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CYANOETHYLATION OF SUBSTITUTED 4-AZAFLUORENES. SYNTHESIS OF SPIRO-[4-AZAFLUORENE-9-CYCLOPENTENES]

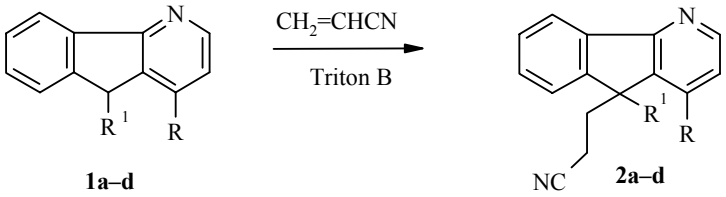
N. M. Mikhailova, A. N. Levov, S. V. Gozun, O. O. Timonina, F. Toze, and A. V. Varlamov

Cyanoethylation of 9-phenacyl(β-hydroxy-β-phenylethyl-, or acetamido)-4-azafluorenes under conditions of the Michael reaction occurs regioselectively at position 9. 1-Amino-4-azafluorene under these conditions forms 1-[N,N-di-(β-cyanoethyl)amino)]-(9-β-cyanoethyl)-4-azafluorene. The cyclization of 9-(β-cyanoethyl)-9-phenacyl-4-azafluorene has been carried out into 1'-cyano-2'-phenylspiro[4-aza-fluorene-9,4'-cyclopentene and 1'-imino-2'-hydroxybenzylidenespiro[4-azafluorene-9.3'-cyclopentane]-substituted in the five-membered fragment.

Keywords: azafluorene, spiroazafluorenecyclopentane, spiroazafluorene-cyclopentene, intramolecular cyclization, cyanoethylation.

4-Azafluorene is readily alkylated under the conditions of the Michael reaction with the formation of 9,9-di-(β-R-ethyl)-substituted derivatives, from which 4-azafluorenes spiroannelated at position 9 may be obtained [1]. Such a family of spiro compounds are of interest from the point of view of their potential biological activity. The behavior under Michael reaction conditions of azafluorenes having two reaction centers has not been studied.

In the present work the regiodirection of cyanoethylation under Michael reaction conditions of 9-phenacyl(β-hydroxy-β-phenylethyl-, or acetamido)-4-azafluorenes **1a-c** and 1-amino-4-azafluorene (**1d**) has been studied in the presence of Triton B. The synthesis of compounds **1c** and **1d** was described in [2, 3]. Azafluorene **1b** was obtained by the reduction of the 9-phenacyl derivative **1a** with lithium aluminum hydride in ether. The Michael reaction of azafluorenes **1a-d** may proceed both at position $C_{(9)}$, and at the methylene (or hydroxyl, amide) group of the substituent at atom $C_{(9)}$ or at the amino group in position 1.



1a–d **2a–d**

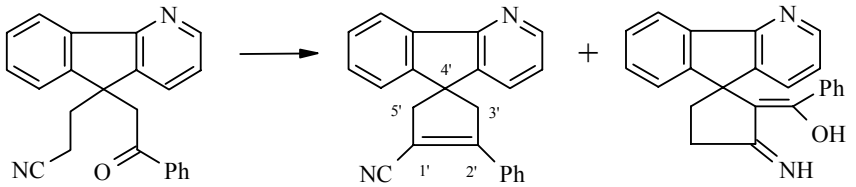
1 a-c R = H, **d** R = NH_2; **2 a-c** R = H, **d** R = $N(CH_2CH_2CN)_2$;
1, 2 a R^1 = CH_2COPh, **b** R^1 = $CH_2CH(OH)Ph$, **c** R^1 = NHAc, **d** R^1 = H

Russian People's Friendship, Moscow 117198; e-mail: avarlamov@sci.pfu.edu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1496-1501, October, 2006. Original article submitted June 14, 2002; revision submitted February 24, 2005.

Cyanoethylation of compounds **1a-c** proceeds regioselectively at the $C_{(9)}$ atom with the formation of β-cyano-substituted azafluorenes **2a-c** in 26-55% yield. Such a direction for the reaction is caused by the high stability of the intermediate $C_{(9)}$-carbanion due to delocalization of the negative charge through the azafluorene system. The cyanoethylation of compound **1d** occurs both at position 9 and at the amino group with the formation of tri-β-cyanoethyl-substituted compound **2d** (30% yield). In the absence of catalyst the cyanoethylation of compound **1d** at the amino group in boiling acetonitrile does not take place, which is probably caused by its low nucleophilicity. Cyanoethylation of compounds **1a-c** was accompanied by resinification. On cyanoethylation of compound **1a** 9-phenacylidene-4-azafluorene is formed in 5% yield, probably due to oxidation of the intermediate $C_{(9)}$-carbanion. Alkylation of the 9-phenacyl-substituted compound **1a** with acrylamide, or ethyl or butyl acrylates under conditions analogous to cyanoethylation was unsuccessful.

Reduction of the carbonyl group in compound **2a** to hydroxyl with sodium borohydride gave azafluorene **2b** in 60% yield which, unlike the product isolated on cyanoethylation of the single isomer **1b**, was a mixture (1:1.5) of two diastereomers (Table 1) according to data of ^{1}H NMR spectra.

Cyclization of compound **2a** was effected by the action of sodium ethylate with the aim of obtaining spiro compounds containing 4-azafluorene, which may be promising in a biological project. Under these conditions both possible directions of cyclization occur with the participation of the methylene groups of both CH_2CN and CH_2CO. 1'-Cyano-2'-phenylspiro[4-azafluorene-9,4'-cyclopentene] (**3**) and 2'-benzoyl-1'-imino-spiro[4-azafluorene-9-3'-cyclopentane] (**4**) (existing in the enolic form according to IR spectroscopy) were isolated chromatographically from the reaction mixture in equal yields (20%).



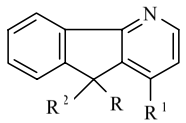
2a **3** **4**

A characteristic band was present in the IR spectra of compounds **2a-d** and **3** at 2218-2252 cm^{-1} for the stretching vibrations of the CN group. The stretching vibration of CO in compound **2a** corresponds to the band at 1670, and in compound **2c** at 1650 cm^{-1}. A broad band for a bonded hydroxyl at 3200 cm^{-1} was present in the IR spectrum of azafluorene **2b**. The absorption bands in the region of CO stretching vibrations were absent from the IR spectrum of spiro compound **4**. An intense band at 1603 cm^{-1} is caused by the presence of the –C(OH)=C–C=NH grouping and shows the existence of compound **4** in the enolic form, stabilized by a hydrogen bond. In the IR spectrum of compound **4** in $CHCl_3$ solution (concn. = 0.0296 M), together with a broad band for the stretching vibrations of NH and OH groups at 3291 cm^{-1}, narrow bands were displayed at 3491 and 3403 cm^{-1}, which may be assigned to the stretching vibrations of OH and NH groups linked by an intramolecular bond with one bridge. Molecular ion peaks of various intensity, corresponding to their empirical formulae, were observed in the mass spectra of compounds **1b**, **2a-c**, **3**, and **4**.

In the ^{1}H NMR spectra of all compounds (Table 1) signals were present for all the protons existing in the molecules. The signals of the pyridine fragment protons of the molecule H-1, 2, 3 are observed as three groups of signals as doublets of doublets with coupling constants J_{12} = 7.6-8.0, J_{13} = 1.5-1.8, and J_{23} = 4.9-5.8 Hz characteristic of pyridines. The methylene protons of the β-cyanoethyl group at $C_{(9)}$ are displayed as two multiplets at 1.36-1.80 (2H) and 2.36-3.22 ppm (2H).

In the ^{1}H NMR spectra of the phenacyl-substituted azafluorene **2a** the protons of the CH_2CN group are chemically nonequivalent and are observed as two multiplets at 2.55-2.80 and 2.90-3.10 ppm, each with an integral intensity of 1H. The methylene protons of the R^1 group on the $C_{(9)}$ atom appear in the spectra of compounds **2a,b** as a doublet of doublets (**2a**) and a multiplet (**2b**) with geminal coupling constants J = 16.8 and J = 14.4 Hz respectively.

TABLE 1. ^{1}H NMR Spectra of Substituted and Spiroannelated Azafluorenes **1-4**



Com-pound*	Chemical shifts, δ, ppm (SSCC, *J*, Hz)						
	R^1	H-2	H-3	H-5, m	H-6-8, m	R^2	R
1a	7.82 (dd, *J* = 7.6, *J* = 1.5)	7.14 (dd, *J* = 7.6, *J* = 4.9)	8.58 (dd, *J* = 1.5, *J* = 4.9)	8.10	7.65-7.35	4.77 (dd, *J* = 5.80, *J* = 8.20)	3.59 (dd, *J* = 18.0, *J* = 5.8, CH_A-$C_{(9)}$); 3.35 (dd, *J* = 18.0, *J* = 8.2, CH_B-$C_{(9)}$); 7.99 (m, C_6H_5)
maj-1b	7.25-8.19 (m)	7.19 (dd, *J* = 7.6, *J* = 5.2)	8.52 (dd, *J* = 5.2, *J* = 1.2)	9.06	9.19-7.25	4.20 (m)	4.93 (m, C<u>H</u>OH); 2.65-1.90 (m, CH_2-$C_{(9)}$); 8.19-7.25 (m, C_6H_5)
min-1b	7.25-8.19 (m)	7.08 (dd. *J* = 7.6, *J* = 5.2)	8.46 (dd, *J* = 5.2, *J* = 1.2)	7.95	8.19-7.25	4.20 (m)	4.93 (m, C<u>H</u>OH); 2.65-1.90 (m, CH_2-$C_{(9)}$); 8.19-7.25 (m, C_6H_5)
2a	7.29 (dd, *J* = 7.6, *J* = 1.5)	7.19 (dd, *J* = 7.6, *J* = 4.9)	8.60 (dd, *J* = 4.9, *J* = 1.5)	8.07	7.74-7.30	3.10-2.90 (m) 2.00-2.55 (m); 1.57 (m)	3.43 and 3.62 (AB) (*J* = 16.8, CH_2CO); 7.74-7.30 (m, C_6H_5)
maj-2b	7.37 (dd, *J* = 8.0, *J* = 1.8)	6.98 (dd, *J* = 8.0, *J* = 5.0)	8.46 (dd, *J* = 5.0, *J* = 1.8)	8.06	8.86-7.11	2.63-2.36 (m); 1.65-1.36 (m)	2.71 and 2.47 (m, *J* = 14.4, CH_2); 4.06 (m, CH); 1.54 (*J* = 4.0, OH); 8.86-7.11 (C_6H_5)
min-2b	7.87 (dd, *J* = 8.0, *J* = 1.8)	7.29 (dd, *J* = 8.0, *J* = 5.0)	8.57 (dd, *J* = 5.0, *J* = 1.8)	7.99	8.86-7.11	2.63-2.36 (m); 1.65-1.36 (m)	2.65 and 2.36 (m, *J* = 14.4, CH_2); 4.06 (m, CH); 1.64 (*J* = 4.0, OH); 8.86-7.11 (C_6H_5)
2c	8.24 (dd, *J* = 7.6, *J* = 1.5)	7.22 (dd, *J* = 7.6, *J* = 4.9)	8.60 (dd, *J* = 4.9, *J* = 1.5)	8.02	7.7-7.4	3.22 (m); 2.82 (m); 1.80 (t, *J* = 7.9)	5.86 (br. s, NH); 1.95 (s, Ac)
2d	—	6.45 (d, *J* = 5.8)	8.40 (d, *J* = 5.8)	8.02	7.30-7.50	2.50-2.30 (m); 1.59 (t)	4.80 (t, H-9); 2.90-2.60 (m, CH_2N)
3	7.79 (dd, *J* = 7.7, *J* = 1.5)	7.20 (dd, *J* = 7.7, *J* = 4.9)	8.60 (dd, *J* = 4.9, *J* = 1.5)	8.04	7.83-7.40	3.52, 3.42, 3.38 and 3.37 (4H, m, *J* = 16.5, *J* = 2.2); 7.83-7.40 (m, C_6H_5)	
4	7.55 (dd, *J* = 7.6, *J* = 1.5)	7.03 (dd, *J* = 7.6, *J* = 4.9)	8.36 (dd, *J* = 4.9, *J* = 1.5)	—*^{2}	7.45-7.25	3.15-2.85 and 2.30-2.20 (4H, m); 6.86-6.16 (m, C_6H_5)	

* maj is the major isomer, min the minor isomer.

*^{2} Due to the overlapping of signals it was not possible to determine the chemical shifts or coupling constants.

EXPERIMENTAL

The IR spectra were obtained on a IR-75 spectrometer in KBr disks. The mass spectra were recorded on a Varian MAT 112 instrument with direct insertion of samples into the ion source at an ionizing voltage of 70 eV. The ^{1}H NMR spectra of ~3% solutions of the synthesized substances in $CDCl_3$ were recorded at 30°C on a Bruker WP 200 (200 MHz) instrument, internal standard was TMS. Silufol UV 254 plates were used for TLC (visualizing with iodine vapor), Al_2O_3 of Brockmann activity grade I was used for column chromatography.

9-Phenacyl-4-azafluorene (1a). Zinc dust (1.85 g, 28.2 mmol) and ammonium acetate (2.17 g, 28.2 mmol) were added to a solution of 9-phenacylidene-4-azafluorene (4 g, 14.4 mmol) in a mixture (140 ml) of ethanol and 25% ammonia solution (1:1) and the mixture boiled for 4 h (check by TLC). The solution was decanted and cooled. The precipitated crystals were filtered off and washed with water. Compound **1a** (3.17 g, 79%) was obtained as colorless crystals; mp 104-106°C (hexane–ethyl acetate, 2:1), R_f 0.53 (hexane–ethyl acetate, 1:1). IR spectrum, ν, cm^{-1}: 1673 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 285 (41) $[M]^+$, 180 (71), 179 (25), 166 (29), 152 (13), 105 (100), 77 (51). Found, %: C 84.01; H 5.14; N 4.77. $C_{20}H_{15}NO$. Calculated, %: C 84.20; H 5.26; N 4.91. M 285.

9-(β-Hydroxy-β-phenylethyl)-4-azafluorene (1b). A fivefold excess of lithium aluminum hydride was added to a solution of compound **1a** (0.41 g, 1.44 mmol) in absolute ether (150 ml). The mixture was stirred for 4 h (check by TLC). The mixture was carefully decomposed with water, and extracted with ether. The extract was dried over $MgSO_4$. Compound **1b** (0.37 g, 92%) was obtained as light yellow crystals; mp 39-42°C, R_f 0.31 (hexane–ethyl acetate, 1:1). IR spectrum, ν, cm^{-1}: 3100-3500 (OH). Found, %: C 83.92; H 6.02; N 4.62. M^+ 287. $C_{20}H_{17}NO$. Calculated, %: C 83.62; H 5.92; N 4.88. M 287.

9-(β-Cyanoethyl)-9-phenacyl-4-azafluorene (2a). A solution of **1a** (3 g, 10.5 mmol), Triton B in alcohol (1.2 ml), and acrylonitrile (8.4 g, 158.5 mmol) in absolute benzene (120 ml) was stirred for 6 h at 20°C (check by TLC). The benzene was distilled off. The residue was chromatographed on aluminum oxide (1 × 20 cm), eluent hexane–ethyl acetate, 1:1. Compound **2a** (1.94 g, 55%) was eluted first as colorless crystals; mp 117-121°C (hexane–ethyl acetate, 1:1), R_f 0.42 (hexane–ethyl acetate, 1:2). IR spectrum, ν, cm^{-1}: 2252 (C≡N), 1670 (C=O). Found, %: C 81.96; H 5.12; N 8.38. M^+ 338. $C_{23}H_{18}N_2O$. Calculated, %: C 81.66; H 5.33; N 8.28. M 338. 9-Phenacylidene-4-azafluorene (0.2 g, 5%) was eluted next; mp 147-149°C (heptane) [4]. Found: M^+ 283. $C_{20}H_{13}NO$. Calculated: M 283.

9-(β-Cyanoethyl)-9-(β-hydroxy-β-phenylethyl)-4-azafluorene (2b). A. A solution of compound **1b** (0.64 g, 2.2 mmol), Triton B (0.25 ml), and acrylonitrile (1.42 g, 27 mmol) in absolute toluene (50 ml) was stirred at 0°C (check by TLC). Water was added, the organic layer was separated, and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$. After distilling off the solvent, the residue (0.6 g) was crystallized from hexane–ethyl acetate. Compound **2b** (0.2 g, 26%) was obtained as colorless crystals of mp 182-184°C, R_f 0.27 (hexane–ethyl acetate, 1:1). IR spectrum, ν, cm^{-1}: 2250 (C≡N), 3100-3300 (OH). Mass spectrum, *m/z* (I_{rel}, %): 340 (12) $[M]^+$; 233 (3.5); 194 (100); 180 (69); 107 (31); 77 (30). Found, %: C 81.40; H 5.91; N 8.40. $C_{23}H_{20}N_2O$. Calculated, %: C 81.18; H 5.88; N 8.24. M 340.

B. Sodium borohydride (0.025 g, 0.59 mmol) was added to a solution of **2a** (0.2 g, 0.59 mmol) in acetonitrile (20 ml) and the mixture was boiled for 1 h (check by TLC). The acetonitrile was distilled off in vacuum, water (20 ml) was added, and the mixture was extracted with ether (3 × 20 ml). The extract was dried over $MgSO_4$. After distillation of the ether, the residue (0.2 g) was crystallized from hexane–ethyl acetate, 1:1. Compound **2b** (0.12 g, 60%) was obtained as colorless crystals; mp 151-155°C, R_f 0.31 (hexane–ethyl acetate, 1:2). IR spectrum, ν, cm^{-1}: 2253 (C≡N), 3100-3300 (OH). Found, %: C 81.48; H 6.13; N 8.38. M^+ 340. $C_{23}H_{20}N_2O$. Calculated, %: C 81.18; H 5.88; N 8.24. M 340.

9-Acetamido-9-(β-cyanoethyl)-4-azafluorene (2c). A solution of compound **1c** (1 g, 4.5 mmol), Triton B (0.6 ml), and acrylonitrile (3.6 g, 67 mmol) in absolute benzene (100 ml) was stirred at 20°C for 4 h (check by TLC). Water (20 ml) was added, the organic layer was separated, and the aqueous layer was extracted with

chloroform. The combined extracts were dried over $MgSO_4$. After distilling off the solvents, the residue was crystallized from ethyl acetate-ethanol. Compound **2c** (0.65 g, 52%) was obtained as colorless crystals; mp 223-225°C, R_f 0.34 (2-propanol). IR spectrum, ν, cm^{-1}: 2250 (C≡N), 1670 (C=O), 3300, 3070 (NH). Found, %: C 73.80; H 5.50; N 15.16. M^+ 277. $C_{17}H_{15}N_3O$. Calculated, %: C 73.65; H 5.42; N 15.16. M 277.

1-[N,N-Di-(β-cyanoethyl)amino]-9-(β-cyanoethyl)-4-azafluorene (2d). A solution of compound **1d** (0.3 g, 1.65 mmol), Triton B (10 drops), and acrylonitrile (1 ml, 16.5 mmol) in absolute benzene (5 ml) was heated for 10 h at 45-50°C (TLC check). The benzene was distilled off, and the residue was chromatographed on aluminum oxide (1 × 30 cm), eluent was hexane–ethyl acetate, 1:1. Compound **2d** (0.16 g, 30%) was isolated as yellow crystals; mp 98-100°C (hexane–ethyl acetate, 1:1), R_f 0.4 (ethyl acetate). IR spectrum, ν, cm^{-1}: 2230 (C≡N). Mass spectrum, *m/z* (I_{rel}, %): 341 (35) $[M]^+$; 301 (30); 287 (100); 260 (15); 246 (30); 234 (40); 219 (22); 194 (20); 178 (150); 166 (10); 151 (15); 139 (5); 126 (5); 110 (10); 83 (15); 54 (30); 43 (25). Found, %: C 74.20; H 5.61; N 20.73. $C_{21}H_{19}N_5$. Calculated, %: C 73.90; H 5.57; N 20.53. M 341.

1'-Cyano-2'-phenylspiro[4-azafluorene-9,4'-cyclopentene] (3) and 1'-Imino-2'-hydroxybenzylidenespiro[4-azafluorene-9,3'-cyclopentane] (4). A solution of compound **2a** (0.5 g, 1.47 mmol) and sodium ethylate (0.3 g, 4.43 mmol) in absolute ethanol (40 ml) was boiled for 2 h (TLC check). The alcohol was distilled off, water (50 ml) was added to the residue, and the mixture was extracted with ether. The extract was dried over $MgSO_4$. After distilling off the ether, the residue was chromatographed on aluminum oxide (1 × 35 cm), eluent was hexane–ethyl acetate, 1:1. Spiro compound **3** (90 mg, 20%) was eluted first as colorless crystals; mp 143-145°C (hexane–ethyl acetate, 1:1), R_f 0.4 (ethyl acetate–hexane, 1:1). IR spectrum, ν, cm^{-1}: 2218 (C≡N). Mass spectrum, *m/z* (I_{rel}, %): 320 (100) $[M]^+$; 319 (75); 293 (10); 267 (12); 243 (15); 193 (8); 180 (12); 166 (22); 103 (9). Found, %: C 86.25; H 5.20; N 8.46. $C_{23}H_{16}N_2$. Calculated, %: C 86.25; H 5.0; N 8.75. M 320. Spiro compound **4** (0.1 g, 20%) was eluted next as yellowish crystals; mp 218-222°C (hexane–ethyl acetate, 1:1), R_f 0.30 (ethyl acetate–hexane, 1:1). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3433-3643 (OH), 3233-3553 (NH), 2276 and 3450 (NH···OH and bonded OH and NH). Mass spectrum, *m/z* (I_{rel}, %): 338 (58) $[M]^+$; 337 (100); 294 (10); 233 (42); 217 (12); 192 (10); 180 (12); 167 (5); 105 (22); 77 (40). Found, %: C 81.89; H 5.40; N 8.19. $C_{23}H_{18}N_2O$. Calculated, %: C 81.66; H 5.33; N 8.28. M 338.

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