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Review

N-Radical enabled cyclization of 1,*n*-enynesWen-Ting Wei ^{a,*}, Qiang Li ^{a,b}, Ming-Zhong Zhang ^c, Wei-Min He ^{d,#}^aState Key Laboratory Base of Novel Functional Materials and Preparation Science, School of Materials Science and Chemical Engineering, Ningbo University, Ningbo 315211, Zhejiang, China^bInstitution of Functional Organic Molecules and Materials, School of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng 252059, Shandong, China^cSchool of Chemistry and Chemical Engineering, Yangtze Normal University, Chongqing 408100, China^dHunan Provincial Key Laboratory of Materials Protection for Electric Power and Transportation, Changsha University of Science and Technology, Changsha 410114, Hunan, China

ARTICLE INFO

Article history:

Received 12 June 2020

Accepted 13 July 2020

Available online 22 September 2020

Keywords:

1,*n*-Enynes*N*-Radical

Cyclization

C–N bond

ABSTRACT

Compared to the widely used carbon-centered radicals, *N*-radicals have been relatively unexplored owing to the lack of practical and convenient production methods. Over the past few years, benefiting from the resurgence of reliable and controllable radical chemistry, *N*-radicals have been produced via thermal decomposition, oxidants, metal salts, or electrocatalysis. Therefore, numerous *N*-radical enabled cyclization of 1,*n*-enynes methods have been developed, providing a versatile and concise synthetic platform for the preparation of complex cyclic systems and natural products containing elaborate ring frameworks. In this review, we will summarize recent advances in the promising field of radical chemistry focusing on the production methods of *N*-radicals and their cyclization patterns, associated mechanisms, unmet challenges, and future opportunities.

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1. Introduction

N-Radicals are versatile intermediates with pivotal roles in the formation of C–N bonds, which are prevalent in pharmaceuticals, natural products, and functional materials [1–7]. However, compared to the extensively used carbon-centered radicals, *N*-radicals have been relatively unexplored owing to the lack of practical and convenient production methods. The earliest example of an *N*-radical was used in an amination process for the synthesis of five-membered nitrogen heterocycles via the Hofmann–Löffler–Freitag reaction more than 130 years ago [8]. Based on this pioneering study, a series of radical initiator-promoted protocols have been developed

for *N*-radical generation via cleavage of N–X (X = Cl, Br, I, N, O, S, Si, among others), N–H, or C–N bonds using (*n*-Bu₃Sn)₂, Et₃B, azodiisobutyronitrile (AIBN), or strong organic oxidants at elevated temperatures [9–13]. Metal coordination is another method used for the production of stable and reactive *N*-radicals [14–21]. This method might be divided into two main pathways: (1) the reactions of transition metals (Rh, Ru, Ag, Fe, Co, Ni, Cu, among others) with nitrogen sources (azide, iminoiodine, hydroxylamine, among others), and (2) the exchange of [M]–OR (M = metal) intermediates with amines. Recently, photoredox catalysis has emerged as a unique platform for efficient and selective preparation of *N*-radicals via single-electron transfer (SET) process under mild conditions

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This work was supported by the National Natural Science Foundation of China (21801142, 21802062), the Fundamental Research Funds for the Provincial Universities of Zhejiang (SJLY2021004) and the Hunan Provincial Natural Science Foundation of China (2019JJ20008).

DOI: 10.1016/S1872-2067(20)63702-0 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 42, No. 5, May 2021

using visible-light as an inexpensive and clean energy source [22–33]. Owing to the advances of electrocatalysis in modern organic synthesis, radical species can be initiated by anodization or cathodic reduction, representing an environmentally-friendly and controllable method for the generation of *N*-radicals [34–37].

Because of its high efficiency in the formation of chemical bonds (two or more new bonds are formed in a single step) and selective introduction of varying external functional groups, 1,*n*-enyne cyclization reaction has been recognized as an indispensable and sustainable methodology for accessing complex cyclic systems and natural products containing elaborate ring frameworks [38–44]. Conventionally, 1,*n*-enyne cyclization approaches are achieved via transition-metal mediation/catalysis using precious metals (Au, Pd, Rh, Ru, among others) and/or initiators [45–47]. A landmark work on the radical induced 1,*n*-enyne cyclization was reported by Curran et al. [48], who described the concise total synthesis of (±)-hirsutene via intramolecular radical cascade cyclization of iodo-enyne (Scheme 1). Benefitting from the resurgence of reliable and controllable radical chemistry as modern synthesis technology evolved, radical induced 1,*n*-enyne cyclization has become the focus of increasing interest over the past few years [49–69]. These processes enable the cyclization of 1,*n*-enyne in a mild and predictable manner with elevated functional group compatibility and atom utilization, frequently without the use of stoichiometric amounts of metals and/or toxic initiators.

Currently, *N*-radical enabled cyclization of 1,*n*-enynes is being intensively investigated as it has proven to be a valuable and environmentally-friendly strategy to construct diversely functionalized nitrogen-containing motifs in synthetic chemistry. However, an exclusive review devoted to this promising topic has not been provided yet [70–72]. Hence, in this review, we summarize the advances in the field of radical chemistry in a timely manner. In general, these *N*-radicals are initiated via thermal decomposition, stoichiometric oxidants, metal salts, or electrocatalysis by cleaving the corresponding N–O, N–Si, or N–H bonds. To date, there are three pathways for initiating these cyclization transformations (Scheme 2): (1) selective *N*-radical addition to the C=C bond followed by intramolecular cyclization to produce the alkenyl radical intermediate, which then undergoes further cyclization, H-abstraction, or radical coupling to yield the final products (Scheme 2.1), (2) selective *N*-radical addition to the C≡C bond, followed by intramolecular cyclization and oxidative dehydrogenation (Scheme 2.2), and (3) intramolecular addition of in situ-generated *N*-radicals, which are then converted into the final product through bicy-

Scheme 1. Intramolecular radical cascade cyclization of iodo-enyne.

Scheme 2. Overview of *N*-radical enabled cyclization of 1,*n*-enynes.

cyclization, SET oxidation, and dehydrogenation (Scheme 2.3). In the following sections, we provide an outline of the recent advances in *N*-radical enabled cyclization of 1,*n*-enynes based on the types of *N*-radical precursors, with particular emphasis on the reaction mechanisms.

2. Cyclization initiated by NO₂ radical

Nitration is one of the most attractive and challenging process in synthetic chemistry owing the application of nitro-compounds in pharmaceuticals, agrochemicals, dyes, and polymers [73–76]. Conventionally, nitro-compounds are generated by electrophilic or nucleophilic substitutions using NO₂⁺ or NO₂[−] [77–79]. Owing to the popularity of radical strategies in modern organic chemistry, nitration can be performed via radical processes, which represent efficient and simple tools for the conversion of C–H bonds to their C–NO₂ counterparts [80–81]. Therefore, a series of nitrating agents, such as *t*-BuONO, NaNO₂, AgNO₂, Fe(NO₃)₃, Cu(NO₃)₂, among others, have been developed for radical nitration [82–87]. Among them, *t*-BuONO has been extensively used because it is a safe, inexpensive, and efficient agent to generate NO₂ radicals under mild conditions [88,89]. The NO₂ radicals can be generated from *t*-BuONO via two pathways: the reaction of *t*-BuONO, H₂O, and O₂ in air, and homocleavage of the unstable N–O bond of *t*-BuONO under thermal conditions and subsequent aerobic oxidation (Scheme 3.1). The chemoselectivity of the NO₂ radical addition to 1,*n*-enynes mainly relies on the substitution effect on the terminal alkene. As showed in Scheme 3.2, NO₂ radical addition across the C≡C bond takes precedence over the C=C bond when 1,*n*-enynes have 1,1-disubstituents at the terminal alkene, whereas terminal alkene radical addition across the C=C bond is preferential.

In 2014, Li et al. [90] reported the first example of NO₂ radical generation from *t*-BuONO in the presence of H₂O to facilitate cascade nitration/cyclization of 1,7-enynes for the synthesis of pyrrolo[4,3,2-de]quinolinones (Scheme 4). The reaction proceeds via alkene nitration, 6-*exo-trig* cyclization, C–H nitration, and redox cyclization, forming four C–N bonds and one C–C bond; as a result, two nitro groups and one amine group

Scheme 3. Generation of NO₂ radical and its chemoselectivity addition to 1,*n*-enynes.

are incorporated into the final product in one step under metal-free conditions. The amount of H₂O used has a fundamental influence on the reaction yield and 4.5 equiv. was proven to be the optimal amount; when 14 equiv. was used, the yield decreased substantially.

According to the controlled experiment using ¹⁸O-labeled H₂¹⁸O under optimized conditions, a mixture of the product [¹⁸O₁] containing one oxygen atom, and the product [¹⁸O₂] containing two oxygen atoms, was detected in a 1:1 ratio, suggesting that H₂O was not the only oxygen atoms source of the nitro groups (Scheme 5). Based on preliminary mechanistic studies, a possible mechanism is proposed for this reaction. As can be seen in Scheme 5, first, the NO₂ radical is formed from *t*-BuONO under H₂O and air. Thereafter, the radical addition and cyclization occurred to generate intermediate **A**, which underwent a sequential reaction with NO or NO₂, electrophilic addition of the N=O group to the phenyl ring, further reaction with NO or NO₂, and a redox reaction to produce the final product **5**.

Shortly thereafter, an improved approach was developed by the same research group [91]. Using 1-ethynyl-2-(vinylxy)benzenes, a selective and simple nitrate cyclization with *t*-BuONO was performed in air at ambient temperature (Scheme 6). The substituents on the 2-position of the alkene moiety (R³) affect the reaction process: when R³ is H, the nitrate cyclization generates benzofurans, and when R³ is alkyl or Ph, benzodihydrofurans are yielded. Air plays a key role in this transformation reaction and no product is detected under degassed N₂-purged EtOAc. However, when using O₂

Scheme 4. Cascade nitration/cyclization of 1,7-enynes for the synthesis of pyrrolo[4,3,2-de]quinolinones.

Scheme 5. ¹⁸O-Labeled experiment and suggested mechanism for cascade nitration/cyclization of 1,7-enynes.

instead of air, the product yield decreased because of the formation of the C–O bond decomposition side-products under the stronger oxidation system.

The ¹⁸O-labeling experiment results show that the OH group originates from H₂O and the oxygen atom of the carbonyl from the O₂ present in the air (Scheme 7.1–7.4). Considering the results discussed here, a possible mechanism is proposed for this transformation (Scheme 7). Initially, the alkenyl intermediate **B** is formed via NO₂ radical addition and intramolecular cyclization. In contrast to the reaction reported in Scheme 5, the alkenyl intermediate **B** is trapped by O₂ to produce the peroxy intermediate, which then undergoes O–O bond cleavage, isomerization, and SET to give the cationic intermediate **C**. Then, intermediate **C** undergoes reduction or nucleophilic addition, based on the R³ group substitution effect, yielding the final products.

In 2015, Liang et al. [92] demonstrated a versatile

Scheme 6. Nitrate cyclization of 1-ethynyl-2-(vinylxy)benzenes.

Scheme 7. ^{18}O -Labeled experiments and suggested mechanism for nitrate cyclization of 1-ethynyl-2-(vinyl)benzenes.

nitro-carbocyclization of 1,6-enynes with *t*-BuONO using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), which represented a rare constructing olefinic $\text{C}(\text{sp}^2)\text{-NO}_2$ bond through the addition of NO_2 radical to internal alkynes (Scheme 8). In contrast to the methods developed by the Li group [90,91], the chemoselectivity of NO_2 radical addition across the $\text{C}\equiv\text{C}$ bond is preferential, as the 1,6-enyne has 1,1-disubstituents at the terminal alkene. Other nitrating agents, such as NaNO_3 , $\text{Bi}(\text{NO}_3)_3$, $\text{Fe}(\text{NO}_3)_3$, and AgNO_2 , also have reactivity in the nitro-carbocyclization; however their reactivities are less pronounced than that of *t*-BuONO. Moreover, TEMPO is proven to be important in this transformation, as the product yield was only 27% in its absence.

The proposed mechanism is shown in Scheme 9. First, NO_2

Scheme 8. Nitro-carbocyclization of 1,6-enynes.

Scheme 9. Suggested mechanism for nitro-carbocyclization of 1,6-enynes.

radical was generated via homocleavage of *t*-BuONO at 70 °C and subsequently oxidized. Then, intermediate **D** was produced upon radical addition to the $\text{C}\equiv\text{C}$ bond, followed by intramolecular cyclization and oxidative dehydrogenation, producing the final product.

In 2018, Wei group described the regioselective nitrative cyclization of 1,6-enynes using *t*-BuONO under metal- and additive-free conditions (Scheme 10) [93]. The key point of this method is the design of a new *N*-linked 1,6-enyne skeleton, leading to the synthesis of 2-pyrrolidinones with high regioselectivity and satisfactory yields, which represents an important class of five-membered *N*-heterocyclic structural core in several natural products and bioactive molecules [94–97]. The reaction pathway involves NO_2 radical addition, followed by 5-*exo*-cyclization, and H-abstraction, allowing the formation of one C–N and one C–C bond. Various *N*-aryl substituted *N*-linked 1,6-enynes, even if they are *N*-alkyl substituents, are useful scaffolds for this nitrative cyclization.

When using anhydrous 1,4-dioxane as the reaction medium, the product yield is only 12%, which suggests that H_2O plays a pivotal role in this reaction (Scheme 11.1). Moreover, the product yield increased to 79% when 1.0 equiv. of H_2O was added to anhydrous 1,4-dioxane, further confirming the pivotal role of H_2O (Scheme 11.2). The deuterium-labeled experimental result suggested that one of the hydrogen atoms at the end of the olefin originated from H_2O (Scheme 11.3). The suggested mechanism for the formation of 2-pyrrolidinones is shown in Scheme 11. Initially, the present system leads to the generation of NO_2 radical. Then, the NO_2 radical addition to the $\text{C}=\text{C}$ bond of 1,6-enyne generated an alkyl radical intermediate, which underwent a sequential radical cyclization and H-abstraction using *t*-BuOH yielding the product.

$\text{Cu}(\text{NO}_3)_2$ is a well-known NO_2 radical precursor; however, it

Scheme 10. Regioselective nitrative cyclization of 1,6-enynes.

3. Cyclization initiated by N_3 radical

Reaction scheme showing the synthesis of 14 from 11 and 13:

11 + 13 $\xrightarrow[\text{DMF, 80 } ^\circ\text{C, Air}]{\text{Oxone (1.2 equiv)}}$ 14, 62%-96% yields

Three specific examples of the reaction are shown below:

- Example 1: 11 (R¹=Ph, R²=Me, R³=NO₂) reacts with 13 to yield 14 (R¹=Ph, R²=Me, R³=NO₂) in 95% yield.
- Example 2: 11 (R¹=Ph, R²=Me, R³=MeNO₂) reacts with 13 to yield 14 (R¹=Ph, R²=Me, R³=MeNO₂) in 68% yield.
- Example 3: 11 (R¹=Ph, R²=Me, R³=PhNO₂) reacts with 13 to yield 14 (R¹=Ph, R²=Me, R³=PhNO₂) in 62% yield.

(1) The generation of N_3 radical

Path I

Path II

$$\text{TMSN}_3 + \text{ML}_n \rightarrow \text{ML}_{n-1} \xrightarrow{\text{N}_3} \dot{\text{N}}_3 + \text{ML}_{n-1}$$

Path III

$$\text{TMSN}_3 \xrightarrow{[\text{O}]} \dot{\text{N}}_3$$

(2) Azidation of 1, n -enynes

Scheme 13. Generation of N_3 radical and azidation of 1,*n*-enynes.

In 2015, Li et al. [118] reported a major breakthrough in azidation of 1,*n*-enynes. They described a copper catalyzed [2+2+1] annulation of 1,*n*-enynes using N₃-containing 2-iodo-benzoate, providing a simple and practical platform to incorporate a nitrogen atom and an azido group into heterocyclic molecules with 100% stereoselectivity (Scheme 14). Under optimized conditions, several N-, O-, C-linked 1,*n*-enynes generated 3*H*-pyrrolo[3,4-*c*]quinolin-4(3*aH*)-ones, chreno[3,4-*c*]pyrrol-4(9*bH*)-ones, and indeno[1,2-*c*]pyrrolines with reasonable yields. Moreover, this reaction was completely sup-

Scheme 14. Copper catalyzed [2+2+1] annulation of 1,*n*-enynes.

Scheme 15. Suggested mechanism for copper catalyzed [2+2+1] annulation of 1,*n*-enynes.

pressed by stoichiometric amounts of radical inhibitors, including TEMPO, hydroquinone, and butylated hydroxytoluene (BHT), indicating that this transformation involved a radical process.

Scheme 15 shows the reaction mechanism proposed for the copper catalyzed [2+2+1] annulation of 1,*n*-enynes. Initially, the N₃ radical is produced using N₃-containing 2-iodo-benzoate with the aid of active Cu²⁺ species under heating conditions. Subsequently, the aminyl radical intermediate **G** is generated via a sequential radical addition, intramolecular bicyclization, releasing N₂. Then, intermediate **G** is transformed into intermediate **H** via H-abstraction or reduction-protonation sequence. Finally, the addition of another N₃ radical to the alkene moiety of intermediate **H** gives the final product.

Diastereodivergent catalysis is undergoing a revival in synthetic chemistry owing to its inherently advantageous properties. It provides straightforward and efficient paths to produce complete sets of diastereomers [119–122]. In 2016, Li et al. [123] disclosed a novel transition-metal controlled diastereodivergent azidation of 1,7-enynes (Scheme 16). They proposed the N₃ transfer from the M–N₃ complex to the alkyl radical; the radical reaction was terminated by the N₃ transfer oxidation step. The Mn(OAc)₃/*N*-fluorobenzenesulfonimide (NFSI)/

Scheme 16. Transition-metal controlled diastereodivergent azidation of 1,7-enynes.

Scheme 17. Suggested model for Mn- and Cu-controlled diastereodivergence.

MeCN-mediated system produces *trans*-fused pyrrolo[3,4-*c*]quinolinones, whereas the Cu(ClO₄)₂/bipyridine (Bipy)/*tert*-butyl peroxybenzoate (TBPB)/MeCN system gives the *cis*-products.

A tentative model for diastereodivergence is outlined in Scheme 17. In the case of the Mn-mediated system, Mn–N₃ possibly coordinates with the nitrogen atoms of the intermediate, followed by N₃ transfer to produce the *trans*-products. When Cu salts are added to the reaction mixture, the pronounced steric repulsion between the phenyl and N₃ groups enables the N₃ attack on the opposite side, generating the *cis*-products.

In 2019, Wei et al. [124] reported a unique azidation/cyclization of 1,6-enynes with N₃ sources for the synthesis of 2-pyrrolidinones using K₂S₂O₈ as oxidant (Scheme 18). The reaction was conducted under metal- and ligand-free conditions by employing an inexpensive and stable inorganic oxidant, and the azidation process was terminated by the hydrogen atom abstraction from the solvent or H₂O. K₂S₂O₈ played a key role in the generation of N₃ radical, and the products were not detected in its absence. Numerous N₃ sources, including TMSN₃, N₃-containing 2-iodo-benzoate, NaN₃, TfN₃, and TsN₃, were effective in this azidation. Moreover, the azidation products can be easily transformed into amino and triazole, demonstrating the synthetic effectiveness of this protocol.

When the reaction was performed in anhydrous MeCN, the product yield was only 11%, which reveals that H₂O is essential for this transformation (Scheme 19.1). The deuterium-labeled experimental results suggested that the hydrogen atoms at the end of the olefin may be originated from H₂O or the solvent (Scheme 19.2). On the basis of these studies, the proposed mechanism is shown in Scheme 19. First, the N₃ radical is gen-

Scheme 18. Azidation/cyclization of 1,6-enynes with N₃ sources.

Scheme 19. Control experiments and suggested mechanism for azidation/cyclization of 1,6-enynes with N_3 sources.

erated from TMSN_3 in the presence of $\text{K}_2\text{S}_2\text{O}_8$. Subsequently, the final product is produced via a sequential radical addition, intramolecular cyclization, and H-abstraction.

In 2016, an efficient and novel haloazidation of 1,7-enynes protocol for the construction of biologically unique azidylated 3,4-dihydroquinolin-2(1*H*)ones was accomplished by Wang et al. [125] (Scheme 20), by using TMSN_3 as the N_3 radical precursor and NXS ($\text{X} = \text{I}, \text{Br}, \text{Cl}$) as the halogen source. The

Scheme 20. Haloazidation of 1,7-enynes for the construction of 3,4-dihydroquinolin-2(1*H*)ones.

Scheme 21. Suggested mechanism for haloazidation of 1,7-enynes.

main challenge of this protocol was the difficulty in controlling N_3 and halogen radicals during the long process of the one-pot operation and its poor selectivity in the radical addition toward alkenyl and alkynyl groups. To solve this problem, a mild oxidation system was introduced and the substrate of 1,7-enynes was reasonably designed, followed by sole azidation and subsequent halogenation. An important characteristic of this process is the cascade-type formation of successive C–N, C–C, and C–X bonds under mild and metal-free conditions, initiated by the addition of an in situ generated N_3 radical.

The proposed mechanism is shown in Scheme 21. Initially, the N_3 and I radicals are generated in the presented system. Then, the N_3 radical attacks the alkenyl moiety of the 1,7-enynes to produce an alkyl radical intermediate trapped by the alkynyl motif to produce a vinyl radical intermediate. Finally, the radical coupling between the vinyl radical intermediate with I radical generates the final 3,4-dihydroquinolin-2(1*H*)-ones.

In 2018, Wei et al. [126] accomplished a similar haloazidation of 1,6-enynes for the synthesis of 2-pyrrolidinones using $\text{PhI}(\text{OAc})_2$ as oxidant at room temperature (Scheme 22). In this reaction, three new chemical bonds, including C–X ($\text{Cl}, \text{Br}, \text{I}$), C–N, and C–C bonds, were formed in one step under metal-free conditions. The current haloazidation was inhibited in the presence of TEMPO or BHT under the standard reaction conditions, suggesting that the

Scheme 22. Haloazidation of 1,6-enynes for the synthesis of 2-pyrrolidinones.

reaction likely involved a radical process. Hence, a radical based reaction mechanism, was proposed for the haloazidation of 1,6-enynes, similar to that reported in a previous work [125].

Meanwhile, Lin et al. [127] reported a novel TBPB promoted iodoazidation of *para*-quinone methides to produce several spiro[4.5]deca-6,9-dien-8-ones, which are a class of spiro skeletons with important biological activities (Scheme 23). This iodoazidation underwent a cascade radical 1,6-addition, 5-*exo-dig* cyclization, radical coupling process, with successive formation of C–N, C–C, and C–I bonds in a one-pot operation with wide functional group tolerance. The product was obtained with 41% yield in the absence of oxidant, and a product trace was detected in the presence of $\text{PhI}(\text{OAc})_2$; however, the study did not provide reasonable explanations for these unusual experimental results.

Recently, Rong et al. [128] disclosed a time-economical haloazidation of 1,6-enynes for the synthesis of succinimide derivatives using $\text{PhI}(\text{OAc})_2$ as oxidant in dichloromethane (DCM) at room temperature (Scheme 24). The advantages of the process includes fast reaction time (3–5 min), excellent *Z/E* ratio (up to 99:1), ease of scale-up synthesis, and mild reaction conditions; therefore, greatly reducing costs, and minimizing the environmental impact.

4. Cyclization initiated by amidyl radical

Over the past years, impressive advances have been achieved in the field of cleavage of weak N–O and N–Si bonds into *N*-radicals, as discussed here. However, the development of more efficient direct conversion of N–H bonds into *N*-radicals under mild conditions is still an attractive but challenging goal in the synthetic chemistry field owing to the high bond dissociation energy. In general, most of the methods developed for direct transformation of N–H bonds into corresponding *N*-radicals still rely on the use of stoichiometric strong oxidants at elevated reaction temperatures [129–134].

Organic electrochemistry has emerged as an environmentally-friendly alternative to traditional synthetic methods because of its unique redox modes and importance in sustainable chemistry [135,136]. It employs traceless electrical current to promote redox reactions and controls the electrode potentials

Scheme 23. Iodoazidation of *para*-quinone methides.

Scheme 24. Haloazidation of 1,6-enynes for the synthesis of succinimide derivatives.

easily during the entire process, eliminating the need of potentially hazardous redox reagents. In this context, a significant achievement has been made by Xu's group in 2019, who developed the efficient synthesis of benzimidazolones and benzoxazolones by building both the benzene and heterocyclic rings via electrochemical dehydrogenative cyclization of arylamine-tethered 1,5-enynes initiated by the intramolecular addition of in situ-generated amidyl radical (Scheme 25) [137]. This electricity-powered oxidative reaction proceeded with H_2 evolution, and without the use of metal catalysts or oxidizing reagents. After reaction optimization, the target product was produced with the highest yield when performing electrolysis at 110 °C and constant current of 15 mA, with a reticulated vitreous carbon (RVC) anode, a platinum plate cathode, 1 equiv. of trifluoroacetic acid (TFA) as the acid additive, and DMF as the solvent.

The proposed reaction mechanism is shown in Scheme 26. Initially, the amidyl radical is generated in the electrochemical system, followed by the attack of the alkynyl moiety of the 1,5-enynes to produce intermediate **I**. Thereafter, the intermediate **I** is converted into intermediate **J** via 6-*endo-trig* cycliza-

Scheme 25. Electrochemical dehydrogenative cyclization of arylamine-tethered 1,5-enynes.

Scheme 26. Suggested mechanism for electrochemical dehydrogenative cyclization of arylamine-tethered 1,5-enynes.

tion (path I) or 5-*exo-trig* cyclization and the subsequent radical ring-opening reaction is performed (path II). Then, intermediate J underwent a SET oxidation and deprotonation to produce intermediate K. Lastly, the final product was generated by the sequential loss of two electrons and two protons from intermediate K.

5. Conclusions and future outlook

Considering the high synthetic efficiency and mild reaction conditions, *N*-radical enabled cyclization of 1,*n*-enynes has attracted considerable attention in the past years. A wide range of rationally designed 1,*n*-enynes (such as aryl, N, O, and C linked-1,*n*-enynes, *n* = 5, 6, 7) in combination with several *N*-radicals (such as NO₂ radical, N₃ radical, and amidyl radical) have been investigated along these lines. Numerous biologically interesting cyclic molecules can be efficiently synthesized with high selectivity, excellent functional group compatibility, and ideal atom utilization. In this review, we demonstrated that oxidative systems are essential for most of the transformations described in the four different radical initiation methods, thermal decomposition, oxidants, metal salts, or electrocatalysis, which occur by cleavage of the N–O, N–Si, or N–H bonds to produce corresponding *N*-radicals. The cyclization of 1,*n*-enynes can be achieved following three different approaches: (1) selective radical addition to the C=C bond followed by intramolecular cyclization, followed by further cyclization, H-abstraction, or radical coupling, (2) selective radical

addition to the C≡C bond, intramolecular cyclization, and oxidative dehydrogenation, or (3) intramolecular addition of in situ-generated radical to the C≡C bond, followed by bicyclization, SET oxidation, and dehydrogenation.

Despite the considerable progress in this rapidly developing research field since 2014, some challenges and opportunities remain: (1) *N*-radical precursors are limited to *t*-BuONO and TMSN₃. One example has been described involving oxidative cleavage of N–H bond of amides [137], which makes the application of more convenient precursors attractive; (2) the oxidative cyclization of 1,*n*-enynes mainly relies on chemical oxidants, such as TBPB, K₂S₂O₈, and PhI(OAc)₂. Therefore, another future goal is the development of an ideal oxidant system, especially using O₂ from air or electrocatalytic oxidation. It is our belief that new strategies for 1,*n*-enynes cyclization and alternative types of easily available *N*-radical precursors will be discovered, and *N*-radical enabled cyclization of 1,*n*-enynes will eventually play an exceptional role in medicinal chemistry and materials science in the near future.

Notes

The authors declare no competing financial interest.

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Graphical Abstract

Chin. J. Catal., 2021, 42: 731–742 doi: 10.1016/S1872-2067(20)63702-0

N-Radical enabled cyclization of 1,*n*-enynes

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This review summarizes the recent advances in *N*-radical enabled cyclization of 1,*n*-enynes, with emphasis on approaches for the generation of *N*-radicals and their cyclization patterns, associated mechanisms, unmet challenges, and future opportunities.

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氮自由基启动的1,*n*-烯炔环化反应

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摘要: C–N键广泛存在于药物、天然产物和功能材料中, 而氮中心自由基在C–N键的构建中起到关键作用。但是, 与广泛使用的碳中心自由基相比, 氮中心自由基由于缺乏实用简便的产生方法而尚未得到充分研究。因此, 发展高效的氮中心自由基引发反应迫在眉睫。在过去的几年里, 得益于可信赖且可控制的自由基化学的兴起, 可以通过热分解、氧化剂促进、金属盐催化或电催化来产生氮中心自由基。

1,*n*-烯炔环化不仅可以一步反应同时构建形成两个或多个新的化学键, 而且可以高选择性引入各种外部官能团, 被认为是构建复杂环状化合物必不可少的方法。传统上, 通过贵金属(例如Au、Pd、Rh、Ru等)和/或引发剂介导/催化来实现1,*n*-烯炔环化反应。1985年, Curran和他的同事报道了具有里程碑意义的工作, 该方法通过碘代烯炔类化合物的分子内自由基串联环化反应实现了(±)-hirsutene的简洁全合成。受该工作的启发, 并伴随着现代合成技术的发展, 自由基启动的1,*n*-烯炔环化由于反应条件温和、具有较高的官能团兼容性、原子利用率高、通常不使用化学计量的金属催化剂和/或有毒引发剂, 因而受到化学家们越来越多的关注。

在此背景下, 化学工作者已经开发了多种氮中心自由基启动的1,*n*-烯炔类化合物环化反应的方法。然而, 据我们所知, 目前还没有专门针对该主题的综述, 因此本文及时进行总结分析。迄今为止, 氮中心自由基启动的1,*n*-烯炔环化反应大概分为三种途径: (1)氮中心自由基选择性的与1,*n*-烯炔的C=C键进行加成反应, 然后通过分子内环化以生成烯基自由基中间体, 最后借助进一步环化反应、氢原子攫取或自由基偶联以得到最终产物; (2)涉及到氮中心自由基与1,*n*-烯炔的C≡C键的选择性加成反应、分子内环化及氧化脱氢; (3)借助分子内原位生成的氮中心自由基来启动的, 随后经过两次分子内环化、单电子转移氧化及脱氢反应转化为最终产物。本文将依据氮中心自由基的类型, 分为硝基自由基、叠氮自由基和酰胺自由基进行讨论, 并将重点放在生成氮中心自由基的方法及其环化模式、相关反应机理以及存在的挑战上。

关键词: 1,*n*-烯炔; 氮自由基; 环化; C–N键

收稿日期: 2020-06-12. 接受日期: 2020-07-13. 上网日期: 2020-09-22.

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基金来源: 国家自然科学基金(21801142, 21802062); 浙江省省属高校基本科研业务费专项资金(SJLY2021004); 湖南省自然科学基金(2019JJ20008).

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