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N-Alkylation of *N*-Trimethylsilylimidazole

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Abstract — The reaction of *N*-trimethylsilylimidazole with alkyl chloroacetates is studied. This process yields a mixture of N-alkylation and quarternization products in the ratio dependent on the reaction conditions. The reaction mechanism is discussed. ^{1}H NMR data show that high melting point and low solubility of 1-imidazolylacetic acid in organic solvents are evidently caused by the formation of strong intermolecular hydrogen bonds, whereas in water zwitterionic structures with the protonation of both nitrogen atoms are formed.

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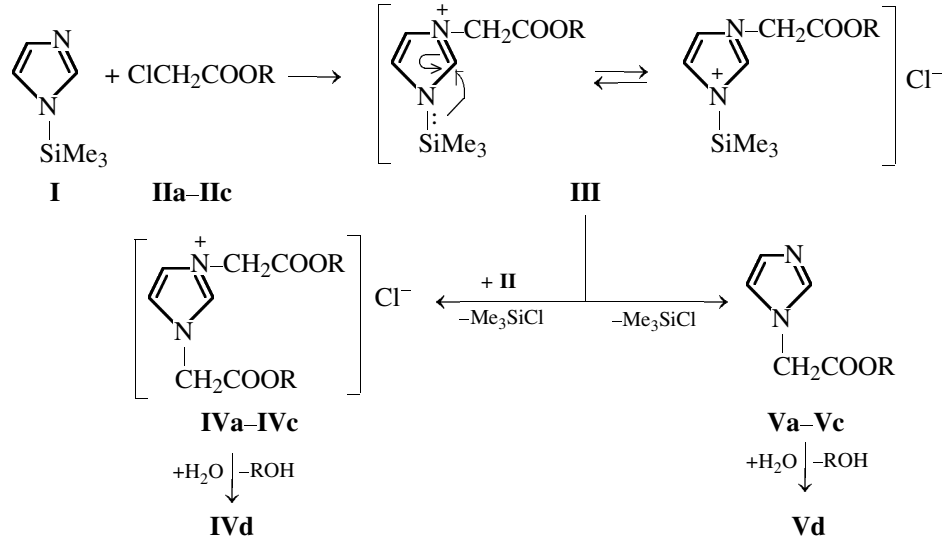
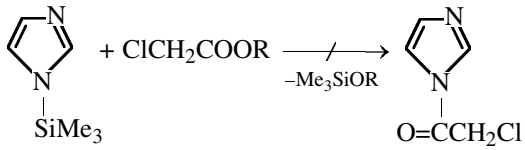
Data on alkylation of aminosilanes of the formula $RNHSiMe_3$ or R_2NSiMe_3 with haloalkanes are practically lacking. This is evidently due to low nucleophilicity of the nitrogen center of the molecule and steric effect of the silyl substituent. At the same time, formally similar reactions of N-alkylation of *N*-silyl-substituted pyrazoles with R–Cl alkylating reagents containing an active C–Cl bond have been reported [1]. Preparative acylation of N-silyl-substituted diazoles with phosgene, cyanogen chloride, acylcarbamoyl chlorides [2], and chloroformates [3] gives the desired products in high yields. Direct alkylation of *N*-trimethylsilylimidazole **I** with trimethylsilyl chloroacetate **IIc**, giving silyl ester of 1-imidazolylacetic acid **Vc** in 63% yield, was also described [3]. In this connection, it seemed promising to study in detail the alkylation of silyl derivative **I** with alkyl chloroacetates as a possible route to 1-imidazolylacetic acid derivatives, which are the starting compounds in the production of zoledronic acid drug [4].

We found that *N*-trimethylsilylimidazole **I** reacts with alkyl chloroacetates **IIa**–**IIc** at elevated temperatures without a solvent to form derivatives **IVa**–**IVc** and **Va**–**Vc**, which are readily hydrolyzed with hot water to give acids **IVd** and **Vd**.

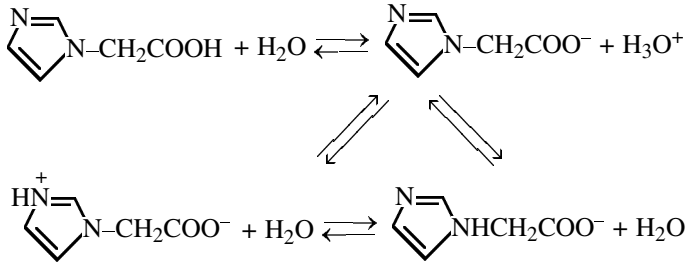


R = Et (**a**); Me (**b**); $SiMe_3$ (**c**); H (**d**).

Note that no silyl interchange product, *N*-chloromethylcarbonylimidazole, was detected in the reaction mixture, although the related transformation is characteristic of pyrazole derivatives [1].



The structure of compounds **IVd** and **Vd** was determined by elemental analysis, mass spectrometry, and ^{1}H NMR spectroscopy. Note that 1-imidazolylacetic acid **Vd** has high melting point and low solubility in organic solvents owing to the formation of strong intermolecular hydrogen bonds, rather than to its existence in the betaine form, as could be expected from the presence of a carboxy group and two nitrogen atoms with free unshared electron pairs. Indeed, the ^{1}H NMR spectrum of **Vd** in DMSO-d_6 contains three signals of the imidazole ring protons at δ 6.92, 7.15, and 7.69 ppm. At the same time, in D_2O the signals of the imidazole ring are revealed at δ 7.64 and 7.65 ppm, whereas the proton in position 2 gives two low-field signals of equal intensity at δ 8.88 and 8.97 ppm which are strongly shifted downfield as compared to the spectrum in DMSO-d_6. So large downfield shift of the signals of the imidazole ring protons is observed only in the case of quarternization of the nitrogen atom. For example, for compound **IVd** containing a quarternary nitrogen atom, the H^2 signal in the ^{1}H NMR spectrum is observed at δ 9.18 ppm in DMSO-d_6 and at δ 8.90 ppm in D_2O. For the hydrochloride of **Vd**, the low-field signal in the ^{1}H NMR spectrum in DMSO-d_6 is observed at δ 9.10 ppm. Thus, the signal of the H^2 proton in the imidazole ring in D_2O is shifted downfield as compared to that in DMSO-d_6. This fact suggests the formation of the zwitterionic structure of **V** only in water. The appearance of two downfield signals of the H^2 proton suggests the existence of two types of the betaine structure with the protonation of both nitrogen atoms according to the following scheme:



When considering the mechanism of alkylation of the silylated imidazole, it should be noted that the direct attack of alkyl halides **IIa**–**IIc** on the *N*-trimethylsilylimidazole nitrogen atom bound with silicon is impossible because of its low nucleophility arising from the partial double bonding with silicon and steric hindrance. The reactions of **I** with **IIa**–**IIc** start only at about 70°C and occur primarily at the "pyridinium" nitrogen atom of the imidazole ring to form intermediate **III**. The similar reaction pathway with the shift of the reaction center was found previously for the reaction of silylpyrazoles with an active halomethylsilane $ClCH_2Si(OEt)_3$ [1]. The results of the reaction in nonpolar toluene count in favor of the initial quaternization. The reaction is significantly decelerated at threefold dilution of the reaction mixture with toluene. After the tenfold dilution, it is completely inhibited even at the toluene boiling point.

The multiplicity of the N–Si bond in intermediate **III** is decreased because of the effect of the CH_2·COOR group and the resonance stabilization of the cation. Hence, it can react further with the internal elimination of the Me_3SiCl molecule and the formation of the alkylation products, alkyl 1-imidazolylacetates **Va**–**Vc**. The reaction with the second molecule of chloroacetates **IIa**–**IIc** leads to the formation of the symmetric alkylation and quaternization products **IVa**–**IVc**. The ratio of the products of the competing strongly exothermic reactions does not depend on the nature of substituent R in esters **IIa**–**IIc**, but is determined by the reaction conditions. When the reaction temperature is maintained in the range 68–70°C, the subsequent hydrolysis gives 1 : 3 ratio of the products **IVd** and **Vd**. Self-heating of the reaction mixture to 90–100°C without external cooling leads to the 4 : 1 product ratio, which is characteristic of the quarternization.

In all the cases the yield of the released trimethylchlorosilane did not exceed 80% based on silylimidazole **I** taken into in the reaction. Therefore, the separation of the reaction mixture involved vacuum distillation of the unchanged compound **I** and the subsequent distillation of esters **Va**–**Vc**. Another procedure involved fractional crystallization of acids **IVd** and **Vc**, among which the first one is poorly soluble in water. The preparative yield of 1-imidazolylacetic acid does not exceed 60% based on silylimidazole **I**. It decreases with an the increase in the amount of the starting compounds, because maintaining the minimum necessary temperature for the synthesis becomes more difficult.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM-360 spectrometer (360.14 MHz) in $CDCl_3$, DMSO-d_6, or D_2O. The mass spectra were measured on an MAT-311A mass spectrometer at the ionizing electron energy of 70 eV, with direct sample inlet.

Reaction of *N*-trimethylsilylimidazole I with alkyl chloroacetates. Compound **I**, 0.4 mol, was treated with 0.4 mol of appropriate ester **IIa**–**IIc**. The reaction mixture was heated with stirring to 75–80°C. The released trimethylchlorosilane was distilled off from the reaction mixture using a descending condenser. The reaction temperature was maintained in the range 67–70°C by boiling and external cooling, or the mixture was allowed to warm up to 90–100°C. After the complete distillation of chlorosilane, which, according to mass spectra, did not contain alkoxytrimethylsilanes and noticeable amounts of hexamethyldisiloxane, the unchanged imidazole **I** and esters **Va**–**Vc** were successively distilled in a vacuum from the reaction mixture. The residue containing mainly salts **IVa**–**IVc** and the distillate consisting of esters **Va**–**Vc** were treated with 100 ml of water, and the mixtures obtained were evaporated until the distillation of water–ethanol azeotrope, methanol, or hexamethyldisiloxane, respectively, was complete. The residues were cooled, treated with 30 ml of acetone and 150 ml of methanol, stirred, and filtered. Pure compounds **IVd** and **Vd**, respectively, were obtained. When the syntheses were carried out without distillation of esters **Va**–**Vc**, the reaction mixture was hydrolyzed with 200 ml of hot water, and the reaction products **IVd** and **Vd** were separated by fractional crystallization from water.

1,3-Bis(carboxymethyl)imidazolium chloride IVd: decomposition point 222–223°C (MeOH/H_2O 1 : 1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.22 s (4H, $2CH_2$), 7.759 s ($1H_{arom}$), 7.764 ($1H_{arom}$), 9.18 s ($1H_{arom}$). ^{1}H NMR spectrum (D_2O), δ, ppm: 5.07 s (4H, $2CH_2$), 7.571 s ($1H_{arom}$), 7.577 s ($1H_{arom}$), 8.90 s ($1H_{arom}$). Found, %: C 38.03, H 4.13. $C_7H_9ClN_2O_4$. Calculated, %: C 38.11, H 4.11.

Ethyl 1-imidazolylacetate Va: bp 108–110°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.41 t (3H, CH_3), 3.95 q (2H, OCH_2), 4.67 s (2H, CH_2), 6.89 s ($1H_{arom}$), 6.99 s ($1H_{arom}$), 7.43 s ($1H_{arom}$).

1-Imidazolylacetic acid Vd: decomposition point 266–269°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.83 s (2H, CH_2), 6.92 s ($1H_{arom}$), 7.15 s ($2H_{arom}$), 7.69 s ($1H_{arom}$). ^{1}H NMR spectrum (D_2O), δ, ppm: 5.12 s (2H, CH_2), 7.64 s ($1H_{arom}$), 7.65 s ($1H_{arom}$), 8.88 s/8.97 s (1/1, $1H_{arom}$). Mass spectrum (*m/z*): 126 ($[M]^{+\cdot}$). $C_5H_6N_2O_2$. Calculated: molecular mass 126.1138.

1-Imidazolylacetic acid hydrochloride Vd · HCl. Compound **Vd** (1 g) and 1 ml of concentrated hydrochloric acid were refluxed for 15 min. Excess acid was removed in a vacuum, and the residue was recrystallized from water–methanol mixture. Hydrochloride of **Vd**, 1.02 g, was obtained. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.15 s (2H, CH_2), 7.65 s ($1H_{arom}$), 7.71 s ($1H_{arom}$), 9.10 s ($1H_{arom}$).

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