STRUCTURE OF DISILYLATED ACETOACETOHYDROXAMIC ACID

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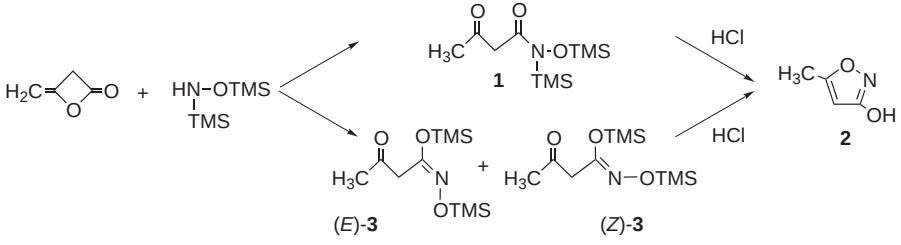
As proved by ^{29}Si and ^{15}N NMR spectra, the reaction of *N*,*O*-bis(trimethylsilyl)hydroxylamine with diketene yields a mixture of *E* and *Z* isomers of *O*,*O*′-bis(trimethylsilyl)acetoacetohydroximic acid ((*E*)-**3** and (*Z*)-**3**), and not the conformers of *N*,*O*-bis(trimethylsilyl)acetoacetohydroxamic acid (**1**), as believed up to now. In contrast, the acetylation of *N*,*O*-dimethylhydroxylamine leads to methyl *N*-methylacetohydroxamate (**5**), analogous to the structure **1**.

Keywords: NMR spectroscopy; Hydroxamic acids; Ketenes; Hydroxylamines; Silyl migration; Silylation; Protecting groups.

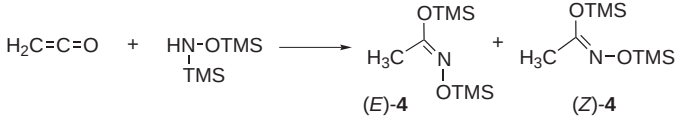
In line with the continuous interest in the chemistry of silylhydroxylamines (e.g., lit.[1–6]), synthetic applications of these compounds have appeared. In one of the first applications an isoxazole derivative was synthesized from *N*,*O*-bis(trimethysilyl)hydroxylamine and diketene (Scheme 1).



SCHEME 1

The intermediate **1** [7,8] was hydrolyzed to yield isoxazole **2** which is a constituent of a variety of physiologically active compounds[7,8]. The isolated mixture of two conformers of the organosilicon intermediate **1** (*N*,*O*-disilyl

derivative of acetoacetohydroxamic acid) was interesting as all our previous attempts to prepare *N*,*O*-disilyl derivatives of hydroxamic acids failed. The so far reported disilyl derivatives of aliphatic or aromatic hydroxamic acids have been shown[9–12] to have the structure of *O*,*O′*-disilyl derivatives (*E* and *Z* isomers) of the tautomeric hydroximic acids, e.g., acetohydroximic acid ((*E*)-**4** and (*Z*)-**4**, Scheme 2) prepared by an analogous reaction of *N*,*O*-bis(trimethysilyl)hydroxylamine with ketene[13] or by the silylation of acetohydroxamic acid[9]. Therefore, we have repeated the synthesis of **1** in order to verify its structure and, if confirmed, to establish the compound **1** as the first true model of the –C(O)–N(Si)–OSi moiety and the above reaction as a method for the synthesis of *N*,*O*-disilyl derivatives of hydroxamic acids.



SCHEME 2

EXPERIMENTAL

Compound Synthesis

Disilylated acetoacetohydroxamic acid (**1**). *N*,*O*-Bis(trimethylsilyl)hydroxylamine (0.5 ml, 2.5 mmol, 97%, Aldrich 23,510-5) was added with stirring at 12 °C to diketene (0.2 ml, 2.5 mmol, stabilized with copper sulfate, Aldrich 42,236-3) placed in a 10-ml round-bottom flask. After 6 h, the flask was connected to a vacuum line and degassed for 10 min. The resulting liquid was subjected to NMR measurements without further purification.

N-Methoxy-N-methylacetamide (**5**) (methyl *N*-methylacetohydroxamate). Acetyl chloride (1.66 ml, 23.3 mmol) and pyridine (4.2 ml, 51.3 mmol) were added with stirring to a mixture of *O*,*N*-dimethylhydroxylamine hydrochloride (2.5 g, 25.6 mmol, 99%, Aldrich 15,941-7) and dichloromethane (36 ml) cooled to 0 °C. The mixture was maintained at this temperature for 30 min and at ambient temperature for another 2.5 h. Then the mixture was shaken with a saturated sodium chloride solution and extracted with two 35-ml portions of ether. The combined organic layers were washed with the sodium chloride solution, the organic layer separated, the ether evaporated and the residue vacuum-distilled. The fraction boiling at 47–52 °C/2600 Pa (1.5 g) was NMR analyzed.

NMR Spectroscopy

The spectra were measured in dry $CDCl_3$ solutions (with 1% of hexamethyldisilane, HMDSS, as an internal reference) at two concentrations (approximately 1 mol/l and 10 mmol/l). ^{1}H, ^{13}C, ^{29}Si, and ^{15}N NMR measurements were performed on a Varian Inova-500 spectrometer (operating at 499.9 MHz for ^{1}H, at 125.7 MHz for ^{13}C, at 99.3 MHz for ^{29}Si, and at 50.7 MHz for ^{15}N NMR) using a 5-mm switchable broad-band probe. All the spectra were recorded at 25 °C. The ^{1}H NMR spectra were measured using the spectral width of 8 kHz and

acquisition time 4 s, FID data were zero-filled to 128 K. The spectra were referenced to internal HMDSS (δ = 0.040 relative to TMS). The ^{13}C NMR spectra were measured using the spectral width 20–30 kHz. GARP decoupling was applied both during acquisition (1–2 s) and relaxation delay (2–5 s). Up to 3000 transients were accumulated. Zero filling to 128 K and a mild line broadening were used in data processing. The spectra were referenced to the solvent line (δ = 76.99 relative to TMS). The ^{29}Si-^{13}C coupling constants were measured[14] on samples of higher concentration by ^{29}Si-^{13}C HMQC using INEPT for ^{29}Si line enhancement in a dedicated $^{29}Si\{^{1}H,^{13}C\}$ pulsed field gradient 5-mm probe (Nalorac). ^{15}N NMR spectra were measured using 90° excitation pulses, 60 s relaxation delay, and 2 s acquisition for the spectral width 30 kHz. The spectra were referenced externally to the ^{15}N NMR line of nitromethane in a 50% solution in the same solvent; no susceptibility correction was applied. The ^{29}Si NMR spectra, referenced to the line of HMDSS at δ = –19.79, were measured by an INEPT pulse sequence optimized for trimethylsilyl groups[15]. The results are summarized in Table I.

TABLE I
NMR chemical shifts in the product mixtures[a]

Comp.	CH_3		C=O	CH_2		C=N/C–N		TMS[b]
	^{1}H	^{13}C	^{13}C	^{1}H	^{13}C	^{13}C	^{15}N	^{29}Si
(*Z*)-**3**	2.167	29.03	203.12	3.186[c]	47.61[d,e]	152.03[f,g]	–82.5[c]	21.89[d,f] 25.33[e,g]
(*E*)-**3**	2.143	29.17	201.96	3.424[h]	43.75[i,j]	160.17[k,l]	–70.6[h]	22.88[i,k] 24.95[j,l]
(*Z*)-**4**[m]	1.827[n]	18.81	–	–	–	154.80	–87.9[n]	19.33, 23.84
(*E*)-**4**[m]	1.936[o]	14.15	–	–	–	163.72	–73.2[o]	20.69 23.26
5[p]	2.129	19.67	171.83	–	–	171.83	–191.4[q]	–

[a] Chemical shifts in δ scale, ^{1}H, ^{29}Si, and ^{13}C relative to tetramethylsilane using secondary reference HMDSS for ^{1}H, δ(^{1}H) = 0.040 and δ(^{29}Si) = –19.79, and solvent line for ^{13}C δ(^{13}C) = 76.99. ^{15}N relative to external 50% nitromethane in the same solvent. [b] ^{29}Si lines could not be assigned to TMS–O–C or TMS–O–N moiety. [c] $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ = 3.1 Hz. [d] $J(^{29}Si\text{-}^{13}C)$ = 1.9 Hz. [e] $J(^{29}Si\text{-}^{13}C)$ not determined. [f] $J(^{29}Si\text{-}^{13}C)$ = 4.2 Hz. [g] $J(^{29}Si\text{-}^{13}C)$ = 5.1 Hz. [h] $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ < 0.5 Hz. [i] $J(^{29}Si\text{-}^{13}C)$ = 2.0 Hz. [j] $J(^{29}Si\text{-}^{13}C)$ not determined. [k] $J(^{29}Si\text{-}^{13}C)$ = 3.1 Hz. [l] $J(^{29}Si\text{-}^{13}C)$ = 5.4 Hz. [m] Data from[9]. [n] $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ = 3.3 Hz. [o] $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ < 0.5 Hz. [p] δ($^{1}H_3C$-N) = 3.184, δ($^{1}H_3C$-O) = 3.696, δ($^{13}CH_3$-N) = 31.87, δ($^{1}H_3C$-O) = 60.96. [q] Broad line.

Computational Details

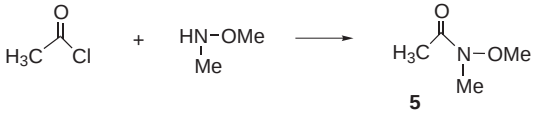
The calculations were performed using the density functional method B3LYP [16,17] in conjunction with the double-ζ basis set 6-31G(d,p) as implemented in the Gaussian 98 suite[18]. For all optimized structures, frequency analysis at the same level of theory was used in order to assign them as genuine minima as well as to calculate zero-point vibrational energies (ZPVEs). Due to the large size of calculated structures (**1**, (*E*)-**3**, and (*Z*)-**3**), a preliminary scan of all possible conformers has been performed using semi-empirical method AM1 [19], in the next step, the two most stable conformers of each isomer were re-optimized at the B3LYP level. The NMR chemical shifts were calculated at B3LYP/6-311+G(2d,p) level.

RESULTS AND DISCUSSION

We have reproduced the synthesis described in[7] except for downscaling the involved amounts of chemicals by a factor of 70 and omitting the final distillation step because of reported explosion hazard[7]. Our yields were somewhat lower and the product was not so pure as claimed[7]. Nevertheless, the NMR spectra of the two main products reproduced well ^{1}H and ^{13}C chemical shifts given[7] for supposedly two conformers (^{1}H chemical shifts agree within 0.02 ppm, most of ^{13}C chemical shifts agree within 0.3 ppm, exceptions being the shifts of the CH_2 and of one of the C=O carbons where the differences amount to 0.7 and 0.6 ppm, respectively). Our products were thus identical with those described in ref.[7]

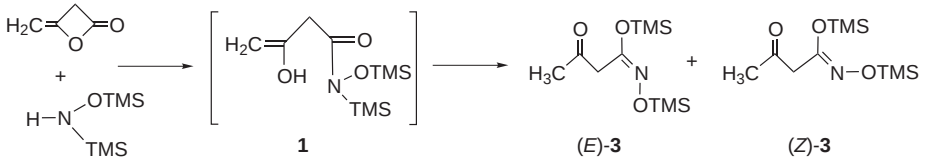
The ^{29}Si NMR spectra reveal that there is no trimethylsilyl group attached to the nitrogen atom, all four ^{29}Si NMR lines being within the region δ = 21–26, i.e., the region common for the silicon of TMS group bound to an oxygen atom, whereas that bound to the nitrogen is expected in the region δ = –2 to 12 [20]. The ^{15}N NMR spectra further prove that the product does not have the structure **1** but **3** and the supposed two conformers of **1** are in fact *E*/*Z* isomers, (*E*)-**3** and (*Z*)-**3**. The chemical shifts (δ = –82.5 and –70.6) and ^{1}H-^{15}N couplings ($^{3}J(^{1}H\text{-C-CO-}^{15}N)$ = 3.1 and < 0.5 Hz, respectively) are similar to those found in *O*,*O*′-bis(trimethylsilyl) derivatives of acetohydroximic acid **4** ((*Z*)-**4** isomer: $\delta(^{15}N)$ = –87.9, $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ = 3.3 Hz; (*E*)-**4** isomer: $\delta(^{15}N)$ = –73.2, $^{3}J(^{1}H\text{-C-CO-}^{15}N)$ < 0.5)[9]. The observed ^{15}N chemical shifts are far away from the shifts found in hydroxamic acids $\delta(^{15}N)$ = –210 to –220 [21,22].

As a check of the above reasoning we have prepared the methyl analogue of **4**, methyl *N*-methylacetohydroxamate (**5**) (*N*-methoxy-*N*-methylacetamide, Scheme 3)[23]. Its NMR spectra, namely the ^{15}N chemical shift which is close to –200 ppm, are in agreement with its structure and fully support the above conclusion.



SCHEME 3

One can speculate about the pathways leading to the products obtained, but we have, besides quantum chemical calculations, no experimental proof. The reaction scheme outlined by Oster and Harris[7] was in agreement with other reactions of diketene[24] including reactions with *N*-alkyl- or *N*-arylhydroxylamines[25] and *N*-phenyl-*O*-benzylhydroxylamine[26], though the mechanisms of these reactions have not been studied. Accordingly, one can assume that the first unstable reaction intermediate of this 1:1 condensation is **1** (Scheme 4), the product of nucleophilic H–N addition on O–C(O) single bond accompanied by the conversion of the enol to the ketone on the other end of the intermediate molecule. The silyl group in the Me_3Si–N–C(O)– moiety is known (for a review of early works see[27]) to have unusually high mobility primarily due to the adjacent carbonyl group. So, similarly as in other compounds with this moiety (e.g., anilides[28]), silyl tautomerism (silatropic tautomeric rearrangement[29]) leads to the more stable position of the silyl group on the oxygen atom. In agreement with the calculated energies (see below), the isolated product is a mixture of (*E*)-**3** and (*Z*)-**3** isomers with hydroximic structure.



SCHEME 4

In order to support these considerations, we have performed explorative calculations of the relative stabilities of the discussed isomers (Table II). (Demanding calculations of the whole potential energy surface of the discussed reaction would be beyond the scope of the present paper.) In agreement with the expectations, *N*,*O*-disilyl derivative **1** is the least stable of the three isomers. Its relative energy is 32.5 kJ/mol higher than the energy of the most stable isomer (*Z*)-**3**; accordingly, **1** isomerizes to **3**. The calculated NMR chemical shifts (Table II) suggest that, if present in sufficient amount, **1** should demonstrate itself by a signal of δ(N) in the range of –190 ppm, no such signal was noticed. *Z* and *E* isomers of **3** are very close in energy, the latter being only 0.9 kJ/mol higher. The presence of both of them in the

product mixture is evidenced by two sets of signals in the NMR spectra, their positions are also in rough agreement with the calculations.

Summarizing, the reaction of *N*,*O*-bis(trimethylsilyl)hydroxylamine with diketene leads to the products, the structures of which are analogous to the products of its reaction with ketene[13], (*E*)-**4** and (*Z*)-**4**, as established by us earlier[9]. The results show that the β-keto group does not affect the chemistry of the hydroxamic/hydroximic part of the molecule. To the best of our knowledge, the –CO–N(Si)–OSi moiety remains without a viable model and the above reaction cannot serve as the method for the synthesis of *N*,*O*-disilyl derivatives. Clearly, this does not detract anything from the synthetic usefulness of the reaction, the reaction just proceeds through a different intermediate than assumed so far.

TABLE II
Calculated relative energies at 0 K (E_{rel})[a] of the most stable conformers of **1**, (*Z*)-**3** and (*E*)-**3**, and their calculated NMR chemical shifts[b]

Comp.	E_{rel} kJ/mol	CH_3		C=O	CH_2		C=N/C–N		TMS
		^1H[d]	^{13}C	^{13}C	^1H[d]	^{13}C	^{13}C	^{15}N	^{29}Si
1	32.5	2.5	33.3	213.7	3.6	48.4	180.6	–190.0	19.9 38.8
(*Z*)-**3**	0[c]	2.1	30.8	213.5	1.7	50.6	160.8	–75.7	26.0 26.8
(*E*)-**3**	0.9	2.1	30.8	210.5	3.6	44.6	169.6	–66.5	24.4 25.4

[a] Relative energies at 0 K are obtained as a sum of total electronic energy and ZPVE. Energies are given in kJ/mol and relative to (*Z*)-**3**. [b] Values of NMR chemical shifts are related to those of tetramethylsilane calculated at the same level of theory (B3LYP/6-311+G(2d,p)): δ(^{1}H) = 31.8221, δ(^{13}C) = 182.4656, and δ(^{29}Si) = 327.3890; δ(^{15}N) = –153.0533 calculated for nitromethane at B3LYP/6-311+G(2d,p) level is used as a reference for ^{15}N chemical shifts. [c] B3LYP/6-31G(d,p) total electronic energy E_e = –1254.470869 Hartree, ZPVE = 0.318487 Hartree. [d] An average value of chemical shifts of all hydrogen atoms of the group.

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