified the work-up procedures, demonstrating the practical applicability of this approach in modern organic synthesis.

Additionally, the integration of microwave-assisted synthesis with other methodologies, such as organocatalysis, has shown promise. Ranjbar et al.[57] explored the use of a visible light-mediated organocatalyst in conjunction with microwave heating to synthesize Pyrano(3,2-c)pyridine derivatives effectively. This dual strategy enhanced the reaction scope and provided conditions for reactions that were otherwise challenging to conduct, contributing further to the diversity of synthetic pathways available for these derivatives.

Pyranopyridines are chemically fascinating molecules because they are structurally related to quinolines, modified pyridines, and benzopyranes[1]. They are also significant intermediates in the creation of physiologically active chemicals. In this study, multicomponent reactions (MCRs) are convergent reactions in which three starting components combine in a single pot to generate a new product containing all or most of the contributing atoms. FATHINEJAD et al.[58] reported An efficient and simple method for synthesizing pyrano[3,2-c]pyridine derivatives using a microwave-assisted technique to condensate malononitrile, ethyl acetoacetate, and aryl aldehydes in the presence of piperazine as a catalyst under solvent-free conditions. Compound structure is confirmed by FTIR, 1H-NMR, and 13C-NMR spectra, as well as elemental analysis.

One challenge that accompanies microwave-assisted synthesis is the need for specialized equipment and the potential for non-uniform heating when scaling up

reactions. Despite these challenges, the advantages provided by this method, particularly in terms of reaction speed and yield, have made it an increasingly popular choice among synthetic chemists Ali et al.[59].

In recent years, the advent of modern synthesis techniques has revolutionized the field of heterocyclic chemistry, including the synthesis of Pyrano(3,2-c)pyridine derivatives. One significant advancement is the application of microwave-assisted synthesis (MAS), which enhances reaction rates while minimizing solvent usage, reaction times, and energy consumption Ali et al.[60]

For example, Hussain et al.[61] reported a microwave-assisted synthesis of Pyrano(3,2-c)pyridine derivatives which resulted in synthesis times reduced to mere minutes and yields increased to 90%. This approach not only truncated the reaction time significantly but also improved the purity of the final product. The employment of microwave technology plays a crucial role in promoting specific interactions at the molecular level, which in turn can facilitate better reaction pathways compared to conventional heating methods Ahmad et al.[62]

In addition to microwave synthesis, there has been a growing interest in green chemistry approaches. These methods leverage eco-friendly solvents and reagents to minimize the environmental impact of chemical synthesis. Jauhar et al.[63] describe a method that integrates ionic liquids as reaction media combined with ultrasound-assisted synthesis to generate Pyrano(3,2-c)pyridine derivatives. This technique reportedly achieved yields surpassing 95% while significantly reducing waste and energy demands.

Conclusion

The synthesis of pyrano[3,2-c]pyridine derivatives showcases a myriad of methodologies, ranging from traditional cyclization techniques to modern green chemistry approaches. Both method presents unique advantages and challenges, influencing their applicability in both academic and industrial contexts. Traditional methods often yield high selectivity but suffer from longer reaction times, while innovative techniques like microwave-assisted synthesis and the use of ionic liquids offer promising alternatives that align with sustainability objectives.

Future research directions involve optimizing these methods further and investigating novel strategies such as biocatalysis to enhance the efficiency and reduce the environmental impact of pyrano[3,2-c]pyridine synthesis. The ongoing commitment to improving synthetic methodologies in this field will not only advance our understanding of these critical compounds but also facilitate their deployment in diverse applications.

In sum, the synthesis of pyrano(3,2-c)pyridine derivatives has evolved through the integration of multicomponent reaction techniques and cyclization methods. The literature evidences a spectrum of products achieved through these methodologies, each presenting unique advantages and challenges. As the field progresses, a continuous emphasis on optimizing reaction conditions and exploring new substrates will be critical for advancing the synthesis of such biologically significant compounds.

In summary, the synthesis of Pyrano(3,2-c)pyridine derivatives has benefited from the development of various innovative methodologies, particularly multicomponent reactions and microwave-assisted synthesis. These approaches not only streamline the synthetic process but also enhance the potential diversity and pharmaceutical applicability of the resulting compounds. As ongoing research continues to refine these methodologies and address synthesis-related challenges, the field is poised for further advances in the generation of these promising heterocyclic compounds.

Acknowledgement: The authors are thankful to Department of Chemical Sciences, Maharaja Ranjit Singh College of professional Sciences, Indore (M.P.) for providing research facilities.

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