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Ring Expansion Reactions *via C-N* Bond Cleavage in the Synthesis of Medium-sized Cycles and Macrocycles

Abstract
The literature review discusses and systematizes synthetic approaches to medium-sized cycles and macrocycles based on ring expansion reactions of bi- or polycyclic systems via *C-N* bond cleavage. Ring expansion reactions of bicyclic ammonium salts proceed *via* thermal decomposition or the action of strong bases. Bi- or polycyclic systems containing a common amine group can be reduced with strong reducing reagents, e.g. lithium aluminum hydride. Ammonium derivatives are much more prone to nucleophilic attack and quite often are used as starting materials for the synthesis of medium-sized cycles. Bicyclic systems containing a common aminal or amidine group are used for the synthesis of medium-sized rings and macrocycles *via* cleavage of the endocyclic *C-N* bond. Various methods of their activation and reduction are discussed in the review.
***Keywords*:** cleavage; ring expansion; aminal; amidines; medium-sized cycles; macrocycles

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Реакції розширення циклу, які супроводжуються розривом *C-N* зв'язку, в синтезі циклів середнього розміру та макроциклів

Анотація
В огляді літератури описано та систематизовано синтетичні підходи до одержання циклів середнього розміру та макроциклів, які засновані на реакціях розширення циклу бі- або поліциклічних систем, що супроводжуються розривом C-N зв'язку. Реакції розширення циклу біциклічних солей амонію протікають шляхом їх термічного розкладання або дії на них сильних основ. Бі- або поліциклічні системи, що містять спільну аміногрупу, можна відновити сильними реагентами, як-от літій алюмогідрид. Похідні амонію значно більш схильні до нуклеофільної атаки, і їх досить часто використовують як вихідні матеріали для синтезу циклів середнього розміру. Біциклічні системи, що містять спільну групу аміналю або амідину, використовують для синтезу циклів середнього розміру та макроциклів шляхом розриву ендоциклічного зв'язку C-N. В огляді наведено різні способи їх активації та методи розщеплення.
Ключові слова: розщеплення; розширення кільця; аміналі; амідини; середні цикли; макроцикли

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■ Introduction

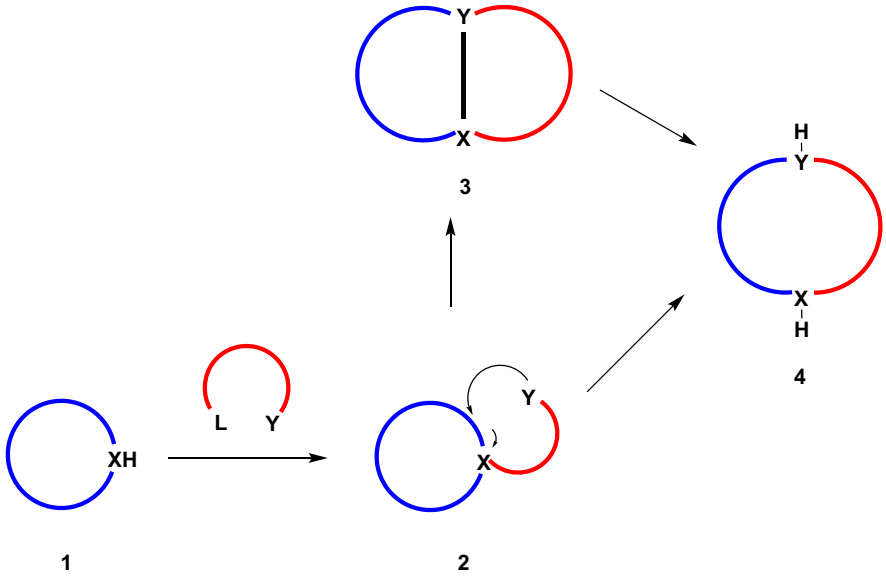
Cyclic systems containing medium rings (i.e., 8–12 membered cycles) are important structural components of various natural molecules, as well as biologically active compounds. However, despite their presence in many important natural products, medium-sized rings are underrepresented in marketed drugs and drug development programs, mainly due to a lack of synthetic methods. While synthetic approaches to 5-, 6-, and 7-membered rings are typically based on cyclization and cycloaddition reactions, these strategies are often ineffective for medium-sized rings due to negative entropic factors and transannular interactions. The kinetic and thermodynamic barriers associated with their synthesis are generally higher than for rings of other sizes, that is, they are large enough for the cyclization of a linear precursor to occur with significant loss of entropy, yet still small enough to experience destabilizing transannular interactions and strain [1]. Therefore, relatively fewer methods based on conventional cyclization or cycloaddition reactions are used to prepare medium-sized rings from acyclic precursors. Nevertheless, some elegant cycloaddition and annulation approaches have proven to be useful for the synthesis of these structures, particularly metal-catalyzed intramolecular cyclization [2–5], metathesis reactions [6], and click chemistry [7]. However, a more effective strategy is the ring expansion method, which allows for avoiding negative effects associated with the cyclization of medium-sized and macrocycle derivatives [8]. The simplest class of ring expansion reactions is based on the cleavage of an endocyclic bond in a fused bi- or polycyclic system. There are two mechanistically related approaches underlying this strategy for constructing medium-sized cycles and macrocycles. One of them is the successive ring expansion methodology (*SuRE*-approach), which has been widely used in the synthesis of medium- and macrocyclic lactams, lactones, and ketones [9] in the 1970s (**Scheme 1**). This approach is based on the sequential introduction of linear fragments into existing cyclic systems **1**, forming a condensed bicyclic system **3** *in situ*. Further fragmentation leads to the ring expansion affording monocyclic compounds with larger ring sizes **4**.

Another approach mechanistically linked to the *SuRE*-method involves cleavage of an endocyclic bond in condensed bi- or polycyclic systems **3** previously synthesized (**Scheme 1**). This approach is more efficient for generating medium-sized cycles and macrocycles, but it requires the starting substrates, which synthesis is not always a trivial task.

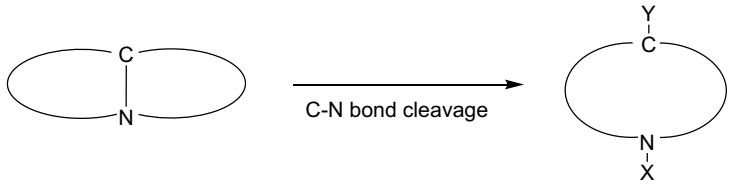
Since synthetic methods based on the *SuRE*-approach have been extensively analyzed in recently published reviews [8, 10], this literature review discusses and systematizes approaches to the synthesis of derivatives of medium-sized cycles and macrocycles based on ring expansion reactions of bi- or polycyclic systems with the *C-N* bond cleavage.

■ *C-N* bond cleavage in bicyclic amines

In the synthesis of medium-sized cycles and macrocycles, reactions involving the cleavage of *C-N* bonds are frequently used. This approach



Scheme 1. The strategy for constructing medium-sized cycles and macrocycles



5 **6**

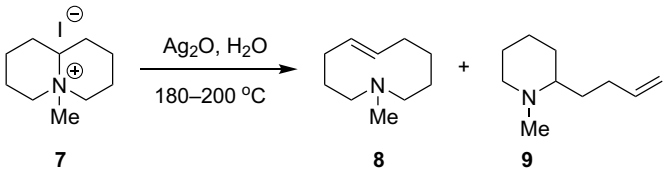
Scheme 2. The *C-N* bond cleavage in bicyclic amines

requires the prior activation of starting materials **5** *via* the acylation or nitrogen atom quaternization. The subsequent fragmentation of activated substrates and the formation of monocyclic compounds **6** can occur *via* the reductive cleavage or the action of nucleophilic reagents (**Scheme 2**).

The historically first example of the *C-N* cleavage in the synthesis of a medium-sized cycle is the work by *Clemo* in 1932 where ammonium salt **7** was used to prepare a 10-membered derivative **8** *via* the Hofmann elimination in the presence of Ag_2O (**Scheme 3**) [11]. However, the cleavage of the *C-N* bond occurs non-selectively, with piperidine derivative **9** being a side product [12].

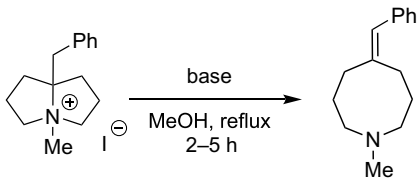
The presence of a benzyl substituent adjacent to the carbon atom makes the elimination process more straightforward (**Scheme 4**) [13].

This approach has been more extensively studied using indolizidine derivatives [14, 15] (**Scheme 5**). It involves the oxidation of compounds **12** with mercuric acetate and the subsequent introduction of a substituent at the carbon atom by the reaction of iminium salts **13** with organometallic reagents (2-pycolyl lithium, Grignard reagents, and Reformatsky-type enolate). The subsequent alkylation of indolizidines **14** with methyl iodide and treatment of the resulting ammonium salts **15** with bases, such as sodium ethoxide, sodium amide, or *n*-butyl lithium, leads to the ring expansion product – 1-azacyclononane **17**.



7 **8** **9**

Scheme 3. The Hofmann elimination in the synthesis of 10-membered derivative

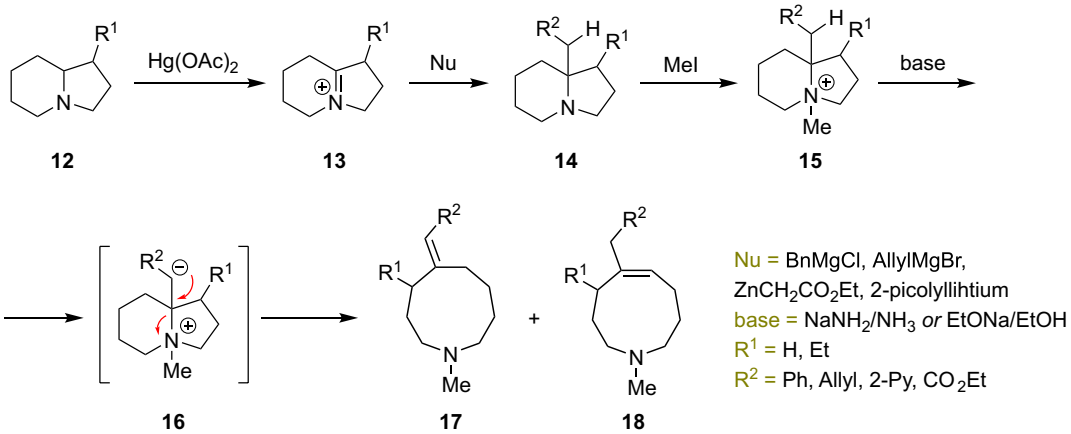


10, *84 %* **1**

Scheme 4. The synthesis of 8-membered cycle **11**

The authors assumed that the *C-N* bond cleavage occurred *via* the ß-elimination with the formation of carbanion **16** as an intermediate. In the presence of a carboxyl group ($R^2 = CO_2Et$), the formation of regioisomer **18** is observed, resulting from the isomerization of compound **17** into the thermodynamically more stable endocyclic olefin.

The authors [15] emphasize that the cleavage of the *C-N* bond can also occur *via* the ß-elimination induced by the thermal decarboxylation of betaine **19** (**Scheme 6**). According to this modification, derivative **20** with an exocyclic double bond was formed, which could not be obtained by the treatment of salts **15** with sodium ethylate.



12 **13** **14** **15** **16** **17** **18**

Scheme 5. Indolizidine derivatives in the synthesis of medium-sized cycles

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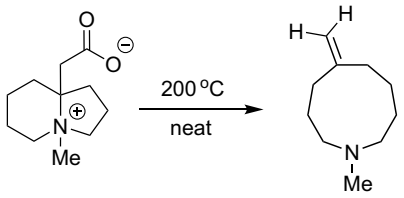


19, *63 %* **20**

Scheme 6. The thermal decarboxylation of betaine **19**

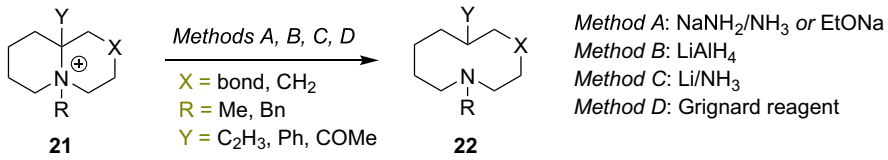
Thus, ring expansion reactions in bicyclic ammonium salts **15** to form unsaturated derivatives can occur *via* the thermal decomposition or the action of strong bases.

It is worth mentioning a series of studies devoted to the synthesis of nitrogen-containing heterocycles with medium-sized ring **22** *via* the cleavage of *C-N* bonds in quarternary salts of indolizidine and quinolizidine **21** (**Scheme 7**) [14–18]. It was demonstrated that the endocyclic *C-N* bond could be easily cleaved under reductive conditions (*methods A–C*) and upon the action of a nucleophilic Grignard reagent (*method D*).

An original approach to the synthesis of 9-indolizidines suitable for their further transformation into 1-azacyclononanes *via* the cleavage of the *C-N* bond was demonstrated [16]. Nitrile **23** was used as the starting compound, wherein the *CN*-group can be easily substituted with a vinyl or acetylenyl residue upon treatment with the corresponding Grignard reagents, forming indolizidines **24** and **25** (with the yields of 94% and 96%, respectively) (**Scheme 8**). The reaction of *N*-alkylated derivative **25** with lithium aluminum hydride leads to the formation of a mixture of regioisomers **26** and **27** in ratios depending on the solvent and concentration of the reactants. Meanwhile, the reaction product of the acetylene derivative **24** with lithium aluminum hydride in THF or ether is allene **28** with the yield of 96%.

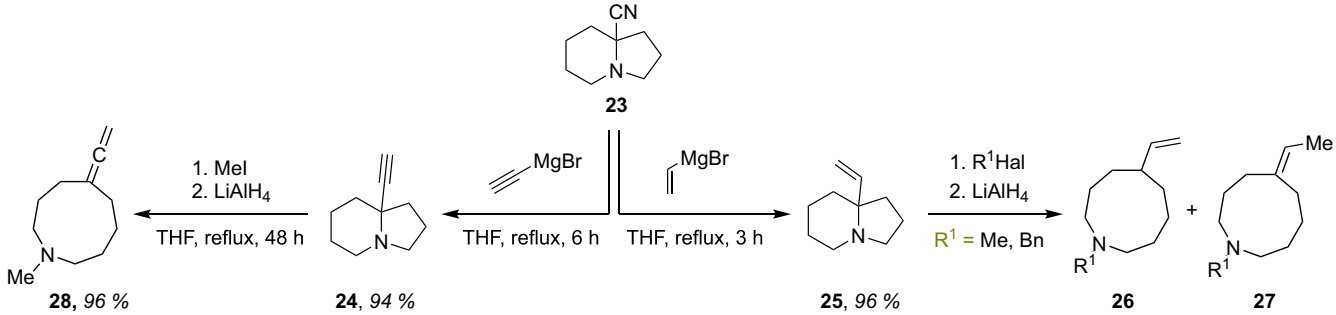
A similar approach based on the activation of bicyclic systems with a nitrogen atom *via* the *N*-alkylation has also been successfully applied to derivatives of benzoindolizidines and benzoquinolizidines **29** (**Scheme 9**) [19–21]. The quaternary ammonium salts **30** underwent reductive cleavage with metallic lithium in liquid ammonia (*Emde-Birch* reaction). In this case, the yield of 10-membered cyclic derivatives **31** (n = 1) was nearly quantitative due to the selective cleavage of the *C-N* bond [20, 21]. At the same time, the formation of 9-membered derivatives **31** (n = 0) occurred selectively only in the presence of an activating phenyl substituent (R^3 = Ph, X = bond). This result is explained [19] by forming a more stable benzhydryl carbanion under the *Emde-Birch* reaction conditions.

Another example of the successful implementation of the above-mentioned approach is the



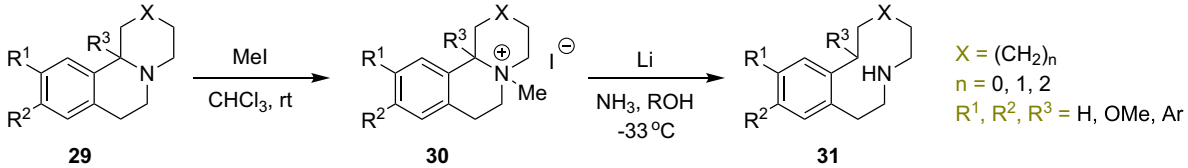
21 **22**

Scheme 7. The *C-N* bond cleavage in quaternary salts of indolizidine and quinolizidine derivatives



28, *96 %* **24**, *94 %* **25**, *96 %* **26** **27**

Scheme 8 Quaternary salts in the ring expansion reaction



29 **30** **31**

Scheme 9. The Emde-Birch reaction in the synthesis of medium-sized cycles

synthesis of 9- and 10-membered derivatives of pyrrole **34** [22]. The treatment of salts **33** with metallic sodium in liquid ammonia leads to the cleavage of the endocyclic *C-N* bond affording the target medium-sized heterocycles **34** (**Scheme 10**).

The application of the *Emde-Birch* reaction for the synthesis of bicyclic structures with medium-sized rings is also known (**Scheme 11**). 1-Azabicyclo[4.4.4]tetradec-5-ene **36** was obtained by cleaving the endocyclic *C-N* bond in **35** with sodium in liquid ammonia in the presence of *tert*-butanol in the yield of 58% [23]. Another example is the synthesis of manxine (1-azabicyclo[3.3.3] undecane) **38** by cleaving azapropellane **37** [24].

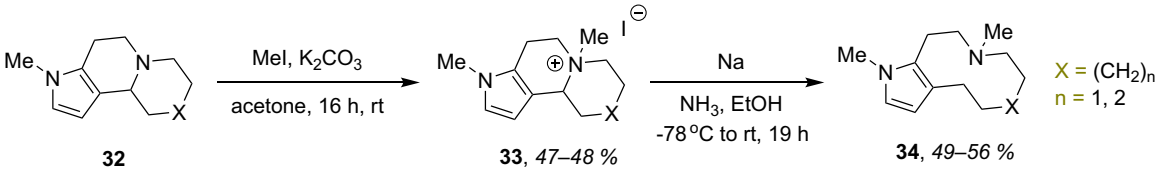
In the above-mentioned examples the activation of endocyclic *C-N* bonds in bicyclic compounds was achieved *via* the quaternization of the nitrogen atom, and the resulting quaternary ammonium salts were used as starting materials in the ring expansion reactions. However, there are other methods for cleaving the *C-N* bond where a sequential action of an electrophile (on the nitrogen atom) and a nucleophile (on the carbon atom) occurs (**Scheme 12**) [25–43]. This approach is illustrated by a ring expansion of well-known derivatives of tetrahydro-ß-carboline **39**. The cleavage of the endocyclic *C-N* bond is often a key step in the synthesis of various alkaloids featuring an indole fragment. It is worth noting that in all cases the derivatives of tetrahydro-ß-carboline **39** are initially treated with alkylating (RX, BrCN) or acylating (RCO_2Cl, $(RCO)_2O$) reagents to increase the electrophilicity of the starting compounds.

Electrophiles and nucleophiles that could be used for this synthetic approach are presented in **Table 1**. The main feature of this method is the use of a wide range of reagents. It allows for synthesizing functionalized derivatives of medium-sized rings **40**, which can be used as building blocks for constructing biologically active compounds.

The ability of the *C-N* bond in derivatives of tetrahydro-ß-carboline **39** for cleavage can be explained by an additional stabilization provided by the indole fragment **43** formed in the first step of quaternary salt **42** (**Scheme 13**) [33]. It is known that the *C-N* bond cleavage in bi- and polycyclic compounds induced by cyanogen bromide is a well-known approach for the synthesis of medium-sized cycles and macrocycles and is a modification of the *von Braun* reaction.

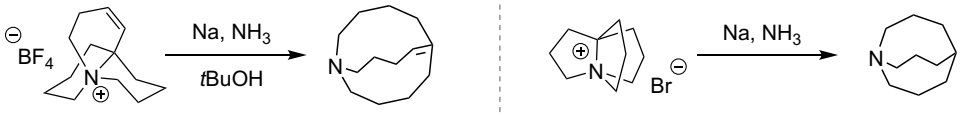
Table 1. The type of electrophile and nucleophile in the ring expansion of tetrahydro-β-carboline derivatives

No.	Electrophile, E	Nucleophile, Nu	Reference
1	RCO_2Cl	H^-	[25–27]
2	RCO_2Cl	ROH, RNH_2	[28–32]
3	BrCN	ROH, H_2O	[33–36]
4	$(RCO)_2O$	$RCOO^-$	[37, 38]
5	RX	Li *or* Na, NH_3	[39–41]
6	RX	CN^-	[134, 135]



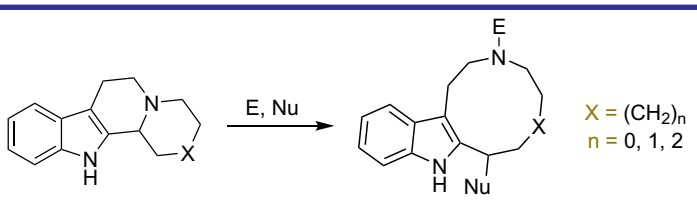
32 **33**, *47–48 %* **34**, *49–56 %*

Scheme 10. The ring expansion reaction of fused pyrrole derivatives



35, *58 %* **36** **37**, *60 %* **38**

Scheme 11. The synthesis of bicyclic structures *via* the *C-N* bond cleavage



39 **40**

Scheme 12. The ring expansion of tetrahydro-β-carboline derivatives

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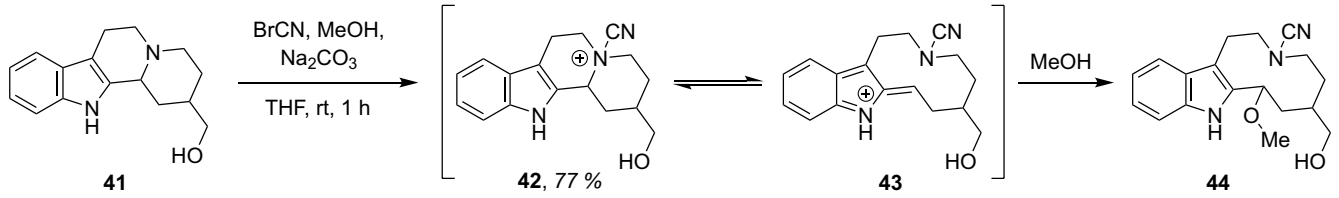


Scheme 13. A modified *von Braun* reaction in the synthesis of 10-membered cycle

Another example is a ring expansion reaction under the action of ethyl chloroformate/lithium aluminum hydride (**Scheme 14**) [17]. The reaction produces a mixture of *N*-methylamines **47**–**48** in the ratio of 40:60. The formation of diene **48** is explained by the elimination of hydrogen from an intermediate carbamate or quaternary salt. The authors did not determine the exact position of the endocyclic double bond.

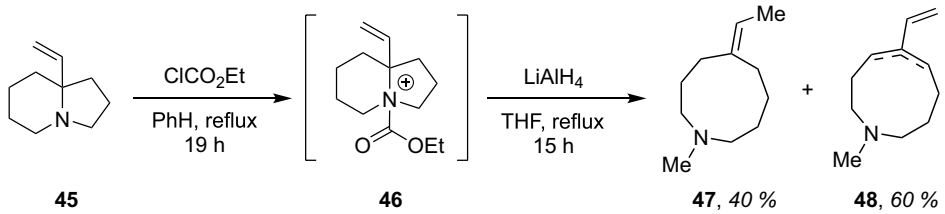
The cleavage of *C-N* bonds in heterocyclic salts is possible not only under conditions of the reductive cleavage, but also under the action of nucleophilic reagents. *Bremner* and *Winzenberg* discovered a photosolvolysis reaction of benzoindolizidines and benzoquinolizidines, as well as their *oxo*-analogs (**Scheme 15**) [44–46]. They demonstrated that the synthesis of 9- and 10-membered heterocyclic systems **50** could be achieved by the ultraviolet irradiation of alcohol or water solutions of salts **49**. It is worth noting that the course of the reaction and the yield critically depends on the structure of the starting material.

For example, the irradiation of quaternary salt **51** leads to the formation of the cleavage product with a much better yield (49%) compared to salt **52** (2%). It is noteworthy that the starting salt **52** was recovered unchanged after the reaction (82%). The authors suggest that the reason for such different reactivity of quaternary salts **51-52** under conditions of the photosolvolysis reaction is the stability of intermediate carbocations **53**–**54** (**Figure 1**). In the case of cation **54**, there is a more effective overlap between the vacant *p*-orbital of the carbon atom and the lone pair of the nitrogen atom compared to carbocation **53**, which likely results in the formation of the starting salt in the reaction mixture.

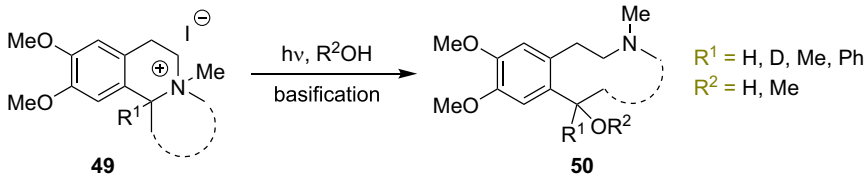
■ The *C-N* bond cleavage in bicyclic amidines and aminals

One method for synthesizing medium-sized cycles and macrocycles is the cleavage of bicyclic systems containing a common aminal or amidine moiety **55** (**Scheme 16**). This type of reaction can serve as a convenient method for obtaining medium-sized cycles with one or more heteroatoms in ring **56**. The cleavage of the *C-N* bond can occur under the action of nucleophiles. It is known that aminals are unstable in the absence of an electron-withdrawing substituent in the α-position and easily undergo hydrolysis in the presence of acid. Another approach to the breaking of the *C-N* bond is the reductive cleavage. It is worth noting that in the case of amidines, the reaction proceeds *via* the formation of intermediate aminal derivatives.

Aminals, which have two nitrogen atoms connected by a sp^3-hybridized carbon, are primarily used for synthesizing medium-sized and macrocyclic heterocycles. For example, the treatment of derivative **58** with hydrochloric acid in dioxane leads to the formation of the *N*-unsubstituted derivative of 1,5-diazocine **59** (**Scheme 17**).



Scheme 14. The ring cleavage of a carbamate derivative



Scheme 15. The photosolvolysis of benzoindolizidines and benzoquinolizidines

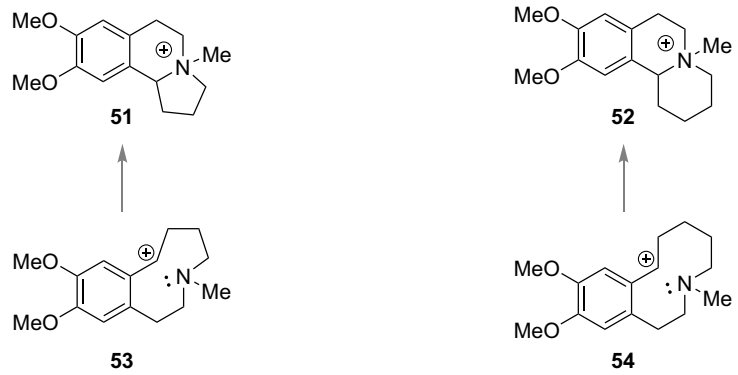
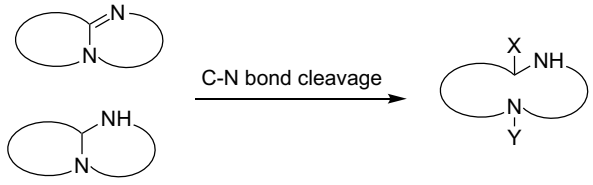


Figure 1. The stability of intermediate carbocations in the photosolvolysis reaction



Scheme 16. The *C-N* bond cleavage in bicyclic amidines and aminals

Meanwhile, the hydrogenation of compound 58 using the Adams catalyst allows for obtaining *N*-methylated derivative **57** (**Scheme 17**) [47].

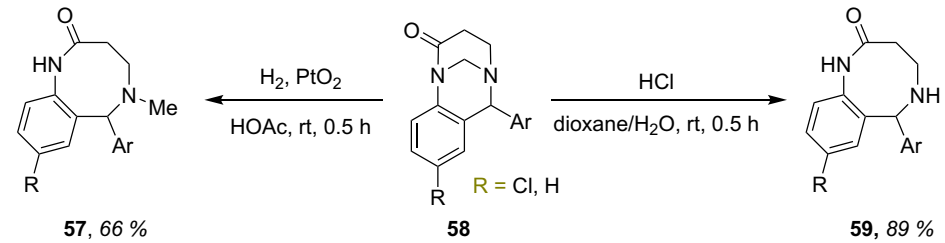
Another example is the cleavage of polynuclear aminals with a common sp^3-carbon atom. The sequential treatment with an alkylating agent and an aqueous acid solution of tricyclic orthoamide **60** leads to the formation of 1,4,7-triazonane **62** with the yield of 79% (**Scheme 18**) [48–51].

A bicyclic quaternary salts of amidines can also form medium-sized rings when reacted with other nucleophiles. For example, an approach to the nitrile derivative 1,4,7-triazacyclononane **65** by the nucleophilic cleavage of the benzylated quaternary salt of octahydroimidazolo[1,2-*a*]-pyrazine **64** with sodium cyanide was developed (**Scheme 19**) [52].

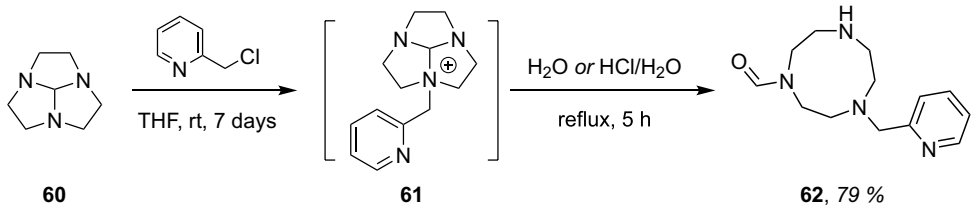
Another example involves the cleavage of 1,2-polymethylene imidazolium salts **66** with potassium cyanide leading to functionalized diazocines **67** and diazocanes **68** (**Scheme 20**) [53].

It has been shown that the hydrolytic cleavage of bicyclic amidines **69** can occur *via* two pathways involving the concurrent cleavage of two *C-N* bonds and critically depends on the size of the saturated cycle (**Scheme 21**) [54]. For instance, alkaline hydrolysis of derivative **69** (n = 2) leads to the formation of 11-membered azalactam **71** by cleaving the endocyclic *C-N* bond. Conversely, reducing the size of the saturated cycle (n = 1) results in derivatives **70**.

Recently, it has been discovered that the hydrolysis of DBU (**72**) leads to the formation of caprolactam derivative **73** (**Scheme 22**). However,



Scheme 17. The synthesis of 1,5-diazocines



Scheme 18. The synthesis of 1,4,7-triazonane derivative *via* the cleavage of a polynuclear aminal

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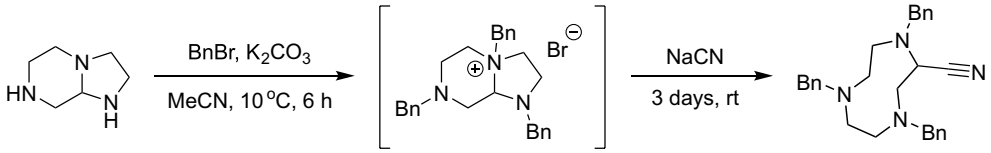
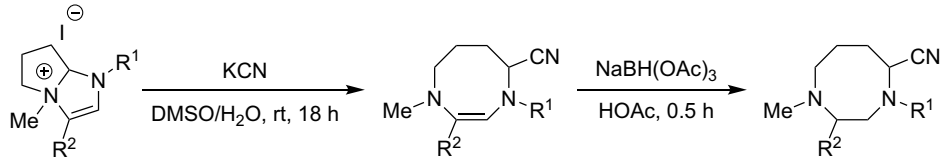


63 **64**, *63 %* **65**

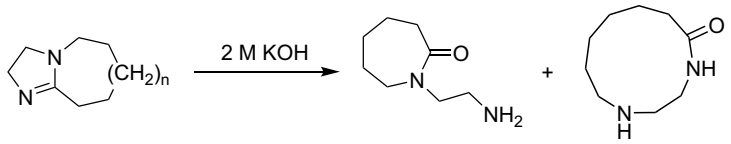
Scheme 19. The nucleophilic cleavage of quaternary salts of octahydroimidazolo[1,2-*a*]pyrazine



66 **67**, *74–93 %* **68**, *57–88 %*

R^1, R^2 = Ar

Scheme 20. The synthesis of diazocines and diazocanes



69 n = 1, 2 **70** for n = 1 **71** for n = 2

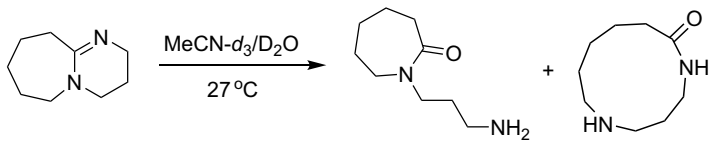
Scheme 21. The hydrolytic cleavage of bicyclic amidines

a small amount of 11-membered azalactam **74** was also found in the reaction mixture; it was confirmed by ^{1}H NMR [55].

It is worth noting that in the hydrolysis of DBU, the yield of medium ring **76** is significantly higher (60%) in the presence of an alkylating agent due to the formation of an intermediate quaternary salt (**Scheme 23**). However, the formation of caprolactam derivative **75** is also observed [56].

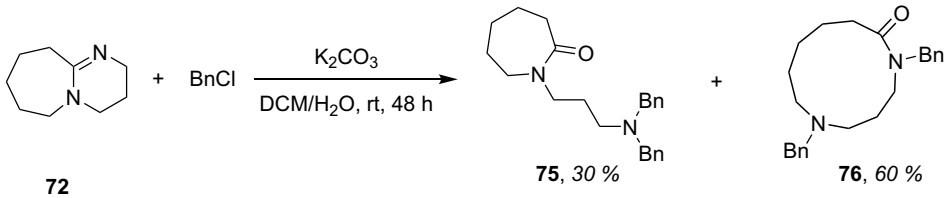
Much more examples of the reductive cleavage of amidines are known in the literature compared to aminals since the synthesis of the latter is often more difficult. Moreover, amidines are frequently used as starting materials for obtaining aminals. It is important to note that, unlike the hydrolysis of bicyclic amidines, the reductive cleavage of these compounds (and therefore, the formation of medium-sized cycles) is an irreversible process, and the selectivity of the reaction is not strongly dependent on the size of the saturated cycle. The reductive cleavage of aminals and amidines is closely interconnected since this process for amidines occurs via the formation of an intermediate of bi- or polycyclic structure with an aminal fragment.

Yamamoto and colleagues demonstrated the possibility of applying the reductive cleavage



72 **73** **74**

Scheme 22. The hydrolysis of DBU



72 **75**, *30 %* **76**, *60 %*

Scheme 23. The hydrolysis of alkylated DBU

reaction of bicyclic derivatives of aminals and amidines **77** using DIBAL-H and proposed a mechanism for this reaction (**Scheme 24**) [57].

It has been shown that the DIBAL-H induced cleavage is an effective synthetic approach not only for the synthesis of medium-sized but also macrocyclic compounds **78** in high yields (**Table 2**).

Other examples of the reductive cleavage of bicyclic aminals are provided, for instance, in the works [58–62].

However, for 1,2-fused benzimidazoles, the reaction outcome largely depends on the size of the saturated ring (**Scheme 25**). Thus, for 7- and 8-membered derivatives **79** (n = 3, 4), the main product of the reaction is diazacycloalkanes **83**, whereas the reduction of 6- and 5-membered derivatives **79** (n = 1, 2) yields approximately the equimolar mixture of **83** and **84** due to the competitive cleavage of *C-N* or *C=N* bonds in intermediate **80**. The result obtained could be explained by steric hindrance in the formation of *N,N'-bis*-amides **81** (*path 1*) in the case of n = 1, 2 [63].

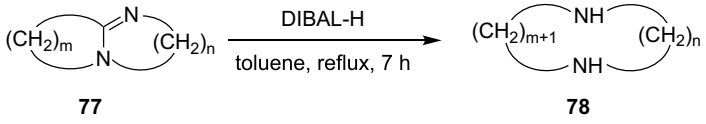
The method developed by *Yamamoto* is highly effective in the synthesis of medium-sized and macrocyclic derivatives of diazaheterocycles. However, the use of a strong reducing agent like DIBAL-H imposes certain limitations on the starting compounds with functional groups and technical difficulties in carrying out the reaction. The activation of aminals or amidines *via* the formation of quaternary salts allows the use of less hazardous reducing agents, such as lithium aluminum hydride ($LiAlH_4$), and in many cases, the reductive cleavage of bicyclic compounds is achieved using sodium borohydride ($NaBH_4$) in water or alcohols.

An example of the application of lithium aluminum hydride $LiAlH_4$ is the synthesis of bicyclic diamines with a medium-ring fragment by reducing derivatives **85** (**Scheme 26**) [64–66]. It has been shown that the reduction of salts **85** with $LiAlH_4$ in DME at room temperature leads to the formation of bicyclic [5.4.2], [5.5.2], [5.4.3], and [5.5.3] diamines **86** in high yields. It is worth noting that the authors have successfully applied this strategy for the synthesis of derivatives of 7–12-membered rings.

Another example of the $LiAlH_4$ application is the approach to synthesizing analogs of azacrown ethers by cleaving tricyclic *ortho*-amides, which was first proposed by *Weisman* and coworkers (**Scheme 27**) [67–82]. The reduction of tricyclic guanidine salts **87** (n = 1, 2) with $LiAlH_4$ in THF leads to the formation of *ortho*-amides **88** with the yield of 75%, while derivative **87** (n = 3) gives a mixture of products due to the reduction

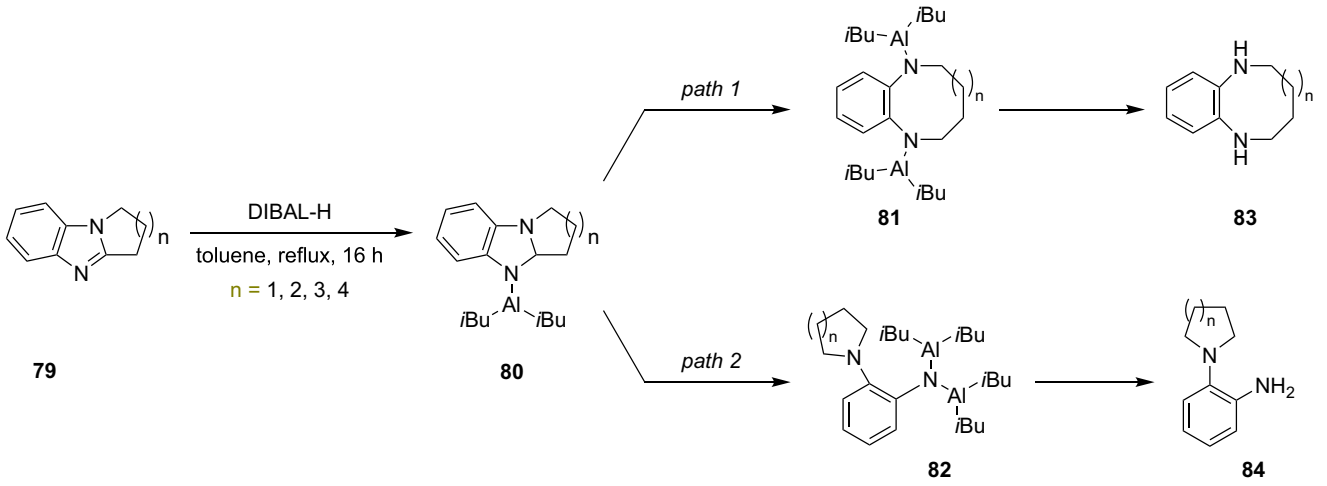
Table 2. Yields of ring cleaved products

m	n	Ring size of **77**	Yield of **78**, %
4	2	9	79
5	3	11	96
7	2	12	90
7	3	13	74
11	2	14	92
11	3	15	83



77 **78**

Scheme 24. The reductive cleavage of bicyclic aminals and amidines derivatives



79 **80** **81** **82** **83** **84**

Scheme 25. The reductive cleavage of 1,2-fused benzimidazoles

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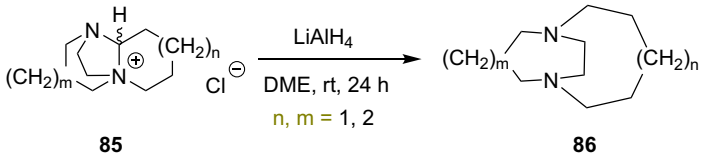
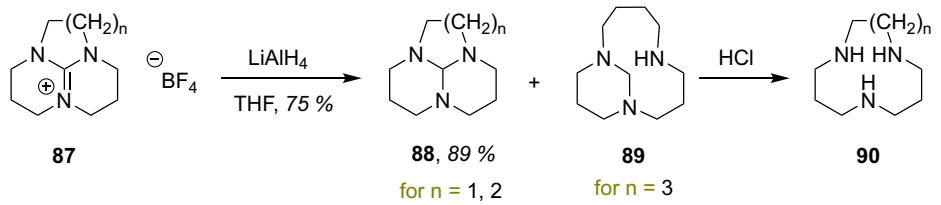


Scheme 26. The application of $LiAlH_4$ is the synthesis of bicyclic diamines



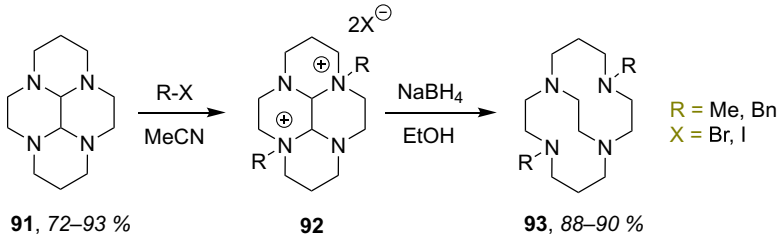
Scheme 27. The cleavage of tricyclic *ortho*-amides

of the *C=N* and *C-N* bond, resulting in **88** and **89**. In all cases, the acidic hydrolysis of orthoamides **88** and **89** obtained allows the formation of monocyclic triamines **90** in nearly quantitative yields [68].

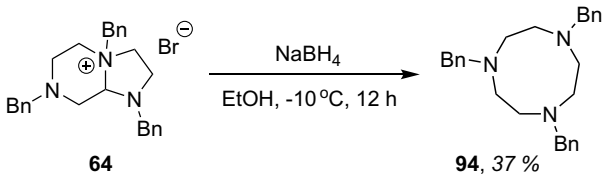
As mentioned above, the *C-N* bond can also be cleaved with $NaBH_4$. This method has been successfully used for the development of synthetic methods for cyclam derivatives **93** (**Scheme 28**) [83–87]. It has been demonstrated that the treatment of salts **92** with sodium borohydride $NaBH_4$ in 95% ethanol at room temperature for 3 to 16 days leads to the formation of derivatives **93** [84]. Attempts to optimize reaction conditions (increasing temperature, varying solvent volume) resulted in the formation of a large amount of side products. Additionally, attempting to reduce the quaternary salt **92** with $LiAlH_4$ in diethyl ether also leads to a mixture of unidentified compounds. It is worth emphasizing that the inactivated compounds **91** do not react with $NaBH_4$ or $LiAlH_4$ and are isolated unchanged after the reaction. These compounds can only be reduced using the *Yamamoto* method [57].

Two more examples of the facile reduction of quaternary salts **64** and **66** with $NaBH_4$ include the synthesis of medium-sized ring derivatives **94** and **96** (**Schemes 29, 30**) [52, 53].

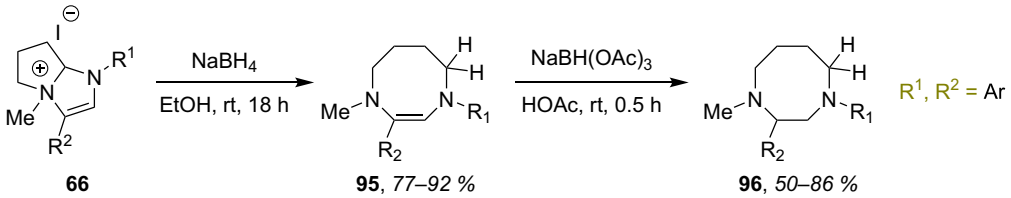
The presence of electron-withdrawing substituents near one of the nitrogen atoms (typically a carbonyl group) in bicyclic amidines or aminals is itself an activating factor that significantly



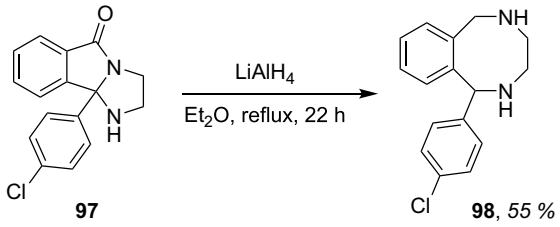
Scheme 28. The synthesis of cyclam derivatives



Scheme 29. The reductive cleavage of octahydroimidazolo[1,2-*a*]pyrazine



Scheme 30. The reductive cleavage of 1,2-polymethylene imidazolium salts



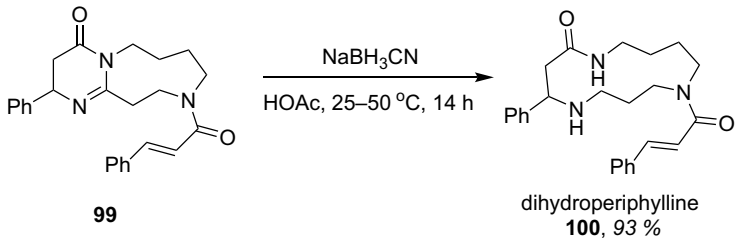
Scheme 31. The reductive cleavage of an isoindole derivative **97**

facilitates the progress of reductive cleavage reactions. As an example, the cleavage of the internal *C-N* bond in an isoindole derivative **97** without prior activation leads to the formation of an 8-membered derivative **98** (**Scheme 31**) [88, 89].

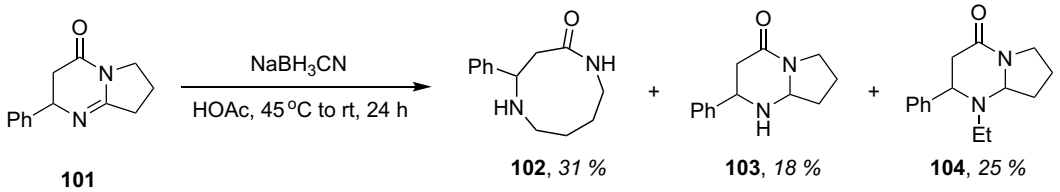
It has also been demonstrated that the cleavage of the *C-N* bond can occur in derivatives of 1,2-fused pyrimidones. The reaction of the reductive cleavage of the amidine bond has been successfully applied in the synthesis of a wide range of spermine and spermidine alkaloids [90–96]. As an example, the final stage of the synthesis of (±)-dihydroperiphylline **100** is the treatment of annulated pyrimidone **99** with 3 equivalents of sodium cyanoborohydride in acetic acid yielding the thirteen-membered heterocycle **100** in the yield 93% (**Scheme 32**).

The striking difference in the progress of a similar reductive cleavage for the derivative of pyrrolo[1,2-*a*]pyrimidine **101** should be noted. Under similar conditions, the yield of the expected 9-membered azalactam **102** was only 31% (**Scheme 33**) [94]. As side products, bicyclic aminals **103** and **104** were formed in the yields of 18% and 25%, respectively. It is worth mentioning that this is the only attempt in synthesizing medium-sized cycles by this method [94].

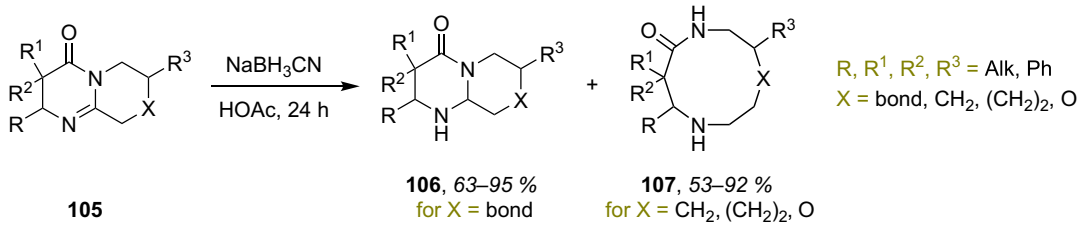
However, a more detailed study of the reductive cleavage reaction of derivatives of 1,2-fused pyrimidines is presented in the work [97]. The authors demonstrated that the cleavage of the derivative of pyrrolo[1,2-*a*]pyrimidine **105** (X = bond) and the formation of a 9-membered **107** (X = bond) azalactam was possible only in the presence of a bulky substituent in position C2 of the heterocyclic system (**Scheme 34**). At the same time, the use of piperidine, morpholine, and azepane derivatives led to the formation of 10- and 11-membered azalactams **107** (X = CH_2, $(CH_2)_2$, O) in the yields of 53–92%.



Scheme 32. The key step in the synthesis of (±)-dihydroperiphylline



Scheme 33. The synthesis of 9-membered azalactam *via* the reductive cleavage of pyrrolo[1,2-*a*]pyrimidine derivative



Scheme 34. The reductive cleavage of 1,2-fused pyrimidines

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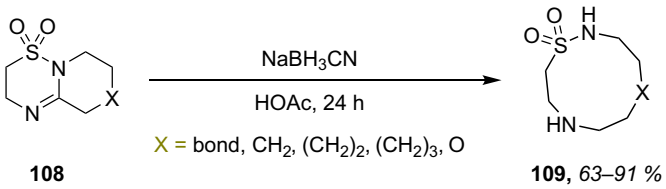

108 **109**, *63–91 %*

Scheme 35. The reductive cleavage of 2,3-fused dihydrothiadiazines

At the same time, the use of derivatives of 2,3-fused dihydrothiadiazines **108** in the ring expansion reaction leads to the formation of azasultam derivatives **109** in the yields of 63–91% [98]. It is worth noting that this reaction depends little on the size or nature of the ring annulated to the 1,2,3-thiadiazine core (**Scheme 35**).

Conclusion

There are various approaches to medium-sized cycles and macrocycles based on reductive cleavage reaction. Two types of bicyclic or polycyclic systems are used as starting materials – derivatives that contain amine or ammonium common fragments and aminal or amidine common fragments. The reductive cleavage proceeds with the splitting of the endocyclic *C-N* bond. Various reducing agents are used for the reaction. A common approach to facilitate the reaction is the quaternization of nitrogen or the introduction of activating groups. Despite the availability of numerous methods, further efforts are required to develop more reliable procedures.

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