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Synthesis, structure and cytotoxic activity of 2-acetyl-5-trimethylsilylthiophene(furan) and their oximes

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5-Trimethylsilylderivatives of 2-acetylthiophene and -furan have been regioselectively prepared by a one-pot procedure from the corresponding 2-acetylfuran or 2-acetylthiophene using lithium *N*-methylpiperazide (LNMP)–butyllithium–trimethylchlorosilane–water as the sequence of reagents. The ketones obtained were converted to the corresponding oximes. The structure of 2-acetyl-5-trimethylsilylthiophene oxime (*E*-isomer) has been studied by X-ray diffraction. Formation of centrosymmetric dimers by means of H-bonds has been observed. The intermolecular hydrogen bond O9–H···N8 length is 2.842(5) Å [H···N8 = 1.87 (6) Å, O9–H···N8 = 157(4)°]. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: 2-acetyl-5-trimethylsilylfuran; 2-acetyl-5-trimethylsilylthiophene; oximes; thiosemicarbazone; aminoguanidine; crystal structure; cytotoxicity; toxicity

INTRODUCTION

Two synthetic methods can be used for the preparation of silylated furan and thiophene ketones: (1) acylation of silylheterocycle; and (2) silylation of acylheterocycle. In the first case the yields of corresponding silylketones are low due to concurrent *ipso*-substitution (yields of target acetyltrimethylsilylthiophene and -furan were only 13 and 25%)[1]. The second method includes protection of the carbonyl group, metallation of the heterocycle, silylation and deprotection in mild condition to save the silyl group. The 1,3-dioxolane protective group has been used for the preparation of 2-acetyl-5-trimethylsilylfuran.[2]

We have elaborated a one-pot procedure for the preparation of 5-trimethylsilyl substituted 2-acetylthiophene from 2-acetylthiophene using lithium *N*-methylpiperazide(LNMP)–butyllithium–trimethylchlorosilane–water as the sequence of reagents. The ketone was converted to the oxime. Its crystal structure and configuration was investigated by X-ray diffraction method. The corresponding furan derivative can be prepared analogously.

The oximes with heterocyclic ring is a prominent structural motif in numerous pharmaceutically active compounds. Indeed, heterocyclic oximes and their derivatives have shown several biological activities such as cardiovascular, sedative, antidepressant, anticonvulsive, analgetic, anti-inflammatory, antiviral, bactericidal, cytotoxic and antitumour.[3–8] On the other hand, the derivatives of furan and thiophene oximes and their derivatives have been scarcely investigated as antitumour agents.[3]

The cytotoxicity of synthesized compounds has been studied *in vitro* on HT-1080, MG-22A and NIH 3T3 cell lines.

MATERIALS AND METHODS

Chemistry

NMR spectra were recorded on a Varian 200 Mercury instrument (200 MHz for ^{1}H, 40 MHz for ^{29}Si) using $CDCl_3$ as a solvent and hexamethyldisiloxane ($\delta = 0.055$ ppm) as internal standard. Mass spectra were registered on GC-MS HP 6890 (70 eV). 2-Acetylthiophene and 2-acetylfuran were synthesized using known methods.[9] *N*-Methylpiperazine and tetrahydrofuran (THF) were dried on CaH_2, and distilled

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prior use. Thin-layer chromatography (TLC) was performed on a Merck silica gel 60 F_{254} with various eluents.

Crystallography

The crystals of oxime, **4**, were grown from a diethyl ether solution of the compound. Crystals of $C_{19}H_{15}NOSSi$, $M = 213.38$, are monoclinic with space group $P2_1/n$: $a = 6.7647(3)$, $b = 21.5207(9)$, $c = 8.6643(5)$ Å, $\beta = 100.162(2)^\circ$; $V = 1241.67(1)$ Å^3, $Z = 4$, $\mu = 0.32$ mm^{-1}, $D_{calc} = 1.142$ g cm^{-3}. Intensity data were collected on a Bruker–Nonius single-crystal diffractometer with graphite-monochromated MoK_α ($\lambda = 0.71073$ Å) radiation on a crystal $0.12 \times 0.23 \times 0.28$ mm. A total of 2867 data were collected at room temperature up to $2\theta_{max} = 52^\circ$. The structure was solved by direct methods and refined by full-matrix least-squares.[10,11] The final R was 0.059 for 1211 reflections with $I > 3\sigma(I)$; CCDC deposition number = 296 067.

Cytotoxicity *in vitro*

Monolayer tumour cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma) and NIH 3T3 (normal mouse fibroblasts) were cultivated for 72 h in standard Dulbecco's modified Eagle's medium (Sigma) without an indicator and antibiotics.[12] After the ampoule was thawed not more than four passages were performed. The control cells and cells with tested substances in the range of $2–5 \times 10^4$ cell/ml concentration (depending on line nature) were placed on separate 96-wells plates. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5 and 6.25 μg/ml. The control cells were treated in the same manner only in the absence of test compounds. Plates were cultivated for 72 h. A quantity of survived cells was determined using Crystal Violet (CV), Neutral Red (NR) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) coloration, which was assayed by multiscan spectrophotometer. The quantity of living cells on control plate was taken in calculations for 100%.[12,13] Concentration of NO was determined according to Fast *et al*.[12] Mean lethal dose (LD_{50}) has been determined on 3T3 cells (alternative to LD_{50} in vivo test) according to the protocols of Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program (NTP) of Interagency Center for the Evaluation of Alternative Methods (NICEATM).

RESULTS AND DISCUSSION

Arylsilanes usually react with electrophiles to give arenes in which the electrophile occupies the position to which the silyl group was previously bonded.[14–16] In contrast to this general statement, some examples have been reported in which electrophilic aromatic substitution of arylsilanes proceeds with retention of the silyl group.[1] In 1948 Benkeser reported that electrophilic acetylation of 2-trimethylsilylfuran and 2-trimethylsilylthiophene does not proceed only with *ipso*-substitution but electrophilic substitution takes place at the 5-position; however, yields of target compounds were low: 25% for furan and 13% for thiophene derivative.[1] The influence of trialkylsilyl groups on the nucleophilic reactivities of furans and thiophenes was determined by kinetic experiments.[17] On the other hand, 2-acetyl-5-trimethylsilylfuran was prepared using a four-step reaction: firstly protection of carbonyl group by introduction of 1,3-dioxolane moiety; secondly metallation by *n*-butyllithium at the position 5 of the furan ring; then reaction with trimethylchlorosilane; and subsequent hydrolysis of the protective group.[2]

We have found that silylsubstituted acetylfuran and -thiophene can be easily prepared using a one-pot procedure from the corresponding 2-acetylfuran and 2-acetylthiophene using LNMP–butyllithium–trimethylchlorosilane–water as the sequence of reagents. After blocking with a suitable aminolithium compound, the carbonyl function is regenerated by hydrolysis in neutral or weakly acid conditions. Mild conditions for the hydrolysis are required to preserve the trimethylsilyl group bound to the heterocycle. In the case of 2-acetylfuran and 2-acetylthiophene this procedure gave regiospecifically the 5-metallated derivatives in good yield (45–60%). 2-Acetyl-5-trimethylsilylthiophene was converted into corresponding ketone oxime, **4**, by reaction with hydroxylamine. To investigate the influence of *N*-substituents on the cytotoxicity of imines, two other iminoderivatives, **5** and **6**, have been prepared by condensation reaction with thiosemicarbazide and aminoguanidine.

The crystal structure of oxime, **4** (*E*-isomer), was studied by X-ray diffraction. There are only a few examples of crystal structure of thiophene ketoximes in the literature. Indeed, a search of the Cambridge Structural Database[18] (CSD Version 5.26) indicated that there are only seven entries of this type of compounds. However, there are no data for silyl-substituted thiophene ketoximes in the CSD. Therefore, we are presenting here the first crystal structure of silylsubstituted 2-acetylthiophene oxime, **4**.

Figure 1 illustrates the molecular structure of **4** giving the atomic numbering scheme followed in the text. Table 1 lists

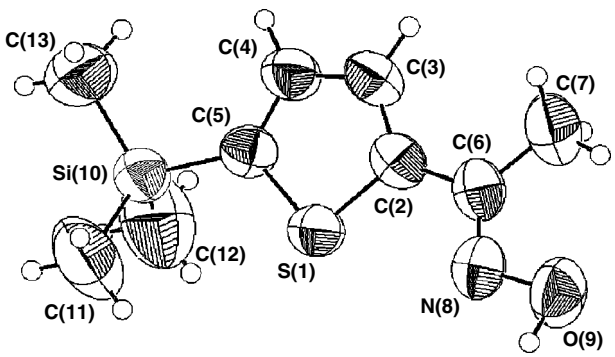

Figure 1. Perspective view and atom numbering scheme of compound **4**.

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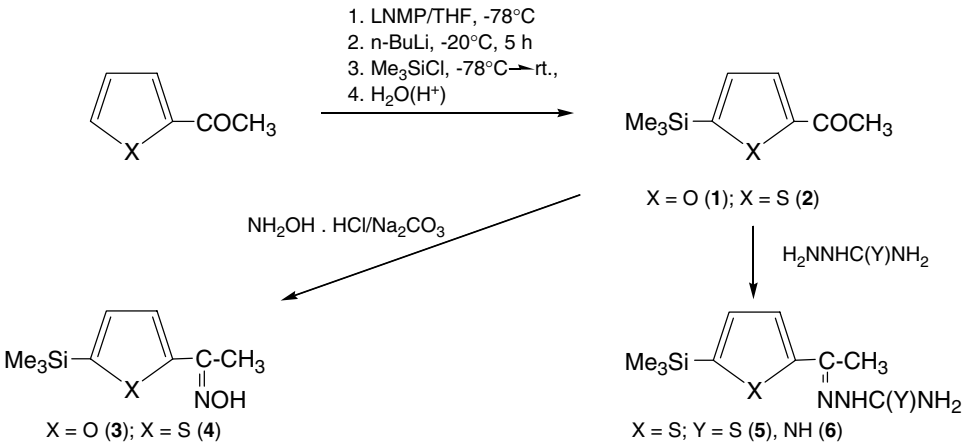

Scheme 1.

Table 1. Interatomic distances (Å) and angles (deg) in the molecule **4** (the average values for selected bond distances and angles for thiophene ketoximes are in square brackets)

S1–C2	1.713(4)	[1.72(1)]	C4–C5	1.367(6)	[1.34(2)]
S1–C5	1.737(4)	[1.70(2)]	C6–C7	1.485(7)	
N8–C6	1.285(5)	[1.28(1)]	Si10–C5	1.847(4)	
O9–N8	1.401(5)	[1.397]	Si10–C11	1.827(7)	
C2–C3	1.371(6)	[1.40(4)]	Si10–C12	1.853(8)	
C2–C6	1.465(6)	[1.46(1)]	Si10–C13	1.824(6)	
C3–C4	1.406(4)	[1.421(9)]			
C2–S1–C5	94.4(2)	[92.0(3)]	C2–C6–N8	115.4(4)	[122(7)]
S1–C2–C3	109.2(3)	[111.1(5)]	N8–C6–C7	125.1(4)	
S1–C2–C6	122.2(3)		C6–N8–O9	113.0(4)	[112(1)]
C6–C2–C3	128.6(4)		C5–Si10–C12	109.3(3)	
C2–C3–C4	113.5(4)	[111(2)]	C5–Si10–C11	109.2(3)	
C5–C4–C3	115.1(4)	[114(1)]	C5–Si10–C13	108.4(2)	
S1–C5–C4	107.8(3)	[112(2)]	C12–Si10–C11	107.0(4)	
S1–C5–Si10	122.8(2)		C12–Si10–C13	109.2(4)	
Si10–C5–C4	129.4(3)		C11–Si10–C13	113.6(4)	
C2–C6–C7	119.6(4)				

the principal bond lengths and angles. The data obtained show that C2–C3 and C4–C5 bonds of the thiophene ring are near to double; the C3–C4 bond order is one and a half. The ketoxime C═N bond is also involved in π–electron delocalization. The geometry of the thiophene ring and the ketoxime fragment corresponds to those in unsubstituted 2-acetylthiophene oxime.[19] The average values for selected bond distances and angles for thiophene ketoximes obtained from CSD are given in square brackets in Table 1. The values of the C2–C6–N8 angle fall into a wide range. The minimum value is 114.1(3)° in 1-[4-bromo-3-(methylsulfanyl)thien-2-yl]ethanone oxime (Mereiter K, Dvorak T, Stanetty P, private communication in CCDB; CCDC number 165 803, 2001) and the maximum value is 130.4(4)° in 2-thiophenealdoxime.[20] The C5–Si10 bond length corresponds to the average value for silylthiophenes, which is 1.87(2) Å.

Figure 2 gives a packing diagram for **4**. The intermolecular hydrogen bond of O9–H···N8 is observed in the crystal structure. The distance of this interaction is 2.842(5) Å [H···N8 = 1.87(6) Å and O9–H···N8 = 157(4)°]. By means of these H-bonds, centrosymmetric dimers are formed in the crystal structure. Similar packing is observed in the crystal structure of 2-acetylthiophene oxime,[19] where the hydrogen bond length is 2.7986 (19) Å.

Compounds **1, 2** and **4–6** were evaluated for their cytotoxic activity *in vitro* against two monolayer tumour cell lines: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) and mouse normal fibroblasts NIH 3T3. The experimental results are presented in Table 2. Compounds **1** and **2** were not cytotoxic compounds; modification of the carbonyl group led to the compound with moderate cytotoxicity and high $NO^{\bullet}$ generation activity. At the same

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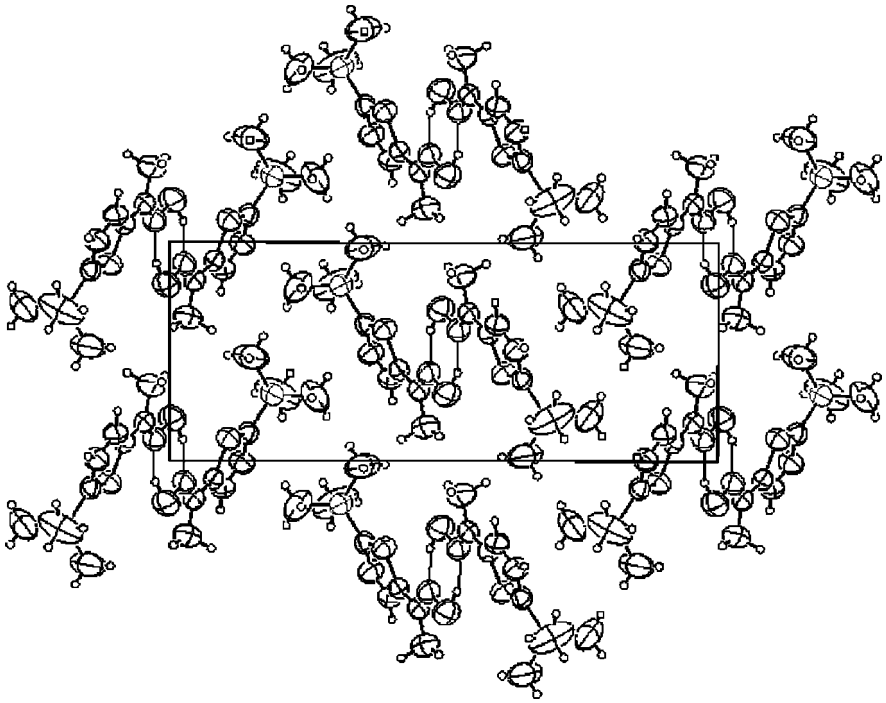

Figure 2. A packing diagram for compound **4**, with hydrogen bonds indicated by dashed lines.

Table 2. Cytotoxicity (IC_{50} μg ml^{-1}) of compounds **1,2** and **4–6**

Cell line	Method	Compounds				
		1	2	4	5	6
HT-1080	CV	nce[a]	nce	7	<1	3
	MTT	nce	nce	13	1.8	1
	$NO^{\bullet}$[b]	5	7	350	633	1600
MG-22A	CV	nce	nce	10	<1	3
	MTT	nce	nce	15	1	2
	$NO^{\bullet}$	5	9	250	189	414
3T3	NR	263	221	73	26	1.6
3T3	LD_{50} (mg kg^{-1})	912	877	555	407	117

IC_{50} (μg ml^{-1}) providing 50% cell killing effect (CV, colouration; MTT, colouration; NR, colouration).
[a] nce, no cytotoxic effect.
[b] $NO^{\bullet}$ generation ability parameter determined according to Fast *et al.*[12] and Veinberg *et al.*[21]

time ketoxime, **4**, was less toxic for normal fibroblasts NIH 3T3 (IC_{50} 73 μg ml^{-1}). Further modification at carbonyl group of 2-acetyl-5-trimethylsilylthiophene (**2**) remarkably improved the cytotoxic activity of the compound (Table 2): thiosemicarbazone of 2-acetyl-5-trimethylsilylthiophene (**5**) is a highly cytotoxic compound for both tumour cell lines ($IC_{50} = \sim 1$ μg ml^{-1}); at the same time this compound was also of moderate toxicity for normal fibroblasts NIH 3T3 ($IC_{50} = 26$ μg ml^{-1}, $LD_{50} = 407$ mg kg^{-1}).

1-(5-Trimethylsilyl-2-thienyl)-1-ethylideneaminoguanidine (**6**) also exhibited high cytotoxic activity and NO generation ability. This compound readily increased the NO concentration in the cultural medium of the HT-1080 cell line, but unfortunately it was toxic for normal fibroblasts 3T3 (IC_{50} 1.6 μg ml^{-1}, LD_{50} 117 mg kg^{-1}).

EXPERIMENTAL

2-Acetyl-5-trimethylsilylfuran (1)

To a suspension of lithium *N*-methylpiperazide, prepared from *N*-methylpiperazine (20 mmol) in 40 ml of dry THF and *n*-BuLi (20 mmol) in hexane at −78 °C, was added 2-acetylfuran (18 mmol) at −78 °C. The mixture was stirred for 15 min and hexane solution of *n*-BuLi (20 mmol) was added and the reaction mixture was stirred at −20 °C for 4 h. A solution of trimethylchlorosilane (20 mmol) in 10 ml THF was added dropwise at −78 °C and the mixture was allowed to warm to room temperature and stirred for 10 h. The mixture was hydrolysed by stirring with 1 M HCl (120 ml) at 0 °C for 10 min and neutralized with aq. Na_2CO_3 solution. The resulting mixture was extracted with Et_2O, the organic layer dried with $MgSO_4$ and concentrated. The mixture was filtered through Al_2O_3; after evaporation of Et_2O the residue was distilled *in vacuo* to yield 1.53 g (45%) of **1**, b.p. 65–68 °C/4 mmHg. MS *m/z* (%): 182 (M^+, 40), 167 (M^+-Me, 100), 151 (20), 136 (9), 125 (9), 97 (15), 75 (50). ^1H NMR (δ, ppm): 0.30 (9H, s, Si-CH_3); 2.48 (3H, s, C-CH_3); 6.68 (1H, d, H^3); 7.14 (1H, d, H^4); $J_{3,4}$ 3.9 Hz.

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2-Acetyl-5-trimethylsilylthiophene (2)

Ketone **2** has been prepared analogously. Yield 2.15g (60%), b.p. 94–95/4 mmHg. MS *m/z* (%): 198 (M^+, 18), 183 (M^+-Me, 100), 167 (7), 84 (8), 75 (8). ^{1}H NMR (δ, ppm): 0.33 (9H, s, Si-CH_3); 2.56 (3H, s, C-CH_3); 7.22 (1H, d, H^3); 7,71 (1H, d, H^4); $J_{3,4} = 3.8$ Hz. ^{29}Si (δ, ppm): −5.26.

Oxime of 2-acetyl-5-trimethylsilylfuran (3)

Ketone **1** (1.5 mmol) in 1 ml of EtOH, NH_2OH. HCl (1.66 mmol) and Na_2CO_3 (0.83 mmol) in 0.5 ml of H_2O were mixed and stirred under reflux for 100 h. The reaction was monitored by TLC and GC-MS. GC-MS detected only traces of target oxime. MS *m/z* (%): 197 (M^+, 69), 182 (M^+-Me, 100), 166 (19), 96 (19), 75 (100).

Oxime of 2-acetyl-5-trimethylsilylthiophene (4)

Ketone **2** (1.5 mmol) in 1 ml of EtOH, $NH_2OH^{\bullet}HCl$ (1.66 mmol) and Na_2CO_3 (0.83 mmol) in 0.5 ml of H_2O were mixed and stirred under reflux for 26 h. The reaction was monitored by TLC. After 26 h, the reaction mixture was cooled and filtered, the resulting precipitate was washed with water. After drying 0.254 g (79.1%) of crude oxime, **4** (*E*-/*Z*-isomers mixture 2 : 1 by ^{1}H NMR), was obtained. MS *m/z* (%): 213 (M^+, 29), 198 (M^+-Me, 100), 182 (17), 77 (15), 58 (17). After recrystalization from diethylether m.p. 38–40 °C. Anal. calcd for $C_9H_{15}NOSSi$ (%) C, 50.66; H, 6.09; N, 6.56; S, 15.03. Found: C, 50.91; H, 6.34; N, 6.60; S 15.22. MS *m/z* (%): 213 (M^+, 31), 198 (M^+-Me, 100), 182 (9), 166 (10), 140 (12), 75 (14). ^{1}H NMR (δ, ppm): 0.31 (9H, s, Si-CH_3); 2.30 (3H, s, C-CH_3); 7.13 (1H, d, H^3); 7,27 (1H, d, H^4); 8.99(1H, bs, OH); $J_{3,4} = 3.4$ Hz. (*Z*-isomer). 0.34 (9H, s, Si-CH_3); 2.56 (3H, s, C-CH_3); 7.23 (1H, d, H^3); 7,72 (1H, d, H^4), 8.99 (1H, bs, OH), $J_{3,4} = 3.6$ Hz (*E*-isomer). ^{29}Si (δ, ppm): −5.89.

Thiosemicarbazone of 2-acetyl-5-trimethylsilylthiophene (5)

Ketone **2** (0.87 mmol) in 5 ml of EtOH and $NH_2NHC(S)NH_2$ (0.87 mmol) were mixed and stirred under reflux for 6 h. The reaction was monitored by TLC. After 6 h, the reaction mixture was cooled and filtered, the resulting precipitate was washed with water. After drying, 0.186 g (78.8%) of crude thiosemicarbazone, **5**, was obtained. After crystallization from EtOH m.p. 165–166 °C. Anal. calcd for $C_{10}H_{17}N_3S_2Si$ (%) C, 43.95; H, 6.14; N, 15.66. Found: C, 44.24; H, 6.09; N, 15.38. ^{1}H NMR (δ, ppm): 0.07 (9H, s, Si-CH_3); 2.17 (3H, s, C-CH_3); 7.15 (1H, d, H^4); 7.29 (1H, d, H^3); 7.53 (2H, m, NH_2); 8.49 (1H, m, NH); $J_{3,4} = 3.4$ Hz. ^{29}Si (δ, ppm): −6.14.

1-(5-Trimethylsilyl-2-thienyl)-1-ethylideneaminoguanidine (6)

A mixture of aminoguanidine bicarbonate (0.15 g, 1.1 mmol) and 0.19 ml concentrated HCl was stirred at ambient temperature few minutes and ketone **2** (0.21 g, 1.1 mmol) in 5 ml of EtOH was added and mixture was stirred under reflux for 4 h. The reaction was monitored by TLC. After 4 h, the reaction mixture was concentrated to approximate half of the original volume, cooled and neutralized with $NaHCO_3$, extracted using Et_2O and dried on Na_2SO_4. After evaporation of ether the residue was washed by hexane and collected by filtration and dried to give 0.064 g (21.4%) of aminoguanidine **6**, m.p. 172–174 °C. Anal. calcd for $C_{10}H_{18}N_4SSi$ (%) C, 47.21; H, 7.13; N, 22.02; S 12.60. Found: C, 47.16; H, 6.82; N, 22.25. S, 12.62. ^{1}H NMR (δ, ppm): 0.3 (9H, s, Si-CH_3); 2.36 (3H, s, C-CH_3); 4.06 (1H, s, NH); 5.08 (1H, s, NH) 7.12 (1H, d, H^3); 7.22 (1H, d, H^4); $J_{3,4} = 3.6$ Hz. ^{29}Si (δ, ppm): −6.60.

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