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Exploring 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkenes: Synthesis of Isoxazolidine Derivatives

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Abstract

Heterocycles have long been pivotal to the advancement of organic chemistry, forming the backbone of numerous compounds with significant chemical, biological, and industrial applications. Among these, isoxazolidines (ISXs) hold particular importance due to their versatility in generating diverse molecular architectures. A prominent synthetic route to ISXs involves the 1,3-dipolar cycloaddition (1,3-DC) of nitrones with alkenes, a reaction valued for its ability to construct chiral molecules with multiple stereogenic centers. The pharmaceutical industry's growing demand for enantiopure compounds has spurred extensive research into asymmetric synthesis, particularly in the context of 1,3-DC reactions. Despite notable advancements, controlling regio-, diastereo-, and enantioselectivity in these reactions remains a significant challenge. This review provides a focused bibliographic overview of nitrone-alkene cycloaddition reactions, highlighting key developments and current challenges in achieving selectivity.

1. Introduction

For almost two centuries, organic chemistry has seen continuous development, especially in the area of heterocyclic synthesis [1]. This is largely due to the significant role of heterocycles, which serve as the core structures for a diverse range of compounds with chemical, biological, pharmacological, and

industrial relevance [2]. Among these compounds, ISXs stand out as particularly valuable structures in organic synthesis due to the diverse molecules that can be generated from the ISX ring [3]. The design of such derivatives often focuses on creating molecules that can target specific biological pathways, or possess desirable physical properties for industrial use [4-8]. One of the most well-known and extensively studied methods for synthesizing this motif is the 1,3-DC of a nitrone to an alkene. This reaction is highly valued because it enables the synthesis of chiral molecules, creating two to three stereogenic centers depending on the structure of the dipole and the dipolarophile. Asymmetric synthesis is a stimulating academic endeavor, especially since most chiral drugs are now considered safer in their enantiopure form. Therefore, the growing demand from the pharmaceutical industry for such compounds makes research in asymmetric synthesis crucial. Numerous studies have aimed to clarify the origins of regio- and stereoselectivity in 1,3-DC reactions [9,10]. However, achieving control over regio-, diastereo-, and enantioselectivity remains challenging and continues to pose a significant hurdle for organic chemists.

In this review, we provide a focused bibliographic summary of the 1,3-DC reaction, with particular emphasis on the nitrone-alkene cycloaddition, shedding light on its complexities and ongoing advancements in the field.

2. Historical Milestones of 1,3-Dipolar Cycloaddition (1,3-DC)

The major 1,3-dipoles used in cycloaddition reactions include azides, diazo compounds, nitrile oxides, and nitrones. Since the 1930s, this topic has been extensively studied, with a substantial number of publications. In the past 15 years alone, over 400 papers and reviews have focused on 1,3-DC reactions involving ISXs.

The history of 1,3-DC, also known as [3+2] cycloaddition, began in 1883 when Curtius discovered diazoacetic ester, the first known 1,3-dipole [11]. Five years later, Buchner investigated the reactivity of this compound with various α,β-unsaturated esters, leading to the first reported 1,3-DC reactions

[12]. In 1898, the discovery of nitrones and nitrile oxides by Beckmann, followed by Werner and Buss, expanded the scope of 1,3-dipoles [13,14]. Since then, numerous 1,3-dipoles have been identified, although only a limited number have achieved widespread use in synthesis [15]. In 1960, Huisgen conducted the first systematic studies on [3+2] cycloaddition, demonstrating that this reaction, through a concerted mechanism, enables the formation of five-membered heterocycles by the addition of a 1,3-dipole to a dipolarophile [16].

1,3-Dipoles are compounds with zwitterionic structures that can engage in 1,3-DC reactions by interacting with multiple bonded systems known as dipolarophiles.

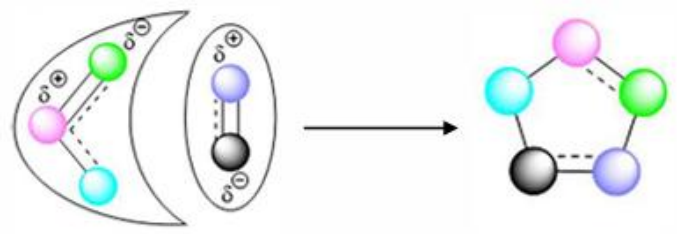


Figure 1. Dipolarophile-Dipole Approach

Among these dipoles, nitrones are distinguished by a carbon-nitrogen double bond and a coordination bond between nitrogen and oxygen. They exhibit a pronounced 1,3-dipolar character and are stabilized through resonance (Figure 2).

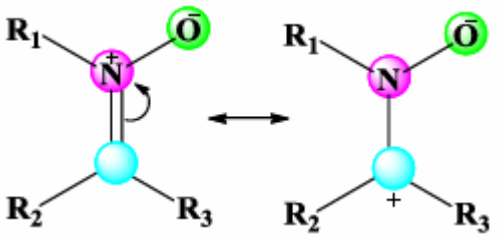


Figure 2. Resonance structures of an acyclic nitrone.

3. Classification and Structural Configurations of Nitrones

Similar to aldehydes and ketones, nitrones are classified into two main types: aldonitrones and ketonitrones, which can be either cyclic or acyclic. In acyclic nitrones, ketonitrones can adopt both Z and E configurations. Aldonitrones, however, are stabilized by hyperconjugation and only exist in the Z configuration, making them typically crystalline and stable. For cyclic nitrones, only the E configuration is possible due to structural limitations.

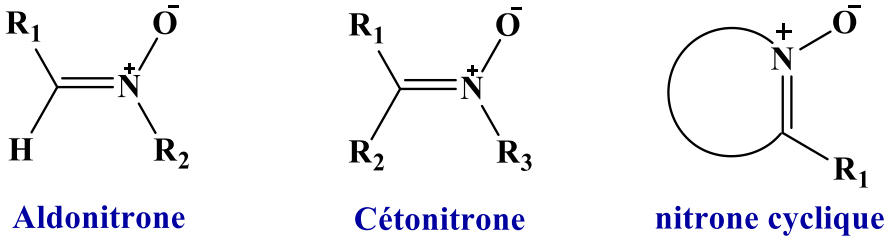


Figure 3. Various types of nitrones.

4. Synthetic Strategies for Nitrones: Key Approaches and Methods

Various methods have been developed for synthesizing nitrones, with the most widely used approaches including: the condensation of an aldehyde or ketone with an N-substituted hydroxylamine [17,18], the oxidation of N,N-disubstituted hydroxylamines, the N-oxidation of an imine [19], the N-alkylation of an oxime [20], and the oxidative cleavage of an ISX ring [21] (Figure 4).

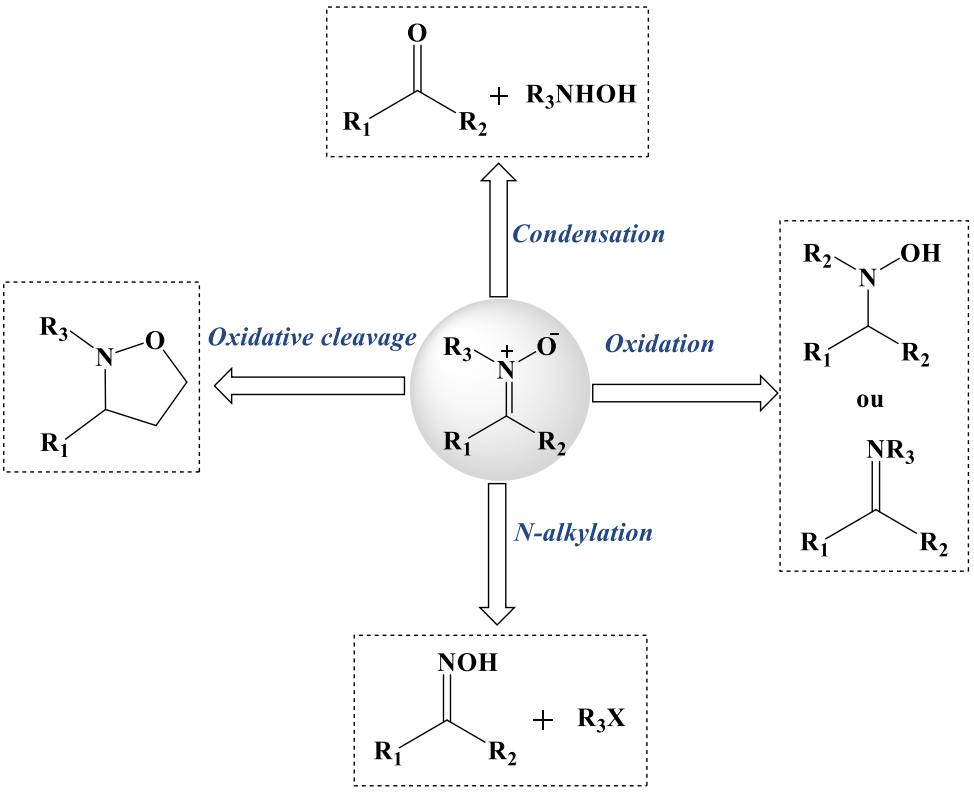


Figure 4. Summary of nitrone synthesis methods.

In cycloaddition reactions, nitrones exhibit distinct behavior depending on whether they are cyclic or acyclic [22]. For acyclic nitrones, the Z configuration is favored, as the E configuration leads to greater steric hindrance (Figure 5).

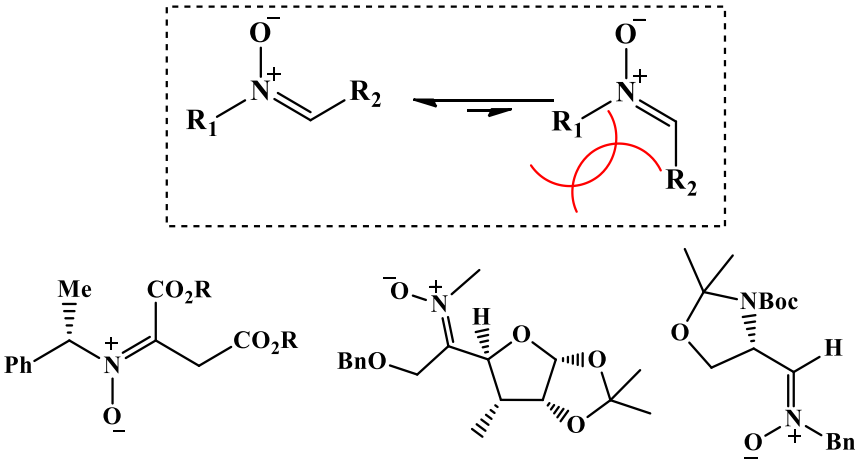
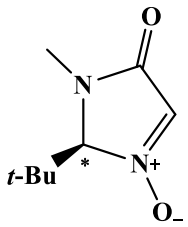
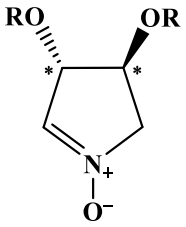


Figure 5. Examples of chiral acyclic nitrones.

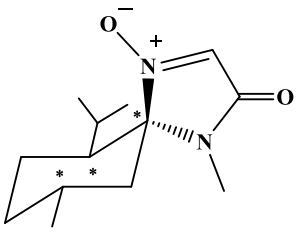
However, for cyclic nitrones, only the E isomer is present due to structural limitations. These compounds typically exhibit faster reactivity than their acyclic counterparts and demonstrate stronger regio- and stereoselectivity (Figure 6).



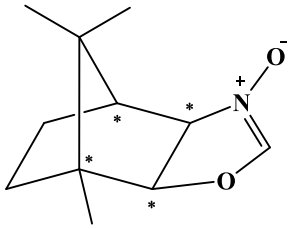
A nitrone with one asymmetric center



A nitrone with two asymmetric centers



A nitrone with three asymmetric centers



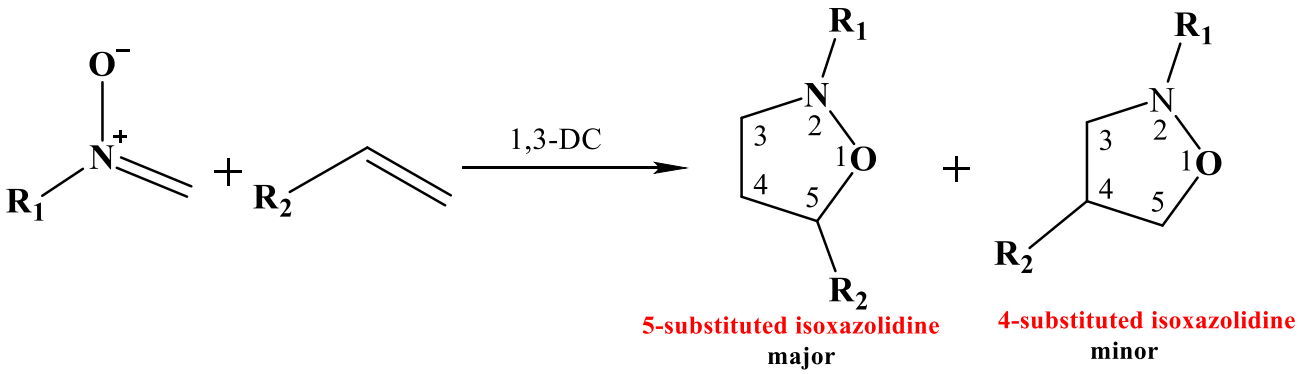
A nitrone with for asymmetric centers

Figure 6. Illustrates some examples of chiral cyclic nitrones.

5. The 1,3-DC involving a nitrone and an alkene

Thanks to their ease of preparation and the variety of synthetic routes available, nitrones have been employed for over 80 years [23] in 1,3-DC reactions with alkenes to synthesize ISXs [24]. The final structure of the resulting ISXs depends on the ability to control the regioselectivity, stereoselectivity, and approach selectivity of the nitrone towards the alkene.

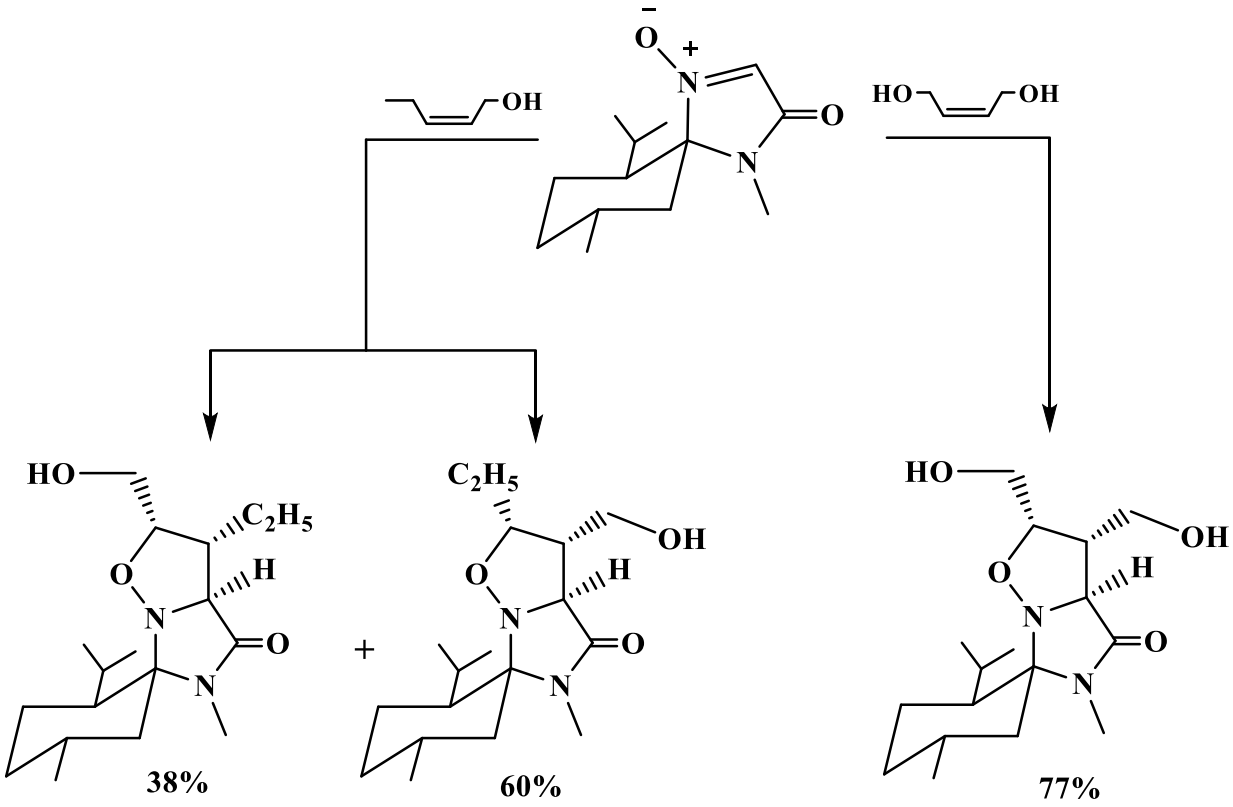
Depending on the substrates and reaction conditions, the [3+2] cycloaddition can lead to two regioisomers [25]. Regioselectivity in the 1,3-DC of nitrones with alkenes is influenced by both electronic and steric factors [26]. For terminal alkenes, steric effects typically favor the formation of 5-substituted ISXs [27], with the nitrone oxygen atom adding to the most substituted carbon (see Scheme 1).



Scheme 1. The regioselective cycloaddition of nitrone

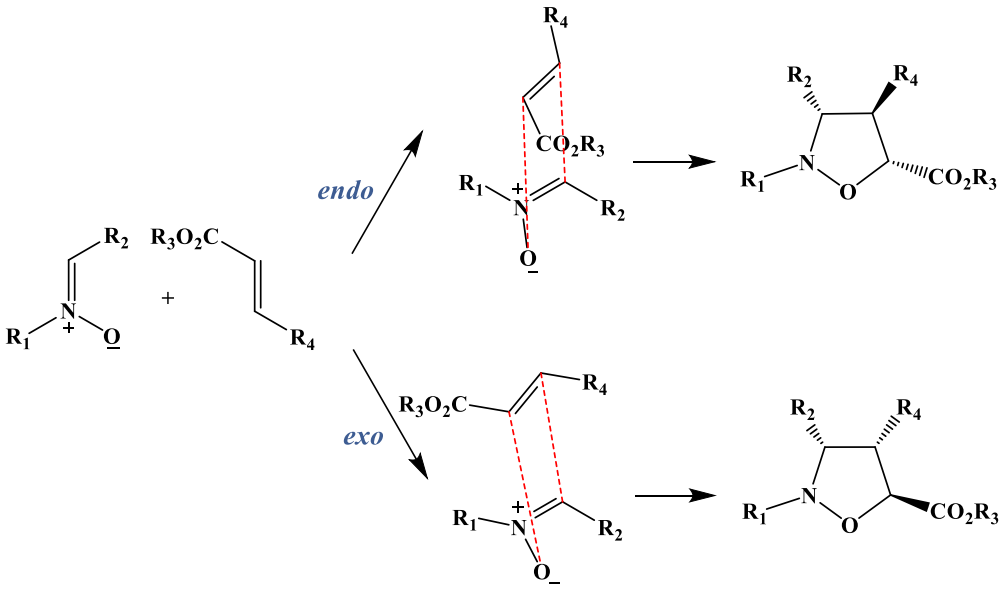
In the case of asymmetric disubstituted alkenes, two orientations of the dipole and dipolarophile can lead to a mixture of two regioisomers. The regioselectivity is governed by both steric and electronic factors. Conversely, for the 1,3-DC of nitrones with symmetric disubstituted alkenes, the regioselectivity issue is absent.

For example, the 1,3-DC of the nitrone derived from (–)-menthone with (Z)-pent-2-enol resulted in a mixture of two regioisomers, one being the predominant product [28]. In contrast, the reaction with (Z)-but-2-en-1,4-diol produced a single regioisomer in good yield [28] (Scheme 2).



Scheme 2. 1,3-DC of the chiral nitrone with (Z)-2-pentenol and/or (Z)-2-but-en-1,4-diol

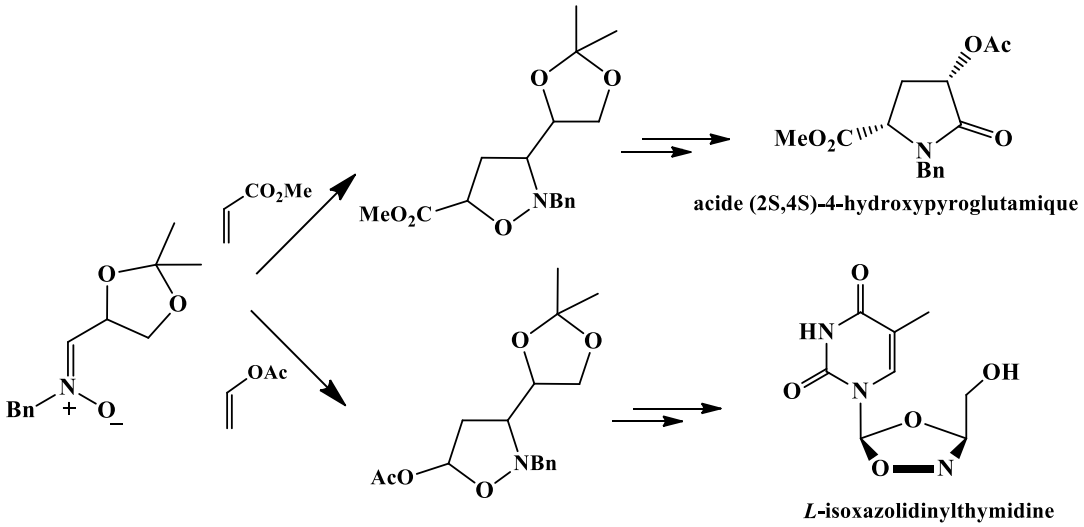
Analogous to the Diels-Alder reaction, the 1,3-DC of nitrones to alkenes can proceed via endo and *exo* approaches. The selectivity of these approaches is primarily governed by steric factors as well as favorable secondary interactions (Scheme 3).



Scheme 3. *Exo/Endo* approach

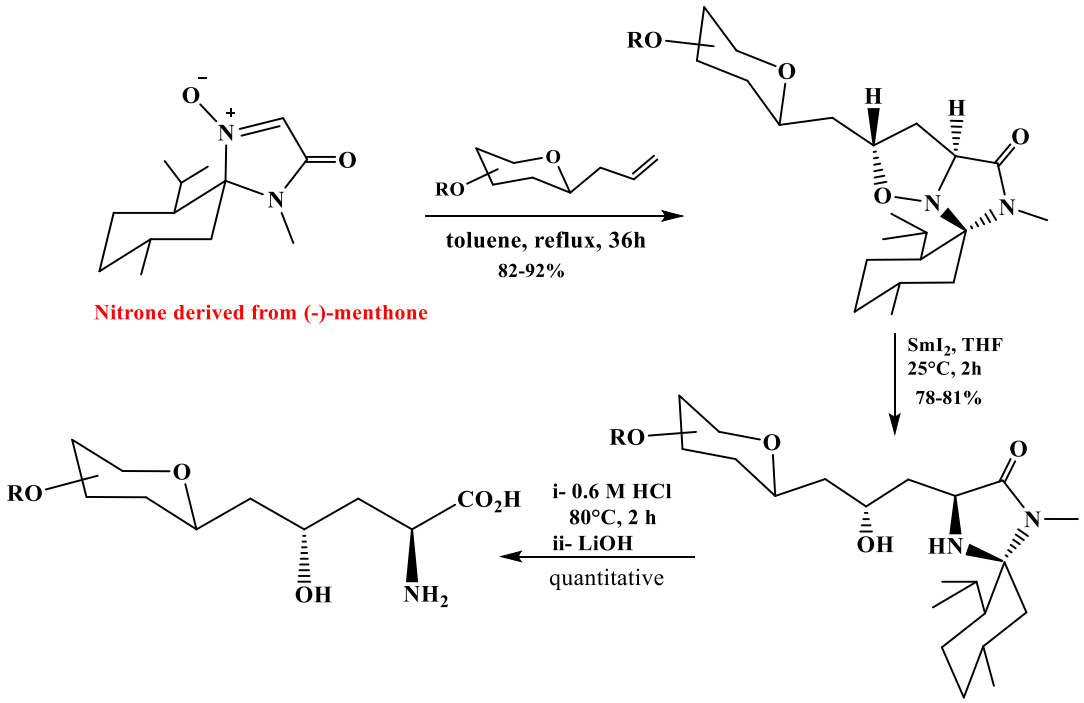
Although the 1,3-DC reaction has been extensively studied in the literature, controlling regioselectivity, diastereoselectivity, and enantioselectivity has become a central objective for chemists. Consequently, numerous efforts have been directed toward developing new methodologies to prepare diastereopure and enantiopure products. This can be achieved through the establishment of asymmetric induction using a nitrone and/or an alkene bearing a chiral auxiliary.

In this context, P. Merino and collaborators [29,30] employed a chiral acyclic nitrone derived from D-glyceraldehyde to synthesize enantiopure ISXs. In this case, the diastereofacial selectivity is controlled by the electronic nature of the dipolarophile. In the presence of methyl acrylate, the cycloadduct obtained arises from an *endo* approach, which is then transformed into protected (2S,4S)-4-hydroxypyroglutamic acid. Conversely, the condensation of the same chiral nitrone with vinyl acetate predominantly leads to a cycloadduct resulting from an *exo* approach, providing access to L-isoxazolidinylthymidine (Scheme 4).



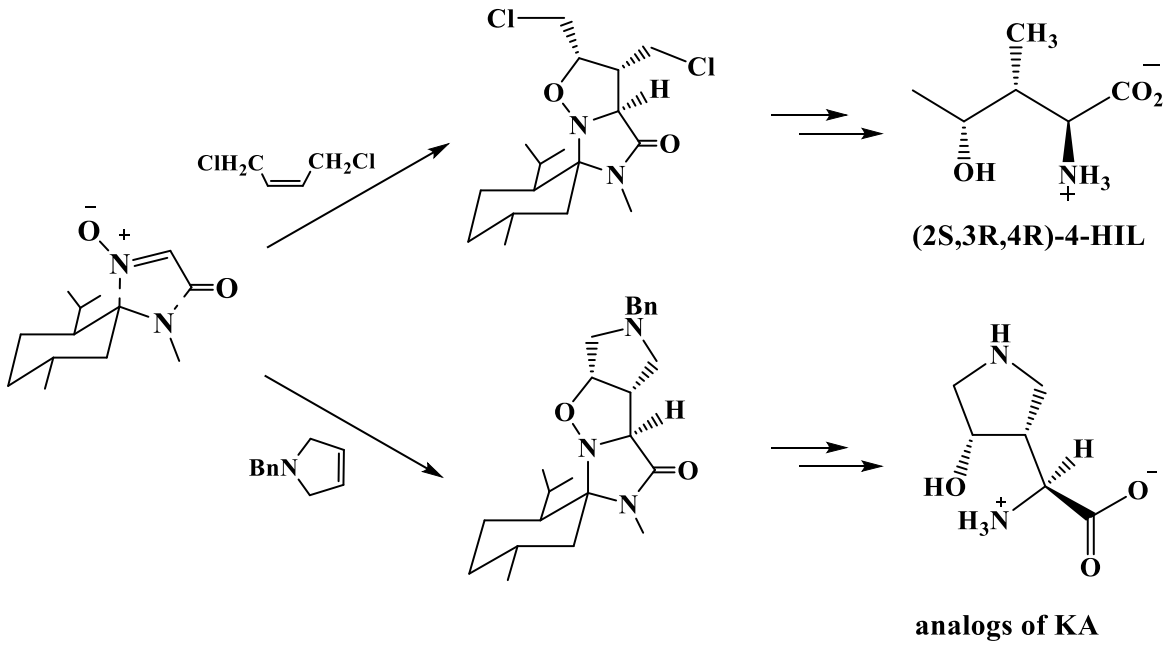
Scheme 4. 1,3-Dipolar cycloadditions using a nitrone derived from D-glyceraldehyde

In 2001, Altenbach et al. [31,32] utilized an innovative chiral cyclic nitrone, derived from (−)-menthone, to synthesize C-glycosyl α-amino acids with high regio- and diastereoselectivity. This nitrone participated in a 1,3-DC with C-vinyl-glycosides, yielding the corresponding ISXs as a single isomer, which was subsequently used as a precursor to produce C-glycosyl α-amino acids (Scheme 5).



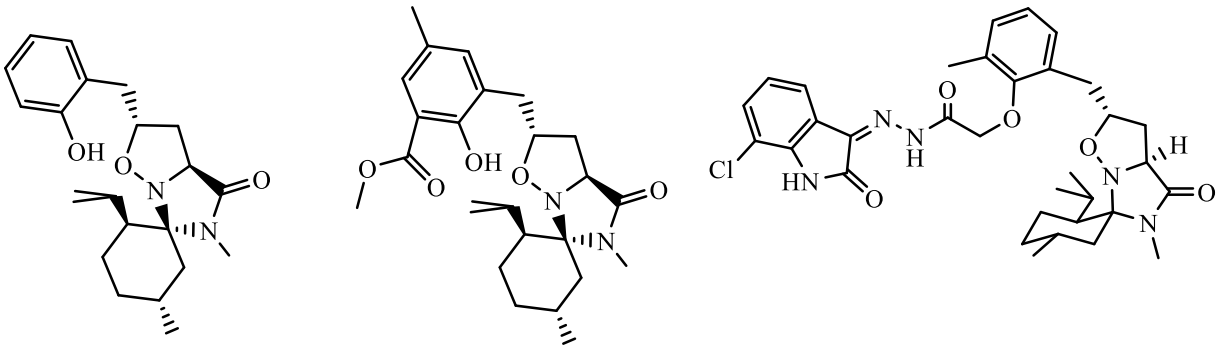
Scheme 5. 1,3-DC of the nitrone derived from (–)-menthone onto *C*-allyl-glycosides.

Our team also employed the same nitrone in 1,3-DCs with various alkenes, enabling the preparation of both natural and non-natural amino acids, such as (2S,3R,4R)-4-hydroxyisoleucine ((2S,3R,4R)-4-HIL) [33], a natural hypoglycemic agent, as well as analogs of kainic acid (KA) [34] (Scheme 6).

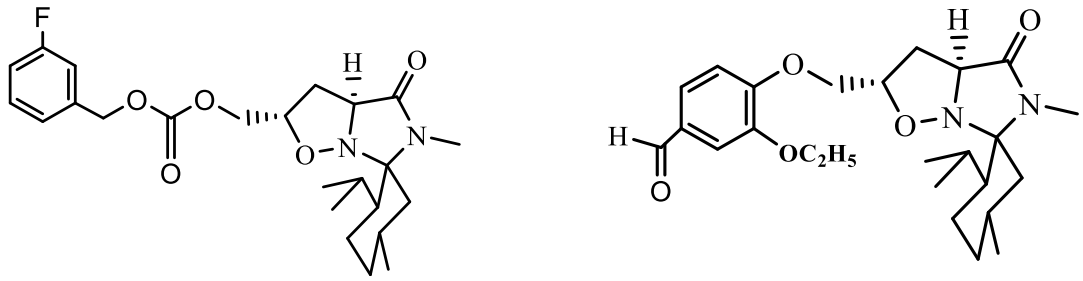


Scheme 6. Synthesis of amino acids from the nitrone derived from (–)-menthone.

Due to the high selectivity of the nitrone derived from (−)-menthone in 1,3-DC reactions, it has been used for the synthesis of a wide range of ISX derivatives, exhibiting various biological activities, including antidiabetic [35–39], anticancer [40], antibacterial [41], antimicrobial [42], and antioxidant properties [43] (Figure 7).



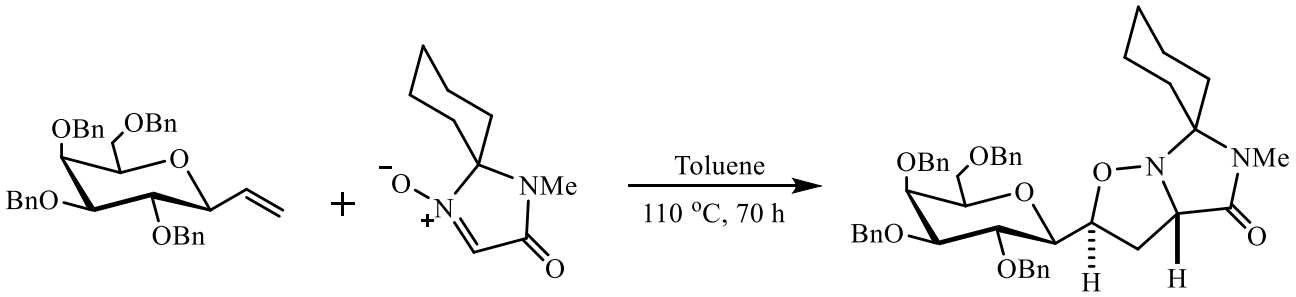
Anticancer activity Antidiabetic



Antioxidant and antibacterial Antidiabetic

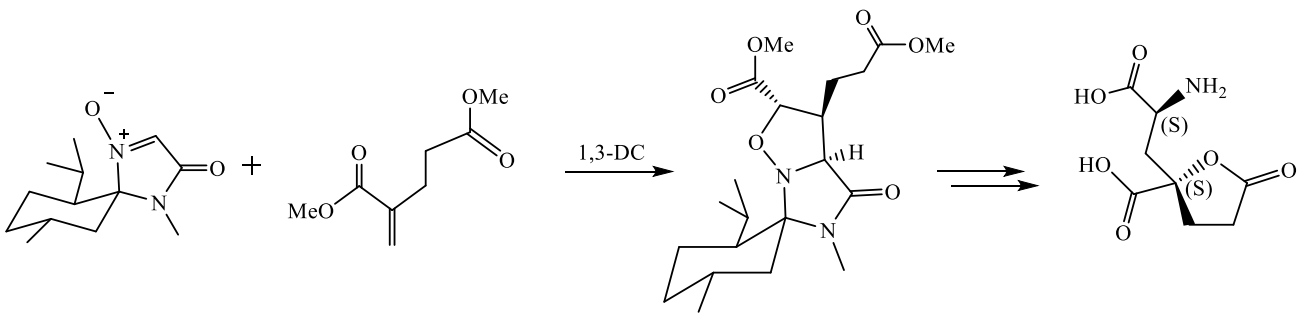
Figure 7. Biologically active isoxazolidine derivatives.

In 2022, Florian Rouzier et al. [44] developed an efficient strategy for the stereoselective synthesis of constrained C-glycosyl amino acid derivatives via C-vinylglycosides, involving a 1,3-DC using the nitrone derived from (−)-menthone as a key step (Scheme 7).



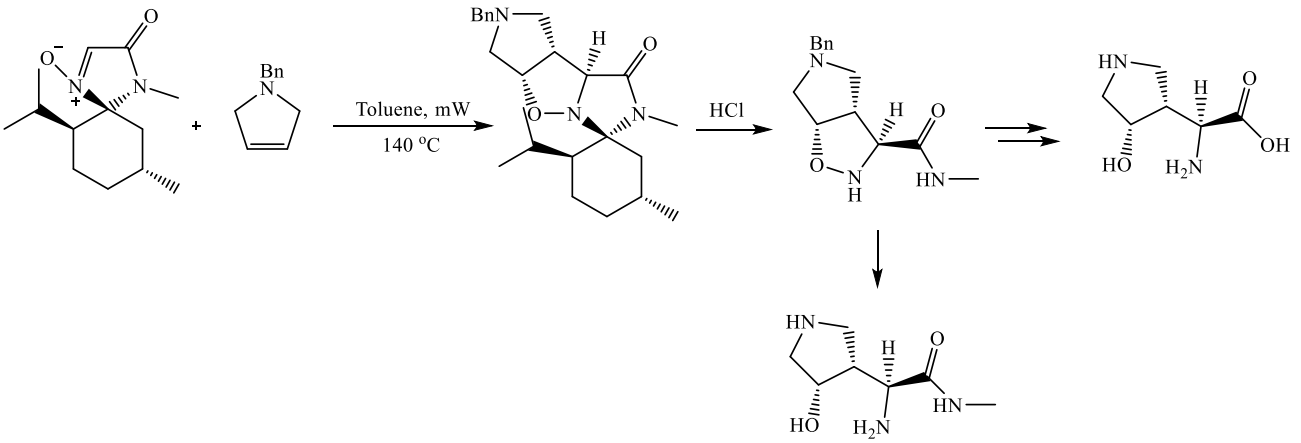
Scheme 7. 1,3-DC between C-vinylglycosides and nitrone

Dimethyl methylidene glutarate and the nitrone derived from (−)-menthone were engaged in a 1,3-DC reaction, leading to the formation of ISX derivatives with moderate selectivity. These derivatives are direct precursors of substituted glutamate in the (2S,4S) configuration [45] (Scheme 8).



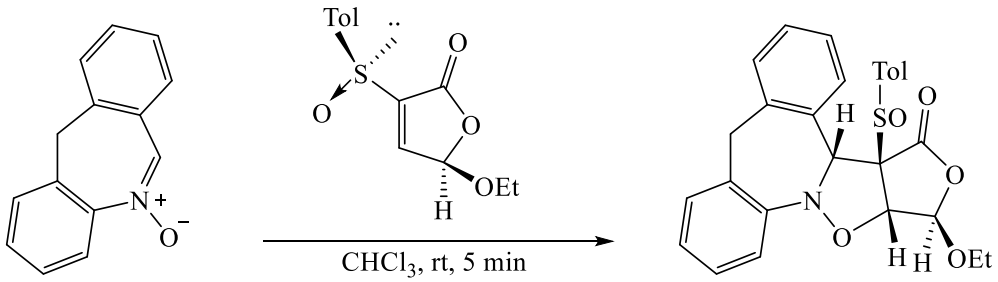
Scheme 8. 1,3-DC of Dimethyl methylideneglutarate with nitrone

Cecioni et al. [46] developed an enantio- and diastereoselective synthetic method to obtain spiro-fused heterocycles via [3+2] cycloaddition between nitrones derived from (+)- or (−)-menthone and N-benzyl-3-pyrroline. The fragility of the N-O bond in the ISX was then exploited to generate a series of enantiopure 4-hydroxy-3-glycinyl-pyrrolidine derivatives (Scheme 9).



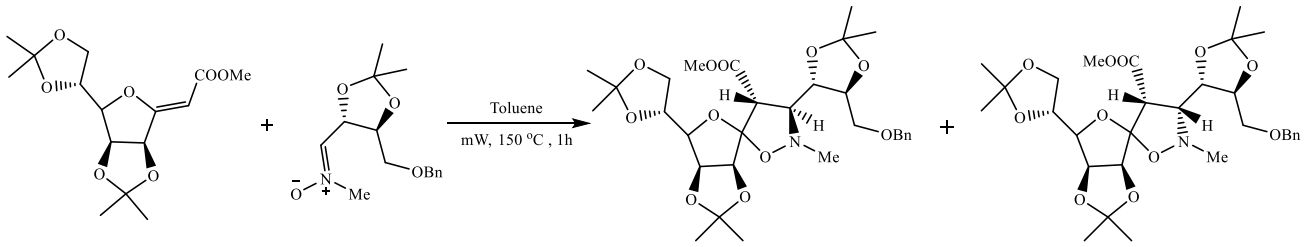
Scheme 9. Synthesis of enantiopure 4-hydroxy-3-glycinyl-pyrrolidine derivatives

Numerous chiral dipolarophiles have been used in 1,3-DC reactions for the stereoselective synthesis of ISXs. In 2004, M. Rosario Martin et al. [47] developed a 1,3-DC between N-oxy-morphanthridine and chiral sulfinylfuranones, resulting in the corresponding ISX as a single diastereoisomer (Scheme 10).



Scheme 10. stereoselective synthesis of ISXs

In 2013, Hassan Oukani et al. [48] investigated thermally and microwave-activated 1,3-DCs involving various α,β-unsaturated esters derived from D-mannose and chiral nitrones from threitol, as model reactions for synthesizing long-chain carbohydrates containing eleven carbon atoms (Scheme 15).



Scheme 11. 1,3-DC utilizing chiral nitrone derived from threitol

6. Biological Activities of ISX Derivatives

6.1. Antibacterial activity

ISX derivatives exhibit remarkable antimicrobial potential, demonstrating effectiveness against various pathogenic microorganisms, such as bacteria, fungi, and certain viruses. Their antimicrobial properties position them as promising candidates for developing novel drugs to address the escalating challenge of antibiotic resistance. For instance, the ISX derivative illustrated in Figure 8 demonstrated exceptional antibacterial activity, making it a promising candidate for further research and potential applications in medicinal chemistry [49].

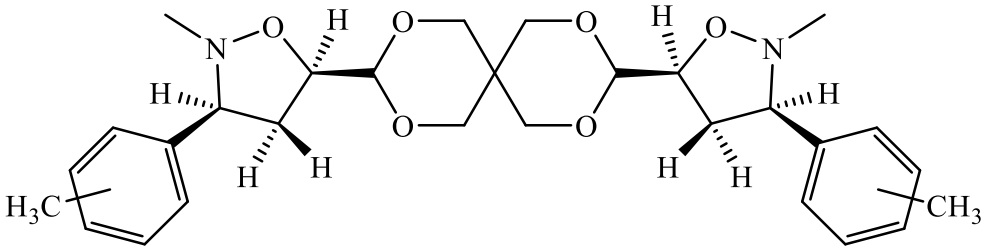


Figure 8. An antibacterial ISX derivative

Several ISX compounds have exhibited significant antifungal properties, showing activity against pathogenic fungi such as Candida albicans, Aspergillus fumigatus, and dermatophytes. These compounds often work by interfering with ergosterol biosynthesis or disrupting fungal cell membrane integrity.

6.2. Antidiabetic activity

Ghannay et al. [36] synthesized a novel series of isoxazolidine-isatin hybrids and revealed that the compound depicted in Figure 9 holds promise as a dual inhibitor of α-amylase and α-glucosidase, offering potential applications in diabetes management.

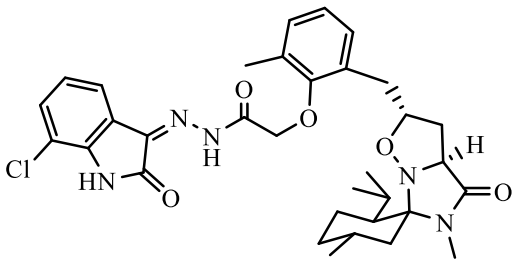


Figure 9. ISX-isatin hybrid

6.3. Anticancer activity

The exploration of ISX derivatives as potential anticancer agents has been an area of intense research in recent years. Many of these compounds have demonstrated significant cytotoxic effects against various cancer cell lines, making them promising candidates for the development of new chemotherapeutic drugs [39,50]. In this context, Eneama et al. [50] reported that compound ISX3

exhibited significant antitumor activity against MCF-7 cells, with an IC50 value of 32.49 µg/mL, showing greater potency compared to HdFn. Meanwhile, compounds ISX1 and ISX2 demonstrated IC50 values of 64 µg/mL and 128 µg/mL, respectively (Figure 10). These results highlight the potential of ISX derivatives as promising candidates for targeted breast cancer therapies.

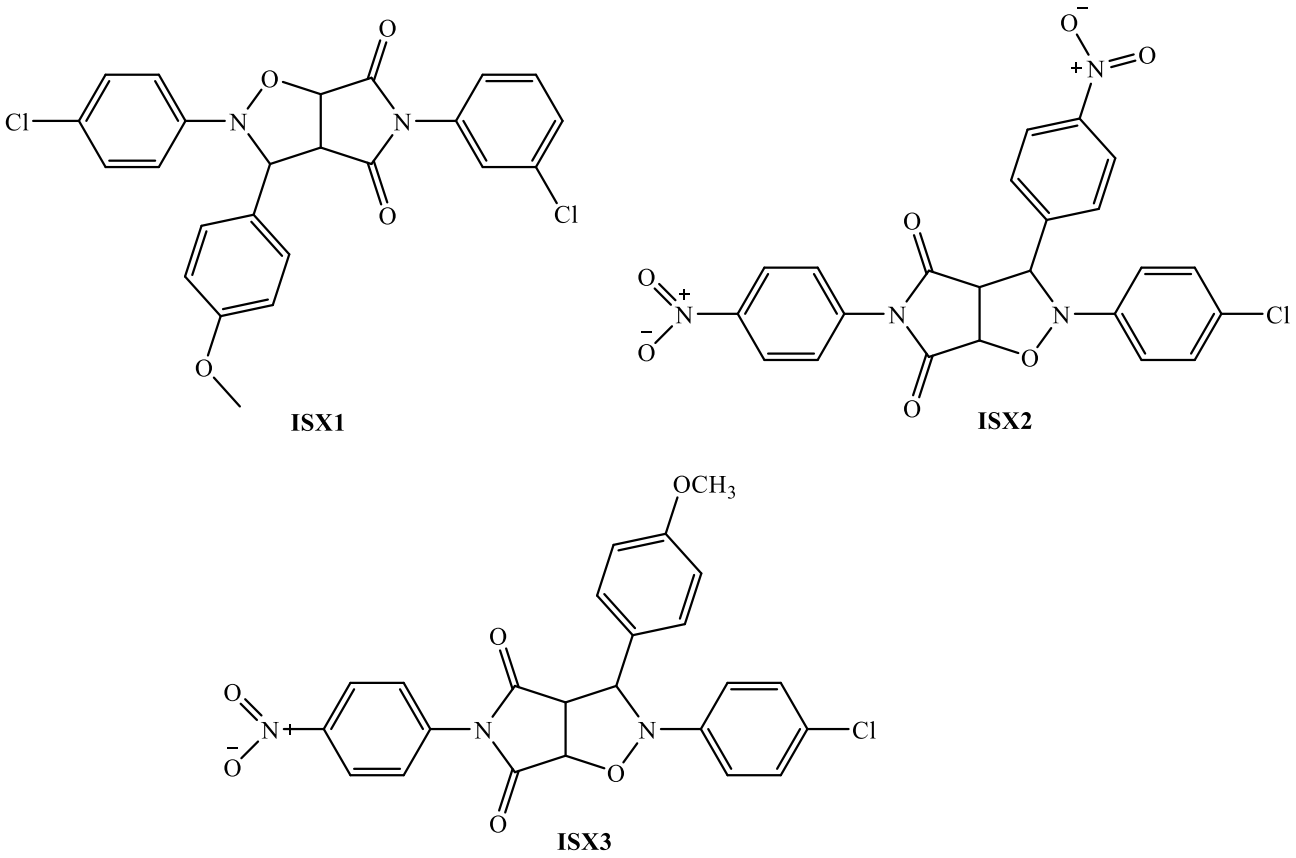


Figure 10. Examples of ISC Derivatives: Promising Candidates for Breast Cancer Targeted Therapies

Alminderej et al. [39] investigated the anticancer activities of ISX derivatives against three human cancer cell lines: MCF-7, A549, and SKOV3. Among the tested compounds, ISX4 and ISX5 demonstrated the highest activity, showing comparable efficacy to the standard drug doxorubicin. Additionally, these compounds exhibited notable EGFR enzyme inhibitory activity, surpassing that of Afatinib (Figure 11).

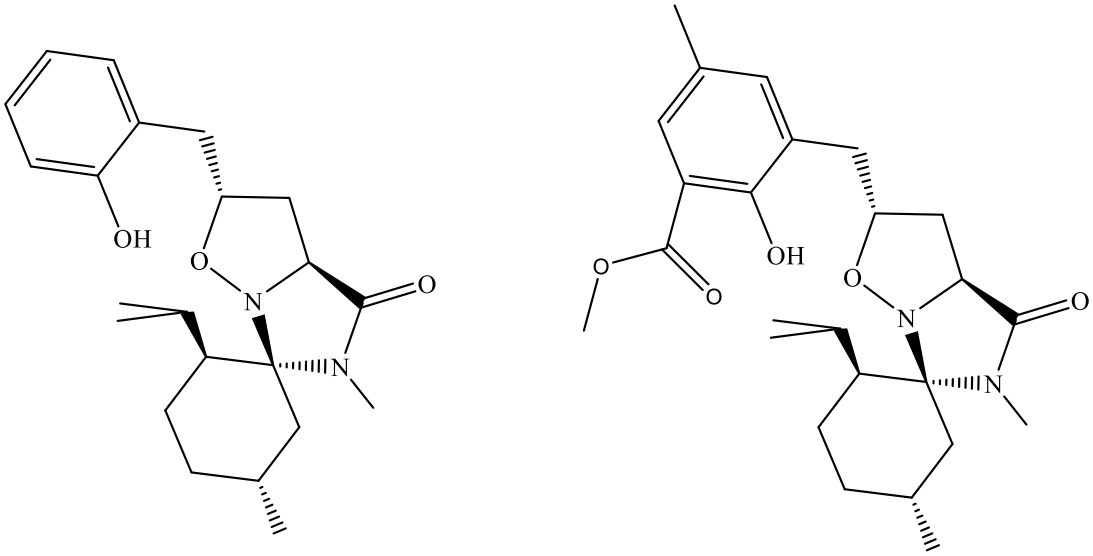


Figure 11. ISX derivatives exhibiting anticancer properties.

Conclusion

In conclusion, the 1,3-DC reaction, particularly between nitrones and alkenes, remains a cornerstone in the synthesis of heterocycles with high regio-, diastereo-, and enantioselectivity. The synthesis of chiral molecules through this method not only advances academic research but also meets the increasing demands of the pharmaceutical industry for enantiopure drugs, which are considered safer and more effective. Despite significant progress in understanding the regio- and stereoselective mechanisms of these reactions, challenges in achieving precise control persist, underscoring the need for continued research in this area. This review offers a focused bibliographic overview of nitrone-alkene cycloaddition reactions, emphasizing key advancements and ongoing challenges in achieving selectivity. It also highlights some of the biological activities associated with isoxazolidine derivatives.

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