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Review on the Application of *O-Alkenylaryl* Isocyanide in Heterocyclic Synthesis

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Abstract: *In recent years, isocyanide compounds have been increasingly used in the field of organic synthetic chemistry, and more and more chemists are using isocyanide compounds to construct N-containing heterocyclic compound frameworks. Therefore, the purpose of this review is to showcase the recent research progress in the synthesis of N-containing heterocyclic compounds using o-alkenylaryl isocyanides.*

Keywords: *Isocyanide, Organic synthesis, quinoline, indole*

1. Introduction

Isocyanide compounds, in recent years, have garnered widespread utilization in the field of organic synthesis. Isocyano, a remarkable functional group, exhibits resonances between neutral iminocarbene and zwitterionic triple bond structures. The presence of the C atom in isocyanide enables both the donation and acceptance of lone pair electrons, thus manifesting properties of nucleophilic and electrophilic, as well as radical reactivity under suitable conditions. This unique characteristic positions isocyanide compounds as crucial active synthons in the efficient synthesis of nitrogen-containing molecules and heterocyclic compounds. Notably, isocyanide compounds offer several advantages, including high regional and stereoselectivity, high compatibility with various functional groups, high conversion rates, and atomic economy. Consequently, researchers have extensively employed isocyanide compounds in a diverse range of organic synthesis reactions, leading to significant advancements in the field.

Owing to its distinctive properties, isocyanide finds application as both a source of C and N atom for the synthesis of various compounds. In contrast, ortho alkenyl aryl isocyanide achieves cyclization by strategically designing a highly reactive site at the ortho position of aryl isocyanide, enabling subsequent reactions. This particular type of ortho alkenyl aryl isocyanide is commonly employed in the synthesis of indole or quinoline compounds. Due to the exceptional efficiency and atomic economy of isocyanide in synthesis, an increasing number of chemists have explored the synthesis of N-containing heterocyclic compounds using *o*-alkenylaryl isocyanide.

2. Synthesis of quinoline with o-alkenylaryl isocyanide

A notable breakthrough in this area occurred in 2015 when Evoniuk's group[1] successfully synthesized a series of 2-substituted quinoline compounds employing ortho olefin-substituted phenyl isocyanide and arylboronic acid as substrates (Figure 1). Notably, this study marked the first application of the free radical 6-endo-trig cyclization of o-alkenylaryl isocyanide in heterocyclic synthesis. The researchers observed that the cyclization of *o*-alkenylaryl isocyanide could be controlled by the substituent groups present at the olefin end. Specifically, the inclusion of alkoxy and phenyl substituents provided the sufficient stability for the formation of quinoline compounds.

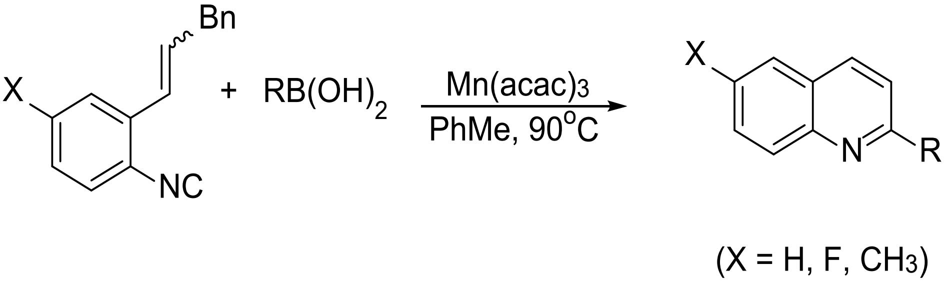

Figure 1. Evoniuk's work[1]

In 2018, Xu's group[2] successfully synthesized a series of quinoline compounds using ortho olefin-substituted phenyl isocyanides as substrates (Figure 2). The ortho alkenyl aryl isocyanide employed in their study featured a conjugated structure, with a carbonyl group serving as the substituent at the other end of the alkenyl group. Under the catalysis of DBN, the dehydrogenation of nitroalkanes led to the formation of carbon negative ions, which underwent Michael addition, 1,3-H migration, and subsequent [5+1] ring closure with nitroalkanes. This reaction selectively yielded 3,4-disubstituted quinoline or 3-nitrodihydroquinoline, and the resulting dihydroquinoline could further undergo ring closure.

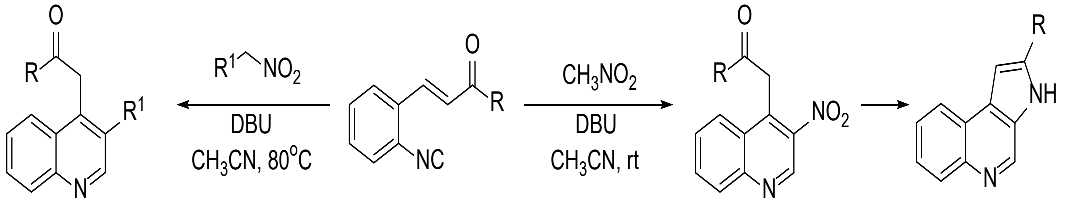

Figure 2. Xu's work [2]

In 2020, Yu's group[3] reported a method for synthesizing quinoline compounds through free radical reactions of o-alkenylaryl isocyanide using Mn as a catalyst. Different Mn (III) salts were employed as free radical initiators to induce aromatic boric acid or diaryl phosphorus oxide to generate free radicals and undergo regioselective attack (Figure 3). This led to a 6-endo-trig cyclization reaction and the formation of two distinct 2-substituted quinoline compounds. This method achieved free radical stabilization by modifying the C=C bond, facilitating the reaction towards quinoline ring formation.

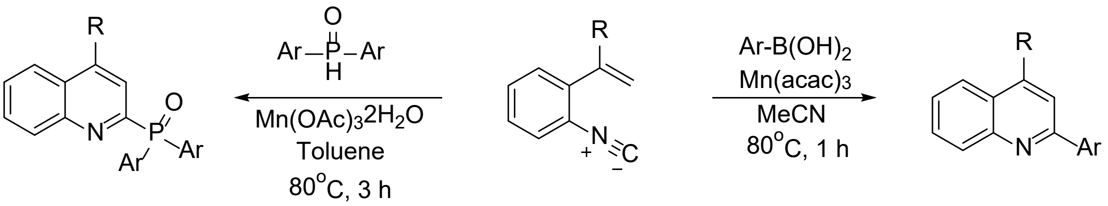

Figure 3. Yu's work [3]

In 2020, Li's group[4] reported a photocatalytic cyclization reaction of ortho alkenyl aromatic isocyanides initiated by free radicals. This reaction utilized ortho alkenyl aniline as the substrate, reacting with Togni reagent to construct the skeleton of fluoroquinoline compounds (Figure 4). Previous studies have shown that when aniline with ortho olefins forms a ring under the action of free radicals, it tends to form a five membered ring dynamically, which is the synthesis of indole compounds in the form of 5-exo-trig. Therefore, by introducing a cyano or ester group at the other end of the alkenyl group, the group aimed to enhance the reaction's advantages in terms of steric hindrance or thermodynamics, favoring the formation of a six-membered ring. This approach enabled the synthesis of quinoline compounds through a 6-endo-trig cyclization.

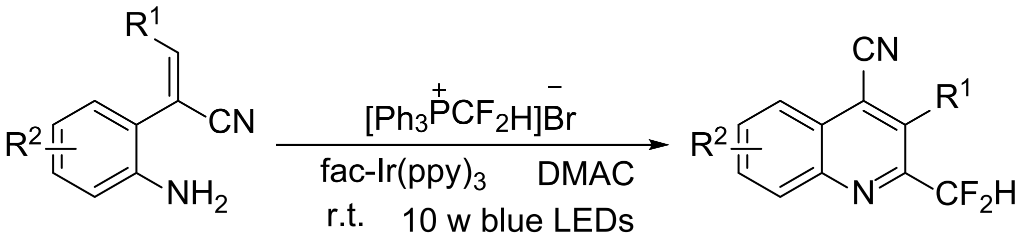

Figure 4. Li's work [4]

3. Synthesis of indole with o-alkenylaryl isocyanide

In 2002, Takahashi's group[5] reported a Pd-catalyzed method for synthesizing indole compounds using ortho alkenyl aryl isocyanide (Figure 5). This method involved the insertion reaction of isocyanide catalyzed by Pd, leading to the formation of indole compounds. The process initiated with the oxidation addition of aromatic halides by Pd, forming a C-Pd bond. The lone pair electrons on the carbon atom of isocyanide then coordinated with Pd and quickly insert adjacent C-Pd bonds (this process is commonly referred to as migration insertion), resulting in the intermediate of iminoyl palladium complex. Finally, this intermediate bonded with C=C to yield a 2-aryl indole compound.

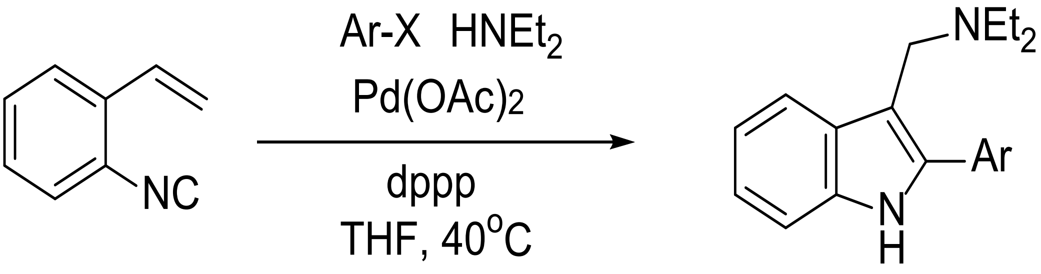

Figure 5. Takahashi's work [5]

In 2018, a research team led by Tang [6] reported a [1+2+3] cycloaddition reaction involving ortho alkenyl aryl isocyanide, leading to the synthesis of carbazole derivatives (Figure 6). The reaction initiated with the nucleophilic attack of the double bond of isocyanide on ketene to generate a zwitterionic intermediate. This intermediate then underwent cyclization and 1,3-hydrogen migration to achieve aromatization, ultimately forming a furan product through a process similar to a normal [1+4] cyclization. Subsequently, the furan molecule underwent a Diels-Alder reaction with the alkenyl group in the isocyanide, forming a bridged intermediate. This intermediate then underwent C-O bond cleavage, 1,3-hydrogen migration, and hydroxyl elimination dehydration through aromatization, leading to the formation of carbazole derivatives. This reaction represented a metal-catalyst-free domino cyclization reaction of isocyanide and enone, providing an important method for synthesizing carbazole alkaloids.

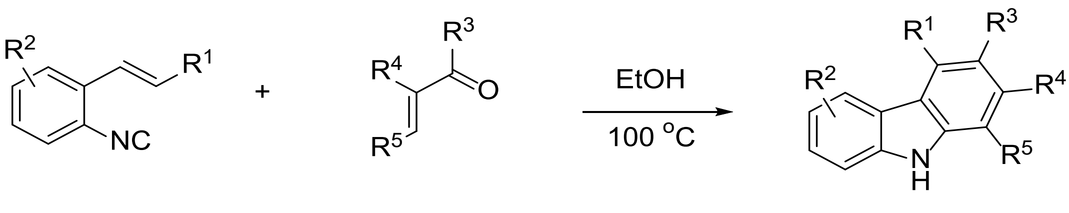

Figure 6. Tang's work [6]

In 2020, Marcio W. Paixao's group[7] reported a method for constructing sulfur-containing indole compounds through intramolecular cyclization of *o*-alkenylaryl isocyanide initiated by sulfur radicals (Figure 7). The reaction obtained sulfur free radicals through visible light catalyzed single electron transfer and hydrogen atom transfer processes. These sulfur free radicals then initiated the 5-exo-trig cyclization reaction of o-alkenylaryl isocyanide. The process concluded with single electron transfer, protonation, and isomerization steps to obtain sulfur-containing indole compounds. The final product can also be oxidized to 2-sulfonylindole using m-chloroperoxybenzoic acid under mild conditions. This method offered mild reaction conditions and good functional group tolerance, making it an efficient approach for synthesizing sulfur-containing indole compounds.

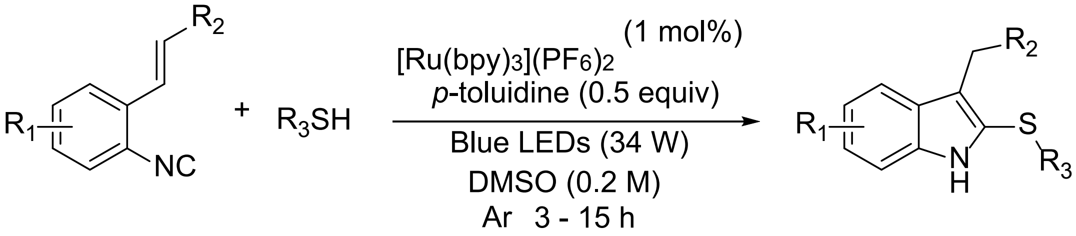

Figure 7. Marcio W. Paixao's work [7]

In 2020, the Yao's group [8] of Shaanxi University of Science and Technology reported a photocatalytic reaction for synthesizing indole compounds using *o*-alkenylaryl isocyanide (Figure 8). The reaction initiated with the excitation of Ir^{3+} under visible light, generating Ir^{3+} radicals. These radicals then undergo radical transfer with benzoic acid, resulting in the formation of benzoyl radicals and the release of CO_2. The benzoyl radical was subsequently captured by isocyanide, which then attacked the intramolecular double bond and underwent 5-exo-trig cyclization. Under the influence of Ir^{2+}, free radicals were reduced to benzyl carbon negative ions, while Ir^{2+} was oxidized back to Ir^{3+} to continue the catalytic cycle. The obtained benzyl carbon negative ions underwent isomerization after proton capture, ultimately forming the desired indole compounds.

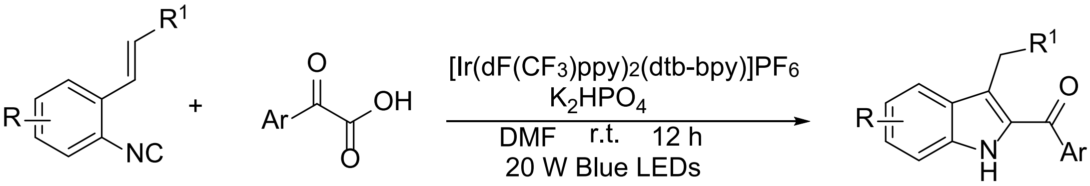

Figure 8. Yao's work [8]

In 2021, Huang's team[9] reported an iron-catalyzed method for the synthesis of indole compounds from ortho aryl isocyanides (Figure 9). This reaction utilized a Fe (III) pre-catalyst, which reacted with silane to form Fe (III)-H, triggering a free radical reaction through hydrogen atom transfer. This process leads to the generation of imide radicals from the isocyanide substrate. These radicals then attacked the C=C bond and underwent aromatization, resulting in the formation of a free radical for indole compounds. Finally, the reaction proceeded through single electron transfer and protonation steps to obtain the final product indole compounds.

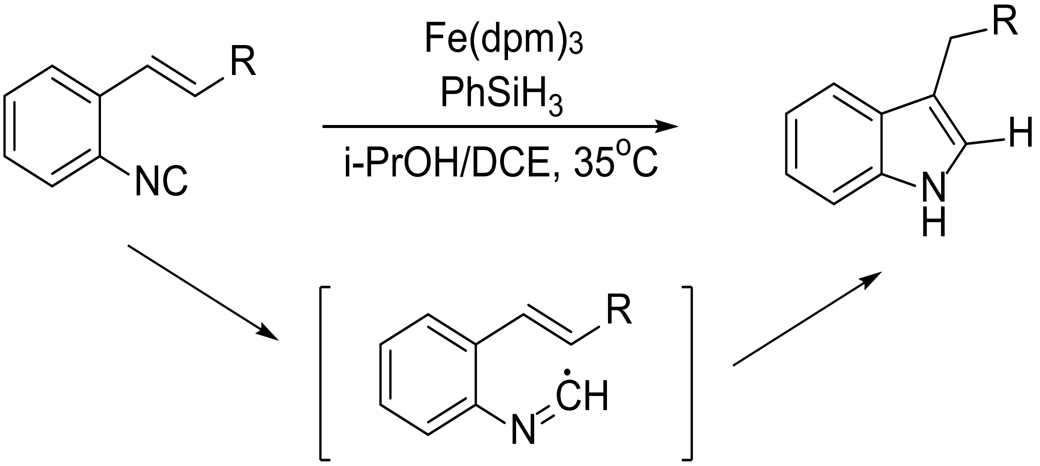

Figure 9. Huang's work [9]

In 2023, Studer's group[10] reported a copper-catalyzed method for the synthesis of chiral indole compounds from ortho alkenyl aryl isocyanide (Figure 10). The reaction began with the generation of free radicals through single electron transfer and mutual activation of a high-valent iodized salt and TMSCN, facilitated by a Cu catalyst. These radicals then underwent a 5-exo-trig cyclization by attacking isocyanide, leading to the formation of racemic indole compounds. These free radicals then captured the copper catalyst and underwent reduction elimination to form a racemized indole compound. However, due to the tautomerism of indole, the formed enantiomers were eliminated, resulting in the highly purified *S*-type products. This method has provided a novel and efficient approach for the synthesis of chiral heterocyclic compounds.

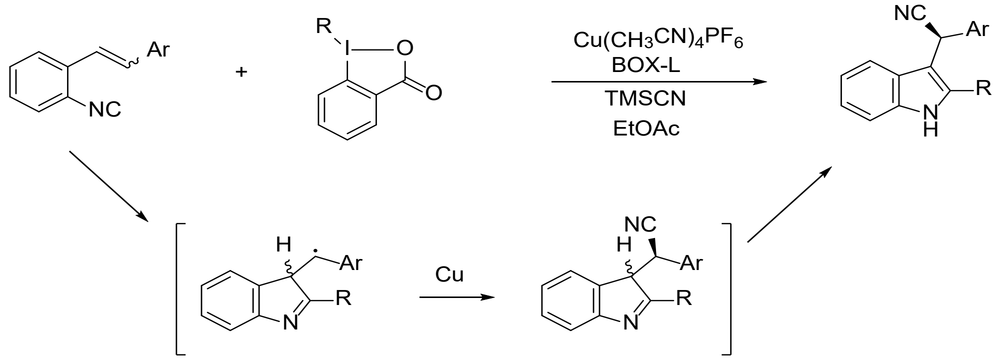

Figure 10. Studer's work [10]

4. Conclusions

Isocyanide compounds have been widely used in the synthesis of heterocyclic compounds, especially in the synthesis of indole and quinoline compounds. *O*-alkenylaryl isocyanides have become an excellent synthetic substrate. The reactions involving *o*-alkenylaryl isocyanide exhibit high reactivity and atomic economy, making it highly suitable for constructing *N*-containing heterocyclic compounds. *O*-alkenylaryl isocyanide has received continuous attention in organic synthesis, and in the future, more methods for synthesizing quinoline and indole compounds through *O*-alkenylaryl isocyanide compounds will be studied and reported.

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