Electrocyclizations of Conjugated Azapolyenes Produced in Reactions of Azaheterocycles with Metal Carbenes

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Abstract: Conjugated azapolyenes (azabuta-1,3-dienes, aza-/diaza-/oxaza-/oxadiazahexa-1,3,5-trienes) are highly reactive in electrocyclization reactions, which makes them convenient precursors for the synthesis of a wide range of four-, five-, and six-membered nitrogen heterocycles that are of relevance for medicinal chemistry. Ring opening reactions of 2H-azirines and azoles containing an N–N or N–O bond, initiated by a transition metal carbene, have become increasingly important in recent years, since they easily allow the generation of azapolyenes with different numbers of double bonds and heteroatoms in various positions. This review summarizes the literature, published mainly in the last decade, on the synthetic and mechanistic aspects of electrocyclizations of azapolyenes generated by the carbene method.

Keywords: electrocyclization; pericyclic reactions; azadienes; rhodium carbenes; isoxazoles; pyrazoles; 2H-azirines; 1,2,3-triazoles; diazo compounds; catalysis

1. Introduction

Conjugated azapolyenes such as azabuta-1,3-dienes and aza-/diaza-/oxaza-/oxadiazahexa-1,3,5-trienes (Figure 1) are valuable building blocks in the synthesis of a variety of acyclic and heterocyclic nitrogen-containing compounds [1–5]. These highly unsaturated compounds are generally classified into three types: electron-rich, neutral, and electron-deficient azapolyenes. The compounds of the latter type, bearing one or more strong electron-withdrawing group in the polyene chain, exhibit especially diverse and sometimes unexpected reactivity. The most common reactions of electron-deficient azapolyenes are nucleophilic additions and pericyclic reactions including cycloadditions [6–8] and electrocyclizations [9–11]. Electrocyclizations of conjugated azapolyenes can occur via pericyclic or pseudopericyclic pathways [12] depending on the nature of the reaction centers in the reacting molecule. Electrocyclizations are of particular importance for the construction of thermally labile heterocycles since they do not require any additional reagents and usually proceed with high regio- and stereoselectivity under mild conditions. However, the use of electrocyclic reactions for the synthesis of heterocyclic compounds involves serious challenges due to the limited synthetic availability of azapolyenes of the required structure. Whereas 1-azabuta-1,3-dienes are readily available from a condensation of unsaturated carbonyl compounds with primary amines [13–15], the methods for the synthesis of their isomers, 2-azabuta-1,3-dienes, which include the Mannich olefination of alkylidene glycinites [16], the Wittig reaction of N-(diphenylmethylidene)oxamates [17], the coupling of imines with activated acetylenes [18], and the aza-Wittig reaction of N-vinylphosphazenes [19–23] are more complicated and allow the introduction of only a limited set of substituents.
In recent years, another convergent approach to azapolyenes based on the ring opening of three- and five-membered heterocycles has been intensively developed (Scheme 1). The reactions are believed to proceed via the formation of metal-bound ylides and metal-free ylides. In this approach, metal carbenes are generated from diazo compounds or their masked analogs, 1H-1,2,3-triazoles, in the presence of rhodium or copper catalysts, which are generally used for the initiation of the denitrogenative decomposition of diazo compounds [24]. This approach to azapolyenes is quite versatile since it allows one to synthesize conjugated N-, N,N-, and N,O-containing butadienes, hexatrienes, and even octatetraenes in one synthetic operation. The unique feature of the approach is the interchangeability of some three- and five-membered heterocycles in the reactions with transition metal carbenes. This allows flexibility of the starting material choice to obtain the azapolyene with the desired substitution pattern and configurations of double bonds.

In this short review, we summarize recent progress on electrocyclic reactions of azapolyenes generated by the transition metal catalyzed reaction of diazo compounds/1,2,3-triazoles with 2H-azirines [25] or azoles containing the weak N-N or N-O bond.
Scheme 1. Transition metal carbene reactions for the synthesis of azapolyenes and heterocycles.

2. 1,4-Electrocyclization of Azabutadienes

Electrocyclization of 2-Azabuta-1,3-dienes to 2,3-Dihydroazetes

Theoretically, a 2-azabuta-1,3-diene fragment can undergo conrotatory 1,4-electrocyclization, which is allowed by the rules of orbital symmetry. Since the four-membered ring of a 2,3-dihydroazete is significantly strained, such cyclization is possible only when at least one substituent is present at the C4 of 2-azadiene and more favorable 1,5- or 1,6-cyclizations are difficult or impossible. In particular, 1,4-cyclization of 3,4-diphenyl-substituted azadiene 13 derived from 2,3-diphenyl-2H-azirine 10 and rhodium carbene 12 gave dihydroazete 14 in good yield under mild conditions (Scheme 2) [26,27]. The analogous reaction of azirine 10 with diazoamidoester 15 in 1,2-dichloroethane (DCE) resulted in the formation of dihydroazete 18 and revealed the stereoselective nature of both the formation of the intermediate azadiene 17 and its cyclization [28]. It is notable that the cyclizations of azadienes 13 and 17 occurred irreversibly in both cases.

Scheme 2. Synthesis of dihydroazetes from azirine 1.

It was found that azadienes bearing one substituent at C4 undergo cyclization more readily if the C=C double bond has the E configuration. For example, dihydroazete 21 was obtained only from azadiene E-20, while its Z isomer was found to be inactive in the cyclization (Scheme 3) [29].
4,4-Disubstituted 2-azabuta-1,3-dienes can be generated by the reactions of azirines or isoxazoles with diazocarbonyl compounds under rhodium catalysis [30,31] (Scheme 4). It was found that a prerequisite for the 1,4-electrocyclization of the resulting 2-azabuta-1,3-dienes 26 is the presence of two electron-withdrawing groups at C1. In most cases, the cyclization reactions occur only at elevated temperatures in reversible fashion. 4-Halo-substituted azadienes 26 with the E configuration of the C=C bond were used to explore the influence of the substituents on the azadiene-dihydroazete equilibrium in C\textsubscript{6}H\textsubscript{6} at 100 °C [31]. It was found that replacing iodine with chlorine led to a change in the azadiene/dihydroazete ratio from 2.6:1 to 1:1.3. The introduction of an electron-donating 4-MeO group to the phenyl ring located at the C3 of the 2-azadiene shifts the equilibrium from a 1:1 to 1:2.5 ratio in favor of dihydroazete 27. A decrease in the electron-withdrawing ability of the substituent at the C1 of the azadiene (replacement of CO\textsubscript{2}Me with CF\textsubscript{3}) shifts the equilibrium toward the azadiene.

Since 3-halo-2,3-dihydroazetes 27 are rather stable at room temperature, their preparation in satisfactory yields turned out to be possible by using repeated heating of the azadiene to obtain an equilibrium azadiene–dihydroazete mixture and separation of the dihydroazete at each stage [31]. The 2-azadiene, prepared from the diazo Meldrum’s acid, also underwent reversible 1,4-electrocyclization upon heating, leading to the spirocyclic derivative of 2,3-dihydroazete 28 [32]. Dihydroazete 28 turned out to be stable at room temperature, which made it possible to isolate it in pure form.

To obtain dihydroazetes with a hydrogen at the C3, an approach was developed based on the hydrodebromination of 3-bromo-2,3-dihydroazetes under the action of tributyltin hydride (Scheme 5) [29]. Using this method, 2,3-dihydroazetes 33 with various substitution patterns were obtained in good yields from both 2-bromoazirine-2-carboxylates 29 and 5-alkoxy-4-bromoisoxazoles 30. It is noteworthy that the replacement of bromine with
hydrogen in 2,3-dihydroazetes led to a significant increase in their thermal stability: in contrast to dihydroazetes \(32\), which undergo the ring opening to azadienes \(31\) at temperatures above 60 °C, dihydroazetes \(33\) are stable even at 150 °C. In addition, the cytotoxic activity of 2,3-dihydroazetes \(32\) and \(33\) on the THP-1 cell line (human monocytic leukemia cells) was studied in vitro. It was found that the maximum apoptotic potential, along with a high cytotoxic and minimal necrotic potential, can be displayed by a representative of 2,3-dihydroazetes \(33\)—trimethyl-4-phenyl-2,3-dihydroazete-2,3,3-tricarboxylate.

Scheme 5. Synthesis of stable 2,3-dihydroazetes via 1,4-electrocyclization–hydrodebromination.

For the synthesis of 2,3-dihydroazetes \(37\) bearing a 2-pyridyl substituent at C3, it was necessary to protect the pyridine nitrogen in the starting 2-(pyridin-2-yl)-2\(H\)-azirines \(34\) in order to avoid deactivation of the rhodium catalyst due to complexation (Scheme 6) [33]. For this purpose, one-pot protection/deprotection with a trimethylsilyl group was successfully used.

Scheme 6. Synthesis of 3-(2-pyridyl)-2,3-dihydroazetes.

The reaction of rhodium carbenes with azirines and isoxazoles is still the only way to synthesize 2,3-dihydroazetes having a carbon substituent at C4. Despite the low thermal stability of many representatives of these compounds, they can be easily detected in reaction mixtures due to the characteristic chemical shift of C4 in the \(^{13}\)C NMR spectra, which is about 190 ppm.

3. 1,6- and 1,5-Electrocyclizations of Aza-, Oxaza-, Diaza-, and Oxadiazahexatrienes

The most common type of electrocyclic reactions of azapolyenes is 1,6-electrocyclization, the products of which are aza and oxaza analogs of cyclohexa-1,3-diene. There are a limited number of reliable methods for the preparation of oxaza analogs of cyclohexa-1,3-diene that makes the 1,6-electrocyclization of azapolyenes a promising synthetic alternative [34–36].
An attractive feature of these compounds is the feasibility of a reverse reaction, ring opening, which determines their use as thermo- and photochromic materials as well as starting compounds for the synthesis of other heterocycles. In addition, under certain conditions, aromatization of the dihydro derivatives can take place to give azines. If a heteroatom is located at the end of the triene system, 1,6-cyclization occurs as a pseudopericyclic process [12]. Such reactions are characterized by a flattened structure of the cyclization transition state; therefore, they proceed through a lower activation barrier than classical 1,6-electrocyclizations, in which carbon atoms are at the ends of the triene system.

3.1. 1,6-Electrocyclization of 1-Oxa-5-azahexa-1,3,5-trienes to 2H-1,3-Oxazines

Manning and Davies reported the rhodium catalyzed synthesis of 2H-1,3-oxazines 42 from diazocarbonyl compounds 35 and isoxazoles 39 (Scheme 7) [37]. The authors proposed the mechanism for the formation of oxazine 42 involving the generation of isoxazolium ylide 40, the ring opening to 1-oxa-5-azatriene 41, followed by 1,6-electrocyclization. The scope of the reaction was further expanded by the work in [38].

Scheme 7. Synthesis of 2H-1,3-oxazines from isoxazoles.

The authors of [38] confirmed the intermediate formation of 1-oxa-5-azatrienes in the reactions of rhodium metal carbenes with isoxazoles by experimental and computational methods. The density functional theory (DFT) calculations revealed that the metal-free isoxazolium ylides 40 are extremely unstable species, which undergo ring opening practically without an energy barrier, and their formation in these reactions therefore seems rather unlikely. The isoxazolium ring undergoes opening, most likely, at the stage of metal-bound ylides 44 (Scheme 8). The latter undergo simultaneous cleavage of the N–C and Rh–C bonds to give oxazatrienes 45 with the Z configuration of the C=C double bond. It is notable that the analogous reaction of 5-alkoxyisoxazoles 43 stops at the stage of oxazatrienes 45, which is one more piece of evidence for the reaction to proceed through the oxazatriene intermediate [38]. The quantum chemical calculations confirmed that oxazatrienes 45 are thermodynamically more stable than their 1,3-oxazine isomers 46 by 16 kcal/mol, and 1,6-electrocyclization in this case is thermodynamically unfavorable.

Scheme 8. Synthesis of 2-alkoxy-1-oxa-5-azahexa-1,3,5-trienes stable to 1,6-electrocyclization.
It was also shown that 2-acyl- and 2-formyl-substituted azirines 47 react similarly and can serve as sources of oxazatrienes 49, which are capable of undergoing 1,6-electrocyclization (Scheme 9). Thus, dimethyl diazomalonate, ethyl 2-cyano-2-diazoacetate, and ethyl 2-diazo-3,3,3-trifluoropropanoate react with azirines 47 under rhodium catalysis to afford 2H-1,3-oxazines 50 in good yields [39,40].

Scheme 9. Synthesis of 2H-1,3-oxazines from 2H-azirines.

It turned out that the obtained 1,3-oxazines are capable of reversible ring opening to 1-oxa-5-azahexatrienes at elevated temperatures (Scheme 10) [40]. 1,3-Oxazine 51 bearing a hydrogen atom at C6 produces oxazatriene 52 upon heating, which undergoes a cascade of transformations, leading to the formation of pyrrolinones 55. This isomerization occurs most easily for the 1,3-oxazines containing a cyano group at C2. The synthesis of pyrrolones 55 can also be carried out starting from azirines and diazo compounds, without isolation of the intermediate 1,3-oxazines.

Scheme 10. Synthesis of pyrrolinones via electrocyclic ring opening of 2H-1,3-oxazines.

3.2. 1,6-Electrocyclization of 1-Oxa-4-azahexa-1,3,5-trienes to 2H-1,4-Oxazines

When an acyl group is introduced into the C1 position of 2-azadiene (1-oxa-5-azahexa-1,3,5-triene), 1,6-electrocyclization to form 2H-1,4-oxazines takes place. It was found that the cyclization of 1-oxa-4-azahexa-1,3,5-trienes 59, derived from azirines 56 and diazo compounds 57 in most cases occurred readily and irreversibly to afford 2H-1,4-oxazines 60 with a wide range of substituents in good yields (Scheme 11) [41–43]. The presence of an electron-withdrawing substituent (ester group) at C6 and an alkyl substituent (methyl) at C5 of the oxazahexatriene impede the cyclization. It should be noted that no cyclization involving the ester group (R4 = OAlk) was observed; the impossibility of such cyclization for both kinetic and thermodynamic reasons was confirmed by the results of quantum chemical calculations.

An interesting feature of the obtained monocyclic 2H-1,4-oxazines 60 is their photo- and thermochromic activity, which is attractive for their practical applications. When irradiated with UV light of a mercury lamp, colorless oxazines (λmax 315–360 nm) convert to oxazatrienes 59, colored from yellow to red (λmax 380–455 nm) [42] (Scheme 12). After the termination of irradiation, the cyclization occurs again. For a series of oxazines, the half-life times of the open-chain form were determined; these were in a range of 0.5–29 h, and these times were highly dependent on the substitution pattern. Thermochromism was most pronounced for spirooxazines containing a fluorene fragment at C2 [42].
Scheme 11. Synthesis of 2H-1,4-oxazines via 1,6-electrocyclization of 1-oxa-4-azahexa-1,3,5-tetraenes.

Scheme 12. Photochromism of monocyclic 2H-1,4-oxazines.

3.3. 1,6-Electrocyclization of 1,5-Diazahexa-1,3,5-trienes to 1,2-Dihydropyrimidines

1,6-Electrocyclization of 1,5-diazahexa-1,3,5-trienes occurs with the formation of 1,2-dihydropyrimidine derivatives. Two complementary approaches have been developed for the generation of 1,5-diazatrienes 65,67, precursors of 1,2-dihydropyrimidines 66,68, based on the reactions of diazocarbonyl compounds 63 with either azirine-2-carbaldimines 61 or pyrazoles 62 (Scheme 13). The use of azirine-2-carbaldimines as the starting material makes it possible to obtain 1,2,2,4,5-pentasubstituted dihydropyrimidines [44]. Due to the peculiarities of the reactivity of pyrazoles (completely substituted pyrazoles do not react with rhodium carbenes), the reactions of pyrazoles are more suitable for obtaining 1,2,2,5,6-pentasubstituted dihydropyrimidines [45].

1,5-Diazahexatrienes 71,75 generated by the reactions of diazo ketones 70,74 have an additional keto group, therefore, they theoretically can undergo two types of 1,6-electrocyclizations: into 1,2-dihydropyrimidines or 2H-1,4-oxazines (Scheme 14). It was found that the 1,6-cyclization of such 1-oxa-4,8-diazaocta-1,3,5,7-tetraenes occurs exclusively onto the C=N bond to give dihydropyrimidine derivatives [44,45].

It is interesting that the synthesized 1,2-dihydropyrimidines exist in an equilibrium with 1,5-diazatrienes in solution at room temperature [44]. An indirect evidence of this fact, which was also confirmed by the results of quantum chemical calculations, is the rapid epimerization of a dihydropyrimidine, which contains two chiral centers. Thus, dihydropyrimidine (RS,RS)-77, which is stable in a solid state, rapidly transforms into a 1:1 mixture of two diastereomers in CDCl₃ solution via the ring opening–cyclization sequence (Scheme 15).
### Scheme 13. Synthesis of 1,2-dihydropyrimidines via 1,6-electrocyclization of 1,5-diazahexa-1,3,5-trienes.

![Reaction Scheme 13](image)

- $R^1 = 4$-MeOC$_6$H$_4$, 4-CIC$_6$H$_4$, Ph, t-Bu; $R^2 = 4$-MeOC$_6$H$_4$, 4-CIC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, Ph, Me;
- $R^3 = Ph$, Bn, CO$_2$Et; $R^4 = 4$-MeOC$_6$H$_4$, 4-CIC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, Ph, Alk, Ts;
- $R^5 = Me$, Et; $R^6 = 4$-MeOC$_6$H$_4$, 4-CIC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, CO$_2$Me, CN, CF$_3$

### Scheme 14. 1,6-Electrocyclization of 1-oxa-4,8-diazaocta-1,3,5,7-tetraenes.

![Reaction Scheme 14](image)

- $R^1 = 4$-ClC$_6$H$_4$, $R^2 = Ph$ (61%)
- $R^1 = 4$-ClC$_6$H$_4$, $R^2 = CO_2$Me (43%)

### Scheme 15. Epimerization of 1,2-dihydropyrimidines via reversible electrocyclic ring opening.

![Reaction Scheme 15](image)

- $(RS,RS)$-77
- $(RS,SR)$-77

### 3.4. 1,6- and 1,5-Electrocyclizations of 1,4-Diazahexa-1,3,5-trienes

Several approaches to the preparation of 1,4-diazahexa-1,3,5-trienes have been studied to date, the 1,6-electrocyclization of which provides access to 1,2-dihydropyrazine derivatives.
The reaction of isoxazoles 79 with rhodium azavinyl carbenes, generated from 1-sulfonyl-1,2,3-triazoles 80 under rhodium(II) catalysis, allows for the generation of 1,4-diazahexa-1,3,5-trienes 81 with a sulfonyl substituent at N1 [46]. In these reactions, two products were formed: 3-aminopyrrole 82 and 1,2-dihydropyrazine 83 (Scheme 16). The result of the reaction turned out to be extremely sensitive to reaction conditions (catalyst, solvent, temperature, etc.). The reaction, carried out in chloroform at 100 °C in the presence of Rh₂(OAc)₄ as a catalyst, is most suitable for the synthesis of 4-aminopyrrole-3-carboxylates 82. The use of dirhodium tetrapivaloate (Rh₂(Piv)₄) in boiling toluene led to the formation of 1,2-dihydropyrazine-2-carboxylates 83 as the major products. The dihydropyrazines 83 were not very stable and gradually underwent dehydrosulfonation; for this reason, they were converted without isolation to aromatic pyrazines 84 in the presence of TsOH.

Scheme 16. Synthesis of 3-aminopyrroles and 1,2-dihydropyrazines from isoxazoles.

The NMR spectroscopy data and quantum chemical calculations showed that both products, pyrrole 92 and dihydropyrazine 93, formed from (5Z)-1,4-diazahexa-1,3,5-triene intermediate Z-90 (Scheme 17) [46]. The formation of pyrrole 92 proceeds via 5-exo-trig-cyclization of diazahexatriene Z-90 to betaine 91. The effect of the catalyst on the reaction direction can be explained by the stabilization of the betaine through coordination of the catalyst with the betaine anionic nitrogen.

Analogous 1,4-diazatrienes with a sulfonyl substituent at the nitrogen can also be generated from 2H-azirines 86 (Scheme 17) [46,47]. In this case, 3-aminopyrroles 92 are predominantly formed. The reason for this is associated with the selective ring opening of azirinium ylides 88 to (5E)-1,4-diazahexa-1,3,5-trienes E-90, which, as follows from quantum chemical calculations, undergo 5-exo-trig-cyclization through a lower energy barrier than the corresponding Z-isomers Z-90 [46]. Isoxazolium ylide complexes 89, due to geometrical reasons, can provide only diazahexatrienes Z-90 with the C=C bond in the Z configuration, which is of crucial importance for the formation of pyrazines 93. On the other hand, it turned out that the introduction of a strong electron-withdrawing substituent at the C5 of 1,4-diazatriene makes the 5-exo-trig cyclization to betaine 91 unfavorable, probably due to a decrease in the nucleophilicity of the C6 of the diazatriene [46]. As a result, in this case, 1,6-electrocyclization to dihydropyrazine 93 predominantly occurs. Furthermore, it is most likely that this fact helped the authors of [48] to synthesize the aromatic pyrazines 97 in good yields (Scheme 18).
Scheme 17. Mechanisms for the formation of 3-aminopyrroles and 1,2-dihydropyrazines.

Scheme 18. Synthesis of pyrazines from ethyl azirine-2-carboxylates and 1,2,3-triazoles.

1,4-Diazahexatrienes 100 containing an aryl or alkyl substituent at the C6 and an aryl substituent at the C5 can be converted to dihydropyrazines 102 or 3-aminopyrroles 103 depending on the reaction conditions (Scheme 19) [49]. Tang and coworkers reported the conditions that provided good yields of both cyclic products. In contrast, 1,4-diazahexatrienes 100 containing an aryl substituent at C6 and an alkyl substituent at the C5 position exclusively underwent 1,6-electrocyclization to give dihydropyrazines 101.

Park and coworkers showed that azirines 104 can react with diazo oxime ethers 105 under catalysis with copper(II) hexafluoroacetylacetonate (Scheme 20) [50]. In this case, 1,4-diazahexatrienes 106 are formed as intermediates, which are capable of undergoing 1,6-electrocyclization to dihydropyrazines 107. Upon further heating of the dihydropyrazines at high temperature, the elimination of methanol takes place, leading to the formation of completely substituted pyrazine-2-carboxylates 108 in good yields.

The reactions of diazoinindolinamines 110 with various 2H-azirines 109 give ortho-fused pyrazines 113 resulting from the 1,6-electrocyclization of intermediate 1,4-diazatrienes 111. These reactions have been studied in detail in the works of three research groups (Scheme 21) [51–53]. In all these studies, the formation of the intermediate 1,2-dihydropyrazines 112 was observed. It was found that the aromatization of the 1,2-dihydropyrazines 112 can occur without any additives (when \( R_2^2 = CO_2Me \)), but at rather high temperature. To carry out this process under milder conditions, it was necessary to add a base (Et₃N, t-BuOK) or TsOH. Under these conditions, 5H-pyrazino[2,3-b]indoles 113 were obtained in good yields.
Scheme 19. Synthesis of 3-aminopyrroles and 1,2-dihydropyrazines from alkyl/aryl-2$H$-azirines.

Scheme 20. Synthesis of pyrazines from 2$H$-azirines and diazo oxime ethers.

To obtain 5$H$-pyrazino[2,3-$b$]indoles 117 containing an ester substituent, according to the results of previous studies, it would be more convenient to use 5-alkoxyisoxazoles 114 rather than azirines 115 (Scheme 22). Unfortunately, however, isoxazoles 114 proved to be inactive toward diazoinodolinimines in the presence of rhodium carboxylates. The authors of the work [53] took advantage of the isomerization of 5-alkoxyisoxazoles 114 to azirine-2-carboxylates 115 found in a previous study. It was found that the isomerization is catalyzed by the same rhodium carboxylate as the subsequent reaction with the diazo compound. Using this procedure, a number of pyrazinoindoles 117 bearing an ester substituent were obtained in good yields.

The rhodium-catalyzed reactions of azirines 120 with ortho-fused triazoles, [1–3]triazolo[1,5-$a$]pyridines 118, have been studied in [54] (Scheme 23). The final products of the reaction were previously unknown 4$H$-pyrido[1,2-$a$]pyrazine derivatives 122, which resulted from 1,6-electrocyclization of 1-(pyridin-2-yl)-2-azabuta-1,3-dienes 121 (1,4-diazahexa-1,3,5-trienes with the terminal C=N bond as part of the pyridine system). This process is quite remarkable because it belongs to a rare type of electrocyclization accompanied by the dearomatization of a pyridine ring.
Scheme 21. Synthesis of 5H-pyrazino[2,3-b]indoles from 2H-azirines.

Scheme 22. Synthesis of 5H-pyrazino[2,3-b]indoles from isoxazoles.

Scheme 23. Synthesis of 4H-pyrido[1,2-a]pyrazines via 1,6-electrocyclization of 1-(2-pyridyl)-2-azabuta-1,3-dienes.

It was found that such 1,6-electrocyclization has limitations with respect to the substituents at the 2-azabutadiene [54]. The cyclization occurs for azadienes 121 bearing an electron-withdrawing substituent at C1 and a hydrogen atom, an alkyl, or aryl group at C4. The 4-alkyl-substituted pyridopyrazines 122 were found to be stable at room temperature and were isolated in moderate yields. Pyridopyrazines 122 with an aryl group at C4 exist in equilibrium with the corresponding 1,4-diazahepta-1,3,5-trienes 121, even
at room temperature. 1,6-Electrocyclization is also possible with the participation of the C=N bond of a quinoline and a benzoxazole (compounds 123 and 124). According to the results of quantum chemical calculations, the 1,6-electrocyclization under consideration is a pseudopericyclic reaction proceeding through a significantly flattened transition state. It is noteworthy that 3-benzoyl-substituted 1,4-diazahexa-1,3,5-triene 125, formed from the corresponding pyridodiazole, undergoes cyclization to 2H-1,4-oxazine 126, rather than to 4H-pyrido[1,2-a]pyrazine 127 (Scheme 24).

Scheme 24. 1,6-Electrocyclization of 1-benzoyl-1-(2-pyridyl)-2-azabuta-1,3-diene.

3.5. 1,6- and 1,5-Electrocyclizations of 2-Azahexa-1,3,5-trienes

The introduction of an alkenyl substituent at C4 of the 2-azabuta-1,3-diene system led to 2-azahexa-1,3,5-trienes, which can undergo 1,6-electrocyclization to dihydropyridines. Indeed, the reaction of alkenyl-substituted azirine E-128 with diazo compound 129 in the presence of Rh2(OAc)4 led to azahexatriene 3E,5E-130 and dihydropyridine 132. A similar reaction of the isomeric azirine Z-128 gave azahexatriene 3Z,5E-130 and pyrrole 131 (Scheme 25) [55,56]. Dihydropyridine 132 is the result of 1,6-electrocyclization of the unstable azatriene 3Z,5E-130 and subsequent prototropic shift, while pyrrole 131 is the product of 1,5-electrocyclization of the unstable azatriene 3Z,5Z-130. Thus, the configuration of the terminal C=C bond in (3Z)-2-azahexa-1,3,5-trienes 130 completely controls the direction of their cyclization. Following from the quantum chemical calculations, in the transition states of the 1,6-electrocyclizations of azatrienes with the Z configuration of the terminal C=C bond, in contrast to the E isomer, there were noticeable steric repulsive interactions created by the CO2Me group at the C6 and a substituent at the C1. As a result, the barrier of the 1,6-electrocyclization increases, and the pseudopericyclic 1,5-electrocyclization becomes more preferable.

Scheme 25. 1,6- and 1,5-electrocyclizations of 2-azahexa-1,3,5-trienes.
The pathways of the azirine ring expansion in the \( \text{Rh}_2(\text{OAc})_4 \)-catalyzed reactions of various 2-carbonylvinyl-substituted azirines 133 with diazo esters 134 were also studied (Scheme 26) [56]. In all cases, the formation of dihydropyridines 136 and pyrroles 137, along with the formation of stable azahexatrienes \( 3E,5E-135 \), was observed, with the proportion of the pyrrole increasing with an increase in volume of a substituent at the C1 (phosphonate, \( R^2 = \text{P}(\text{O})(\text{OMe})_2 \)) or C6 (benzoyl group, \( R^1 = \text{Ph} \)) of the azahexatriene.

\[ \begin{align*}
\text{Scheme 26.} \quad & \text{Synthesis of pyrroles and dihydropyridines via electrocyclizations of 2-azahexa-1,3,5-trienes.} \\
& \text{2-Azadienes 139 (2-azahexa-1,3,5-trienes with the terminal C=C bond as a part of the benzene system) containing two phenyl substituents at the C4 and two electron-withdrawing groups at the C1 undergo unusual 1,5-electrocyclization involving the C=C bond of the aromatic ring to give indole derivatives 140 (Scheme 27). On the basis of this reaction, an efficient method for the synthesis of N-substituted indoles 140 from 2,2-diphenyl-2H-azirines 138 and diazocarbonyl compounds 24 without isolation of the intermediate azahexatrienes 139 was developed [28]. It was found that an increase in the electron-withdrawing ability of substituents at the C1 of 2-azabutadienes facilitates the indole formation. Particularly, the azahexatriene containing an alkoxycarbonyl and cyano group at C1 isomerized smoothly to the corresponding indole, even at room temperature.}
\end{align*} \]

\[ \begin{align*}
\text{Scheme 27.} \quad & \text{Synthesis of indoles via 1,5-electrocyclization of 4-phenyl-2-azabuta-1,3-dienes.} \\
& \text{According to the results of the DFT calculations, the activation barrier of 1,5-electrocyclization of azadiene 141 to indolium ylide 142 turned out to be lower than those of 1,4-electrocyclization to dihydroazete 145 and 1,6-electrocyclization to dihydroisoquinoline 146 (Scheme 28) [28]. Further intramolecular prototropic shift in indolium ylide 142 has an extremely low barrier. In contrast to the 1,4- and 1,6-cyclization, the formation of indolium ylide 142 is a pseudopericyclic cyclization, the structure of the transition state of which is significantly flattened. This, together with the effective stabilization of the emerging anionic center by electron-withdrawing substituents, determines the preference of the 1,5-electrocyclization.}
\end{align*} \]
It was found that at elevated temperature, 2,2-diphenyl-substituted 2H-1,4-oxazines 147 obtained in the rhodium-catalyzed reaction of 2,2,3-triphenyl-2H-azirine with diazo keto esters or diazo diketones exist in equilibrium with the corresponding 1-oxa-4-azaocta-1,3,5,7-tetraenes 148 (Scheme 29) [28]. In turn, this intermediate, which is formed in small amounts, undergoes irreversible 1,5-electrocyclization to an indole derivative, thereby shifting the oxazine–oxazatetraene equilibrium until the complete conversion of the oxazine is achieved. In particular, the thermolysis of 2,2-diphenyl-2H-1,4-oxazines 147 led to N-substituted indoles 149 in good yields.

The reaction of 2,2-disubstituted 1,2-dihydropyrazines, obtained from 1-sulfonyl-1,2,3-triazoles and 2,2-diaryl-substituted 2H-azirines, proceeded in a similar manner [57]. In particular, dihydropyrazine 150 was found to be a stable compound at room temperature, however, upon heating, it underwent reversible ring opening to 1,4-diazaocta-1,3,5,7-tetraene 151 (Scheme 30). Eventually, prolonged heating of dihydropyrazine 150 led to the formation of aminovinylindole 152 in moderate yield.
the reaction mixture containing the initially formed dihydropyrazine (Scheme 31) [57]. A number of aminovinylindoles have been obtained by this procedure in good yields. All indoles were obtained as a single stereoisomer with the Z configuration of the C=C double bond.

Scheme 31. Synthesis of (2-aminovinyl)indoles from 2H-azirines and 1,2,3-triazoles.

The data of DFT calculations showed that the most low-barrier cyclization of 6,6-diphenyl-1,4-diazahexa-1,3,5-trienes 156 is the 1,6-electrocyclization to dihydropyrazines 157 (Scheme 32) [57]. The ring opening of dihydropyrazine 157 has a relatively low barrier, and it can be overcome upon moderate heating. The reversible cyclization of azapolyene 156 to diazabicyclohexene 158 has a larger activation barrier. Thus, before irreversible cyclization of diazaoctatetraene 156 to indole occurs, it exists in an equilibrium with dihydropyrazine 157 and diazabicyclohexene 158. Indolium ylide 159 is an extremely unstable compound, which transforms to indole 160 through the barrierless prototropic shift.

Scheme 32. Calculation data for the electrocyclizations of 6-phenyl-1,4-diazahexa-1,3,5-trienes.

The presence of a fluorene system at C4 of 2-azabutadiene moiety (2-azahexa-1,3,5-trienes with the terminal C=C bond as a part of the fluorene system) led to a change in the reaction course from 1,5-cyclization to 1,6-cyclization, giving rise to azafluoranthen derivative [28]. In particular, azahexa-1,3,5-trienes 161 was converted by heating at 170 °C in o-xylene to 2-azafluoranthenes 163 in moderate yields (Scheme 33). The change in the cyclization mode on going from the gem-diphenyl to the fluorene system can be explained by a decrease in stability of the transition state, leading to a strained indeno[1,2,3-cd]indolium ylide 164.
Scheme 33. Synthesis of 2-azafluoranthenes via 1,6-electrocyclization of 2-azahexa-1,3,5-trienes.

Analogously, the formation of indoles did not occur in the case of fluorene and anthrone derivatives of 1,4-diazahexa-1,3,5-triene (Scheme 34) [58]. As in previous cases, the rhodium-catalyzed reaction of azirines 165 with 1,2,3-triazoles 166 resulted in the initial formation of dihydropyrazines 167, which upon further heating afforded spirocyclic 3H-pyrroles 169, 170 via the 5-exo-trig-cyclization of azapolyene 168, rather than indoles resulting from its 1,5-electrocyclization.

Scheme 34. Synthesis of 3H-pyrroles via electrocyclic ring opening of 1,2-dihydropyrazines.

3.6. 1,6-Electrocyclization of 3-Azahexa-1,3,5-trienes to Dihydropyridines

A rhodium(II)-catalyzed reaction of diazo compounds 172, containing an alkenyl substituent, with 2,3-disubstituted 2H-azirines 171 was used to generate 3-azahexa-1,3,5-trienes 173 (Scheme 35) [59,60]. These intermediates readily underwent 1,6-electrocyclization to 3,4-dihydropyridines 174, which tautomerized to 1,4-dihydropyridines 175. The oxidation of the latter in a one-pot mode by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) allowed the preparation of pyridines 176 bearing a wide range of substituents in moderate to high yields. In one case, the authors were able to isolate a 3-azaheptatriene intermediate, which was transformed to a pyridine derivative at elevated temperature.
In a similar manner, isoxazoles can be successfully used in rhodium-catalyzed reactions with diazo compounds bearing an alkenyl substituent for the preparation of substituted pyridines. Manning and Davies reported the reaction of isoxazoles with diazo compounds catalyzed with Rh$_2$(OAc)$_4$ at 60 °C, which afforded 1,3-oxazines (Scheme 36) [61]. When refluxed in toluene, the latter were converted to 3,4-dihydropyridines. This transformation can be assumed to proceed either through the Cope rearrangement or through the ring opening to 1-oxa-5-azaoctatetraenes, followed by 1,6-electrocyclization. Further oxidation of the dihydropyridines with DDQ led to the formation of pyridines with a carbonyl substituent at C3.

In the reaction of 1,2,4-oxadiazoles with rhodium carbenes generated from α-diazoesters, 1-oxa-3,5-diazahexa-1,3,5-trienes were generated as reactive intermediates (Scheme 37) [62]. Despite the possibility of several directions of electrocyclization, heteropolyenes underwent 1,6-electrocyclization involving the carbonyl group (both ketone and ester one) located at the nitrogen atom. As a result, a wide variety of 2H-1,3,5-oxadiazines were obtained in good yields. Interestingly, the reaction can be efficiently catalyzed not only by rhodium compounds, but also by cheaper copper compounds. The involvement of an ester group in the electrocyclization process is rather unexpected, since no electrocyclization products with the participation of such groups were observed in previous studies. According to the data of the DFT calculations, in this case, the cyclization onto the ester group is favorable for both kinetic and thermodynamic reasons.
Scheme 37. Synthesis of 2H-1,3,5-oxadiazines via 1,6-electrocyclization of 1-oxa-3,5-diazahexa-1,3,5-trienes.

3.8. 1,6-Electrocyclization of 1,4,5-Triazahexa-1,3,5-trienes to 3,4-Dihydro-1,2,4-triazines

1,4,5-Triaza-1,3,5-hexatrienes 188, generated by the reaction of 1-alkyl-1H-1,2,3-triazoles 187 with rhodium α-carbonyl carbenes 186, derived from diazocarbonyl compounds 183, underwent 1,6-electrocyclization to 3,4-dihydro-1,2,4-triazines 189 (Scheme 38) [63]. Under the reaction conditions, the latter rapidly rearranged to pyrrolin-2-ones 190, which was accompanied by a nitrogen evolution, ring contraction, and 1,2-migration of the alkoxy substituent. To prove the intermediate formation of the 3,4-dihydro-1,2,4-triazines, the reaction of triazole 191 with 2-diazo-3,3,3-trifluoropropanoate 129 was carried out under milder reaction conditions. In this case, it was possible to isolate and characterize 3,4-dihydro-1,2,4-triazine 192, which turned out to be quite stable in pure form. Heating its solution in DCE in the presence of catalytic amounts of Rh$_2$(OAc)$_4$ led to a triazine ring contraction to give pyrrolinone 193.

Scheme 38. Synthesis of 4-pyrrolin-2-ones via electrocyclic formation of 3,4-dihydro-1,2,4-triazines.

The reaction of 1-alkyl-1,2,3-triazoles 194 with rhodium azavinyl carbenes 195, derived from 1-sulfonyl-1,2,3-triazoles 154, begins in a similar manner via the 1,6-electrocyclization of azapolyenes 196 to unstable 1,3,4-triazines 197, which undergo, under the reaction conditions, denitrogenative ring contraction to give 3-sulfonamidopyrroles 198 (Scheme 39) [64]. According to the DFT calculations, the formation of pyrroles 198 from triazines 197 proceeds via a concerted rearrangement with a simultaneous nitrogen evolution followed by a 1,2-prototropic shift.
Scheme 39. Synthesis of 3-aminopyrroles via electrocyclic formation of 3,4-dihydro-1,2,4-triazines.

4. Conclusions

Reactions of transition metal carbenes with 2H-azirines and azoles containing an N-N or N-O bond is becoming an active field of research, as justified by the growing number of papers covered in this review. This approach is a novel versatile tool for the design of new reactive azapolyene intermediates suitable for the synthesis of various heterocycles via an electrocyclization (i.e., under atom-economical conditions). In contrast to other known methods, the present one features a wide diversity of accessible azapolyenes and, therefore, is able to provide a powerful impetus for the further development of the electrocyclization strategy in heterocyclic synthesis. The method has been exploited for the synthesis of unique 2,3-dihydroazetes, 2H-1,3-oxazines, 2H-1,4-oxazines, 1,2-dihydropyrimidines, various pyrazine and pyridine derivatives, etc. Moreover, the method provided azapolyenes, which are capable of undergoing an unprecedented 1,5-electrocyclization to pyrrole and indole derivatives.

Although a great number of studies has been conducted, the described approach is just at the beginning stage. We believe that the use in the reactions of azirines and azoles containing polyene and heteropolyene substituents seems to be promising for further unlocking the potential of the method. Furthermore, the reactions of transition metal carbenes with azoles ortho-fused with aromatic and heteroatomatic rings remain practically unexplored. At the same time, these reactions should result in the formation of azapolyenes, which are most promising for the development of new photochromic materials. Another fruitful area of upcoming research, in our opinion, is switchable electrocyclizations of azapolyenes upon treatment by a specific catalyst, providing selective access to several heterocyclic systems from the same starting materials. In this context, it seems prospective to intensify the search for cheaper catalytic systems for azapolyene generation and pay attention to the reactions of azoles and their derivatives with copper carbenes. It also seems promising to study the transformation of non-aromatic diaza- and oxaza-derivatives of a cyclohexa-1,3-diene to stable aromatic heterocycles.

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