The role of pH in the synthesis of diaziridines 2.* The effect of pH on the synthesis of diaziridines from amines, carbonyl compounds and NaOCl

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In the synthesis of diaziridines from amines, carbonyl compounds, and NaOCl in water, the yields of 1,2-dialkyldiaziridines and of 1,2,3-trisubstituted diaziridines prepared from amines with electron-withdrawing subsituents in the side chain are less sensitive to changes in pH than the yields of 1,2,3-trialkyldiaziridines with simple alkyl substituents. The formation of 1,5-diazabicyclo[3.1.0]hexanes is insensitive to the pH in 6.5—13.0 range. This difference is explained by the occurrence of two competing pathways to the key intermediate, *N*-chloroaminal.

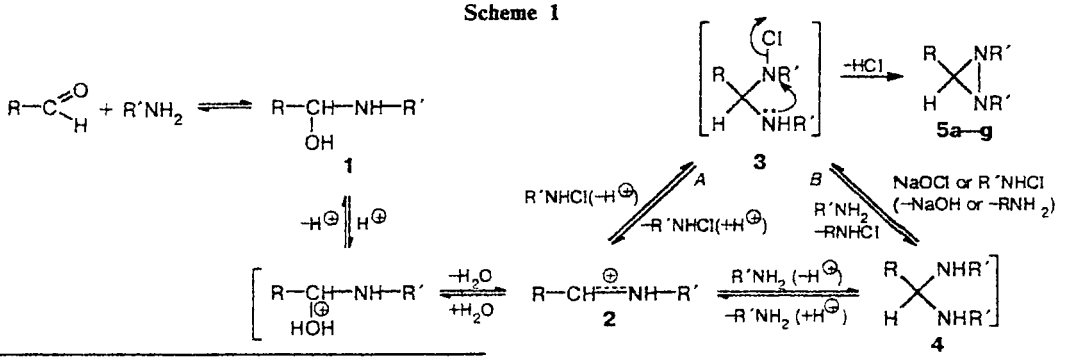
Key words: 1,2-dialkyldiaziridines, 1,2,3-trisubstituted diaziridines, 1,5-diazabicyclo[3.1.0]hexanes.

Previously[1] we showed that in the synthesis of diaziridines from carbonyl compounds, amines, and aminating reagents in water, the highest yield is achieved at a certain pH_{opt}, which shifts to the less alkaline region as the $-I$-effect of the substituents in the carbonyl compound increases and the pK_{BH^+} value of the amine decreases. The role of the pH was explained by the fact that favorable conditions for the transformation of α-aminocarbinol (**1**) into an immonium ion (**2**), a precursor of *N*-chloroaminal (**3**), (Scheme 1, pathway *A*) are created at a certain pH value. However, depending on the character of the substituents in the initial compounds, not only does the value of pH_{opt} vary but so does its range. In the present study, using the synthesis of 1,2-di- and 1,2,3-trialkyl-substituted diaziridines from primary aliphatic amines, formaldehyde (or acetaldehyde), and NaOCl as an example, we attempt to elucidate the reasons for these variations.

Analysis of the correlations between the pH and the yields of diaziridine in these reactions (Fig. 1) has shown that the curves for compounds **5a—c** have a less clear-cut maximum and a wider range of pH_{opt} than the curves for diaziridines **5d,e**. This means that the yields of 1,2-dialkyldiaziridines such as **5a** or **5b** and the yield of 1,2,3-trialkyldiaziridine **5c**, which have an electron-withdrawing substituent in a side chain, are less sensitive to changes in the pH of the medium than the yields of 1,2,3-trialkyldiaziridines **5d,e** (Fig. 1). This fact is difficult to explain in terms of merely the mechanism proposed previously.[1] Apparently, it should be assumed that in the case of diaziridines **5a—c**, intermediate **3** can also arise *via* a different pathway that is less sensitive to the acid-base properties of the medium.

This route could include preliminary formation of aminal **4** followed by its halogenation to give **3** (Scheme 1, pathway *B*), as has been assumed[2] for the

Scheme 1



* For Part 1, see Ref. 1.

† Deceased.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1410—1412, July, 1997.

1066-5285/97/4607-1354 $18.00

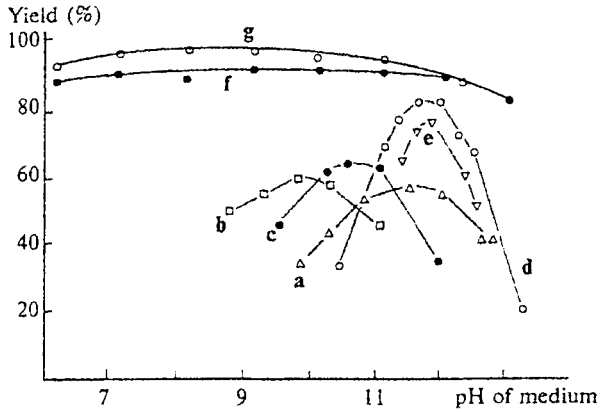


Fig. 1. Dependence of the yield of diaziridines **5a—g** on the pH of the medium. Designations of the curves correspond to the codes of the compounds.

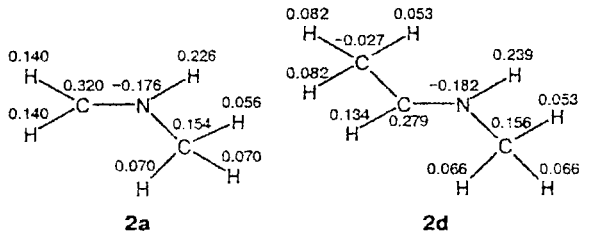
Table 1. Diaziridines synthesized

Compound	R	R′ [R′—R′]	B.p./°C (*p*/Torr)	M.p./°C	Ref.
5a	H	Me	49 (760)	—	2
5b	H	$MeCONHCH_2CH_2$	—	131—134 (from acetone)	1
5c	Me	$MeCONHCH_2CH_2$	Oil $n^{20}_D = 1.491$		1
5d	Me	Me	74—76 (760)	—	4, 1
5e	Me	Et	53—55 (70)	—	5
5f	H	$[(CH_2)_3]$	163 (760)	–15	6, 7
5g	Me	$[(CH_2)_3]$	79—81 (18)	—	7

synthesis of 1,2-dialkyldiaziridines from primary aliphatic amines, CH_2O, and NaOCl in 2 *N* NaOH. Formaldehyde is known to be prone to forming aminals with primary aliphatic amines in weakly alkaline media. If the above assumption is true, the reaction with 1,3-diaminopropane, which forms stable cyclic aminals with carbonyl compounds,[3] will occur predominantly by pathway *B*, and the yields of products, 1,5-diazabicyclo[3.1.0]hexanes, will depend only slightly on the pH of the medium. In fact, the yields of diaziridines **5f,g** are nearly quantitative and almost do not vary in the pH range of 6.5—13 (Fig. 1).

Conversely, the immonium ion **2** formed from methylamine or ethylamine with acetaldehyde is stabilized due to the $+I$-effect of the alkyl groups, and, therefore, the reaction mostly follows pathway *A*, and the yields of the resulting diaziridines **5d,e** are very sensitive to variation of the pH of the medium (see Fig. 1).

The absence of a σ-donating substituent in the initial formaldehyde or the introduction of an electron-withdrawing substituent to the β-C atom of the initial alkylamine causes the stability of ion **2** to decrease, and causes aminal **4**, conversely, to become more stable. Consequently, the contribution of pathway *B* to the formation of intermediate **3** increases, and the dependence of the yield of diaziridine on the pH of the medium becomes less pronounced, as observed for diaziridines **5a—c** (see Fig. 1). These assumptions are also confirmed by the fact that, according to MO LCAO calculations carried out in the MNDO approximation with full optimization of the geometry by a program reported previously,[8] the degree of charge delocalization on the atoms in immonium ion **2d** is higher than that in ion **2a**.



Thus, the clear-cut maximum on the yield—pH plot (Fig. 1) can be regarded as an indication of the contributions of the two pathways, *viz.*, addition of the aminating reagent to immonium ion **2** (pathway *A*) or formation of gem-diamine **4** followed by its halogenation (pathway *B*), to the formation of intermediate **3**. The more pronounced the maximum, the greater the contribution of the former route to the formation of **3**.

Experimental

IR spectra were recorded on a UR-20 spectrometer in pellets with KBr for **5b,c**, or in thin films between KBr glasses for the rest of compounds. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz), and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument (75.5 MHz). In both cases, tetramethylsilane was used as the internal standard. TLC was carried out on Silufol UV-254 plates, which were visualized by I_2 vapor or by spraying with a solution of diphenylamine in acetone followed by heating. Elution was carried out with a $MeOH—H_2O—NH_3$ mixture (95 : 4 : 1). Refractive indices were measured on an IRF-72 refractometer. The yields of diaziridines were determined by iodometric titration, and the pH of the medium was monitored using an EV-74 ionometer. Compounds synthesized were identified by comparison with samples prepared by known procedures.

Synthesis of 1,2-disubstituted and 1,2,3-trisubstituted diaziridines and 1,5-diazabicyclo[3.1.0]hexanes (general procedure). A carbonyl compound (0.05 mol) was added dropwise (CH_2O and MeCHO were used as 20% and 50% aqueous solutions, respectively) to an amine (0.1 mol) or 1,3-diaminopropane (0.05 mol). The required pH value of the mixture was established by adding 15% HCl dropwise. Then at 0—5 °C, aqueous NaOCl (0.05 mol) was added dropwise at such a rate

as to maintain constant pH. The mixture was kept for 24 h at 0 °C, and the pH value was maintained by the dropwise addition of a 20% aqueous solution of NaOH; then an additional 5 mL of 20% NaOH was added, and the mixture was kept for an additional 72 h at 20 °C in order to decompose the remaining chloramines. The yield of diaziridine was determined by iodometric titration of the mixture taking into account the results of blank entries.

To isolate 1,2-dimethyl- (**5a**), 1,2,3-trimethyl- (**5d**), 1,2-diethyl-3-methyldiaziridines (**5e**), 1,5-diazabicyclo[3.1.0]hexane (**5f**), and 6-methyl-1,5-diazabicyclo[3.1.0]hexane (**5g**), the reaction mixture was saturated with NaOH at 20—30 °C, and the upper layer was separated, dried with NaOH, and distilled three times.

To isolate 1,2-di(β-acetaminoethyl)diaziridine (**5b**) and 3-methyl-1,2-di(β-acetaminoethyl)diaziridine (**5c**), the reaction mixture was acidified at 0—5 °C with 50% H_2SO_4 to pH 7.0, half of the water was evaporated on a rotary evaporator, and the residue was diluted with a fivefold volume of MeOH. The mixture was kept for 30 min at 0 °C, the precipitate was filtered off, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and dried with K_2CO_3. Diaziridines were isolated on a column with silica gel L 40/100; elution was carried out with $CHCl_3$ washed twice with an equal volume of 25% aqueous NH_3.

Blank entries with RNHCl. An aqueous solution of NaOCl (0.05 mol) was added dropwise at 0 °C to a solution of an amine (0.1 mol) in 30 mL of H_2O. The mixture was kept for 24 h at 0 °C and for 72 h at ~20 °C. The content of RNHCl was determined by iodometric titration (as a rule, it was 0—3% of the initial amount).

The authors are grateful to K. I. Rezchikova, a senior research worker of the N. D. Zelinsky Institute of Organic Chemistry of the RAS, for her assistance in performing the quantum-chemical part of this study.

This work was carried out with financial support from INTAS (Grant 94-03-08730) and from the Russian Foundation for Basic Research (Project No. 97-03-33021a).

References

1. V. V. Kuznetsov, N. N. Makhova, Yu. A. Strelenko, and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2861 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2496 (Engl. Transl.)].
2. R. Ohme, E. Schmitz, und P. Dolge, *Chem. Ber.*, 1966, **99**, 2104.
3. E. Bergman, D. Herman, und E. Zimkin, *J. Org. Chem.*, 1948, **13**, 353.
4. B. Carboni, F. Tonnard, and R. Carrie, *Bull. Soc. Chim. Fr.*, 1987, **3**, 525.
5. M. Komatsu, N. Nishikaze, M. Sakamoto, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, 1974, **39**, 3198.
6. BASF AG, Pat. BRD, No 3607993, 11.03.1986, C.A. 1987, **107**, 236687h.
7. G. V. Shustov, S. N. Denisenko, I. I. Chervin, N. L. Asfandiarov, and R. G. Kostyanovsky, *Tetrahedron*, 1985, **41**, 5719.
8. I. Clark, *A Handbook of Computational Chemistry*, J. Wiley and Sons, New York, 1985.

Received February 26, 1997

Synthesis and molecular structure of *trans*-2,6-dimethallyl-1,1-dimethyl-1,2,3,6-tetrahydropyridinium iodide

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The structure of *trans*-2,6-dimethallyl-1,1-dimethyl-1,2,3,6-tetrahydropyridinium iodide was established by X-ray structural analysis. The corresponding base was synthesized by reductive diallylation of pyridine with trimethallylborane in the presence of 2-propanol.

Key words: allylboration, pyridine, trimethallylborane, *trans*-2,6-dimethallyl-1,2,3,6-tetrahydropyridine, X-ray structural analysis.

Complexes of triallylborane with pyridine and its various derivatives are stable under an inert atmosphere but undergo complete rearrangement under the action of alcohols, water, or R_2NH to form the corresponding *trans*-2,6-diallyl-1,2,3,6-tetrahydropyridines (in yields of 70—97%).[1—3] This stereospecific reaction occurs with "destruction of aromaticity" and is not complicated by

† Deceased in 1995.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1413—1415, July, 1997.

1066-5285/97/4607-1356 $18.00