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Pyridinium salts as versatile reactive platforms in organic synthesis

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Dedicated to Professor Teresa M.V.D. Pinho e Melo in recognition of her scientific contributions to the field of organic chemistry

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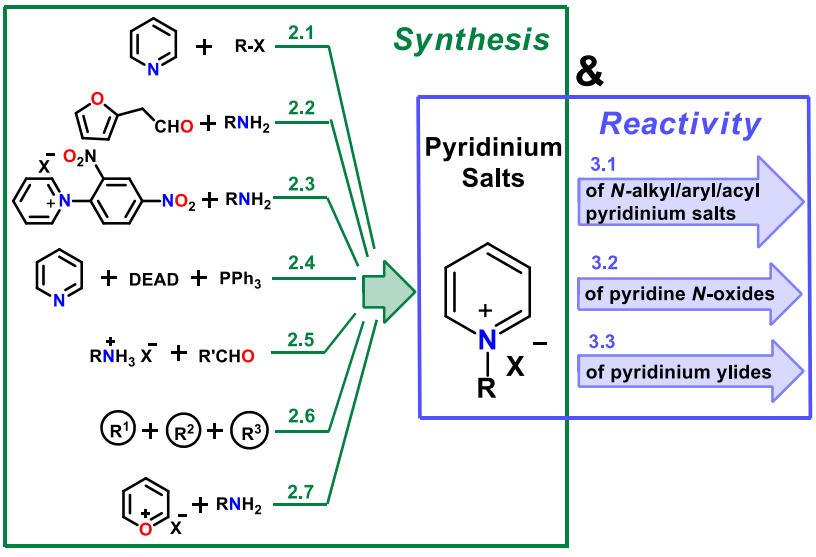
Abstract

Pyridinium salts are an important class of heterocyclic compounds widely used in industry and medicinal chemistry. In addition to applications in surfactants, dyes, and cosmetics, they exhibit diverse biological activities, including antimicrobial, antifungal, antimalarial, and anticancer effects. The positively charged nitrogen atom enhances the electrophilicity of the pyridine ring, enabling versatile synthetic transformations. This review provides an overview of the key synthetic approaches to pyridinium salts and highlights representative studies illustrating their diverse reactivity and synthetic utility in organic chemistry.



Keywords: Pyridinium salts, pyridine *N*-oxides, pyridinium ylides, synthesis, reactivity.

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1. Introduction

Among the vast and diverse family of heterocyclic compounds,[1] the pyridine nucleus stands out as one of the most extensively studied scaffolds.[2] Its aromatic six-membered ring, in which one carbon atom is replaced by a nitrogen atom, imparts a unique balance of electronic properties that enables both electrophilic and nucleophilic reactivity, making pyridine a versatile and widely used starting material for the synthesis of functional derivatives.

The pyridine motif is frequently found in natural products and plays a central role in the development of biologically active compounds. Pyridinium salts, generated through quaternization of the pyridine nitrogen, constitute an important class of derivatives with broad applicability. These compounds have been employed in the preparation of surfactants, cosmetics,[3] dyes, and numerous other functional materials.[4]

Pyridinium salts are of particular interest due to their enhanced reactivity toward nucleophilic attack on the aromatic ring, a consequence of the positively charged nitrogen atom, which strongly activates the system toward substitution and transformation reactions. This reactivity has been widely exploited in synthetic chemistry, where pyridinium salts serve as valuable intermediates and building blocks for a variety of chemical transformations. In addition, these compounds have attracted considerable attention in medicinal chemistry, displaying a wide range of biological activities, including antimicrobial,[5] antimalarial, antifungal, and anticancer properties.[6]

Given this sustained interest, the present review focuses on the synthesis and reactivity of pyridinium salts, highlighting recent advances and key developments in the field.

2. Synthesis of pyridinium salts

2.1 By alkylation of the pyridine nitrogen

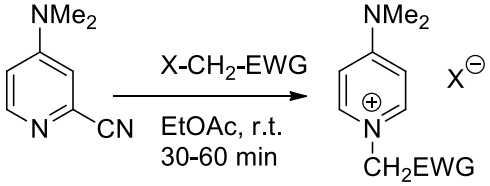
From all the available routes to pyridinium salts, alkylation is still the most widely used. In general, the reaction occurs via nucleophilic substitution, following a S_N2 mechanism, involving a pyridine and an alkyl halide, at room temperature. Scheme 1 shows an example of methylation, in which the authors used methyl iodide in acetone and the product was isolated in 50% yield after 8h under reflux.[7]

Scheme 1. Formation of a pyridinium salt by the reaction of a pyridine with methyl iodide.

However, this method was not considered viable for the synthesis of chiral pyridinium salts when the stereocenter is directly linked to the ring nitrogen, due to the high risk of racemization occurring by the concurrent S_N1 process.[8]

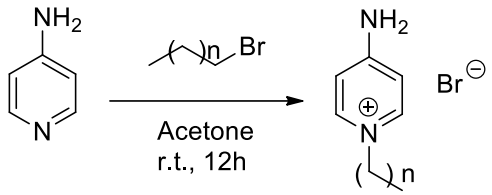
Some studies reported the synthesis of different 4-amino-1-alkylpyridinium salts with long alkyl chains using this pyridine alkylation strategy.

Nallu et al.[9] synthesized this type of pyridinium salts from 4-dimethylaminopyridine, a very active nucleophile in substitution reactions, by reaction with alkyl chlorides, bromides or iodides with electron-withdrawing groups (EWG) and using ethyl acetate as solvent (scheme 2), leading to excellent yields of the product (72-90%). In comparative terms, phenacyl bromide yielded higher product yields than phenacyl chloride, due to the easier cleavage of the C-Br bond. The same occurred in the reaction with phenacyl iodide, compared to the bromide analogue. Some studies reported the synthesis of different 4-amino-1-alkylpyridinium salts with long alkyl chains using this pyridine alkylation strategy.



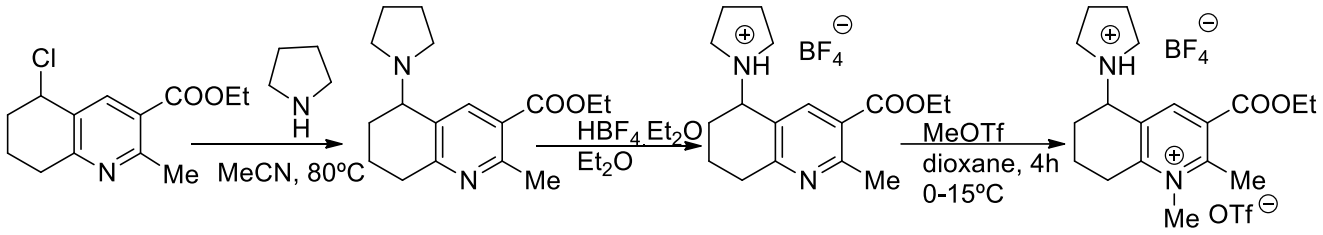
Scheme 2. Synthesis of 4-dimethylamino-1-alkylpyridinium salts.

In 2010, Ilangovan and colleagues[10] carried out the synthesis of pyridinium salts by reacting 4-aminopyridine with alkyl bromides with chains of variable length (C1-C7, C9, C13 and C15). The reaction occurred in a single step and the products were obtained as white solids in 85-93% yield (scheme 3). These compounds were tested for their antibacterial and antifungal activity.



Scheme 3. Synthesis of 4-amino-1-alkylpyridinium bromides.

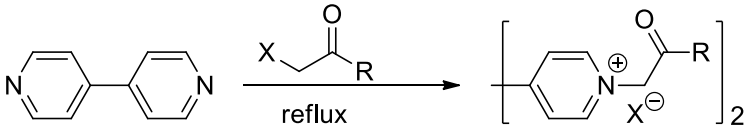
In both cases, the formation of the corresponding pyridinium salts was possible considering that the ring nitrogen has a greater affinity for the proton than the nitrogen atom of the exocyclic amino group, facilitating its quaternization.[9] However, in a study carried out by Pfaltz,[11] this was not the case as the amine function was not directly linked to the pyridine ring. In this work, the authors intended to synthesize pyridinium salts functionalized with a substituent incorporating a tertiary amino group. Starting from the reagent identified in scheme 4, they incorporated a cyclopentylamine and studied the best experimental conditions for the selective alkylation of the pyridine ring. They concluded that it was necessary to protect the tertiary amine as an ammonium salt, using tetrafluoroboric acid that proved to be superior in the selective monoprotonation of this nitrogen when compared with tosylic acid and triflic acid. This salt was alkylated at the pyridine nitrogen using methyl triflate, at 0-15 °C, allowing the product to be isolated in quantitative yield.



Scheme 4. Synthesis of pyridinium salts with a tertiary amino group not directly linked to the pyridine ring.

Other reactions needed heating to occur, as was the case with the synthesis of pyridinium salts with long alkyl chains. In Ilangovan's study,[10] it was necessary to use reflux conditions in acetone to generate pyridinium salts with C13 and C15 alkyl chains from the reaction of pyridine with alkyl bromides. Similarly, another study was carried out by K. Kuca et al.[12] that used a similar reaction to synthesize pyridinium salts with alkyl chains between C8 and C20, to be applied as surface cationic agents. The experimental conditions involved reflux in ethanol and the products were obtained in 13-99% yield after recrystallization. Pyridinium salts with shortest chains (C8-C10) were more difficult to purify, requiring several recrystallizations, and leading to relatively low isolated yields (13-43%). Salts with alkyl chains between C12-C20 were isolated in considerably higher yields (76-99%).

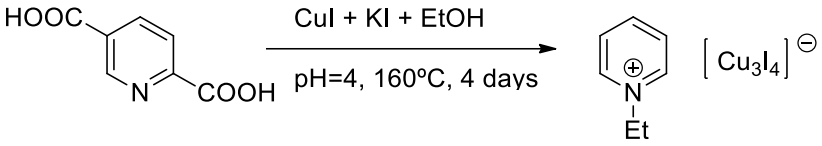
Furdui,[5] synthesized diquaternary bispyridinium salts to investigate their antimicrobial activity, under reflux conditions. Previous reports showed that acetonitrile was the best choice to carry out this reaction. This solvent also proved useful in the isolation of the pure products (scheme 5).



Scheme 5. Synthesis of bis-pyridinium salts.

Aiming to prepare new polymers by reaction of 2,5-(CO_2H)2py and CuI in ethanol, Hou and collaborators[13] unexpectedly obtained *N*-ethylpyridinium salts with a copper complex counter anion (scheme 6). Ethanol,

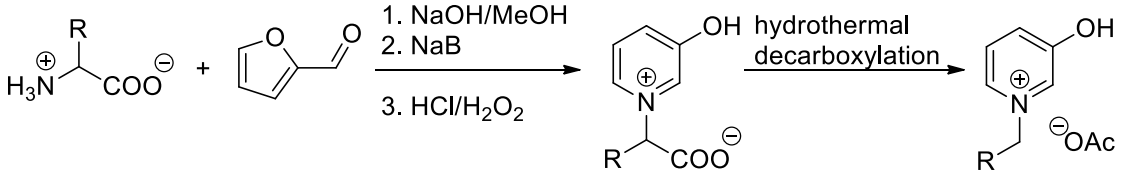
used as solvent, was involved in the alkylation process of pyridine and the formation of the final product occurred after a sequence of decarboxylation and alkylation reactions.



Scheme 6. Formation of pyridinium salts by reaction with copper and potassium iodide in ethanol.

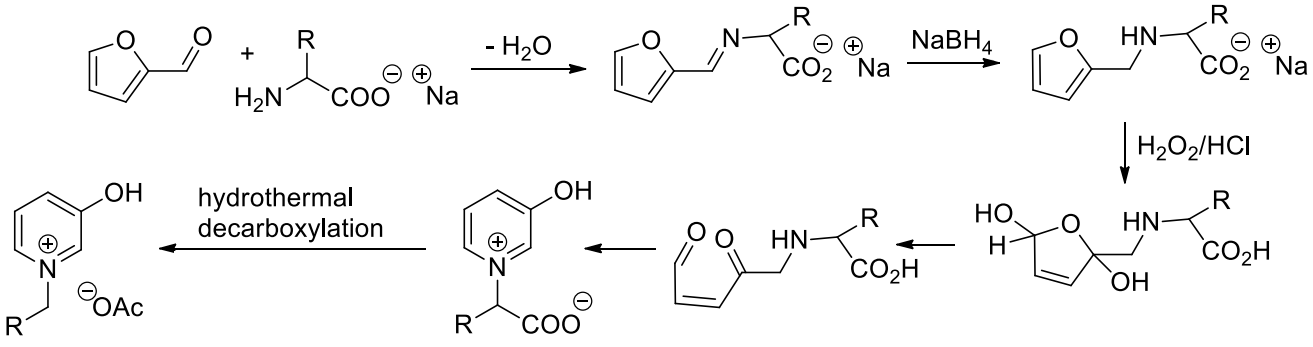
2.2 From furfural

Esposito et al. recently reported the synthesis of ionic liquids derived from pyridinium salts through the condensation of furfural with amino acids.[14] The transformation was performed via a one-pot protocol and proceeded through decarboxylation of an initially generated zwitterionic pyridinium intermediate, in water or ethanol/water, using 2-4 equivalents of acetic acid, at 200-250 ºC and 120 bar for 4 minutes (scheme 7).



Scheme 7. Synthesis of pyridinium salts from furfural.

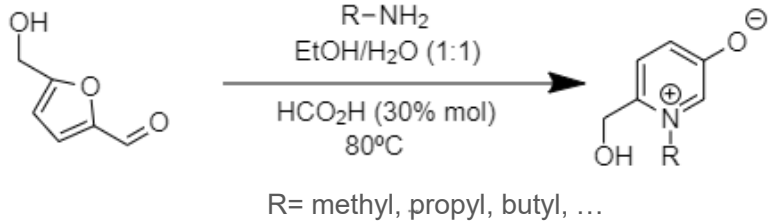
Formation of this intermediate is proposed to occur through the sequence outlined in scheme 8, involving: (i) generation of the amino acid sodium salt; (ii) condensation with furfural to afford the corresponding imine; (iii) reduction of the imine intermediate; and (iv) subsequent oxidation to furnish the zwitterionic pyridinium species. Excellent yields were obtained for most amino acids investigated, including alanine, leucine, β-alanine, and glycine (71.9–100%), whereas phenylalanine afforded the desired product in a comparatively lower yield (55.4%).



Scheme 8. Proposed mechanism for the formation of pyridinium salts by reaction of furfural with amino acids.

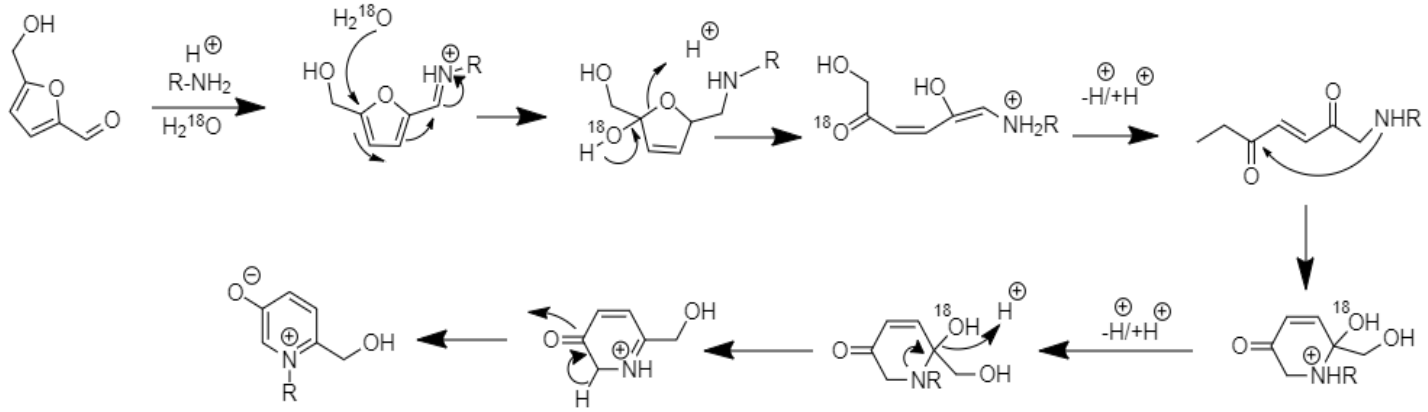
C. Afonso reported the use of hydroxymethylfurfural (HMF) as a precursor for the synthesis of pyridinium salts via reaction with primary amines.[15] The transformation required careful temperature control, with optimal results obtained at 70–80 °C (scheme 9). Reactions conducted at lower temperatures proceeded slowly and remained incomplete, whereas higher temperatures led to rapid decomposition of HMF without formation of the desired products. Under the optimized conditions depicted in scheme 9, the corresponding pyridinium

salts were obtained in yields ranging from 13 to 82% after 2–3 days of reaction. The observed variation in yield was found to depend primarily on the nature of the amine employed, with shorter-chain alkyl amines displaying higher reactivity.



Scheme 9. Synthesis of pyridinium salts starting from hydroxymethylfurfural.

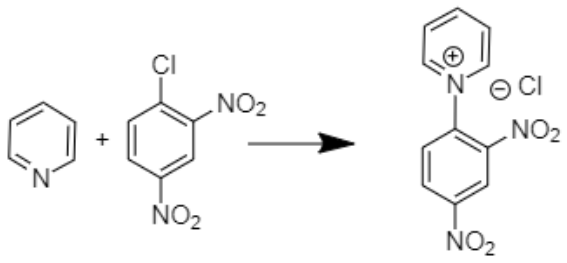
Finally, to gain mechanistic insight into the reaction pathway, isotopically labeled water ($H_2{}^{18}O$) was employed to determine whether water present in the reaction medium was incorporated into the final product. Analysis of the product revealed no incorporation of the ^{18}O label, indicating that water does not participate directly in product formation. Based on these findings, the authors proposed the reaction mechanism depicted in scheme 10.



Scheme 10. Proposed plausible mechanism for the formation of pyridinium salts from hydroxymethylfurfural.

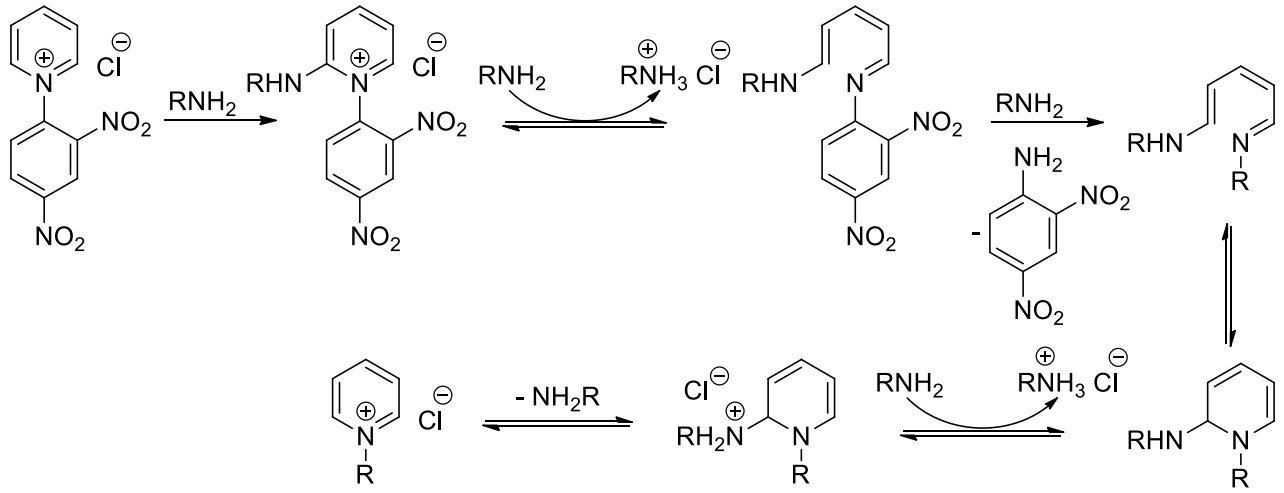
2.3 From Zincke salts

N-(2,4-dinitrophenyl)pyridinium chloride salts or simply Zincke salts are highly electrophilic compounds that can be obtained by the reaction between a pyridine and 1-chloro-2,4-dinitrobenzene (scheme 11).[16]



Scheme 11. Formation of the Zincke salt.

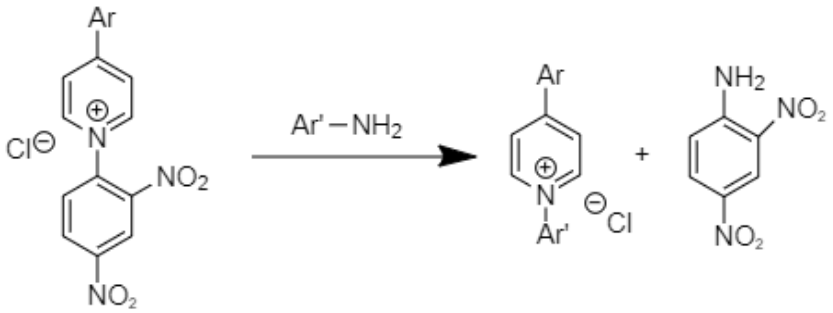
Zincke salt reacts with primary amines through nucleophilic attack of the amine to the carbon atom *ortho* to the positively charged nitrogen center, ultimately leading to formation of a new pyridinium salt according to the mechanism depicted in scheme 12. Since cleavage of the C–N bond of the primary amine does not occur during the process, the stereochemical configuration of chiral amines is retained in the final product.[8]



Scheme 12. Mechanism of the Zincke reaction for the synthesis of pyridinium salts.

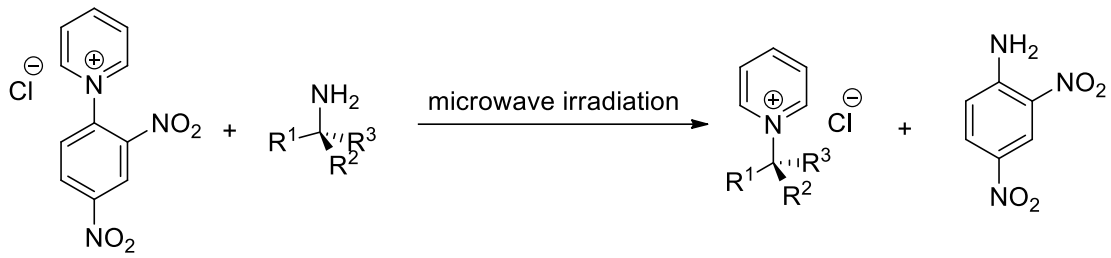
Consequently, the use of Zincke salts represents a versatile and highly efficient synthetic approach toward a broad range of pyridinium salts and constitutes one of the principal methodologies for the preparation of chiral pyridinium derivatives.

Marvel and Ise[17-20] were among the first researchers to investigate this reaction mechanism and are recognized as pioneering contributors to the synthesis of aryl pyridinium salts from Zincke salts (scheme 13).



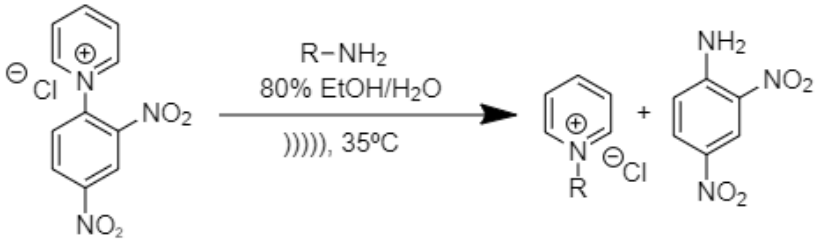
Scheme 13. Synthesis of *N*-aryl pyridinium salts from a Zincke salt.

Viana and colleagues reported the synthesis of chiral pyridinium salts under microwave irradiation conditions.[8] The methodology proved to be highly effective, leading to a substantial reduction in reaction time from 15 h to only 10 min, while simultaneously improving product yields from 29–85% to 57–98% (scheme 14). These results demonstrated that microwave-assisted synthesis constitutes a simple and significantly more efficient alternative to conventional thermal heating methods for the preparation of chiral pyridinium salts.



Scheme 14. Zincke reaction using microwave irradiation.

Considering the well-established advantages of ultrasound-assisted organic synthesis, including reduced reaction times, improved yields and milder reaction conditions, Zhao investigated the preparation of alkyl pyridinium salts under ultrasonic irradiation.[21] The reactions were carried out in an 80% methanol/water mixture at an optimized temperature of 35 °C (scheme 15). The results demonstrated that ultrasound irradiation significantly enhanced the efficiency of the process, reducing the reaction time from 12 h to 80–100 min while affording higher yields, when compared with the conventional procedure employing only magnetic stirring. In the synthesis of 1-(4-methoxyphenyl)pyridinium chloride, for example, yields increased from 75% under conventional conditions to 86% after 80 min and 87% after 100 min under ultrasonic irradiation.

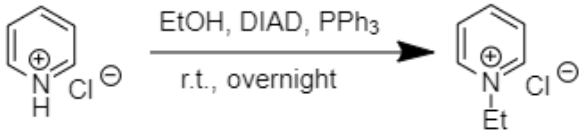


Scheme 15. Zincke reaction using ultrasound.

2.4 By the Mitsunobu reaction

Originally developed by Mitsunobu in 1967,[22] the Mitsunobu reaction has become a widely employed transformation in organic synthesis, particularly for the preparation of esters from primary alcohols. The reaction is typically mediated by triphenylphosphine and either diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). In this process, the presence of an acidic nucleophile is required to protonate DEAD or DIAD, thereby minimizing the occurrence of undesired side reactions.[23]

This methodology has also been investigated in the context of the synthesis of *N*-alkylated pyridinium salts. Petit and collaborators employed pyridinium chloride in ethanol at room temperature in the presence of DIAD and triphenylphosphine, obtaining the corresponding pyridinium salt in 45% yield under the conditions illustrated in scheme 16.[24]

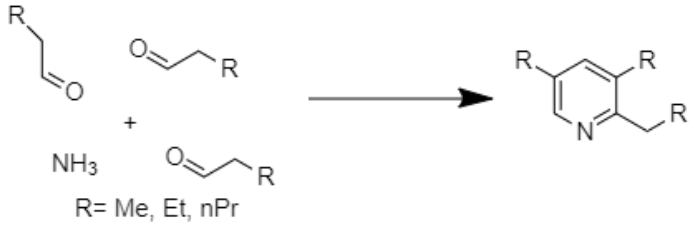


Scheme 16. Synthesis of pyridinium salts by the Mitsunobu reaction.

In a second approach, using acetonitrile as solvent, the reaction of primary alcohols afforded the desired pyridinium salts in excellent yields (86–100%). Secondary alcohols were also evaluated and when isopropanol was employed as the substrate, the corresponding product was obtained in a comparatively lower yield (60%). This methodology has therefore proven to be an effective and practical alternative for the synthesis of *N*-alkyl pyridinium salts.

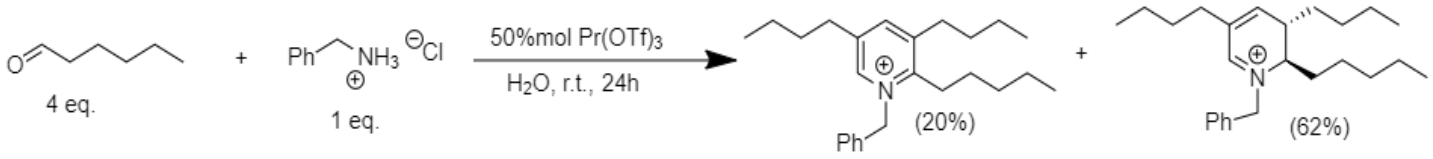
2.5 By the Chichibabin reaction

Chichibabin reported, in 1905, the synthesis of trisubstituted pyridines through the reaction of aldehydes with ammonia under conditions of high temperature and pressure (scheme 17).[25]



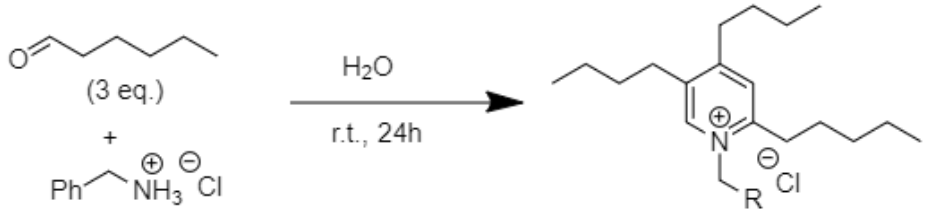
Scheme 17. The Chichibabin Reaction

Nearly a century later, Yu et al., inspired by Chichibabin's pioneering work and by the observation that lanthanide triflates are highly effective catalysts for the reaction between aldehydes and amines leading to 2,3-dihydropyridinium salts, developed a methodology for the synthesis of tetrasubstituted pyridinium salts catalyzed by lanthanide triflates.[26] In their study, $Dy(OTf)_3$, $Yb(OTf)_3$ and $Pr(OTf)_3$ were evaluated as catalysts. The best results were obtained with $Pr(OTf)_3$, affording a tetrasubstituted 1,2,3,5-pyridinium salt together with its corresponding dihydro derivative in 82% yield. The structures of the isolated products are presented in scheme 18.



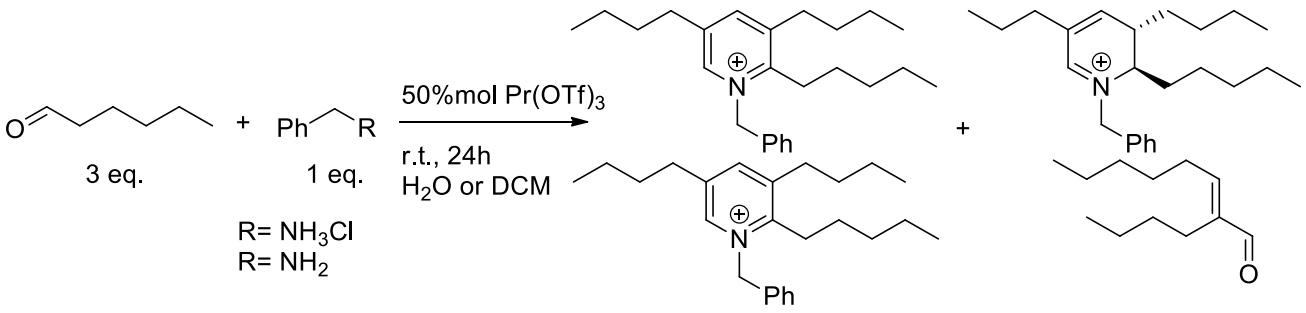
Scheme 18. The Chichibabin reaction for the formation of pyridinium salts.

More recently, Imura and colleagues investigated the methodology developed by Yu both in the presence and absence of $Pr(OTf)_3$ catalysis.[25] In the absence of the catalyst, the reactions performed with the amines evaluated afforded only very low yields (10–17%). Nevertheless, the authors succeeded in isolating a novel tetra-substituted pyridinium salt, namely a 1,2,4,5-tetrasubstituted derivative (scheme 19).



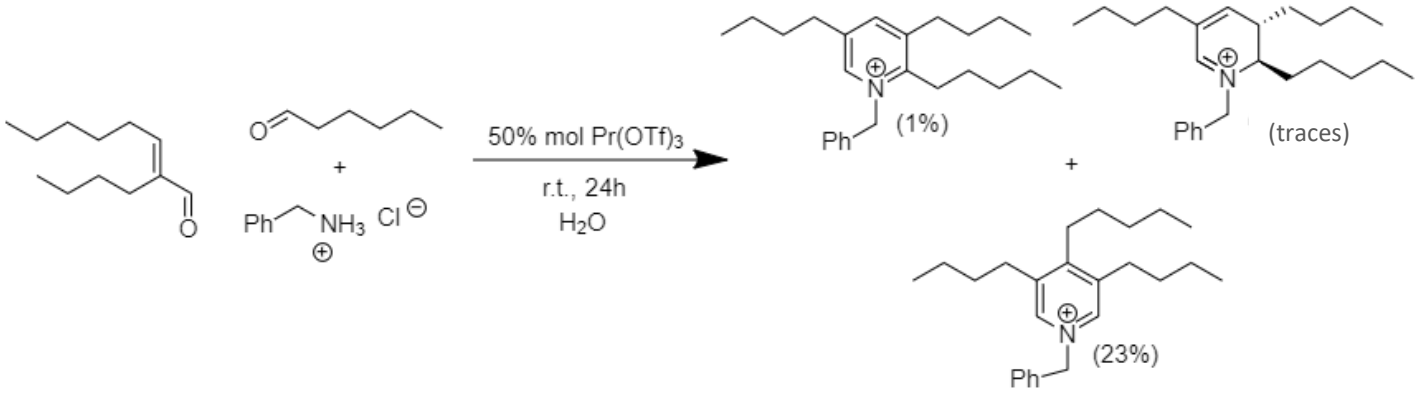
Scheme 19. Synthesis of pyridinium salts without metal catalysis.

In the presence of catalytic $Pr(OTf)_3$, the reaction afforded a mixture of products, including the 1,2,3,5-tetrasubstituted pyridinium salt, its corresponding dihydro derivative, the 1,3,4,5-tetrasubstituted pyridinium salt, and a product arising from aldol condensation (scheme 20).

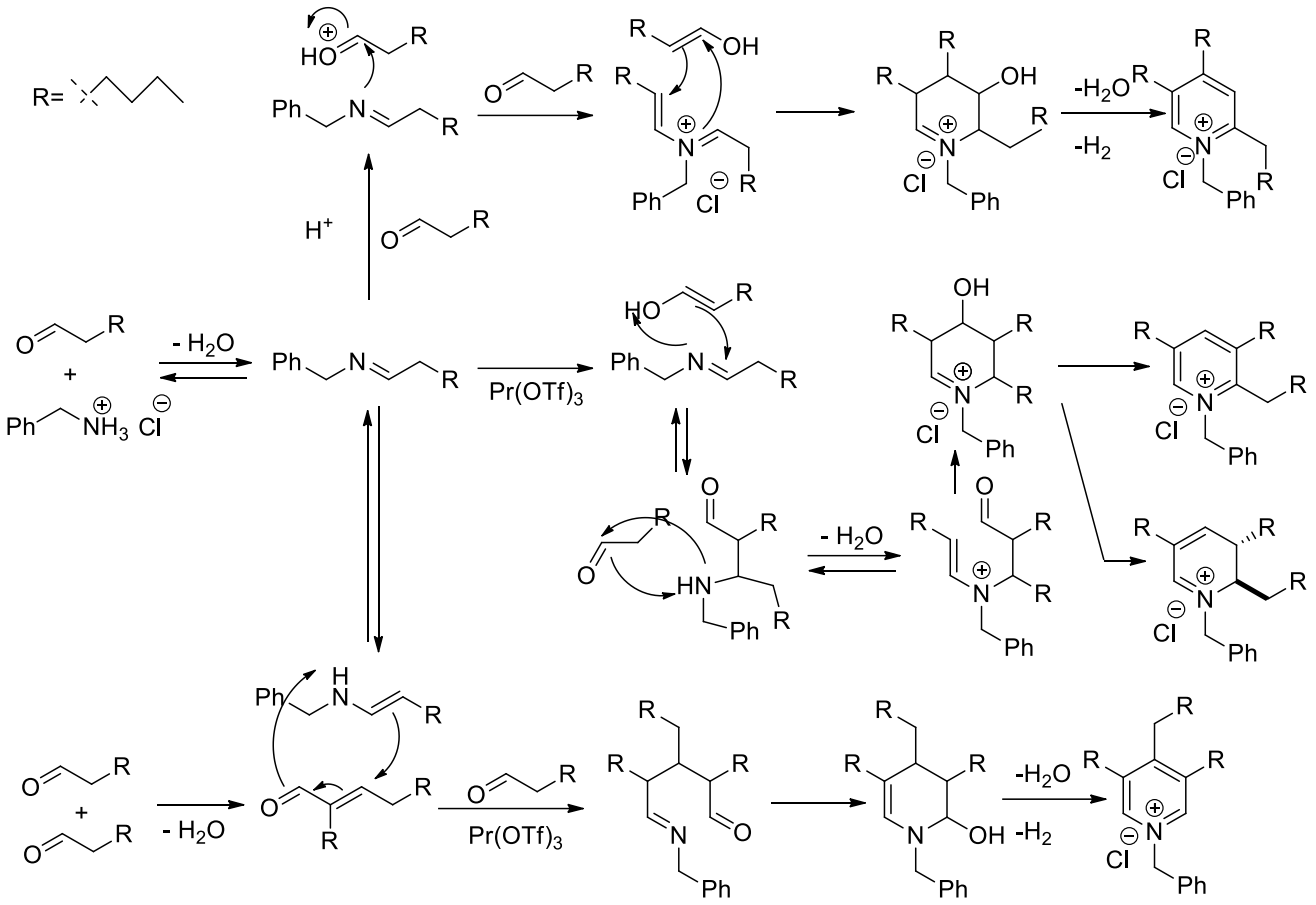


Scheme 20. Products obtained in the synthesis of pyridinium salts using $Pr(OTf)_3$ catalyst.

The authors proposed that the latter compound acts as an intermediate in the formation of the 1,3,4,5-tetrasubstituted pyridinium salt (scheme 21). The mechanistic pathways proposed for the different transformations are summarized in scheme 22.

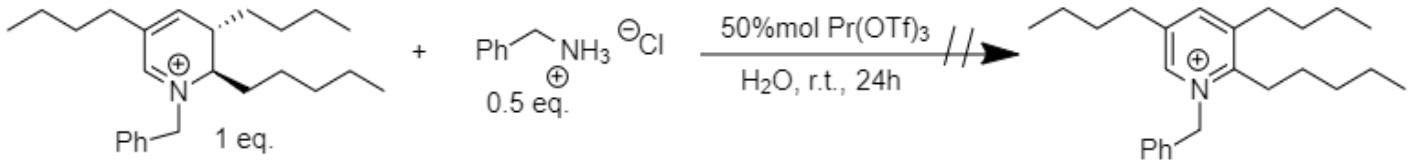


Scheme 21. Formation of pyridinium salts from the aldol condensation product.



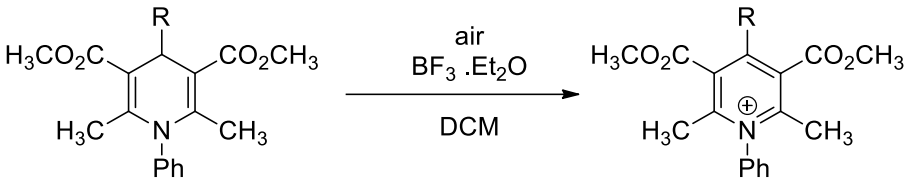
Scheme 22. Proposed mechanism for the reactions leading to the different pyridinium salts.

At the conclusion of this study, Imura also investigated the conversion of the dihydropyridinium derivative into the corresponding pyridinium salt under the optimized reaction conditions previously reported by Yu et al.[26] (scheme 23). However, no reaction was observed, which was attributed to the inability of these conditions to promote oxidation and the subsequent aromatization of the heterocyclic ring.



Scheme 23. Unsuccessful attempt to transform the 2,3-dihydropyridinium salt into the corresponding pyridinium salt.

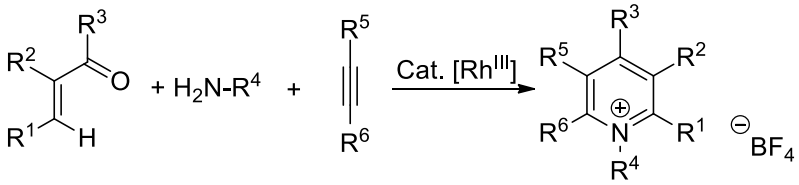
Guanaes investigated the transformation of 1,4-dihydropyridines into the corresponding pyridinium salts using BF_3OEt_2 in dichloromethane (DCM) at low temperature (0 °C) under atmospheric conditions (scheme 24).[27] The methodology was evaluated using a variety of substituents at the 4-position of the heterocyclic ring, affording the corresponding pyridinium salts in moderate to good yields (40–80%). Lower yields were observed for substrates bearing electron-withdrawing substituents at this position, indicating a significant electronic effect on the efficiency of the transformation.



Scheme 24. Oxidation of dihydropyridines.

2.6 By multicomponent reactions

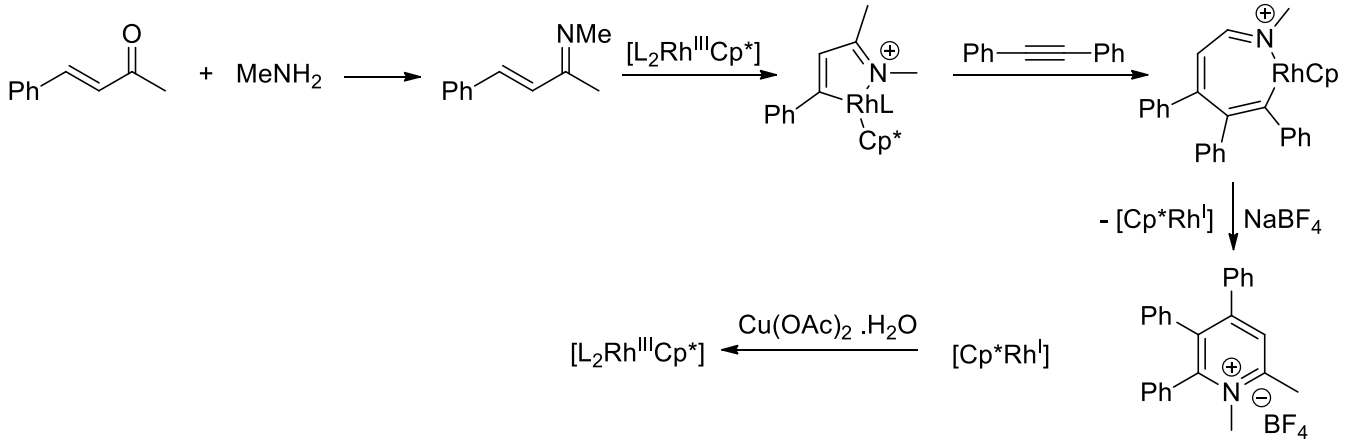
Transition metals have been extensively used as catalysts in the synthesis of a wide range of organic compounds. More recently, a synthetic methodology for the preparation of highly substituted pyridinium salts was reported, involving the reaction of a vinyl ketone or an α,β-unsaturated aldehyde with an amine and an alkyne in the presence of a rhodium(III) catalyst (scheme 25).[28] The transformation provides an efficient route toward structurally diverse pyridinium derivatives through metal-catalyzed multicomponent coupling reactions.



Scheme 25. Synthesis of pyridinium salts by a multicomponent reaction using a rhodium catalyst.

The proposed mechanism involves the initial formation of an α,β-unsaturated imine, followed by activation and cleavage of the vinylic C–H bond in a rhodium-catalyzed step, leading to cyclization of the intermediate (scheme 26). Subsequent insertion of the alkyne affords a seven-membered rhodacyclic intermediate. Finally, reductive elimination from the rhodium center generates the corresponding pyridinium salt together with rhodium(I), which is then reoxidized to rhodium(III) by $Cu(OAc)_2$, thereby regenerating the active catalytic species.

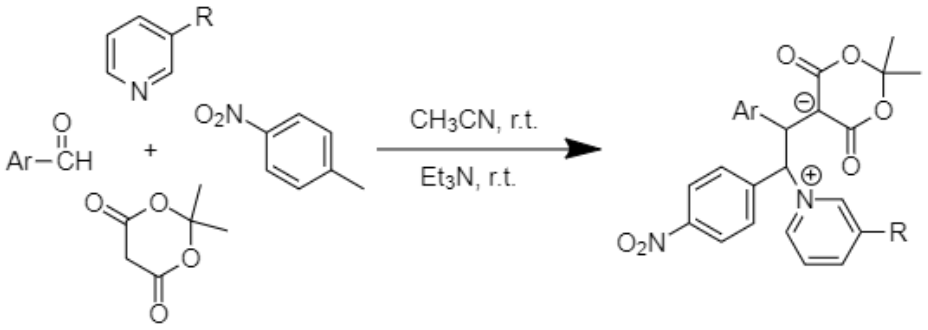
The methodology proved to be highly efficient, with most substrate combinations affording yields above 80% when the reactions were conducted at 80 °C for 16–24 h. These results demonstrate the broad applicability of the rhodium-catalyzed protocol toward the synthesis of highly substituted pyridinium salts.



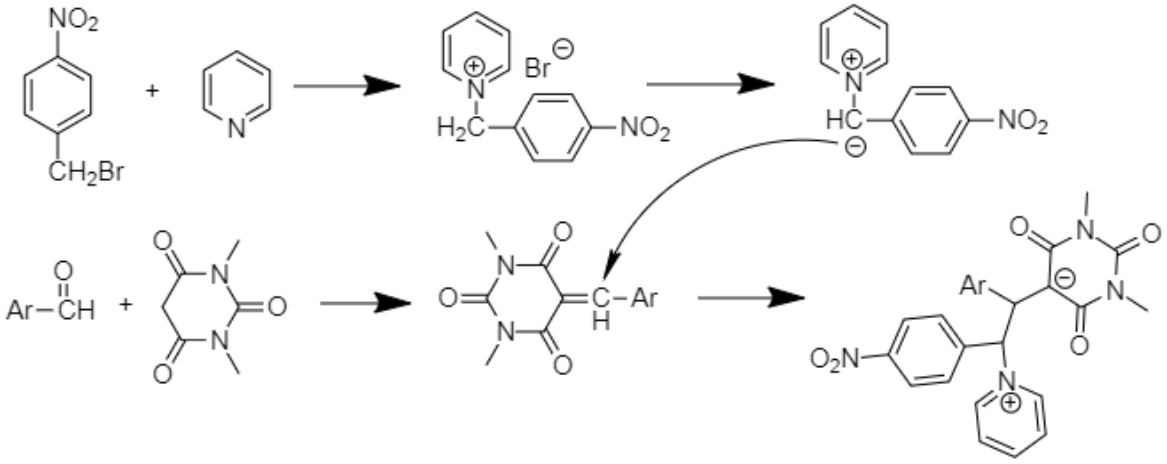
Scheme 26. Proposed reaction mechanism for the synthesis of a pyridinium salt using a rhodium catalyst.

Hui and colleagues reported the preparation of a zwitterionic pyridinium salt through a four-component reaction involving pyridine, an aromatic aldehyde, Meldrum's acid, and 1-(bromomethyl)-4-nitrobenzene.[29] In an initial approach, the reaction was carried out in acetonitrile at room temperature. After 2 h, the reaction mixture afforded *p*-nitrobenzylpyridinium salt together with the benzylidene derivative of Meldrum's acid. However, no further conversion to the desired product was observed even after 2 days. The authors attributed the lack of reactivity to the weak basicity of pyridine, which was considered insufficient to promote formation of the corresponding pyridinium ylide intermediate. To overcome this limitation, one equivalent of triethylamine was added to the reaction mixture. Under these modified conditions, the zwitterionic pyridinium salt was formed after 20 h at room temperature and isolated in 78% yield (scheme 27).

The resulting compound, characterized by high polarity and a high melting point, possesses a positive charge localized on the pyridinium nitrogen and a negative charge on the methylene carbon derived from Meldrum's acid, stabilized by resonance with the two adjacent carbonyl groups. A plausible mechanism for the transformation is proposed in scheme 28.



Scheme 27. Formation of a zwitterionic pyridinium salt.



Scheme 28. Proposed mechanism for the formation of the zwitterionic pyridinium salt.

2.7 From pyrylium salts

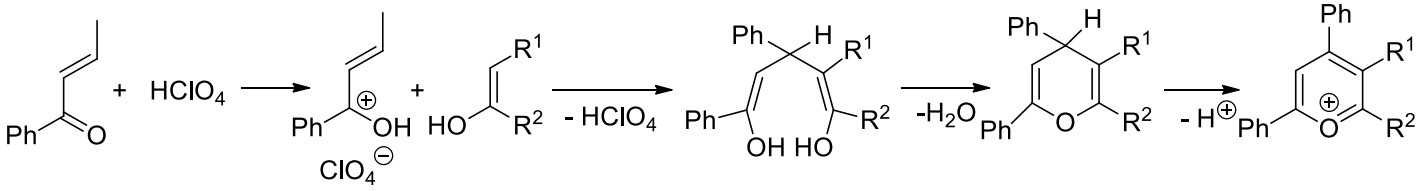
Pyrylium salts are six-membered aromatic heterocycles in which one of the carbon atoms of the ring is replaced by a positively charged oxygen atom. Owing to the high electronegativity of oxygen combined with its formal positive charge, a significant perturbation of the π-electron system is generated. Therefore, the electron density at the *ortho* and *para* positions is substantially reduced, making these positions particularly susceptible to nucleophilic attack.[30,31]

The reaction of pyrylium salts with primary amines constitutes a simple and efficient methodology for the synthesis of pyridinium salts and enables access to derivatives that are difficult or inaccessible through more conventional synthetic routes.[32] This strategy provides a straightforward approach to highly substituted pyridinium salts, such as 2,4,6-trisubstituted derivatives.[33] The transformation proceeds through ring opening of the pyrylium system, generating an intermediate capable of recyclization to form the corresponding *N*-substituted pyridine ring in a process analogous to that observed for Zincke salts.

Despite their synthetic utility, pyrylium salts, similarly to pyridinium salts, are not always commercially available and often require prior synthesis. Several methodologies have been reported for their preparation, including one-component reactions involving 2- or 4-pyrones,[34] as well as two- and three-component approaches, with the reaction mechanisms depending strongly on the nature of the substrates and substituents employed.[35]

An illustrative example of a two-component synthesis involves the preparation of 2,4,6-triarylpyrylium salts through the reaction of chalcones with ketones in the presence of perchloric acid ($HClO_4$). Dorofeenko and Olekhnovich used this methodology for the synthesis of 2,3,4,6-tetrasubstituted pyrylium salts bearing different substituents at the 2- and 3-positions.[36]

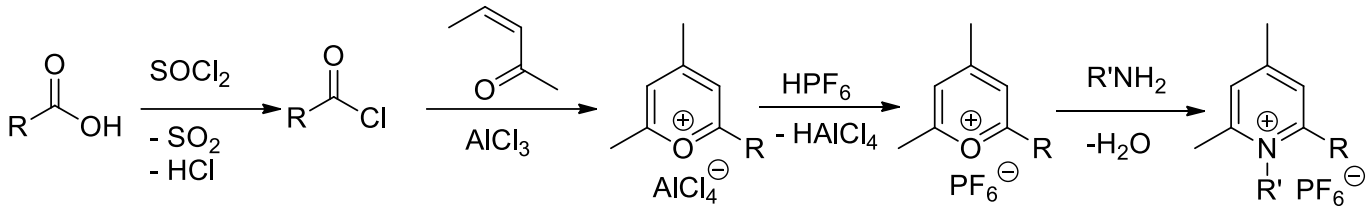
The proposed mechanism (scheme 29) involves initial Michael addition of the ketone to the chalcone, leading to formation of a 1,5-diketone intermediate. This intermediate subsequently undergoes intramolecular cyclization followed by deprotonation to afford the corresponding pyrylium salt. Although the methodology enabled access to a variety of substituted products, the isolated yields were relatively modest, ranging from 7.5 to 45%.



Scheme 29. Synthesis of pyrylium salts by a two-component reaction.

Another representative two-component approach to pyrylium salts involves the condensation of an acylating agent with an aryl methyl ketone, affording 2,4-diaryl-6-*R*-pyrylium salts.[37]

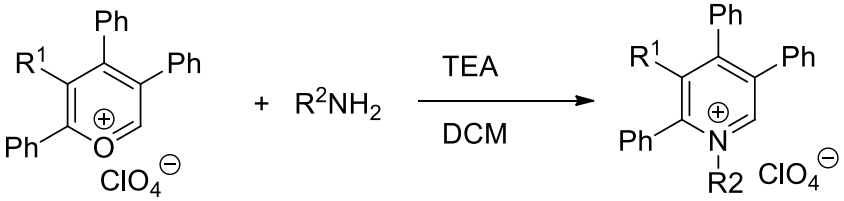
Ilies and co-workers[38] reported the synthesis of a novel class of pyridinium salts bearing long alkyl chains, designed for application as ionic lipids. In this methodology, long-chain alkyl carboxylic acids (C10–C17) were first converted into the corresponding acyl chlorides using thionyl chloride. In the presence of a Lewis acid, generation of a reactive carbocation intermediate enabled subsequent reaction with an α,β-unsaturated carbonyl compound, followed by cyclization to furnish the corresponding pyrylium salts. Conversion into the target pyridinium salts was then achieved by treatment with primary amines containing long alkyl chains (C10–C18) in a medium containing hexafluorophosphoric acid (scheme 30).



Scheme 30. Synthesis of pyridinium ionic lipids from a pyrylium salt.

In the early 1980s, Alan R. Katritzky reported several studies concerning the transformation of pyrylium salts into pyridinium salts.[39-41] In one of these investigations, it was proposed that the formation of aryl pyridinium salts from the corresponding pyrylium precursors required substitution at both ortho positions of the ring.[42] However, this assumption was later challenged by the work of Ning and co-workers in 2012.[32] In that study, one-pot syntheses were carried out using 2,4,5-triphenyl- and 2,3,4,5-tetraphenylpyrylium salts (R^1 = H or Ph) reacted with primary amines bearing either electron-withdrawing substituents (halogens) or electron-donating groups (pyridinyl and aminophenyl moieties) (scheme 31). The yields obtained for the triphenylpyridinium salts were comparable to those observed for the tetraphenyl analogues (70–89% versus 68–86%). Nevertheless, the formation of triphenylpyridinium salts generally proceeded in shorter reaction times (4–18 h) compared with the tetraphenyl derivatives (6–24 h).

The study further demonstrated that pyridinium salts containing electron-donating substituents were typically obtained in higher yields and within shorter reaction times. These findings indicated that, in the synthesis of ortho-monosubstituted pyridinium salts, the number of phenyl substituents attached to the pyrylium framework plays a significant role, owing to both steric and electronic effects that influence the course of the reaction.



Scheme 31. Synthesis of tri-/tetraphenylpyridinium salts from pyrylium salts.

3. Reactivity of Pyridinium Salts

Due to the presence of a formal positive charge on the nitrogen atom, pyridinium salts are highly reactive intermediates that may act either as electrophilic species or as 1,3-dipoles, enabling a wide range of transformations. Among the most representative reactions involving these compounds are condensation processes, Michael-type additions, and 1,3-dipolar cycloadditions.

Within the pyridinium ring, the nitrogen atom exerts a strong electron-withdrawing effect. Resonance stabilization of the cationic system promotes delocalization of the positive charge over the *ortho* and *para* positions of the ring (positions 2, 4, and 6). Consequently, these positions become the most electrophilic sites and are therefore particularly susceptible to nucleophilic attack.

3.1 Reactivity of *N*-alkyl/aryl/acyl pyridinium salts

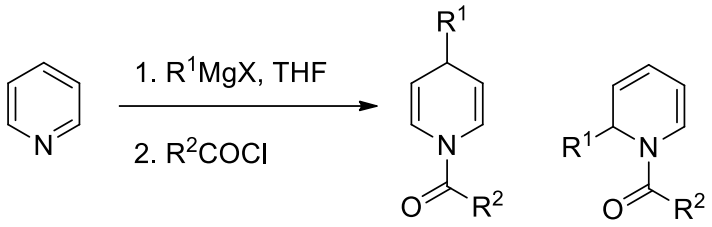
Nucleophilic addition reactions constitute one of the most characteristic transformation pathways of pyridinium salts, which can react with a broad range of nucleophilic species. Such reactions have been reported to afford diverse partially or fully reduced nitrogen-containing heterocycles, including 2,3-dihydro-4-pyridones, piperidines, tetrahydropyridines, and substituted dihydropyridines. In several cases, the latter products are obtained as mixtures of 1,2- and 1,4-dihydropyridine regioisomers.

3.1.1 Reaction with organometallic compounds. Reactions of pyridinium salts with organometallic reagents constitute an important strategy for the introduction of nucleophilic substituents at the 2- and 4-positions of the heteroaromatic ring. In these transformations, regioselectivity represents a major challenge, since nucleophilic attack at either the 2- or 4-position is strongly influenced by both the nature of the organometallic reagent and the reaction conditions employed.

In general, Grignard reagents preferentially attack the *ortho* position of the pyridinium ring, whereas organocuprates tend to promote addition at the *para* position. Nevertheless, the presence of substituents on the ring may alter this selectivity through steric and electronic effects, directing the nucleophilic attack toward alternative positions.[6]

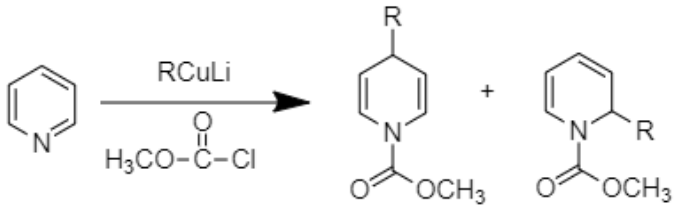
The studies discussed herein concerning this type of transformation were primarily performed using *N*-acylpyridinium salts. In this context, Dennis L. Comins conducted several investigations into the regioselectivity of nucleophilic additions to these intermediates.[43-45] In one representative study,[46] dihydropyridines were synthesized directly through a one-pot procedure involving unsubstituted pyridines, acyl chlorides, and Grignard reagents in tetrahydrofuran (THF) (scheme 32). Owing to the rapid formation of the *N*-acylpyridinium salt from the reaction between pyridine and the acyl chloride, competitive reaction between the Grignard reagent and the acyl chloride was effectively suppressed, enabling efficient one-pot synthesis.

The results demonstrated that alkyl Grignard reagents generally exhibited low regioselectivity, whereas aryl Grignard reagents underwent nucleophilic addition predominantly at the 2-position of the pyridinium ring. In contrast, addition at the 4-position was favored when steric hindrance at the 2-position increased, particularly due to the steric bulk of substituents present in the acyl moiety.



Scheme 32. Synthesis of 1,2- and 1,4-dihydropyridines by nucleophilic attack to the pyridine nucleus using Grignard reagents.

In 1974, Edward Piers and Pierre Soucy investigated a straightforward methodology for the synthesis of substituted dihydropyridines in which nucleophilic addition occurred predominantly at the 4-position of the pyridinium ring, a transformation that had previously been difficult to achieve selectively.[47] Their approach involved the reaction of diaryl or dialkyl lithium cuprates with pyridine in the presence of an electrophilic activating agent, such as methyl chloroformate (scheme 33). Under these conditions, regioselective nucleophilic addition at the *para* position was favored, providing an efficient route to 4-substituted dihydropyridine derivatives.

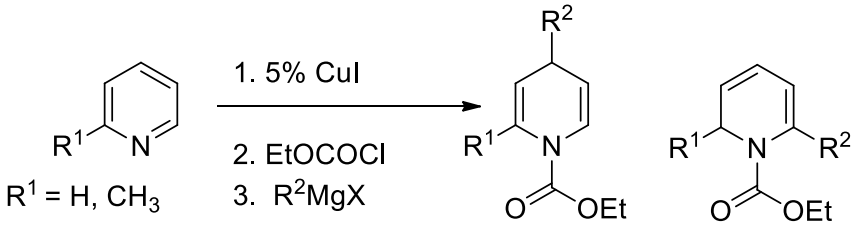


Scheme 33. Synthesis of 1,2 and 1,4-dihydro pyridines by nucleophilic attack to the pyridine nucleus by organocuprates.

The results obtained demonstrated that cuprates bearing linear alkyl substituents exhibited higher regioselectivity toward nucleophilic addition at the 4-position of the pyridinium ring (94:6 and 98:2 C4/C2 ratios) compared with aryl-substituted cuprates (90:10 and 92:8) or cuprates containing branched alkyl groups (89:11).[47]

Building on these findings, Dennis L. Comins, in the study previously discussed,[46] investigated the influence of copper iodide on the regioselectivity of nucleophilic additions involving Grignard reagents, aiming to enhance selectivity for the 4-position of the pyridinium ring. In this methodology, ethyl formate and a Grignard reagent were employed in the presence of catalytic CuI (5 mol%) (scheme 34).

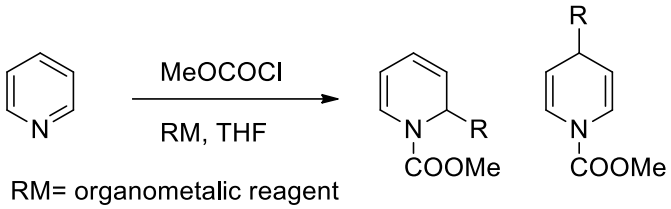
The results revealed the almost exclusive formation of 4-substituted pyridinium derivatives when pyridine was used as the starting substrate, with C4/C2 ratios ranging from 99.1:0.9 to 100:0 and isolated yields between 62 and 77%. Similar regioselectivity was observed for reactions involving 2-picoline (C4/C2 ratios of 98.8:1.2 to 100:0), although lower product yields were obtained (27–55%). The methodology was also extended to 3-picoline derivatives, for which higher yields were achieved relative to the 2-picoline substrates. Because all three reactive positions of the ring remained accessible for nucleophilic attack in this system, formation of the three possible regioisomeric products was detected. Nevertheless, the presence of CuI strongly favored nucleophilic addition at the 4-position, providing regioselectivities exceeding 92%.



Scheme 34. Synthesis of 1,2- and 1,4-dihydropyridines from Grignard reagents and pyridines by the addition of copper iodide.

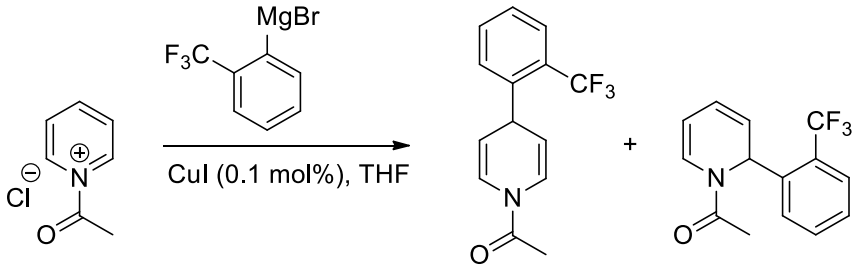
Yamaguchi also carried out a systematic investigation of nucleophilic additions to pyridinium salts using a variety of organometallic reagents.[48,49] The study demonstrated that reactions involving alkyl Grignard reagents generally produced mixtures of products, with regioselectivity strongly dependent on both the nature of the metal center and the structure of the alkyl substituent. Consequently, these transformations could not be considered fully selective.

Among the reagents evaluated, MeMgI displayed good regioselectivity toward nucleophilic addition at the 2-position of the pyridinium ring, providing a C2/C4 ratio of 92:8. Furthermore, Grignard reagents bearing alkenyl or alkynyl substituents exhibited almost complete selectivity for attack at the 2-position, with nucleophilic addition ratios exceeding 99% (scheme 35).



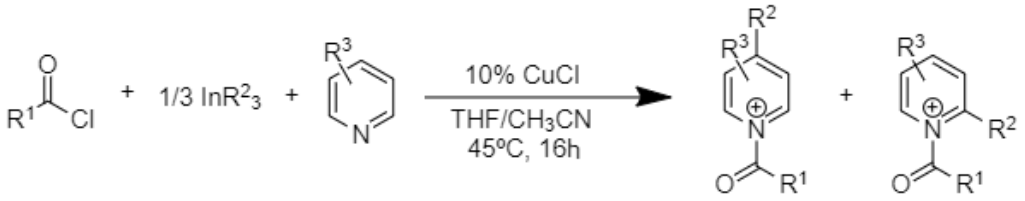
Scheme 35. Synthesis of 1,2- and 1,4-dihydropyridines by nucleophilic attack of various organometallic compounds to the pyridine ring.

Tang and co-workers[50] developed a synthetic methodology for the preparation of dihydropyridines, as outlined in scheme 36. The reaction employed acetyl chloride, pyridine, and a 2-trifluoromethylphenyl Grignard reagent in the presence of copper(I) iodide as catalyst, using THF as solvent. This protocol afforded the desired dihydropyridines in 76% yield. Notably, the nucleophilic addition to the pyridinium ring occurred with remarkable regioselectivity, proceeding predominantly at the C4 position, with a C4 selectivity ratio of 97:3.



Scheme 36. Synthesis of a 1,2- and 1,4-aryldihydropyridine from a *N*-acylpyridinium chloride

Arndtsen and co-workers[51] also investigated the regioselectivity of organoindium reagents in nucleophilic additions to pyridinium salts, as illustrated in scheme 37.



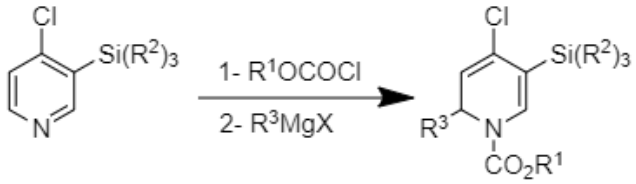
Scheme 37. Synthesis of 1,2 and 1,4 dihydropyridines by addition of organoindium compounds to a *N*-acylpyridinium salt.

The products obtained demonstrated that, under these conditions, nucleophilic attack occurred preferentially at the C4 position of the pyridinium ring. In the cases where addition at the C2 position was observed, the C4 position was already substituted or sterically hindered.

In another study, Comins[52] demonstrated that the introduction of a bulky substituent, such as a trialkylsilyl group, at the C3 position of the pyridinium ring directed the nucleophilic addition preferentially toward the C6 position.

In this work, 4-chloro-3-trialkylsilyl-*N*-acylpyridinium salts were employed as substrates. Since the C4 position of the pyridinium ring was blocked, nucleophilic addition could occur only at the C2 and C6 positions. However, the steric hindrance imposed by the trialkylsilyl group disfavored attack at C2, resulting in

preferential addition at C6. Notably, bulkier silyl substituents, such as triisopropylsilyl groups, led to exclusive regioselectivity for the C6 position, as illustrated in scheme 38.

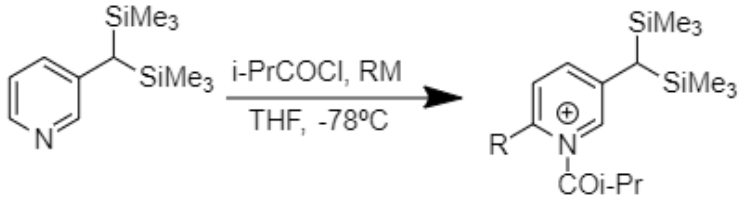


Scheme 38. Nucleophilic substitution by Grignard reagents in pyridinium salts substituted at the C3 and C4 positions.

The *N*-acylpyridinium salt lacking the chlorine substituent was also investigated. In this case, nucleophilic addition could, in principle, occur at the C2, C4, and C6 positions of the pyridinium ring. Nevertheless, the presence of the bulky triisopropylsilyl group once again directed the reaction exclusively toward the C6 position, resulting in complete regioselectivity for nucleophilic addition at this site.

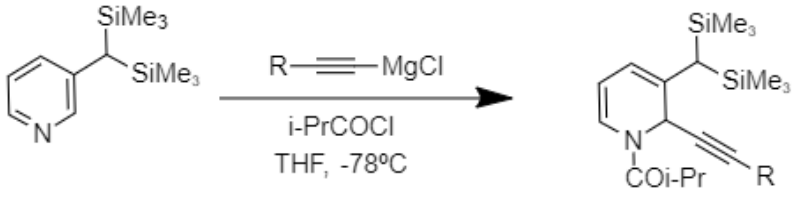
However, the regioselectivity of the nucleophilic attack strongly depends on the substituent present at the C3 position of the pyridinium ring. Small substituents, such as methyl, methoxyl, or halogen groups, generally continue to favor 1,2-addition due to their directing effects.

A study conducted by Song[53] investigated the influence of a geminal bis(trimethylsilyl) group at the C3 position of the pyridinium ring as a directing group for nucleophilic addition at the C6 position (scheme 39). Owing to the considerable steric bulk of this substituent, it was anticipated that strong steric hindrance would be exerted at the C2 and C4 positions, thereby favoring nucleophilic attack at C6. Indeed, when alkyl-, vinyl-, and phenyl-substituted Grignard reagents were employed, nucleophilic addition occurred almost exclusively at the C6 position, with only trace amounts of products resulting from addition at the C4 position.



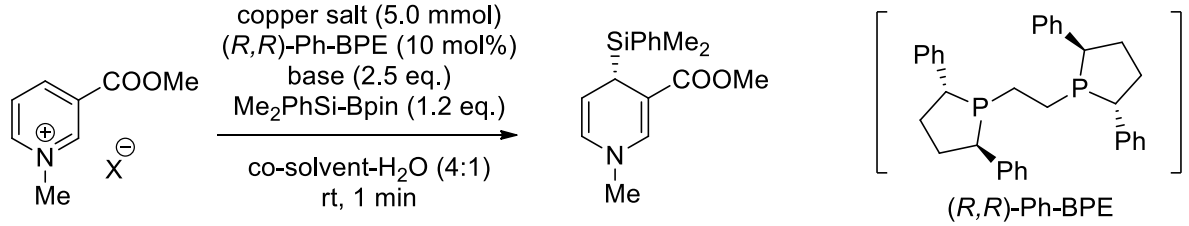
Scheme 39. Effect of the bis(trimethylsilyl) geminal group at the C3 position of the pyridinium salt on nucleophilic attack by organometallic compounds.

A different regioselectivity pattern was observed when alkynyl-substituted Grignard reagents were employed. In this case, the authors unexpectedly found that nucleophilic addition occurred preferentially at the C2 position of the pyridinium ring, rather than at C6, as shown in scheme 40.



Scheme 40. Synthesis of a 1,2-dihydropyridine.

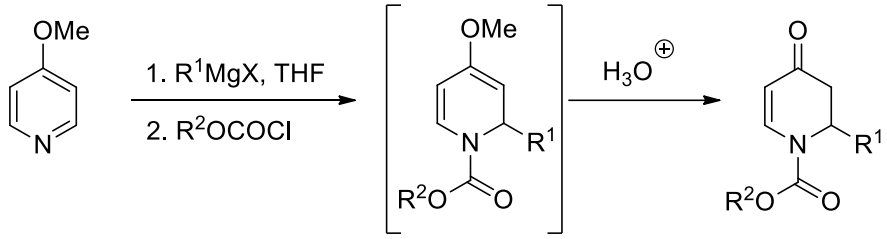
Oestreich and co-workers[54] developed an enantioselective dearomatization od *N*-alkyl pyridinium salts, generating 4-silylated 1,4-dihydropyrimidines with up to 99% ee (scheme 41). The reaction was performed in the presence of base, a copper salt, Me_2PhSi-Bpin and a chiral catalyst, (*R,R*)-Ph-BPE. The success of the synthetic method is strongly related to the presence of a carbonyl group at C3 of the pyridinium triflate salt, to direct the addition of the silicon nucleophile to C4. This leads to an excellent regioselectivity in the formation of the silylated 1,4-dihydropyrimidine, a valuable synthetic intermediate in the formation of functionalized piperidine derivatives.



Scheme 41. Enantioselective synthesis of 4-silylated 1,4-dihydropyrimidines using a chiral catalyst.

3.1.2 Synthesis of 2,3-dihydro-4-pyridones. These studies also employed *N*-acylpyridinium salts bearing an alkoxyl substituent at the 4-position of the pyridine ring, such as *N*-acyl-4-methoxypyridinium salts, which undergo reaction with nucleophiles. Since the *para* position is blocked by the alkoxyl group, nucleophilic addition preferentially occurs at the *ortho* positions of the ring.

Comins[55] reported the synthesis of 2,3-dihydro-4-pyridones through the nucleophilic addition of Grignard reagents to an *N*-acylpyridinium intermediate generated *in situ* from 4-methoxypyridine. Owing to the pronounced hydrolytic instability of the resulting *N*-acyl-4-methoxy-1,2-dihydropyridine intermediate, subsequent treatment under aqueous 10% HCl conditions promoted hydrolysis, affording the corresponding 2,3-dihydro-4-pyridones in isolated yields ranging from 72–91% (scheme 42).



Scheme 42. Synthesis of a 2,3-dihydro-4-pyridone.

Analysis of the structural features of these compounds reveals their potential applicability in a broad range of synthetic transformations, including cycloaddition reactions, electrophilic substitutions, 1,2- and 1,4-nucleophilic additions, as well as enolate-mediated alkylation reactions (figure 1). Consequently, these molecular frameworks represent versatile synthetic intermediates that can be employed as valuable starting materials for the preparation of structurally diverse compounds with potential biological activity.

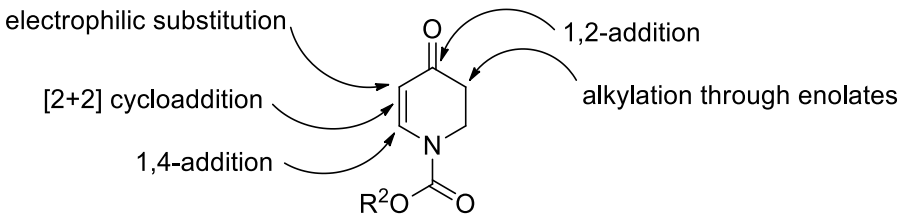
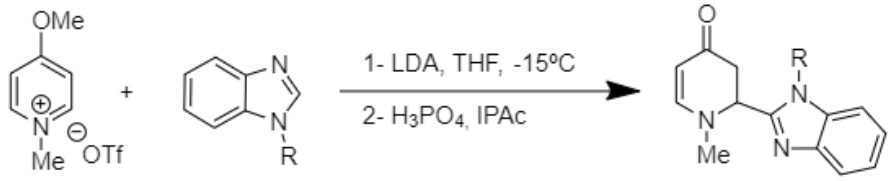


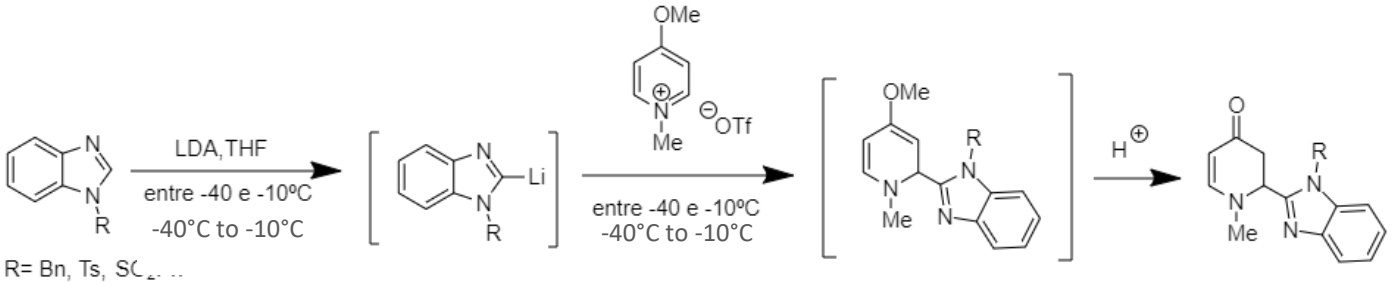
Figure 1. Possible reactions from 2,3-dihydro-4-pyridones.

An example of this application was reported in the study by Clarke et al.[56] in which a dihydropyridone intermediate was synthesized as part of the preparation of a Smoothened (SMO) receptor inhibitor. The reaction employed 4-methoxy-*N*-methylpyridinium triflate and protected benzimidazoles bearing either benzyl or sulfonyl protecting groups, using lithium diisopropylamide (LDA) as the base and tetrahydrofuran (THF) as the solvent (scheme 43). Initially, LDA deprotonated the acidic methylene position located between the two nitrogen atoms of the benzimidazole derivative, generating a stabilized carbanion. Coordination with lithium afforded the corresponding lithium benzimidazolide species, which subsequently reacted with the pyridinium salt to produce the dihydropyridine intermediate. Subsequent hydrolysis under mildly acidic conditions yielded the corresponding dihydropyridone (scheme 44).

Regarding the reaction efficiency, the use of benzyl-protected benzimidazole afforded overall yields of 50–60%, with 30–40% of the starting material remaining unreacted. In contrast, sulfonyl-protected benzimidazoles provided improved overall yields of 70–80%, with only 10–20% of the starting material recovered. The incomplete conversion of the reagents was attributed to partial reprotonation of the lithium benzimidazolide intermediates upon addition of the pyridinium salt, regenerating the starting benzimidazole derivatives. The proposed mechanism for this reaction is presented in scheme 44.



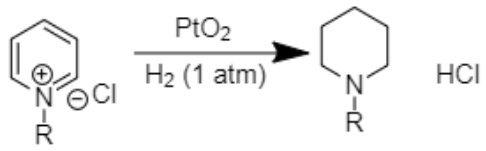
Scheme 43. Formation of 2,3-dihydro-4-pyridone by the reaction of a pyridinium salt with benzimidazole.



Scheme 44 Proposed mechanism for the reaction of benzimidazole with the pyridinium triflate salt, based on spectroscopic evidence.

3.1.3 Catalytic reduction of pyridinium salts. The catalytic reduction of pyridinium salts represents a widely employed strategy for the conversion of pyridines into the corresponding piperidines. These hydrogenation reactions are typically conducted either at room temperature or under elevated thermal

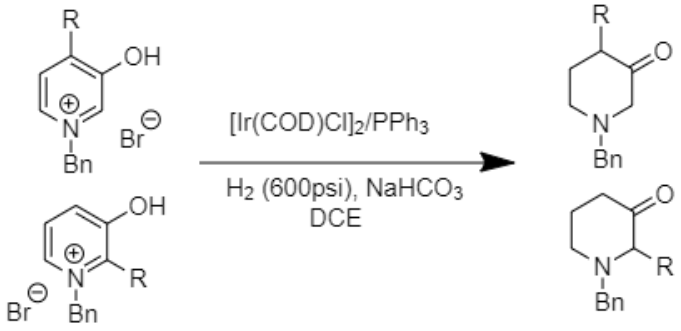
conditions. A variety of catalysts have been reported for this transformation, including supported metal catalysts such as Pd/C, Ru/C, and Ni, as well as metal oxides including PdO and PtO. The reactions are generally performed under a hydrogen atmosphere, with the applied H_2 pressure varying depending on the reaction conditions and substrate scope (scheme 45).[6]



Scheme 45. Catalytic reduction of pyridinium salts with H_2.

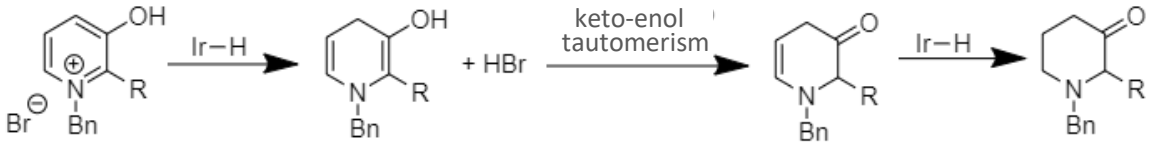
Zhou et al.[57] reported a novel synthetic route toward 3-piperidinone, an important intermediate in the synthesis of numerous pharmaceuticals and natural products. The methodology involved the hydrogenation of an *N*-benzyl-3-hydroxypyridinium salt, catalyzed by an iridium complex (scheme 46).

A comprehensive investigation of both the catalyst system and the reaction parameters was carried out to optimize the synthetic procedure. Different catalysts, including Pd/C, Rh/C, and iridium complexes, were evaluated, alongside variations in solvent, temperature, reaction time, and the addition of inorganic bases. Optimal reaction conditions were achieved using dichloroethane (DCE) as solvent, sodium bicarbonate as base, and $Ir(COD)Cl_2$ as catalyst. Under an H_2 atmosphere (600 psi) at 50 °C for 20 h, the desired product was isolated in yields ranging from 83–88%.



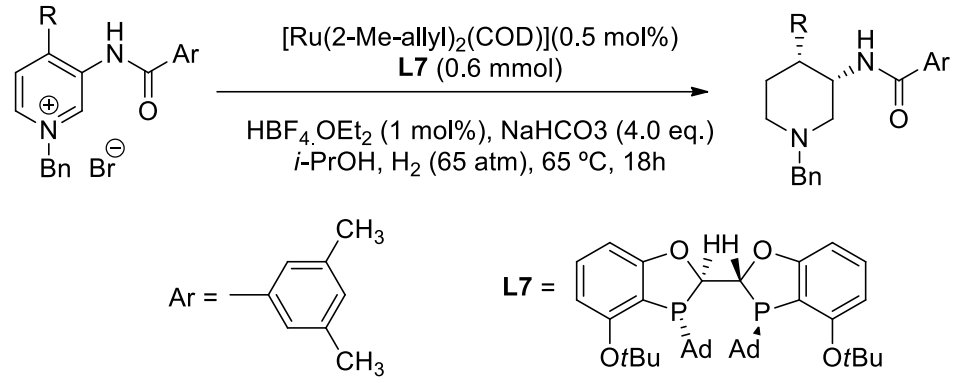
Scheme 46. Synthesis of a piperidinone by catalytic reduction of a pyridinium salt.

This methodology enabled the selective synthesis of a range of 3-piperidinone derivatives substituted at the C2 or C4 positions of the piperidine ring, without any competing cleavage of the *N*-benzyl protecting group. According to the authors, the transformation is proposed to proceed via the mechanistic pathway outlined in scheme 47.



Scheme 47. Proposed mechanism for the formation of the piperidinone ring.

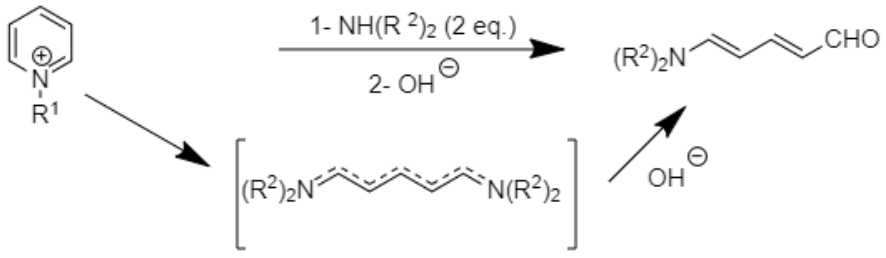
Tang and co-workers[58] developed an efficient method for the enantioselective synthesis of 3-amino-4-substituted piperidines from substituted 3-acylamino pyridinium salts. The reaction involved a ruthenium-catalyzed hydrogenation performed in the presence of a sterically bulky Ad^P-tBuO-BIBOP ligand, as represented in scheme 48. The presence of two adamantyl groups on the phosphorous center, prepared in this work, greatly improved the isolated yield and the ee of the asymmetric hydrogenation product.



Scheme 48. Synthesis of 3-amino-4-substituted piperidines from substituted 3-acylamino pyridinium salts.

3.1.4 Miscellaneous reactions. The nucleophilic addition of an amine to the pyridinium ring induces a significant perturbation of the aromatic π-system, ultimately leading to ring opening. Once the ring is opened, the resulting intermediate can undergo base-mediated hydrolysis to afford aldehydic products. These aldehydes, embedded within a five-carbon conjugated polyene chain, can be readily functionalized through a variety of transformations, thereby enabling access to a broad range of compounds with potential biological activity. This versatility renders this transformation particularly valuable in synthetic chemistry.

A representative class of such structures corresponds to the so-called Zincke aldehydes, which are formed through the reaction of pyridinium salts activated via the König or Zincke pathway with two equivalents of a secondary amine, promoting ring opening. Subsequent hydrolysis under basic conditions yields 5-amino-2,4-pentadienal. A proposed mechanism for this transformation is illustrated in scheme 49.[59, 6]

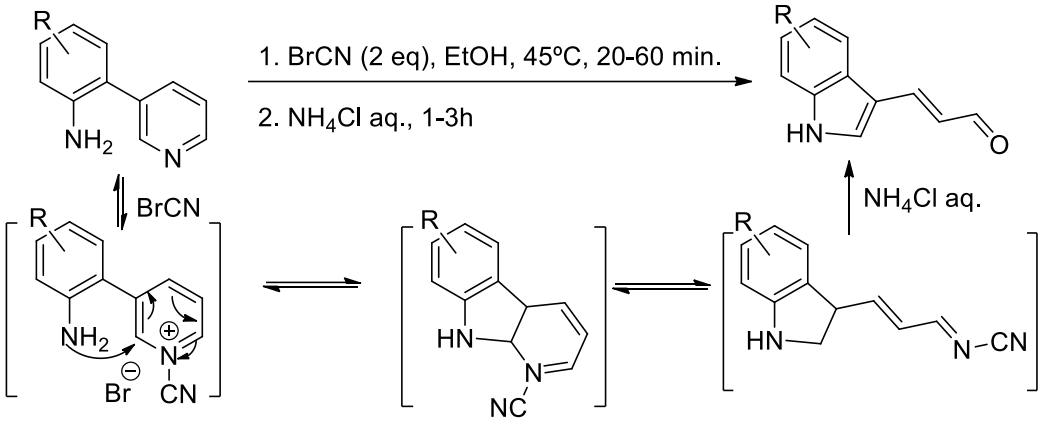


Scheme 49. Synthesis of a 5-amino-2,4-pentadienal.

The formation of these aldehydes may also proceed via an intramolecular pathway. In a study by Vanderwal et al.[60] a pyridinium salt bearing an aniline substituent at the C3 position was shown to undergo cyclization to afford an indole-3-propenal derivative.

The corresponding pyridinium salt was first generated from the parent pyridine via activation using the König method in ethanol, involving treatment with BrCN, in a process analogous to the established pyridine alkylation protocol. Following formation of the pyridinium intermediate, intramolecular nucleophilic attack by

the aniline amino group at the *ortho* position onto C2 of the pyridinium ring induced ring opening. The resulting intermediate subsequently underwent base-mediated hydrolysis to furnish the aldehyde functionality, consistent with the mechanistic sequence depicted in scheme 50.



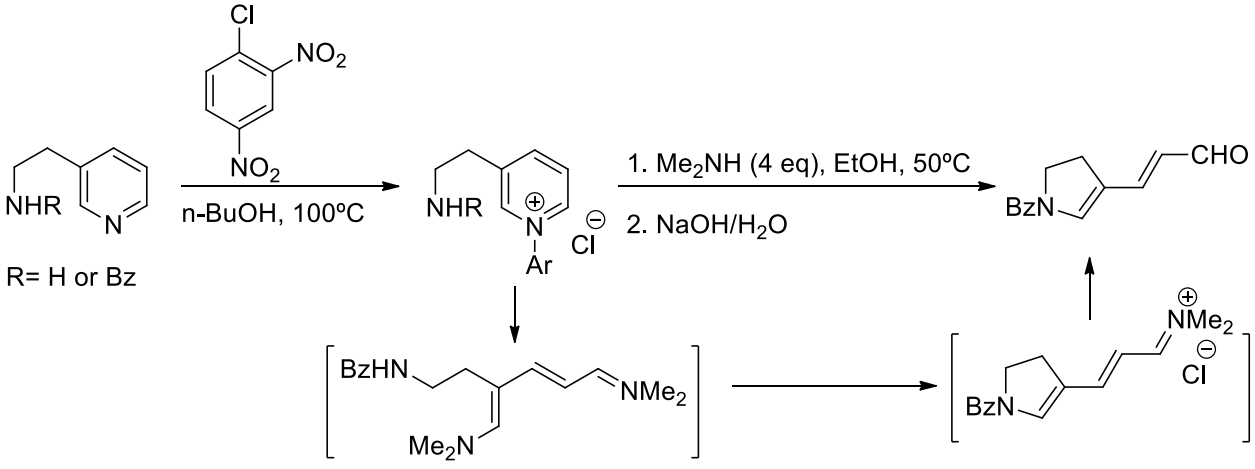
Scheme 50. Proposed mechanism for the synthesis of an indole-3-propenal by an intramolecular reaction.

In this study, a range of substituents on the aniline moiety was evaluated, affording the corresponding products in moderate to good yields (63–80%), thereby demonstrating the broad functional group tolerance and versatility of this methodology for the synthesis of substituted indole frameworks.

The synthetic strategy was also extended to an analogous substrate bearing a methyl substituent on the 4-position of the pyridine ring, which similarly furnished the desired product in 67% yield.

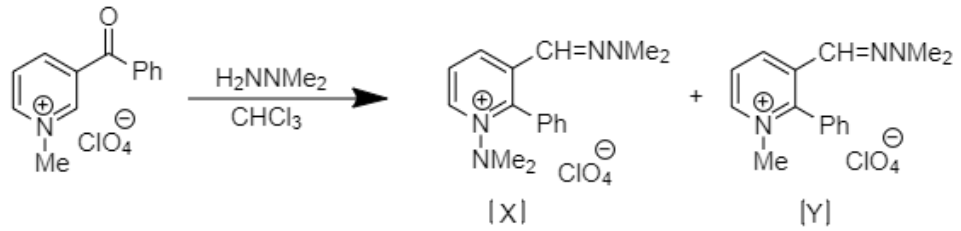
When 2-aminopyridine was employed as the substituent at the C3 position, the corresponding transformation enabled the synthesis of 7-azaindole in 80% yield.

The reaction of an *N*-arylpyridinium salt with excess dimethylamine (scheme 51) afforded *N*-benzoyl dihydropyrrole in 57% yield. The proposed mechanism involves initial activation of the pyridine ring via the Zincke reaction, followed by nucleophilic ring opening through attack of dimethylamine at the C2 and C6 positions. Subsequent intramolecular cyclization, arising from the reaction between the secondary amine and the iminium carbon, leads to formation of the dihydropyrrole framework.



Scheme 51. Proposed mechanism for the synthesis of *N*-benzoyl dihydropyrrole.

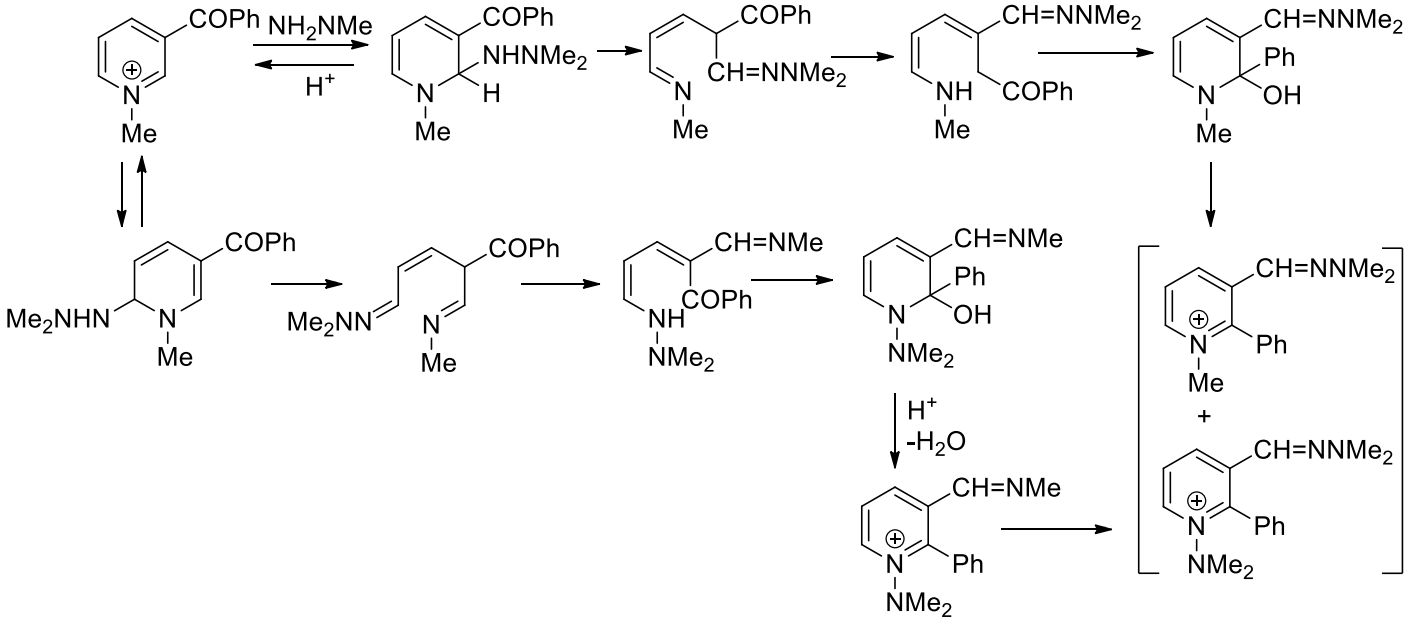
Nucleophilic substitution in azines, diazines, and triazines commonly proceeds via the "Nucleophilic Addition, Ring Opening, Ring Closure" (SN(ANRORC)) mechanism. Lund and Skov[61] demonstrated that this pathway also accounts for the formation of the products observed in the reaction between the perchlorate salt of 3-benzoyl-1-methylpyridinium and *N*,*N*-dimethylhydrazine (scheme 52).



Scheme 52. Reaction of a pyridinium salt with *N*,*N*-dimethylhydrazine.

In this reaction, a mixture of two *N,N*-dimethylhydrazone derivatives was obtained, namely the perchlorate salts of 1-dimethylamino-2-phenyl-3-formylpyridinium and 1-methyl-2-phenyl-3-formylpyridinium. The former arises from nucleophilic attack at the C6 position of the pyridinium nucleus, whereas the latter is formed via nucleophilic attack at C2.

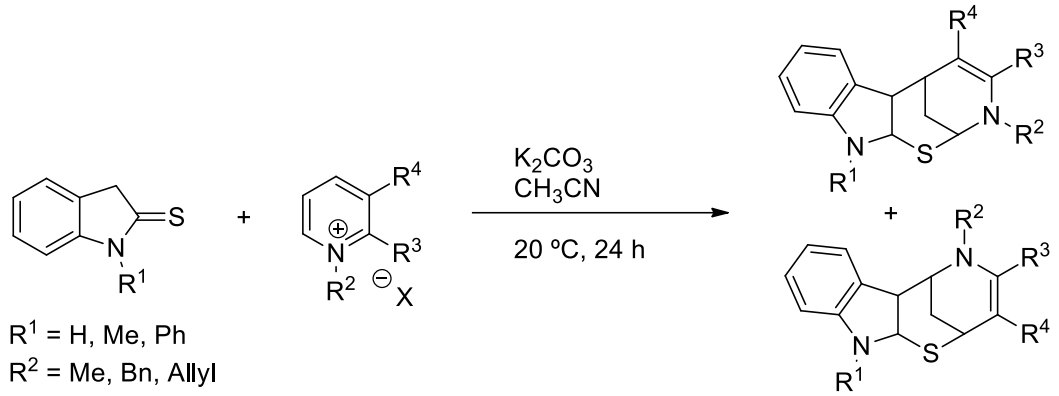
The product distribution was found to be solvent-dependent. In methanol, a ratio of 3:1 (X:Y) was observed, while in acetonitrile or chloroform the ratio shifted to 1:2. The authors attributed this effect to differential solvation of the carbonyl group in protic versus aprotic media. In methanol, enhanced solvation is proposed to influence the reaction pathway, whereas in aprotic solvents such as acetonitrile and chloroform, the absence of such stabilization alters the relative rates of nucleophilic attack at C2 and C6, leading to a reversal in selectivity, with attack at C2 being disfavored for steric and stereoelectronic reasons. The proposed reaction mechanism is shown in scheme 53.



Scheme 53. Suggested mechanism for the reaction of 3-benzoylpyridinium salt with *N*,*N*-dimethylhydrazine.

In several reported studies, pyridinium salts have been shown to act as 1,3-dielectrophiles. This reactivity enables the formation of pyrrole and indole derivatives via formal [3+3] cycloaddition processes.

In this context, Iaroshenko et al.[62] reported the synthesis of thiazocino[2,3-*b*]indoles through the reaction of thiooxindoles with substituted pyridinium salts (scheme 54).



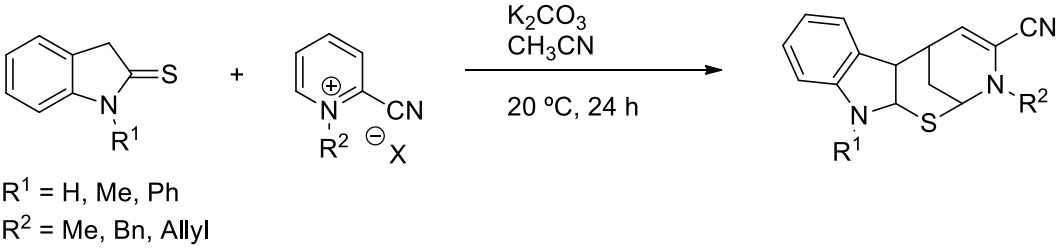
Scheme 54. Synthesis of thiazocine[2,3-*b*]indoles.

During optimization of the experimental conditions, it was observed that the presence of a base is crucial for the transformation, as no reaction was detected in its absence. The authors initially explored the reaction scope using a variety of thiooxindoles in combination with different bromide and iodide salts of 3-acylpyridinium derivatives. Under the optimized conditions, the corresponding products were obtained in good to excellent yields (56–99%) with high regioselectivity.

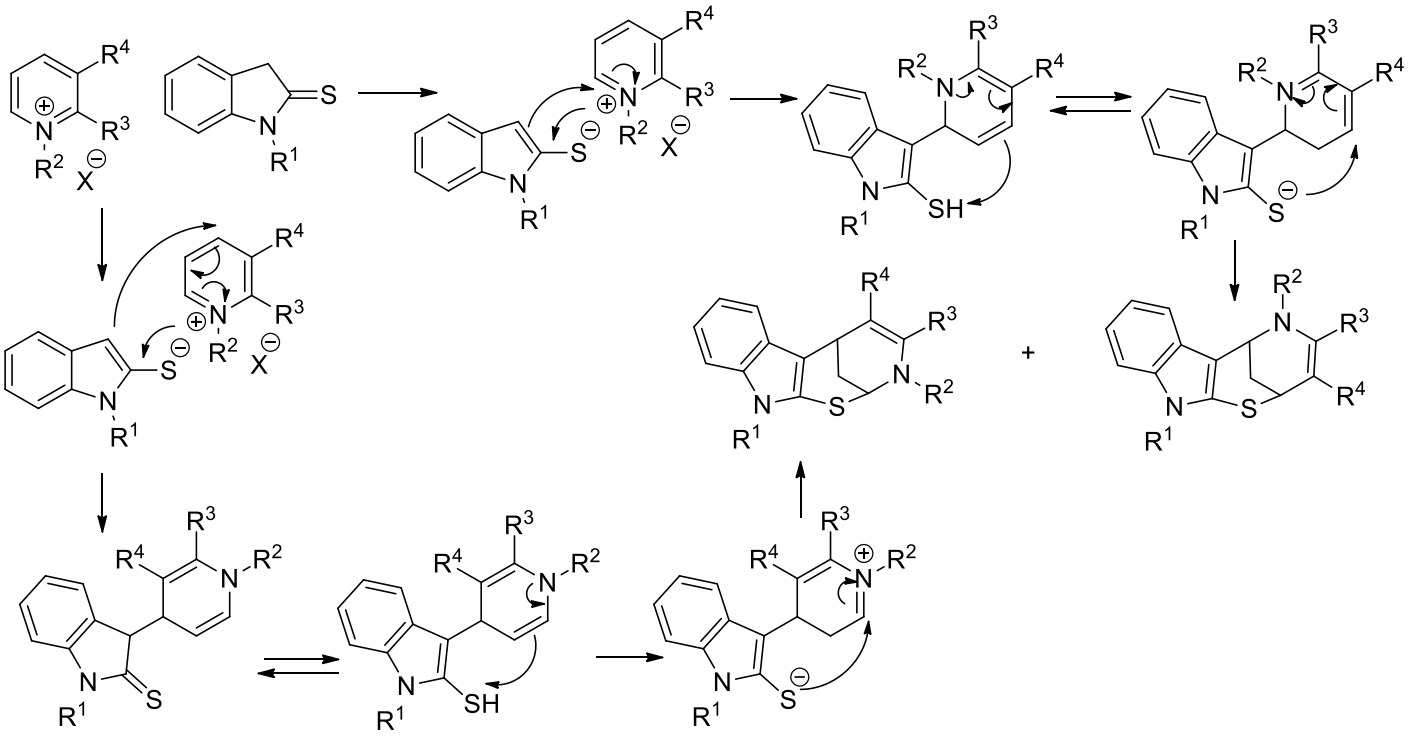
A key limitation of the methodology is the requirement for *N*-substituted thiooxindoles, which cannot undergo competitive deprotonation, thereby favoring product formation. In addition, it was found that the pyridinium salts must bear electron-withdrawing substituents to enable efficient reactivity.

In fact, the reaction between 3-cyanopyridinium salts and thiooxindoles afforded the same mixture of products in overall yields ranging from 64–88% (scheme 54, R_1 = H, Me, Ph; R_2 = Me, Bn, allyl; R_3 = H; R_4 = CN).

Finally, the reaction was extended to 2-cyanopyridinium salts. In this case, the formation of product mixtures was no longer observed, and the reaction proceeded with comparable yields (65–92%). Since the C2 position of the pyridinium ring is already substituted, nucleophilic attack occurs selectively at the C6 position, leading to a single regioisomeric outcome (scheme 55). The mechanism proposed by the authors for these reactions is presented in scheme 56.

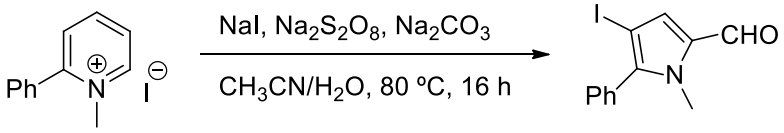


Scheme 55. Synthesis of thiazocino[2,3-*b*]indoles from 2-cyanopyridinium salts.



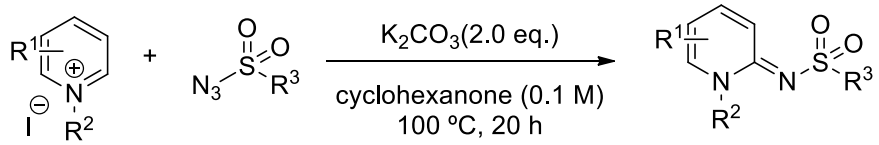
Scheme 56. A plausible mechanism for the formation of thiazocino[2,3-*b*]indoles.

Hua Chen[63] reports a cascade reaction from *N*-methyl pyridinium iodide salts to generate 4-iodopyrrole-2-carbaldehydes in the presence of sodium iodide and an oxidizing agent ($Na_2S_2O_8$). When the reaction mixture was heated at 80 ºC in acetonitrile/water with the addition of sodium carbonate, the product was isolated in good to excellent yield (scheme 57). The selective incorporation of the iodine and formyl groups in the pyrrole ring are an important asset if further chemical transformations are required.



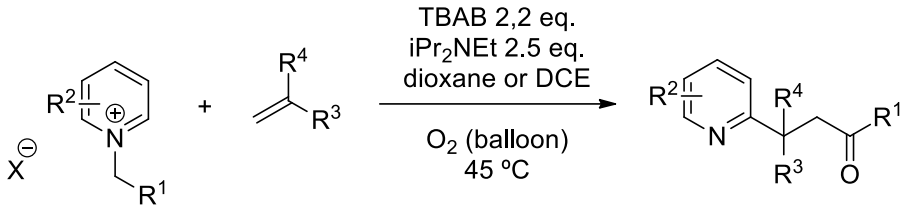
Scheme 57. Synthesis of 4-iodopyrrole-2-carbaldehydes by a cascade reaction

N-Alkyl pyridinium iodides were reacted with sulfonyl azides in the presence of base (K_2CO_3) and heating at 100 ºC using cyclohexanone as solvent (scheme 58). The work, reported by Haiyan Fu and co-workers,[64] allowed the formation of a wide range of sulfonyl iminopyridine derivatives, isolated in good to excellent yield under metal-free conditions.



Scheme 58. Synthesis of sulfonyl iminopyridines by reaction of sulfonyl azides with pyridinium salts.

Yijin Su and co-workers[65] reported a C2-selective alkylation of *N*-alkyl pyridinium salts by a three-component reaction where the pyridinium salt is combined with an alkene and O_2, usually in dioxane, at 45 ºC (scheme 59).

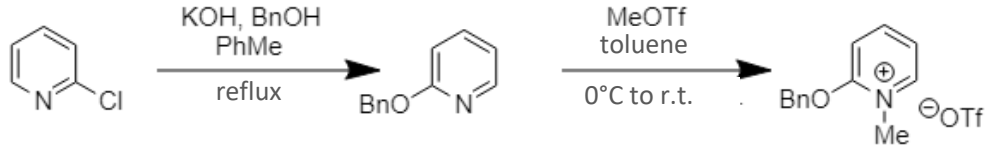


Scheme 59. C2-selective alkylation of *N*-alkyl pyridinium salts by a three-component reaction

A complex reaction mechanism was proposed, involving an intermediary cycloadduct that was isolated and further transformed into the product by a dearomative cycloaddition and rearomative ring opening oxygenation. Further studies are required to support the proposed mechanism.

Benzyl ethers are important functional units in organic synthesis, primarily employed as protecting groups due to their high stability under a wide range of reaction conditions.

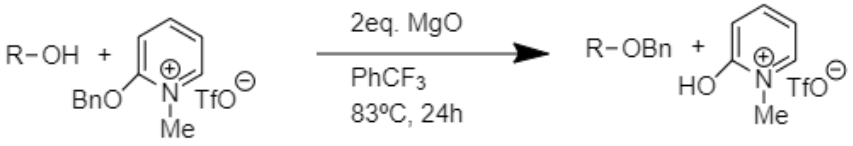
In a study by Dudley[66] 2-benzyloxy-1-methylpyridinium triflate was synthesized and evaluated as a benzyl-transfer reagent for the protection of alcohols via ether formation. The corresponding pyridinium salt was prepared through the reaction of 2-chloropyridine with benzyl alcohol, followed by alkylation with methyl triflate in toluene (scheme 60).



Scheme 60. Preparation of 2-benzyloxy-1-methylpyridinium triflate.

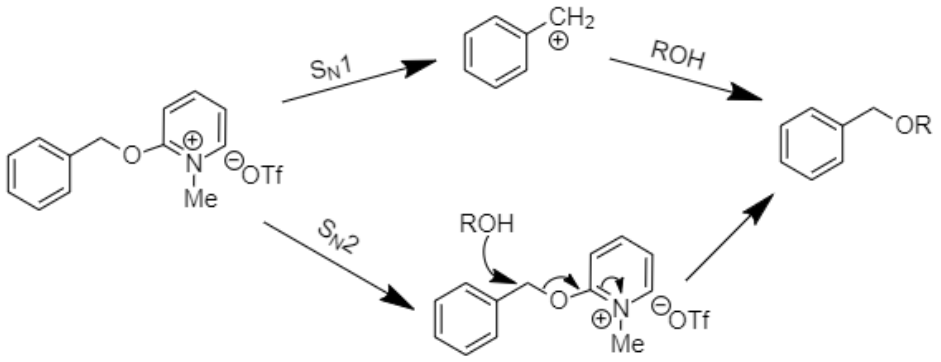
The scope of the reaction was subsequently evaluated with a range of alcohol substrates under the optimized conditions described in scheme 61. The methodology proved effective for primary, secondary, and tertiary alcohols, as well as phenols.

Primary alcohols afforded the corresponding benzyl ethers in high yields (93–95%), while secondary alcohols gave slightly lower yields (83–88%). In contrast, tertiary alcohols and phenols showed more modest conversions, with yields ranging from 44–80%. The authors proposed that the transformation proceeds via an S_N1-type mechanism. Although no kinetic studies were performed, the observation of solvent alkylation by-products when the reaction was conducted in toluene supports the intermediacy of a benzyl cation species.



Scheme 61. The use of 2-benzyloxy-1-methylpyridinium triflate as a benzyl-transfer reagent for the protection of alcohols.

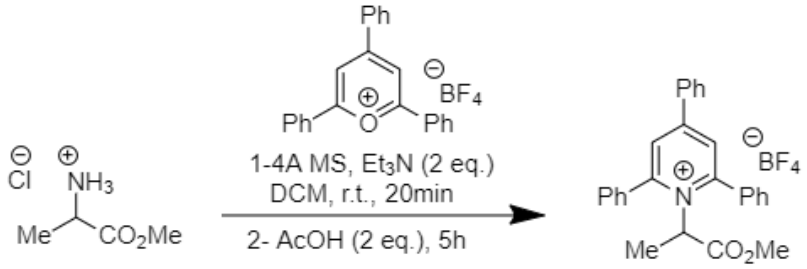
Regarding mechanistic considerations, the authors proposed that the formation of benzyl ethers may proceed through either S_N1 or S_N2 pathways, as illustrated in scheme 62.



Scheme 62. S_N1 *vs* S_N2 mechanistic observations for the synthesis of benzyl ethers.

Pyridinium salts have also been shown to be effective intermediates in metal-catalyzed deaminative arylation reactions of amino acids and their derivatives. Watson et al.[67] reported a synthetic approach based on a Suzuki–Miyaura-type coupling involving the reaction of a pyridinium salt with an arylboroxine.

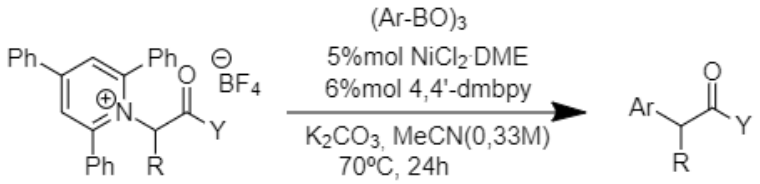
In this work, the required pyridinium intermediate was generated from an amino ester via reaction with 2,4,6-triphenylpyrylium tetrafluoroborate. The transformation was carried out in dichloromethane at room temperature in the presence of two equivalents of triethylamine and 4 Å molecular sieves, followed by neutralization with acetic acid (scheme 63).



Scheme 63. Synthesis of a pyridinium salt bearing an amino acid derivative through the ring nitrogen.

The pyridinium salt bearing the amino acid derivative through the amine functionality was efficiently converted into the corresponding α-aryl ester or amide via reaction with a range of arylboroxines. The optimized protocol employed a nickel(II) chloride catalyst in ethylene glycol dimethyl ether, in combination with the 4,4′-dimethyl-2,2′-bipyridine ligand (scheme 64).

The highest yields were obtained using arylboroxines, although boronic acids could also be employed when 4 Å molecular sieves were present to remove water generated *in situ*, thereby maintaining reaction efficiency. In addition, the presence of a base (K_2CO_3) and heating at 70–80 °C in acetonitrile were required to promote the transformation. Under these optimized conditions, the desired products were isolated in moderate to good yields (42–87%).



Scheme 64. Deaminative arylation reaction of amino acids and derivatives.

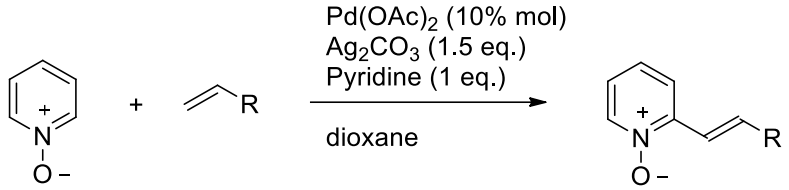
3.2 Reactivity of pyridine *N*-oxides

At the beginning of the 21st century, a new synthetic strategy for the preparation of functionalized pyridines was developed, starting from pyridine *N*-oxides in metal-catalyzed transformations. This approach is based on the enhanced reactivity and regioselectivity typically exhibited by pyridine *N*-oxides in such reactions.

3.2.1-Alkenylation. Substituted pyridines can also be accessed from halogenated pyridines; however, this approach typically requires multistep sequences and may be associated with undesired side reactions. In this context, Chang et al.[68] developed an alternative method for the synthesis of 2-substituted pyridines starting from pyridine *N*-oxides, inspired by the Fujiwara–Moritani reaction, in which alkenes are coupled directly to aromatic systems.

In a first approach, a range of alkenes was reacted with pyridine *N*-oxides to incorporate the alkenyl unit at the C2 position of the pyridine ring, affording the corresponding products in yields of 53–91%. In a complementary study, the reverse substrate scope was investigated using various pyridine *N*-oxides with a common olefin (*tert*-butyl acrylate), giving products in 63–88% yield. In this case, *N*-oxides bearing a substituent at C2 underwent functionalization preferentially at the C6 position.

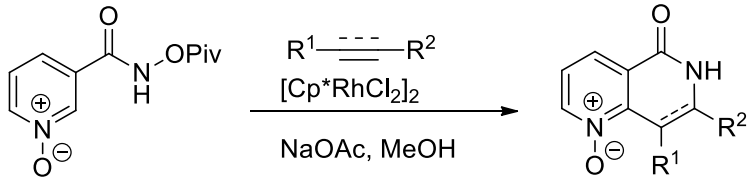
In both approaches, the alkenylation reactions were performed using palladium acetate and silver carbonate in 1,4-dioxane at 100 °C for 12 h (scheme 65).



Scheme 65. Alkenylation of pyridine *N*-oxides.

More recently, the development of rhodium-catalyzed [4+2] annulation reactions between carboxamides and alkynes has provided an efficient strategy for the synthesis of heterocycles bearing 2-pyridone motifs.

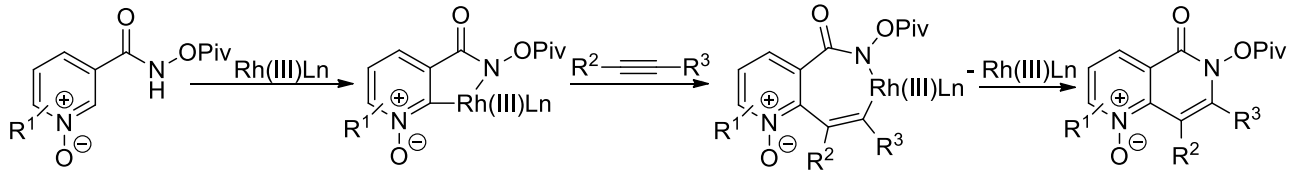
In Huckins' study[69] a nicotinamide *N*-oxide was employed as the starting material, and its reactivity toward alkenes and alkynes was investigated. The transformation proceeded with high regioselectivity in the presence of a low loading of rhodium catalyst (2 mol%). The optimized conditions required sodium acetate as base and methanol as solvent. Under these conditions, alkyne coupling occurred at room temperature (20 °C), affording the corresponding products in good to excellent yields (64–92%) (scheme 66).



Scheme 66. Reaction of nicotinamide *N*-oxide with alkynes and alkenes.

For the corresponding reaction with alkenes, performed under analogous conditions, higher temperatures (65 °C) were required to achieve efficient conversion. Under these conditions, the desired products were obtained in moderate yields ranging from 46–63% (scheme 66).

The reaction mechanism, depicted in scheme 67, highlights the role of the rhodium catalyst in the selective activation of the C2–H bond of nicotinamide *N*-oxide. This activation enables regioselective insertion of alkenes and alkynes, ultimately leading to the formation of naphthyridinone derivatives.

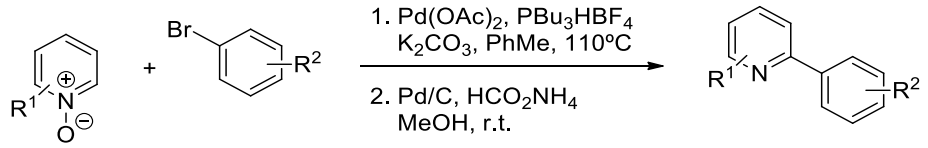


Scheme 67. Proposed mechanism for the rhodium-catalyzed reaction of nicotinamide *N*-oxide with an alkyne, based on deuterium labeling studies.

3.2.2 Arylation. In 2005, Fagnou et al.[70] reported an economical method for the synthesis of 2-arylpyridines via direct arylation of pyridine *N*-oxides. This transformation proceeded with complete selectivity for the C2 position of the pyridine ring when aryl bromides were employed as coupling partners.

Under the optimized conditions shown in scheme 68, a broad range of aryl bromides was successfully coupled with pyridine *N*-oxide, affording the corresponding products in good to excellent yields (74–97%). However, the use of stoichiometric limitations of the *N*-oxide influenced the reaction efficiency; when only 1 equivalent was employed, the yield decreased to 45%.

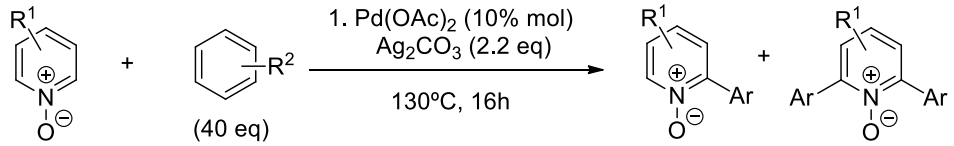
The resulting *N*-oxide intermediates were subsequently reduced to the corresponding 2-arylpyridines using ammonium formate in methanol at room temperature in the presence of Pd/C as catalyst.



Scheme 68. Synthesis of 2-arylpyridines from pyridine *N*-oxides.

In Chang's study[68] the reaction conditions for the arylation of pyridine *N*-oxides with arenes were further optimized, as shown in scheme 69. The procedure was analogous to that employed for the alkenylation reactions, requiring elevated temperatures and extended reaction times (130 °C for 16 h).

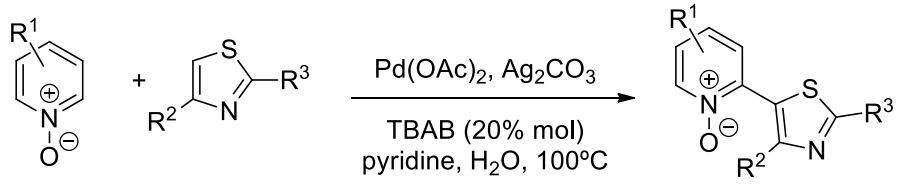
A variety of pyridine *N*-oxides were reacted with benzene, as well as with several mono- and disubstituted benzene derivatives. In all cases, mixtures of mono- and di-arylated products were obtained. The reactions proceeded in moderate to good yields (40–79%), with the mono-arylated product predominating, typically in ratios ranging from 2.5:1 to 20:1. In certain cases, complete selectivity for the mono-arylated product was observed, particularly when substitution at the C2 position of the pyridine ring was present.



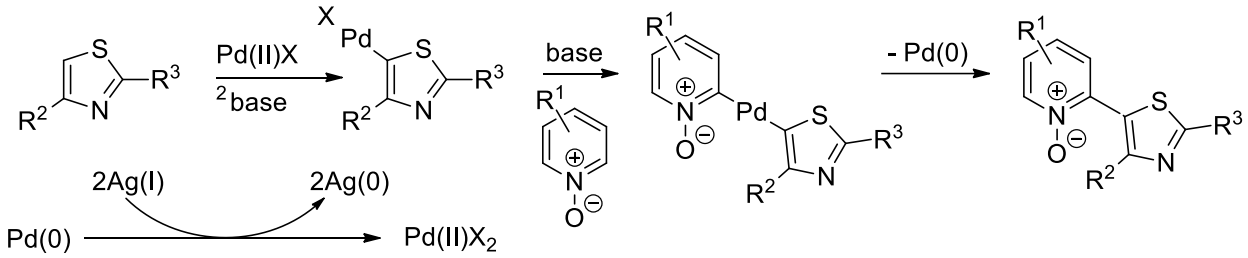
Scheme 69. Arylation reaction of a pyridine *N*-oxide.

Willis and Smith[71] extended this type of transformation to reactions involving thiazoles in aqueous medium. Under the optimized conditions shown in scheme 70, it was established that tetra-n-butylammonium bromide (TBAB) is essential for the reaction to proceed efficiently.

The process was carried out using a range of pyridine *N*-oxides and dimethyl thiazole, affording the corresponding products in moderate to good yields (58–77%). However, the use of halogenated *N*-oxide substrates resulted in significantly reduced yields (26–31%). This study also demonstrated a broad substrate scope with respect to the thiazole component, which tolerated a variety of substituent groups. The mechanism proposed for this reaction is presented in scheme 71.



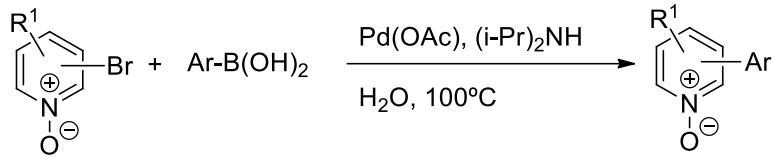
Scheme 70. Reaction of pyridine *N*-oxides with thiazoles.



Scheme 71. Proposed mechanism for the reaction of pyridine *N*-oxides with thiazoles.

The reaction of pyridine *N*-oxides with arylboron compounds has also been investigated. Liu et al.[72] employed arylboronic acids in aqueous medium to promote the arylation of pyridine *N*-oxides. The use of water as solvent offers several advantages, including its low cost, availability, and non-toxic nature.

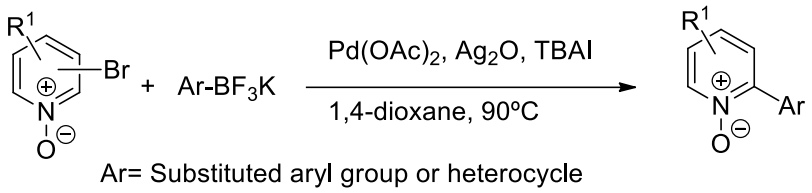
Under the optimized conditions shown in scheme 72, a range of brominated pyridine *N*-oxides was evaluated, affording the corresponding products in yields ranging from 35–96%.



Scheme 72. Arylation of pyridine *N*-oxides with arylboronic acids.

In the study by Li et al.[73] several 2-arylpyridines were synthesized from the corresponding *N*-oxides via reaction with potassium aryltrifluoroborates under palladium catalysis in the presence of Ag_2O.

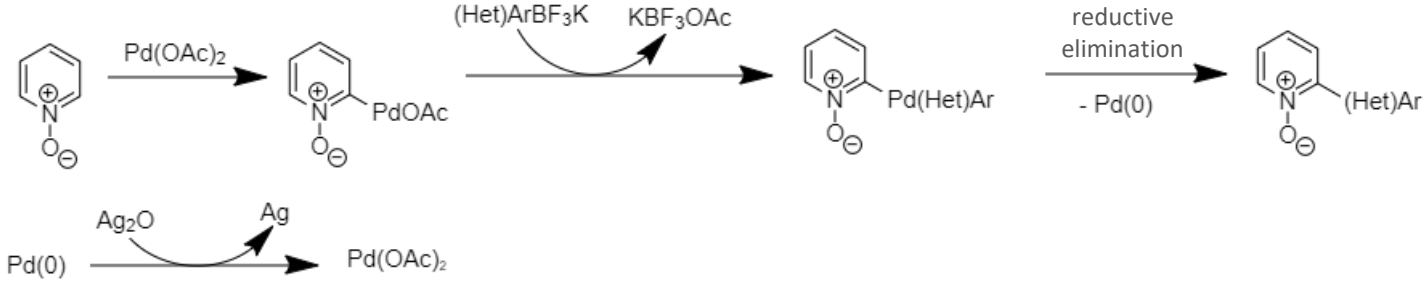
Under the optimized conditions shown in scheme 73 (where TBAI = tetrabutylammonium iodide), the reaction between pyridine *N*-oxide and a broad range of potassium aryltrifluoroborates was successfully carried out.



Scheme 73. Arylation of pyridine *N*-oxides with aryl potassium trifluoroborate salts.

Based on the observed yields (51–98%), it was concluded that this methodology enables the incorporation of a wide range of substituted arylborates into the pyridine framework, including substrates bearing both electron-donating and electron-withdrawing groups, as well as heteroaromatic moieties.

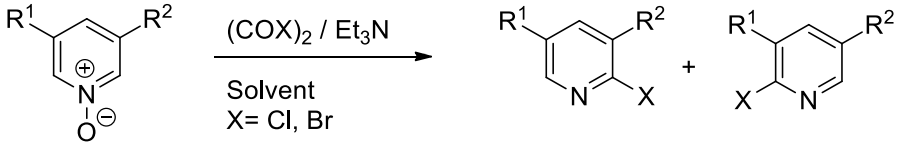
On this basis, the reaction between potassium phenyltrifluoroborate and various pyridine *N*-oxides was further evaluated, affording the corresponding products in comparable yields (56–98%). In cases where the *N*-oxide substrate contained a substituent at the C3 position, functionalization occurred selectively at the C6 position. The proposed reaction mechanism is presented in scheme 74.



Scheme 74. Proposed mechanism for the reaction of pyridine *N*-oxides with aryl potassium trifluoroborate salts.

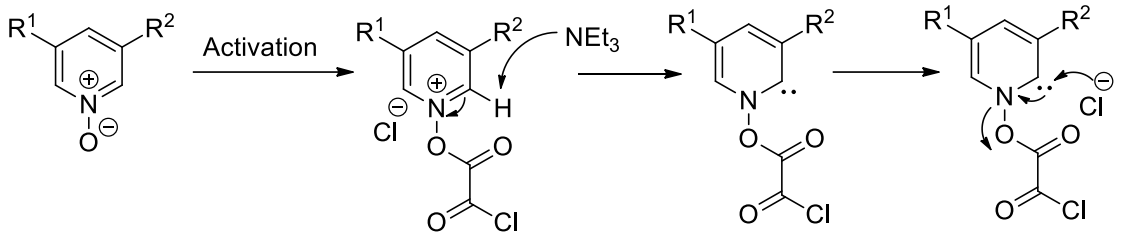
Substituted pyridine *N*-oxides can serve as precursors for the selective formation of halogenated pyridines at either the C2 or C6 positions. Chen et al.[74] developed a simple and cost-effective method for the synthesis of 2-chloro- and 2-bromo-3,5-disubstituted pyridines from the corresponding 3,5-disubstituted pyridinium *N*-oxides via reaction with oxalyl chloride or oxalyl bromide.

The transformation was carried out at 0 °C in the presence of triethylamine, using dichloromethane or dibromomethane (DCM/DBM) as solvent, and the products were isolated after 30 min. A broad range of *N*-oxide substrates, including both electron-rich and electron-poor derivatives, was evaluated. In most cases, mixtures of regioisomers were obtained due to competing substitution at the C2 and C6 positions, with the outcome depending on the substitution pattern at C3 and C5 of the *N*-oxide ring. In some cases, exclusive formation of a single product was observed (scheme 75). In reactions employing oxalyl chloride in dichloromethane, monochlorinated pyridines were isolated in overall yields of 75–94%.



Scheme 75. Introduction of a halogen atom into the pyridine *N*-oxide ring to prepare 2-chloropyridines.

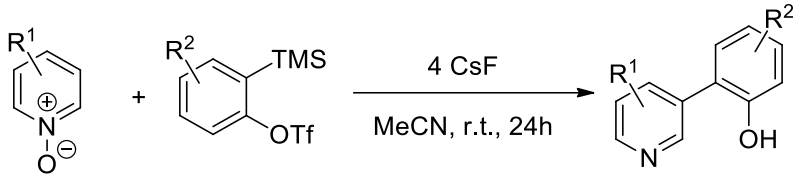
This procedure was also applied using oxalyl bromide in dibromomethane, affording the corresponding monobrominated pyridines in comparable yields (73–86%). The proposed reaction mechanism is shown in scheme 76.



Scheme 76. Proposed mechanism for the *ortho*-chlorination reaction of pyridine *N*-oxides.

Larock[1] reported the synthesis of 3-(2-hydroxyphenyl)pyridines from the corresponding pyridine *N*-oxides and silylaryl triflates via a CsF-catalyzed reaction in acetonitrile.

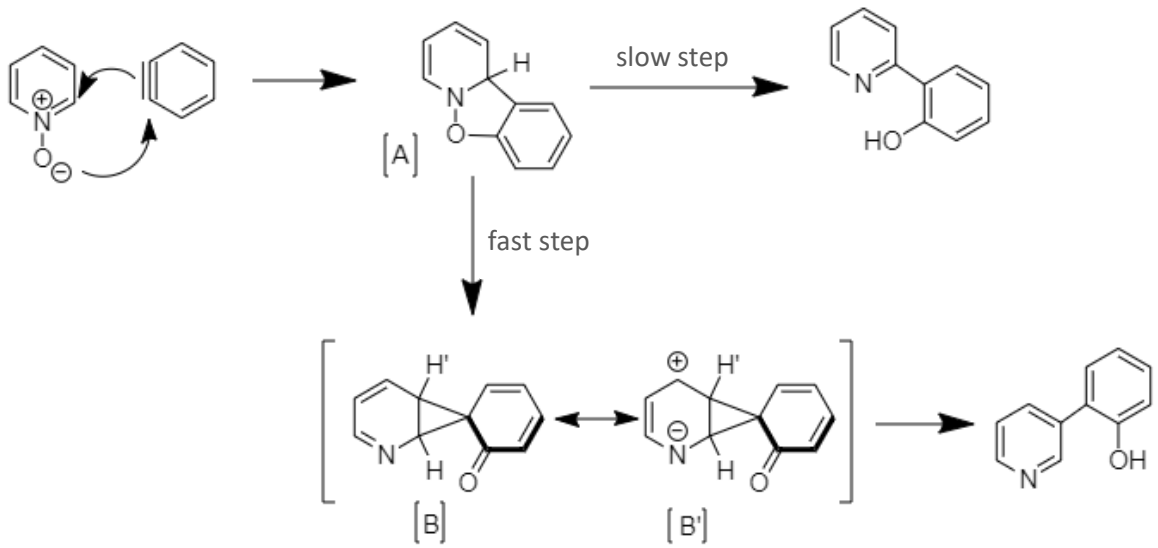
In this methodology, a variety of *N*-oxide substrates were employed, including unsubstituted derivatives as well as compounds substituted at the 2-, 4-, and 6-positions. A broad range of silylaryl triflates was also evaluated, encompassing both electron-rich and electron-poor systems, as well as symmetric and asymmetric derivatives. The corresponding products were obtained in good to excellent yields (75–92%) (scheme 77).



Scheme 77. Synthesis of 3-(2-hydroxyphenyl)pyridines.

To investigate the regioselectivity of these transformations, asymmetric silylaryl triflates were employed, leading to the formation of product mixtures arising from the two possible 1,3-dipolar cycloaddition pathways. A similar experiment was performed using 2-methylpyridine *N*-oxide as the asymmetric substrate. In this case, the major product was the pyridine derivative substituted at the C5 position, obtained in an overall yield of 81%. This outcome indicates that the presence of the methyl substituent exerts a significant steric influence on the reaction pathway.

The proposed mechanism involves a 1,3-dipolar cycloaddition to a benzyne intermediate, generating an initial adduct that rapidly undergoes rearrangement to afford a cyclopropane-containing intermediate. The authors suggest that the B’ resonance structure, characterized by charge separation, accounts for the increased acidity of the H’ proton relative to the H proton. Consequently, preferential deprotonation at H’ facilitates proton transfer to the carbonyl oxygen, ultimately leading to formation of the major isolated product (scheme 78).



Scheme 78. Proposed mechanism for the synthesis of 3-(2-hydroxyphenyl)pyridines.

3.3 Reactivity of pyridinium ylides

Pyridinium ylides, generated from pyridinium salts upon treatment with base, have been widely employed as key intermediates in the synthesis of diverse molecular frameworks. The stability of these species is attributed to the multiple resonance structures, which demonstrate delocalization of the negative charge either within the heteroaromatic ring or onto the exocyclic R^1 and R^2 substituents, typically electron-withdrawing groups that further stabilize the ylide system (figure 2).[6]

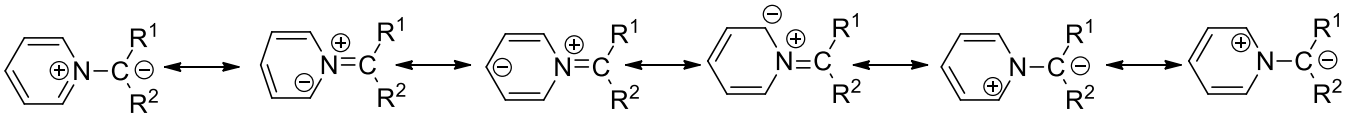
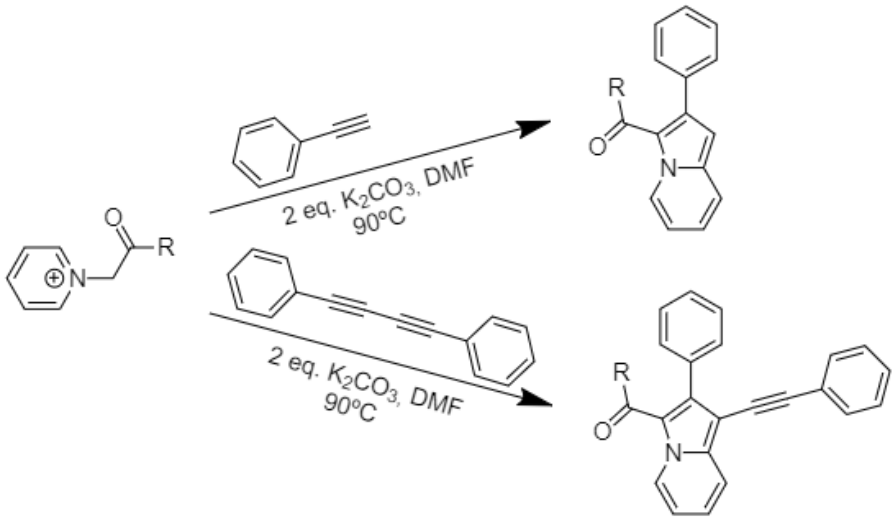


Figure 2. Resonance structures of pyridinium ylides.

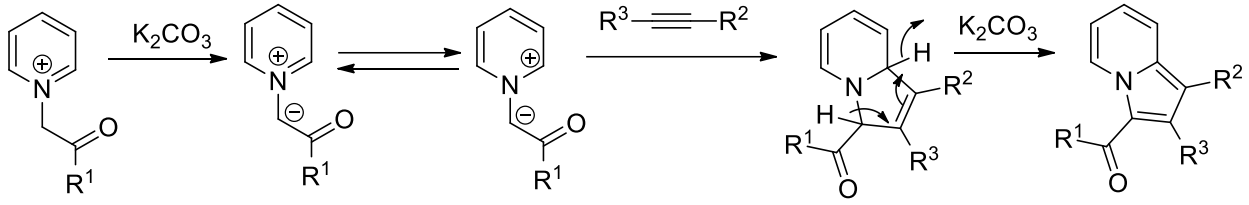
Given the significant biological relevance of indolizines, this section will address the discussion of their synthesis that has been performed through a variety of synthetic methodologies.

In this context, Shang et al.[75] demonstrated an efficient metal-free approach based on a 1,3-dipolar cycloaddition between a pyridinium ylide and an alkyne under basic conditions. In this transformation, deprotonation of the pyridinium precursor occurs at the position activated by the adjacent electron-withdrawing carbonyl group and the positively charged nitrogen atom, generating the corresponding ylide as the reactive 1,3-dipole. The process proceeds without the need for metallic catalysis, highlighting its operational simplicity and synthetic efficiency.

Using this strategy, the authors successfully prepared di- and tri-substituted indolizines in generally excellent yields (78–93%). However, substrates bearing strongly electron-withdrawing substituents led to a marked decrease in reaction efficiency, affording only trace amounts to moderate yields (0–40%) (scheme 79). The proposed reaction mechanism is shown in scheme 80.



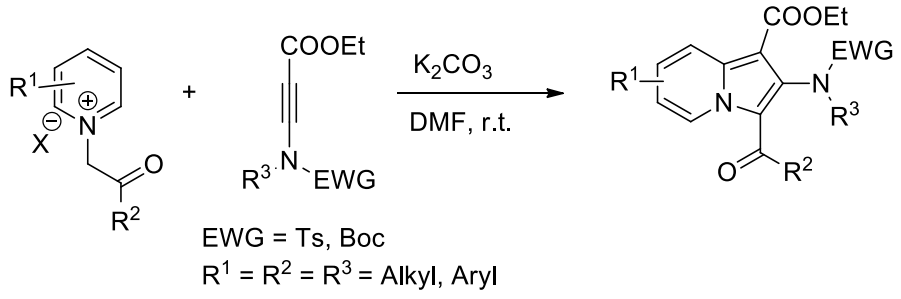
Scheme 79. Synthesis of di- and tri-substituted indolizines.



Scheme 80. Proposed mechanism for the synthesis of di- and tri-substituted indolizines

This outcome established the transformation as an important synthetic route toward indolizine scaffolds and stimulated further investigations into the preparation of highly functionalized derivatives. Ongoing efforts have focused on the development of more efficient and economical approaches to access these compounds from simple and readily available starting materials.[76]

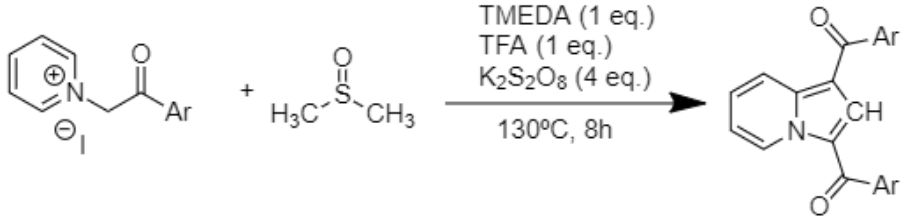
Meyer[77] reported the synthesis of functionalized 2-aminoindolizines from electron-deficient inamides, which are stabilized by either ester or ketone substituents. Comparable yields were obtained for both classes of inamides, ranging from 52–70% and 45–83%, respectively (scheme 81).



Scheme 81. Synthesis of indolizines by reaction of pyridinium ylides and inamides.

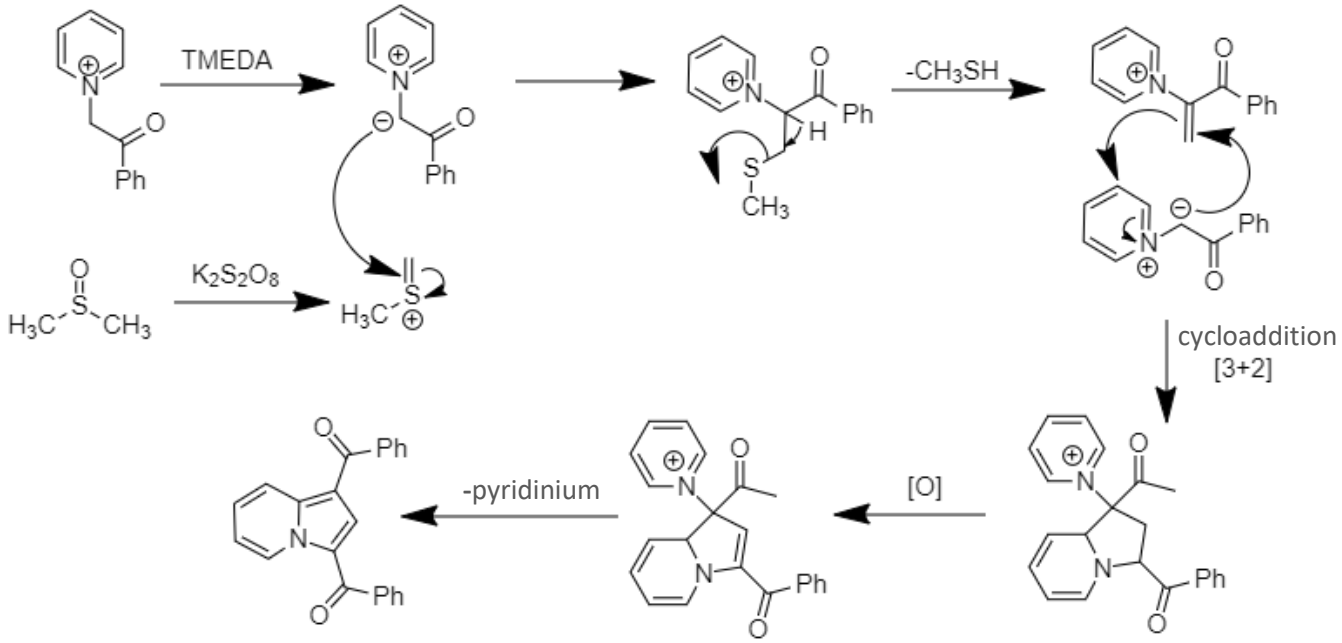
Shu et al.[76] reported the synthesis of indolizines using a combination of trifluoroacetic acid (TFA), trimethylethylenediamine (TMEDA), potassium thiosulfate, and dimethyl sulfoxide (DMSO), which also served as both solvent and carbon source.

In this study, a cascade sequence involving oxidation and cycloaddition steps occurred, ultimately affording the desired indolizine products in good yields. Notably, DMSO played a dual role in the reaction system, functioning both as reaction medium and as a carbon source incorporated into the final heterocyclic framework (scheme 82).



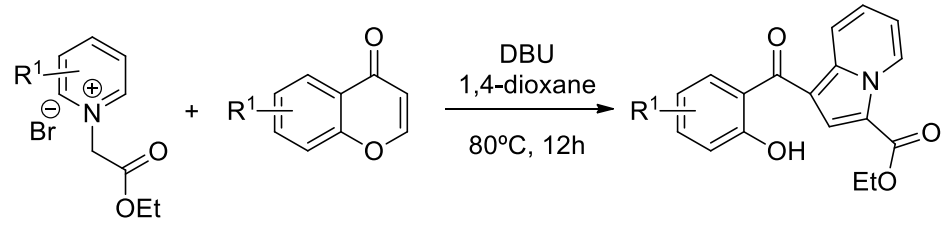
Scheme 82. Synthesis of indolizines in a reaction mediated by DMSO.

The products obtained by varying the substituent in the aryl group were isolated with yields ranging from 65 to 92%. The proposed mechanism for this reaction is shown in scheme 83.



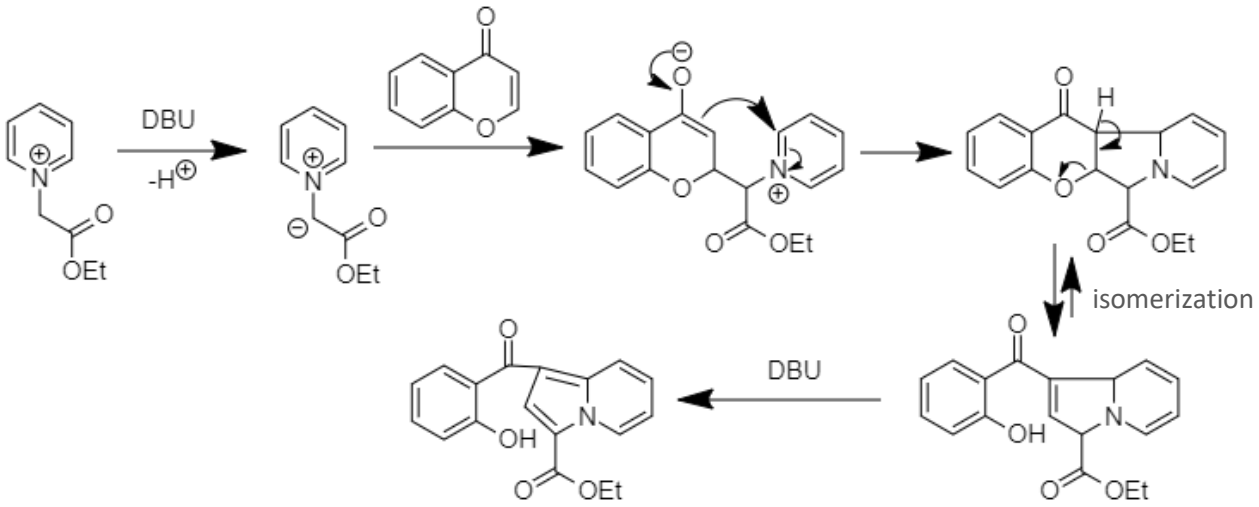
Scheme 83. Possible mechanism for the DMSO-mediated synthesis of indolizines.

Dong and Huang[78] reported the synthesis of novel indolizine derivatives via the addition of pyridinium ylides to a range of chromones (scheme 84). The corresponding products were obtained in moderate to good yields (60–82%). These results suggest that this methodology constitutes a valuable synthetic route for the preparation of indolizines bearing phenolic functionalities.



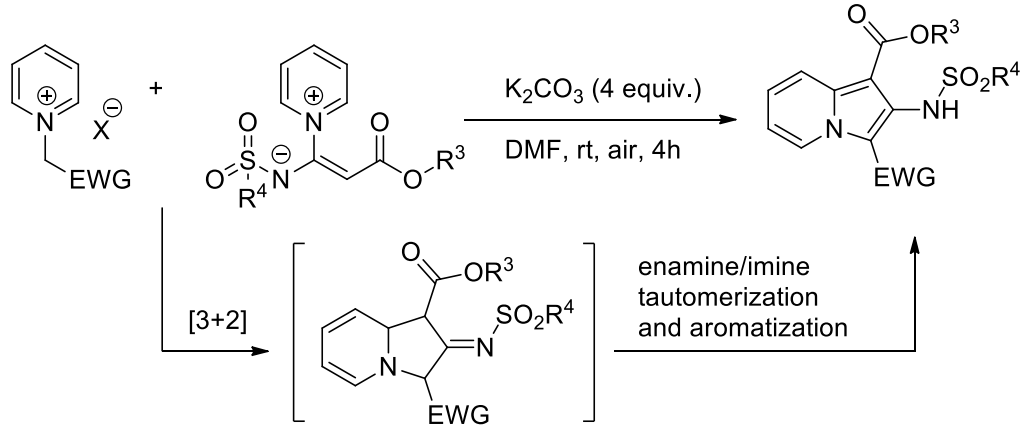
Scheme 84. Synthesis of indolizines by reaction between chromones and pyridinium ylides.

The reaction is proposed to proceed via an initial 1,3-dipolar cycloaddition of the pyridinium ylide to the chromone framework, followed by subsequent ring opening of the intermediate adduct. This sequence ultimately leads to the formation of the indolizine scaffold bearing a phenolic substituent. The proposed mechanistic pathway is illustrated in scheme 85.



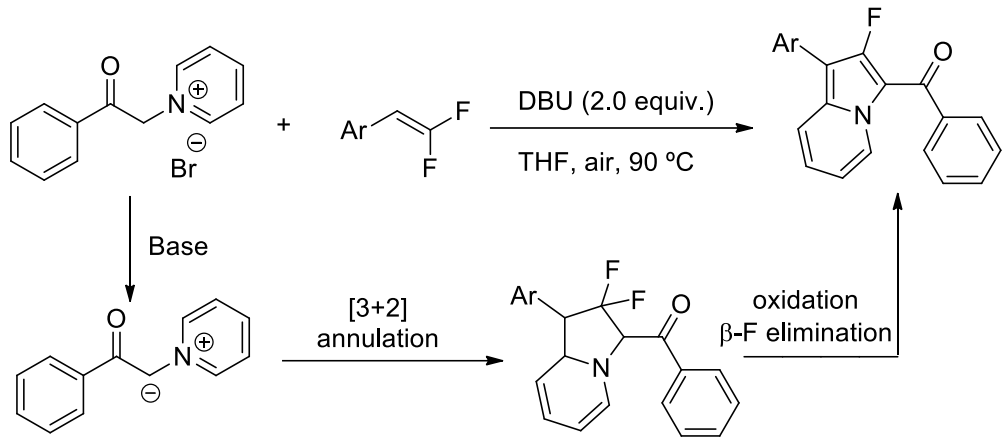
Scheme 85. Plausible reaction mechanism for the synthesis of indolizines from chromones and pyridinium ylides.

Balalaie[79] reported the synthesis of functionalized indolizines by a 1,3-dipolar cycloaddition of zwitterionic ketenimines to pyridinium salts (scheme 86). The synthesis does not require the use of metal catalysis or the presence of an oxidizing agent and occurs at room temperature leading to the product in moderate to good yields. The reaction involves an intramolecular [3+2] cycloaddition, followed by enamine/imine tautomerization and aromatization, in a one-step process.



Scheme 86. Synthesis of functionalized indolizines by a 1,3-dipolar cycloaddition of zwitterionic ketenimines to pyridinium salts.

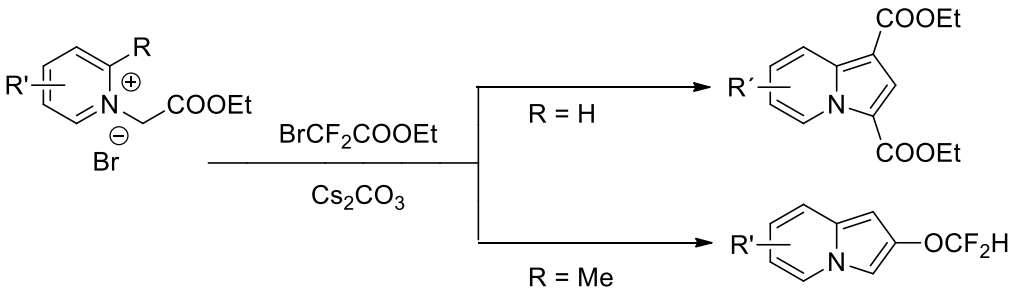
Jin-Bao Peng and co-workers[80] developed a synthetic approach to the synthesis of highly substituted 2-fluoroindolizines by an oxidative [3+2] annulation of pyridinium salts with *gem*-e-fluoroalkenes (scheme 87). The reaction was performed in THF, at 90 °C and using DBU as base.



Scheme 87. Synthesis of 2-fluoroindolizines by an oxidative [3+2] annulation of pyridinium salts with *gem*-e-fluoroalkenes.

A plausible reaction mechanism may involve deprotonation of the pyridinium salt upon treatment with base, generating pyridinium ylide that participated in the [3+2] annulation with the alkene. A stepwise anionic mechanism or a concerted pathway followed by β-F elimination and oxidative aromatization lead to the final 2-fluoroindolizines in good to excellent yield.

Another approach for the synthesis of indolizines, reported by G. Wang,[81] uses the reaction of the pyridinium salts with $BrCF_2COOEt$ in the presence of base (Cs_2CO_3). The substitution pattern in the product is determined by the α-substitution in the pyridine nucleus. The presence of a proton or a methyl group results in different reaction pathways with the regioselective formation of 1,3-dissubstituted or 2-substituted indolizines (scheme 88)



Scheme 88. Synthesis of indolizines from the reaction of the pyridinium salts with $BrCF_2COOEt$.

4. Conclusions

This work highlights the existence of multiple synthetic approaches for the preparation of pyridinium salts. These species can be obtained from pyridine through alkylation, arylation, or acylation reactions. Alternatively, they may also be generated via condensation of amines with furfural, as well as through transformations involving Zincke salts or pyrylium salts. Additional routes include their formation via the Mitsunobu reaction and the Chichibabin reaction.

Owing to their enhanced reactivity relative to the corresponding parent pyridines, pyridinium salts serve as versatile intermediates in a broad range of transformations leading to structurally diverse compounds of

significant biological relevance. Consequently, their study has attracted considerable attention in synthetic chemistry.

The reactivity of pyridinium salts is closely associated with delocalization of the positive charge over the nitrogen atom and the *ortho*- and *para*-positions of the heteroaromatic ring, thereby facilitating nucleophilic attack at these positions. Representative transformations include reactions with Grignard reagents, reduction processes, and the synthesis of conjugated dienes bearing terminal aldehyde functionalities, among others. 4-methoxypyridinium salts have been shown to afford 2,3-dihydropyridones through nucleophilic addition followed by acid-catalyzed hydrolysis of the alkoxyl group. These 2,3-dihydropyridone scaffolds constitute valuable intermediates for a wide range of further chemical transformations.

Although the synthesis of *N*-oxides has not been extensively discussed, aspects of their reactivity with alkenes and alkynes, as well as with aryl halides leading to ring arylation, are also considered. Notably, several of these transformations are initiated by 1,3-dipolar cycloaddition processes and may proceed through unexpected rearrangement pathways.

Overall, the surveyed literature demonstrates that the diverse reactivity of pyridinium salts enables access to a wide variety of molecular architectures and supports the design of novel compounds, including fused heterocyclic ring systems.

Acknowledgements

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