N-Alkylation of diaziridines

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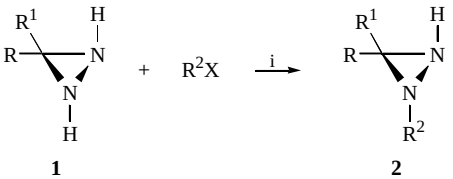
1,2-*H*-Diaziridines can be successfully alkylated only at one of the ring nitrogen atoms, whereas preliminary metalation is required for introducing an alkyl substituent at the second nitrogen atom; this metalation was performed using *N*-sodium salts as an example.

It is well known that alkyl derivatives of diaziridines have a pronounced action on the central nervous system, and this action depends on the structure and number of substituents.[1,2] Diaziridines with alkyl substituents at nitrogen atoms are commonly prepared by direct synthesis from corresponding amines.[3] The published data on the N-alkylation of 1-(1,2)-unsubstituted diaziridines are scanty. Only an example of the N-monoalkylation of 1,2-*H*-diaziridines **1** was described, *viz*., the synthesis of 3,3-dimethyl-1-methoxymethyldiaziridine by alkylation of 3,3-dimethyldiaziridine with methyl chloromethyl ether.[4] The possibility of introducing a substituent at the second nitrogen atom of 1-propyl-3,3-pentamethylenediaziridine by alkylation of the *N*-lithium derivative with ethyl iodide was referred to in a review;[5] however, any experimental information is absent. At the same time, the alkylation reaction can be extremely useful for preparing 1-(1,2)-substituted diaziridines, which are difficult to synthesise directly from amines. Here, we report the results of the first systematic study on the N-alkylation reaction of diaziridines.

The basicity of diaziridines is rather low (pK_a 4.5–5.5).[6] In this connection, the alkylation would be expected to require polar (or dipolar aprotic) solvents and the presence of inorganic bases. On the other hand, diaziridines are cyclic hydrazines. However, it is well known[7] that alkylation of hydrazines at both of the nitrogen atoms is difficult because the second molecule of an alkyl halide is directed to the alkylated nitrogen atom at which the electron density is higher than that at the unalkylated atom. This was a prerequisite for this study.

As starting compounds **1** we examined 3,3-pentamethylene-, 3,3-dimethyl- and 3-methyldiaziridines **1a**–**c**, respectively. Alkyl chlorides, alkyl bromides, alkyl iodides and dimethyl sulfate were used for the alkylation. The **1**:alkylating agent ratio was varied from 1:1 to 1:3, and the temperature, from 0 to 80 °C. The reaction was performed in water, water–ethanol or acetonitrile in the presence of KOH, K_2CO_3 or $NaHCO_3$. We found experimentally that an increase in the **1**:alkylating agent molar ratio did not result in the formation of dialkylation products. In all experiments, only monoalkylated compounds **2**† were obtained, and their yields were not higher than 50% (Scheme 1, Table 1). Carbonyl compounds (precursors of the starting diaziridines) were isolated as by-products (demonstrated using **1a** as an example).

Among alkyl halides, alkyl bromides were found to be the most effective agents. The yield of alkylation product **2** decreased with the use of alkyl chlorides. In the reaction with alkyl chlorides, the addition of NaBr in an equimolar amount is equivalent to the alkylation with alkyl bromides. In the alkylation with alkyl iodides at an equimolar ratio between the



1 **2**

1a R + R¹ = $(CH_2)_5$
1b R = R¹ = Me
1c R = H, R¹ = Me

X = Br, Cl, SO_3OMe

Scheme 1 *Reagents and conditions*: i, see Table 1.

† All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by IR, ^1H and ^{13}C NMR spectroscopy. IR spectra were measured on an UR-20 spectrometer in thin films of pure substances; ^1H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively (TMS was used as an internal standard). 1-Methyl-3,3-pentamethylenediaziridine **2a**, 1-propyl-3,3-pentamethylenediaziridine **2c**, 3,3-dimethyl-2-isopropyldiaziridine **2f** and 2-butyl-3-methyldiaziridine **2i** had the characteristics consistent with the literature data[8–11] (Table 1).

General procedure for the alkylation of N-monosodium salts of 1,3-dialkyl- and 1,3,3-trialkyldiaziridines **4**: Starting diaziridine **2** (0.1 mol) was added to a suspension of powdered $NaNH_2$ (0.12 mol) in 75 ml of THF in a nitrogen atmosphere at 20 °C, and the mixture was stirred until the completion of ammonia evolution (6 or 18–20 h for 1,3-dialkyldiaziridines or 1,3,3-trialkyldiaziridines, respectively). Next, alkyl bromides were added at –30 to –15 °C for 10–15 min, the temperature was increased to 20 °C, the mixture was stirred for several hours and left to stand overnight. The precipitate formed was filtered off and washed with THF, the solvent was distilled off in a vacuum, and the residue was distilled in the presence of solid KOH in a flow of nitrogen. If the alkylation was performed in the presence of tetraalkylammonium halides, these compounds were added to the prepared sodium salt in an amount of 5% of theory, and an alkyl halide was added dropwise at –40 to –30 °C. If the alkylation was performed with alkyl iodides, they were added at –40 to –30 °C; next, the temperature was increased to 0 °C, and the reaction mixture was stirred for 1.5 h at this temperature. Thereafter, the reaction mixture was poured into an equal volume of diethyl ether or hexane, the precipitate formed was filtered off, the solvent was distilled off, and the residue was distilled over solid KOH in a flow of nitrogen.

1-Ethyl-3,3-pentamethylenediaziridine **2b**: bp 74–76 °C (12 Torr), n_D^{22} 1.4725. ^1H NMR ($CDCl_3$) δ: 1.05 (t, 3H, Me, ^3J 6 Hz), 1.54 [br. s, 10H, $(CH_2)_5$], 1.75 (br. s, 1H, NH), 2.36 (AB, dq, 2H, CH_2, ^2J 12 Hz, ^3J 6 Hz). IR (ν/cm^{-1}): 3190 (NH).

1-Allyl-3,3-pentamethylenediaziridine **2d**: bp 104–106 °C (18 Torr), n_D^{22} 1.4891. ^1H NMR (CCl_4 + $CDCl_3$) δ: 1.55 [br. s, 10H, $(CH_2)_5$], 1.92 (br. s, 1H, NH), 3.04 (AB, dq, 2H, NCH_2, ^2J 6 Hz, ^3J 2 Hz), 5.02 (m, 2H, CH_2=, ^3J 9 Hz), 5.78 (m, 1H, CH=, ^3J 9 Hz). IR (ν/cm^{-1}): 3210 (NH), 3085 (=CH_2 as), 1650 (C=C), 1620 (NH_2 def).

1-Propargyl-3,3-pentamethylenediaziridine **2e**: bp 80–82 °C (3 Torr), mp 39–40 °C (pentane), n_D^{20} 1.5005. ^1H NMR ($CDCl_3$) δ: 1.49 and 1.53 [br. d, 10H $(CH_2)_5$], 1.94 (br. s, 1H, NH), 2.14 (t, 1H, ≡CH, ^4J 2.6 Hz), 3.14 (AB, dq, 2H, NCH_2, ^2J 12 Hz, ^4J 2.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.8, 25.4, 30.3, 38.1 (C in C_5H_{10}), 42.0 (N–C), 61.3 (C diaziridine ring), 72.5 (C≡C), 80.7 (*C*–C≡). IR (ν/cm^{-1}): 3305 (≡CH), 3192 (NH), 2125 (C≡C).

1-Allyl-3,3-dimethyldiaziridine **2g**: bp 42–44 °C (17 Torr), n_D^{19} 1.4508. ^1H NMR (CCl_4 + $CDCl_3$) δ: 1.25 (s, 3H, Me), 1.30 (s, 3H, Me), 2.08 (br. s, 1H, NH), 3.00 (AB, dq, 2H, N–CH_2, ^2J 5.5 Hz, ^3J 1.5 Hz), 5.05 (m, 2H, CH_2=), 5.88 (m, 1H, CH=). IR (ν/cm^{-1}): 3200 (NH), 3080 (=CH_2 as), 1640 (C=C).

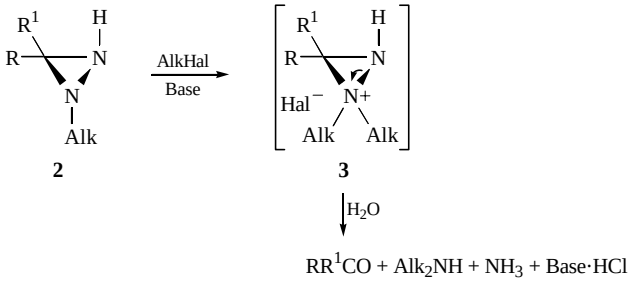
1-Propargyl-3,3-dimethyldiaziridine **2h**: bp 55–58 °C (20 Torr), n_D^{22} 1.4671. ^1H NMR (CCl_4 + $CDCl_3$) δ: 1.26 (s, 3H, Me), 1.31 (s, 3H, Me), 2.05 (br. s, 1H, NH), 2.21 (t, 1H, ≡CH, ^3J 2.5 Hz), 3.11 (AB, dq, 2H, N–CH_2, ^2J 16 Hz, ^3J 2.5 Hz). IR (ν/cm^{-1}): 3300 (≡CH), 3200 (NH), 2125 (C≡C).

3-Methyl-1-(2-nitrazapropyl)diaziridine **2j**: bp 89–90 °C (0.5 Torr), n_D^{22} 1.4951. ^1H NMR ($CDCl_3$) δ: 1.45 (d, 3H, Me, ^3J 6.1 Hz), 2.05 (br. s, 1H, NH), 2.84 (q, 1H, CH, ^3J 6.1 Hz), 3.63 (s, 3H, Me), 3.89 and 4.90 (AB, 2H, N–CH_2, ^2J 12 Hz). IR (ν/cm^{-1}): 3250 (NH), 1510, 1525 (NO_2).

Table 1 Conditions and results of the alkylation of 1,2-*H*-diaziridines **1**.

Starting diaziridine	Alkylating agent (mol)	Alkaline reagent (mol)	*T*/°C	*t*/h	Solvent	End product	Yield (%)
1a	Me_2SO_4 (2.5)	KOH (2.5)	0–5	3	H_2O	**2a**[8]	21
1a	EtCl/NaBr (3.0)	KOH (3.0)	60	15	H_2O	**2b**	44
1a	PrCl (2.0)	KOH (2.0)	80	12	H_2O	**2c**[9]	26
1a	CH_2=$CHCH_2Br$ (1.1)	KOH (1.1)	50–60	2	H_2O	**2d**	45
1a	HC≡CCH_2Br (1.1)	KOH (1.1)	50–60	8	H_2O	**2e**	41
1b	Pr^iBr (1.2)	$NaHCO_3$ (1.2)	50–60	15	H_2O	**2f**[10]	40
1b	CH_2=$CHCH_2Br$ (1.1)	$NaHCO_3$ (1.1)	50–60	12	H_2O	**2g**	30
1b	HC≡CCH_2Br (1.2)	$NaHCO_3$ (1.2)	50–60	15	H_2O	**2h**	30
1c	BuBr (1.2)	KOH (1.2)	70–80	25	H_2O–EtOH	**2i**[11]	35
1c	$MeN(NO_2)CH_2Br$ (1.2)	K_2CO_3 (1.2)	5–10	2	MeCN	**2j**	43
			20	15			

reactants, desired compounds **2** were not formed at all, and starting compound **1** was decomposed. For example, cyclohexanone (detected as the semicarbazone) and tetraallylammonium iodide rather than **2d** were isolated in small yields from a mixture of **1a**, allyl iodide and KOH in water. At first glance this result seems to be surprising because it is well known that diaziridines oxidise the iodide ion in an acidic rather than alkaline medium.[12,13] However, we found in special experiments that 3,3-pentamethylenediaziridine **1a** undergoes decomposition in the presence of NaI in neutral and weakly alkaline media to form cyclohexanone. We succeeded in preparing desired compound **2d** in 18% yield from **1a** and allyl iodide only in a fivefold excess of KOH.

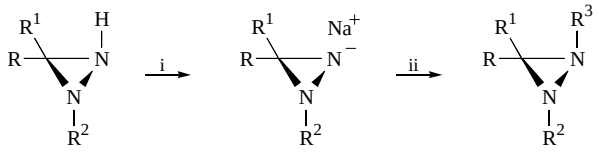


2 **3**

Scheme 2

The low yields of monoalkylation products **2**, the absence of dialkylation products and the occurrence of a carbonyl compound, which is used for the synthesis of starting diaziridine **1**, in the reaction products indicate that the behaviour of diaziridines in the alkylation reaction is really similar to the behaviour of hydrazines in this reaction. It is evident that the second alkyl halide molecule can be directed to the alkylated nitrogen atom of the ring to form diaziridinium cation **3**. This cation decomposes in the presence of water with ring opening and formation of carbonyl compounds and amines (Scheme 2).

It is likely that, for successful alkylating the second nitrogen atom in *N*-monoalkyldiaziridines **2**, the electron density at this atom should be significantly increased in comparison with the alkylated atom. For this purpose, we prepared *N*-sodium salts **4** by the interaction of **2** with sodium amide in anhydrous dipolar aprotic solvents (THF, dioxane). Reagent-grade $NaNH_2$, which was powdered in a mortar under a layer of the solvent, was used in this reaction. The salt formation was finished upon completion of ammonia evolution. After the addition of an alkyl halide to salt **4**, desired 1,2-dialkyldiaziridines **5**‡ were isolated in reasonable yields (Scheme 3, Table 2).



2 **4** **5**

Scheme 3 *Reagents and conditions*: i, $NaNH_2$ (1.2 mol), THF; ii, R^3Hal (or R^3Hal + $Alk_4N^+Br^-$) (see the general procedure).

The rate of formation of sodium salts **4** increased with decreasing alkyl substitution in the molecule of starting compound **2**. Thus, 3-butyl-1-methyldiaziridine **2i** and 1,3-dimethyldiaziridine **2k** rapidly react with sodium amide (heating up, violent evolution of ammonia). The formation of salts **4i** and **4k** was completed in 5 to 6 h. The time taken to prepare sodium salt **4a** from 1-methyl-3,3-pentamethylenediaziridine **2a** was 18–20 h; this is evidently due to the less acidic character of the NH unit in **2a** in comparison with that in **2i** or **2k**. Because the reaction was performed in an anhydrous medium, it was possible to use not only alkyl chlorides and bromides (alkyl bromides gave better results of the reaction than alkyl chlorides), but also alkyl iodides. In the latter case, the reaction rate increased dramatically. After the addition of alkyl chlorides and bromides, the reaction mixture should be stirred at 20 °C for several hours, whereas the reaction with more reactive alkyl iodides was completed in 1–1.5 h at 0 °C.

The rate of alkylation of salts **4** also increased on the addition of tetraalkylammonium salts to the reaction mixture. In this case, alkylation can be performed even in diethyl ether or hexane. It is likely that sodium salt **4** is undissociated under water-free conditions and occurs as an intimate ion pair in which the negative charge at the nitrogen atom is substantially neutralised by the neighbouring sodium cation. With a tetraalkylammonium cation in place of a sodium cation, the distance between the ions increased, and the nitrogen anion became significantly more accessible for the attack of the alkyl halide;

Table 2 Conditions and results of alkylation of *N*-sodium salts **4** of 1,3-dialkyl- and 1,3,3-trialkyldiaziridines **2**.

Starting diaziridine	Alkyl halide	Tetraalkyl-ammonium salt	Solvent	End product	Yield (%)
1-Butyl-3-methyl-diaziridine **2i**	BuBr	—	THF	1,2-Dibutyl-3-methyl-diaziridine **5a**[14]	60
2i	BuI	—	THF	**5a**	65
2i	BuBr	EtN^+Br^-	THF	**5a**	65
2i	BuBr	$Et_3C_{12}H_{25}N^+Br^-$	THF	**5a**	77
2i	BuBr	$Et_3C_{12}H_{25}N^+Br^-$	hexane	**5a**	31
2i	BuBr	$Et_3C_{12}H_{25}N^+Br^-$	Et_2O	**5a**	39
1,3-Dimethyl-diaziridine **2k**[11]	$PhCH_2Br$	$Et_4N^+Br^-$	THF	2-Benzyl-1,3-dimethyl-diaziridine **5b**	47
1-Methyl-3,3-penta-methylene-diaziridine **2a**	BuBr	—	THF	1-Methyl-2-butyl-3,3-pentamethylene-diaziridine **5c**	57

‡ *2-Benzyl-1,3-dimethyldiaziridine* **5b**: bp 56–57 °C (1 Torr), a mixture of diastereoisomers, n_D^{20} 1.5016. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.26 and 1.34 (dd, 3H, Me–C, ^3J 5.5 and 5.4 Hz), 2.32 and 2.38 (ds, 3H, N–Me), 2.64 and 2.75 (dq, 1H, CH, ^3J 5.5 and 5.4 Hz), 3.40, 3.62 and 3.53, 3.58 (2AB, 2H, CH_2, ^2J 13.6 and 9.8 Hz), 7.3 (m, 5H, Ph). ^{13}C NMR ([$^2H_6$]DMSO) δ: 11.53 and 12.0 (*Me*–C), 39.6 and 47.3 (N–Me), 55.04 and 59.4 (CH_2), 60.9, 63.6 (diaziridine ring), 126.5, 126.7, 128.0, 128.13, 128.25, 128.5, 138.7, 139.4 (C in Ar). IR (ν/cm^{-1}): 3000, 3030, 3065 (CH), 1610 (Ar).

1-Methyl-2-butyl-3,3-pentamethylenediaziridine **5c**: bp 92–93 °C (8 Torr) n_D^{20} 1.4669. ^{1}H NMR (CCl_4 + $CDCl_3$) δ: 0.92 (t, 3H, Me–C, ^3J 3.0 Hz), 1.55 [br. s + m, 14H, $(CH_2)_5$, $(CH_2)_2$], 2.35 (br. s + m, 5H, N–Me, N–CH_2). IR (ν/cm^{-1}): 2780 (CH in N–Me).

this fact is favourable for increasing rate of the reaction. Table 2 summarises the examples of alkylation of *N*-sodium salts **4** of 1,3-dialkyl- and 1,3,3-trialkyldiaziridines **2**. An attempt to prepare 1,2-disodium salts from 1,2-*H*-diaziridines **1** and two moles of $NaNH_2$ followed by dialkylation under the conditions examined was unsuccessful. Only monoalkylation products in small yields were isolated. This is likely due to the fact that the monosodium salt produced at the first step of the reaction forms a precipitate and does not further react with sodium amide.

Thus, full alkylation of diaziridines at both nitrogen atoms was performed for the first time. The first nitrogen atom was alkylated by alkylating agents in the presence of bases, and the second nitrogen atom was alkylated only after preliminary preparation of the *N*-sodium salt.

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