Russian Chemical Bulletin, International Edition, Vol. 55, No. 11, pp. 2056—2060, November, 2006

New method for the synthesis and the mechanism of formation of 1,2-di- and 1,2,3-trialkyldiaziridines*

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A new simple approach to the synthesis of 1,2-di- and 1,2,3-trialkyldiaziridines has been developed based on direct chlorination of a mixture of the corresponding aldehyde and an excess of primary aliphatic amine in water. The mechanism of this reaction is proposed and confirmed by quantum chemical calculations at the density functional theory level.

Key words: 1,2-di- and 1,2,3-trialkyldiaziridines, direct chlorination, aldehydes, primary aliphatic amines, mechanism, quantum chemical calculations, B3LYP, PCM.

In recent years, we have concerned ourselves with the development of optimal approaches to the synthesis of differently substituted diaziridines.[1a—c] These studies were stimulated by the use of the resulting diaziridines in ring expansion reactions with electrophilic reagents (ketenes, isocyanates, or isothiocyanates), which led to the development of new simple methods for the preparation of both known and previously unknown heterocyclic systems.[2a—e] Diaziridines are among a few objects containing nitrogen atoms configurationally stable under usual conditions and, consequently, these compounds are used for studying the stereochemistry of nitrogen.[3,4] In addition, they are of interest as psychotropic active compounds.[5—7] Hence, a search for new more efficient methods for the synthesis of diaziridines remains an important problem. The simplest methods for the synthesis of 1,2-di- and 1,2,3-trialkyldiaziridines **1** and **2** are based on the reaction of carbonyl compounds, primary aliphatic amines, and *N*-haloalkylamines (aminating agents), which are prepared by the reactions of hypohalites with the corresponding amines. In the course of optimization of this method for the synthesis of diaziridines **1** and **2** in an aqueous medium, it was demonstrated that the maximum yield can be achieved at particular pH (pH_{opt}), which is shifted to less alkaline values as the $-I$ effect of the substituents in carbonyl compounds increases and pK_{BH^+} of amines decreases.[1a,b] Diaziridines **1** and **2** containing identical substituents at the nitrogen atoms were synthesized by the reaction of NaOCl or NaOBr with a mixture of two moles of amine and one mole of aldehyde. The required pH was achieved by adding HCl or HBr (Scheme 1).

Scheme 1

1, **2**

X = Cl, Br

The aim of the present study was to further optimize procedures for the synthesis of 1,2-di- and 1,2,3-trialkyldiaziridines **1** and **2** by searching for new simpler approaches to the formation of pH_{opt} without the use of alkali metal hypohalites, which are unstable under standard conditions.

Earlier, it has been found[1a,b] that pH_{opt} in the synthesis of 1,2-diethyldiaziridine **1a** ($R^1 = H$, $R^2 = Et$) and 1,2-diethyl-3-methyldiaziridine **2a** is 11.2—12.1 and 11.6—11.9, respectively. We expected that pH_{opt} could be efficiently achieved by passing the calculated amount of gaseous chlorine through a mixture of a carbonyl compound and an excess of primary aliphatic amine. Initially, we examined the synthesis of 1,2-diethyldiaziridine **1a** from formaldehyde and ethylamine. Formaldehyde and ethylamine were mixed as 30% aqueous solutions at 15—20 °C, and then the calculated amount of chlorine was bubbled through the reaction mixture at 0—5 °C. The theoretically required $EtNH_2 : CH_2O : Cl_2$ molar ratio (4 : 1 : 1) was used in first experiments. However, pH_{opt} was not achieved under these conditions. The use of stan-

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* Dedicated to Academician O. M. Nefedov on the occasion of his 75th birthday.

† Deceased.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1978—1982, November, 2006.

dard buffer solutions, such as a phosphate buffer (pH 9.13) or a sodium tetraborate solution (borax, pH 9.7), instead of water also did not provide the formation of pH_{opt}. After the addition of the reagents to the buffer solutions, pH of the reaction mixture was close to the optimal value. However, pH was shifted to more acidic values as chlorine was passed through the reaction mixture. The addition of one mole of $EtNH_2 \cdot HCl$ appeared to be more efficient. In this case, pH_{opt} was close to the required value in the course of the reaction; however, it did shift to more acidic values, which did not allow us to achieve the maximum yield.

The necessary pH_{opt} (11.7—11.5) in the final reaction step was achieved only with the use of the molar ratio $EtNH_2 : CH_2O : Cl_2 = 10 : 1 : 1$. Under these conditions, the yield of diaziridine **1a** was 94% (iodometric titration of the reaction mixture, Table 1). A further variation of the $EtNH_2 : CH_2O : Cl_2$ ratio (8 : 1 : 1, 12 : 1 : 1, or 14 : 1 : 1) led to a decrease in the yield of diaziridine **1a** (84, 87 and 77%, respectively).

Therefore, using the synthesis of 1,2-diethyldiaziridine **1a** as an example, we developed a new simple procedure for the preparation of 1,2-dialkyldiaziridines **1** based on direct chlorination of a mixture of formaldehyde and primary aliphatic amine, which gave the final product in virtually quantitative yield. These conditions appeared to be suitable for the synthesis of other 1,2-dialkyldiaziridines **1** as well as of 1,2,3-trialkyldiaziridines **2**. In the latter case, the reaction was carried out with both monoaldehydes (acetaldehyde and propionaldehyde) and dialdehydes (glutaraldehyde) (see Scheme 2). In all cases, the yields of the final products estimated by iodometric titration of the reaction mixture were higher than 90%. After isolation, the yields of the products were 60—70% because of losses during distillation of diaziridines, which have low boiling points (Table 2).

Table 1. Dependence of pH of the reaction mixture and the yield of 1,2-diethyldiaziridine **1a** on the reaction conditions of direct chlorination of a mixture of the starting compounds with gaseous chlorine in water

Reagent ratio[a]	pH[b]				Yield of **1a**[c] (%)
	A	B	C	D	
4 : 1 : 1	13.4	11.6	11.1	9.95	63
4 : 1 : 1[d]	11.75	10.6	10.6	10.6	69
10 : 1 : 1	13.4	12.4	11.7	11.7—11.5	94

[a] The $EtNH_2 : CH_2O : Cl_2$ molar ratio.

[b] pH of the reaction mixture before chlorination (A), after passing of 50% (B) and 100% of Cl_2 (C), and after storage at 0—5 °C for 1 h (D).

[c] Iodometric titration.

[d] An additive of $EtNH_2 \cdot HCl$ (0.25 mol).

Table 2. Yields and selected physicochemical characteristics of diaziridines **1** and **2**

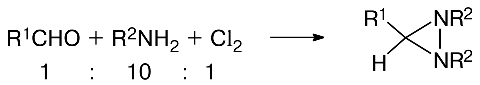
Compound	Yield[a] (%)	B.p./°C (*p*/Torr)	B.p./°C (*p*/Torr)[b]
1a	94/62	96—98 (760)	96—97 (760)[8]
1b	93/60	48—49 (760)	49 (760)[8,9]
1c	91/66	51—52 (15)	37.5—38.0 (11)[1c,8]
1d	90/70	96—98 (10)	34—36 (0.015)[8]
2a	92/66	76—78 (760)	76—78 (760)[1c,10]
2b	94/68	43—45 (20)	43—45 (20)[1a,11]
2c	81/61	113—115 (10)	—[c]

[a] Data from iodometric titration/the yield of the isolated product.

[b] Literature data.

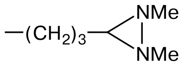
[c] The compound was not described in the literature.

Scheme 2



1, 2

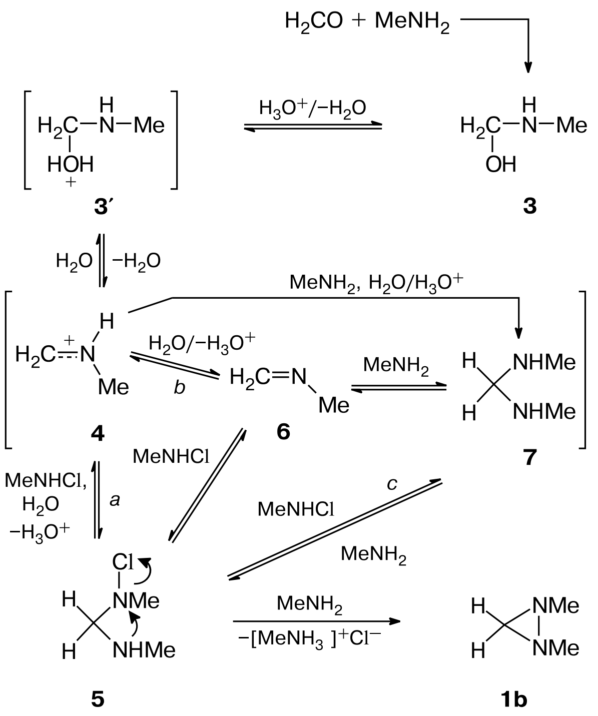
Conditions: 1) 2 h at 0—5 °C; 2) 24 h at 20 °C.

Compound	R¹	R²
1a	H	Et
1b	H	Me
1c	H	Pr
1d	H	Bu
2a	Me	Et
2b	Et	Me
2c		Me

The new method for the synthesis of 1,2-diethyldiaziridine **1a** was tested on a pilot apparatus at the Russian Scientific Center "Applied Chemistry," which enabled the optimization of the reaction conditions: the temperature is 0—5 °C, the passing rate of chlorine is 5—6 L h^{-1}, the starting concentration of ethylamine is 20%, the concentration of the final product is 6.5—8%, and the yield estimated by iodometric titration is 90—96%. In addition to the formation of pH_{opt}, the high yields of diaziridines **1** and **2** prepared according to this method are achieved due to the fact that carbonyl compounds are not oxidized with chlorine in the presence of excess amine. The new method has the following advantages over the known method[8] based on the use of NaOCl for this purpose: 1) the step of the preparation of NaOCl, which requires complex apparatus (particularly, under the conditions of industrial production), is excluded, 2) the concentration of the final diaziridine in the reaction mixture increases by a factor of two (6—8% instead of 3—4%), which substantially simplifies the isolation, and 3) the yield of the final diaziridine increases by ~30%.

Earlier,[1a,b] it has been hypothesized that the role of pH in the synthesis of diaziridines is to provide the most favorable conditions for each particular aldehyde—amine pair in protonation of the product of their reaction, *viz.*, α-aminocarbinol **3**, and its subsequent dehydration giving rise to carbenium-iminium cation **4**. Cation **4** reacts with *N*-haloalkylamine to form intermediate **5**, which is transformed into final diaziridines **1** or **2** (Scheme 3, path *a*) through the intramolecular S_Ni reaction. (In Scheme 3, the possible pathways of the formation of diaziridines **1** and **2** are exemplified by the synthesis of 1,2-dimethyldiaziridine **1b** from formaldehyde, methylamine, and *N*-chloromethylamine. The latter can be prepared either in advance or directly in the course of the reaction by passing the required amount of chlorine through a mixture of formaldehyde and methylamine.) However, it is not improbable that carbenium-iminium cation **4** can be transformed into intermediate **5** according to alternative schemes, in particular, through the formation of imine **6** followed by its reaction with *N*-chloromethylamine (Scheme 3, path *b*) or through the formation of aminal **7** followed by its exchange chlorination in the reaction with *N*-chloromethylamine (Scheme 3, path *c*).

Scheme 3



To reveal the optimal pathway of the transformation of carbenium-iminium ion **4** into diaziridines **1** and **2**, we performed quantum chemical calculations for the synthesis of the simplest representative of 1,2-dialkyldiaziridines, *viz.*, 1,2-dimethyldiaziridine **1b**, according to Scheme 3. The quantum chemical calculations were carried out by density functional theory (B3LYP) taking into account the solvent effect with the use of the PCM model. The calculated relative energies (Δ*E*) and the free energy changes (Δ*G*) for stationary points **1b, 3**, **3′**, and **4—7** are given in Table 3. Since the free energy change most fully describes the nature of processes in the system, we chose these parameters for the detailed discussion. The optimized molecular structures of the compounds under study are shown in Fig. 1. The potential energy surface is presented in Fig. 2.

Table 3. Relative energies and the free energy changes for stationary points **1b**, **3**, **3′**, and **4—7** calculated at the PCM-B3LYP//6-31G* level

Stationary points	Δ*E*	Δ*G*
	kcal mol^{-1}	
1b	−30.04	−35.67
3	0.00	0.00
3′	−4.91	−3.66
4	3.47	−9.02
6	9.75	−4.34
7	−6.14	−4.82
5	−8.82	−8.06

In the calculations, we failed to find the stationary point corresponding to the product of protonation of **3**, *viz.*, cation **3′**, because the geometry optimization led to elimination of the water molecule giving rise to structure **4**. The estimated energy for **3′** presented in Table 3 and Fig. 2 was obtained by the geometry optimization with the fixed C—O bond length of 1.4 Å. Since the formation of cationoid species **4** is accompanied by a substantial gain in energy (9.02 kcal mol^{-1}), dehydration of compound **3** is presumably barrierless. The further transformation of carbenium-iminium cation **4** can proceed either directly through intermediate **5** (Scheme 3, path *a*) or through intermediate imine **6** (path *b*) or, alternatively, through *gem*-diamine **7** (path *c*). As can be seen from Table 3 and Fig. 2, the results of calculations confirmed the mechanism of the transformation of carbenium-iminium cation **4** into diaziridine **1b** through intermediate **5**, which we have proposed earlier. It appeared that the path *a* involving the direct reaction of cation **4** with *N*-chloromethylamine is the energetically most favorable pathway of this transformation in an aqueous solution. The reaction can also proceed through the path *b* or *c*, although these pathways are less probable because the energies of possible intermediates **6** and **7** are higher than that of intermediate **4** (see Fig. 2). The formation of reaction product **1b** is accompanied by a larger gain in energy (35.67 kcal mol^{-1}), which provides the required driving force for the transformation.

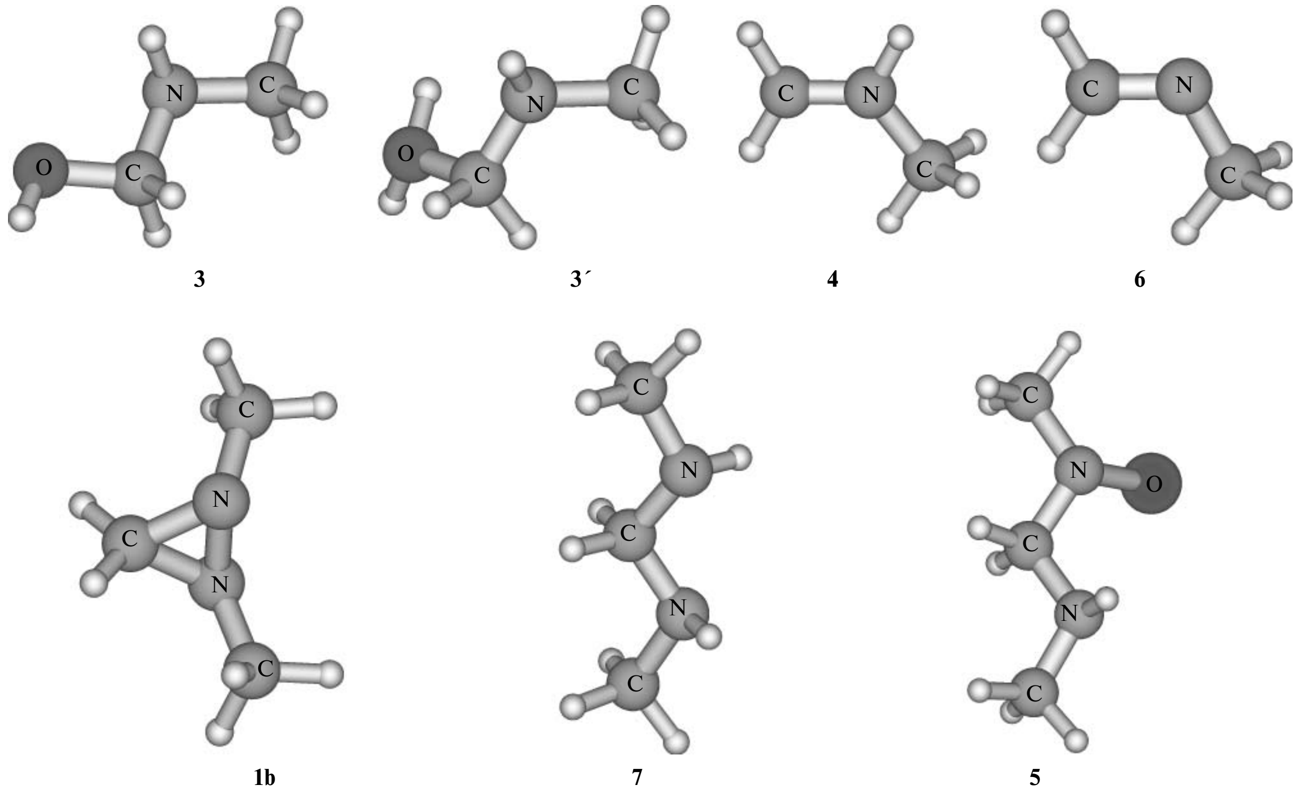


Fig. 1. Molecular structures of **1b**, **3**, **3**′, **4—7**, and those optimized at the B3LYP//6-31G* level.

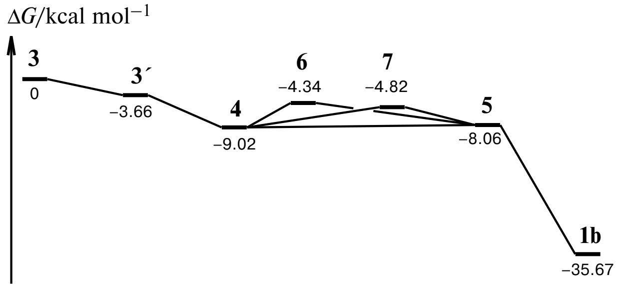


Fig. 2. Potential energy surface calculated at the PCM-B3LYP//6-31G* level.

Experimental

The IR spectra were recorded on a UR-20 spectrometer in thin films of the individual compounds. The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer (250 MHz). The ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (75.5 MHz); the chemical shifts are given on the δ scale relative to the signal of Me_4Si. Thin-layer chromatography was carried out on Silufol UV-254 plates; spots were visualized using iodine vapor and independently by spraying with a solution of diphenylamine in acetone followed by heating of the plates.

Synthesis of 1,2-dialkyl- and 1,2,3-trialkyldiaziridines 1 and 2 by direct chlorination of a mixture of aldehyde and primary aliphatic amine (general procedure). The corresponding aldehyde (0.3 mol) was added dropwise to a solution of primary aliphatic amine (3.0 mol) in water (100 mL) at 15—20 °C. Then the reaction mixture was cooled to 0—5 °C, and gaseous chlorine (0.33 mol) was bubbled through the resulting solution with vigorous stirring at this temperature for 1 h (the amount of the added chlorine was monitored based on the weight increase). The reaction mixture was stirred at 0—5 °C for 2 h and kept at room temperature for 24 h. Then the yield of the resulting diaziridine was determined by iodometric titration, the reaction mixture was saturated with KOH, the upper layer was separated, and the unconsumed amine was distilled off. After titration, the latter was used in the subsequent experiments, and the corresponding diaziridine was twice distilled over solid K_2CO_3. The characteristics of the reaction products were identical to those of the authentic structures described in the literature (see Table 2).

3,3′-Propylenebis(1,2-dimethyldiaziridine) (2c). A 25% aqueous glutaraldehyde solution (56 mL, 0.14 mol) was added dropwise to a 30% aqueous methylamine solution (360 mL, 2.8 mol) at 5—20 °C. Then the reaction was performed according to the general procedure for the synthesis of diaziridines **1** and **2**, including distillation of methylamine. The yield of diaziridine **2c** determined by iodometric titration was 81%. Then the reaction mixture was saturated with NaCl, extracted with chloroform (4×100 mL), and dried with K_2CO_3. The solvent was evaporated. The residue was twice distilled and the fraction with b.p. 113—115 °C (10 Torr) was collected. The yield was 15.7 g (0.085 mol), 61%, n_D^{20} 1.4900. ^{1}H NMR ($CDCl_3$), δ: 1.59 (m, 6 H, $(CH_2)_3$); 2.32 (m, 14 H, 4 Me + 2 CH_{cycl}). ^{13}C NMR ($CDCl_3$), δ: 23.5 (t, $CH_2—\underline{C}H_2—CH_2$, $^1J = 115.6$ Hz); 25.8 (t, $\underline{C}H_2—CH_2—\underline{C}H_2$, ^1J = 128.1 Hz); 38.8 (d, Me—N,

^1J = 134.8 Hz); 47.5 (d, Me—N, ^1J = 134.8 Hz); 65.8 (d, CH_{cycl}, ^1J = 169.9 Hz). IR, ν/cm^{-1}: 792, 1080, 1120, 1288, 1396, 1460, 2924, 2988. Found (%): C, 58.45; H, 11.05; N, 30.10. $C_9H_{20}N_4$. Calculated (%): C, 58.66; H, 10.94; N, 30.40.

Quantum chemical calculations. The geometry optimization and energy calculations were carried out with the use of the B3LYP hybrid functional[12—14] and the standard 6-31G* basis set.[15] The character of stationary points **1b**, **3**, **3´**, and **4—7** was controlled by calculating the eigenvectors of the matrix of second derivatives of the energy (the absence of imaginary frequencies for intermediates). The thermodynamic functions were calculated in terms of the harmonic oscillator—rigid rotator model. The solvent effect was taken into account with the use of single-point calculations in terms of the PCM model for modeling an aqueous medium.[6—18] All calculations were carried out with the use of the Gaussian 98 program package.[19] The molecular structures and vibrations were visualized with the use of the MOLDEN graphics package.[20]

This study was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32799).

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Received September 15, 2006;
in revised form October 2, 2006