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Aromatic *N*-Oxide rearrangements in modern organic synthesis

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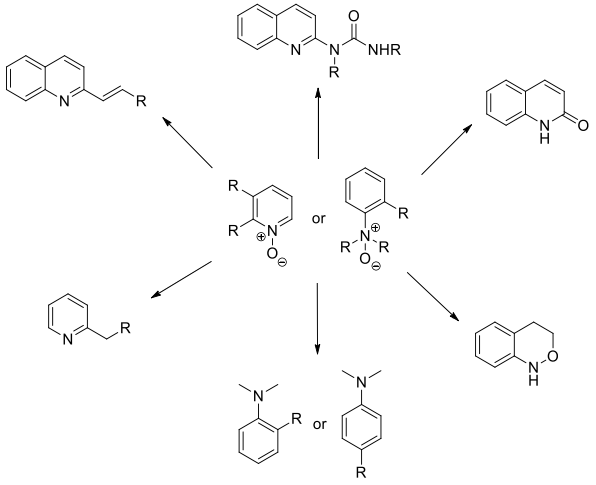
Dedicated to Professor Teresa Pinho e Melo, as a celebration of her achievements and contributions to the field of heterocyclic and organic chemistry

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Abstract

Rearrangements of aromatic *N*-oxides represent a versatile and significant class of transformations in heterocyclic and synthetic organic chemistry, offering efficient routes to the regioselective functionalization and skeletal diversification of nitrogen-containing aromatic compounds. This review outlines the fundamental mechanistic features, scope, and synthetic applications of the most prominent *N*-oxide rearrangements, including the Boekelheide and Meisenheimer rearrangements, as well as related migratory processes. Emphasis is placed on the synthetic utility of these transformations in the preparation of structurally diverse molecules, especially pharmaceuticals, natural products, and functional materials. Collectively, these examples highlight the enduring relevance of aromatic *N*-oxide rearrangements as powerful tools in modern organic synthesis.



Keywords: Aromatic *N*-oxide, rearrangement, heterocyclic chemistry, regioselective, azaheterocycles

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1. Introduction

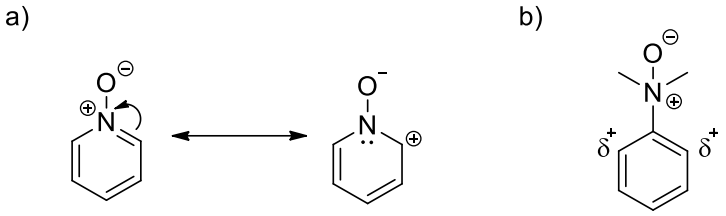
N-oxides are a class of organic compounds containing a nitrogen–oxygen bond formally generated by oxidation of tertiary amines or nitrogen-containing heteroaromatic systems such as pyridines, quinolines, and isoquinolines.[1] This oxidation can happen by reaction with a peracid (e.g. *m*-CPBA) or hydrogen peroxide.[2,3] The N-O bond that is formed is dative, since both electrons are given by the nitrogen atom.[4] This gives a formal negative charge to the oxygen, while the nitrogen is formally positive. This, in turn, gives *N*-oxides several unique properties.[5] They are highly polar, which enables the formation of highly stable hydrogen bonds. This, paired with the zwitterionic character of the N-O bond, is translated in increased solubility in aqueous medium, a desired trait in compounds such as highly lipophilic drug candidates. They can also be used to design hypoxia-activated prodrugs, since they can be reduced *in vivo* by metabolism. *N*-oxides also find applications in industrial chemistry. One notable example is the use of *N*-methylmorpholine *N*-oxide (NMMO) in the industrial production of the semi-synthetic fiber Lyocell.[6] NMMO can directly dissolve cellulose by forming strong hydrogen-bonding interactions with the polymer, making it an effective solvent for this process.

Another important aspect of *N*-oxides is their distinctive reactivity. Aromatic *N*-oxides are particularly valuable as internal oxidants and directing groups, enabling the selective functionalization of aromatic rings, predominantly at the *ortho* position.[7,8] Such transformations can be achieved under a variety of catalytic conditions.[1,9] In addition, aromatic *N*-oxides undergo numerous rearrangement reactions in which the N–O bond is typically reduced while a new functional group is introduced at the *ortho* position or an existing ortho alkyl substituent is modified.[10–12] These reactivity patterns arise from the electronic structure of the *N*-oxide functionality. Delocalization of the positive charge on nitrogen over the aromatic system stabilizes the cationic center while increasing the negative charge density on oxygen, thereby enhancing its nucleophilicity. Simultaneously, charge redistribution generates increased electrophilic character at the C2 position, rendering it susceptible to nucleophilic attack (Scheme 1).[9,13] Consequently, *N*-oxides readily react with electrophiles and, through a range of rearrangement pathways, provide access to C2-substituted products. Owing to this unique combination of directing ability and synthetic versatility, aromatic *N*-oxides constitute highly valuable intermediates for the synthesis of diverse substituted aromatic compounds.

Rearrangements are a fundamental class of organic transformations in which the connectivity of a molecule is reorganized through the migration of atoms, groups, or bonds, leading, in most cases, to the formation of structural isomers. These processes often proceed through reactive intermediates and generally lead to thermodynamically more stable products. In the context of aromatic *N*-oxides, a wide variety of

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rearrangement reactions have been described, many of which can be rationalized by ionic, radical, or concerted mechanisms, with experimental evidence supporting each of these pathways. Accordingly, this review focuses on the principal rearrangements involving aromatic *N*-oxides, examining their mechanistic details, scope and synthetic applications.



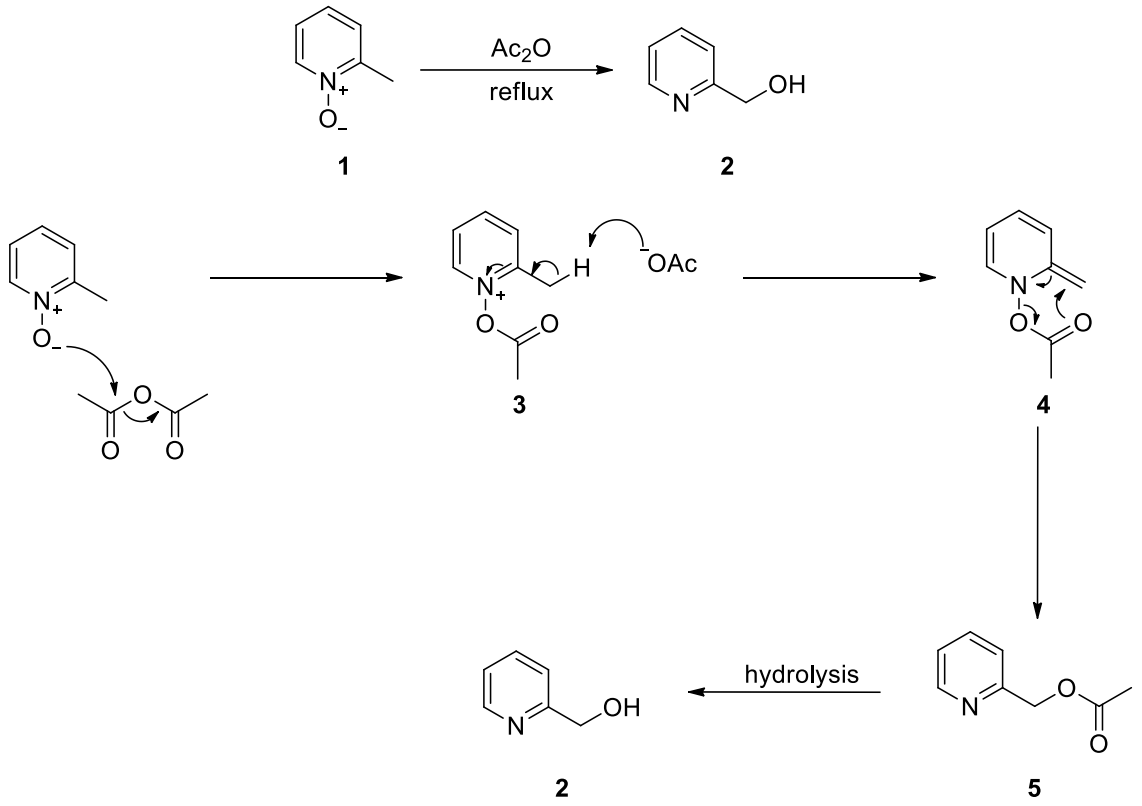
Scheme 1. Activation of aromatic *N*-oxides for nucleophilic substitution at C2: a) by resonance in pyridine *N*-oxides and other similar systems; b) by inductive effect in aniline *N*-oxides.

2. Boekelheide rearrangement

Nitrogen-containing heterocycles are omnipresent in biologically active molecules. In particular, pyridine is regarded as a privileged building block in medicinal chemistry. Just in the period between 2013 and 2023, 54 new FDA-approved drugs contained a pyridine moiety.[14] Furthermore, these aromatic rings are also applied in coordination chemistry, thanks to their unique electronic properties.[15] As such, synthetic methods that allow for the modification and diversification of pyridine rings are of vital importance.[11]

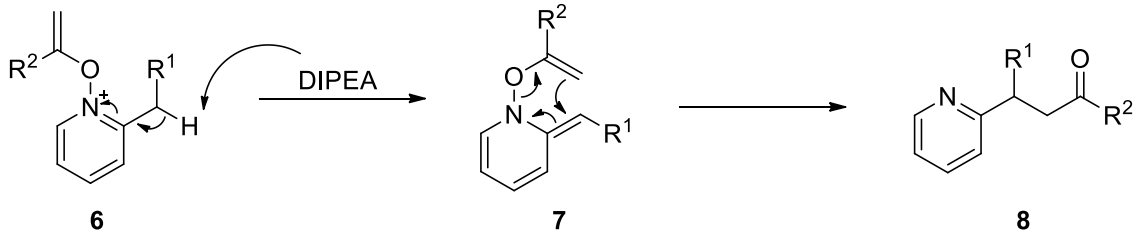
One such method is found in the Boekelheide rearrangement. It was first reported in 1953, and was described as a [3,3]-sigmatropic rearrangement of 2-picoline *N*-oxide to pyridin-2-ylmethyl acetate, in the presence of acetic anhydride, followed by hydrolysis to give pyridin-2-ylmethanol (Scheme 2). The reaction was actually reported by three different research groups at the latter part of 1953: by Boekelheide's group (from whom the reaction was named),[16] by Kobayashi's group,[17] and by Bullitt's group.[18] After its discovery, its field of application was expanded, with rearrangements involving other nitrogen-containing heterocycles, such as pyrimidines, quinolines, quinines, and others, as well as other aromatic rings substituted in carbons further from the nitrogen atom.[19,20] The mechanism by which these rearrangement occurs can vary. Besides the concerted mechanism, there is also evidence for the involvement of ionic and radical species.[21,22] For a more in-depth review on the applications of the Boekelheide rearrangement, please check the excellent 2025 review written by Zhu et al.[11]

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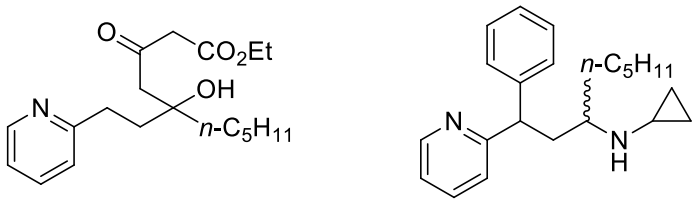
Scheme 2. The Boekelheide rearrangement of 2-picoline *N*-oxide and its mechanism.

In 2020, Liu et al. reported the use a Boekelheide-type rearrangement to synthesize a series of 2-pyridin2-ylalkyl ketones from *N*-alkenoxypyridiniums (Scheme 3).[23] This approach proved to be very efficient (with yields around 58-92%), highly site-selective, and also compatible with a broad arrange of substrates, including ones with bulky groups and unprotected alcohols. Other methods of synthesis of these compounds, such as electrochemical and photochemical approaches, are characterized for low selectivity and limited subtract scope, which the authors proved this reaction could overcome. This synthetic strategy was demonstrated to be extremely useful in the preparation of biologically active molecules, such as a HIV protease inhibitor precursor **9** and pheniramine analogues **10** (Figure 1).



Scheme 3. The mechanism of the Boekelheide rearrangement of *N*-alkenoxypyridiniums.

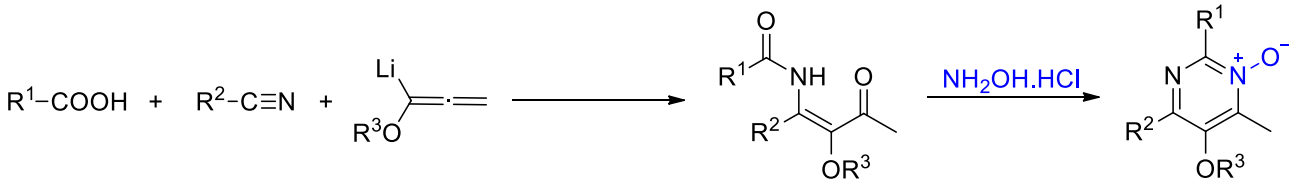
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9 (60%) **10** (78%, dr = 1.8:1)

Figure 1. HIV protease inhibitor precursor (on the left) and the pheniramine analogues precursor (on the right).

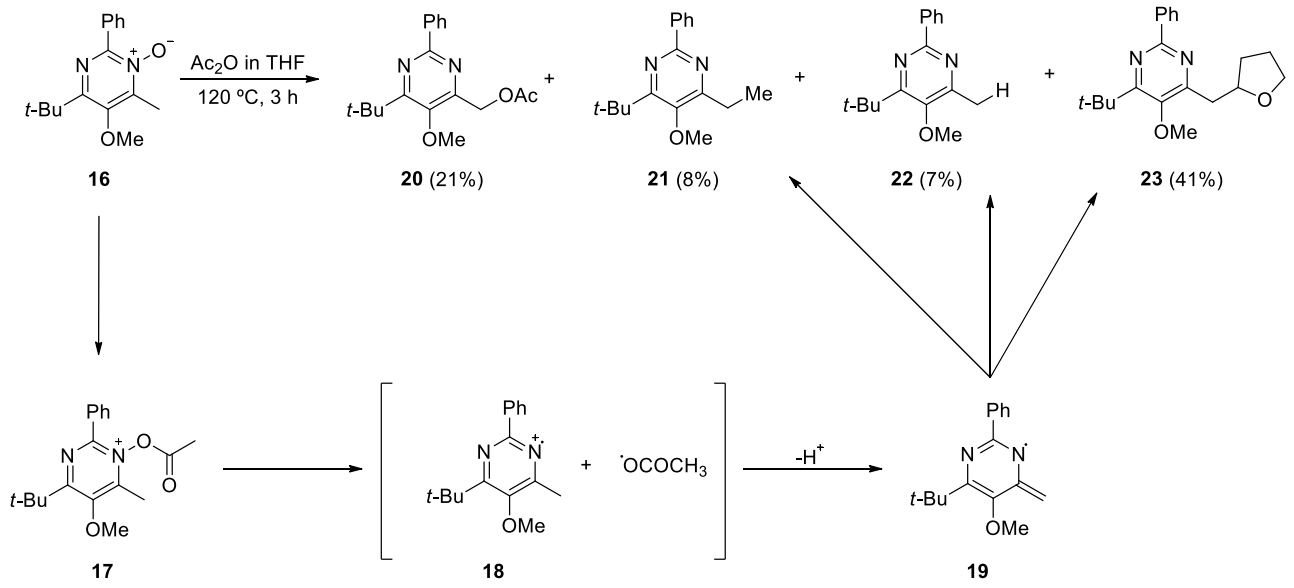
The application of the Boekelheide rearrangement to pyrimidines remained largely underexplored for many years, primarily because of the poor regioselectivity associated with oxidation of the ring nitrogen atoms. This limitation was overcome in 2010 when Reissig et al. introduced the LANCA cyclization strategy (Scheme 4).[24] This multicomponent process provides a functionalized enamide that can be condensed with hydroxylamine hydrochloride to furnish 2,4,6-trisubstituted pyrimidine *N*-oxides, with the *N*-oxide formed regioselectively at a single nitrogen atom. The availability of these well-defined substrates enabled a systematic investigation of the Boekelheide rearrangement as a tool for the selective functionalization of pyrimidine scaffolds. In subsequent studies published in 2018[25] and 2023[10], Reissig and co-workers demonstrated the utility of this rearrangement for the modification of substituents adjacent to the *N*-oxide functionality. During these investigations, however, several side products were detected, including methylated derivatives. To account for their formation, the authors proposed that a radical pathway might operate in parallel with the conventional concerted mechanism (Scheme 5). This hypothesis was supported experimentally by the use of radical initiators, which influenced the product distribution, and by conducting the reaction in the absence of light. Under dark conditions, the yield of product **20** increased dramatically from 69% to 99% (when the reaction was performed without THF), providing strong evidence for the involvement of photochemically induced radical processes. DFT calculations also demonstrated that both the concerted mechanism and the stepwise processes (either ion pair or radical) are energetically feasible.



11 **12** **13** **14** **15**

Scheme 4. The LANCA-cyclization strategy to obtain pyrimidine *N*-oxides.

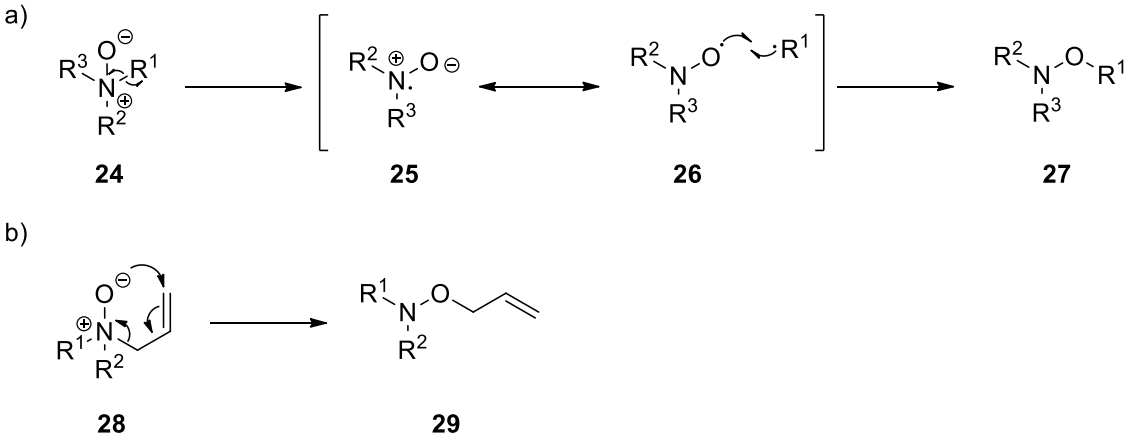
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Scheme 5. The Boekelheide rearrangement of pyrimidine *N*-oxide **16** in THF.

3. Meisenheimer rearrangement

The Meisenheimer rearrangement is described as a [1,2] or [2,3]-migration of tertiary amines - mostly benzylic and allylic - to afford *O*,*N*,*N*-trisubstituted hydroxylamines. This reaction was first observed in 1919 by Jakob Meisenheimer, while conducting experiments on the thermal behavior of tertiary amine *N*-oxides. Although both migration pathways are classified as a Meisenheimer rearrangement, they occur via different processes: while the [1,2]-variant involves formation of radical species, with homolytic cleavage of the carbon-nitrogen bond and subsequent migration of the alkyl group (Scheme 6a), the [2,3]-variant goes through a concerted pericyclic pathway (Scheme 6b).[26,27] This last variant is most common in allylic systems.

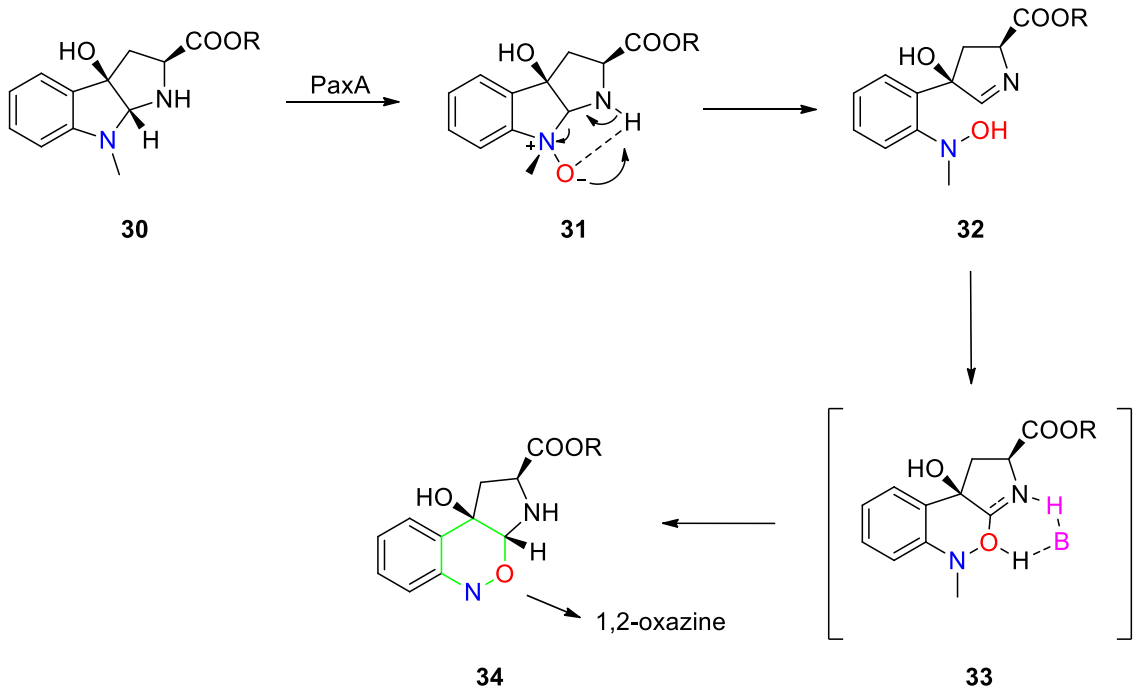


Scheme 6. The Meisenheimer rearrangement: a) [1-2]-variant; b) [2-3]-variant.

The [1,2]-migration represents the most significant rearrangement of aromatic amine *N*-oxides. This process is inaccessible to pyridines and related heterocycles, as it would necessitate cleavage of the aromatic

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framework. Conversely, anilines and analogous systems can undergo [1,2]-migration, a transformation that has been implicated in the biosynthesis of structurally complex natural products. An illustrative example was reported by Yan et al. in 2022, who elucidated the biosynthetic pathway of the insecticidal natural product paeciloxazine and identified a crucial *N*-oxide-mediated rearrangement in its formation.[28] The team identified the biosynthetic gene cluster responsible for the production of this compound from *Penicillium janthinellum*. They found that PaxA, a flavin-dependent monooxygenase, is the key enzyme responsible for catalyzing the formation of the 1,2-oxazine core. The enzyme catalysis the *N*-oxidation of the ring, that then undergoes a Meisenheimer rearrangement to afford the 1,2-oxazine core. DFT calculations determined that the typical mechanism for the rearrangement involving a homolytic cleavage of the carbon-nitrogen bond is not favored, with a bond dissociation energy (BDE) of 38.7 kcal·mol^{-1}. A mechanism involving a heterolytic cleavage seems also unlikely to occur spontaneously due to relatively high barriers. Indeed, it seems the rearrangement may occur via a proton transfer-promoted bond cleavage and nucleophilic addition, assisted by a polar molecule (BH) (Scheme 7). This may be one of the carboxyl or guanidine containing amino acids present close to the substrate. The synthesis of other 1,2-oxazine-containing natural products involving a Meisenheimer rearrangement are also reported in the literature, which could also be the mechanism of biosynthesis for other similar natural products.[29–34]



Scheme 7. The mechanism of PaxA-catalyzed Meisenheimer rearrangement.

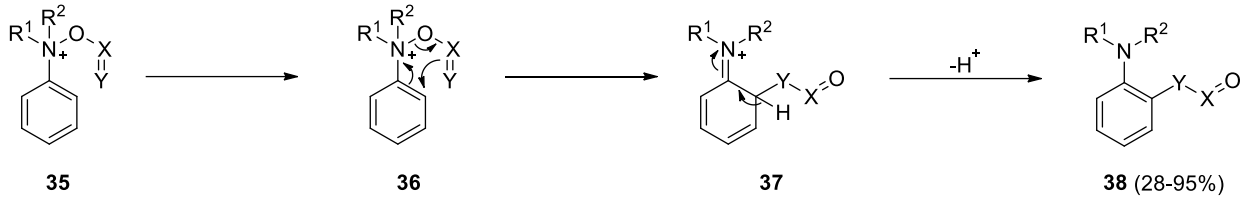
4. Aniline *N*-Oxide rearrangements

Aniline and aminophenol derivatives are fundamental structural motifs in synthetic chemistry, enabling the synthesis of a wide range of functionalized aromatic compounds. Their prevalence in pharmaceuticals and other biologically active molecules further underscores their importance as key intermediates in medicinal

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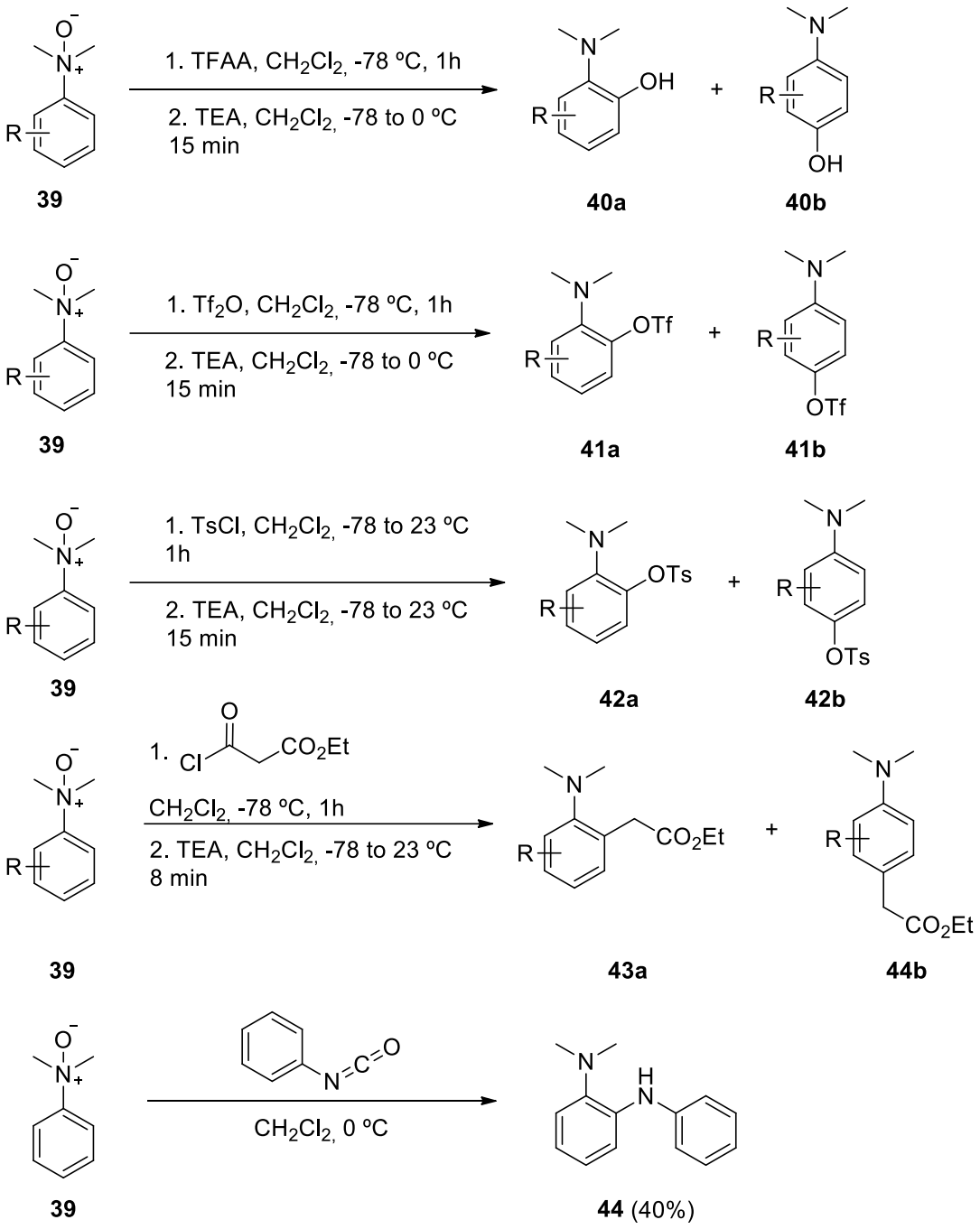
chemistry. Nevertheless, the selective and controlled preparation of these scaffolds remains a significant synthetic challenge, and general methods for their regioselective elaboration are comparatively scarce. [35]

In 2014, Lewis et al. reported a new, simple and single step approach to the synthesis of aminophenols, aminoarylsulfonates, alkylated anilines and amino anilines from the corresponding aniline *N*-oxides, in 28-95% yields (Scheme 8). [12] The aniline functionalization primarily occurs *ortho*, but it can also occur in the *para* position, less efficiently. This happens because this reaction most likely is driven by different mechanistic pathways, in accordance to what was discussed above. The most favored one involves a Cope rearrangement which leads to *ortho* substitution (Scheme 9). The authors were able to greatly favor this reaction by optimizing the reaction conditions. In particular, performing the reaction at -78 °C, an uncommon condition for sigmatropic rearrangements, allowed for a cleaner reaction, with less side products. The *para* substitution may happen by a radicular or ionic mechanism.



Scheme 8. The [3,3]-sigmatropic rearrangement of *N*,*N*-dialkylaniline *N*-oxides.

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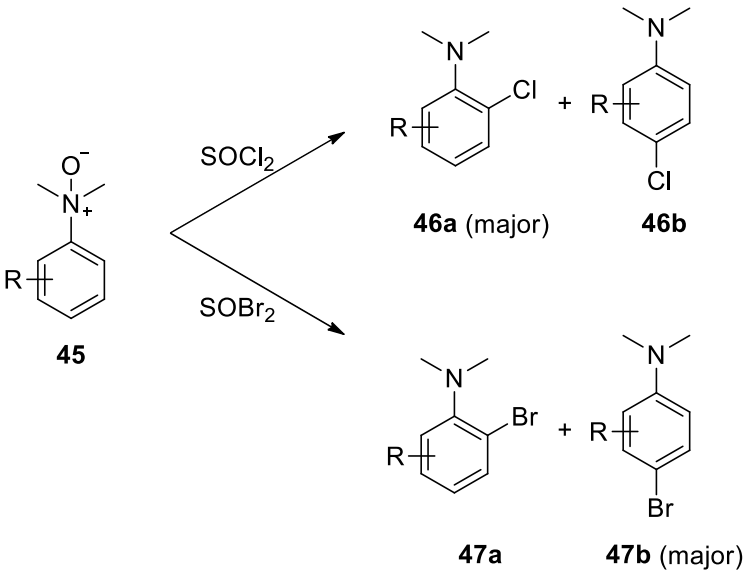


Scheme 9. The different possible transformations of *N*,*N*-dialkylaniline *N*-oxides by rearrangement described by Lewis et al.

Similarly, in 2018, Reed et al. reported the synthesis of halogenated anilines by reaction of the corresponding aniline *N*-oxide with thionyl chloride and thionyl bromide (Scheme 10). [36] These useful aryl halides are widely used in the construction of C-C bonds in synthetic chemistry.[37] Besides this, they are also heavily present in biologically active molecules.[38] Their classical preparation methods (e.g., electrophilic aromatic substitution) sometimes prove to be challenging, owing to the electron rich nature of the aniline ring, much like in the case discussed previously. Utilizing the aniline *N*-oxide, the team was able to overcome this problem, with the reaction being performed mild, low temperature conditions similar to the ones described by Lewis et al. Interestingly, the chlorination occurred preferably at C2, while the bromination

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occurred preferably at C4. Although not fully understood, the reaction most likely proceeds via different pathways for each case: the *ortho* chlorination is consistent with a [3,3]-sigmatropic rearrangement of the *O*-acylated *N*-oxide, while the *para* bromination may involve radical or ionic species.



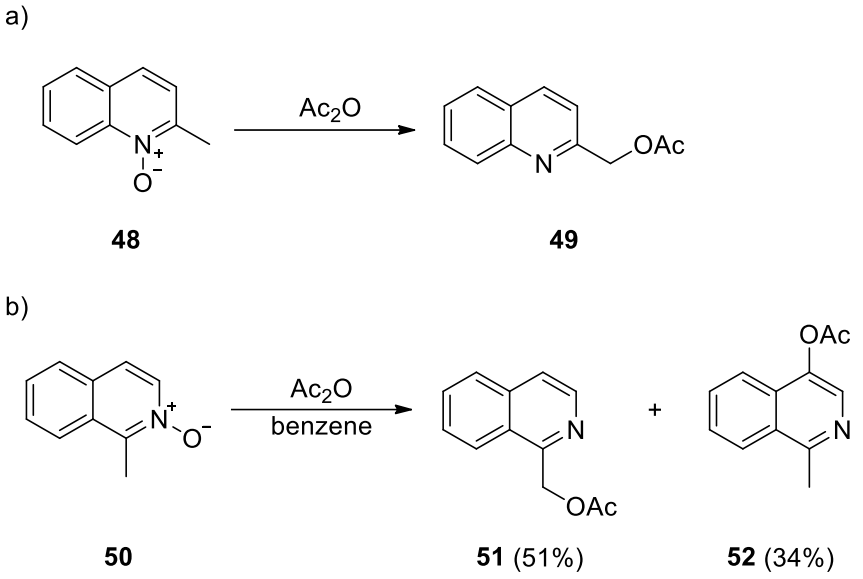
Scheme 10. The halogenation of aniline *N*-oxides described by Reed et al.

5. Quinoline and isoquinoline *N*-Oxide rearrangements

Quinolines are one of the most prevalent structures in biologically active compounds, natural and synthetic, with emphasis in antimarial drugs.[39,40] Naturally, they constitute a privileged scaffold for drug development, and methods for their functionalization are highly desirable. However, direct functionalization of quinoline rings is generally considered very difficult, because of the low reactivity and poor selectivity that comes from its π-system with lower energy.[41] To overcome this, a simple strategy is to use quinoline *N*-oxides, which are easily obtained, are more reactive, and demonstrate increased regioselectivity. Some the reactions that can be done using these systems involve rearrangements of the *N*-oxide in order to, primarily, derivatize the closest position to the nitrogen.[11]

A classic example is the application of the Boekelheide rearrangement. This can be achieved with both quinolines and isoquinolines. Both these transformations were investigated by Oae et al., in 1970.[42] Utilizing the same synthetic strategy used by Boekelheide with 2-picoline *N*-oxide, the team studied the transformation of 2-methyl quinoline *N*-oxide to the corresponding 2-acetoxy product **49** (Scheme 11a). Similarly, when applying these reaction conditions to 1-methylisoquinoline *N*-oxide the team obtained the predicted Boekelheide rearrangement product **51** (Scheme 11b).

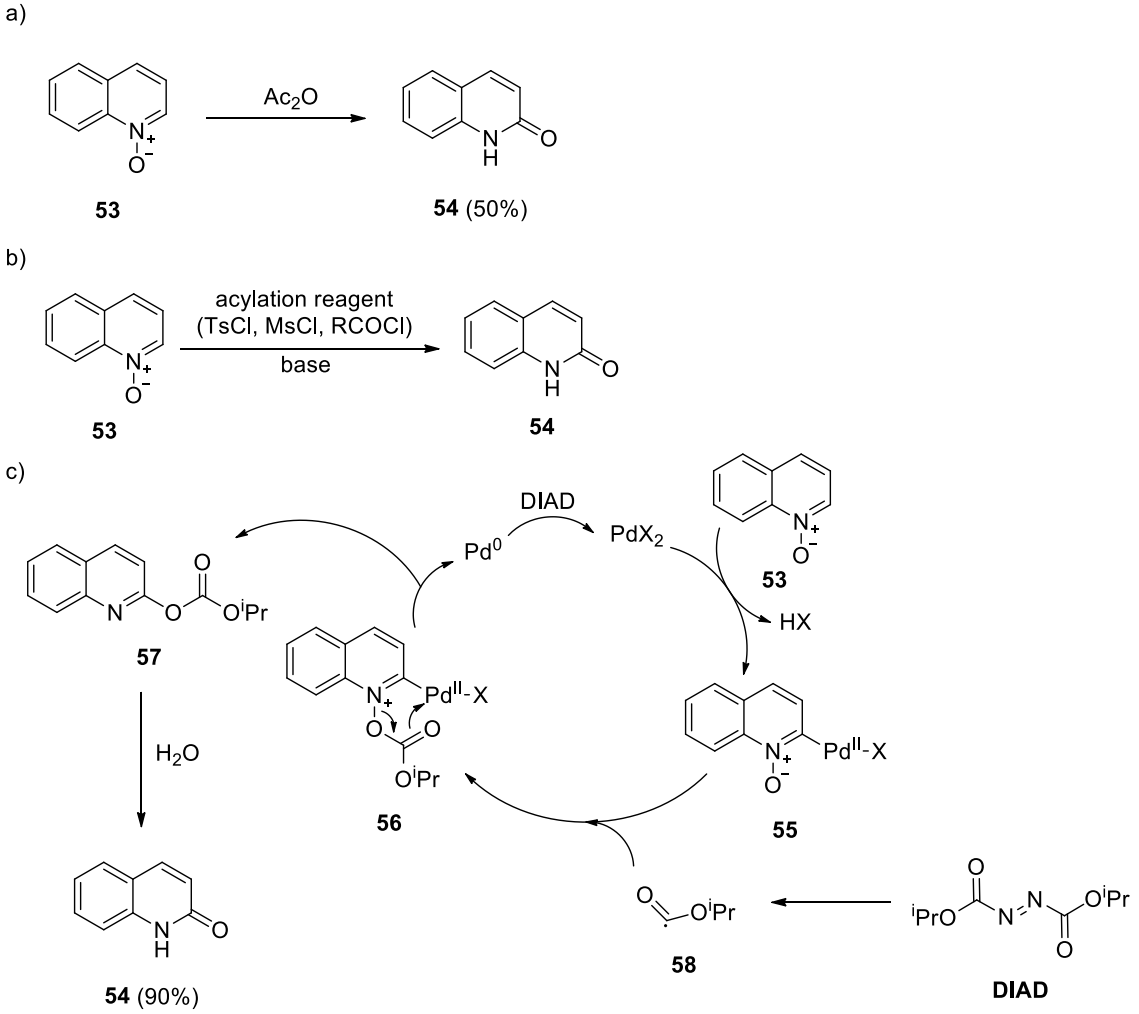
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Scheme 11. The Boekelheide rearrangement of: a) 2-methylquinoline *N*-oxide; b) 1-methylisoquinoline *N*-oxide.

The rearrangement of quinoline *N*-oxides as also been applied to the construction of quinolin-2(*1H*)-ones.[43] These constitute an important family of heterocycles that are present in many natural products, pharmaceuticals and fluorescent markers.[44] Obtaining these compounds can be achieved from the corresponding quinoline *N*-oxide by several ways, including a Katada-type oxidation[45] (Scheme 12a) or through a Reissert-Henze type reaction[46] (Scheme 12b). Recently, in 2018, Peng et al. reported a novel synthesis of a family of quinolin-2(*1H*)-ones via a Pd(II)-catalyzed strategy in the presence of DIAD (Scheme 12c).[43] The reaction occurs via the formation of carbonate **57** by rearrangement and reductive elimination of molecule **56**, followed by hydrolysis to give the targeted quinolin-2(*1H*)-one in moderate to high yields, depending on the substrate (36-90%).

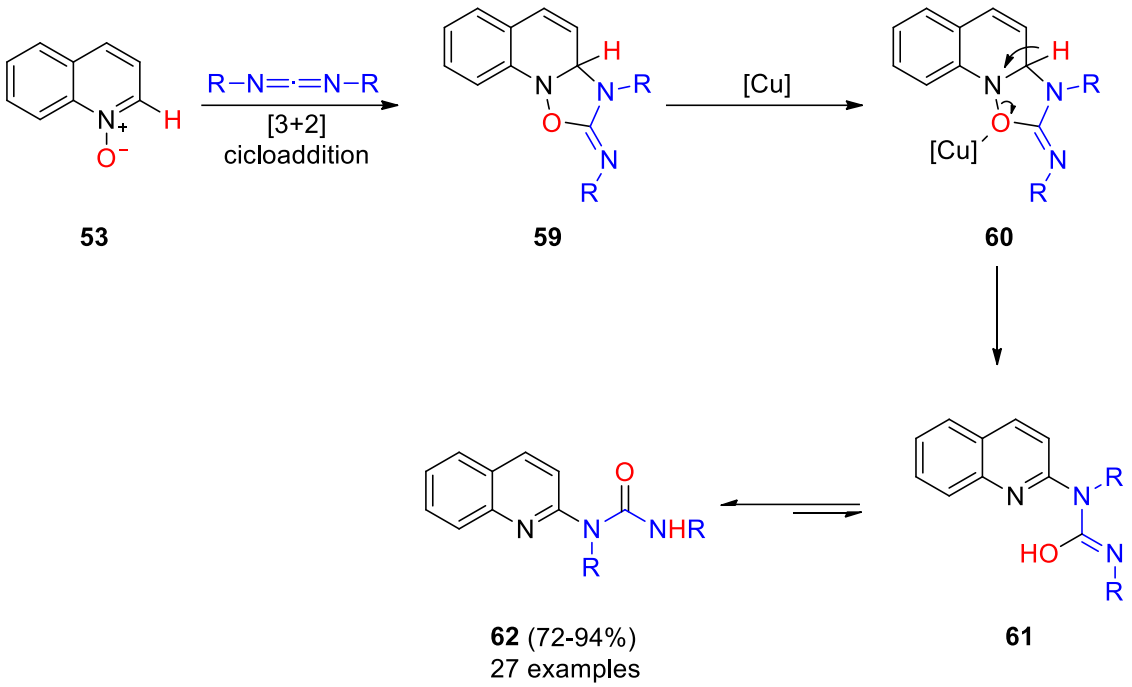
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Scheme 12. Methods to obtain quinolin-2(*1H*)-ones from quinoline *N*-oxides: a) via a Katada-type oxidation; b) via a Reissert-Henze type reaction; c) via a Pd(II)-catalyzed rearrangement.

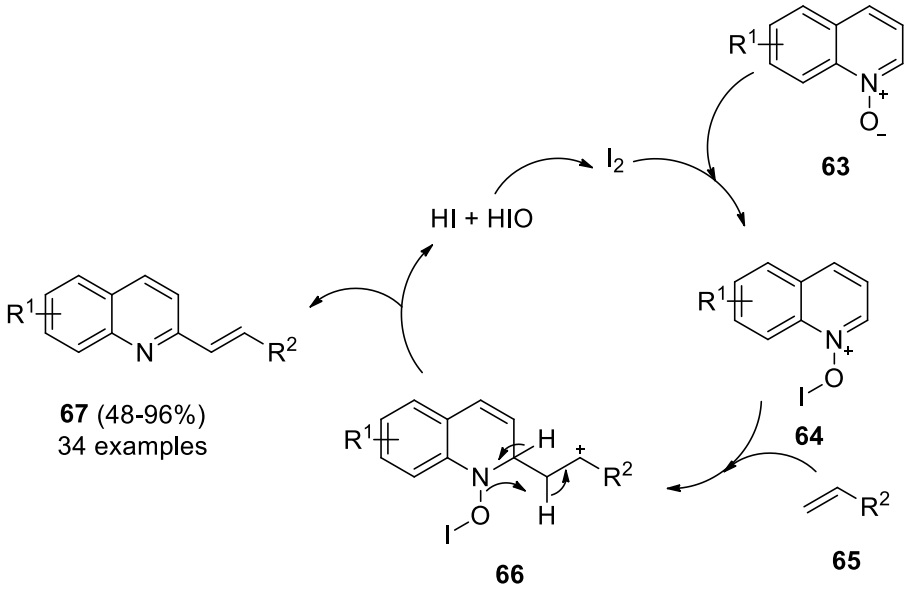
The urea motif is regarded as a privileged motif in medicinal chemistry, due to its chemical properties.[47] They can be fine-tuned to increase a drugs solubility, they can increase binding affinity by efficient hydrogen bonding, and they are highly versatile building blocks.[48,49] As such, establishing protocols to incorporate these motifs into other valuable scaffolds is of practical importance. One such scaffold is quinolines. The existing methods for this, such as the reaction of quinolines with highly toxic amidating agents, are neither efficient nor green.[50] However, in 2019, Xie et al. reported a new, simple, green, scalable and clean preparation of quinolin-2-yl substituted ureas in water.[51] The team, using this innovative method, were able to build a library of 27 compounds, with high to very high yields (72-94%). The method involves the reaction of the desired quinoline *N*-oxide with the appropriate carbodiimine by a [3+2] cycloaddition (Scheme 13). Then, a copper-assisted intramolecular rearrangement gives rise to isourea **61**, which is quickly converted to the much stabler urea **62**, with an overall 100% atom economy.

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Scheme 13. Mechanism of reaction proposed by Xie et al. for the synthesis of quinolin-2-yl substituted ureas.

Styryl quinolines comprise a family of versatile organic compounds characterized for their utility in medicinal chemistry[52–54], and in optical and material science[55]. This can be attributed to their extended π-conjugation system, giving them special properties. In 2017, Zhang et al. reported a new, mild, highly efficient and regioselective synthetic strategy to obtain these compounds utilizing quinoline *N*-oxides, in a metal and external oxidant free manner.[56] The reaction, catalyzed by molecular iodine, proceeds via *O*-iodation of the quinoline *N*-oxide, followed by addition of the corresponding alkene **65** to the C2 position of the ring (Scheme 14). Finally, by an intramolecular rearrangement, the desired (*E*)-2-styrylazaheterocycle **67** can be obtained in moderate to very high yields.



Scheme 14. Reaction mechanism proposed by Zhang et al. for the formation of styryl quinolines from quinoline *N*-oxides.

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6. Conclusions and future perspectives

In summary, azaheterocycles *N*-oxides have attracted sustained interest since the 1950s, and rearrangements involving these compounds continue to constitute a versatile and powerful class of transformations in organic chemistry. These reactions provide highly regioselective routes for the functionalization and diversification of heteroaromatic scaffolds, with notable applications in medicinal chemistry and materials science. Future developments in the field will likely focus on achieving a deeper mechanistic understanding of these processes, enabling more precise control over reactivity and selectivity. Additional efforts may be directed toward expanding substrate scope, developing more sustainable reaction protocols, and improving overall efficiency. As a result, aromatic *N*-oxide rearrangements are well positioned to remain an indispensable component of the synthetic chemist's toolbox.

7. Acknowledgements

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