Synthesis of monocyclic diaziridines and their fused derivatives

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Abstract
Diaziridines and their fused analogues have a wide-range potential as a test subjects for theoretical and practical application. This review covers our investigations focused on the development of optimal methods for the synthesis of monocyclic and fused diaziridine derivatives. Several approaches to the preparation of monocyclic diaziridine derivatives were developed: (1) a synthesis of 3,3-di- and 1,3,3-trialkylmono- and α,ω-o-bis(diaziridin-1-yl)alkanes from ketoxime O-sulfonates and ammonia, and primary aliphatic amines, respectively, as well as of practically previously inaccessible 3-monoalkyldiaziridines from ammonium salts of aldoxime O-sulfonic acids and ammonia (2) a synthesis of diaziridines from carbonyl compounds, primary aliphatic amines, and aminating reagents in water (or a water–MeOH mixture) at controlled pH of the medium, as well as from carbonyl compounds, amines and N-chloroalkylamines in aprotic solvents in the presence of K₂CO₃, and (3) a synthesis of 1,2,3-trialkyldiaziridines from N-chloroalkylamines without carbonyl compounds in the presence of primary aliphatic amines at high pressure. As regards fused diaziridine derivatives, general and simple methods were developed to prepare four types of these structures: 1,5-diazabicyclo[3.1.0]hexanes, 1,6-diazabicyclo[4.1.0]heptanes, 1,3,5-triazabicyclo[3.1.0] hexanes, including the parent compound and 2,4-nonsubstituted structures, and 1,3,6-triazabicyclo[3.1.0]hexanes, the latter being previously unknown. The diastereomers have been isolated for 3,3′-bi- and 1,1′-alkylenebisdiaziridines. As a whole the investigations performed in our laboratory have resulted in the simple and general methods for preparing any kind of monocyclic and fused diaziridine derivatives that give high opportunities in the study of their chemical and stereochemical properties, and applications.

Keywords: Monocyclic diaziridines, bi(bis)diaziridines, fused diaziridines, general methods for the synthesis, mechanism, pH_opt, diastereomers, racemate, meso form
1. Introduction

Diaziridines (1,2-diazacyclop propane) were first synthesized in 1959 by three groups of investigators who employed analogous methods.\textsuperscript{1-3} During the first 20 years the most essential contribution to this chemistry was made by Prof. E. Schmitz.\textsuperscript{4-6} Since that time several reviews on the synthesis and chemical properties of diaziridines have been published.\textsuperscript{4-9} Diaziridines proved to be unique chemical objects. First of all, diaziridines are among a few matters that contain nitrogen atoms which are configuration-stable under trivial conditions (inversion barriers 20-27 kcal/mol), and, consequently, these compounds have been extensively used to investigate stereochemistry of nitrogen.\textsuperscript{10,11} This side of diaziridine chemistry was studied basically by Prof. R. G. Kostyanovsky.\textsuperscript{9,11} Secondly, diaziridine derivatives are of interest as neurotropically active compounds.\textsuperscript{12-15} Furthermore, diaziridines are prone to ring expansion reactions with electrophilic reagents (ketenes, isocyanates, isothiocyanates, and acylating reagents), which led to the development of new simple methods for the preparation of both known and previously unknown heterocyclic systems.\textsuperscript{8,16-20} And, finally, diaziridines have a high formation enthalpy as a result of the input both of the hydrazine fragment and three-member strained cycle and of low toxicity, which can be potentially useful for replacing hydrazine derivatives in rocket propellants. However some diaziridines had been absolutely or almost inaccessible (e.g. 3-monoalkyldiaziridines, diaziridines with functional groups incorporated in the substituents, and
some fused diaziridine-containing systems). Moreover, most of the methods for the diaziridine preparation had not been optimized. Over the last years we have studied in detail the known approaches to the synthesis of monocyclic diaziridines as well as to their different fused derivatives and developed convenient and optimal methods (including previously unknown) to prepare any of these structures. These results have been provided in this review that comprises the Introduction (Section 1), two main issues – synthesis of monocyclic diaziridines (Section 2) and synthesis of fused diaziridines (Section 3), and references.

2. Synthesis of Monocyclic Diaziridine

The formation of the diaziridine ring resulting in monocyclic diaziridines 1 is based on intramolecular $S_{N1}$ cyclization of $N$-X-aminal 2 that theoretically can be obtained through any of three ways: (1) an interaction of primary aliphatic amines or ammonia with the condensation product 3 of carbonyl compounds and aminating reagents ($N$-galogenamines, hydroxylamine-$O$-sulfonic acid (HASA) or hydroxylamine $O$-esters) (Scheme 1a), (2) an interaction of imines 4 (the condensation products of carbonyl compounds and primary aliphatic amines) with aminating reagents, (Scheme 1b) and (3) mixing of the three components (carbonyl compounds, primary aliphatic amines or ammonia, and aminating reagents) (Scheme 1c).

\[
\text{Scheme 1. The most general approaches to the synthesis of monocyclic diaziridines 1.}
\]

According to literature data available prior to our researches, not all of the above substrates could enter these three reactions. Our results regarding the study of each of the three approaches to the synthesis of monocyclic diaziridines as well as regarding the development of a new method based on an interaction of $N$-chloroalkylamines and primary aliphatic amines at high pressure are discussed in this Section.
2.1. Monocyclic diaziridines and α,ω-bis(diaziridin-1-yl)alkanes from oxime O-esters and primary aliphatic amines or ammonia

A synthesis of 3,3-di- and 1,3,3-trisubstituted diaziridines from ketoxime O-sulfonates 5 and ammonia and primary aliphatic amines, respectively, had been described only for ketones with electron-withdrawing substituents – hexafluoracetone and dimethylmesoxalate (Scheme 1a, R = R’ = CF3, CO2Me; X = OSO2C6H4Me-4). The use of ketoxime O-sulfonates 5 obtained from aliphatic ketones raised doubts in view of their higher inclination to Beckman rearrangement.

We studied the possibility of preparing 3,3-di- and 1,3,3-trialkyldiaziridines using as a model 3,3-dimethyl-6a and 1-alkyl-3,3-dimethyldiaziridines 7a-f from acetonoxime O-sulfonates 5a-c and from other acetonoxime O-esters (acyloximes 8, phosphates 9, sulfinates 10, and picrate 11) and ammonia or primary aliphatic amines, respectively, in aprotic organic solvents (ether, dioxane, CHCl3, and CH2Cl2).

There are at least two electrophilic centers in oxime O-esters 5 and 8-11, to which a nucleophilic attack can be applied – the oxime carbon atom and central atom of the acidic fragment. The amine attack at the central atom of the acidic fragment in acetonoxime O-sulfonates 5 is sterically hindered. So 1-alkyl-3,3-dimethyldiaziridines 7a-c were successfully synthesized from all oxime O-esters 5a-c and primary aliphatic amines at room temperature (Scheme 2). As the temperature increased, the yields of 7 reduced given Beckman rearrangement of initial esters 5. 3,3-Dimethyldiaziridine 6a was prepared in an autoclave at 9 MPa.

\[
\begin{align*}
\text{Me} & \quad \text{NOSO}_2\text{R} \quad \text{Me'} \quad + \quad \text{R'}\text{NH}_2 \\
5 & \quad 2 - 10 \text{ days} \\
\text{a, } & \quad R = \text{Bu} \\
\text{b, } & \quad R = \text{Ph} \\
\text{c, } & \quad R = \text{C}_6\text{H}_4\text{Me}-4
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{H} \quad \text{R'} \quad \text{NH}_2 \\
6a & \quad R' = \text{H} (90.5\%) \\
7a & \quad R' = \text{Pr} \\
7b & \quad R' = \text{Bu} \\
7c & \quad R' = (\text{CH}_2)_2\text{OH} (88-89.5\%)
\end{align*}
\]

Scheme 2. Synthesis of 3,3-dimethyl-(6a) and 1-alkyl-3,3-dimethyldiaziridines 7 from acetonoxime O-sulfonates 5.

A synthesis of diaziridines from other acetonoxime O-esters 8-11 was carried out on example of their reaction with propylamine. It was found that only phosphates 9a,b were capable to form 1-propyl-3,3-dimethyldiaziridines 7a in moderate yields (52-67%). Not very high yields in this case were probably associated with side alkylation or phosphorylation reactions where to these esters had a tendency. In acyloximes 8a-d the carbon atom of the acyl fragment appeared to be the strongest electrophilic centre, and thus corresponding amides were obtained. 1-Propyl-3,3-dimethyldiaziridine 7a in the yield 82% was achieved only when sterically hindered
O-mesitylcarbonyl acetonoxime 8e was used. Sulfinates 10a,b and picrate 11 did not form diaziridine 7a similarly to O-esters 8a-d (equation 1).

\[
\begin{align*}
\text{Me} & \quad \text{NO-} & \quad \text{X} + \text{PrNH}_2 & \quad \rightarrow \quad \text{Me} & \quad \text{N} & \quad \text{N} \\
8e, 9a,b & \quad \text{Pr} & \quad 7a
\end{align*}
\]  
(eq. 1)

8 X = COR  
a R = Me, b R = Ph, c R = CH\(_2\)Cl, d R = CCl\(_3\)  
e R = C\(_6\)H\(_2\)Me\(_3\)-2,4,6  
9 X = P(O)R\(_2\)  
a R = OPh, b R = OPri  
10 X = S(O)R  
a R = OMe, b R = OC\(_6\)H\(_4\)Me-4  
11 X = C\(_6\)H\(_2\)(NO\(_2\))\(_3\)-2,4,6

A reaction of ketoxime O-p-toluenesulfonates 5c,d with 1,ω-diaminoalkanes was utilized for the synthesis of α,ω-bis(3,3-dialkyldiaziridin-1-yl)alkanes 12. The diastereomeric racemate 15S*,2S*,1′S*,2′S* and meso-15S*,25S*,1′R*,2′R* were isolated for α,ω-bis(3,3-dimethyl Diaziridin-1-yl)ethane 12a by fractional crystallization and the meso structure confirmed by X-ray diffraction analysis (Scheme 3).

\[
\begin{align*}
\text{R}^1 & \quad \text{NOSO}_2\text{C}_6\text{H}_4\text{Me}-4 & \quad + \quad \text{H}_2\text{N} & \quad \text{NH}_2 & \quad \rightarrow \quad \text{R}^1 & \quad \text{N} & \quad \text{N} & \quad \text{R}^1 \\
5 & \quad \text{c} & \quad \text{R} = \text{R}^1 = \text{Me}, & \quad \text{n} = \text{1 - 5} & \quad \text{Et}_3\text{N} & \quad \text{CH}_2\text{Cl}_2 & \quad \rightarrow & \quad \text{12} & \quad (47 - 77.5\%) \\
& \quad \text{d} & \quad \text{R} - \text{R}^1 = -(\text{CH}_2)_{5-}
\end{align*}
\]

Scheme 3. Synthesis of α,ω-bis(3,3-dialkyldiaziridin-1-yl)alkanes 12.

The developed method for the synthesis of 3,3-dimethyl Diaziridine 6a from acetonoxime O-sulfonates 5 according to Scheme 2 was considered unsuitable for preparing, practically, previously inaccessible 3-monoalkyldiaziridines 13 from analogous derivatives of aldehydes. This is because aldoxime O-sulfonates as well as aldoxime O-sulfonic acids 14 decompose immediately after formation to give corresponding nitriles and sulfonic or sulfuric acids, respectively. We showed for the first time that aliphatic aldoxime O-sulfonic acids 14 could be stabilized as ammonium or alkylammonium salts 15a,b. It was found that alkylammonium salts 15b were stable at room temperature but that ammonium salts 15a only survived in saturated aqueous solution of NH\(_3\) (> 40%) at a lower temperature. To prepare 15a, aqueous NH\(_3\) was saturated with gaseous NH\(_3\) under cooling, and then a freshly prepared cold solution of 14 was
added. A flow of gaseous NH$_3$ passing through solution of 15a at a lower temperature resulted in 3-alkyldiaziridines 13 in moderate yields. 1,3-Dialkyldiaziridines 16a-c were prepared by the interaction of primary aliphatic amines with salts 15b in H$_2$O or in MeOH–H$_2$O mixture$^{27}$ (Scheme 4).

\[
\begin{align*}
\text{RCHO + H$_2$NOSO$_3$H} & \rightarrow \text{RCH(NOSO$_3$)NH$_4$}^+ \\
& \rightarrow \text{RCH(NOSO$_3$)NH$_3$} \\
& \rightarrow \text{RCH(NOSO$_3$)NH$_3$R}^+ \\
& \rightarrow \text{R'NH$_2$} \\
\end{align*}
\]

\[
\begin{align*}
14 & \rightarrow 15a \rightarrow 13 \quad (22 - 32\%) \\
& \rightarrow 15b \rightarrow 16 \quad (32 - 44\%) \\
\]

\[\text{a, R = Me, R'} = \text{Pr} \]
\[\text{b, R = Et, R'} = \text{Bu} \]
\[\text{c, R = Pr, R'} = \text{CH$_2$Ph} \]

**Scheme 4.** Synthesis of 3-mono-(13) and 1,3-disubstituted diaziridines 16 from aldoxime O-sulfonic acids salts 15a,b.

2.2. 3,3’-Biodiaziridines from diimines of glyoxal and 1,2-bis(methylamino)ethane-1,2-diol dihydrochloride

The second approach to the synthesis of monocyclic diaziridines (Scheme 1b) had been rather well developed by E. Schmitz.$^{5,6}$ Using this approach we managed to synthesize the first representatives of 3,3’-biodiaziridines 17 from diimines 18 of glyoxal.$^{28}$ It was found that this approach could be used only for diimines 18 with branched alkyl substituents. Reactions of glyoxal with primary aliphatic amines containing normal aliphatic radicals did not terminate at the stage of diimines as they underwent further condensation or polymerization.$^{29}$ Reactions of diimines 18 with HASA in the presence of TEA in MeOH at -5 → 20 °C afforded 1,1’-dialkyl-3,3’-biodiaziridines 17 in high yields. These compounds were generated as a mixture of several diastereomers as evidenced by the $^1$H NMR spectra of the crude products because 1,1’-dialkyl-3,3’-biodiaziridines 17 contained besides nitrogen atoms one more chiral centre, viz. the carbon atom of the diaziridine ring. However, isolation of the final products by vacuum distillation or sublimation always afforded a mixture of only the two most thermodynamically favorable diastereomers in a ratio from 2:1 to 9:1. The NOE experiments and X-ray diffraction analysis of one of the synthesized diaziridines demonstrated that the isolated diastereomers were the (1$^S$,2$^S$,3$^R$,1’$^S$,2’$^S$,3’$^R$) racemate 17a and the (1$^S$,2$^S$,3$^R$,1’$^R$,2’$^R$,3’$^S$) meso form 17b (Scheme 5)
Scheme 5. Synthesis of 1,1′-dialkyl-3,3′-bidiaziridines 17 with branched alkyl substituents.

To prepare bidiaziridines with normal aliphatic radicals at nitrogen atoms an attempt was made to stabilize the diimine of glyoxal and methylamine at the instant of its formation as the dihydrochloride salt 19. Thus, treatment of the organic layer formed after mixing of aqueous solutions of reagents with conc. HCl followed by twofold treatment with K₂CO₃ led only to bis(methylamino)ethane-1,2-diol dihydrochloride 20 whose structure was established as a mixture of two diastereomers by ¹H NMR with use 2D COSY-LR experiment, ¹³C NMR and MS (Scheme 6). This showed for the first time that aliphatic α-aminocarbinoles can be stabilized as hydrochlorides.³⁰

To synthesize 1,1′,2,2′-tetramethyl-3,3′-bidiaziridine 21 dihydrochloride 20 was added to a solution of N-chloromethylamine in an aprotic organic solvent (CHCl₃ or CH₂Cl₂) in the presence of different bases (TEA, diethylamine or K₂CO₃). In the presence of organic bases, dihydrochloride 20 liberates free bis(methylamino)ethane-1,2-diol, which at once enters a self-condensation reaction that results in oligomers. The synthesis of bidiaziridine 21 was successful only in heterogeneous media in the presence of K₂CO₃ as base. According to the NMR spectroscopic data, compound 22 was a mixture of two diastereomers - racemate 21a and meso-21b in a ratio ≈ 3:2 (Scheme 6), from which 21b was isolated in the individual state and its structure was established by X-ray diffraction analysis. The kinetics of inversion of diastereomers 21a and 21b was studied by ¹H NMR spectroscopy at heating in CHCl₃.³⁰ Each of the individual diastereomers formed an initial mixture of racemate 21a and meso-21b (ca. 3:2) in ~ 5 h.

Scheme 6. Synthesis of 1,1′,2,2′-tetramethyl-3,3′-bidiaziridine 21.
The mixtures of diastereomers of 3,3′-bidiaziridines 17a,b (R = t-Bu) and 21a,b were resolved into three stereoisomers - meso and two enantiomers by the gas-chromatography using the chiral stationary phase – Chirasil-β-Dex, where permethylated β-dextrin was linked to polyoxymethylene through an undecamethylene 11C-spacer.

2.3. Monocyclic diaziridines by mixing carbonyl compounds, primary aliphatic amines and aminating reagents

2.3.1. In water at controlled pH of the medium. Among the three approaches to diaziridine ring formation the simplest is based on an interaction of the carbonyl compound, primary aliphatic amine (or ammonia), and an aminating reagent (HASA or N-halogenamines) (Scheme 1c). However, yields of diaziridines 1 in these reactions were often not quantitative. We have examined the proposed mechanism of the diaziridine ring formation to identify those factors that most likely influence the reaction.32-34 We found that yields of monocyclic diaziridines 1 synthesized by mixing the three components in water depended on pH of the reaction medium. To explain this effect we assumed that N-X-aminal 2, in this case, was generated through α-aminomethylation, the result of which depended on the acid-base properties of the reaction medium and electronic effects of substituents in the initial components.32,33 If so, the first step of the diaziridine synthesis is an interaction of the carbonyl compound with primary aliphatic amine (or ammonia) leading to α-aminocarbinol 22. The transformation of this then occurs via protonation with formation of oxonium ion 23 followed by its dehydration into carbenium-iminium cation 24, and should depend upon pH of the medium by analogy with the other α-aminomethylation reactions. Further interaction between cation 24 and the aminating reagent results in N-X-aminal 2 that rapidly cyclizes into product diaziridine 1 (Scheme 7). In order to check this hypothesis, we looked at the synthesis of diaziridines 1 from carbonyl compounds and amines that contained substituents with different I-effects, and aminating reagents (HASA or N-chloroalkylamines) at different fixed pH values. The effect of the substituents in amines was evaluated relative to their pK_BH+ values, whereas the effect of the carbonyl compounds was evaluated relative to the sum of Taft induction constants \( \Sigma \sigma^* \) of the substituents at the carbonyl groups.

![Scheme 7. Possible scheme for diaziridine ring formation from carbonyl compounds, primary aliphatic amines, and aminating reagents in water.](image)
Indeed, it was found that the highest yield of diaziridines 1 in water was achieved at an optimum pH ($pH_{\text{opt}}$) that shifts to a less alkaline region as the $-I$-effect of the substituents in the carbonyl compound increased and the $pK_{BH^+}$ value of amine decreases.\textsuperscript{32,33} The dependence of the 1,3,3-trialkyldiaziridines 25 and 1,2,3-trialkyldiaziridines 26 yields upon the pH of the reaction medium is presented in Figs. 1 and 2 according to equations 2 and 3, respectively.

As seen from Figures 1 and 2, diaziridine ring formation from amines with electron-withdrawing substituents in the side chain is less sensitive to pH than from the amines with simple alkyl substituents. The formation of the 1,5-diazabicyclo[3.1.0]hexanes 29 is practically insensitive to pH over the 6.5 – 13.0 pH range.

![Figure 1](image.png)

**Figure 1.** The yields of the 1,3,3-trialkyldiaziridines 25 at $pH_{\text{opt}}$ according to equation 2:

1. $R = R^1 = \text{Me}$; 2. $R = \text{Me}$, $R^1 = (\text{CH}_2)_2NHAc$; 3. $R = \text{CH}_2NHAc$, $R^1 = (\text{CH}_2)_2OH$; 4. $R = \text{CH}_2NHAc$, $R^1 = (\text{CH}_2)_2NHAc$.

![Figure 2](image.png)

**Figure 2.** The yields of the 1,2,3-trialkyldiaziridines 26 according to equation 3.

![Equation 2](image.png)

(eq. 2)

![Equation 3](image.png)

(eq. 3)
Figure 2. The yields of the 1,2,3-trialkyldiaziridines 26 and 1,5-diazabicyclo[3.1.0]hexanes 29 at pH_{opt} according to equation 3: (1) R = R^1 = Me; (2) R = Me, R^1 = Et; (3) R = Me, R^1 = (CH_2)_2NHAc; (4) R = H, R^1 = Me; (5) R = H, R^1 = (CH_2)_2NHAc; (6) R = H, R^1-R^1 = (CH_2)_3; (7) R = Me, R^1-R^1 = (CH_2)_3.

These differences may be explained by different competing pathways leading to the key intermediate, N-X-aminal 2 (Scheme 8) (this Scheme is for N-chloroalkylamine R^2NHCl as an aminating reagent): the aforesaid Path A through iminium cation 24, the formation of imine 27 followed by its reaction with N-chloroalkylamine (Path B), and the preliminary formation of aminal 28 followed by its exchange chlorination in the reaction with N-chloroalkylamine (Path C). The formation of diaziridines 1 follows from a loss of HCl.

To identify the optimal pathway of the transformation of iminium cation 24 quantum chemical calculations for the synthesis of the simplest product 1a (R = R^1 = H, R^2 = Me) were performed. The calculations were carried out on a basis of the density functional theory (B3LYP) with account for solvent effect using the PCM model.35 The calculated potential energy surface with stationary points corresponding 22a, 23a, 24a, 27a, 28a, 2a and 1a is shown in Fig. 3.

The stationary point corresponding to the protonation product of intermediate 22a, viz cation 23a was not found because the geometry optimization led to the elimination of the water molecule giving rise to structure 24a. The estimated energy for 23a was obtained by the geometry optimization with the fixed C-O bond length of 1.4 Å. Since the formation of cationoid species 24a is accompanied by a substantial gain in energy (9.02 kcal/mol), dehydration of compound 23a is presumably barrierless. The calculations showed that Path A was the most energetically favorable pathway for the transformation of cation 24a in aqueous solution. The reaction can also follows by paths B or C though these are less probable. The formation of reaction product 1a is accompanied by a larger energy gain (35.67 kcal/mol) that provides the driving force needed for the overall transformation. Path C is evidently most favorable for the synthesis of bicyclic products 29.
Scheme 8. The possible pathways for the key intermediate 2 formation in reaction of carbonyl compound, primary aliphatic amine and N-chloroalkylamine in water.

Figure 3. Potential energy surface calculated for the transformation of α-aminocarbinol 22a into 1,2-dimethyldiaziridine 1a calculated at the PCM-B3LYP/6-31G* level.

The medium pH-dependent approach to diaziridine synthesis from amines, carbonyl compounds and aminating reagents in water (or the water–MeOH mixture) allowed to prepare a lot of diaziridines 1 with different kinds of substituents in both carbonyl compounds and amines, including reagents with electron-withdrawing substituents, sterically hindered...
1-aminoadamantane,α-acetylenic aldehydes, and to synthesize derivatives previously inaccessible, e.g. 30-32.

As the final result of this part researches, we developed a new and simpler approach to the synthesis of 1,2-di- and 1,2,3,-trialkyldiaziridines based on direct chlorination of a mixture of a carbonyl compound with an excess of primary aliphatic amine in water. In this case the optimum pH was determined by the carbonyl compound to amine molar ratio (~ 1:8-10). This approach was used to develop a method for the preparation of 1,2-dialkyldiaziridines suitable for technological application.

2.3.2. In aprotic organic solvents in the presence of K₂CO₃. Unfortunately, the methods based on reactions in aqueous media cannot be extended to the synthesis of diaziridines from water-insoluble reagents. One of the approaches to the synthesis of 1,2-disubstituted diaziridines from such reagents was alkylation of N-monoalkylidiaziridines after preparation of their sodium salts under the action of NaNH₂. However this method demands the use of strictly anhydrous dipolar aprotic solvents and strong bases (Scheme 9).

Scheme 9. Synthesis of 1,2-disubstituted diaziridines by N-alkylation of 1-monoalkyl diaziridines sodium salts.

To synthesize diaziridines from water-insoluble reagents a new approach based on the interaction of carbonyl compounds, primary aliphatic amines and N-chloroalkylamines in aprotic organic solvents in the presence of K₂CO₃ was offered. A preliminary ¹H NMR study of a model interaction between allylamine and formaldehyde showed that α-aminicarbinol (R = R¹ = H, R² = CH₂CH=CH₂) could survive in the aprotic organic solvent containing K₂CO₃ for a reasonably long time without conversion to hexahydro-1,3,5-triazine (R = R¹ = H)
(Scheme 10). K$_2$CO$_3$, which exhibits both basic and dehydration properties, is likely to result in stabilization of α-aminocarbinol 22. However, in order to perform the reaction successfully the reaction mixture needs to be continuously and efficiently stirred for contact with K$_2$CO$_3$. In our test, when stirring stopped, a water layer appeared within a few minutes, and hexahydro-1,3,5-triazine 36a was formed. Based on these results, we explored the synthesis of 1,2-disubstituted diaziridines by adding an N-chloroalkylamine 37 to the mixture of carbonyl compound and primary aliphatic amine in the presence of K$_2$CO$_3$ (in CHCl$_3$ or CH$_2$Cl$_2$ under intensive stirring). N-Chloroalkylamines 37 were generated by the reaction of corresponding amines with NaOCl followed by extraction with CHCl$_3$ or CH$_2$Cl$_2$ used as reaction solvents. In the case of amine and N-chloroalkylamine 37 with identical alkyl groups, 1 mol t-BuOCl was added to 2 moles of amine in the same solvents.

This approach proved to be very fruitful. Carbonyl compounds and primary aliphatic amines with different substituents, including functional and sterically hindered amines, were introduced to this reaction and a variety of 1,2-di-(38), 1,2,3-tri-(26) and 1,2,3,3-tetraalkylidiaziridines 39 was synthesized in 35-70% yields. Evidently, under these conditions, the interaction of α-aminocarbinols 22 and N-chloroalkylamines 37 resulted in N-chloroaminals 2 that further cyclized to the diaziridine products (Scheme 10).

Scheme 10. Synthesis of monocyclic diaziridines 26, 38 and 39 from carbonyl compounds, primary aliphatic amines and N-chloroalkylamines 37 in aprotic organic solvents in the presence of K$_2$CO$_3$.

2.4. 1,2,3-Trialkylidiaziridines from N-chloroalkylamines and primary aliphatic amines at high pressure

During the optimization of the above method for the synthesis of 1,2-di-, 1,2,3-tri- and 1,2,3,3-tetraalkylidiaziridines 38, 26 and 39, we studied the behavior of N-chloroalkylamines 37 in the presence of an excess of corresponding amine in chlororganic solvents. It was found that such reactions with an amine carrying the same alkyl fragment, in the presence of K$_2$CO$_3$ and
a small amount of water at room temperature resulted in 1,2,3-trialkyl diaziridines 26 where the 3-alkyl fragment contains one CH₂ group less than the alkyl fragment of the initial compounds as it becomes the carbon centre of the three-membered ring. Given the structure of the products, we assumed that the first step of this reaction is the conversion of N-chloroalkylamines 37 into aldimines 40 by E₂-loss of HCl in the presence of amine. Hydrolysis of 40 by the water would then give aldehydes 41, which can enter into reaction with amines and N-chloroalkylamines 37 leading to 1,2,3-trialkyl diaziridines 26 by analogy with the method described above (Scheme 11). 34

\[
\begin{align*}
\text{RCH₂NHCl} & \xrightarrow{\text{K₂CO₃, CHCl₃}} \text{RCH=NH} & \xrightarrow{\text{H₂O}} \text{RCHO} & \xrightarrow{\text{RCH₂NH₂ + 37}} \text{RNCH₂CH₃} \\
\end{align*}
\]

**Scheme 11.** Synthesis of 1,2,3-trisubstituted diaziridines 26 from N-chloroalkylamines 37 and primary aliphatic amines in aprotic solvents in the presence of K₂CO₃.

However, the slow rate of this reaction impedes its application. For aliphatic N-chloroalkylamines 37, the reaction requires several days, and for those synthesized from amines with lower basicity it takes several weeks. Anyhow, this variant of the synthesis of diaziridines 26 could be useful in those cases where carbonyl compounds are less accessible than the corresponding amines. In light of these findings, we used high pressure to accelerate this reaction. The reactions were carried out in a Teflon ampoule placed in a special reaction block at 300, 500, and 700 MPa. The reaction kinetics were examined for the interaction of N-chloroethylamine 37a (R = Me) and ethylamine and revealed that these reactions were the second order at all the pressures (Figure 4).

Thus, the limiting step of the process is the bimolecular interaction of N-chloroethylamine 37a with ethylamine followed by elimination of the HCl molecule. It was found that the optimal conditions for this reaction resulting 1,2-diethyl-3-methyl diaziridine 26a in yield 95% are a molar ratio of N-chloroethylamine 37a to ethylamine of 1:2.5 with 0.5 mol of K₂CO₃, 1-2% of water (by volume) and 500 MPa pressure at 15 °C. A several other N-chloroalkylamines 37b-f were used in the analogous reaction under the identified conditions. In all cases the taget 1,2,3-trialkyl diaziridines 26b-f were prepared in high yields (Scheme 12). 41
Figure 4. Kinetic curves for the formation of 1,2-diethyl-3-methyl diaziridine \( 26a \) (R = Me) from \( N \)-chloroethylamine \( 37a \) and EtNH\(_2\) at high pressure. Curves 1 and 3 correspond to consumption of \( N \)-chloroethylamine \( 37a \) while curves 2 and 4 correspond to accumulation of diaziridine \( 26a \). Curves 1 and 2 were recorded at 300 MPa and curves 3 and 4 were recorded at 500 MPa.

So, a new method for preparing 1,2,3-trialkyl diaziridines \( 26 \) in high yields based on the transformation of \( N \)-choloralkylamines \( 37 \) without using carbonyl compounds, but in the presence of primary aliphatic amines with the same alkyl fragment, potassium carbonate and a small amount of water at high pressure was developed.

\[
\begin{align*}
RCH_{2}NHCl & \quad \xrightarrow{RCH_{2}NH_{2}, K_{2}CO_{3}, CHCl_{3}, P = 500 \text{ MPa}, 15 \, ^{\circ}C, 12 - 48 \text{ h}}
RCH_{2}NH_{2}, \quad & \text{R} \end{align*}
\]

\( 26 \) (78 - 95%)

\( \text{a,} \ R = \text{Me}; \)
\( \text{b,} \ R = \text{Et}; \)
\( \text{c,} \ R = \text{CH}_{2}\text{Ph}; \)
\( \text{d,} \ R = \text{CH}_{2}\text{OMe}; \)
\( \text{e,} \ R = \text{CH}_{2}\text{NHCOMe}; \)
\( \text{f,} \ R = -(\text{CH}_{2})_{2}\text{N}^{\text{N}} \)

Scheme 12. Synthesis of 1,2,3-trialkyl diaziridines \( 26a-f \) from \( N \)-chloroalkylamines \( 37a-f \) and corresponding alkylamines at high pressure.

3. Synthesis of Fused Diaziridine Derivatives

In addition to the methods for the synthesis of monocyclic diaziridines we have also developed methods for the preparation of four types of fused derivatives of monocyclic diaziridines:
1,5-diazabicyclo[3.1.0]hexanes 42, 1,6-diazabicyclo[4.1.0]heptanes 43, 1,3,5-triazabicyclo[3.1.0]hexanes 44, and 1,3,6-triazabicyclo[3.1.0]hexanes 45. Compounds 42–44 and 47,48 had been described in literature, and we elaborated new and simpler approaches to their preparation and synthesized the parent and 2,4-unsubstituted structures 44. Only one example of bicycle 43 had been described,43 and we proposed a general method for the synthesis of a range of derivatives. Bicyclic compounds 45 were hitherto unknown.

3.1. 1,5-Diazabicyclo[3.1.0]hexanes and 1,6-diazabicyclo[4.1.0]heptanes

Earlier,42–44 1,5-diazabicyclo[3.1.0]hexanes 42 had been synthesized by halogenation of 1,3-diazacyclohexanes 46, formed from aldehydes and 1,3-diaminopropane with NaOCl in water, followed by intramolecular cyclization of ensuing cyclic N-Cl-aminal 47a. We used this variant of the synthesis of bicycles 42 in a combination with controlled pH of the medium (9.5-10.5) to prepare the first representative of 6,6′-bis(1,5-diazabicyclo[3.1.0]hexanes) 48 from glyoxal and 1,3-diaminopropane. According to X-ray diffraction data both bicyclic fragments in compound 48 exist in boat conformation45 (Scheme 13).

\[
\begin{align*}
RCHO + H_2N(CH_2)_3NH_2 & \rightarrow R\begin{array}{c}N\end{array}H \quad \text{NaOCl}\quad \text{NaOH} \quad \begin{array}{c}N\end{array}H\begin{array}{c}N\end{array}N \quad \begin{array}{c}Cl\end{array} \rightarrow \begin{array}{c}N\end{array}H\begin{array}{c}N\end{array}N \quad 42 \\
OHC-CHO + H_2N(CH_2)_3NH_2 & \rightarrow \begin{array}{c}N\end{array}\begin{array}{c}N\end{array} \quad \text{NaOCl} \quad \text{pH 9.5 - 10.5} \quad \begin{array}{c}N\end{array}\begin{array}{c}N\end{array} \quad 48 (61\%) \\
\end{align*}
\]

Scheme 13. The known method for the preparation of 1,5-diazabicyclo[3.1,0]hexanes 42 and synthesis of 6,6′-bis(1,5-diazabicyclo[3.1,0]hexanes) 48.

The procedure to give monocyclic diaziridines in aprotic solvents39 was extended to the synthesis of 1,5-diazabicyclo[3.1.0]hexanes 42 and 1,6-diazabicyclo[4.1.0]heptanes 43 (an interaction of equimolar amounts of carbonyl compounds, 1,3-diaminopropane or 1,4-diaminobutane, respectively, and t-BuOCl in the presence of K₂CO₃ in CHCl₃).46 This variant allowed bicycles 42 and 43 to be more easily isolated and in increased yields (50-52%). However, this procedure appeared unsuitable for reactions with carbonyl compounds carrying substituents sensitive to strong halogenating reagents such as NaOCl or t-BuOCl. To overcome this limitation
1,3-diaminopropane or 1,4-diaminobutane were first halogenated to their monochloro derivatives 49 and 50, respectively, and the condensation with carbonyl compounds then followed. This gave 1,3-diaza- or 1,4-diaza-1-chlorocycloalkanes 47a and 51 subsequently transformed to 6-substituted 1,5-diazabicyclo[3.1.0]hexanes 42 and 7-substituted 1,6-diazabicyclo[4.1.0]heptanes 43 under the action of bases. The study of the base nature’s effect indicated that the best results were obtained where starting diamines were used in an equimolar excess (Scheme 14) 46.

\[
\begin{align*}
&\text{H}_2\text{N} - \text{NH}_2 \\
&\text{t-BuOCl} \\
&\text{H}_2\text{N} - \text{NH}_2 \\
&\text{RCH} = \text{O} \\
&\text{Cl} \\
&\text{H}_2\text{N} - \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
&42, 49, 47a (n = 1), 50 (n = 2) \\
&42 n = 1 (59 - 89\%) \quad 43, 50, 51 n = 2; R = \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, 2-\text{Cl-5-NO}_2\text{C}_6\text{H}_3, \text{N} \quad \text{N} \\
&43 \quad \text{N} \quad \text{N} \\
&42, 49, 47a (n = 1), 51 (n = 2)
\end{align*}
\]

**Scheme 14.** Synthesis of 1,5-diazabicyclo[3.1.0]hexanes 42 and 1,6-diazabicyclo[4.1.0]heptanes 43 from N-monochloroalkylenediamines.

### 3.2. Parent and 2,4-unsubstituted 1,3,5-triazabicyclo[3.1.0]hexanes

The known synthesis of 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes 52 is based on two reactions: cyclization of the corresponding 2,4,6-trialkyl(aryl)hexahydro-1,3,5-triazines 36 with t-BuOCl 47 (path A, Scheme 15) or interaction of aldehydes, N-chloroamine and ammonia at low temperature 48 (path B, Scheme 15). Path B evidently includes the formation of 3-monosubstituted diaziridines 13 followed by their condensation with two moles of aldehyde and one mole of ammonia. We used pathway A to synthesize parent 1,3,5-triazabicyclo[3.1.0]hexane 44a from the equilibrium mixture of CH2O and NH3 condensation products in water (after its treatment with K2CO3 - “Henry solution”) with NaOCl at low temperature (−20 °C). 49 As shown in that work, 49 this solution contained a small amount of unsubstituted hexahydro-1,3,5-triazine 36b. Path B in this reaction should be excluded because the parent unsubstituted diaziridine 53 (if it would be formed) in these conditions must be oxidized to parent diazirine 54. The yield of 44 (b.p. = 74 °C/1 Torr) was only 5% and urotropin 55 was the main reaction product. The structure of compound 44a was based upon by 1H, 13C and 15N NMR data, and on the basis of conversion into phenylisocyanate derivative 56 (Scheme 15). 50
Scheme 15. Synthesis of parent 1,3,5-triazabicyclo[3.1.0]hexane 44a and its phenylisocyanate derivative 56.

It had been earlier shown\textsuperscript{12,51} that diaziridines containing one or two unsubstituted nitrogen atoms behaved as NH acids in the Mannich reaction and only underwent $\alpha$-aminomethylation. The absence of the $\alpha$-aminomethylation ability in aziridines\textsuperscript{24-54} and oxaziridines\textsuperscript{55} is a generic property of these three-membered nitrogen-containing heterocycles. Therefore, in order to use path B of Scheme 15 to prepare 2,4-unsubstituted 1,3,5-triazabicyclo[3.1.0]hexanes 44, it is necessary to carry out Mannich condensation of 1,2-unsubstituted diaziridines with ammonia which is more basic. Attempts to implement Mannich condensation of 3-monoalkyldiaziridines 13a,b or 3,3-dimethyldiaziridine 6a with NH$_3$ and CH$_2$O in both aqueous and methanolic media, and in an aprotic organic solvent failed – in all the cases urotropin 55 was produced. The best conditions for the synthesis of compounds 44b,c proved to be condensation of diaziridines 13a,b with NH$_3$ and CH$_2$O in water with subsequent twofold treatment with K$_2$CO$_3$, extraction of the resulting organic layer into the aprotic organic solvent, and exposure to a basic dehydrating reagent such as K$_2$CO$_3$ or BaO (Scheme 16).\textsuperscript{56,57} The yields of compounds 44b,c under these conditions were 85-91\%, and the yield of by- 55 did not exceed 5\%.

Presumably, the first step of this reaction in water is kinetically controlled $\alpha$-aminomethylation of diaziridines 13a,b to give an intermediate of type 57, which unless it is diverted, is in the equilibrium with the starting materials and gradually decomposes giving 55 as thermodynamic the product of reaction. However, removal of intermediate 57 into an aprotic phase that contains dehydrating reagents facilitates its condensation into bicycles 44b,c. The synthesized compounds were readily derivatized at N(3) to give phenylsulfonamides 58, trimethylsilylanes 59, and nitroso 60 (Scheme 16).\textsuperscript{57}
Scheme 16. Synthesis of 2,4-unsubstituted 1,3,5-triazabicyclo[3.1.0]hexanes 44b,c and their derivatives 58-60.

Condensation of 3,3-dialkyldiaziridines 6a and 6b with NH₃ and CH₂O under these latter conditions gave a complex mixture of products. However when NH₃ was replaced by primary aliphatic amines or amino acids the reaction was unambiguously in giving 3-substituted 1,3,5-triazabicyclo[3.1.0]hexanes 44d-n. 3-Methyl diaziridine 13a also also entered this reaction successfully (Scheme 17).57,58.

Scheme 17. Synthesis of 3-substituted 1,3,5-triazabicyclo[3.1.0]hexanes 44d-n.

3.3. 1,3,6-Triazabicyclo[3.1.0]hexanes

The regularity of the diaziridine behaviour that we observed in the Mannich reaction indicates that intramolecular α-aminomethylation of the diaziridine nitrogen atoms could be possible if an amino group, more basic than diaziridine was introduced into the ring as a C-substituent. Indeed,
the interaction of 3-aminomethyldiaziridines **61a,b** with CH$_2$O in CHCl$_3$ in the presence of K$_2$CO$_3$ under heat led to the formation of the first representatives of the new 1,3,6-triazabicyclo[3.1.0]hexane heterocyclic system **45**, which were characterized as phenylisocyanate and phenylsulfonate derivatives **62** and **63** (Scheme 18).$^{56}$

![Scheme 18. Synthesis of the first examples of 1,3,6-triazabicyclo[3.1.0]hexanes 45.](image)

The reaction of diaziridine **61b** with aromatic and heteroaromatic aldehydes proceeded diastereoselectively to form a mixture of two racemates 1$^R$,2$^R$,5$^R$,6$^R$ **64a-d** and 1$^R$,2S$^R$,5$^R$,6$^R$ **65a-d** in a ratio of (3-20) : 1. The predominant diastereomers was isolated in all the cases$^{59}$ and X-ray diffraction showed that 1$^R$,2R$^R$,5R$^R$,6R$^R$-2-(2-bromothien-5-yl)-1,3,6-triazabicyclo[3.1.0]hexane **64d** crystallized as a conglomerate. The reaction with symmetric ketones (R$_1$ = R$_2$ = Me) gave rise exclusively to the (1$^R$,5R$^R$,6R$^R$) racemate **64e** (Scheme 19).

![Scheme 19. Synthesis of 2-substituted 1,3,6-triazabicyclo[3.1.0]hexanes diastereomers 64 and 65.](image)

The methods so developed allowed the synthesis of both monocyclic and fused diaziridine derivatives with any kinds of substituents and in high yields, provided excellent opportunities for their applications in organic and pharmaceutical chemistry as well as their stereochemistry to be explored.
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