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TRIMETHYLSILYLCYANATION OF N-[3-(2-FURYL)-2-PROPENYLIDENE]-TRIFLUOROMETHYLANILINES

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The addition of Me_3SiCN to N-[3-(2-furyl)-2-propenylidene]trifluoromethylanilines, differing in the position of the CF_3 group in the benzene ring and in the presence or absence of a methyl group in the heterocycle, was studied in the presence of aluminum bromide as catalyst. The direction of the process (1,2-addition in all cases) was determined, and certain other features of the reactions were discovered. A series of the corresponding unsaturated heterocyclic α-amino nitriles were synthesized. The molecular and crystal structures of one of them were determined by X-ray crystallographic analysis.

Keywords: α-Amino nitriles, N-[3-(2-furyl)-2-propenylidene]anilines, Lewis acid, trimethylsilyl cyanide, catalysis.

Recently we synthesized a series of new N-[3-(2-furyl)-2-propenylidene]trifluoromethylanilines [1-3] by the condensation of furylacroleins with 2-, 3-, and 4-trifluoromethylanilines. In a continuation of the previous investigations [4-6] in the present work we studied the trimethylsilylcyanation of a series of new aldimines by the reaction of trimethylsilyl cyanide with various azomethines. There are no published data on the reaction of trimethylsilyl cyanide with propenylideneamines. During investigation of the hydrosilylation of furylacrolein and its derivatives and analogs containing conjugated O=C–C=C bonds it was shown that 1,2- and 1,4-addition products are formed in these processes [7]. On the basis of this it seemed of interest to determine the direction of the processes in the trimethylsilylcyanation of the system of N=C–C=C bonds.

It was established in [4, 5] that among the employed Lewis acids the most active catalyst of the addition of trimethylsilyl cyanide to various heterocyclic aldimines is aluminum bromide in the presence of 4A molecular sieves. This catalytic system was therefore also used in the present investigation. The reaction of the 2-, 3-, and 4-trifluoromethyl derivatives of N-(3-hetaryl-2-propenylidene)anilines **1a-f** (where hetaryl = 2-furyl and 5-methyl-2-furyl) with trimethylsilyl cyanide was studied. The reactions were conducted in methylene chloride or acetonitrile at 40 or 65°C with the substrate and silyl cyanide in a molar ratio of 1:1.2 and the catalyst at a concentration of 20 mole %.

During study of the reaction of the substrates **1a-f** with trimethylsilyl cyanide it was found that compounds containing a 4-CF_3 group in the benzene ring have the highest reactivity. The methyl group of the furan ring has practically no effect on the rate of the process on account probably of the distance from the reacting bond. During trimethylsilylcyanation of the aldimines **1a-f** after hydrolysis and separation of the reaction mixtures by preparative liquid column chromatography the 1,2-addition products, i.e., the respective α-amino nitriles of N-(1-cyano-3-hetaryl-2-propenyl)trifluoromethylanilines **3a-f**, were obtained in all cases with yields of 57-85% (Scheme 1, Table 1). It should be noted that in contrast to trimethylsilylated azomethines

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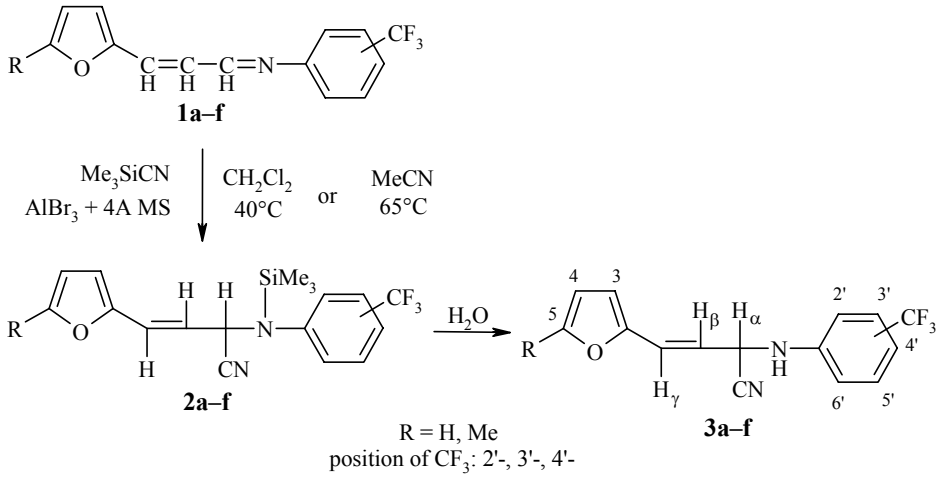
Scheme 1



hydrolysis of the N–Si bond in the intermediate products **2a-f** takes place under very mild conditions by the action of moist acetone at room temperature. Thus, in the investigated processes the trimethylsilyl cyanide adds selectively at the N=C bond of the initial imines without affecting the C=C double bond.

All the obtained compounds were oily or crystalline yellow substances, and their ^{1}H NMR spectra (Table 2) and the elemental analysis of the solid compounds (Table 1) corresponded to the structure of the required products. In the ^{1}H NMR spectra of all the synthesized nitriles **3a-f** the spin–spin coupling constant of the protons at the $H_\beta C=CH_\gamma$ double bond amounted to 15.4-15.8 Hz, indicating the *trans* position for the indicated hydrogen atoms.

The GLC mass spectra of compounds **3a-f** could not be recorded as a result probably of the thermal instability of the synthesized α-amino nitriles, as reflected in the loss of gaseous HCN by these molecules and the formation of the corresponding amines under the conditions of analysis.

In order to obtain additional information revealing the structure of the substances an investigation by 2D-COSY and ^{13}C NMR methods was undertaken for compound **3b**. The results fully supported the proposed structure of the final product (see Scheme 1).

TABLE 1. The Characteristics of the Reactions and the Products

Compound	R	Position of CF_3	T, °C/ Time, h (solvent)	Empirical formula (M_{calc})	Found, % / Calculated, %			mp, °C	Yield, %
					C	H	N		
3a	H	2'-	40/25, 65/6 (MeCN)	$C_{15}H_{11}N_2OF_3$ (292.26)	—	—	—	Oily liquid	71
3b	H	3'-	40/6 (CH_2Cl_2)	$C_{15}H_{11}N_2OF_3$ (292.26)	61.70 / 61.65	3.89 / 3.79	9.05 / 9.58	87-88	72
3c	H	4'-	40/4 (CH_2Cl_2)	$C_{15}H_{11}N_2OF_3$ (292.26)	61.50 / 61.65	3.74 / 3.79	9.36 / 9.58	136-137	85
3d	Me	2'-	40/15 (CH_2Cl_2)	$C_{16}H_{13}N_2OF_3$ (306.29)	—	—	—	Oily liquid	57
3e	Me	3'-	65/5 MeCN)	$C_{16}H_{13}N_2OF_3$ (306.29)	—	—	—	Oily liquid	70
3f	Me	4'-	40/3 (CH_2Cl_2)	$C_{16}H_{13}N_2OF_3$ (306.29)	62.47 / 62.74	4.34 / 4.28	8.90 / 9.15	115-116	75

TABLE 2. The ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shift ($CDCl_3$), δ, ppm, SSCC (*J*, Hz)					
	CH_3, s	NH, d	CHN, dd	CH_β, dd	CH_γ, dd	Ring protons
3a	—	4.51 (*J* = 7.8)	5.08 (*J* = 5.4, 7.8)	6.19 (*J* = 5.4, 15.7)	6.91 (*J* = 15.7)	6.42 (2H, s, H-3, H-4), 6.9-7.0 (2H, m, H-5', H-6'), 7.40 (1H, s, H-5), 7.5-7.6 (2H, m, H-3', H-4')
3b	—	4.53 (*J* = 8.6)	5.05 (*J* = 5.4, 8.6)	6.17 (*J* = 5.4, 15.6)	6.83 (*J* = 15.6)	6.40 (2H, s, H-3, H-4), 6.9-7.0 (2H, m, H-2', H-6'), 7.12 (1H, d, *J* = 8.0, H-5'), 7.35 (1H, s, H-5), 7.39 (1H, m, H-2')
3c	—	4.20 (*J* = 8.4)	5.09 (*J* = 5.3, 8.4)	6.20 (*J* = 5.3, 15.8)	6.86 (*J* = 15.8)	6.42 (2H, s, H-3, H-4), 6.81 (2H, d, *J* = 8.4, H-2', H-6'), 7.41 (1H, s, H-5), 7.51 (2H, d, *J* = 8.4, H-3', H-5')
3d	2.32	4.50 (*J* = 7.2)	5.06 (*J* = 5.2, 7.2)	6.12 (*J* = 5.2, 15.8)	6.80 (*J* = 15.8)	6.02 (1H, d, *J* = 3.0, H-4), 6.31 (1H, d, *J* = 3.0, H-3), 6.9-7.0 (2H, m, H-5', H-6'), 7.5-7.6 (2H, m, H-3', H-4')
3e	2.32	4.07 (*J* = 8.2)	5.05 (*J* = 4.8, 8.2)	6.10 (*J* = 4.8, 15.4)	6.77 (*J* = 15.4)	6.01 (1H, d, *J* = 3.1, H-4), 6.30 (1H, d, *J* = 3.1, H-3), 6.9-7.0 (2H, m, H-2', H-6'), 7.12 (1H, d, *J* = 7.4, H-5'), 7.35 (1H, m, H-2')
3f	2.31	4.20 (*J* = 8.8)	5.04 (*J* = 5.4, 8.8)	6.09 (*J* = 5.4, 15.6)	6.80 (*J* = 15.6)	6.01 (1H, d, *J* = 3.4, H-4), 6.29 (1H, d, *J* = 3.4, H-3), 6.75 (2H, d, *J* = 8.4, H-2', H-6'), 7.54 (2H, d, *J* = 8.4, H-3', H-5')

The ^{13}C NMR spectrum of compound **3b** contained the following chemical shifts, δ, ppm (SSCC, C–F, *J*, Hz): 47.18 C_α, 110.76 (4.0) C(2'), 111.18 and 111.70 C(3) and C(4), 116.68 (4.0) C(4'), 116.95 (1.1) C(5'), 117.04 C≡N 118.21 C(6), 123.31 C_β, 123.93 (272.2) CF_3, 130.07 C_γ, 131.85 (32.1) C(3'), 143.31 C(5), 144.67 C(1'), 150.35 C(2). The spectrum confirms the presence of the C_β=C_γ double bond and the presence of the N≡C substituent at the C_α atom. In addition, the recorded spectrum agrees with the conclusion reached for the structure of **3b** by means of the HOSE (Hierarchical Ordered Spherical Description of Environment) codes [8].

In order to establish the structure of compound **3f** conclusively single crystals were prepared, and X-ray crystallographic analysis was performed. A three-dimensional model of the molecule showing the designations of the atoms and the ellipsoids of the thermal vibrations is shown in Fig. 1. Table 3 give the principal bond lengths and bond angles. In the molecule of **3f** it is possible to distinguish two approximately planar fragments: The furan ring together with the C(7) and C(8) atoms and the phenyl ring with the N(12), C(9), C(10), and N(11) atoms. The C(7)–C(8)–C(9)–N(12) torsion angle, characterizing the mutual rotation of the planar fragments, is 117.1(8)°C. The results of the X-ray investigation indicate the *syn-trans* configuration for the compound, and this agrees with ^{1}H NMR data concerning the arrangement of the protons at the C_β=C_γ double bond.

In the structure of **3f** the fluorine atoms are randomly arranged, like the structures **5b** and **5c** in [3]. The *g* values for all six fluorine atoms are 0.5. In the crystal structure there is a forked hydrogen atom of the NH···N type with bond lengths 3.207(5)Å (N(12)–H(12)···N(11) = 148(4)°, H(12)···N(11) = 2.45(6)Å) and 3.136(5)Å (N(12)–H(12)···N(11) = 121(4)°, H(12)···N(11) = 2.61(6)Å). These lengths are somewhat longer than the statistical mean value for the length of a hydrogen bond of this type 2.98 Å [9]. Figure 2 shows a fragment of the molecular packing and indicates the positions of the hydrogen bonds in the crystal. The crystals of compound **3f** are centrosymmetric and contain equal amounts of the molecules of the *S*- and *R*-enantiomers.

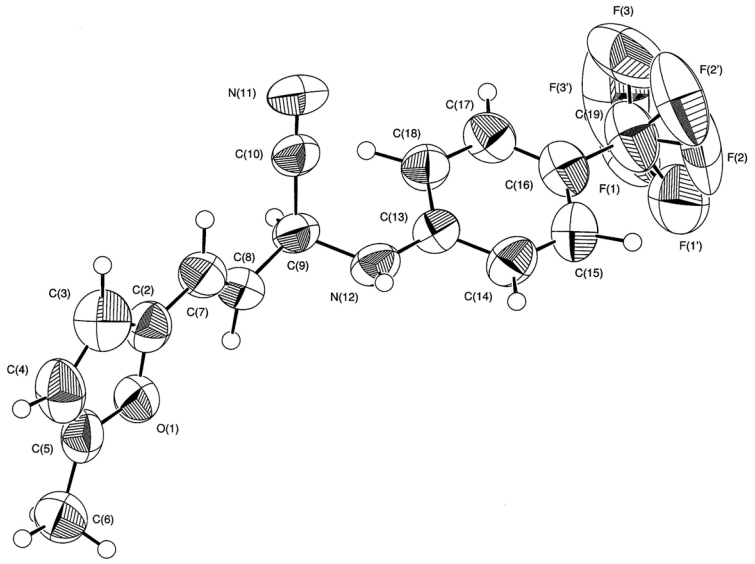


Fig. 1. A three-dimensional model of the molecule of N-[1-cyano-3-(5-methyl-2-furyl)-2-propenyl]-4-trifluoromethylaniline (**3f**).

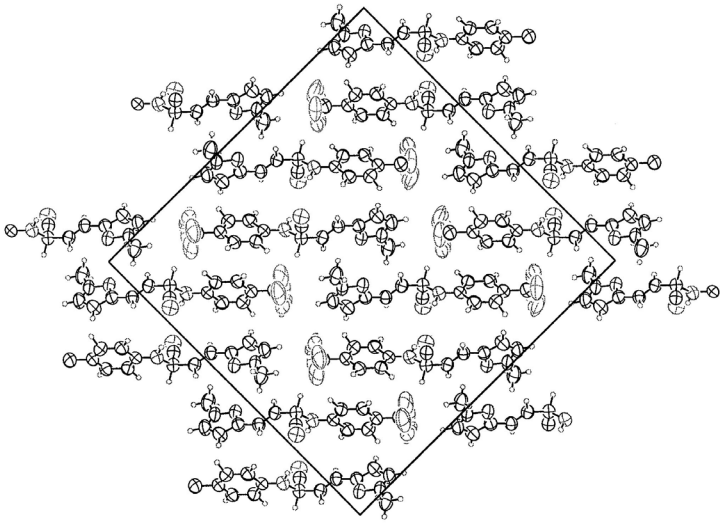


Fig. 2. A fragment of the crystal structure of compound **3f**.

TABLE 3. The Principal Bond Lengths (*d*) and Bond Angles (θ) in the Molecules of Compound **3f**

Bond	*d*, Å	Angle	θ, deg.	Angle	θ, deg.
1	2	3	4	5	6
O(1)–C(5)	1.371(5)	C(5)–O(1)–C(2)	106.6(4)	F(3)–C(19)–F(2')	61.4(14)
O(1)–C(2)	1.375(5)	C(13)–C(18)–C(17)	120.0(4)	F(3)–C(19)–F(3')	50.(2)
C(18)–C(13)	1.403(5)	N(12)–C(9)–C(10)	111.5(3)	F(1')–C(19)–F(2')	100.0(14)
C(18)–C(17)	1.389(6)	N(12)–C(9)–C(8)	110.5(3)	F(1')–C(19)–F(3')	113.(2)
C(9)–N(12)	1.451(5)	C(10)–C(9)–C(8)	111.4(3)	F(2')–C(19)–F(3')	102.(2)
C(9)–C(10)	1.489(6)	C(9)–N(12)–C(13)	123.6(3)	C(19)–F(2)–F(1')	64.0(11)

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were investigated on a Varian Mercury spectrometer at 200 and 50.3 MHz respectively for solutions in deuterochloroform with TMS as internal standard. The acetonitrile (special purity) was used without further purification, and the methylene chloride was distilled over phosphorus pentoxide. Trimethylsilyl cyanide (Aldrich) was used without further purification. Aluminum bromide (Fluka), 4A molecular sieves (VEB Laborchemie Apolda), and silica gel for column chromatography (Kieselgel 60, 0.063-0.200 mesh, Merck) were used. Analyses by TLC were conducted on Kieselgel 60 F_{254} (Merck) plates.

General Procedure for Trimethylsilylcyanation. A 5-cm^3-Pierce reaction tube was blown with argon, and dry solvent (2 ml), the initial amine (0.5 mmol), aluminum bromide (0.1 mmol), and the molecular sieves (0.5 g) were placed in it. Trimethylsilyl cyanide (0.6 mmol) was then added to the mixture with a syringe. The reaction was conducted at 40 or 65°C, and samples were taken periodically and analyzed by TLC and GLC-MS. At the end of the reaction (the reaction times are given in Table 1) the mixture was filtered and evaporated at reduced pressure (30°C/15 mm Hg), and acetone was added. A white precipitate of compounds containing the Me_3Si group separated. The mixture was filtered and evaporated, and ether was added. The mixture was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was separated by liquid chromatography on a column of silica gel with 9.5:0.2 benzene–ethyl acetate as eluent.

X-ray Crystallographic Analysis. Single crystals of compound (**3f**) were grown from a 1:3 mixture of benzene and ethyl acetate. The diffraction pattern was recorded at 20°C on an automatic Nonius Kappa CCD diffractometer (MoKα radiation) to $2\theta_{max} = 51°$. The crystals belong to the monoclinic system and have the following parameters: $a = 22.4388(8)$, $b = 5.9784(2)$, $c = 22.758(1)$ Å; $\beta = 90.745(1)°$; $V = 3052.7(2)$ Å^3; $d = 1.333$ g/cm^3; $Z = 8$; $F(000) = 1264$; $\mu = 0.11$ mm^{-1}. The structure was interpreted by the direct method and refined by full-matrix least-squares treatment in anisotropic approximation. The hydrogen atoms were found from a difference synthesis and refined anisotropically. Of 3050 symmetrically independent reflections 1536 reflections with $I > 3\sigma(I)$ were used in the calculations. The final divergence factor was 0.094. All the calculations were performed using software in [10, 11].

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