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Syntheses of 1,2-di- and 1,2,3-trialkyldiaziridines

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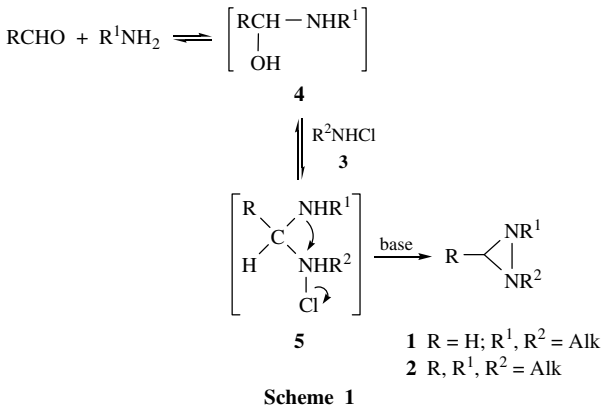
The reactions of 1,3,5-trialkylhexahydro-1,3,5-triazines with *N*-chloroalkylamines resulted in 1,2-dialkyldiaziridines, whereas the reactions of *N*-chloroalkylamines or *N*,*N*-dichloroalkylamines with an excess of primary aliphatic amines gave 1,2,3-trialkyldiaziridines.

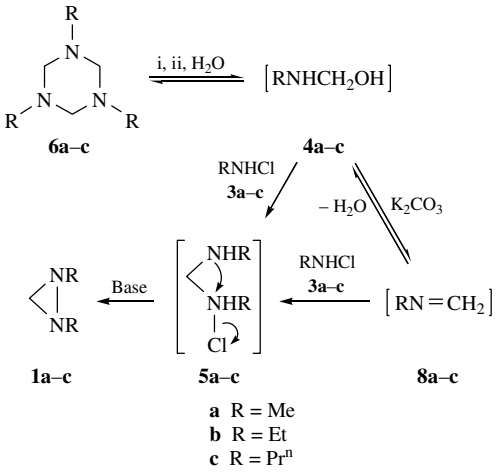
The simplest synthesis of 1,2-dialkyldiaziridines **1** involves the treatment of a mixture of formaldehyde and 2 mol of primary aliphatic amines with NaOCl, whereas the synthesis of 1,2,3-trialkyldiaziridines **2** is based on the action of *N*-chloroalkylamines **3** on Shiff bases, which in turn are obtained from aldehydes and primary aliphatic amines.[1] When optimising the synthesis of diaziridines **1** from weakly basic amines and developing a one-stage synthesis of 1,2,3-trialkyldiaziridines **2**, we found that a maximum yield of diaziridines **1** and **2** in water was reached at a certain value of the solution pH (pH_{opt}).[2,3] For sterically hindered amines and carbonyl compounds that are poorly soluble in water, we elaborated a method based on the reaction in organochlorine solvents ($CHCl_3$, CH_2Cl_2) in the presence of potassium carbonate.[4,5] It was assumed that the reaction occurred by the same scheme in both solvents: at the first stage, a carbonyl compound and an amine were condensed into α-aminocarbinols **4**, which underwent α-aminoalkylation of *N*-chloroalkylamines **3** to give *N*-chloroaminals **5**; the latter underwent cyclisation into **1** or **2** due to an S_N^i process in the presence of a base (Scheme 1).

In order to optimise the synthesis of diaziridines **1** and **2** and to understand its mechanism, we studied the behaviour of 1,3,5-trialkylhexahydro-1,3,5-triazines **6** in the presence of *N*-chloroalkylamines **3** and an inorganic base in both aqueous media and organochlorine solvents, as well as the behaviour of *N*-chloroalkylamines **3** and *N*,*N*-dichloroalkylamines **7** in organochlorine solvents in the presence of an excess of a corresponding amine and an inorganic base. These compounds were chosen because they were present in reaction mixtures during the synthesis of diaziridines **1** and **2** by the methods developed previously.[2–5]



Scheme 1

The reactions of 1,3,5-trialkylhexahydro-1,3,5-triazines **6a–c** with *N*-chloroalkylamines **3a–c** both in water in the presence of an alkali and in $CHCl_3$ in the presence of K_2CO_3 gave 1,2-dialkyldiaziridines **1a–c**, whose yields were as small as 9–12% in water and 45–68% in $CHCl_3$. It was found that a successful synthesis of diaziridines **1** by the reaction of compounds **6** and **3** in organochlorine solvents in the presence of K_2CO_3 required the presence of water traces; water probably serves as a catalyst of hexahydro-1,3,5-triazine ring opening to give α-aminocarbinol **4**, which reacts with *N*-chloroalkylamine **3** to give *N*-chloroaminal **5** and then 1,2-dialkyldiaziridine **1**.† Due to the dehydrating properties of K_2CO_3, α-aminocarbinol **4** can be transformed into



Scheme 2 *Reagents and conditions*: i, $CHCl_3$, K_2CO_3, traces of water, 10–15 °C, 48–60 h; ii, H_2O, NaOH, 0–5 °C, 48–60 h.

Schiff base **8**, which reacts with *N*-chloroalkylamine **3** to give *N*-chloroaminal **5** (Scheme 2). Unlike the well-known methods for the synthesis of diaziridines,[1–5] it takes much longer (48–60 h) to complete the process under these conditions.

† All new compounds gave satisfactory elemental analyses and their structures were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. IR spectra were measured on a UR-20 spectrometer in thin films of pure substances; ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer (300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR).

Initial 1,3,5-trialkylhexahydro-1,3,5-triazines **6** were prepared according to the following methods: trimethyl- **6a**,[11] triethyl- **6b**,[12] and tripropyl- **6c**.[13]

General procedure for the synthesis of 1,2-dialkyldiaziridines **1a–c** *from 1,3,5-trialkylhexahydro-1,3,5-triazines* **6a–c** *and* N*-chloroalkylamines* **3a–c** *in* $CHCl_3$ *in the presence of* K_2CO_3. Finely powdered K_2CO_3 (20.7 g, 0.15 mol), a few drops of water and 0.05 mol of 1,3,5-trialkylhexahydro-1,3,5-triazine **6** were added to a 10–12% solution of *N*-chloroalkylamine **3** (0.15 mol) in $CHCl_3$ at 15 °C. The reaction mixture was kept for 48–60 h at 15–18 °C and was stirred for 1 h every 6–8 h. The end of the reaction was detected by the disappearance of signals of *N*-chloroamines **3** in ^{1}H NMR spectra.[13] The precipitate was filtered off and washed with 30–50 ml of $CHCl_3$. The yields of resulting diaziridines **1a–c** were found by iodometric titration: 45% for **1a**, 66.5% for **1b** and 60% for **1c**. The pure diaziridines were isolated by distillation at atmospheric (compound **1a**) or reduced pressure (compounds **1b**,**c**). Their characteristics were identical to published data for these compounds.[14,15] The ^{13}C NMR spectra of compounds **1b**,**c** were not described.

1,2-Diethyldiaziridine **1b**: ^{13}C NMR ($CDCl_3$) δ: 12.7 (q, *Me*CH_2, ^1J 125.8 Hz, ^2J 3.2 Hz), 54.9 (t, *C*H_2Me, ^1J 135.2 Hz), 55.7 (t, C_{ring}, ^1J 173.3 Hz).

1,2-Dipropyldiaziridine **1c**: ^{13}C NMR ($CDCl_3$) δ: 11.6 (*Me*CH_2), 21.8 (Me*C*H_2CH$_2$), 56.6 (Me CH_2*C*H), 63.0 (C_{ring}).

General procedure for the synthesis of 1,2-dialkyldiaziridines **1a**,**b** *from 1,3,5-trialkylhexahydro-1,3,5-triazines* **6a**,**b** *and* N*-chloroalkylamines* **3a**,**b** *in water.* A freshly prepared 25% aqueous solution of NaOCl (0.15 mol) with a 10–15% excess of NaOH was added dropwise to a 20–25% aqueous solution of an alkylamine (0.15 mol) at 0–5 °C with vigorous stirring. The yields of *N*-chloroalkylamines **3a**,**b** were determined by iodometric titration. Then, corresponding 1,3,5-trialkylhexahydro-1,3,5-triazines **6a**,**b** (0.05 mol) were added, and the reaction mixture was kept for 48 h at 4–6 °C and for 12 h at 18–22 °C. The end of the reaction was determined by the disappearance of *N*-chloroamines **3** according to UV spectra (λ_{max} = 250 nm). The yields of diaziridines **1a**,**b** were found by iodometric titration to be 10.2% for **1a** and 12% for **1b**.

General procedure for the synthesis of diaziridines **1a** *and* **2b**,**c** *from* N*-chloroalkylamines* **3a–c** *(or* N,N*-dichloroamines* **7a–c***) and primary aliphatic amines in* $CHCl_3$. Finely powdered K_2CO_3 (20.7 g, 0.15 mol), a few drops of water and 0.45 mol of a primary aliphatic amine were added to a 10–12% solution of *N*-chloroalkylamine **3a–c** (0.15 mol) (or 0.075 mol of *N*,*N*-dichloroamine **7a–c**) in $CHCl_3$ at 15 °C. The reaction mixture was kept for 72 h at 15–18 °C with stirring for 1 h every 6–8 h. The completion of the reaction was detected by the disappearance of the signals of *N*-chloroamines **3** in ^{1}H NMR spectra.[13] The precipitate was filtered off and washed with 30–50 ml of $CHCl_3$. The yields of the resulting diaziridines were found by iodometric titration: ~34% for **1a**, 95% for **2b** and 84.5% for **2c** from *N*-chloroamines **3** and 24.3%, 42% and 60%, respectively, from *N*,*N*-dichloroamines **7**. The pure diaziridines were isolated by distillation. Compound **1a** was characterized in refs. 14 and 15; only bp has been published for compound **2b**,[16] whereas compound **2c** has not been described in the literature.

1,2-Diethyl-3-methyldiaziridine **2b**: bp 43–45 °C (20 Torr) (lit.,[16] bp 43–45 °C), n_D^{20} 1.4210. ^{1}H NMR ($CDCl_3$) δ: 1.09 (t, 3H, *Me*CH_2, ^3J 7.0 Hz), 1.16 (t, 3H, *Me*CH_2, ^3J 7.0 Hz), 1.29 (d, 3H, *Me*–C_{ring}, ^3J 5.4 Hz), 2.37 (m, 2H, H_aH_bCN, ABX_3 spectrum, $\Delta\nu$ 54 Hz, ^2J –12 Hz, $^3J_{AX}$ 7.0 Hz, $^3J_{BX}$ 7.2 Hz), 2.45 (m, 2H, H_aH_bCN, ABX_3 spectrum, $\Delta\nu$ 33 Hz, ^2J –11.5 Hz, $^3J_{AX}$ 6.50 Hz, $^3J_{BX}$ 6.7 Hz), 2.57 (q, 1H, CH_{ring}, ^3J 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 11.7 (q, *Me*–C_{ring}, ^1J 129 Hz, ^2J 4.0 Hz), 13.1 (q, *Me*CH_2, ^1J 129 Hz), 13.6 (q, *Me*CH_2, ^1J 128 Hz), 45.9 (t, CH_2N, ^1J 131.0 Hz, ^2J 3.3 Hz), 55.0 (t, CH_2N, ^1J 132.0 Hz, ^2J 3.4 Hz), 60.0 (d, C_{ring}, ^1J 170.0 Hz). IR (ν/cm^{-1}): 2972, 2936, 2872, 1452, 1400, 1380, 1344, 1280, 1216, 1180, 1104, 948, 756, 664.

1,2-Dipropyl-3-ethyldiaziridine **2c**: bp 71–73.5 °C (12 Torr), n_D^{20} 1.4322. ^{1}H NMR ($CDCl_3$) δ: 0.84 (t, 3H, *Me*CH_2CH_2N, ^3J 7.3 Hz), 0.87 (t, 3H, *Me*CH_2CH_2N, ^3J 7.3 Hz), 0.99 (t, 3H, *Me*CH_2–C_{ring}, ^3J –7.5 Hz), 1.51 (m, 6H, MeC*H*$_2$CH$_2$N, MeC*H*$_2$–C_{ring}), 2.33 (m, 5H, MeCH$_2$C*H*$_2$N, CH_{ring}). ^{13}C NMR ($CDCl_3$) δ: 10.4 (*Me*CH–C_{ring}), 11.4 (*Me*CH_2CH_2N), 11.5 (*Me*CH_2CH_2N), 19.5 (*C*H_2–C_{ring}), 21.6 (Me*C*H_2CH_2N), 22.3 (Me*C*H_2CH_2N), (CH_2N), 63.2 (CH_2N), 66.5 (C_{ring}). IR (ν/cm^{-1}): 2968, 2856, 2788, 1676, 1448, 1380, 1344, 1276, 1228, 1160, 1052, 972, 928, 756, 664.

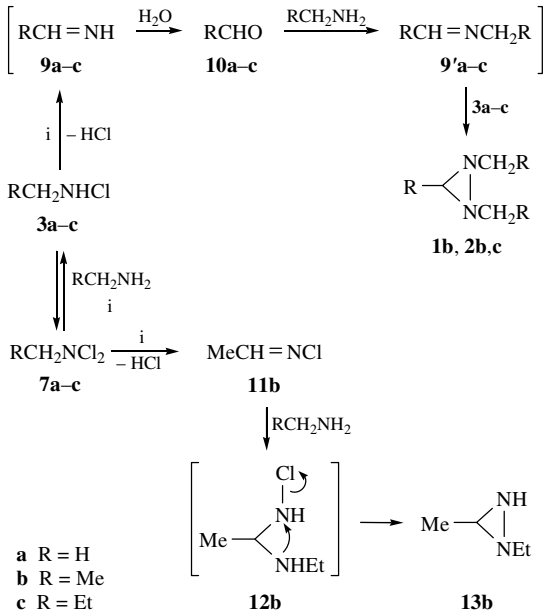
At first glance, the low yields of 1,2-dialkyldiaziridines **1** from 1,3,5-trialkylhexahydro-1,3,5-triazines **6** and *N*-chloroalkylamines **3** in aqueous media seem unexpected, since an excess of water should favour ring opening in the molecule of **6** and thus facilitate the reaction as a whole. However, additional kinetic studies‡ demonstrated that the stability of *N*-chloroalkylamines **3** in weakly basic aqueous media is low (MeNHCl **3a**, E_{decomp} = 17.8 kcal mol^{-1}, n = 1) in comparison with the stability in chloroform (E_{decomp} = 22 kcal mol^{-1}, n = 0); the formally estimated decomposition rates of compound **3a** at 20 °C differ by more than two orders of magnitude in these solvents. This is probably the decisive circumstance in the successful synthesis of 1,2-dialkyldiaziridines **1** from 1,3,5-trialkylhexahydro-1,3,5-triazines **6** and *N*-chloroalkylamines **3** in organochlorine media.

The reactions of *N*-chloroalkylamines **3a–c** with primary aliphatic amines containing the same alkyl fragment in the absence of a carbonyl compound unexpectedly gave 1,2,3-trialkyldiaziridines **2b**,**c** from *N*-chloroethyl- and *N*-chloropropylamines **3b**,**c** in 81 and 98% yields, respectively, and 1,2-dimethyldiaziridine **1a** from *N*-chloromethylamine **3a** in ~30% yield. The reaction was carried out with an excess of the corresponding amine in $CHCl_3$ in the presence of K_2CO_3. As follows from the structure of the products obtained, the first stage of the reaction apparently involves the conversion of *N*-chloroalkylamines **3** into aldimines **9** as a result of E_2 elimination of HCl (by analogy with reactions reported in ref. 6) in the presence of a base; compounds **9** are hydrolysed into corresponding aldehydes **10**. The latter react with unreacted *N*-chloroalkylamine **3** and excess amine to give diaziridines **2b**,**c** and **1a** (Scheme 3). In this case, a prerequisite for this process to occur successfully is that the reaction mixture must contain a small amount of water, which apparently participates both in the first stage of the reaction, that is, elimination of HCl by the inorganic base, and in the second stage, *viz.*, hydrolysis of aldimines **9a–c**.

Similar results were obtained in the reactions of *N*,*N*-dichloroalkylamines **7a–c** with an excess of the corresponding amines in $CHCl_3$ in the presence of K_2CO_3. Apparently, in this case, the presence of excess amine at the first step of the reaction results in the disproportionation of *N*,*N*-dichloroalkylamines **7a–c** to give *N*-monochloroalkylamines **3a–c**,[7,8] whereas the subsequent process does not differ from their conversion to 1,2-dialkyl- **1** and 1,2,3-trialkyldiaziridines **2** discussed above (Scheme 3). The yields of diaziridines **2b**,**c** from *N*,*N*-dichloroalkylamines **7b**,**c** were 40–60%, while that of diaziridine **1a** was about 20%. However, the latter reaction in the case of dichloroamine **7b** was found to give yet another type of diaziridine, *viz.*, 1-ethyl-3-methyldiaziridine **13b**, in 5% yield. Apparently, the conversion of *N*,*N*-dichloroamines **7** involves the elimination of HCl on treatment with a base to give *N*-chloroaldimine **11**, the reaction of which with the corresponding amine *via* *N*-chloroaminal **12** in the presence of a base gives 1,3-dialkyldiaziridine **13** (Scheme 3).

In order to confirm this assumption, we synthesised authentic *N*-chloroaldimine **11b**.§ For this purpose, a solution of *N*,*N*-dichloroamine **7b** in $CHCl_3$ was stirred in the presence of humid K_2CO_3 followed by distillation of the resulting solution at room temperature *in vacuo*. Compound **11b** was detected by ^{1}H and

‡ The values of E_{decomp} for *N*-chloroalkylamine **3a** were obtained as the slopes of straight lines in the Arrhenius coordinates. The reaction rate constants were calculated by relating the initial rate of decomposition of a compound to its initial concentration. The determination of the decomposition rate was based on changes in the concentration of starting compound **3a**, which was measured by iodometric titration or by ^{1}H NMR spectroscopy in the temperature range from –18 to +35 °C in $CHCl_3$ and from –5 to +30 °C in water. All experimental data were processed by the least-squares method. The E_{decomp} value for compound **3a** in aqueous solutions is 17.8 kcal mol^{-1} and the reaction is of the first order. In chloroform, the E_{decomp} is 22 kcal mol^{-1} and the reaction is of zero order. The formally estimated decomposition rate of compound **3a** at 20 °C in the aqueous medium is two orders of magnitude higher than that in chloroform.



Scheme 3 *Reagents and conditions*: i, $CHCl_3$, K_2CO_3, traces of water, 10–15 °C, 72 h.

^{13}C NMR spectroscopy in the solution obtained after distillation, which showed it was contained in a mixture with the solvent, parent $EtNCl_2$ **7b**, acetonitrile (which is a product of deeper decomposition of compound **11b**; the synthesis of nitriles from *N*-chloroalkylamines was described previously[9]), and an impurity of EtNHCl **3b**. The compound was treated with $EtNH_2$ in $CHCl_3$ in the presence of humid K_2CO_3. Vacuum distillation gave 1-ethyl-3-methyldiaziridine **13b** formed in this reaction as a mixture with diaziridine **2b** in a ratio of 1:4, which was determined by ^1H and ^{13}C NMR (the DEPT technique). For comparison, we recorded the ^1H and ^{13}C NMR spectra of compounds **2b** and **13b** (like for the other diaziridines reported previously[2–5]), which were obtained by independent syntheses[§] according to the known procedures.[10]

Thus, we optimised the synthesis of 1,2-di- and 1,2,3-trialkyldiaziridines **1** and **2** in organochlorine solvents in the presence of K_2CO_3. We found that a small amount of water should be added to the reaction mixture in order to prevent the formation of 1,3,5-trialkylhexahydro-1,3,5-triazines **6** in the synthesis of 1,2-dialkyldiaziridines **1** from formaldehyde, primary aliphatic amines and *N*-chloroalkylamines **3** in an organic solvent in the presence of K_2CO_3. In this case, water facilitates the conversion of 1,3,5-trialkylhexahydro-1,3,5-triazines **6** (if any have formed) to desired 1,2-dialkyldiaziridine **1**. The synthesis of 1,2,3-trialkyldiaziridines **2** from carbonyl compounds, primary aliphatic amines and *N*-chloroalkylamines **3** under these conditions should not be carried out either with an excessive or insufficient amount of an amine, which may give undesired products, such as, 1,2,3-trialkyldiaziridines of other structures or 1,3-dialkyldiaziridines.

[§] *Synthesis of* N-*chloroaldimine* **11b** *and diaziridines* **2b** *and* **13b**. Finely powdered K_2CO_3 (20.7 g, 0.15 mol) was added to a 15–20% solution of $EtNCl_2$ **7b** (0.15 mol) in $CHCl_3$ synthesised according to ref. 7. The reaction mixture was kept for 72 h at 15–18 °C with stirring for 1 h every 6–8 h. The concentration of compound **11b** in solution was determined by ^1H NMR (0.047 mol, 31% yield). After that, ethylamine (0.3 mol) was added, the reaction mixture was stirred for 6 h at 20–25 °C, the precipitate was filtered off, and 1,2-diethyl-3-methyldiaziridine **2b** (0.03 mol, 20%) and 1-ethyl-3-methyldiaziridine **13b** (0.0075 mol, 5%) were isolated by repeated distillation. The bp of **13b** was similar to that reported in ref. 17(*a*).

N-*Chloroaldimine* **11b**: ^1H NMR ($CDCl_3$–$CHCl_3$, 1:1) δ: 2.07 (d, 3H, Me, ^3J 6.7 Hz), 8.23 (q, 1H, CH, ^3J 6.7 Hz). ^{13}C NMR ($CDCl_3$–$CHCl_3$, 1:1) δ: 21.0 (Me), 173.5 (CH).

1-Ethyl-3-methyldiaziridine **13b**: ^1H NMR ($CDCl_3$) δ: 1.17 (t, 3H, *Me*CH_2, ^3J 7.5 Hz), 1.32 (br. s, 1H, NH), 1.36 (d, 3H, *Me*–C_{ring}, ^3J 5.2 Hz), 2.23 (m, 1H, CH_aN), 2.55 (m, 2H, CH_bN, CH_{ring}). ^{13}C NMR ($CDCl_3$) δ: 13.2 (*Me*CH_2), 20.2 (*Me*–C_{ring}), 55.2 (CH_2N), 55.8 (C_{ring}).

The two new reactions for the synthesis of alkyl-substituted diaziridines are promising from the methodological point of view: these are the syntheses of 1,2-dialkyldiaziridines **1** in the reactions of 1,3,5-trialkylhexahydro-1,3,5-triazines **6** with *N*-chloroalkylamines **3** and 1,2,3-trialkyldiaziridines **2** in the reactions of *N*-chloroalkylamines **3** or *N*,*N*-dichloroalkylamines **7** with an excess of a primary aliphatic amine. The latter reaction makes it possible to synthesise 1,2,3-trialkyldiaziridines **2** in the absence of a carbonyl compound.

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