



Synthesis of six-membered Si-containing heterocycles based on acetoacetanilide



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ABSTRACT

The interaction of acetoacetanilide with diorganilydichlorosilanes Me_2SiCl_2 , MePhSiCl_2 and Ph_2SiCl_2 led to the formation previously unknown polyfunctional six-membered Si-containing heterocycles. Their structure was characterized by NMR, IR and X-ray crystallography.

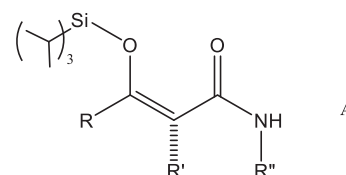
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1. Introduction

β -Ketoamides are typical representatives of β -dicarbonyl compounds: the rich chemistry of the amide functional group $-\text{C}(\text{O})-\text{NRR}'$ ($\text{R}, \text{R}' = \text{H}, \text{Alk}, \text{Ar}$) makes it possible to expand the number of a chemical transformations of β -ketoamides compared to β -ketoesters [1]. The combination of amide, ketone, and activated methylene groups in one molecule, as well as the ability of β -ketoamides to undergo tautomeric isomerization [2], provide their high synthetic potential [3–12]. β -Ketoamides exhibit a wide range of a biological activity [13–16], including derivatives of β -ketoanilides [17–19].

A silyl modification of the organic compounds is a promising method for designing of the new compounds [20–24]. The introduction of a silyl group into any organic molecule leads to a change of its stereoelectronic structure and, as a consequence, its physico-chemical properties and biological activity [25,26]. The first C-, O-, and N-silylated derivatives of β -ketoamides were first obtained by the reaction of diketene with N-silylamines and N-silylamides [27–32].

There is scant research concerning silylation reactions of β -ketoamides. We found only two articles that describe the preparation of their O-triisopropylsilyl ethers **A**. Thus, O-triisopropylsilyl ethers of β -ketoanilides were synthesized by the interaction of triisopropylsilyl ester of trifluoromethanesulfonic acid (triisopropylsilyl triflate) with β -ketoanilides [33]. O-Triisopropylsilyl ethers **A** are formed by the reaction of the corresponding β -ketoamides with triisopropylchlorosilane in the presence of NaH (sodium hydride) as a base. They were used as intermediates in the stereoselective synthesis of *anti*- α -substituted- β -hydroxyamides [34]. Unfortunately, the authors of this work give spectral characteristics for a single silicon-containing compound **A** ($\text{R} = \text{Ph}, \text{R}' = \text{R}'' = \text{Me}$), and there are no data confirming the structure of other O-silylated β -ketoamides.



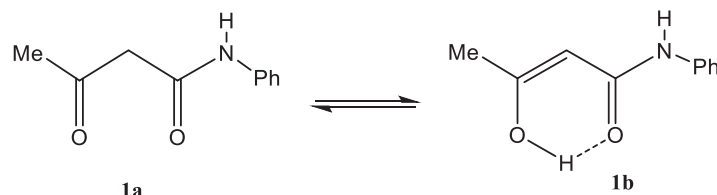
$\text{R} = \text{Et}, \text{Pr}, i\text{-Pr}, \text{Bu}, \text{C}_7\text{H}_{15}, \text{Ph};$

$\text{R}' = \text{Me}, \text{Et}, \text{Pr};$

$\text{R}'' = \text{H}, \text{Me}, \text{Ph}, 4\text{-MeOC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4\text{CH}_2$

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Scheme 1. The keto–enol tautomerism of acetoacetanilide **1**.

We recently studied the structure of acetoacetanilide **1** using IR spectroscopy and quantum chemistry and showed that this compound exists mainly in the form of two tautomers: β -ketoamide **1a** and its enol form **1b** with a strong intramolecular hydrogen bond C=O...HO (Scheme 1) [35].

The aim of this work was to study the interaction of acetoacetanilide **1** with diorganoyldichlorosilanes $RR'SiCl_2$ and we described the obtained results.

2. Experimental

2.1. Material and methods

Acetoacetanilide, triethylamine and silanes are commercial products. Acetoacetanilide was dried in desiccator over P_2O_5 at 20 °C for 24 h. Silanes and triethylamine were purified by distillation before use. The solvents were purified by standard procedures prior to use [36]. All reactions and other manipulations were carried out in thoroughly dried glassware in argon atmosphere.

1H , ^{13}C , ^{29}Si NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13, 100.61 and 79.5 MHz, respectively) with cyclohexane or $(Me_3Si)_2O$ as an internal standard. FTIR spectrum was taken on FT-IR Varian 3100 spectrometer in film. Elemental analysis is performed on the Thermo Scientific Flash 2000 Automatic CHNS Analyzer. Melting points were determined using the Boetius Block apparatus.

2.2. Synthesis

2.2.1. 2,2,6-Trimethyl-3-phenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **2**

Method 1. Dimethyldichlorosilane (1.936 g, 15 mmol) was slowly added with vigorous stirring to a mixture of acetoacetanilide (2.658 g, 15 mmol) and triethylamine (3.036 g, 30 mmol) in benzene (30 ml). The reaction mixture was stirred at the room temperature for 2 days. The precipitate of triethylamine hydrochloride was filtered off and washed with benzene (2×10 ml). Benzene was removed from the combined filtrate in vacuo. The residue was washed with dry diethyl ether (2×10 ml) and dried in vacuo to constant weight. Yields of compound **2** are 87 % (3.045 g).

Method 2. Dimethyldichlorosilane (0.387 g, 3 mmol) was added to the solution of compound **5** (0.965 g, 3 mmol) in pentane (15 ml). The resulting reaction mixture was kept at room temperature for 4 days. The formed colorless crystalline product was filtered off, washed with pentane (2×5 ml) and dried in vacuo to constant weight. Yields of compound **2** are 92 % (0.644 g).

M. p. = 114–115 °C. NMR 1H ($CDCl_3$, δ , ppm): 0.37 (s, 6H, Me-Si); 1.98 (s, 3H, Me-C); 5.24 (s, 1H, C=CH); 6.95–7.45 (m, 5H, Ph). NMR ^{13}C ($CDCl_3$, δ , ppm): -0.71 (Me-Si); 22.06 (Me-C); 101.69 (C=CH); 126.91, 128.55, 129.18, 137.30 (Ph); 162.66 (Me-C); 166.46 (C=O). NMR ^{29}Si ($CDCl_3$, δ , ppm): 10.37. IR (film from $CDCl_3$), ν , cm^{-1} : 1663, 1721 (C=O, C-N). Anal. Found, %: C 61.93; H 6.43; N 5.86. Calcd for $C_{12}H_{15}NO_2Si$, %: C 61.77; H 6.48; N 6.00.

2.2.2. 2,6-Dimethyl-2,3-diphenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **3**

Method 1. Methylphenyldichlorosilane (2.294 g, 12 mmol) was slowly added with vigorous stirring to a mixture of acetoacetanilide (2.126 g, 12 mmol) and triethylamine (2.429 g, 24 mmol) in benzene (30 ml). The reaction mixture was stirred at the room temperature for 2 days. The precipitate of triethylamine hydrochloride was filtered off and washed with benzene (2×10 ml). Benzene was removed from the combined filtrate in vacuo. The residue was washed with dry diethyl ether (2×10 ml) and dried in vacuo to constant weight. Yields of compound **3** are 71 % (2.517 g).

Method 2. Methylphenyldichlorosilane (0.382 g, 2 mmol) was added to the solution of compound (0.643 g, 2 mmol) in pentane (15 ml). The resulting reaction mixture was kept at room temperature for 14 days. The formed colorless crystalline product was filtered off, washed with pentane (2×5 ml) and dried in vacuo to constant weight. Yields of compound **3** are 85 % (0.502 g).

M.p. = 133–135 °C. NMR 1H ($CDCl_3$, δ , ppm): 0.64 (s, 3H, Me-Si); 2.02 (s, 3H, Me-C); 5.35 (s, 1H, C=CH); 6.77–7.73 (m, 10H, Ph-N + Ph-Si). NMR ^{13}C ($CDCl_3$, δ , ppm): -3.30 (Me-Si); 22.24 (Me-C); 102.06 (C=CH); 126.94, 128.18, 128.75, 129.11, 131.48, 132.58, 133.66, 137.12 (Ph-N + Ph-Si); 163.35 (Me-C); 166.87 (C=O). NMR ^{29}Si ($CDCl_3$, δ , ppm): -4.1. IR (film from $CDCl_3$), ν , cm^{-1} : 1663, 1720 (C=O, C-N). Anal. Found, %: C 69.68; H 6.61. Calcd for $C_{17}H_{17}NO_2Si$, %: C 69.12; H 5.80.

2.2.3. 6-Methyl-2,2,3-triphenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **4**

Method 1. Diphenyldichlorosilane (3.798 g, 15 mmol) was slowly added with vigorous stirring to a mixture of acetoacetanilide (2.658 g, 15 mmol) and triethylamine (3.036 g, 30 mmol) in benzene (50 ml). The reaction mixture was kipped at the room temperature for 5 months. The precipitate of triethylamine hydrochloride was filtered off and washed with benzene (2×10 ml). Benzene was removed from the combined filtrate in vacuo. The residue was washed with dry diethyl ether (2×10 ml) and dried in vacuo to constant weight. Yields of compound **4** are 76 % (4.076 g).

M. p. = 157–159 °C. NMR 1H ($CDCl_3$, δ , ppm): 2.05 (s, 3H, Me-C); 5.42 (s, 1H, C=CH); 6.85–7.69 (m, 15H, 3Ph). NMR ^{13}C ($CDCl_3$, δ , ppm): 22.32 (Me-C); 102.52 (C=CH); 126.89, 128.14, 128.91, 129.29, 129.70, 131.65, 134.24, 134.29, 134.39, 134.43; 135.14, 137.07 (3Ph); 163.38 (Me-C); 167.07 (C=O). NMR ^{29}Si ($CDCl_3$, δ , ppm): -19.69. IR (film from $CDCl_3$), ν , cm^{-1} : 1663, 1716 (C=O, C-N). Anal. Found, %: C 73.75; H 5.33; N 3.84. Calcd for $C_{22}H_{19}NO_2Si$, %: C 73.92; H 5.36; N 3.92.

2.2.4. N-Phenyl-N-trimethylsilyl-3-(trimethylsilyloxy)but-2-enamide **5a** and O-trimethylsilyl-N-phenyl-3-(trimethylsilyloxy)but-2-enimide **5b**

Trimethylchlorosilane (16.700 g, 153.72 mmol) was added dropwise to a mixture of (9.080 g, 51.24 mmol) acetoacetanilide and triethylamine (15.600 g, 153.72 mmol) in 200 ml of thoroughly dried benzene. The reaction mixture was stirred at room temperature for 1.5 h and for 25 h at 75 °C. The precipitated triethylamine hy-

Table 1Crystal data, details of intensity measurements, and structure refinement for compounds **2** and **4**

Compound	2	4
Empirical formula	C ₁₂ H ₁₅ NO ₂ Si	C ₂₂ H ₁₉ NO ₂ Si
Formula weight / g·mol ⁻¹	233.34	357.47
Crystal system	monoclinic	orthorhombic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> na2 ₁
<i>a</i> / Å	9.2136(3)	15.946(8)
<i>b</i> / Å	8.6722(3)	15.569(8)
<i>c</i> / Å	15.8207(6)	7.563(4)
α , β , γ / °	90, 98.9120(10), 90	90, 90, 90
Volume / Å ³	1248.85(8)	1877.5(15)
<i>Z</i>	4	4
Density (calculated) / g·cm ⁻³	1.241	1.265
Absorptions coefficient / mm ⁻¹	0.174	0.140
Radiation (λ / Å)	MoK α (0.71073)	MoK α (0.71073)
Temperature / K	293(2)	296(2)
2 θ range / °	4.80 – 60.08	3.65 – 54.27
Crystal size / mm	0.40 × 0.44 × 0.45	0.20 × 0.20 × 0.50
Crystal habit	colorless prism	colorless prism
F(000)	496	752
Index ranges	-11 ≤ <i>h</i> ≤ 12; -12 ≤ <i>k</i> ≤ 12; -22 ≤ <i>l</i> ≤ 22	-20 ≤ <i>h</i> ≤ 19; -19 ≤ <i>k</i> ≤ 19; -9 ≤ <i>l</i> ≤ 9
Reflections collected	33300	0.0852
Independent reflections	3637	3465
Max. and min. transmission	0.6992 / 0.7460	0.5782 / 0.7453
Number of ref. parameters	148	236
R ₁ / wR ₂ (all data)	0.0424 / 0.1186	0.0691 / 0.2081
Goodness-of-fit on F ²	1.049	1.272
Largest diff. peak and hole / e·Å ⁻³	0.249 / -0.228	0.382 / -0.521
Weight scheme, where P=(F _o ² + 2F _c ²)/3	w=1/[\sigma ² (F _o ²) + (0.0550 P) ² + 0.3170 P]	w=1/[\sigma ² (F _o ²) + (0.0960 P) ² + 1.2866 P]

drochloride was filtered off and washed with dry benzene (2 × 25 ml), and the combined filtrate was evaporated under reduced pressure. The residue was distilled in vacuo and mixture of tautomers **5a,b** was obtained. B. p. = 143–144 °C/4 mm Hg. Yield 12.690 g (77%). NMR ¹H (CDCl₃, δ , ppm): -0.07 (s, 9H, Me₃SiOC=CH); 0.21, 0.26 (broad s, 9H, Me₃Si amide); 2.24 (s, 3H, MeC=CH); 6.52–7.39 (m, 5H, Ph). NMR ¹³C (CDCl₃, δ , ppm): -0.32 (Me₃SiO); 0.27 (Me₃Si-N); 20.48 (CH₃C=); 101.86 (=CH); 126.48, 129.07, 129.17 (br, C_{o,m}), 142.53 (Ph), 165.58 (C=N), 166.98 (MeC=C); 172.73 (C=O). NMR ²⁹Si (CDCl₃, δ , ppm): 19.03 (Me₃SiOC=C); 8.17 (broad s, Me₃Si-amide). Anal. Found, %: C 59.44; H 8.41; N 4.35. Calcd for C₁₆H₂₇NO₂Si₂, %: C 59.76; H 8.46; N 4.36.

2.3. X-ray study and refinement

The single crystals of compounds **2** and **4** were obtained by recrystallization from benzene solution. In order to investigate the molecular structure and intermolecular interactions in the solid state, X-ray structure analysis of the single crystal of compounds **2** and **4** was carried out. Crystal data, data collection and structure refinement details are summarized in Table 1.

For compound **2**: crystal data were collected on a Bruker D8 Venture diffractometer with MoK α radiation (λ = 0.71073) using the φ and ω scans. For compound **4**: crystal data were collected using SMART APEX II single crystal diffractometer (Bruker AXS) equipped with a CCD-detector, graphite monochromator and Mo K α radiation (λ = 0.71073) source. These structures were solved and refined by direct methods using the SHELX programs set [37]. Data were corrected for absorption effects using the multi-scan method (SADABS). Nonhydrogen atoms were refined anisotropically using SHELX programs set [37]. All the hydrogen atoms were

positioned geometrically as riding on their parent atoms with d(C–H) = 0.97 Å for the C–H bonds and U_{iso}(H) = 1.2U_{eq}(C). The structural tests for the presence of missing symmetry elements and possible voids were produced using the PLATON program [38]. The crystallographic data are deposited in Cambridge Crystallographic Data Centre (CCDC 2174580 and CCDC 2253792). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3. Results and discussion

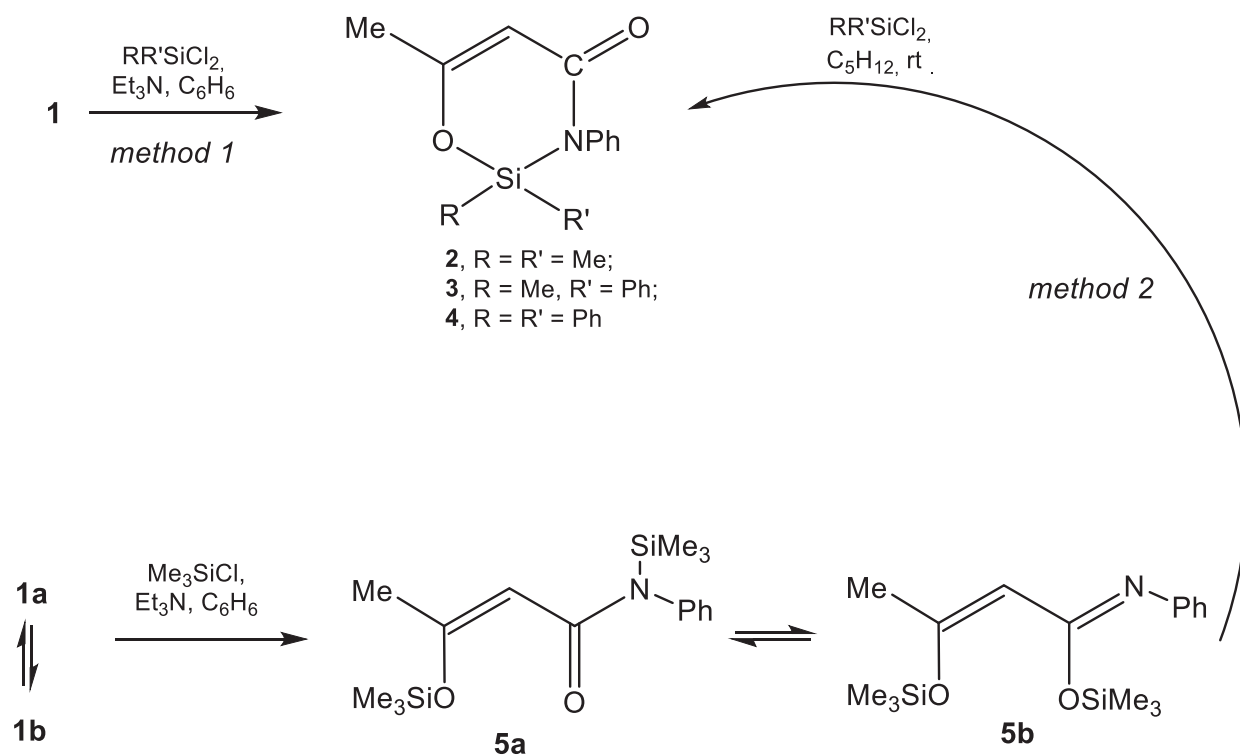
3.1. Synthesis

Diorganodichlorosilanes Me₂SiCl₂, MePhSiCl₂ and Ph₂SiCl₂ react with compound **1** to form 2,2,6-trimethyl-3-phenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **2**, 2,6-dimethyl-2,3-diphenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **3** and 6-methyl-2,2,3-triphenyl-2,3-dihydro-4H-1,3,2-oxazasilin-4-one **4** (Scheme 2). These reactions were performed at room temperature in benzene in the presence of triethylamine as base. It should be noted that the time required to complete this reaction depends on the substituents at the silicon atom. The cyclization of Me₂SiCl₂ and MePhSiCl₂ is completed in 2 days, but heterocycle from Ph₂SiCl₂ formed only after 5 months. Attempts to accelerate the response Ph₂SiCl₂ with compound **1** by heating in various solvents (C₆H₆, PhMe, THF) in the presence of different bases (Et₃N, Py, DABCO) failed. Compound **4** is formed under these conditions, however, products of partial silylation and unidentified products are formed simultaneously. Unfortunately was not successful in isolating compound **4** in pure form from these mixtures.

An alternative method for the synthesis of such Si-containing heterocycles consists in preliminary silylation of compound **1** by trimethylchlorosilane. Trans-silylation of the compound **5** by the corresponding diorganodichlorosilanes leads to the formation of Si-containing heterocycles (Scheme 2). Compounds **2** and **3** are formed during prolonged storage a solution of the equimolar mixture of reagents in dry pentane. However, compound **4** could not be obtained by this method. The structure of compounds **2–5** was proved by IR and multinuclear NMR spectroscopy, and their composition by elemental analysis. The structure of compounds **2** and **4** was examined by X-ray crystallography analysis.

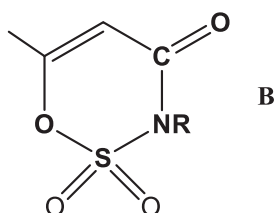
Note that the compound **5** was obtained by interaction of acetoacetanilide **1** with trimethylchlorosilane in thoroughly dried benzene in the presence of triethylamine as base. The spectral characteristics indicate that in solution CDCl₃ at the room temperature compound **5** exists as a mixture of two tautomers: N-phenyl-N-trimethylsilyl-3-(trimethylsilyloxy)but-2-en amide **5a** and O-trimethylsilyl-N-phenyl-3-(trimethylsilyloxy)but-2-en imide **5b** (Scheme 2). At present, the structure of tautomers of compound **5** and related compounds is being studied by spectroscopy and quantum chemistry methods, and the results will be published later.

The signals of SiMe groups in the ¹H NMR spectra of compounds **2** and **3** are 0.37 and 0.64 ppm, respectively. The signals of the methyl groups and the C–H of vinyl fragments MeC=CH of the compounds **2–4** are in the 1.98–2.05 ppm and 5.24–5.42 ppm, respectively. The signals in the range of 21.90–22.44 ppm in the ¹³C NMR spectra of compounds **2–4** belong to the carbon atoms of methyl groups (=CMe). The intervals of values of the carbon atoms of the vinyl groups C=CH in the ¹³C NMR spectra of compounds **2–4** are 162.66–163.38 ppm and 101.69–102.52 ppm, respectively. The signals of carbon atom (C=O) of the amide group in the ¹³C NMR spectra of compounds **2–4** are within the range of 166.46–167.07 ppm. These values of chemical shifts of –OC(Me)=CH–C(O)–



Scheme 2. Synthesis of compounds 2-5.

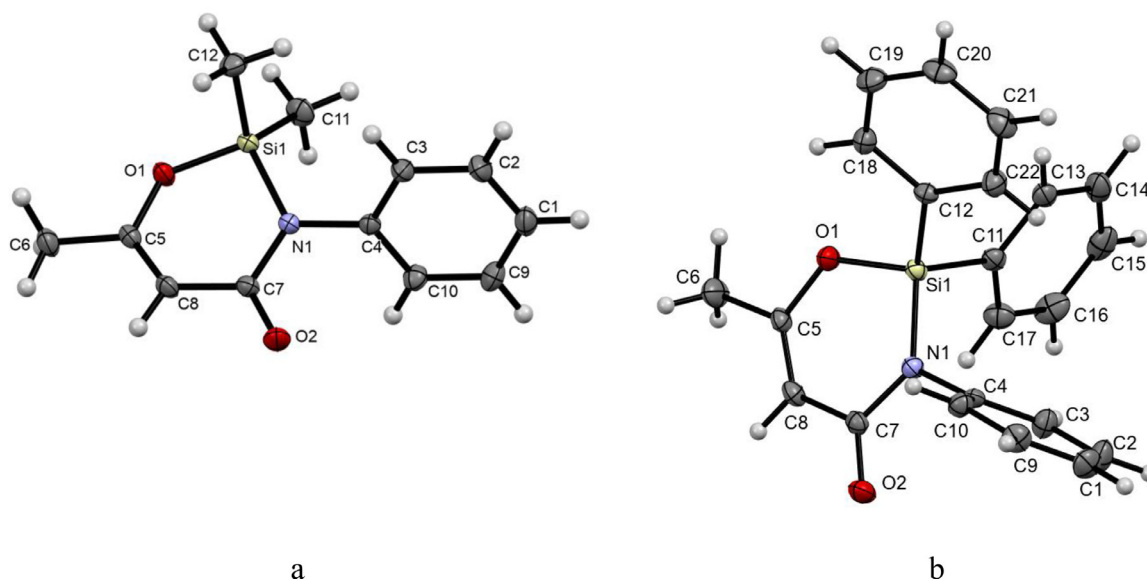
N groups of compounds 2-4 agree closely with those of the structurally similar derivatives of acesulfamates **B** [39,40].



3.2. X-ray single crystal structure analysis

The single crystals of **2** and **4** were obtained by re-crystallization from benzene solution. In order to investigate the molecular structure and intermolecular interactions in the solid state, X-ray structure analysis of the single crystal of compounds **2** and **4** was carried out. The molecular structures are depicted in Fig. 1. Principal bond distances, bond angles and torsion angles are presented in Supp. Inf.

Molecules of compound **2** crystallize in monoclinic space group $P2_1/c$. Molecules of compound **4** crystallize in orthorhombic space

Fig. 1. Molecular structures of compounds **2** (a) and **4** (b) (ORTEP, 20% probability ellipsoids)

group *Pna*₂₁. Geometrical parameters (bond length and angles, Table 1S) of compounds **2** and **4** are very close. In molecule **2** Si-O, Si-N and Si-C bond lengths are 1.659, 1.754 and 1.837 Å respectively, in compound **4** these bond lengths are 1.650, 1.749 and 1.848 Å. Unfortunately, we were unable to find structural analogues of compounds **2** and **4** containing the C-C-N-Si-O-C cycle, but Si-O, Si-N and Si-C bond lengths in compounds **2** and **4** have meaning closed to that in other structures containing four-coordinated silicon [41–43]. C-C-N-Si-O-C cycles are near plane, Si atom out of plane is 0.327 Å in molecule **2** and 0.277 Å in molecule **4** (Fig. S1).

In the crystal molecules of **2** connected by short contacts CH[⋯]O and CH[⋯]π by lengths 2.541 and 2.905 Å respectively (Fig. S2, a) whereas crystal structure of compound **4** forms only CH[⋯]O short contacts (2.505, 2.557 and 2.693 Å, Fig. S2, b).

4. Conclusion

In conclusion, it should be stressed that we described practical protocols for the synthesis of the previously unknown polyfunctional Si-containing heterocycles. The procedures are experimentally simple and provide cost-effective synthesis of these heterocycles from commercially available chemicals as starting materials: acetoacetanilide and diorganodichlorosilanes. Heterocycles have been described by use of NMR spectroscopy and structure of two compounds was examined by X-ray crystallography analysis. The molecules of these heterocycles contain the several reaction centers: double bond, amide bond, Si-O and Si-N bonds. Due to extraordinary polyfunctionality such heterocycles will be used in organic synthesis and medicinal chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jorgchem.2023.122777](https://doi.org/10.1016/j.jorgchem.2023.122777).

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