Chemistry of Heterocyclic Compounds, Vol. 41, No. 6, 2005

SYNTHESIS AND STEREOISOMERIZATION OF 2-(1-ALKOXYIMINO-2,2,2-TRIFLUOROETHYL)-5-TRIMETHYLSILYLFURANS

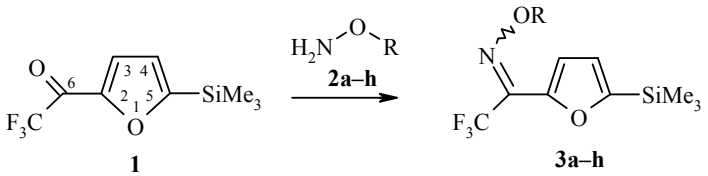
Yu. Melnik, M. Vorona, G. Veinberg, J. Popelis, L. Ignatovich, and E. Lukevics

2-(1-Alkoxyimino-2,2,2-trifluoroethyl)-5-trimethylsilylfurans were synthesized by the condensation of 2-(trifluoroacetyl)-5-trimethylsilylfuran with alkoxyamines. According to ^{1}H and ^{19}F NMR spectroscopic data, the alkoxyimino group in the E-isomers descreens the H-3 and H-4 protons of the furan ring more strongly than in the Z-isomers, shifting their signals downfield. The fluorine atoms of the α-trifluoromethyl group in the Z-isomer are characterized by a downfield shift in relation to the E-isomer.

Keywords: 2-(1-alkoxyimino-2,2,2-trifluoroethyl)-5-trimethylsilylfurans, *syn,anti* stereoisomerism, ^{1}H, ^{19}F spectroscopy.

The presence of furan in various types of organic compounds is a determining factor in their display of biological activity, the effectiveness of which depends on the structure of substituents at positions 2 and 5 of the heterocycle. This tendency was observed, in particular, during a comparative study of the toxicity of our previously synthesized 5-alkyl-, 5-trialkylgermyl-, and 5-trialkylsilyl-2-trifluoroacetylfurans [1].

In order to develop further the synthetic basis for the production of new biologically active substances based on 2-(trifluoroacetyl)-5-trimethylsilylfuran (**1**) we realized the alkoxyimination of this compound and studied the stereoisomerism of the products.

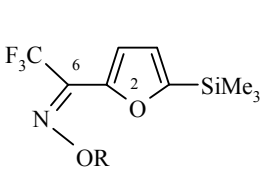


2, **3 a** R = Me, **b** R = Et, **c** R = *n*-Pr, **d** R = *i*-Pr, **e** R = *n*-Bu, **f** R = *n*-C_8H_{17}, **g** R = $CH_2CH{=}CH_2$, **h** R = CH_2Ph

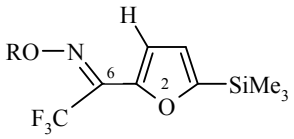
Alkoxyimination of the trifluoroacetyl group in the initial furan **1** with the hydrochlorides of alkoxyamines **2a-h** was carried out in boiling ethanol in the presence of sodium acetate. Compounds **3a-h** were isolated from the reaction mixture by column chromatography with yields of 7-70%. Their chromatomass-spectrometric analysis indicates that apart from the methoxyimino derivative **3a**, which consists of two isomers, the other alkoxyimino derivatives **3b-g** are represented almost entirely by only one isomeric form (Table 1).

Latvian Institute of Organic Synthesis, Riga; e-mail: veinberg@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 834-838, June, 2005. Original article submitted December, 7, 2004.

Analysis of the ^{1}H and ^{19}F NMR spectra (Table 2) showed that the trifluoroacetyl group in compound **3a** is arranged in two ways in relation to the $C_{(2)}$–$C_{(6)}$ bond. Besides each conformer **A** and **B** corresponds to fixed *anti*-(*E*) of *syn*-(*Z*) arrangement of the methoxy group.



A (*E*)



B (*Z*)

This could be indicated in the spectrum of the conformer **B** by the presence of long-range spin–spin coupling constants for the H-3 proton and fluorine nuclei ($^{5}J_{HF}$ = 1.7-2.2 Hz), due to the W-conformation of the five chemical bonds situated between them, which absent in the structure of conformer **A**.

As far as the hydroxyimino group in 2-(α-alkoxyiminoethyl)furans is concerned, it is known that this group descreens the H-3 and H-4 protons of the furan ring more strongly than in the *E*-isomers, leading to a downfield shift of their signals. A similar descreening effect from the methoxyimino group in the *Z*-isomer appears in relation to the protons of the α-methyl group, shifting their signals downfield compared with the *E*-isomers [2, 3].

According to the above-mentioned data, the chemical shifts of the H-3 protons in the furan ring show unambiguously that the methoxy group has *E*-geometry in conformer **A** of compound (**3a**) (7.34 ppm) (Table 2) and *Z*-geometry in conformer **B** (6.75 ppm). [With identical spatial orientation for the isomeric alkoxyimines both in our synthesized compounds and in those described in [2, 3] their nomenclature in the case of **3a-g** is reversed in so far as the replacement of hydrogen atoms by fluorine atoms changes the seniority of the

TABLE 1. The Physicochemical Characteristics of 2-(1-Alkoxyimino-2,2,2-trifluoroethyl)-5-trimethylsilylfurans **3a-h**

Compound	R_f*	*E*/*Z* isomers	MS-GC, *m/z* (I_{rel},%)	Yield, %
E-**3a**	0.23	93/7	265 [M^+] (25), 250 [M^+ –Me] (36), 123 (9),	7
Z-**3a**	0.23, 0.14*[2]	20/80	89 (32), 77 (100) 265 [M^+] (27), 250 [M^+ –Me] (30), 123 (7), 89 (41), 77 (100)	63
E-**3b**	0.28	>99/<1	279 [M^+] (62), 264 [M^+ –Me] (39), 236 (17), 103 (55), 77 (100)	58
Z-**3b**			279 [M^+] (33), 264 [M^+ –Me] (100), 236 (21), 150 (36), 73 (16)	
E-**3c**	0.36	>99/<1	251 [M^+ –C_3H_6] (4), 236 [M^+ –Me] (33), 220 (48), 77 (35), 43 (100)	29
E-**3d**	0.26	100/0	251 [M^+ –C_3H_6] (31), 236 [M^+–Pr–Me] (76), 123 (10), 75 (100)	7
E-**3e**	0.38	98/2	307 [M^+] (14), 292 [M^+ –Me] (7), 236 (52), 220 (66), 123 (14), 77 (100)	23
E-**3f**	0.34	100/0	363 [M^+] (6), 348 [M^+ -Me] (4), 262 (35), 236 (47), 220 (98), 123 (16), 73 (67), 43 (100)	12
E-**3g**	0.32	98/2	291 [M^+] (31), 276 [M^+ –Me] (3), 128 (22), 73 (100), 41 (63)	65
E-**3h**	0.31	98/2	341 [M^+] (4), 326 [M^+ –Me] (3), 91 (100), 77 (11)	28

* Data from TLC, 1:10 ethyl acetate–petroleum ether system.

*[2] A chromatically inseparable mixture.

TABLE 2. The ^{1}H and ^{19}F NMR Spectra of 2-(1-Alkoxyimino-2,2,2-trifluoroethyl)-5-trimethylsilylfurans **3a-h**

Com-pound	Conformer	Chemical shifts δ, ppm., SSCC (*J*, Hz)				
		H-3, d	H-4, d	$Si(CH_3)_3$	R	CF_3
E-**3a**	**A**	7.34 (*J* = 3.4)	6.71 (*J* = 3.4)	0.28	4.14 (3H, s, OCH_3)	-66.12
Z-**3a**	**B**	6.75 (*J* = 3.4, 2.2*)	6.65 (*J* = 3.4)	0.29	4.12 (3H, s, OCH_3)	-63.83
E-**3b**	**A**	7.34 (*J* = 3.4)	6.70 (*J* = 3.4)	0.28	1.37 (3H, t, *J* = 6.6, $CH_2\underline{CH_3}$); (2H, q, *J* = 6.6, $\underline{CH_2}CH_3$)	-66.10
E-**3c**	**A**	7.34 (*J* = 3.4)	6.71 (*J* = 3.4)	0.28	0.91 (3H, t, *J* = 6.6, $CH_2CH_2\underline{CH_3}$); 1.70-1.87 (2H, m, $CH_2\underline{CH_2}CH_3$); 4.36 (2H, t, *J* = 6.6, OCH_2)	-66.12
E-**3d**	**A**	7.33 (*J* = 3.5)	6.71 (*J* = 3.5)	0.28	1.36 (6H, d, *J* = 6.6, $2CH_3$); 4.47-4.65 (1H, m, OCH)	-66.43
E-**3e**	**A**	7.33 (*J* = 3.3)	6.71 (*J* = 3.3)	0.28	0.95 (3H, t, *J* = 7.2, $CH_2CH_2CH_2\underline{CH_3}$); 1.35-1.56 (2H, m, $CH_2CH_2\underline{CH_2}CH_3$); 1.68-1.85 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$); 4.37 (2H, t, *J* = 7.2, OCH_2)	-66.04
E-**3f**	**A**	7.33 (*J* = 3.5)	6.71 (*J* = 3.5)	0.28	0.87 (3H, t, *J* = 6.5, $C_7H_{14}\underline{CH_3}$); 1.22-1.47 (10H, m, $CH_2CH_2(\underline{CH_2})_5CH_3$); 1.70-1.85 (2H, m, $CH_2\underline{CH_2}C_6H_{13}$); 4.34(2H, t, *J* = 6.5, OCH_2);	-66.06
E-**3g**	**A**	7.36 (*J* = 3.4)	6.71 (*J* = 3.4)	0.28	4.86(2H, d, *J* = 5.9, OCH_2); 5.26-5.45 (2H, m, $CH_2CH=\underline{CH_2}$); 5.97-6.18 (1H, m, $CH_2\underline{CH}=CH_2$)	-66.03
E-**3h**	**A**	7.35 (*J* = 3.5)	6.69 (*J* = 3.5)	0.28	5.43 (2H, s, CH_2); 7.38-7.50 (6H, m, C_6H_5)	-66.37

* SSCC ^{5}J (H–CF_3).

trifluoromethyl group.] The opposite tendency could be observed in the case of the fluorine atoms of the α-trifluoromethyl group, which unlike the protons of the α-methyl group are characterized by a more downfield signal (-63.83 ppm) for the *Z*-isomer than for the *E*-isomer (-66.12 ppm).

The chemical shifts of the H-3 protons in the other alkoxyimino derivatives of furan **3b-h** in the region of 7.33-7.66 ppm indicate that they are all represented almost entirely by only one **A** conformer with *E*-geometry for the alkoxyimino group (Table 2).

Determination of the cytotoxic characteristics of the synthesized substances *in vitro* according to the standard procedure [4] showed that only compounds **3a**,**d** at concentrations of 50-100 μg/ml caused the destruction of 50% of monolayer tumor cells of the HT-1080 line (human fibrosarcoma). Compounds **3c**,**d**,**h** did not exhibit cytotoxic characteristics.

The investigation has made it possible to synthesize low-toxicity alkoxyimino derivatives of 2-(trifluoroacetyl)-5-trimethylsilylfurans **3a-h** and also to identify the spatial arrangement of the alkoxy- and trifluoromethyl groups on the basis of data from ^{1}H and ^{19}F NMR spectroscopy.

EXPERIMENTAL

The NMR spectra were recorded on a Varian 200 Mercury spectrometer (200 MHz for ^{1}H, internal standard TMS, and 188 MHz for ^{19}F, external standard $CFCl_3$) in $CDCl_3$. The mass spectra were obtained on an HP6890 GC-MS chromato-mass spectrometer (70 eV). The reaction was monitored by TLC on Merck Kieselgel plates with development in UV light. Merck Kieselgel silica gel (0.063-0.230 mm) was used for preparative column chromatography. Reagents and materials from Acros were used in the experiments. The hydrochlorides of the alkoxyamines **2a-h** were synthesized by O-alkylation of N-hydroxysuccinimide with the respective alkyl halides followed by hydrolysis of the obtained N-alkoxysuccinimides with dilute hydrochloric acid.

Production of 2-(1-Alkoxyimino-2,2,2-trifluoroethyl)-5-trimethylsilylfurans (3a-h) (General Procedure). Sodium acetate (463 mg, 5.71 mmol) and the alkoxyamine **2a-h** hydrochloride (3.17 mmol) were added to a solution of 2-trifluoroacetyl-5-trimethylsilylfuran (450 mg, 1.90 mmol) in ethanol (15 ml). The mixture was boiled for 4 h, and the solvent was evaporated under vacuum. The residue was chromatographed on a column of silica gel in 1:10 ethyl acetate–petroleum ether. In the case of **3a** (R = Me) the *E*-isomer was isolated from the fraction with R_f 0.23, while a mixture of *E*/*Z*-isomers was isolated from the inseparable mixture of fractions with R_f 0.23 and R_f 0.14 respectively. The fractions from which the other substances **3b-h** were obtained were characterized almost entirely by the presence of only one stereoisomer.

REFERENCES

1. L. Ignatovich, D. Zarina, I. Shestakova, S. Germane, and E. Lukevics, *Metal-Based Drugs*, **8**, 211 (2002).
2. E. Abele, Yu. Popelis, E. Lukevics, M. Shimanska, and Yu. Goldberg, *Khim. Geterotsikl. Soedin.*, 18 (1994).
3. A. S. Demir, O. Sesenoglu, D. Ulku, and C. Arici, *Helv. Chim. Acta*, **86**, 91 (2003).
4. G. A. Veinberg, I. Shestakova, N. Grigan, D. Musel, I. Kanepe, I. Domrachova, V. Grigoryeva, O. Zharkova, I. Turovskis, I. Kalvinsh, A. Strakovs, and E. Lukevics, *Eur. J. Med. Chem.*, **33**, 755 (1998).