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A NEW METHOD FOR THE SYNTHESIS OF SILICON- AND GERMANIUM-CONTAINING 2-ACETYLFURANS AND 2-ACETYLTHIOPHENES

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A new method was developed for the synthesis of silicon- and germanium-containing acetylfurans and acetylthiophene by metallation of 2-acetylfuran or 2-acetylthiophene with n-BuLi at low temperature after protection of the carbonyl group with lithium N-methylpiperazide and reaction of the lithium derivative with various trialkyl-, alkylphenyl-, and cycloalkylchlorosilanes or trialkylchloro-(bromo)germanes. The cytotoxic activity of the new compounds was studied, and it was established that the silicon- and germanium-containing acetylfurans and acetylthiophenes are substances with low toxicity (LD_{50} 312->2000 mg/kg) and have low cytotoxicity toward HT-1080 and MG-22A tumor cells.

Keywords: 2-acetyl-5-alkylphenylsilylthiophenes, 2-acetyl-5-alkylphenylsilylfurans, 2-acetyl-5-sila-cycloalkylthiophenes, 2-acetyl-5-silacycloalkylfurans, 2-acetyl-5-trialkylsilyl(germyl)thiophenes, 2-acetyl-5-trialkylsilyl(germyl)furans, synthesis, toxicity, cytotoxicity, ^{1}H, ^{13}C, ^{29}Si NMR.

The presence of a heterocycle in various types of organic compounds plays a significant role in their manifestation of biological activity [1, 2]. The type and effectiveness of the biological action depend both on the nature of the heterocycle and on the structure and position of the substituents in the ring. Thus, many preparations contain a furan ring: Ranitidine and lupitidine (for the treatment of stomach ulcers) furosemide and mefruside (diuretics), bufetol, prazosin, tetrazosin, and alfuzosin (antihypertensive agents), furodazole (antihelminthic preparation), dantrolene (muscle relaxant), furagin and solafur (antibacterial preparations), naftidrofuril (vasodilator), ipomeanols and ftorafur (antitumor agents). 2-Furyloxocarboxylic acid was used in the synthesis of the cephalosporin antibiotic cerufoxime, and thienylacetic acid was used in the synthesis of cefalotine [1]. It is interesting to note that if there is a 4-nitrophenyl group at position 5 of the furan ring the product from condensation with aminohydantoin – dantrolene – can be used as a muscle relaxant; however, if the nitro group is directly attached to the furan ring the antibacterial agent nitrofurantoin is obtained.

It is known that the presence of a silyl or germyl group in an organic compound substantially increases the lipophilicity of the substance, i.e., its ability to pass through cell membranes, which in many cases substantially increases the biological activity of the compound compared with the carbon analogs [3].

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Comparative study of the toxicity of our synthesized 5-alkyl-, 5-trialkylgermyl-, and 5-trialkylsilyl-2-trifluoroacetylfurans and their oximes also showed a definite dependence of the toxicity on the substituents at position 5 [4]. Thus, modification in the organic substituent, condensation of the carbonyl group in 2-trifluoroacetyl-5-trimethylsilylfuran with hydroxylamine, leads to a compound with cytotoxicity for two lines of tumor cells HT-1080 and MG-22A (LC_{50} 0.3 and 0.8 μg/ml respectively) [5], while further transformation of the oxime to an alkoxyimine group leads to total loss of cytotoxicity by the compound [6].

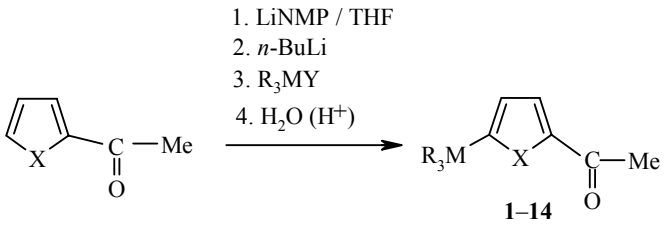
In order to develop further the synthetic base for the production of new biologically active substances based on 2-acetylfuran and 2-acetylthiophene we worked out a new method for the synthesis of silicon- and germanium-containing acetylfurans and acetylthiophenes and studied their biological activity.

The acyl derivatives of furan and thiophene are usually obtained by acylation of the respective heterocycle with acetic anhydride in the presence of catalytic amounts of iodine or phosphoric acid [7, 8]. Recently Bowman analyzed and summarized published data on the acylation of thiophene over the last 60 years [9]. Kinetic investigations showed that the α-position of furan is $7 \cdot 10^4$ times more reactive than the β-position [10].

The presence of the silicon- or germanium-containing substituent in the heterocycle significantly complicates the classical Friedel–Crafts acylation since it is accompanied by *ipso* substitution of the heteroatomic substituent. This reaction is widely used in organic synthesis for the selective introduction of a substituent into an aromatic or heteroaromatic ring [11].

However, the authors in [12] were able to realize the acylation of 2-trimethylsilylfuran and 2-trimethylsilylthiophene with acetic anhydride in the presence of iodine and obtain 2-acetyl-5-trimethylsilylfuran and 2-acetyl-5-trimethylsilylthiophene with small yields (25 and 13% respectively).

We developed a new method for the synthesis of silyl- and germyl-substituted acetylfurans and acetylthiophenes by metallation of commercially available 2-acetylfuran and 2-acetylthiophene with *n*-BuLi at low temperature after first protecting the carbonyl group with lithium N-methylpiperazide (LiNMP) *in situ* and reaction of the obtained lithium derivative with the corresponding chloro(bromo)silane or chloro(bromo)germane. By the proposed method we were able to obtain a wide range of silicon- and germanium-substituted acetylfurans and acetylthiophenes with yields of 27-78% and to study their cytotoxic activity.



1–14

X = O, S; Y = Cl, Br

The yields and physicochemical characteristics of the synthesized compounds are given in Table 1. The IR and ^{13}C and ^{29}Si NMR spectra are given in Table 2.

Comparison of the $\delta^{29}Si$ chemical shifts of the organosilicon derivatives of furan **1**, **2**, and **5-7** and their thiophene analogs **8**, **9**, and **12-14** shows that the ^{29}Si signals of all the furan derivatives appear in the upfield region (by 3.22-3.85) from the signals of the corresponding thiophene derivatives.

To determine the effect of the nature of the heteroatomic substituent in the ketones **1-14** on the antitumor activity we studied their cytotoxicity (Table 3) for two lines of tumor cells: HT-1800 (human

fibrosarcoma) and MG-22A (mouse hepatoma). For comparison we studied the cytotoxicity of these compounds for normal NIH 3T3 cells (the normal fibroblasts of mouse embryos) and their toxicity (LD_{50}, mg/kg). The investigation showed that all the studied ketones **1-14** are weakly toxic substances with lethal doses (LD_{50}) in the range of 312->2000 mg/kg (Table 3). It is interesting to note that 2-acetyl-5-triethylsilylthiophene **9** was ~4 times more toxic than the furan analog **2**. Substitution of one methyl group in 2-acetyl-5-trimethyl-silylthiophene by phenyl [compound **12**] reduces the toxicity of the compound by half. Substitution of the trimethylsilyl substituent by trimethylgermyl substantially reduces the toxicity of the compound both in the thiophene and in the furan series [compounds **1** and **3** and **8** and **10**]. Unfortunately, compounds **1-14** hardly exhibited any cytotoxic activity against HT-1080 and MG-22A tumor cells and proved toxic against normal NIH 3T3 cells. Only 2-acetyl-5-triethylsilylthiophene **9** proved moderately cytotoxic against tumor and normal cells. It also had the highest NO generating activity.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded on a Varian Mercury-200 spectrometer (200, 50, and 40 MHz respectively) in $CDCl_3$ with standards HMDS (δ 0.055 ppm) for ^{1}H, TMS (external) for ^{29}Si, and the signal of the residual proton of the solvent (δ 77.05 ppm) for ^{13}C. The mass spectra were recorded on a GC-MS HP 6890 mass spectrometer with 70 eV ionizing electrons. The 2-acetylthiophene and 2-acetylfuran were obtained from Acros. The N-methylpiperazine and THF were dried over CaH_2 and distilled.

The cytotoxicity of compounds **1-14** (Table 3) was determined by the procedure described in [13]. The acute toxicity (LD_{50}, mg/kg) on a culture of 3T3 cells (alternative LD_{50} in an *in vivo* test) was determined according to protocols [14].

2-Acetyl-5-trimethylsilylfuran (1) and 2-Acetyl-5-trimethylsilylthiophene (8). These compounds were obtained from the corresponding acetyl derivatives by the method described in [13].

2-Acetyl-5-triethylgermylthiophene (11). In a three-necked flask fitted with a reflux condenser, a thermometer, a magnetic stirrer, and a rubber stopper in a stream of argon we placed 2.0 g (20 mmol) of freshly distilled N-methylpiperazide, dissolved in 40 ml of absolute TFH. The flask with the solution was cooled to -78°C, and 9.1 ml (20 mmol) of a 2.2 N solution of *n*-BuLi in hexane was slowly added drop by drop with a syringe so that the temperature in the flask did not exceed -78°C. When all the *n*-BuLi had been added the mixture was stirred for 15 min at -78°C, and 2.27 g (20 mmol) of 2-acetylthiophene in 7 ml of THF was added drop by drop. When all the 2-acetylthiophene had been added the mixture was stirred for 20 min, and 9.1 ml (20 mmol) of a 2.2 N solution of *n*-Buli in hexane was added drop by drop. When all the butyllithium had been added the temperature was raised to -20°C, and the mixture was stirred at this temperature for 4 h 30 min. The mixture was cooled to -78°C, and a solution of 4.7 g of triethylbromogermane in 10 ml of THF was slowly added drop by drop. After the addition of the triethylbromogermane the mixture was stirred at -78°C for 15 min, the temperature was slowly raised to room temperature, and the mixture was stirred for 10 h. The reaction mixture was hydrolyzed with 120 ml of 1 M HCl at 0°C for 10 min and neutralized with a saturated solution of sodium carbonate. The product was extracted with ether (50 ml×3), and the extracts were combined and dried over magnesium sulfate. The mixture was passed through a layer of Al_2O_3, and the ether was evaporated to dryness. The residue was distilled under vacuum at 130-132°C (5 mm Hg), and 4.0 g (78%) of the ketone **11** was obtained.

The ketones **2-7**, **9**, **10**, and **12-14** were obtained similarly.

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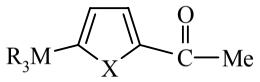
TABLE 1. The Characteristics of 2-Acetyl-5-silyl(germyl)furans(thiophenes)



1–**7** X = O, **8**–**14** X = S

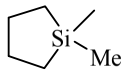
Com-pound	R_3M	mp, °C (mmHg.)	^{1}H NMR spectrum, δ, ppm. (*J*, Hz)	Mass spectrum, *m/z* (I_{rel}, %)	Yield, %
1	2	3	4	5	6
1	Me_3Si	65-68 (3)	0.30 (9H, s, $Si(CH_3)_3$); 2.48 (3H, s, CCH_3); 6.68 (1H, d, H-3); 7.14 (1H, d, $J_{3,4}$ = 3.9, H-4)	182 $[M]^+$ (40), 167 [M^+–Me] (100), 151 (20), 136 (9), 125 (9), 97 (15), 75 (50)	45
2	Et_3Si	100-102 (6)	0.77-1.03 (15H, m, $SiEt_3$); 2.46 (3H, s, CCH_3); 6.68 (1H, d, H-3); 7.14 (1H, d, $J_{3,4}$ = 3.8, H-4)	224 $[M]^+$ (13), 195 [M^+–Et] (100), 167 (60), 137 [M^+–3Et] (20), 95 (10), 43(10)	58
3	Me_3Ge	78-82 (6)	0.44 (9H, s, $Ge(CH_3)_3$); 2.46 (3H,s, CCH_3); 6.60 (1H, d, H-3); 7.14 (1H, d, $J_{3,4}$ = 3.8, H-4)	228 $[M]^+$ (18), 213 [M^+–Me] (100), 183 [M^+–3Me] (16), 143 (18), 119 (16), 109 (20), 89 (30), 43 (30)	48
4	Et_3Ge	105-110 (5)	1.04-1.08 (15H, m, $GeEt_3$); 2.47 (3H, s, CCH_3); 6.69 (1H, d, H-3); 7.17 (1H, d, $J_{3,4}$ = 3.4, H-4)	270 $[M]^+$ (8), 241 [M^+–Et] (100), 213 (70), 185 (90), 113 (15), 103 (10), 91 (9), 65 (9), 43 (20)	52
5	Me_2PhSi	130-133 (5)	0.60 (6H, s, $Si(CH_3)_2$); 2.49 (3H, s, CCH_3); 6.70 (1H, d, H-3); 7.15 (1H, d, $J_{3,4}$ = 3.6, H-4); 7.30-7.41 (4H, m, C_6H_5); 7.55–7.58 (1H, m, C_6H_5)	244 $[M]^+$ (50), 229 [M^+–Me] (100), 211 (41), 183 (8), 167 [M^+–Ph] (11), 151 [M^+–MePh] (30), 136 [M^+–Me_2Ph] (17), 105 (19), 77 [Ph] (15), 53 (8), 43 (26)	40
6		103-105 (5)	0.41 (3H, s, $SiCH_3$); 0.64–1.00 (4H, m, $SiCH_2$); 1.66-1.69 (4H, m, CH_2CH_2); 2.47 (3H, s, CCH_3); 6.72 (1H, d, H-3); 7.14 (1H, d, $J_{3,4}$ = 3.6, H-4)	208 $[M]^+$ (86), 193 [M^+–Me] (91), 179 (67), 165 [M^+–Me–CO] (81), 152 [M^+–$(CH_2)_4$] (67), 137 [M^+–$(CH_2)_4Si$] (100), 125 (17), 117 (18), 109 [M^+–$(CH_2)_4SiCH_3$] (38), 93 (33), 83 (19), 77 (29), 65 (33), 55 (30), 43 [SiMe] (90)	48

TABLE 1 (continued)

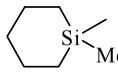
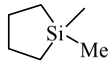
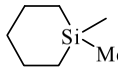
1	2	3	4	5	6
7		107-110 (5)	0.30 (3H, s, $SiCH_3$); 0.55–1.81 (4H, m, $SiCH_2$); 1.56-1.81 (6H, m, $(CH_2)_3$); 2.49 (3H, s, CCH_3); 6.73 (1H, d, H-3); 7.16 (1H, d, $J_{3,4}$ = 3.4, H-4)	222 $[M]^+$ (35), 207 $[M^+–Me]$ (100), 193 (8), 179 $[M^+–Me–CO]$ (52), 167 (36), 161 (8), 153 (63), 137 (35), 131 (9), 125 (15), 112 (38), 103 (10), 97 (29), 84 (38), 77 (37), 69 (21), 61 (13), 55 (19), 43 [SiMe] (77)	45
8	Me_3Si	94-95 (4)	0.33 (9H, s, $Si(CH_3)_3$); 2.56 (3H, s, CCH_3); 7.22 (1H, d, H-3); 7.71 (1H, d, $J_{3,4}$ = 3.8, H-4)	198 $[M]^+$ (18), 183 $[M^+–Me]$ (100), 167 (7), 84 (8), 75 (8)	60
9	Et_3Si	119-124 (5)	0.79-1.03 (15H, m, $Si(C_2H_5)_3$); 2.57 (3H, s, CCH_3); 7.25 (1H, d, H-3); 7.73 (1H, m, $J_{3,4}$ = 3.6, H-4)	240 $[M]^+$ (10), 211 $[M^+–Et]$ (90), 183 $[M^+–2Et]$ (100), 155 (100), 139 (5), 109 (5), 77 (8), 43 (40)	27
10	Me_3Ge	98-105 (5)	0.46 (9H, s, $Ge(CH_3)_3$); 2.52 (3H, s, CCH_3); 7.15 (1H, d, H-3); 7.69 (1H, d, $J_{3,4}$ =3.6, H-4)	244 $[M]^+$ (9), 229 $[M^+–Me]$ (100), 199 (9), 119 $[Me_3Ge]$ (6), 89 [MeGe] (10), 43 (20)	69
11	Et_3Ge	130-132 (5)	1.04–1.07 (15H, m, $GeEt_3$); 2.54 (3H, s, CCH_3); 7.15 (1H, d, H-3); 7.73 (1H, d, $J_{3,4}$ = 3.4, H-4)	286 $[M]^+$ (5), 257 $[M^+–Et]$ (100), 229 $[M^+–2Et]$ (60), 109 (40), 101 (10), 77 (10), 65 (10), 43 (40)	78
12	Me_2PhSi	130-132 (3)	0.30 (6H, s, $Si(CH_3)_2$); 2.56 (3H, s, CCH_3); 7.24 (1H, d, H-3); 7.30-7.40 (4H, m, C_6H_5); 7.53-7.58 (1H, m, C_6H_5); 7.72 (1H, d, $J_{3,4}$ = 3.6, H-4)	260 $[M]^+$ (19), 245 $[M^+–Me]$ (100)	65
13		128-130 (6)	0.45 (3H, s, $SiCH_3$); 0.74-0.93 (4H, m, $SiCH_2$); 1.60-1.74 (4H, m, CH_2CH_2); 2.56 (3H, s, CCH_3); 7.25 (1H, d, H-3); 7.71 (1H, d, $J_{3,4}$ = 3.8, H-4)	224 $[M]^+$ (54), 209 $[M^+–Me]$ (100), 196 $[M^+–CO]$ (18), 181 $[M^+–Me–CO]$ (29), 168 $[M^+–C_4H_8]$ (58), 153 $[M^+–(CH_2)_4Si]$ (42), 137 (7), 125 $[M^+–(CH_2)_4SiMe]$ (7), 109 (27), 99 $[M^+–C_4H_2SC(O)Me]$ (17), 91 (7), 85 (12), 77 (15), 65 (10), 53 (12), 43 [SiMe] (43)	55
14		130-132 (5)	0.29 (3H, s, $SiCH_3$); 0.70-1.82 (4H, m, $SiCH_2$); 1.58-1.82 (6H, m, $(CH_2)_3$); 2.53 (3H, s, CCH_3); 7.24 (1H, d, H-3), 7.70 (1H, d, $J_{3,4}$ = 3.6, H-4)	238 $[M]^+$ (37), 223 $[M^+–Me]$ (100), 195 $[M^+–COMe]$ (100), 182 (17), 169 (50), 153 (28), 109 (13), 97 (15), 85 (14), 77 (10), 43 (23)	54

TABLE 2. The Spectral Characteristics of the Ketones **1-14**

Compound	IR spectrum, ν, cm^{-1} (C=O)	^{13}C NMR spectrum, δ, ppm							^{29}Si NMR spectrum, δ, ppm
		R_3M	$CO\underline{C}H_3$	C(4)	C(3)	C(5)	C(2)	C=O	
1	1680	-1.92	26.16	116.97	121.26	156.53	166.45	190.41	-9.11
2	1685	-2.01	26.13	117.28	119.87	156.48	168.15	186.75	-2.03
3	1685	3.00, 7.17	26.20	116.53	122.38	156.84	164.67	187.10	-
4	1685	4.37, 8.76	26.11	116.84	121.08	156.79	166.56	186.80	-
5	1681	3.17	26.26	116.78	122.72	157.86	164.58	187.35	-14.41
6	1681	4.20, 12.00	27.12	116.92	122.04	156.84	165.33	186.99	5.97
7	1681	-4.55, 12.31	26.27	116.80	122.01	156.73	165.53	187.10	-13.26
8	1670	-0.41	27.25	133.01	134.40	148.71	150.82	190.41	-5.26
9	1675	-0.72	27.10	132.94	133.36	148.27	152.48	190.17	1.19
10	1663	4.11, 7.18	27.23	132.99	135.12	147.58	148.80	190.39	-
11	1670	5.36, 8.72	27.13	132.92	134.13	148.47	149.40	190.16	-
12	1663	1.68	27.28	133.01	133.84	148.57	149.32	190.20	-10.61
13	1664	2.97, 13.32	27.03	132.90	134.83	148.84	149.10	189.98	9.19
14	1669	-2.98, 13.64	27.26	132.98	134.88	148.40	149.16	190.63	-9.55

TABLE 3. The Cytotoxic Activity (LC_{50}, μg/ml)* of the Ketones **1-14**

Compound	HT–1080			MG–22A			3T3	
	CV	MTT	NO	CV	MTT	NO	NR	LD_{50}, mg/kg
1	**	**	5	**	**	5	263	912
2	**	**	5	**	**	6	339	1237
3	**	100	16	**	**	16	**	>2000
4	**	**	27	**	**	**	122	804
5	34	60	73	52	28	62	151	831
6	**	**	14	**	**	25	259	958
7	**	>100	35	100	**	29	251	1001
8	**	**	7	**	**	9	221	877
9	29	17	350	23	16	300	17	312
10	**	>100	16	**	**	18	527	1433
11	**	>100	5	27	32	100	126	855
12	53	>100	27	>100	**	14	1000	1979
13	**	**	10	**	**	12	117	718
14	**	>100	12	>100	**	15	200	930

* CV = crystal violet (action on cell membranes); MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (effect on the activity of mitochondrial enzymes in the cell); NR = neutral red; NO = the degree of generation of NO, determined and calculated according to the procedure in [15].

** There is no cytotoxic effect.

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