Picoline and Its Oxidized Derivatives: A Platform for Synthetic Innovation and Multifaceted Applications

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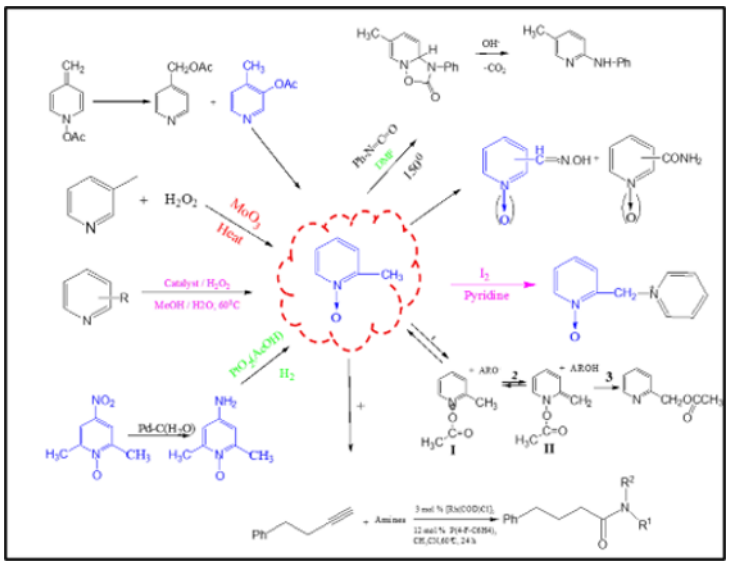
ABSTRACT

Picoline, a methyl-substituted pyridine isomer, and its oxidized derivatives, particularly picoline N-oxides, have garnered significant attention due to their versatile roles in synthetic chemistry and pharmaceutical development. This review comprehensively explores the structural evolution, synthetic methodologies, and biomedical relevance of picoline and its derivatives. Emphasis is placed on the strategic incorporation of picoline scaffolds in drug design, highlighting their physicochemical adaptability and bioisosteric potential. The abstracted data delineate the progression from foundational synthetic routes to advanced, regioselective and environmentally benign protocols for picoline N-oxide formation. Diverse oxidation strategies, including catalytic, electrochemical, and green chemistry approaches, are critically examined, with comparative insights into yield optimization, functional group tolerance, and scalability. Furthermore, the review underscores the pharmacological significance of picoline-based frameworks, particularly in neuroprotective, anti-inflammatory, and antimicrobial applications, supported by recent structure–activity relationship (SAR) studies. The role of N-oxide intermediates in modulating solubility, metabolic stability, and target specificity is also discussed, reinforcing their utility in rational drug design. By bridging synthetic innovation with therapeutic relevance, this article aims to provide a consolidated platform for researchers engaged in heterocyclic chemistry, medicinal chemistry and pharmaceutical research and development. The compiled synthesis pathways and derivative profiles consolidate existing literature but also as a springboard for future exploration into novel picoline-based entities with enhanced bioactivity and clinical promise.

Keywords : Picoline , Picoline N-oxide, structure activity relationship, pyridine isomer, drug design

GRAPHICAL ABSTRACT



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INTRODUCTION

Picoline, a methyl-substituted pyridine, represents a class of heteroaromatic compounds with three positional isomers 2-picoline (α-picoline), 3-picoline (β-picoline), and 4-picoline (γ-picoline) each defined by the location of the methyl group on the pyridine ring. These isomers are structurally simple yet chemically versatile, serving as foundational scaffolds in the synthesis of more complex nitrogen-containing heterocycles[1][2]. Their aromaticity, moderate basicity, and nucleophilicity make them valuable intermediates in organic synthesis, particularly in the pharmaceutical, agrochemical, and dye industries, as well as in biotechnology and life sciences, industrial and material sciences, and environmental and analytical chemistry. Among these, 2-picoline and 4-picoline are most commonly employed due to their favorable reactivity profiles and accessibility from coal tar or via catalytic methylation of pyridine[1].

The transformation of picoline into its N-oxide derivative picoline N-oxide marks a significant chemical modification that alters both the electronic and physicochemical properties of the molecule. Picoline-N-oxides are a class of heterocyclic compounds derived from the oxidation of methylpyridine isomers. Picoline N-oxides are formed through oxidation at the nitrogen atom of the pyridine ring, typically using oxidizing agents such as hydrogen peroxide, m-chloroperbenzoic acid (m-CPBA), or peracetic acid[3].

The oxidation of methyl-substituted pyridines to their corresponding N-oxides introduces a significant electronic perturbation at the nitrogen center, resulting in enhanced polarity, altered hydrogen bonding capacity, and modified reactivity. The N→O functionality imparts a zwitterionic resonance structure that facilitates diverse chemical transformations and influences solubility, permeability, and intermolecular interactions. These properties are particularly relevant in medicinal chemistry, drug metabolism, and bioactivation strategies, where N-oxides serve as bioreversible prodrugs and redox-active intermediates. Their selective activation under physiological conditions such as hypoxia-triggered reduction in tumor microenvironments has been exemplified by agents like tirapazamine[4].

Furthermore, the N-oxide moiety functions as a directing group in metal-catalyzed C–H activation, enabling regioselective functionalization of the pyridine ring. Synthetic access to picoline N-oxides is typically achieved via oxidation at the ring nitrogen using reagents such as hydrogen peroxide, m-chloroperbenzoic acid, or peracetic acid, with reaction outcomes influenced by the electronic environment dictated by methyl group positioning[5].

Historical Background and Early Investigations

The exploration of pyridine N-oxides began in the mid-20th century, with pioneering studies by Ross et al. (1956) that elucidated the donor-acceptor interactions of N-oxide systems[3]. These investigations laid the foundation for understanding the electronic perturbations induced by N-oxidation and their implications for aromatic reactivity. The subsequent decades witnessed a surge in interest surrounding N-oxide derivatives, including picoline-N-oxides, as chemists recognized their potential in facilitating novel transformations and enhancing molecular functionality.

Advances in the Synthesis and Mechanistic Understanding of Picoline N-Oxides

Recent developments in the synthesis of picoline N-oxides have transitioned from conventional batch oxidation protocols to more refined and sustainable methodologies. Controlled oxidation using aqueous hydrogen peroxide in the presence of catalytic system such as transition metals or supported reagents has demonstrated high selectivity and yield, though optimization remains critical to suppress overoxidation and ring degradation.

Innovations in flow chemistry and microreactor platforms have significantly enhanced process safety, scalability, and energy efficiency. These continuous systems offer precise modulation of reaction parameters, including temperature, residence time, and stoichiometry, thereby minimizing side reactions and streamlining product isolation. In parallel, electrochemical oxidation has emerged as a green alternative, circumventing the use of stoichiometric oxidants and aligning with environmentally responsible synthesis.

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Mechanistically, N-oxidation of picoline proceeds via nucleophilic attack of the oxidant on the pyridine nitrogen lone pair, generating a transient peroxy intermediate that rearranges to the N-oxide. The rate and efficiency of this transformation are governed by the electronic environment of the nitrogen atom, which is influenced by the positional orientation of the methyl substituent. Notably, 4-picoline[6] exhibits enhanced reactivity due to increased electron density at the nitrogen site, in contrast to the relatively inert 3-isomer[7][8][9]

Mechanistic Insights into N-Oxidation

The oxidation of picoline involves a peracid intermediate that facilitates oxygen transfer to the nitrogen center. The process is exothermic and sensitive to reaction conditions, including temperature, solvent polarity, and oxidant concentration. Mechanistic studies have revealed that the electron-rich nature of the methylpyridine ring enhances susceptibility to electrophilic attack, particularly in the 2-position isomer[10][11].

Physicochemical Properties and Analytical Considerations

The physicochemical attributes of picoline-N-oxides such as melting point, boiling point, solubility, and polarity are influenced by isomeric structure. Analytical techniques including NMR spectroscopy, IR spectroscopy, and mass spectrometry are routinely employed to confirm N-oxide formation and assess purity. Thermal analysis (DSC/TGA) further aids in characterizing stability and decomposition profiles.

Safety and Handling

Picoline-N-oxide compounds are generally regarded as low-hazard substances; however, standard laboratory safety protocols must be strictly observed during their handling and storage. Although not acutely toxic, these compounds may cause mild irritation upon contact with skin or eyes, and inhalation of dust or vapors should be avoided due to potential respiratory discomfort.

Exposure Control

All manipulations should be conducted in a well-ventilated fume hood. Personnel must wear appropriate personal protective equipment, including nitrile gloves, safety goggles, and laboratory coats. In cases of prolonged exposure or large-scale operations, respiratory protection may be warranted.

Storage Conditions:

Materials should be stored in airtight containers under dry, cool, and ventilated conditions. Picoline-N-oxides are sensitive to moisture and light; therefore, desiccation and protection from direct sunlight are recommended to maintain chemical stability.[12]

Spill and Disposal Protocols

In the event of accidental release, containment using inert absorbents (e.g., silica, vermiculite) is advised. Waste material should be collected and disposed of in accordance with institutional hazardous waste guidelines and local environmental regulations. Incineration under controlled conditions is preferred for disposal of N-oxide derivatives[13].

Regulatory Status

Picoline-N-oxides are not classified under major international hazard categories (e.g., GHS Category 1), but users should consult relevant national chemical inventories and safety data sheets for specific compliance requirements[14].

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Synthetic Methodologies

- **Classical Oxidation Techniques**

Traditional synthesis of picoline-N-oxides involves oxidation using peracids such as m-chloroperbenzoic acid (m-CPBA) or hydrogen peroxide under acidic conditions. These reactions proceed via electrophilic oxygen transfer to the pyridine nitrogen, forming the N-oxide moiety.

- **Catalytic and Green Chemistry Approaches**

Recent advancements have emphasized environmentally benign protocols. For example, phosphotungstic acid catalyzed oxidation using hydrogen peroxide yields 4-chloro-3-methoxy-2-picoline-N-oxide with high efficiency and minimal waste. These methods align with green chemistry principles, promoting atom economy, reduced toxicity, and scalability.

- **Synthetic Utility and Functional Transformations**

Picoline-N-oxides serve as versatile intermediates in organic synthesis due to their nucleophilic character and ability to undergo rearrangement reactions.

-Boekelheide Rearrangement:

Enables α-functionalization adjacent to the nitrogen atom, yielding hydroxymethylated derivatives.

-Electrophilic Substitution:

Facilitated by the electron-donating nature of the N-oxide group, allowing regioselective transformations. These reactions expand the synthetic repertoire for constructing complex heterocycles and functionalized aromatic systems.

-Applications of Picoline N-Oxides Across Scientific Domains

1.Medicinal Chemistry and Drug Development

- **Prodrug Strategy:** Enhance solubility and enable site-specific activation; exemplified by tirapazamine.
- **Redox Modulation:** Support oxidative stress regulation, biosensors, and redox-sensitive therapeutics.
- **C–H Activation:** Direct regioselective pyridine functionalization in drug discovery.
- **Metabolic Profiling:** Serve as phase I metabolites and LC-MS/MS standards.

2. Co-ordination Chemistry

- **Ligand Design:** Act as bidentate ligands with transition metals.
- **Catalysis and Assembly:** Enable oxidation catalysis and supramolecular architectures.

3. Agrochemical and Environmental Chemistry

- **Herbicide/Pesticide Synthesis:** Improve enzymatic binding for selective inhibitors.
- **Plant Growth Regulators:** Mimic auxin-like activity via hydroxypicoline derivatives.
- **Sustainable Chemistry:** Support green synthesis with low toxicity and biodegradability.

4. Synthetic Methodology

- **King-Type Transformations:** Enable electrophilic activation for pyridinium iodide synthesis.
- **Rearrangement Reactions:** Undergo Boekelheide and Meisenheimer rearrangements with high selectivity.

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5. Emerging Technologies and Material Science

- **Polymeric Integration:** Explore drug delivery and sensing platforms.
- **Computational Design:** Guide functionalization via quantum chemical studies.
- **Photoredox and Flow Chemistry:** Expand scalable synthetic access.

6. Pharmaceutical Sciences

- **Prodrug Design:** Improve solubility, permeability, and site-specific activation.
- **Redox-Sensitive Therapeutics:** Enable ROS-targeted therapies and biosensing.
- **Drug Metabolism:** Aid in metabolite profiling and LC-MS/MS analysis.
- **Synthetic Utility:** Facilitate regioselective C–H activation for SAR studies.

7. Heterocyclic and Coordination Chemistry

- **Ligand Design:** Form stable metal complexes for catalysis and recognition.
- **Electrophilic Activation:** Enable selective rearrangements for functionalized scaffolds.
- **King-Type Transformations:** Highlight N→O activation in heterocyclic synthesis.
- **Emerging Methodologies:** Advance photo-redox, flow, and computational chemistry.

8. Agrochemical and Environmental Chemistry

- **Herbicide Development:** Enhance specificity via nucleophilic interactions.
- **Plant Growth Regulation:** Influence physiological processes with tailored regulators.
- **Sustainable Design:** Align with eco-friendly, biodegradable synthesis.
- **SAR and Analog Generation:** Accelerate agrochemical discovery through modular chemistry

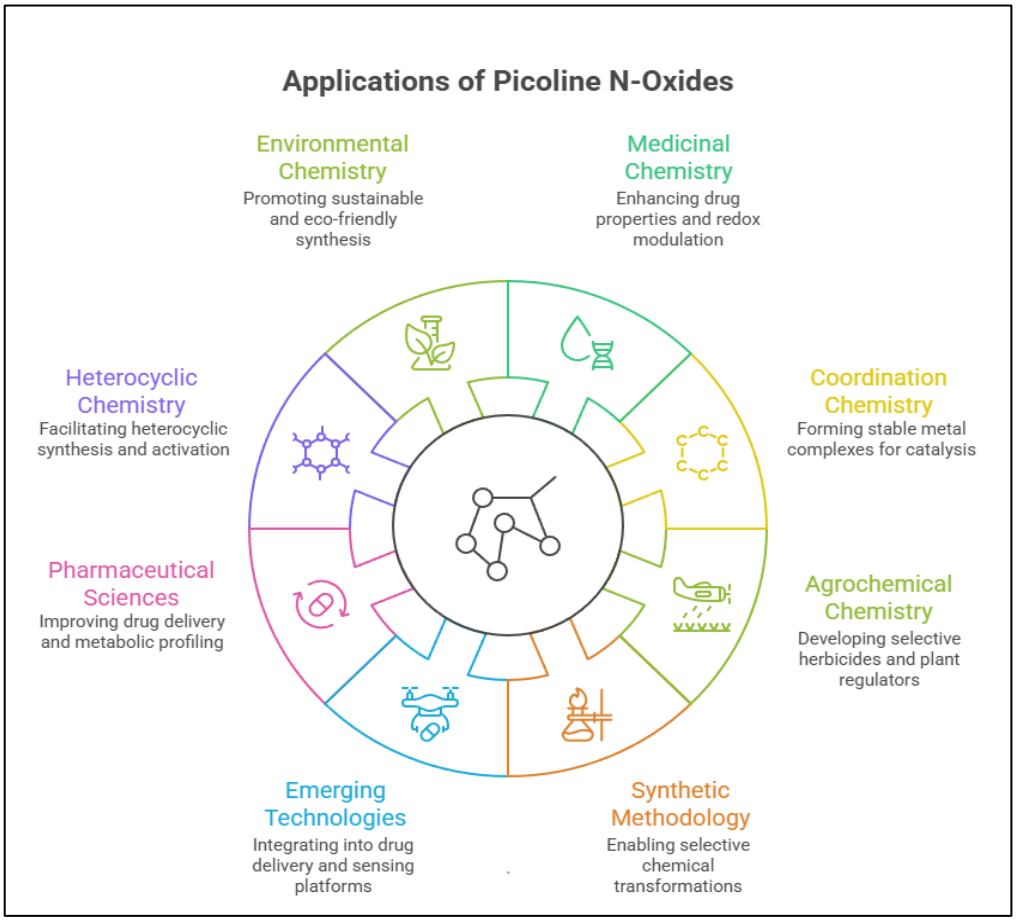


Figure No. 1: Applications of Picoline-N-Oxide in various Fields

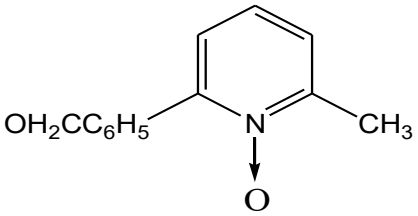
Design Constraints of Picoline N-Oxides

Despite their promising attributes, the use of picoline N-oxides in drug development is not without challenges. Their increased polarity can sometimes hinder passive diffusion across lipid membranes, necessitating the use of transporters or formulation strategies to ensure adequate bioavailability. Additionally, the stability of N-oxides under physiological conditions must be carefully evaluated, as premature reduction or hydrolysis can compromise therapeutic efficacy.

From a synthetic perspective, regioselective oxidation of picoline isomers remains a topic of ongoing research. Achieving high selectivity without overoxidation or side reactions requires precise control over reaction parameters and catalyst design. The development of asymmetric oxidation methods and chiral N-oxide derivatives also presents opportunities for expanding the chemical space of bioactive molecules.

Synthetic approaches to picoline-N-oxide and related derivatives:

1. Adams et al. report the synthesis of ethyl 6-benzyloxy-2-pyridylacetate via condensation of 6-benzyloxy-2-pyridylacetic acid derivatives, followed by debenzylation and rearrangement. Comp. A is identified as a key intermediate in the total synthesis of cytisine, a bioactive alkaloid. Additionally, 6-bromo-2-methylpyridine undergoes nucleophilic substitution with sodium benzyloxide to yield 6-benzyloxy-2-methylpyridine, which is subsequently oxidized with peracetic acid to form its N-oxide derivative. These transformations highlight the strategic application of benzyloxy protection and pyridine N-oxidation in heterocyclic synthesis[15].



2. In continuation of synthetic investigations on 4-substituted picolines, **Herz et al.** explored the preparation of 4-nitro- and 4-amino-3-picoline via pyridine N-oxide intermediates. Building on prior findings by Ochiai and den Hertog regarding electrophilic substitution on pyridine N-oxides, the authors achieved selective nitration of 3-picoline N-oxide to yield 4-nitro-3-picoline N-oxide. This intermediate was synthesized by oxidation of 3-picoline with peracetic acid, followed by nitration using potassium nitrate in sulfuric acid.

Reduction of the nitro N-oxide over palladium-black in acetic acid/acetic anhydride afforded 4-amino-3-picoline, crystallizing as colorless needles (m.p. 107.4–108.6 °C), with confirmation via picrate and N-acetyl derivatives. Alternatively, direct reduction of 4-nitro-3-picoline N-oxide with phosphorus trichloride in chloroform yielded 4-nitro-3-picoline (m.p. 27–29 °C), which was further reduced catalytically to 4-amino-3-picoline. The synthetic route thus provides a convenient and regioselective method for accessing 4-substituted 3-picoline derivatives via N-oxide intermediates[16].

3. Kato et al. (1956) investigated the reduction behavior of 4-nitro-2,6-lutidine 1-oxide (Ia) and 4-nitro-3-picoline 1-oxide (Ib), extending prior findings by Ochiai et al. on the resistance of N-oxide functionalities to reduction relative to nitro groups. Catalytic hydrogenation using Pd-C in aqueous media afforded the corresponding 4-amino 1-oxides (IIa, IIb) with uptake of three equivalents of hydrogen. Reaction kinetics were influenced by catalyst loading and temperature; low Pd-C concentrations favored formation of azo by-products (Va, Vb), whereas higher loadings yielded IIa and IIb efficiently.In methanolic and dilute hydrochloric acid media, incomplete reduction and competitive azo formation were observed. Conversely, reduction in glacial acetic acid with acetic anhydride or in the presence of platinum oxide proceeded smoothly to the amino derivatives (IIIa, IIIb).Alternative reductions using hydrogen sulfide, sodium nitrite, or zinc dust yielded azo (Va, Vb) and azoxy (IVa, IVb) derivatives. Product isolation and characterization were facilitated by differential solubility profiles, enabling effective separation of amino oxides from by-products.These findings underscore the nuanced reactivity of nitro-N-oxide systems and provide optimized conditions for selective synthesis of amino-substituted pyridine N-oxides[17].

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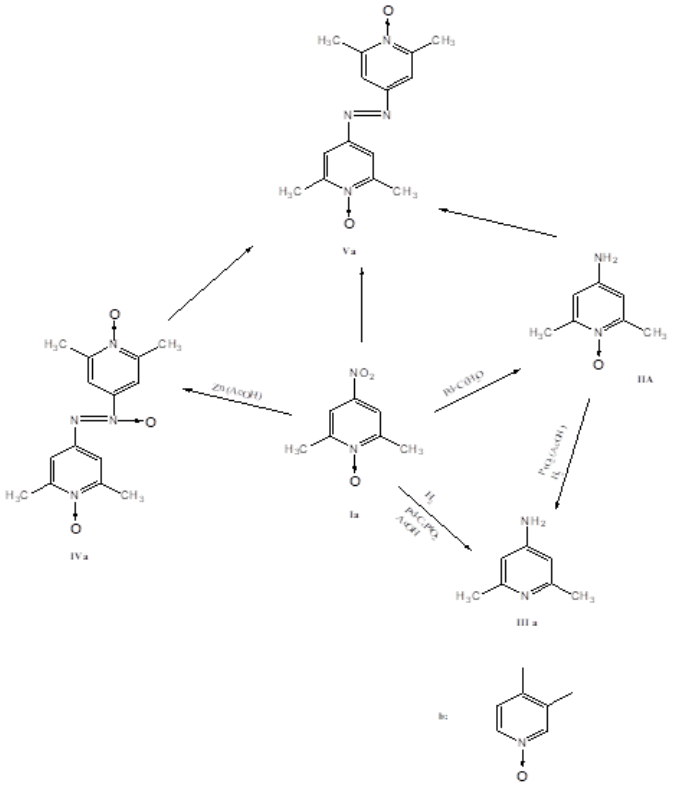
Scheme 1:

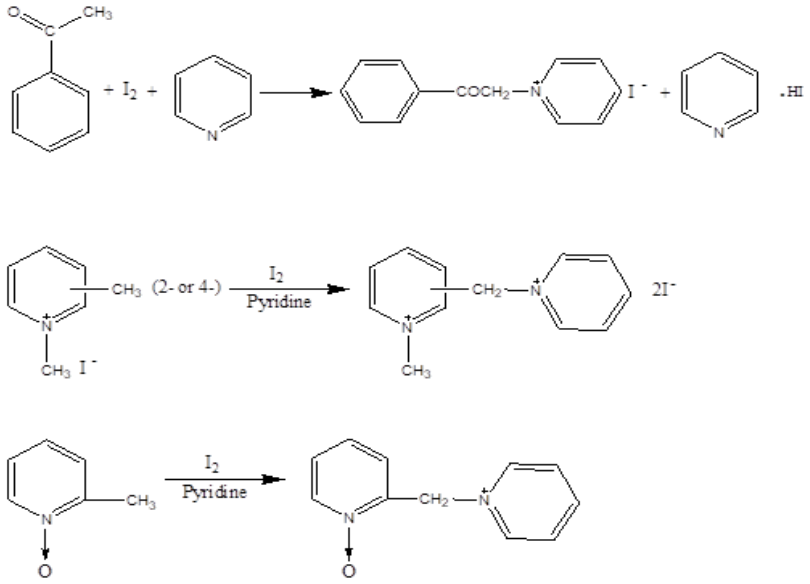


4. Masatomo Hamana et al. investigated the reactivity of 2-picoline 1-oxide in the context of the King reaction, originally reported in 1944, wherein aryl methyl ketones react with iodine and pyridine to yield 1-aroylmethylpyridinium iodides (e.g., acetophenone → 1-phenacylpyridinium iodide). This transformation has since been extended to various N-heterocycles bearing active hydrogen, including 1-methyl-2- or -4-picolinium iodide, quinaldine, lepidine, 6-methylquinaldine, and 1-methylisoquinoline.

Kröhnke later demonstrated that unquaternised 2- or 4-picoline fails to undergo this reaction, whereas their quaternised analogues do, highlighting the role of methyl group activation via quaternisation. However, the influence of N-oxidation remained unexplored.

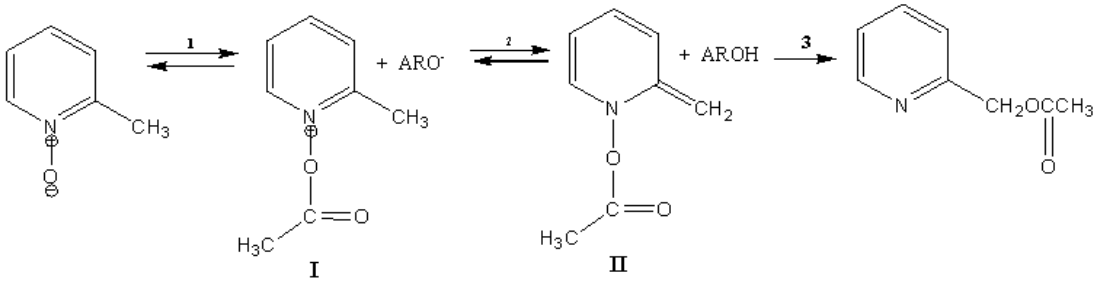
Hamana et al. addressed this gap by refluxing 2-picoline 1-oxide with equimolar iodine and excess pyridine, successfully synthesizing 1-(1-oxido-2-pyridylmethyl) pyridinium iodide (I) -(m.p. 180-181 °C, decomp.), which formed a dipicrate derivative (m.p. 142–143 °C). These findings underscore the activating effect of N-oxidation in facilitating the King-type transformation of picoline derivatives[18]**.**

Scheme 2: King reaction



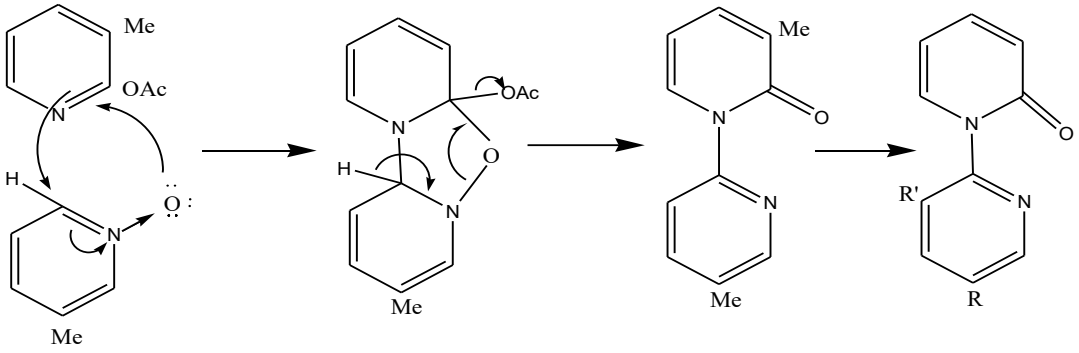
5. **Traynelis et al**. investigated the reactions of picoline N-oxide with various phenyl acetates - m- and p-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trichlorophenyl-yielding pyridylmethyl acetates. Mechanistic insights were supported by the formation of a 1:1 adduct between picryl acetate and picoline N-oxide, identified as 1-acetoxy-2-methylpyridinium picrate. Treatment with triethylamine converted this intermediate to pyridylmethyl acetate and triethylamine picrate, providing chemical evidence for the involvement of the 1-acetoxy-2-methylpyridinium cation as the key reactive species. The reaction of 4-picoline N-oxide with 2,4,6-trichlorophenyl acetate yielded 4-pyridylmethyl acetate along with minor alkylpyridine byproducts, further substantiating the proposed mechanism[19].

Scheme 3 : Substitution reaction



6. Under the conditions described by **B.M. Bain** et al., the reaction of 3-picoline N-oxide with acetic anhydride yielded several pyridone derivatives. Among these, two notable products were isolated: 3-methyl-1-(5-methyl-2-pyridyl)-2-pyridone and 1-(3-methyl-2-pyridyl)-2-pyridone. The formation of these compounds supports a mechanistic pathway involving nucleophilic attack at the 2-position of a substituted pyridine by the N-oxide function, followed by internuclear oxygen transfer. This mechanism, previously proposed for similar systems, appears applicable here despite the absence of direct evidence for oxygen migration. Importantly, the isolation of 1-(3-methyl-2-pyridyl)-2-pyridone challenges earlier steric hindrance arguments that had been used to explain its non-formation in reactions involving 2-bromopyridine. These findings suggest that steric factors may not be the primary determinant in the formation of such pyridone derivative[20][21][22][23].

Scheme 4: Nucleophilic Substitution reaction

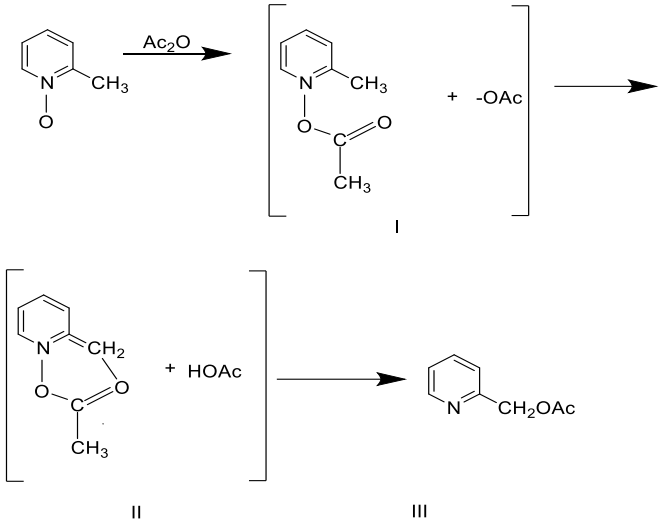


7. Shigeru Oae et al. investigated the mechanistic pathway of the rearrangement reaction between 2-picoline N-oxide and acetic anhydride using oxygen-18 isotopic labeling. The study revealed that both the carbonyl and ether oxygen atoms in the product, 2-acetoxymethylpyridine, incorporated equal amounts of oxygen-18, indicating complete scrambling of the labeled oxygen atoms. Hydrolysis of the ester yielded 2-pyridinemethanol, which retained the isotopic distribution, further supporting the proposed mechanism.

Control experiments with radical scavengers (e.g., DPPH) and varying solvent volumes showed no significant impact on product yield, suggesting that the reaction proceeds via a solvent-caged radical pair rather than a free radical chain or ionic pathway. The authors ruled out intramolecular cyclic rearrangement and nucleophilic attack mechanisms based on the isotopic data and reaction behavior.

The findings support a homolytic cleavage of the N-O bond in the anhydrobase intermediate, followed by recombination of the acetoxy and picolyl radicals within the solvent cage. This mechanistic insight distinguishes the behavior of 2-picoline N-oxide from its 4-isomer and contributes to a deeper understanding of tertiary amine N-oxide rearrangements[24][25][26].

Scheme 5: Rearrangement reaction

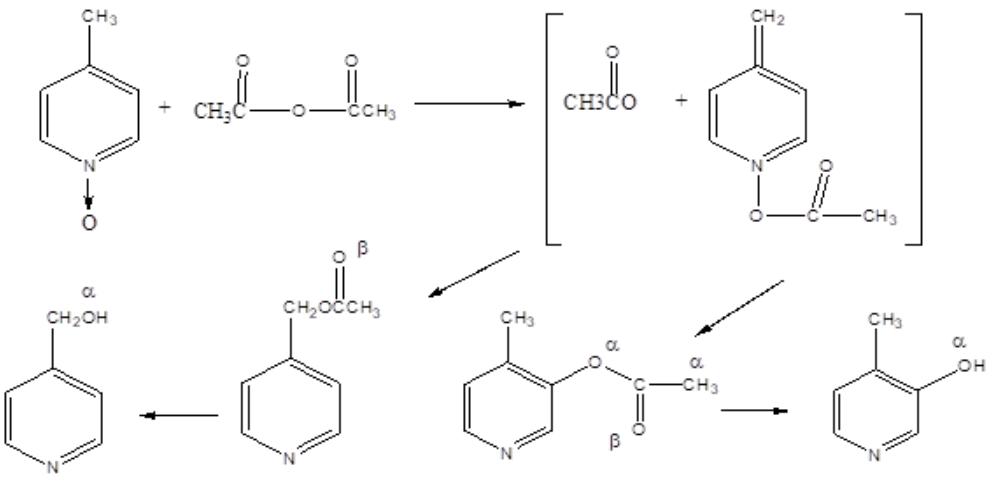


8. Shigeru Oae et al. investigated the mechanistic pathway of the rearrangement reaction between 4-picoline N-oxide and acetic anhydride, focusing on the origin and distribution of oxygen atoms in the resulting 4-acetoxymethylpyridine. Using oxygen-18 labeling, the study revealed that the carbonyl oxygen in the ester product originates exclusively from acetic anhydride, while the ether oxygen is retained from the N-oxide moiety. This selective incorporation contrasts with the behavior observed in the 2-picoline N-oxide system, indicating a distinct mechanistic route.

The authors proposed a concerted rearrangement mechanism involving an anhydrobase intermediate, where the acetyl group migrates to the methyl position without homolytic cleavage of the N–O bond. Supporting evidence includes the absence of radical inhibition effects and the lack of isotopic scrambling. The reaction proceeds efficiently under mild conditions and does not involve free radical intermediates, as confirmed by control experiments with radical scavengers.

These findings provide critical insight into the stereoelectronic factors governing N-oxide rearrangements and highlight the positional influence of the methyl group on reaction pathways. The study contributes to a broader understanding of heterocyclic N-oxide chemistry and its synthetic applications in regioselective functionalization.[27]

Scheme 6: Rearrangement reaction



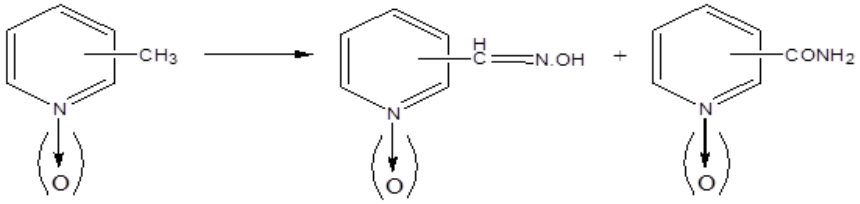
9. **Tetsuzo Kato et al.** investigated the reactivity of picolines and their N-oxides with amyl nitrite under various conditions in liquid ammonia, employing sodium or potassium amide as base. While picolines showed limited reactivity, their N-oxides underwent smooth transformation to yield aldoximes and acid amides. Notably, 2-picoline 1-oxide afforded picolinaldehyde 1-oxide oxime with minor formation of picolinamide 1-

oxide. Reactivity varied with substitution: the methyl group at the 4-position was most reactive, followed by the 2-position, while the 3-position remained largely inert.

The study revealed that aldoximes formed under these conditions were predominantly syn-type, stabilized via intramolecular hydrogen bonding. Anti-type aldoximes, formed at room temperature, readily converted to nitriles or amidines upon further treatment with sodium amide. Additionally, 4-picoline 1-oxide yielded isonicotinonitrile 1-oxide and isonicotinamide 1-oxide, demonstrating unique nitrile formation. Comparative reactions with non-oxidized picolines confirmed the enhanced reactivity conferred by N-oxidation.

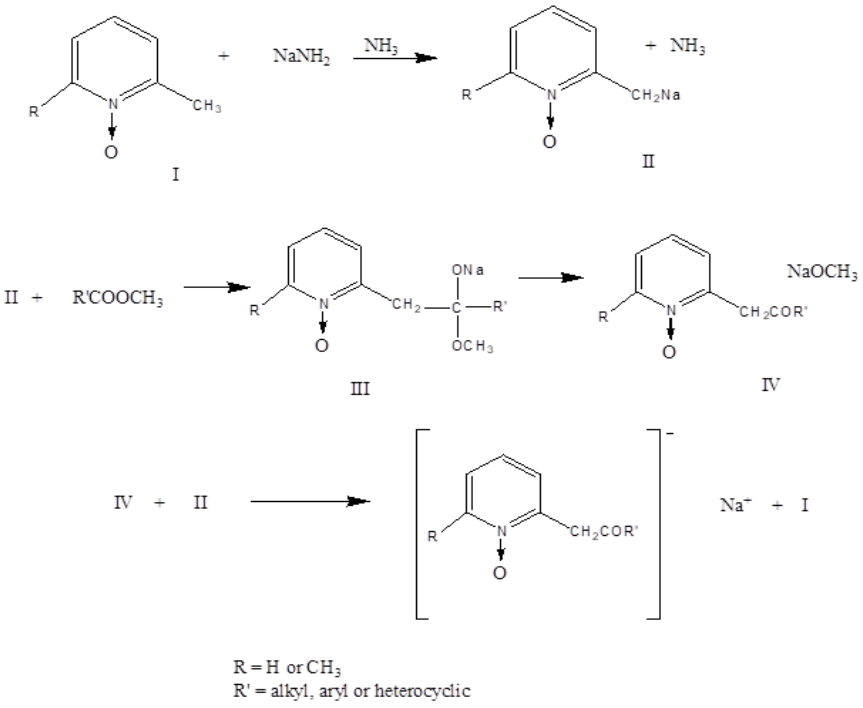
These findings underscore the influence of positional substitution and N-oxidation on methyl group activation in pyridine derivatives, offering mechanistic insights and synthetic routes to functionalized heterocycles via nitrosation in ammonia media[28].

Scheme 7: substitution and N-oxidation



10. David Osborne et al. report the efficient acylation of 2-picoline N-oxide and 2,6-lutidine N-oxide using sodium amide in liquid ammonia as the condensing agent, with various aliphatic, aromatic, and heterocyclic esters. The reaction of 2-picoline N-oxide with methyl benzoate yielded 2-phenacylpyridine N-oxide, isolated as a water-insoluble solid with a melting point of 158 °C. Similarly, 2,6-lutidine N-oxide reacted with methyl nicotinate to afford 2,6-lutidyl 3-pyridyl ketone N-oxide, a water-soluble compound with a melting point of 133–134 °C. In another variation, the reaction of 2,6-lutidine N-oxide with ethyl isobutyrate produced 2,6-lutidyl isopropyl ketone N-oxide, which was isolated by vacuum distillation and characterized by a boiling point of 140–146 °C at 0.5 mmHg and a melting point of 91–92 °C. These results demonstrate the versatility and effectiveness of sodium amide-mediated acylation of pyridine N-oxides under anhydrous conditions[29][30][31][32][33].

Scheme 8: Acylation reaction



11. S. Oae et al. investigated the isotopic behavior of 2-picoline and 4-picoline N-oxides reacting with uniformly acetic anhydride in various solvents. For 2-picoline N-oxide, the solvent had no effect on the distribution in the major product, 2-acetoxymethylpyridine, indicating a solvent-independent intramolecular

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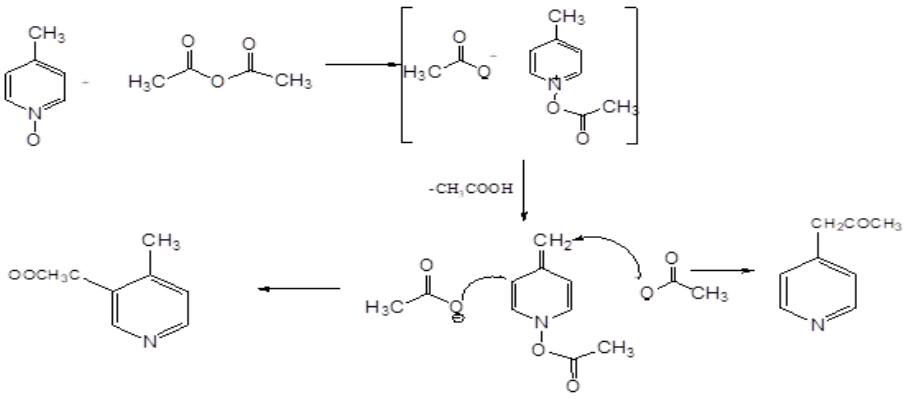
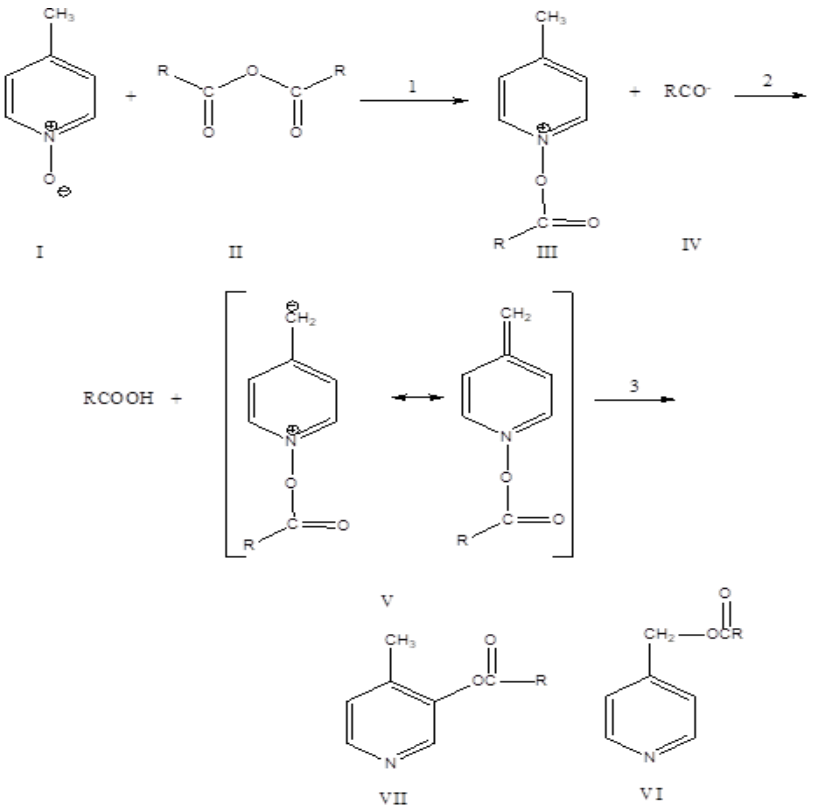
radical cage mechanism involving homolytic N–O bond cleavage and recombination. In contrast, the reaction of 4-picoline N-oxide yielded a mixture of 3-acetoxy-4-methylpyridine and 4-acetoxymethylpyridine with incorporation patterns consistent with an intermolecular pathway. This involves nucleophilic attack by acetoxy anions at the methylene or C-3 position of the pyridine ring, accompanied by heterolytic N–O bond cleavage. These findings highlight distinct mechanistic pathways for structurally related N-oxides and underscore the influence of substitution patterns on reaction dynamics[34][35][36][37].

Scheme 9: nucleophilic substitution reaction



12.Traynelis and Gallagher et al. report a product study of 4-picoline N-oxide reactions with acetic, isobutyric, and pivalic anhydrides. The reaction yielded carbon dioxide, esters namely 4-acyloxymethylpyridine and 3-acyloxy-4-methylpyridine and a range of alkylpyridines including 4-alkyl-, 3,4-dialkyl-, and 2,4-dialkylpyridines. The observed product distribution is rationalized through an intramolecular radical-pair mechanism involving an anhydro base intermediate, offering mechanistic insight into N-oxide reactivity with aliphatic anhydrides[38].

Scheme 10: Photoredox reaction



13. P.W. Ford et al. revisited the reaction of 2-picoline N-oxide with acetic anhydride, previously assumed to yield a single product 2-acetoxymethylpyridine. Their analytical study, including NMR, IR, and mass spectrometry, revealed that the reaction actually produces a mixture of three regioisomeric acetoxypicolines: 2-acetoxymethylpyridine (major, ~66%), 3-acetoxy-2-picoline (~15–18%), and 5-acetoxy-2-picoline (~16–

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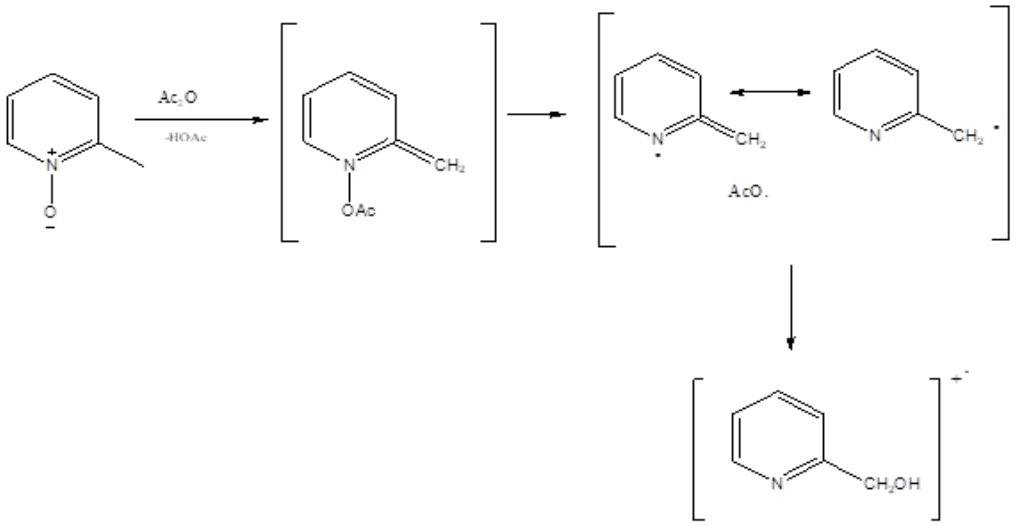
18%). These isomers were separated and structurally confirmed via preparative gas chromatography and spectral comparison with authentic samples.

The formation of 3-acetoxy-2-picoline and 5-acetoxy-2-picoline is attributed to a free radical pathway involving homolytic cleavage of an N-acetoxy intermediate. The resulting picolyl radical exhibits delocalization across the 2-, 3-, and 5-positions, enabling recombination with the acetoxy radical at multiple sites. This mechanism is supported by isotopic labeling studies and aligns with the observed product distribution, ruling out ionic rearrangement as the dominant pathway.

This work refines the understanding of N-oxide reactivity with acetic anhydride and highlights the regioselective complexity inherent in pyridine N-oxide transformations[39][40][41][42][43].

Scheme 11: Homolytic fission of N-acetoxy anhydro base



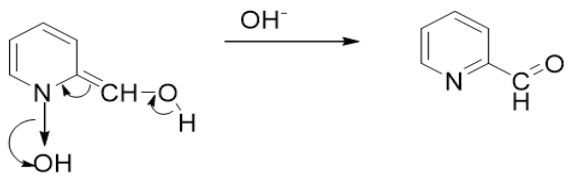
14. W. S. Chilton et al. report an efficient method for synthesizing pyridine-2- and -4-carboxaldehyde derivatives via a base-catalyzed intramolecular oxidation of hydroxymethylpyridine N-oxides. This transformation proceeds through a distinct NO heterolysis pathway, differing from previously proposed intermolecular mechanisms.

Hydroxymethylpyridine was first obtained via acylative rearrangement of picoline N-oxide and subsequently oxidized to its N-oxide form. Treatment of 2-hydroxymethylpyridine N-oxide with phenylhydrazine in dilute sodium hydroxide yielded pyridine-2-carboxaldehyde phenylhydrazone. Control experiments confirmed that phenylhydrazine does not act as the oxidant, as comparable yields were obtained based on its stoichiometry, and no product formed in the absence of base or N-oxide functionality.

Further mechanistic evidence was provided by reactions involving excess 2-ethylpyridine N-oxide, which failed to produce intermolecular oxidation products, indicating that the alcohol is oxidized at the expense of the N-oxide via an intramolecular process. The proposed mechanism involves enolization to an enolamine intermediate, followed by base-induced elimination and NO bond cleavage, analogous to the oxidative step in osazone formation.

No reaction was observed with the methyl ether analog, supporting the requirement for a free hydroxyl group. These findings expand the synthetic utility of picoline N-oxides in aldehyde synthesis and highlight a novel intramolecular redox pathway[44].

Scheme 12: Intramolecular oxidation reaction



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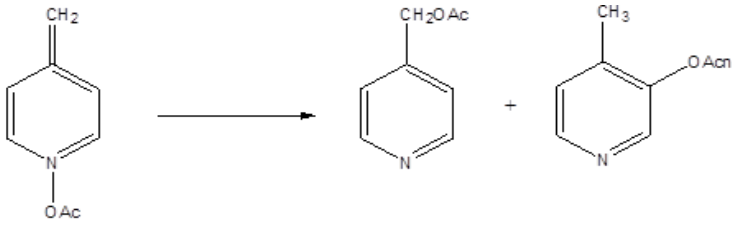
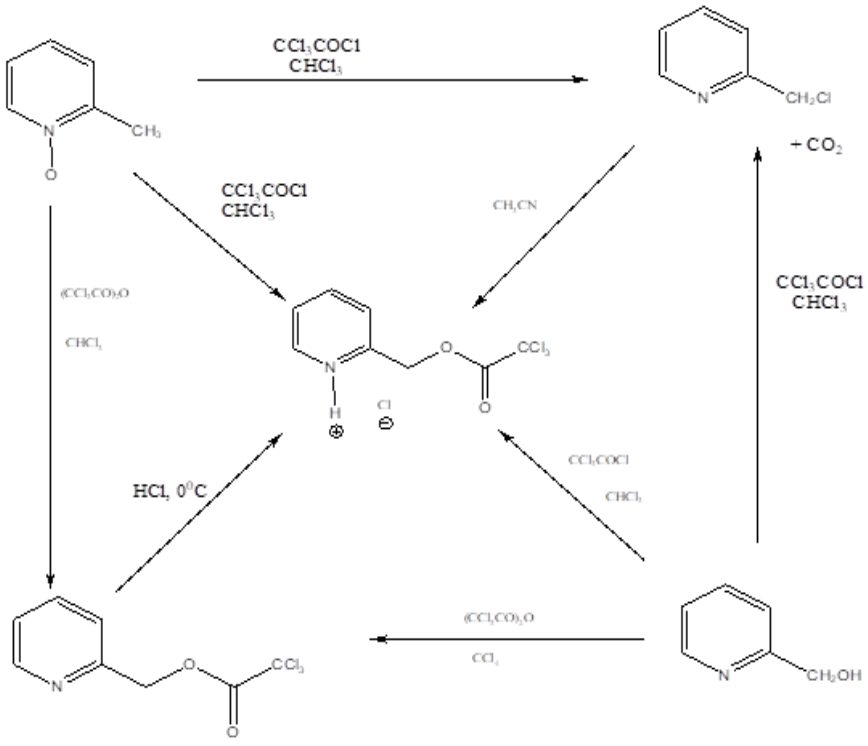
15.Cohen et al. proposed that the N–O bond in the anhydrobase intermediate, derived from 4-picoline N-oxide and acetic anhydride, undergoes heterolytic cleavage to yield an acetate anion and a picolyl cation. This cationic species may subsequently be intercepted by either internal or external acetate or acetic acid, rationalizing the formation of products via a unified cleavage pathway. Supporting evidence for this mechanism includes the formation of substantial ester products in reactions involving 2-picoline N-oxide with phenylacetic and trichloroacetic anhydrides. However, analogous results with 4-picoline N-oxide have also been interpreted in favor of a radical-pair mechanism. To probe the intermediacy of the picolyl cation, reactions were conducted in anisole and benzonitrile. In anisole, a 20% yield of three picolylanisole isomers was obtained, with meta and para derivatives confirmed by comparison to authentic samples. The observed meta:para ratio of 0.25 aligns with electrophilic aromatic substitution by a cationic species rather than radical attack, which typically yields higher meta selectivity. These findings lend credence to a cationic pathway under specific conditions, although mechanistic ambiguity persists due to competing interpretations[45].

Scheme 13: Rearrangement reaction



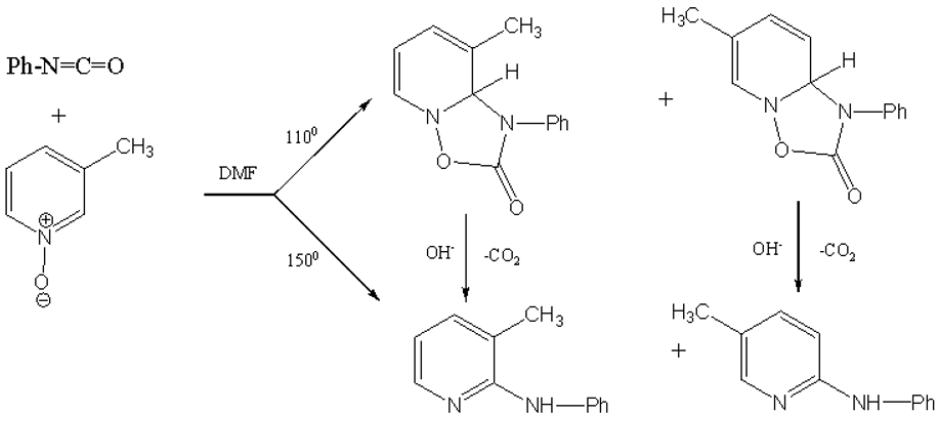
16. T. Coenig et al. report that the reaction of trichloroacetyl chloride with 2-picoline N-oxide in refluxing chloroform leads to the formation of 2-pyridylmethyl chloride and carbon dioxide in high yield. The transformation proceeds via the intermediate formation of a trichloroacetate ester, as confirmed by ^{1}H NMR spectroscopy (singlet at 5.8 ppm). Upon extended reflux, this ester undergoes conversion to the chloride product, evidenced by the emergence of a new singlet at 5.1 ppm and progressive CO_2 evolution. After 12 hours, the ester is nearly consumed, and the final product is isolated . The same chloride product is obtained when 2-pyridylcarbinol is treated with trichloroacetyl chloride or its anhydride, indicating a general pathway involving ester formation followed by chloride substitution. This study highlights a practical route for synthesizing pyridylmethyl chlorides via N-oxide activation and ester-mediated halogenation[46][47][48][49][50]**.**

Scheme 14: Substitution reaction



17.Hisano *et al*. report the isolation and characterization of two isomeric cycloadducts (III and IV) formed from the reaction of 3-picoline-N-oxide with phenylisocyanate in DMF at 110 °C. The adducts, obtained in 34% and 24% yields respectively, exhibit identical molecular weights (m/z 228) and elemental compositions ($C_{13}H_{12}N_2O_2$), consistent with 1:1 stoichiometry. Spectroscopic analyses (IR, NMR, UV) confirm the presence of carbonyl functionalities and distinguish the isomeric nature of the products. Upon alkaline hydrolysis, III and IV convert to 2-anilino-3-methylpyridine (V) and 2-anilino-5-methylpyridine (VI), respectively. Elevated reaction temperatures (150 °C) favor direct formation of V and VI, with minimal recovery of III. Mechanistic considerations suggest either distinct transition states or a common ionic intermediate capable of cyclization at alternate ring positions. The study represents the first documented isolation of primary cycloadducts from an N-oxide–isocyanate system and underscores the subtle influence of methyl substitution on regioselectivity and thermal stability[51].

Scheme 15: Aza- Diels Alder reaction



18. Karayannis et al. synthesized and characterized cobalt(II), nickel(II), and copper(II) complexes with 2-, 3-, and 4-picoline N-oxides (picO) using ligand-to-metal ratios of 2:1 and 8:1. Complexes formed under 2:1 conditions exhibited mono- or binuclear structures with coordinated nitrate groups, including [M(2-picO)$_2$(ONO$_2$)(O$_2$NO)] (M = Co, Ni), [Cu(2-picO)$_2$(ONO$_2$)$_2$], and [Co(3-picO)$_2$(O$_2$NO)$_2$]. Binuclear architecture was proposed for Co(NO$_3$)$_2$·(4-picO). In contrast, 8:1 ligand-rich conditions yielded ionic complexes such as M(2-picO)$_4$(ONO$_2$) and Cu(2-picO)$_{42}$. For Cu(NO$_3$)$_2$·4(3-picO), spectroscopic data supported either a monomeric or binuclear formulation. These findings highlight the influence of ligand ratio and picoline isomer on coordination geometry and nuclearity[52].

19. Jerry A. Jenkins et al. conducted a detailed mechanistic investigation into the reaction of 2-picoline N-oxide with phenylacetic anhydride, which proceeds via two competing pathways: a rearrangement route yielding picolyl phenylacetate, 2-(3-phenylethyl)pyridine, minor products, and CO_2; and an oxidative cleavage pathway producing benzaldehyde, 2-picoline, and CO. The relative dominance of each pathway is highly sensitive to isotopic substitution, providing a robust framework for evaluating hydrogen isotope effects.

A significant primary kinetic isotope effect (KIE = 3.8–4.2) was observed in the rearrangement pathway when comparing methyl-deuterated and undeuterated 2-picoline N-oxide, indicating that formation of the anhydro base intermediate is rate-limiting. Conversely, the oxidation pathway displayed an inverse isotope effect (KIE = 0.76–0.81) upon deuteration at the methylene group of phenylacetic anhydride, consistent with reversible enol/enolate formation preceding an SN1'-type carbocationic transition state.

Solvent polarity was found to moderately influence the pathway distribution, with evidence supporting ion-pairing interactions and a dual fragmentation mechanism of the anhydro base. These insights advance the mechanistic understanding of N-oxide chemistry and highlight the strategic use of isotopic labeling and solvent effects in elucidating complex reaction pathways[53].

Scheme 16 : Rearrangement reaction

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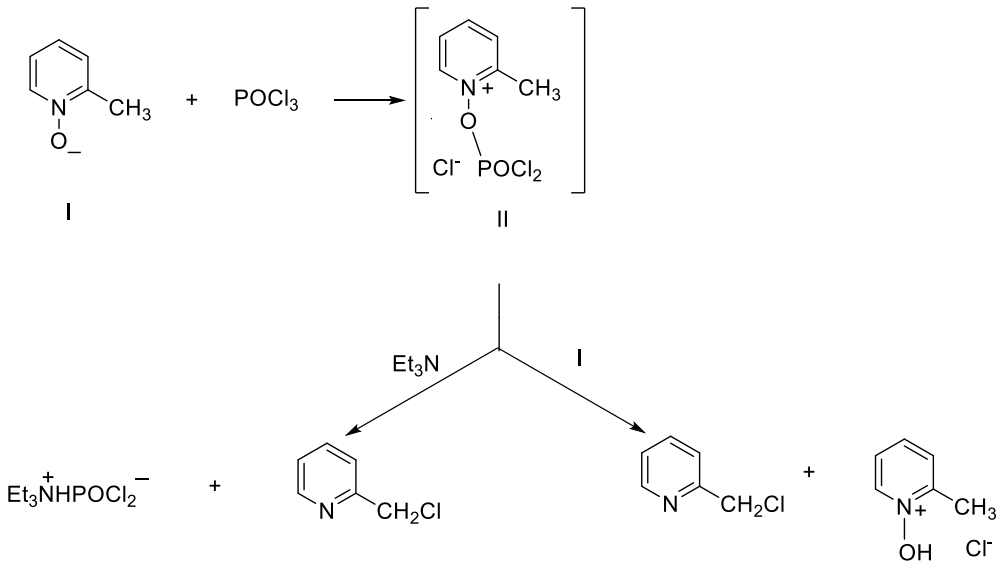
20. Mary Lynne Ash et al. report an efficient method for synthesizing 2-chloromethylpyridine via the reaction of 2-picoline-N-oxide with phosphoryl chloride in the presence of triethylamine. This protocol achieves 90% conversion with 98% selectivity, outperforming previously reported chlorination methods that suffered from low yields or excessive byproduct formation. The reaction proceeds through an intermediate complex, which, when stabilized by triethylamine, avoids decomposition and side reactions such as aromatic substitution.

A comparative evaluation of alternative chlorinating agents including titanium tetrachloride, zinc chloride, sulfuryl chloride, phosgene, and chloroacetyl chloride revealed inferior yields or selectivity, with some reagents merely deoxygenating the N-oxide to picoline. The authors emphasize the critical role of reaction timing and reagent addition sequence in optimizing product formation. Specifically, maintaining a controlled presence of the intermediate complex during triethylamine addition was essential to suppress undesired pathways.

This study establishes phosphoryl chloride, in conjunction with triethylamine, as a cost-effective and scalable route for producing 2-chloromethylpyridine with minimal waste. The mechanistic insights and procedural refinements presented by Ash et al. offer valuable guidance for synthetic applications involving pyridine derivatives and halomethylation strategies[54].

Scheme 17: Hantzsch pyridine synthesis



21. **Hiroshi Igeta et al**. demonstrated that flash vacuum pyrolysis (FVP) of 2-picoline N-oxide leads to the formation of 2-picoline, pyridine, 2-vinylpyridine, bis(2-pyridyl)methane, and 1,2-bis(2-pyridyl)ethane. These products arise through radical pathways, with strong evidence supporting the intermediacy of the 2-picolyl (2-pyridylmethyl) radical.

The pyrolysis initiates with homolytic cleavage of the N–O bond in 2-picoline N-oxide, generating the 2-picolyl radical. This radical undergoes:

- **Hydrogen abstraction** to form 2-picoline and pyridine.
- **Radical coupling** to yield bis(2-pyridyl)methane and 1,2-bis(2-pyridyl)ethane.
- **β-Elimination** to produce 2-vinylpyridine.
- **Cross-coupling** with solvent-derived radicals (e.g., benzyl radicals from toluene) to form mixed products.

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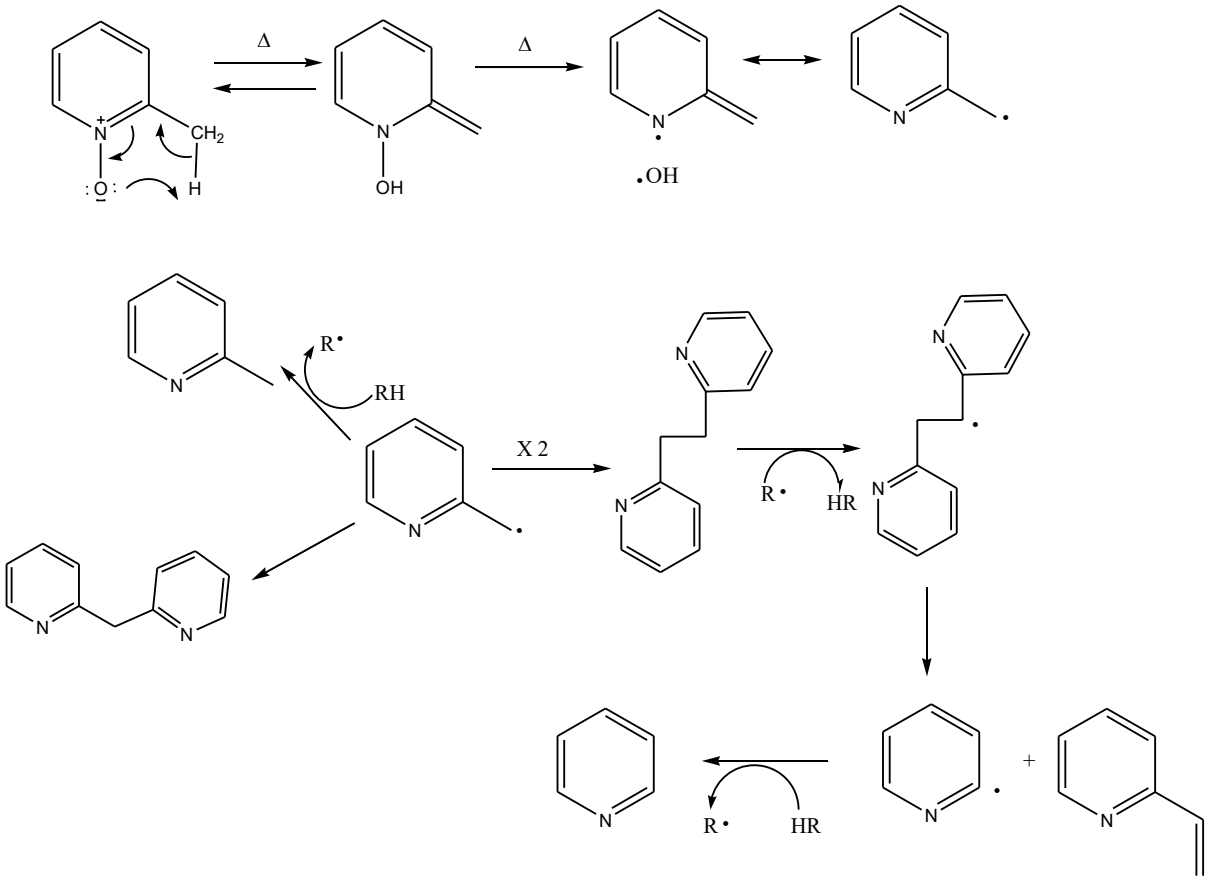
The formation of these compounds under low-pressure, nonpolar conditions confirms the radical nature of the process. The stability and reactivity of the 2-picolyl radical are further supported by its persistence even at low concentrations and its participation in diverse radical transformations. These findings provide direct mechanistic insight into the thermal decomposition of heterocyclic N-oxides via radical pathway[55].

Scheme 18: Intermolecular reaction

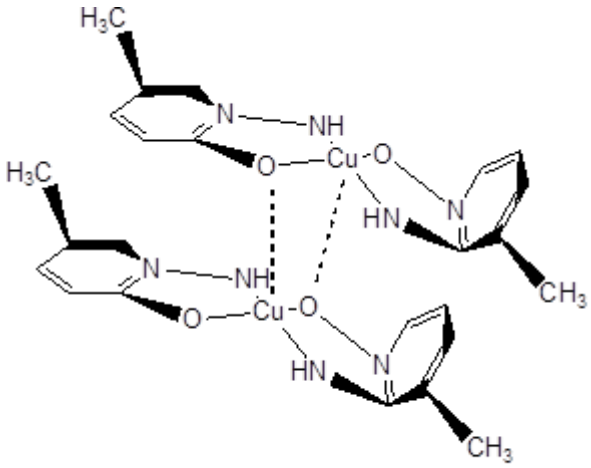


22.Noiusuke Hata et al. conducted a detailed investigation into the gas-phase photolysis of 2-picoline N-oxide under monochromatic irradiation at 3261 Å and 2537 Å. Irradiation at 3261 Å, corresponding to the n→π* transition, led to a photochemical rearrangement yielding 2-pyridinemethanol, whereas exposure to 2537 Å (π→π* transition) induced N→O bond cleavage, producing 2-picoline. Temperature-dependent quantum yield measurements indicated that the formation of intermediate fraction C is thermally activated. The activation energies for 2-pyridinemethanol and 2-picoline formation were determined to be 3.4 kcal mol^{-1} and 1.1 kcal mol^{-1}, respectively. These results highlight two distinct mechanistic pathways governed by the nature of electronic excitation and thermal conditions. A comprehensive mechanistic analysis of post-excitation processes is in progress[56].

23.Douglas et al. investigated copper(II) complexes of 2-amino-3-picoline N-oxide, isolating a series of salts including perchlorate, tetrafluoroborate, nitrate, chloride, and bromide. These complexes were characterized using infrared, UV-visible, and electron spin resonance spectroscopy. By varying the ligand-to-metal ratio, they obtained compounds with empirical formulas such as $Cu(L)_4X_2$, $Cu(L)_2X_2$, and $Cu(L)X_2$, where L represents 2-amino-3-picoline N-oxide and X denotes the counterion. A deprotonated complex, $Cu(L–H)_2$, was also synthesized via base treatment and is proposed to adopt a square planar geometry, forming dimers in nonpolar solvents.

Complexes with weakly coordinating anions like perchlorate and tetrafluoroborate exhibit 1:2 electrolyte behavior, indicating uncoordinated anions, while nitrate complexes show 1:1 conductivity, suggesting partial coordination or ion pairing. Halide-derived complexes are non-electrolytes and sparingly soluble, consistent with polymeric structures involving coordinated halide ions. Spectral data reveal that coordination occurs through the N-oxide oxygen, not the amino group, as evidenced by shifts in ν(NO) bands below 1200 cm^{-1}

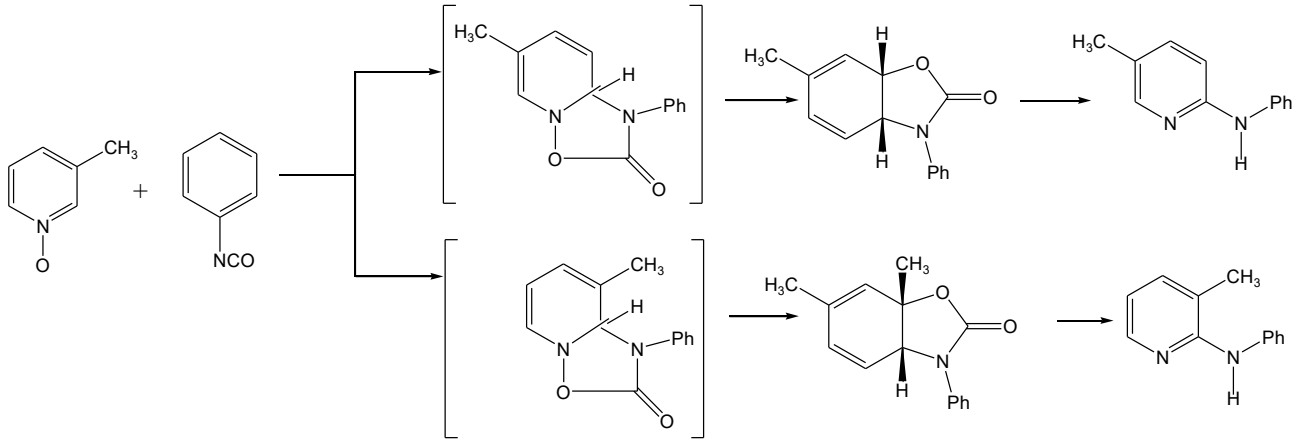
and elevated ν(NH_2) frequencies. The Cu–O stretching bands between 430–440 cm^{-1} further support N-oxide coordination. Deviations in anion vibrational bands suggest weak hydrogen bonding interactions, particularly with larger polyatomic anions. These findings expand the understanding of ligand behavior in copper(II) coordination chemistry and highlight the steric and electronic influences on complex formation[57][58].



Proposed strycture of $[Cu(3MA\text{-}H)_2]_2$

24.**Tazuko Hisano et al.** investigated the 1,3-dipolar cycloaddition of pyridine N-oxides with phenyl isocyanate, emphasizing the influence of solvent-mediated charge-transfer complexes on regioselectivity. Spectroscopic and kinetic analyses revealed that phenyl isocyanate forms stable charge-transfer complexes with both pyridine N-oxides and aromatic solvents, affecting transition state geometry and orbital interactions. In reactions involving 3-methylpyridine N-oxide, two regioisomeric products form via a concerted mechanism, with their ratio (A/B) varying by solvent: equal in sulfolane and favoring product A in 3-methylpyridine. These findings highlight that regioselectivity is governed not only by steric and electronic factors but also by π–π stacking and charge-transfer stabilization[57][59][60].

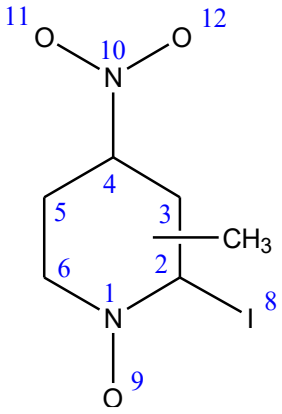
Scheme 19: cycloaddition of pyridine N-oxides with phenyl isocyanate



25.Vicentini et al. (1992) synthesized and characterized a series of lanthanoid picrate complexes coordinated with 4-picoline-N-oxide (4-picNO), replacing most of the hydration water in previously known compounds. The complexes, with varying stoichiometries depending on the lanthanoid ion (La, Pr, Nd, Eu, Gd, Yb), were analyzed through elemental analysis, IR and UV-visible spectroscopy, conductance measurements, and thermal techniques (TG/DSC). The study revealed that coordination occurs via oxygen atoms, and the bonding is predominantly electrostatic with minimal 4f orbital participation. Thermal decomposition pathways were proposed, showing high enthalpies and explosive tendencies, especially under rapid heating. These findings underscore the stability and reactivity of such complexes, with implications for their handling and potential applications in coordination chemistry[61].

26.Aniela Puszko et al. investigated the UV-visible spectral and electronic properties of 2-iodopicolines, their N-oxides, and 2-iodo-4-nitropicoline N-oxides in ethanol. Using modified INDO calculations, they assigned electronic transitions and evaluated substituent effects on molecular orbitals, charge distribution, and dipole moments. All compounds exhibited characteristic π→π* transitions between 200–300 nm, while nitro-substituted N-oxides showed an additional charge-transfer band at 300–400 nm, arising from electron delocalization between N-oxide and nitro groups via the pyridine ring. Ortho methyl substituents modulated this interaction through steric and electrostatic effects, as reflected in calculated twist angles.

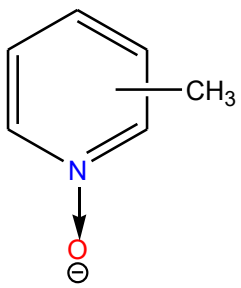
N-oxidation elevated HOMO energies (−10.01 to −9.55 eV), whereas nitration lowered them (−10.19 eV); methyl substitution had minimal impact. Charge density analysis revealed enhanced intramolecular charge transfer in 4-nitro derivatives, correlating with their reactivity during ethanolysis. Dipole moment calculations aligned with experimental values, confirming molecular geometries. N-oxides exhibited the highest dipole moments, while nitro substitution reduced them due to opposing electron-withdrawing effects. Methyl groups at position 5 increased dipole moments by 20–25%. Upon excitation, dipole shifts ranged from 1.00–2.73 D, with nitro derivatives showing the most pronounced changes, consistent with charge-transfer behavior[62].



27.Michael Murray et al. evaluated the biological effects of three isomeric picoline N-oxides 2-, 3-, and 4-methylpyridine N-oxides as oxidized metabolites of industrial pyridine derivatives. Following a single dose (100 mg/kg) in rats, the 3- and 4-isomers significantly induced cytochrome P450 enzymes, particularly CYP2B, as confirmed by immunoblotting and increased microsomal substrate oxidation. The 2-isomer did not elevate CYP2B but upregulated CYP2E1 expression to 160–200% of control.

All three isomers enhanced aniline 4-hydroxylation, consistent with CYP2B/2E1 induction. Additionally, 3- and 4-isomers increased 4-nitrophenol 2-hydroxylation and CYP1A-mediated 7-ethylresorufin O-de-ethylation, while CYP3A-dependent androstenedione 6-hydroxylation was suppressed most notably by the 2-isomer.

Importantly, lipid peroxidation during NADPH-supported CCl_4 oxidation was elevated in microsomes from 3- and 4-isomer-treated rats, implicating CYP2B in this oxidative stress, as confirmed by inhibition with orphenadrine but not 4-methylpyrazole. These results suggest that selective induction of CYP2B and CYP2E1 by picoline N-oxides may contribute to pyridine-associated hepatotoxicity via enhanced microsomal lipid peroxidation[63][64][65][66].



28.Rodolfo Moreno-Fuquén et al. reported the crystal structure of the molecular complex $2C_6H_7NO{\cdot}C_6H_6O_2$, derived from 3-picoline N-oxide and hydroquinone. The formation of the complex is attributed to

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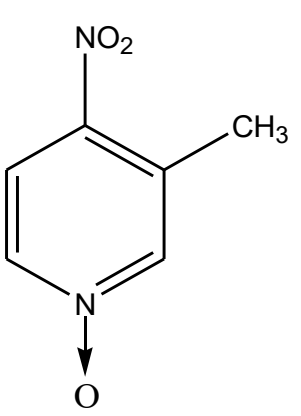
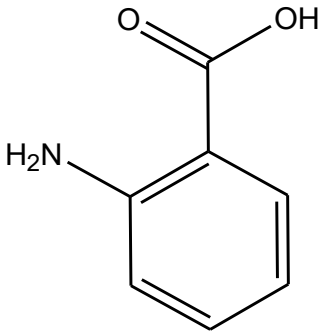
intermolecular hydrogen bonding between the N-oxide oxygen of 3-picoline and the hydroxyl oxygen of hydroquinone. The structure exhibits a dihedral angle of 48.16(5)° between the aromatic rings and reveals π–π stacking interactions along the crystallographic axis. Comparative analysis highlights structural parallels with analogous hydrogen-bonded systems[67].



POM

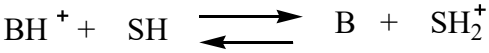


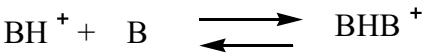
OABA

29.Lech Chumurzynski et al. investigated the acid–base properties of substituted pyridine N-oxidesspecifically, 2-halo (Cl, Br, I)-4-nitropicoline N-oxides bearing methyl groups at positions 3, 5, or 6 via potentiometric titration in acetonitrile. Acid dissociation constants (pKa) of the protonated species were determined and compared with those of mono- and disubstituted analogues. Substitution effects revealed significant suppression of basicity due to the combined electron-withdrawing influence of nitro and halogen groups, yielding pKa values below 5 (maximum 5.56 for 2I-4NO_2-5PicO), in contrast to unsubstituted pyridine N-oxide (pKa = 10.04).

Relative to carboxylic acids and phenols (pKa = 16–27), these cationic acids are markedly stronger in acetonitrile, yet weaker than mineral acids such as H_2SO_4 and HCl (pKa ≈ 7.9–8.9). The conjugate bases are thus classified as very weak, comparable to 4-nitropyridine N-oxide and 3-bromo-4-nitropyridine N-oxide. Attempts to determine cationic homoconjugation constants in acetonitrile were unsuccessful, indicating methodological limitations. These findings contribute to a deeper understanding of substituent effects on N-oxide acidity and offer predictive insights into aqueous behavior via solvent correlation models[68].

Scheme 20: Substitution reaction





In these equations B stands for an N-oxide molecule and SH for an acetonitrile molecule, the latter being an aprotic polar solvent of weak amphiprotic properties.

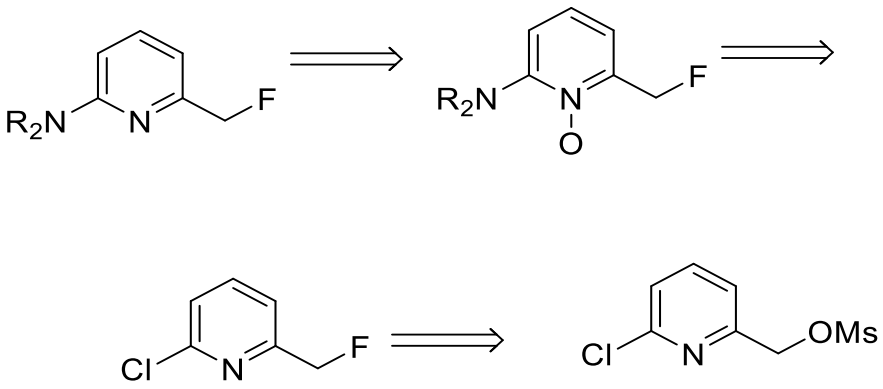
30. Kyo Chul Lee et al. report an efficient two-step synthetic strategy for the preparation of fluoromethylpyridyl-substituted amines, designed for incorporation of the short-lived positron-emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min). The sequence involves nucleophilic fluorination of methanesulfonate (mesylate) derivatives of 6-chloro-α-hydroxy-2- and -3-picolines, followed by N-arylation with chloropicoline. This tandem process, termed *fluorination–N-arylation*, was demonstrated using 1-phenylpiperazine as a model substrate.

Two key intermediates were synthesized: the 2-picoline-derived mesylate in four steps from 6-chloro-2-picoline (78% overall yield), and the 3-picoline-derived mesylate in three steps from 6-chloronicotinic acid. The fluorination step proceeds via fluoride ion displacement under mild conditions, enabling rapid and

selective introduction of the fluoromethyl group. Subsequent arylation affords structurally diverse pyridyl-substituted amines suitable for radiolabeling.

This methodology offers a robust and scalable platform for the synthesis of fluorine-18 labeled amine derivatives, with potential applications in positron emission tomography (PET) imaging and radiopharmaceutical development. The operational simplicity, high efficiency, and compatibility with short-lived isotopes underscore its value in medicinal and diagnostic chemistry[69].

Scheme 21: Nucleophilic substitution



31. M. Ramkrishna et al. report a sustainable and efficient protocol for the selective mono-N-oxidation of heterocycles, particularly substituted pyrazines and pyridines, using 30% aqueous H_2O_2 as a green oxidant in the presence of redox-active molecular sieves (TS-1, Ti–ZSM-5(30), Ti–MCM-41). Among these, TS-1 (Si/Ti = 33) exhibited superior catalytic activity and selectivity, especially in aqueous media and in the presence of electron-withdrawing substituents, except for cyano derivatives. The methodology is operationally simple, employs reusable solid catalysts (5 wt.%), and generates water as the sole by-product, underscoring its eco-friendly nature and practical applicability for scalable N-oxide synthesis[70].

32. Franz A. Mautner et al. report the synthesis and structural characterization of three novel one-dimensional polymeric azido complexes: $Zn(N_3)_2(pyNO)(H_2O)_2$, $Zn(N_3)_2(3picNO)_2(H_2O)_2$, and $Cd(N_3)_2(3picNO)_2(H_2O)_2$. X-ray crystallography reveals that all complexes feature trans-$[M(N_3)_2(H_2O)_2]_n$ chains stabilized by noncoordinated pyridine-N-oxide or 3-picoline-N-oxide molecules. In $Zn(N_3)_2(pyNO)(H_2O)_2$, the pyNO ligand remains uncoordinated, forming three hydrogen bonds with adjacent aqua ligands, while the metal center adopts a distorted octahedral geometry via double end-on azido bridges.

Complexes containing 3-picNO are isomorphous, with each ligand forming two hydrogen bonds. The azido groups exhibit asymmetric bridging (μ-1,1), and the Zn–Zn and Cd–Cd separations fall within expected ranges for such architectures. IR spectroscopy supports the structural findings, with characteristic ν_as(N_3) and δ_s(N_3) bands indicating vibrational coupling and hydrogen bonding effects.

These results demonstrate the structural versatility of pyridine-N-oxide derivatives in stabilizing azido-bridged metal chains and highlight the influence of ligand substitution on hydrogen bonding and coordination geometry. The study expands the understanding of azido coordination polymers and their supramolecular assembly[71].

33.Deoxygenation of N-Oxides with Triphenylphosphine Catalyzed by Dichlorodioxomolybdenum(VI) **Sanz et al**. report a chemoselective protocol for the deoxygenation of heteroaromatic c N-oxides under mild conditions, employing triphenylphosphine (PPh_3) as an oxygen acceptor and dichlorodioxomolybdenum(VI) [MoO_2Cl_2] as catalyst. The method demonstrates efficient oxo-transfer catalysis, affording complete conversion to the corresponding amines in common solvents. The authors highlight the superior reactivity observed in THF, likely attributed to enhanced solubility of the catalytic species. This strategy provides a practical and selective alternative to existing deoxygenation methods, with broad applicability in heterocyclic synthesis[72].

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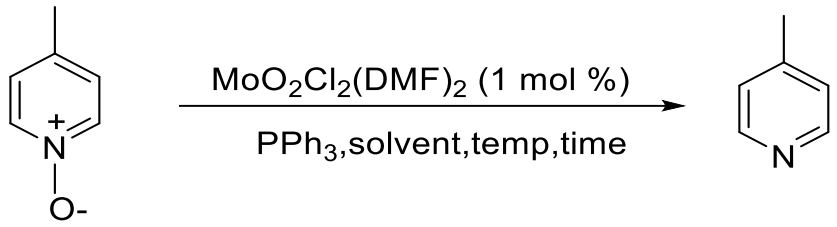
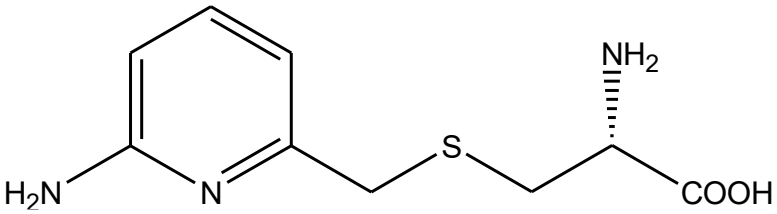
Scheme 22: Deoxygenation of N-oxides



34. Ijuin et al. designed and synthesized a novel class of L-amino acids incorporating pyridine moieties to evaluate their inhibitory potential against human nitric oxide synthase (NOS) isozymes. Among the synthesized analogs, the 2-aminopyridine-based derivative exhibited potent and broad-spectrum inhibition across all NOS isoforms, attributed to favorable hydrogen bonding and electrostatic interactions within the active site. In contrast, regioisomers with substitutions at the 4- and 5-positions, as well as derivatives containing 2-methylpyridine or sulfonyl linkers, showed markedly reduced activity, highlighting the critical role of amino group positioning for effective binding. Computational docking studies corroborated these findings, demonstrating that optimal orientation of the amidino moiety and pyridine nitrogen enhances interaction with key residues such as Glu377 and Arg388. These results underscore the importance of precise structural features in modulating NOS inhibition and suggest that 2-aminopyridine-based L-amino acids serve as promising scaffolds for future development of selective NOS inhibitors. [73].



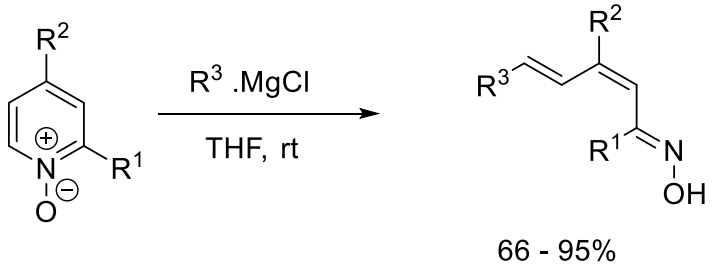
2-aminopyridinyl-thio-L-amino acid

35. Hans Andersson et al. report a highly efficient and stereo-defined method for synthesizing substituted di-enal oximes through the direct addition of Grignard reagents to pyridine N-oxides under mild conditions. This transformation proceeds rapidly and affords the desired olefinic oximes in good to excellent yields, with precise control over stereochemistry.

The methodology offers a streamlined approach to constructing functionalized olefins, which are valuable both as bioactive scaffolds and as versatile intermediates in complex molecule synthesis. The use of pyridine N-oxides as electrophilic partners enhances reactivity and selectivity, enabling the formation of structurally defined products without the need for harsh conditions or extensive purification.

This protocol expands the synthetic utility of N-oxide chemistry and demonstrates the potential of Grignard reagents in stereo controlled C–C bond formation. The resulting di-enal oximes may serve as precursors for further elaboration in medicinal chemistry, agrochemical development, or materials science, underscoring the broad applicability of this strategy in modern organic synthesis[74].

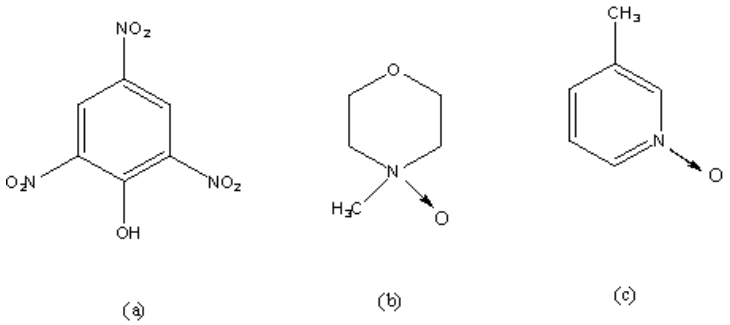
Scheme 23: Direct addition of Grignard reagents



36. Zukerman-Schpector et al. report the synthesis and characterization of two 1:1 hydrogen-bonded co-crystals formed between 2,4,6-trinitrophenol (picric acid) and 4-methylmorpholine-N-oxide or 3-picoline-N-oxide. Single-crystal X-ray diffraction revealed well-defined packing motifs comprising cation–anion pairs stabilized by hydrogen bonding through nitro and phenolate oxygen atoms.

Semi-empirical (AM1) and DFT/B3LYP(6-31G) calculations were employed to evaluate the (hyper)polarizabilities of both crystallographic and optimized geometries. The scalar properties α and γ exhibited consistent trends across both methods, while β- being vectorial- showed irregular variation with geometry optimization. Notably, β values for the complexes exceeded the additive contributions of individual components, indicating significant electrostatic enhancement without substantial charge transfer.

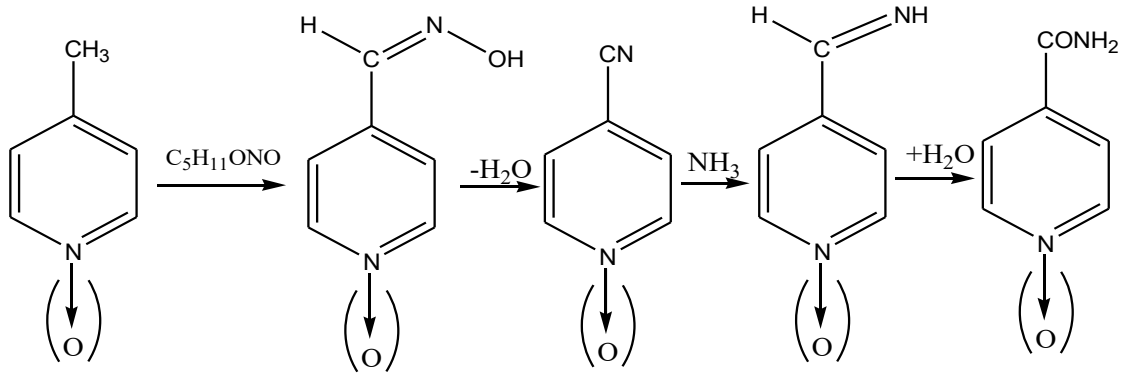
These findings underscore the utility of picric acid as a supramolecular scaffold for designing nonlinear optical (NLO) materials. The congruence between AM1 and DFT results suggests that AM1 may serve as a cost-effective preliminary screening tool for NLO candidates prior to high-level computational refinement[75].



37. Louis-Charles Campeau et al. report a palladium-catalyzed direct arylation methodology applicable to a wide array of azine and azole N-oxides. Regioselectivity was systematically investigated for non-symmetrical azines, revealing that both ligand selection and substituent patterns critically influence regioisomeric outcomes. For azole N-oxides, arylation proceeds preferentially at the C-2 position under mild conditions, followed sequentially by C-5 and C-4 functionalization.

This strategy demonstrates broad functional group tolerance and offers a streamlined alternative to conventional cross-coupling techniques for heterobiaryl synthesis. Its synthetic utility is exemplified in the preparation of bioactive compounds, including a sodium channel inhibitor and a Tie2 tyrosine kinase inhibitor. The findings establish foundational insights into azine/azole C–H activation mechanisms and provide a platform for further mechanistic and medicinal chemistry exploration[76].

Scheme 24: Palladium-catalyzed direct arylation



38. V.N. Kalevaru et al. synthesized a series of titania-supported vanadium phosphorus oxide (VPO) catalysts with varying VPO loadings (5–50 wt%) and evaluated their performance in the selective ammoxidation of 3-picoline to nicotinonitrile . Characterization via ICP-OES, TG/DTA, BET, XRD, FTIR (Py-ads), and XPS confirmed the formation of the active $(VO)_2P_2O_7$ phase and revealed a correlation between VPO content, surface acidity, and catalytic behavior. FTIR studies indicated the presence of both Lewis and Brønsted acid sites, with optimal proportions observed at 20 wt% VPO loading.

Catalytic testing in a fixed-bed reactor demonstrated superior activity and selectivity for supported catalysts compared to bulk VPO. The 20 wt% VPO/TiO_2 catalyst exhibited nearly complete conversion of 3-picoline and an NN yield of 83%, attributed to balanced acidity and enhanced surface area. Thermal analysis confirmed phase transformation and removal of residual solvents and sulfates. XPS data showed stable vanadium oxidation states across fresh and spent samples.

These findings underscore the potential of supported VPO systems for industrial nitrile synthesis and highlight the critical role of acid site distribution and support interaction in optimizing catalytic performance[77].

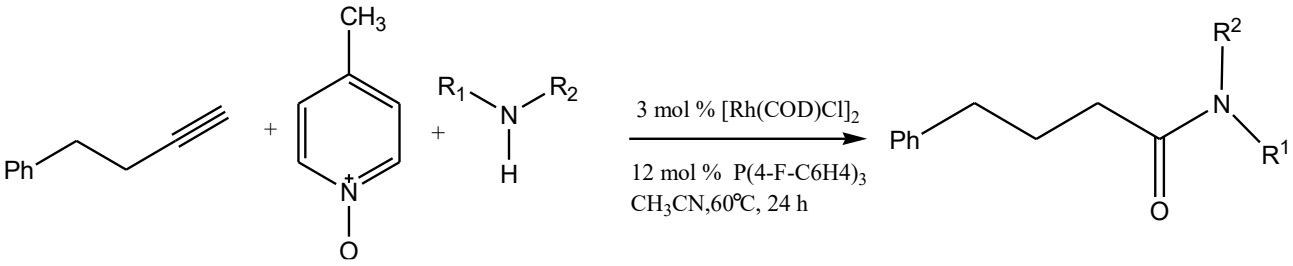
39. Insu Kim et al. developed a rhodium-catalyzed oxygenative addition protocol for the direct transformation of terminal alkynes into esters, amides, and carboxylic acids using azine and azole N-oxides as oxidants. The methodology demonstrates broad substrate scope and functional group tolerance under mild conditions, with regioselectivity governed by ligand choice and substituent effects. Intramolecular and intermolecular variants were optimized using $[Rh(COD)Cl]_2$ and

$P(4\text{-}F\text{-}C_6H_4)_3$, enabling efficient coupling with alcohols, amines, and water.

Mechanistic studies, including deuterium labeling and control experiments, suggest a non-oxirene pathway and implicate N-oxide-mediated C–H activation. The transformation proceeds without exclusion of air or moisture, offering practical advantages. Gram-scale synthesis of bioactive esters further illustrates the synthetic utility of the method.

This work provides a valuable alternative to traditional cross-coupling strategies for heterobiaryl construction and lays mechanistic groundwork for future exploration of rhodium-catalyzed oxidative transformations in medicinal chemistry[78].

Scheme 25: Oxidation of alkynes



40. Zhao-bian Xie et al. employed molecular dynamics simulations, alongside M06-2X and MP2(full) quantum chemical methods, to investigate the binding energies, mechanical properties, and sensitivity modulation of HMX/2-picoline-N-oxide cocrystals across various molar ratios. Their findings demonstrate that co-crystallization is energetically and structurally favored at 1:1, 2:1, and 3:1 ratios, which exhibit enhanced binding energies and improved ductility. Cooperativity effects validated through reduced density gradient and surface electrostatic potential analyses are prominent in cyclic CH_4 complexes (low dielectric), whereas HF (high dielectric) induces anti-cooperativity, destabilizing the cocrystal. Strengthening of the N–NO_2 bond and intermolecular hydrogen bonding contribute to reduced impact sensitivity, as evidenced by lower VS,max, smaller σ^{2+}, and higher ν values. Solvent polarity plays a critical role, with low-dielectric media promoting cooperative interactions and facilitating cocrystal formation. Additionally, cocrystals in the 5:1–10:1 range exhibit satisfactory explosive characteristics, underscoring their potential utility in energetic material applications[79].

41. Kari Rissanen et al. report the formation and characterization of host–guest complexes between Cethyl-2-methylresorcinarene and a series of aromatic and aliphatic N-oxides. These interactions are governed by a combination of intra- and intermolecular hydrogen bonding, C–H···π, π···π, and C–I···π interactions. The host exhibits conformational adaptability, adopting a flexible geometry to accommodate 3-methylpyridine N-oxide, while maintaining a crown-like conformation for 2-methyl- and 4-methoxypyridine N-oxides, underscoring the influence of guest substituents.

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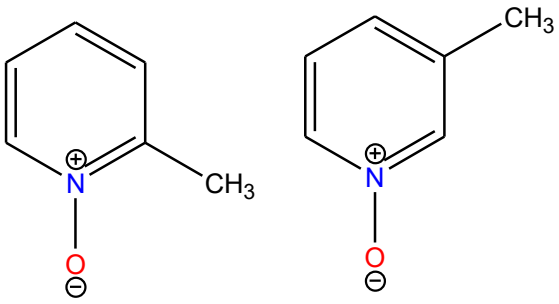
In the case of N-methylmorpholine N-oxide, the equatorial N–CH_3 group penetrates deeply into the cavity, significantly altering the host's geometry. Notably, 2-iodopyridine N-oxide forms a unique 2:2 pseudocapsular complex, facilitated by the disruption of its native halogen-bonded polymeric structure and stabilized through C–I···π interactions between adjacent host–guest pairs.

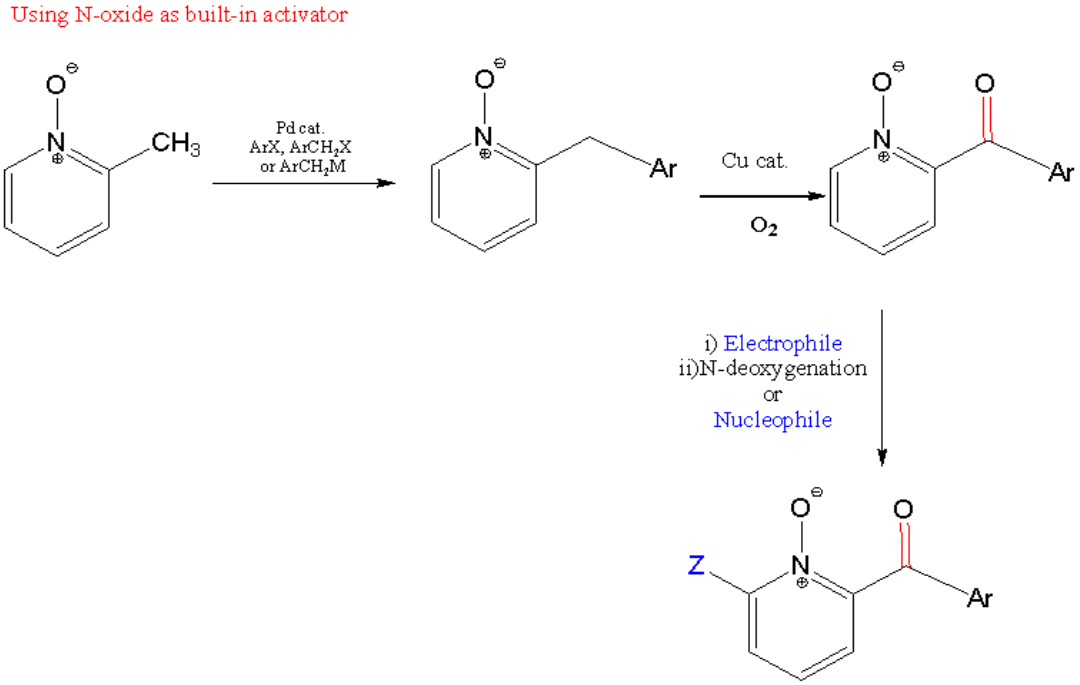
Structural elucidation via single crystal X-ray diffraction and solution-phase ^1H NMR spectroscopy confirms the spatial arrangement and binding modes of the complexes. These findings highlight the suitability of N-oxides as versatile guests for resorcinarene-based assemblies and their potential utility as ligands in organometallic frameworks[80][81][82][83].



2MePyNO 3MePyNO

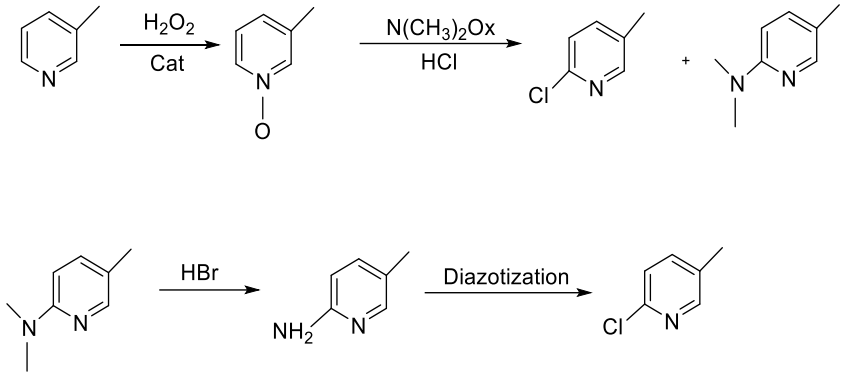
42. Maes et al. report a copper-catalyzed aerobic oxidation of benzylpyridine N-oxides employing molecular oxygen under additive-free conditions. The N-oxide moiety functions as an intrinsic activator for benzylic methylene oxidation, enabling selective transformation while suppressing undesired N-deoxygenation pathways via intermolecular oxygen transfer. .2-Benzylpyridine N-oxides exhibited higher reactivity than their 4-substituted analogs, with electronic properties influencing product distribution. The N-oxide group plays a tripartite role: (i) facilitating synthesis from readily available pyridine N-oxides, (ii) promoting Cu-catalyzed oxidation, and (iii) enabling diverse post-functionalizations on the pyridine ring including C–C, C–N, C–O, and C–Cl bond formations with both nucleophilic and electrophilic partners. These transformations are inaccessible on the corresponding deoxygenated benzoylpyridines.The methodology's synthetic utility is exemplified in a formal route to the antihistaminic drug Acrivastine, involving three sequential N-oxide-directed C–H functionalization starting from picoline N-oxide. This work highlights the strategic value of N-oxide activation in site-selective oxidation and downstream diversification of heteroaromatic scaffolds[84].

Scheme 26: Copper-catalyzed aerobic oxidation

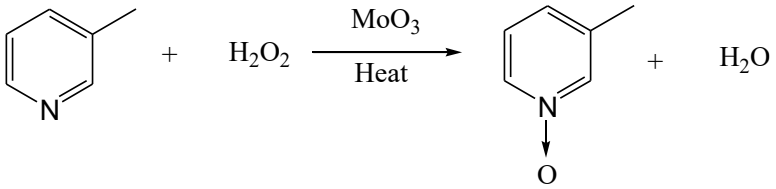


43. Xu *et al.* present a comparative study on the synthesis of 3-methylpyridine-N-oxide, a key intermediate in the production of 2-chloro-5-methylpyridine, which serves as a precursor for neonicotinoid insecticides such as imidacloprid and acetamiprid. Due to the exothermic nature and hazardous properties of 3-methylpyridine, conventional semi-batch oxidation methods pose significant safety and efficiency limitations. To address these challenges, three methodologies were evaluated: traditional semi-batch, co-current microreaction, and circular microreaction systems. Among them, the circular microreaction approach demonstrated superior performance, yielding ~90% product with minimal side reactions and enhanced process control. Optimization of catalyst loading (MoO_3),and reaction temperature (90 °C) further improved yield. The integration of high-throughput micromixers suggests promising scalability for industrial application[85].

Scheme 27(a): Schiff base formation reaction

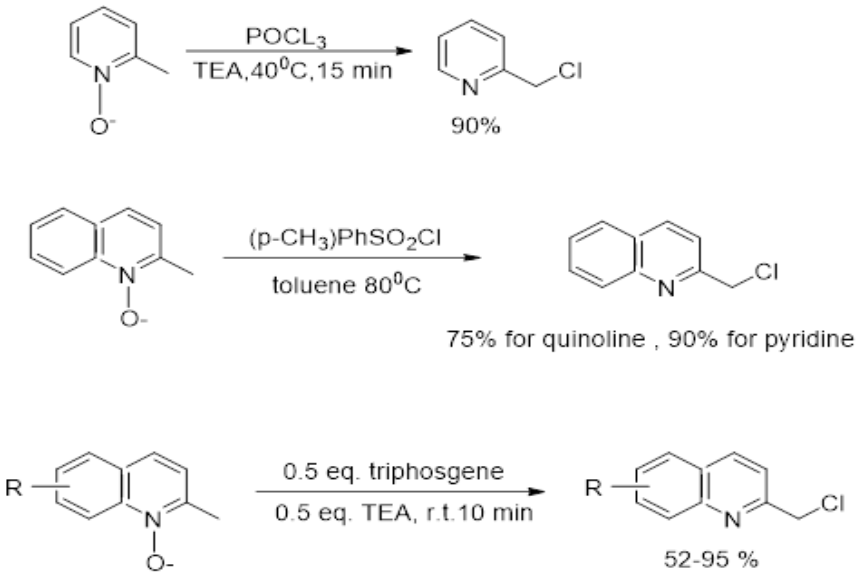


Scheme 28 (b):



44. Song *et al.* have developed a highly efficient and operationally simple one-pot method for synthesizing 2-chloromethylpyridines via chlorination of 2-alkylpyridine N-oxides using triphosgene (BTC) and triethylamine (TEA) at room temperature. The protocol accommodates a broad substrate scope including 2-alkylpyridines, 2-methylquinolines, and phenanthroline N-oxides yielding products with HCl and CO_2 as the only byproducts. Mechanistic studies, particularly with 2-methylquinoline derivatives, confirm a reversible [3,3]-sigmatropic rearrangement. [86].

Scheme 29 : Claisen rearrangement



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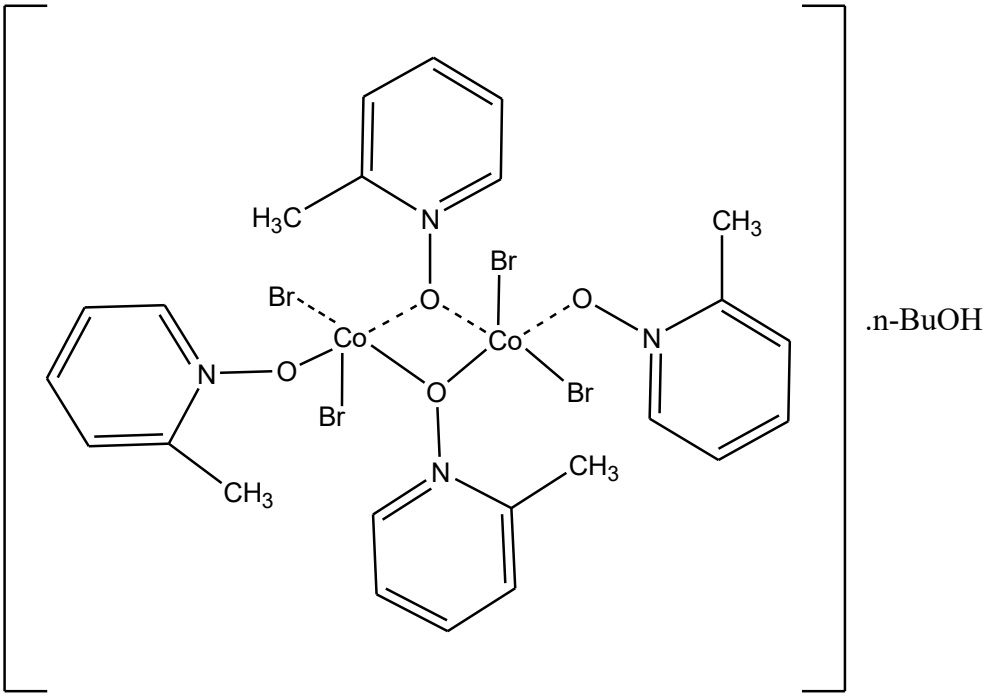
45.The synthesis and crystal structure of a novel dinuclear cobalt(II) complex, $[Co_2Br_4(C_6H_7NO)_4]\cdot C_4H_{10}O$, has been elucidated by **Christian Näther et al.** through the reaction of $CoBr_2$ with 2-methylpyridine N-oxide in n-butanol. Structural analysis via single-crystal X-ray diffraction reveals that each cobalt center adopts a five-coordinate geometry, involving two bromide ions and three N-oxide ligands one terminal and two bridging resulting in centrosymmetric Co_2O_2 ring motifs. The n-butanol solvent, disordered around an inversion center, participates in O–H···Br hydrogen bonding, stabilizing the extended chain structure.

Thermal analysis indicates solvent loss below 523 K, leading to a distinct crystalline phase with modified cobalt coordination, as verified by PXRD and IR spectroscopy. Notably, this phase transition also occurs slowly under ambient conditions, suggesting inherent thermal sensitivity. Comparative structural data show analogs among other transition metals, yet no precedent exists for cobalt(II) halide complexes incorporating methylpyridine N-oxide.

These findings, as presented by Näther and colleagues, underscore the versatility of pyridine N-oxide ligands in coordination chemistry and highlight their utility in designing thermally responsive molecular architectures[87].



.n-BuOH

46. Maurizio D'Auria *et al.* report that the photochemical isomerization of 2-picoline N-oxide proceeds via the formation of oxaziridine intermediates, which subsequently rearrange into oxazepine derivatives. These oxazepines undergo further transformation into pyrrole-based compounds, with a pronounced selectivity toward 5-methyl-2-formylpyrrole. Complete Active Space Self-Consistent Field (CASSCF) calculations reveal the presence of a single conical intersection that facilitates the formation of 2-methyl-7-oxa-1-azabicyclo[4.1.0]hepta-2,4-diene, thereby rationalizing the observed product distribution.

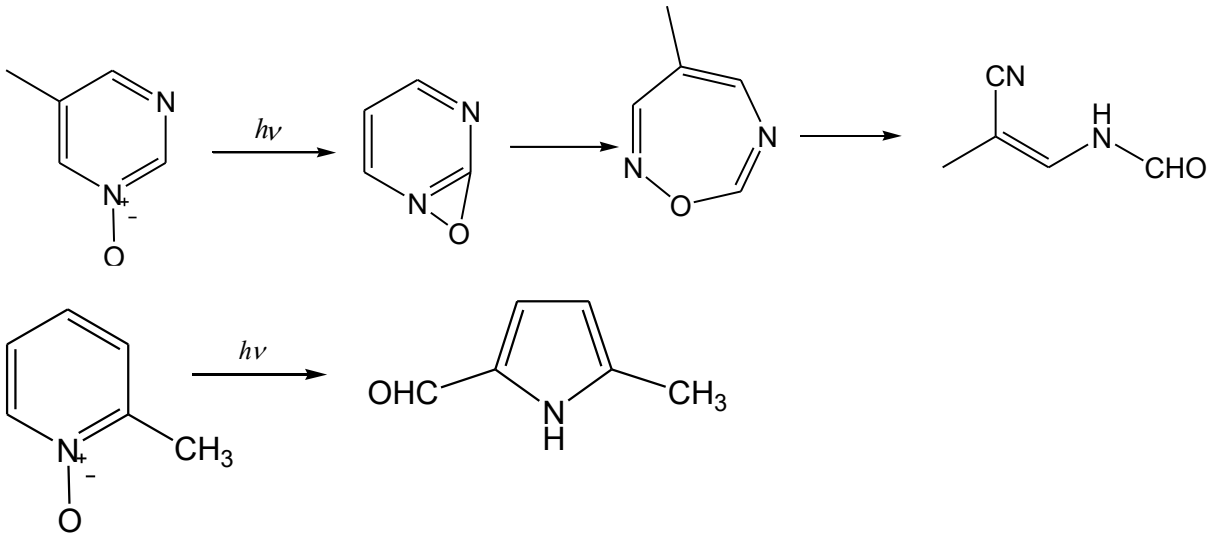
Density Functional Theory (DFT) investigations of 4,6-dimethylpyrimidine N-oxide indicate the formation of both oxaziridine and oxadiazepine species. Notably, the most thermodynamically stable oxaziridine corresponds to a minor reaction product, a phenomenon attributed to the topology of conical intersections accessed from the excited singlet state. A similar mechanistic profile is observed in the DFT analysis of 2-methoxypyrimidine N-oxide, which also supports the formation of both oxaziridine and oxadiazepine derivatives.

In contrast, prior studies on pyridazine N-oxide have demonstrated the absence of oxaziridine intermediates; instead, the excited singlet state directly evolves into a ring-opened species bearing a diazo moiety. The present findings underscore that, in the absence of this diazo functionality, the ring-opening pathway is effectively suppressed, thereby favoring the oxaziridine–oxadiazepine transformation sequence[88].

47. Pyridine N-oxide–silver(I) trifluoroacetate (PyNO-AgTFA) complexes exhibit selective gelation behavior governed by the electronic nature of the PyNO substituents and solvent polarity, as demonstrated by **Rakesh Puttreddy et al.** Among 27 PyNOs studied, only those bearing electron-donating groups formed gels across solvents such as benzene, toluene, ethyl acetate, and acetone, while electron-withdrawing or mixed substituents failed to gel. Interestingly, binary mixtures of donor and acceptor PyNOs yielded gels, suggesting that gel-forming PyNOs can override non-gelling partners. Control experiments confirmed that pyridine analogues lacking the N-oxide group do not gel, underscoring the essential role of the N–O oxygen in coordinating silver(I) and immobilizing solvent molecules. Structural analysis of 65 X-ray crystal structures revealed four dominant PyNO-AgTFA motifs, independent of solvent or stoichiometry, and DFT calculations showed stabilizing non-covalent interactions ranging from −1 to −92 kJ mol^{-1}. The resulting gels are mechanically robust, self-healing, and capable of forming free-standing shapes at the centimeter scale, stabilized by dense silver(I) coordination networks and hydrogen/fluorine-based contacts. However, gelation fails in highly polar solvents like water, DMF, DMSO, and ethanol, limiting immediate biomedical applications. These findings lay the groundwork for future development of biocompatible hydrogels and nanoparticle-infused materials with enhanced mechanical properties.[80]

48. Maurizio D'Auria et al. conducted a computational investigation into the photochemical isomerization of 2-picoline N-oxide, revealing a mechanistic sequence involving oxaziridine and oxazepine intermediates. In the Photochemical Reactivity of 5-Methylpyrimidine N-oxide, the transformation proceeds via an oxaziridine intermediate to yield an α,β-unsaturated nitrile, highlighting the reactivity of pyrimidine N-oxides under UV irradiation. The Photochemical Isomerization of 2-Picoline N-oxide demonstrates that upon excitation, the N-oxide undergoes rearrangement to form 5-methylpyrrole-2-carbaldehyde, with the oxaziridine intermediate playing a central role. The Proposed Mechanism for the Photochemical Isomerization of 2-Picoline N-oxide outlines a stepwise pathway: initial formation of an oxaziridine, followed by conversion to a methylpyridone and then to an oxazepine. The Possible Photochemical Isomerizations of 2-Picoline N-oxide detail two competing routes—one via oxaziridine leading to pyrrole derivatives through low-energy transition states, and another via oxazepine intermediates requiring higher activation energies. CASSCF calculations confirm that only one conical intersection favors the formation of a specific oxaziridine, rationalizing the selective product outcome and emphasizing the role of excited-state dynamics in N-oxide photochemistry[88][89][90][91][92].

Scheme 30 : Photochemical reaction of 5-methoxyl pyrimidine N-oxide



49. Rakesh Puttreddy et al. report the X-ray crystal structure of the centrosymmetric complex $[Ag(\mu\text{-}O_3SCF_3)_2\{(4MePyNO)_2I\}]_2$ (1-AgI), which features a rare combination of orthogonal bonding motifs: a three-center, four-electron $[O–I–O]^+$ halogen bond and two symmetric $I^+–Ag^+$ coordination bonds. The $[O–I–O]^+$ interaction is stabilized by 4-methylpyridine N-oxide ligands, while the $I^+–Ag^+$ bonds (2.8625(16) Å) fall within the range typical of genuine metal–metal interactions, such as $Au^+–Ag^+$ and $Cu^+–Ag^+$.

The orthogonality of the halogen and coordination bonds arises from the spatial distribution of the iodine(I) cation's p-hole and electron belt, allowing both interactions to coexist independently within the molecular

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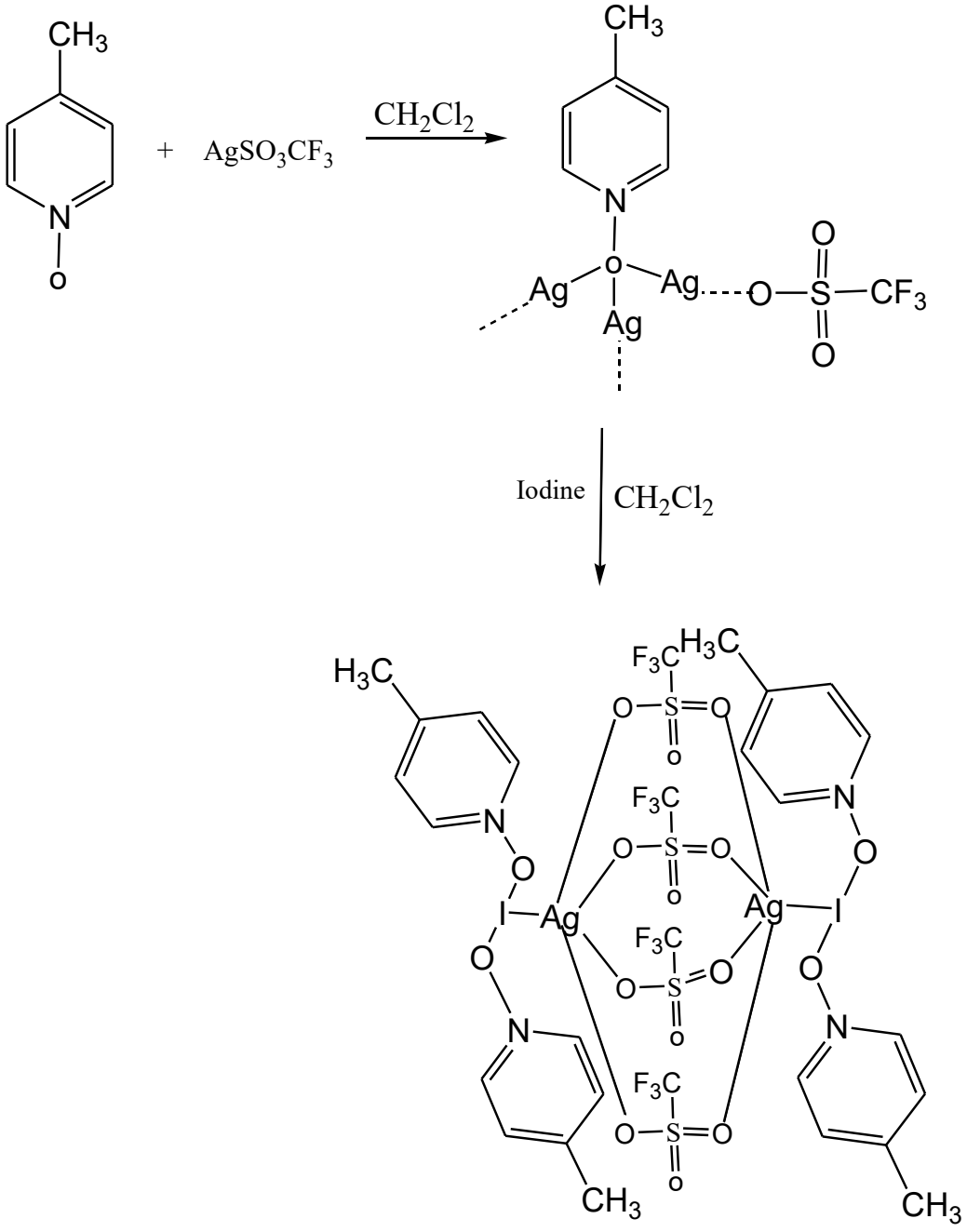
framework. DFT calculations confirm that the I^+–Ag^+ bond is a closed-shell interaction with significant covalent character. This study provides the first atomically resolved structural evidence for $[O–I–O]^+$ halogen bonding in such systems and establishes a precedent for non-metal–metal cation bonding. Future work will explore the generality of I^+ coordination with other metals and N-oxide ligands to develop new supramolecular architectures[93][94][95][96].

Scheme 31: Metal-Ligand co-ordination reaction

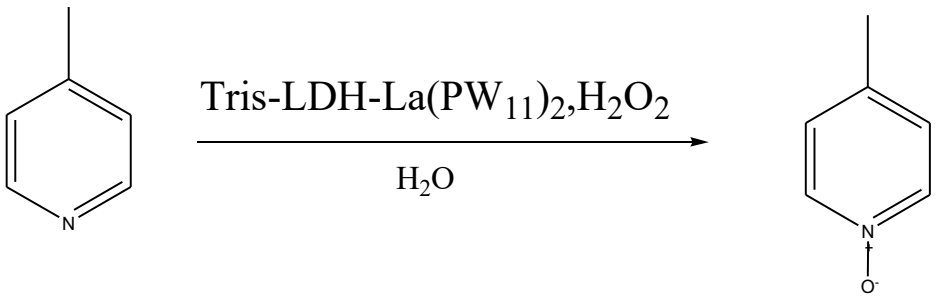


50. By Yu-Fei Song et all

The catalytic N-oxidation of 4-picoline using hydrogen peroxide (H_2O_2) as the oxidant and a heterogeneous Lewis acid catalyst, Tris-LDH-La(PW_{11})$_2$, under aqueous conditions at room temperature. The reaction proceeds efficiently, converting 4-picoline into 4-picoline N-oxide with high selectivity and yield.

Comparative studies with other catalysts (e.g., Na-PW_{12}, K-P_2W_{18}, La_2O_3, $LaCl_3$) demonstrate the superior performance of the La-containing POM composite. The high turnover number (TON = 235) confirms the catalyst's efficiency[97][98][99][100][101].

Scheme 32 : Catalytic N-oxidation



This transformation highlights the potential of Tris-LDH-La(PW_{11})$_2$ as a robust, recyclable, and environmentally benign catalyst for the selective N-oxidation of pyridine derivatives under mild conditions.

CONCLUSIVE SUMMARY

Picoline N-oxides, derived from methyl-substituted pyridines, represent a class of heterocyclic compounds with significant synthetic and pharmacological importance. Their unique structural features particularly the presence of an N-oxide functional group impart distinct electronic and steric properties that influence reactivity, solubility, and biological activity. The position of the methyl group on the pyridine ring (2, 3, or 4-picoline) plays a critical role in determining regioselectivity during oxidation and subsequent transformations.

These compounds serve as versatile intermediates in organic synthesis, acting as oxygen donors, directing groups, and precursors to various functionalized heterocycles. Their ability to undergo electrophilic substitution, nucleophilic addition, and rearrangement reactions makes them valuable tools in constructing complex molecular architectures. Moreover, picoline N-oxides are employed as ligands in coordination chemistry, where their electron-rich nitrogen and oxygen atoms facilitate metal binding and catalysis.

In medicinal chemistry, picoline N-oxides have shown promise due to their enhanced water solubility and potential bioactivity. They are explored as prodrug candidates, redox-sensitive agents, and modulators of enzyme activity. Their incorporation into drug molecules can improve pharmacokinetic profiles and target specificity. Additionally, their role in agrochemicals and materials science such as in the development of herbicides, dyes, and polymer additives further underscores their broad applicability.

Recent advancements in synthetic methodologies, including catalytic oxidation, electrochemical approaches, and green chemistry protocols, have improved the efficiency and sustainability of picoline N-oxide production. These innovations address challenges related to regioselectivity, scalability, and environmental impact.

This review consolidates foundational knowledge and emerging trends surrounding picoline N-oxides, highlighting their multifaceted roles across chemical disciplines. Future research may focus on chiral N-oxide derivatives, photoredox applications, and computational modeling to unlock new functionalities and therapeutic potentials. Overall, picoline N-oxides stand as indispensable entities in the evolving landscape of heterocyclic chemistry, offering rich opportunities for innovation in synthesis, catalysis, and biomedical science.

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Declaration of Competing Interest

The authors declare no conflict of interest, financial or other- wise.

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