Chemistry of Heterocyclic Compounds, Vol. 39, No. 6, 2003

TRIMETHYLSILYLCYANATION OF HETEROCYCLIC ALDIMINES – DERIVATIVES OF 2-TRIFLUOROMETHYLANILINE

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The addition of trimethylsilyl cyanide to the CH=N bond of furan, thiophene, and pyridine azomethines in the presence of aluminum bromide as catalyst was studied. The effect of the CF_3 group in the aldimines produced by the condensation of O-, S-, and N-heteroaromatic aldehydes with 2-trifluoromethylaniline on the reaction and also other relationships of the investigated processes were studied. The corresponding furan, thiophene, and pyridine α-amino nitriles were synthesized.

Keywords: α-amino nitriles, heterocyclic Schiff bases, Lewis acid, trimethylsilyl cyanide, catalysis.

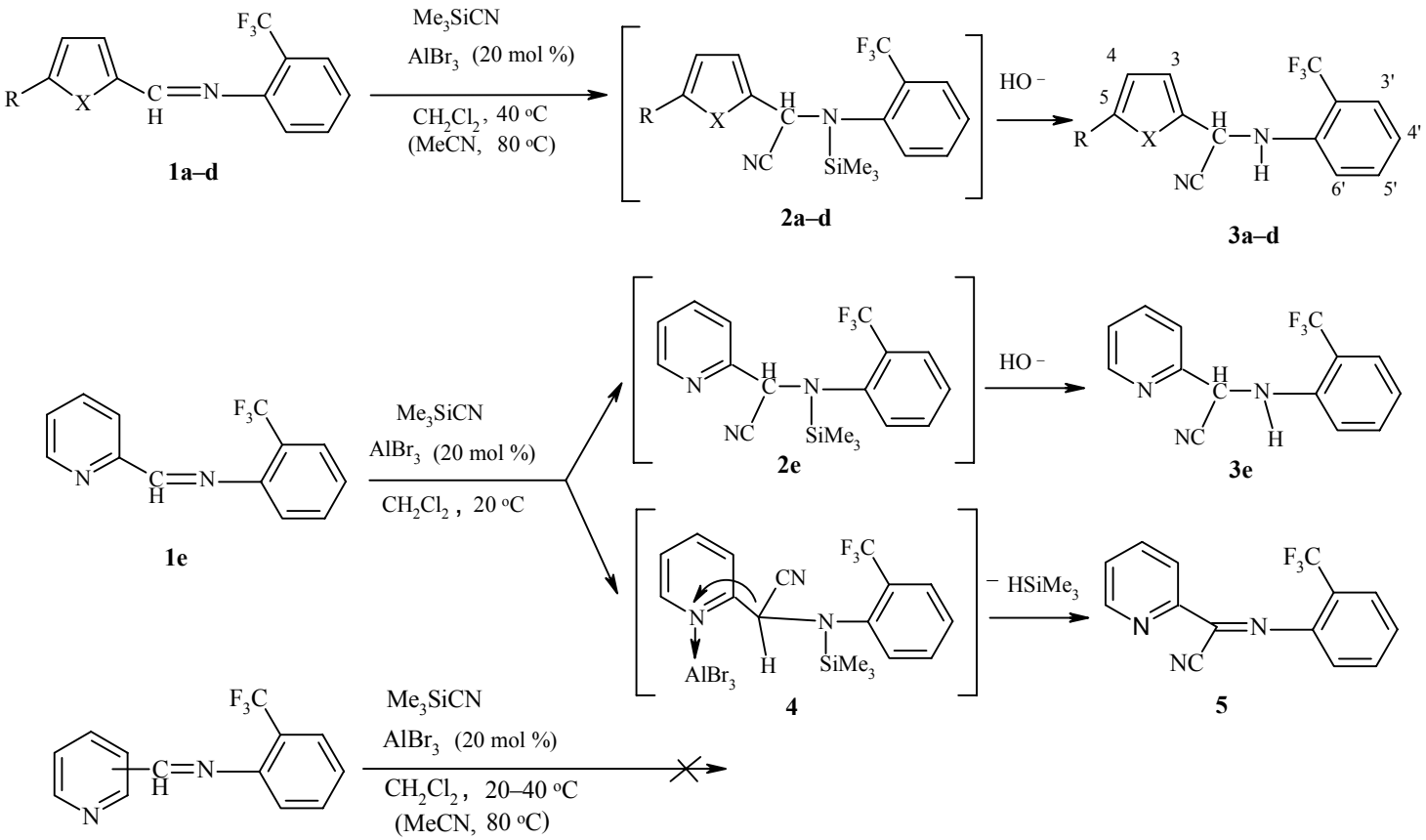
Recently we synthesized a series of new heterocyclic aldimines [1] by the condensation of furan, thiophene, and pyridine aldehydes with 2-trifluoromethylaniline. During investigation of the hydrosilylation of the azomethines it was found [2] that the 2-CF_3 group has a significant effect on the reactions. In the light of these results in the present work, which continues the previous investigations [3, 4] into the reaction of trimethylsilyl cyanide with various imines, we studied the trimethylsilylcyanation of a series of new aldimines.

The most active catalyst for the addition of trimethylsilyl cyanide to the CH=N bond of the various heterocyclic aldimines from the employed Lewis acids ($AlCl_3$, $AlBr_3$, YCl_3, $LaCl_3$, ZnI_2) is aluminum bromide [3, 4]. In addition, to prevent hydrolytic dissociation of the initial imines it is useful to employ zeolites as dehydrating medium. Therefore, in the present investigation we used $AlBr_3$ as catalyst, and the reaction was conducted in the presence of freshly calcined 4Å molecular sieves. The reaction of N-(hetarylmethylene)-2-trifluoromethylanilines **1a-g** (where Het = 2-furyl, 5-methyl-2-furyl, 2-thienyl, 5-methyl-2-thienyl, 2-, 3-, and 4-pyridyl). The reactions were conducted in methylene chloride at 20 or 40°C and also in benzene or acetonitrile at 80°C (substrate–silyl cyanide molar ratio 1:1.2, catalyst concentration 20 mole %).

During investigation of the reaction of the furan and thiophene substrates **1a-d** with trimethylsilyl cyanide it was found that compared with the 3- and 4-trifluoromethyl-substituted analogs [3] the imines with the CF_3 group at the second position of the aromatic ring are significantly less reactive – the processes hardly go at all in methylene chloride at room temperature, and the products are only formed after heating (40°C) for 24-51 h (Table 1). The reasons for the reduced reactivity are probably the steric hindrances arising on account of the presence of the bulky CF_3 group at the position adjacent to the reacting CH=N group. During the trimethylsilylcyanation of the aldimines **1a-d** after hydrolysis and separation of the reaction mixtures by liquid column chromatography in all cases the corresponding N-(hetarylcyanomethyl)-2-trifluoromethylanilines **3a-d** are obtained with preparative yields of 40-80% (Table 1, Scheme). The aldimine **1d** has the lowest reactivity. An attempt was made to increase the conversion of this substrate and the product yield by conducting the reaction at 80°C in more high-boiling solvents – benzene and acetonitrile. However, in the first case the

Latvian Institute of Organic Synthesis, Riga; e-mail: iovel@est.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 847-852, June, 2003. Original article submitted January 21, 2003.

0009-3122/03/3906-0721$25.00



1–3 a, c R = H, **b, d** R = Me; **a, b** X = O, **c, d** X = S

TABLE 1. The Conditions for the Trimethylsilylcyanation of the Imines **1a-g**

Initial aldimine	Solvent	Temperature, °C	Time, h	Conversion, %	Eluant	Reaction product	Yield, %
1a	CH_2Cl_2	40	24	95	PhH–EtOAc, 9.5 : 0.2	**3a**	80
1b	CH_2Cl_2	40	24	85	PhH–EtOAc, 9.5 : 0.2	**3b**	55
1c	CH_2Cl_2	40	27	80	PhH–EtOAc, 9.5 : 0.2	**3c**	50
1d	CH_2Cl_2	40	51	63	PhH–EtOAc, 9.5 : 0.2	**3d**	40
	PhH	80	26	10	—	—	
	MeCN	80	50	70	PhH–EtOAc, 9.5 : 0.2	**3d**	45
1e	CH_2Cl_2	20	13	90	CH_2Cl_2–MeOH, 9.5 : 0.2	**3e** **5**	40 30
1f	CH_2Cl_2	40	10	10	—	—	
	MeCN	80	45	15	—	—	
1g	CH_2Cl_2	20	8	~ 0	—	—	
	MeCN	80	54	18	CH_2Cl_2–MeOH, 9 : 1	—	

conversion did not exceed 10% as a result of probably of the poor solubility of the catalyst, while in the second prolonged heating only slightly improved the results on account possibly of partial coordination of the aluminum bromide with the acetonitrile. The reactivity of both furan substrates **1a**,**b** was higher than that of the

TABLE 2. The Mass Spectra of the Synthesized Nitriles

Com-pound	*m/z* (I_{rel}, %)*
3a	266 (20, M^+), 246 (10, $[M - HF]^+$), 240 (8, $[M - CN]^+$), 239 (22, $[M - HCN]^+$), 220 (7, $[M - HCN - F]^+$), 210 (5, $[M - HCN - HCO]^+$), 199 (5, $[M - Fur]^+$), 191 (4), 172 (4, $[M - HCN - Fur]^+$), 170 (5, $[M - HCN - CF_3]^+$), 152 (7), 145 (17, $[C_6H_4CF_3]^+$), 125 (9), 114 (9), 106 (100, $[FurCHCN]^+$), 95 (8), 78 (15), 75 (9), 69 (2, $[CF_3]^+$), 63 (8), 51 (24)
3b	280 (12, M^+), 254 (7, $[M - CN]^+$), 253 (35, $[M - HCN]^+$), 252 (13, $[M - HCN - H]^+$), 236 (2), 234 (2, $[M - CN - F]^+$), 218 (5, $[M - HCN - HF - Me]^+$), 210 (25, $[M - HCN - MeCO]^+$), 191 (5), 172 (5), 161 (14), 152 (5), 145 (23, $[C_6H_4CF_3]^+$), 125 (8), 121 (9), 120 (100, $[MeC_4H_2OCHCN]^+$), 95 (10), 75 (8), 69 (5, $[CF_3]^+$), 65 (14), 53 (13), 51 (15), 50 (10)
3c	282 (22, M^+), 255 (37, $[M - HCN]^+$), 254 (45, $[M - HCN - H]^+$), 236 (4), 234 (4, $[M - CN - F]^+$), 152 (6), 145 (25, $[C_6H_4CF_3]^+$), 122 (100, $[C_4H_3SCHCN]^+$), 114 (5), 105 (5), 95 (17), 91 (5), 84 (2, $[ThH]^+$), 77 (11), 69 (12, $[CF_3]^+$), 63 (7), 58 (7), 51 (7)
3d	296 (6, M^+), 269 (14, $[M - HCN]^+$), 268 (18, $[M - HCN - H]^+$), 161 (10), 145 (11, $[C_6H_4\text{-}CF_3]^+$), 137 (12), 136 (100, $[MeC_4H_2SCHCN]^+$), 125 (5), 109 (14), 95 (7), 83 (3), 69 (8, $[CF_3]^+$), 65 (6), 59 (5), 51 (7)
3e	277 (73, M^+), 256 (22, $[M - F - 2H]^+$), 231 (27, $[M - HCN - F]^+$), 208 (60, $[M - CF_3]^+$), 204 (12), 181 (100, $[M - HCN - CF_3]^+$), 179 (23), 154 (27), 152 (57), 132 (38, $[M - C_6H_4CF_3]^+$), 127 (13), 126 (28), 125 (17), 119 (20), 118 (48, $[PyCH_2CN]^+$) 107 (32), 105 (56), 102 (22), 95 (26), 80 (33), 79 (90, $[PyH]^+$), 78 (95, $[Py]^+$), 77 (25), 75 (21), 69 (28, $[CF_3]^+$), 64 (30), 63 (49), 62 (37), 52 (54), 51 (54), 50 (9), 39 (35), 38 (29)
5e	274 (5, $[M - H]^+$), 256 (4, $[M - F]^+$), 207 (16), 206 (100, $[M - CF_3]^+$), 181 (1), 154 (4), 145 (14, $[C_6H_4CF_3]^+$), 125 (7), 104 (2), 95 (9), 78 (10, Py^+), 75 (9), 69 (5, $[CF_3]^+$), 51 (14)

* The signals of the characteristic ions are indicated; Fur = furyl, Th = thienyl, and Py = pyridyl.

TABLE 3. The ^{1}H NMR Spectra of the Synthesized Nitriles

Compound	Chemical shifts ($CDCl_3$), δ, ppm; (SSCC, *J*, Hz)			
	CH_3, s	NH, d	CHCN, d	Ring protons
3a	—	4.82	5.55	6.45 (1H, dd, *J* = 1.8, *J* = 2.8, H-4); 6.61 (1H, dd, *J* = 2.8, H-3); 6.97 (2H, m, H-3', H-5'); 7.4-7.6 (3H, m, H-5, H-4', H-6')
		J = 7.8		
3b	2.32	4.78	5.47	6.01 (1H, m, *J* = 2.8, *J* = 0.6, H-4); 6.47 (1H, d, *J* = 2.8, H-3); 6.96 (2H, m, H-3', H-5'); 7.50 (2H, m, H-4', H-6')
		J = 7.6		
3c	—	4.80	5.69	6.9-7.0 (2H, m, H-3', H-5'); 7.07 (1H, dd, *J* = 5.0, *J* = 3.6, H-4); 7.3-7.4 (2H, m, H-3, H-5); 7.5-7.6 (2H, m, H-4', H-6')
		J = 8.4		
3d	2.49	4.75	5.60	6.70 (1H, d, *J* = 3.2, H-4); 6.9-7.1 (2H, m, *J* = 7.4, H-3', H-5'); 7.16 (1H, d, *J* = 3.2, H-3); 7.4-7.7 (2H, m, *J* = 7.4, H-4', H-6')
		J = 7.8		
3e	—	6.02	5.13	6.42 (1H, m, *J* = 8.2, H-3); 7.1 (2H, m, *J* = 8.4, H-3', H-5'); 7.40 (1H, m, *J* = 8.2, *J* = 4.4, H-5); 7.5 (2H, m, *J* = 8.4, H-4', H-6'); 7.60 (1H, dt, *J* = 8.2, *J* = 1.4, H-4); 8.70 (1H, m, *J* = 4.4, H-6)
		J = 5.4		
5e	—	—	—	7.21 (1H, d, *J* = 8.6, H-3'); 7.43 (1H, t, *J* = 8.6, H-5'); 7.53 (1H, m, *J* = 8.0, *J* = 5.2, *J* = 1.0, H-5); 7.67 (1H, t, *J* = 8.6, H-4'); 7.78 (1H, d, *J* = 8.6, H-6'); 7.91 (1H, dt, *J* = 8.0, *J* = 2.0, H-4); 8.29 (1H, dt, *J* = 8.0, *J* = 1.0, H-3); 8.83 (1H, m, *J* = 5.2, H-6)

thiophene compounds **1c**,**d**, while the introduction of a methyl group into the heterocycle reduced the activity both of the furan and of the thiophene azomethines. These data agree with the results obtained for the 3- and 4-CF_3-substituted isomeric heterocyclic aldimines [3].

During investigation of the trimethylsilylcyanation of the pyridine aldimines **1f**,**g** it was found that the reactivity of the β and γ isomers was extremely low; the conversion was low, and products could not be obtained either in methylene chloride or in acetonitrile at 40 and 80°C. Only the α-azomethine **1e** reacted at room temperature, and here two products were isolated, i.e., the expected α-aminonitrile N-(2-pyridylcyanomethyl)-2-trifluoromethylaniline **3e** and the unsaturated nitrile N-(2-pyridylcyanomethylene)-2-trifluoromethylaniline **5**. The last reaction path is uncharacteristic of furan and thiophene substrates, and it can therefore be supposed that the donor nitrogen atom of the pyridine ring takes part in the formation of the intermediate coordination structure **4e**, leading to cleavage of the C–H and C–Si bonds and the formation of the corresponding unsaturated product **5** (scheme). Similar relationships were observed during investigation of the trimethylsilylcyanation of other O-, S-, and N-heterocyclic aldimines [3, 4].

EXPERIMENTAL

The ^{1}H NMR spectra were investigated on Varian Mercury (200 MHz) and Bruker WH-90/DS (90 MHz) spectrometers with TMS as internal standard. The mass spectra were obtained on an HP 6890 GC/MS chromato-mass spectrometer with an HP-5 MS capillary column (30.0 m × 250 μ × 0.25 μ) with programmed temperature from 70 to 260°C (10 deg/min). Acetonitrile (special purity grade) was used without previous purification, and the other solvents were distilled before use (methylene chloride over P_2O_5, benzene over CaH_2). Trimethylsilyl cyanide (Aldrich) was used without further purification. Aluminum bromide (Fluka), molecular sieves 4Å (VEB Laborchemie Apolda), and silica gel for column chromatography (Kieselgel 60, 0.063-0.200 mesh, Merck) were used. Thin-layer chromatography was performed on Kieselgel 60 F_{254} plates (Merck).

Trimethylsilylcyanation (General Procedure). A 5-cm^3 Pierce reaction tube was blown with argon, and dry solvent (2 ml), the initial imine (0.5 mmol), $AlBr_3$ (0.1 mmol), and the molecular sieves (0.5 g) were placed in it. Then trimethylsilyl cyanide (0.6 mmol) was added to the mixture. The reaction was conducted at 20, 40, or 80°C, and samples were taken periodically and analyzed by TLC and GLC-MS. At the end of the reaction (see Table 1) the mixture was filtered and evaporated at reduced pressure at 30°C (15 mm Hg), and the ^1H NMR spectra were recorded. Hydrolysis was then performed with the addition of methanol (2.5 ml) and 10% aqueous solution of sodium bicarbonate (0.5 ml). The mixture was extracted with ether, the extract was dried over anhydrous sodium sulfate, and the mixture was then filtered and evaporated. The residue was separated by liquid chromatography on a column of silica gel with benzene–ethyl acetate as eluant for the furan and thiophene derivatives and methylene chloride–methanol for the pyridine derivatives.

All the obtained products (with the exception of the nitrile **3a**) were yellow oily substances. The elemental analysis of the solid α-aminonitrile of N-(2-furylcyanomethyl)-2-trifluoromethylaniline **3a** (mp 47-48°C) agreed with the calculated values. Found, %: C 58.63; H 3.39; N 10.11. $C_{13}H_9N_2OF_3$. Calculated, %: C 58.65; H 3.41; N 10.521. The compounds were characterized by the ^1H NMR and mass spectra, which corresponded to their structures (Tables 2 and 3).

The authors thank the Latvian Science Council for financial support (Grant No. 181).

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