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Cyanarylation of Fluorinated Benzonitriles with Terephthalonitrile Dianion

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Abstract

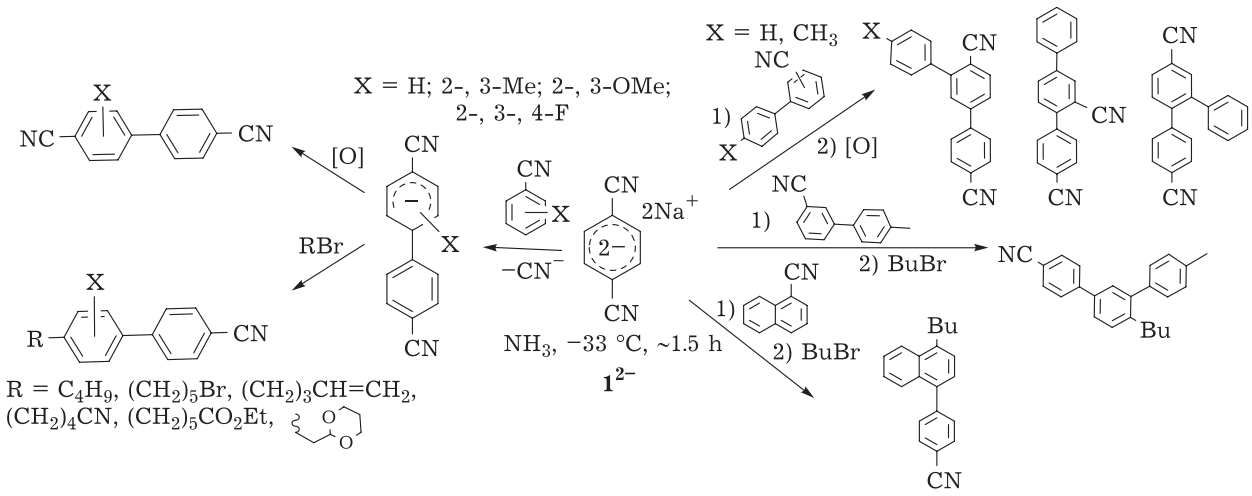
The dianion generated by the reduction of terephthalonitrile with sodium in liquid ammonia arylates di- and trifluorobenzonitrites replacing the *ortho*- and *para*-fluorine atoms, as well as the *para*-hydrogen atom, with the *para*-cyanophenyl fragment. The orientation of the interaction, the structure of the resulting fluorinated 4,4′- and 2,4′-dicyanobiphenyls, and reaction productivity are determined by the location and number of fluorine atoms in the starting benzonitrile.

Keywords: dicyanobiphenyls, cyanarylation, fluorinated benzonitriles, nucleophilic substitution of fluorine

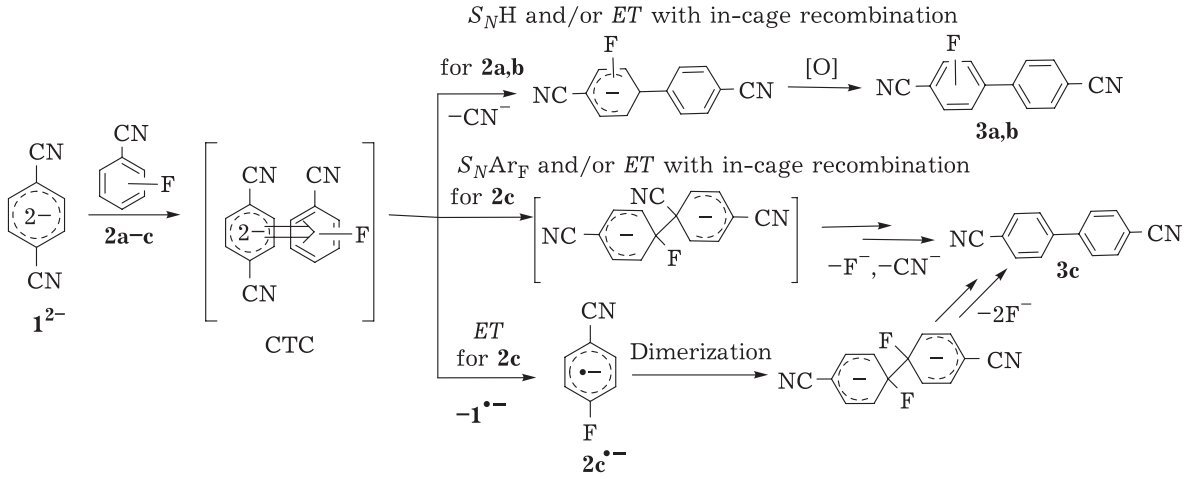
INTRODUCTION

Fluorinated cyanodiphenyls combining in their structure the privileged biphenyl fragment [1, 2] with the groups that are convenient for further nucleophilic modification [3] and heterocyclization [4–8], namely cyano groups and fluorine atoms, are widely used as universal precursors of functional materials and biologically active compounds [9–11]. The demand for such structural blocks stimulates the development of new methods to synthesize them. Previously we have proposed an economical non-catalytic one-pot approach to cyanobisarenes, involving the interaction of the disodium salt of terephthalonitrile dianion ($\mathbf{1}^{2-}$) with neutral aromatic nitrile in liquid ammonia. Dianion $\mathbf{1}^{2-}$ successfully arylates benzonitrile [12, 13], 2- and 3-cyanobiphenyls [14], 1-cyanonaphthalene [15], substituting hydrogen atom in the neutral substrate by *para*-cyanophenyl fragment. On this basis, convenient one-pot synthesis procedures have been developed for biphenyl-, terphenyl-, phenylnaphthalenecarbonitriles and their alkyl derivatives in good yields (30–90 %, Scheme 1).

It is demonstrated that dianion $\mathbf{1}^{2-}$ is productive with respect to monofluorinated benzonitriles: the cyanophenyl fragment of dianion $\mathbf{1}^{2-}$ enters the *para*-position of 2-fluoro- (**2a**), 3-fluoro- (**2b**) and 4-fluorobenzonitrile (**2c**), to form the corresponding 4,4′-dicyanobiphenyls **3a–c** as reaction products in the yield of 53, 32 and 35 %, respectively (Scheme 2) [13]. Biphenyls **3a** and **3b** are formed within the nucleophilic substitution of hydrogen atom and/or electron transfer, followed by in-cage recombination (ET mechanism). Unlike these compounds, 4,4′-dicyanobiphenyl **3c** may be a result of either substitution of the *para*-fluorine atom in **2c** by the cyanophenyl fragment of dianion $\mathbf{1}^{2-}$ or dimerization of anion radical $\mathbf{2c}^{\bullet-}$, which, in turn, may be formed due to electron transfer from dianion $\mathbf{1}^{2-}$ to fluorobenzonitrile **2c**.



Scheme 1. Cross-coupling of terephthalonitrile dianion $\mathbf{1}^{2-}$ with cyanoarenes, a long-living intermediate and products.



Scheme 2. Interaction of terephthalonitrile dianion $\mathbf{1}^{2-}$ with monofluorinated benzonitriles, possible reaction pathways, intermediates and products [13]. CTC – charge-transfer complex.

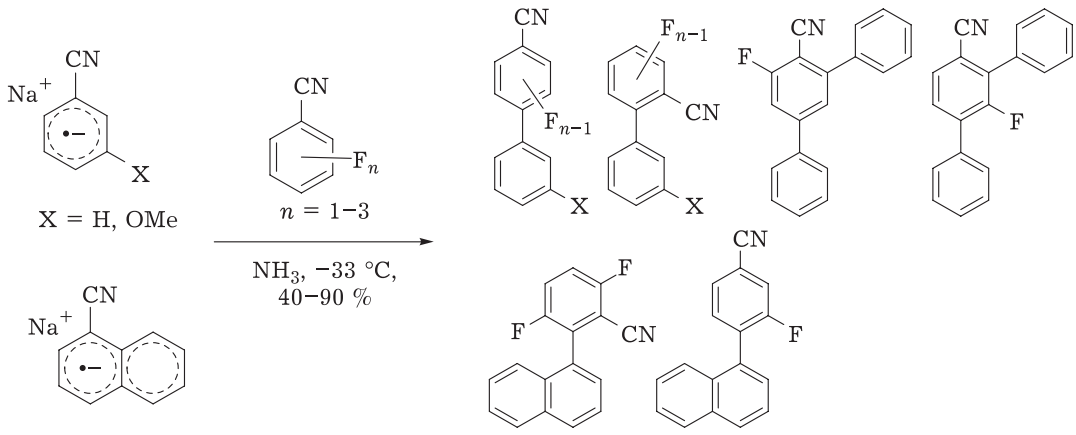
As a development of the approach involving anionic reduced forms of cyanoarenes for arylation of neutral aromatic compounds, we have demonstrated that anion radicals generated by the reduction of benzonitrile, 3-methoxybenzonitrile and 1-cyanonaphthalene by metal sodium in liquid ammonia efficiently substitute *ortho*- and *para*-fluorine atoms in fluorinated benzonitriles for 1-phenyl or 1-naphthyl fragment forming the corresponding monocyanobisarenes (Scheme 3) [16]. The revealed orientation of arylation and the absence of products in reactions with *meta*-fluorinated benzonitriles agree with the manifestation of nucleophilic properties by monocyanoarene anion radicals and with the occurrence of transformations within the mechanism of nucleophilic aromatic substitution of fluorine atom (S_NAr_F).

The goal of the present work is to establish the nature of reactivity and synthetic productivity of dianion $\mathbf{1}^{2-}$ in the aromatic substitution of fluorine atom for the interaction of this dianion with di- and trifluorobenzonitriles as examples.

EXPERIMENTAL

Materials

Liquid NH_3 was purified by dissolving metal Na in it, with subsequent distillation into a reaction vessel cooled to −70 °C. The oxidized surface was removed from metal Na under hexane layer. Terephthalonitrile (Acros Organics, USA) was purified by sublimation in vacuum. Fluorinated benzonitriles (Alfa Aesar, USA) were used with-



Scheme 3. Arylation of fluorinated benzonitriles by anion radicals of benzo- and naphthonitrile [16].

out additional purification. Diethyl ether, hexane, acetone were purified by distillation.

Investigation procedures

Generation of the disodium salt of terephthalonitrile dianion and its interaction with fluorinated benzonitriles. Metal Na (75 mg, 3.26 mmol) was introduced under stirring into the suspension of terephthalonitrile **1** (200 mg, 1.56 mmol) in liquid ammonia (~40 mL) in the atmosphere of evaporating ammonia at a temperature of −33 °C. The resulting dark brown suspension of the salt of dianion $\mathbf{1}^{2-}$ was stirred for 5 min, then fluorinated benzonitrile (2,4- (**2d**), 3,4- (**2e**), 2,6- (**2f**), 2,3- (**2g**) difluorobenzonitrile, 2,3,6-trifluorobenzonitrile **2h** 1.80 mmol) was added, and stirring continued for 1−1.5 h. The reaction mixture was brought in contact with air, Et_2O was added (25 mL), stirring continued till complete evaporation of ammonia. Water (25 mL) was added to the residue. The solid organic products were separated by filtering, washed with water (2 × 10 mL), diethyl ether (2 × 10 mL), dried in the air to the constant mass. The products from the liquid fraction were extracted with Et_2O (3 × 30 mL). The united ether extract was washed with water to neutral pH, dried with $MgSO_4$, and the solvent was evaporated. The composition of thus obtained solid fraction and ether-dissolved fraction was analyzed by means of ^1H, ^{19}F nuclear magnetic resonance (NMR) and gas chromatography − mass spectrometry (GC-MS). Cyanobiphenyls **3a**,**b**,**f**,**g**,**h** and **4h** were separated using preparative thin-layer chromatography (TLC) on glass plates with the fixed sorbent layer (silica gel 60 PF_{254} with gypsum added, Merck), elution was carried out with a mixture of solvents, hexane/diethyl ether at the volume ratio of 8 : 2. The fraction containing product **3h** and dinitrile **1** was additionally recrystallized from acetone. The spectral characteristics of 3-fluoro-[1,1′-biphenyl]-4,4′-dicarbonitrile **3a** and 2-fluoro-[1,1′-biphenyl]-4,4′-dicarbonitrile **3b**, obtained in the reaction of dianion $\mathbf{1}^{2-}$ with difluorobenzonitriles **2d** and **2e**, respectively, are in complete agreement with those reported by us previously [13].

3,5-Difluoro-[1,1′-biphenyl]-4,4′-dicarbonitrile (3f) [6−8]. Yield 82 mg (22 %), light-coloured powder. The ^1H NMR spectrum (400.13 MHz, $(CD_3)_2CO$, δ, ppm, *J*, Hz): 8.03 d (2H, $H^{3',5'}$, J = 8.8), 7.96 d (2H, $H^{2',6'}$, J = 8.8), 7.76 d (2H, $H^{2,6}$, J = 8.9). The ^{13}C NMR spectrum (100.61 MHz, $(CD_3)_2CO$, δ, ppm, *J*, Hz): 164.1 d (2C, $C^{3,5}$, J = 256.7), 148.1 t (1C, C^1, J = 10.3), 141.9 t (1C, $C^{1'}$, J = 2.4), 133.8 s (2C, $C^{3',5'}$), 129.2 s (2C, $C^{2',6'}$), 118.8 s (1C, CN at $C^{4'}$), 114.2 s (1C, CN at C^4), 112.1 d.d (2C, $C^{2,6}$, J = 3.8, 21.6), 109.7 s (1C, $C^{4'}$), 92.2 t (1C, C^4, J = 22.2). The ^{19}F NMR spectrum (376.46 MHz, $(CD_3)_2CO$, δ, ppm, *J*, Hz): 58.8 d (2F, J = 8.9). IR spectrum (KBr), ν, cm^{-1}: 2231 (C≡N). Found: m/z 240.0494 [M^+]. $C_{14}H_6N_2F_2$. Calculated: m/z 240.0489. Mass spectrum (EI), m/z (I_{rel}, %): 240 (100) [M^+], 213 (9).

6-Fluoro-[1,1′-biphenyl]-2,4′-dicarbonitrile (3g). Yield 87 mg (25 %), light-coloured powder, m. p. 154−155 °C. The ^1H NMR spectrum (400.13 MHz, $(CD_3)_2CO$, δ, ppm, *J*, Hz): 7.79 d (2H, J = 8.8), 7.61 m (3H), 7.53−7.48 m (1H), 7.46−7.41 (1H). The ^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 159.3 d (1C, C^6, J = 251), 136.1 s (1C, $C^{1'}$), 132.5 s (1C, $C^{3',5'}$), 131.2 d (1C, C^1, J = 17.9), 130.9 d (1C, C^4, J = 9.0), 130.8 d (2C, $C^{2',6'}$, J = 9.0), 129.8 d (1C, C^3, J = 4.0), 121.2 d (1C, C^5, J = 22.7), 118.4 s (1C, CN at $C^{4'}$), 116.8 d (1C, CN at C^2, J = 4.2), 114.0 d (1C, C^2, J = 4.2), 113.4 s (1C, $C^{4'}$). The ^{19}F NMR spectrum (376.46 MHz, $(CD_3)_2CO$, δ, ppm, *J*, Hz):

49.2 d.d (1F, F^6, J = 8.6, 5.3). IR spectrum (KBr), ν, cm^{-1}: 2227 (C≡N), 2239 (C≡N). Mass spectrum (EI), m/z (I_{rel}, %): 222 (100) [M+], 195 (10). Found, %: C 75.51, H 3.71, F 8.54, N 11.55. Calculated, %: C 75.67, H 3.18, F 8.55, N 12.61.

3,6-Difluoro-[1,1′-biphenyl]-2,4′-dicarbonitrile (3h). Yield 34 mg (9 %), whitle fine crystals. The ^{1}H NMR spectrum (500.13 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 8.01 d (2H, $H^{3',5'}$, J = 8.6), 7.84 d.m (2H, $H^{2',6'}$, J = 8.6), 7.75 t.d (1C, H^4, J = 9.3, 9.3, 4.6), 7.59 d.d.d (1C, H^5, J = 9.2, 8.4, 4.0). The ^{13}C NMR spectrum (125.75 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 161.0 d.d (1C, C^3 or C^6, J = 254, 2.8), 156.2 d.d (1C, C^6 or C^3, J = 245, 2.8), 136.5 d (1C, $C^{1'}$, J = 1.6), 133.4 s (2C, $C^{3',5'}$, 132.7 d.d (1C, C^1, J = 20.6, 1.0), 131.8 d (2C, $C^{2',6'}$, J = 1.9), 123.8 d.d (1C, C^4, J = 25.8, 9.3), 118.7(9) d.d (1C, C^5, J = 22.8, 9.1), 118.7(8) s (1C, CN at $C^{4'}$), 114.3 s (1C, $C^{4'}$), 112.7 d (1C, CN at C^2, J = 3.4), 103.4 d.d (1C, C^2, J = 18.2, 4.7). The ^{19}F NMR spectrum (282.36 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 51.8 d.d.d (1F, F^6, J = 16.6, 8.3, 4.3), 44.7 d.d.d (1F, F^3, J = 16.6, 9.0, 4.0). Mass spectrum (EI), m/z (I_{rel}, %): 240 (100) [M^+], 220 (10), 213 (15).

3,6-Difluoro-[1,1′-biphenyl]-2-carbonitrile (4h). Yield 45 mg (13 %), white powder. The ^{1}H NMR spectrum (300.13 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 7.68 t.d (1H, H^5, J = 9.2, 4.7), 7.57 m (5H, $H^{2',3',4',5',6'}$), 7.50 d.d.d (1H, H^4, J = 9.3, 8.4, 4.0). The ^{13}C NMR spectrum (125.75 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 160.1 d.d (1C, C^3, J = 252, 2.5), 155.5 d.d (1C, C^6, J = 252, 2.5), 133.7 d (1C, C^1, J = 21.4), 131.0 d (1C, $C^{1'}$, J = 1.3), 129.7 d (2C, $C^{2',6'}$, J = 2.5), 129.6 s (1C, $C^{4'}$), 128.6 s (1C, $C^{3',5'}$), 122.5 d.d (1C, C^5, J = 26.3, 9.4), 116.7 d.d (1C, C^4, J = 22.8, 9.1), 112.1 d (1C, CN, J = 3.8), 102.7 d.d (1C, C^2, J = 17.5, 5.0). The ^{19}F NMR spectrum (282.36 MHz, $(CD_3)_2CO$, δ, ppm, J, Hz): 51.3 d.d.d (1F, F^6, J = 13.0, 8.3, 4.6), 44.3 d.d.d (1F, F^3, J = 13.0, 9.0, 3.9). IR spectrum (KBr), ν, cm^{-1}: 2237 (C≡N). Mass spectrum (EI), m/z (I_{rel}, %): 215(100) [M^+],195 (10), 188 (15). Found: m/z 215.0539 [M^+]. $C_{13}H_7NF_2$. Calculated: m/z 215.0541.

Investigation methods

The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded with the help of AV 300 and Avance III 500 spectrometers (Bruker, Germany) for ~5 % solutions in acetone-d_6, the internal standard was admixture of proton-containing solvent or hexafluorobenzene, chemical shifts are shown in the δ scale. Signal assignment in NMR spectra was made relying on the data of heteronuclear correlations HSQC and HMBC, for fluorinated compounds also on the basis of the analysis of spin-spin coupling constants for $^{13}C-^{19}F$. IR spectra were obtained using a Vector-22 spectrometer (Bruker, Germany) in KBr. Identification of the components by means of GC-MS was carried out with the help of a G1081A chromatograph (Hewlett Packard, USA). The exact values of molecular ion masses were determined using a high-resolution mass spectrometer DFS (Thermo Scientific, USA). The data of elemental analysis were obtained with the help of automatic analyzer Carlo Erba 1106 (Italy).

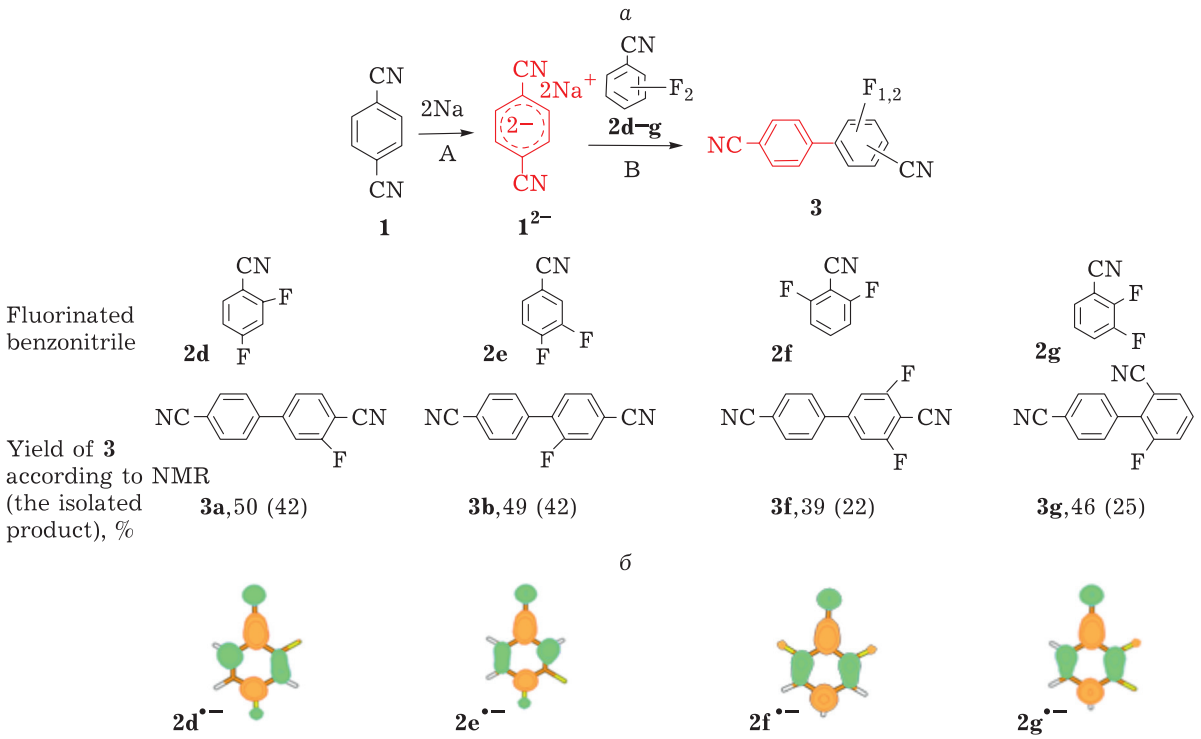
The electronic structure of anion radicals of benzonitriles **2d–g** was calculated by means of DFT B3LYP/6-31+G(d) using US GAMESS software package [17].

RESULTS AND DISCUSSION

Determination of the productivity of dianion $\mathbf{1}^{2-}$ in the aromatic substitution of fluorine atom requires expansion of the range of fluorinated substrates. Their choice is limited by the necessity to use liquid ammonia as solvent. Tetra- and pentafluorobenzonitrile are efficiently aminodefluorinated by the solvent [18], so the substrates in the present study were di- and trifluorobenzonitriles.

The formation of fluorinated dicyanobiphenyls **3** was detected for four of six isomeric difluorobenzonitriles (Scheme 4). Reactions participated by 2,4-difluoro- (**2d**) and 3,4-difluorobenzonitrile **2e** proceeded as the substitution of *para*-fluorine atom and resulted in the formation of monofluorodicyanobiphenyls **3a** and **3b**, respectively. In the case of 2,6-difluorobenzonitrile **2f**, substitution of *para*-hydrogen atom occurred, which led to 3,5-difluoro-4,4′-dicyanobiphenyl **3f**. Involvement of 2,3-difluorobenzonitrile **2g** into the reaction resulted in the formation of 6-fluoro-2,4′-dicyanobiphenyl **3g** due to the substitution of *ortho*-fluorine atom. The reactions of dianion $\mathbf{1}^{2-}$ with 2,5-difluoro- and 3,5-difluorobenzonitrile, which are less activated for nucleophilic substitution and contain acidic hydrogen atoms between the cyano group and fluorine atoms, resulted in multicomponent mixtures containing initial compounds and products with the masses corresponding (according to the data of GC-MS) to di- and trimers of initial compounds.

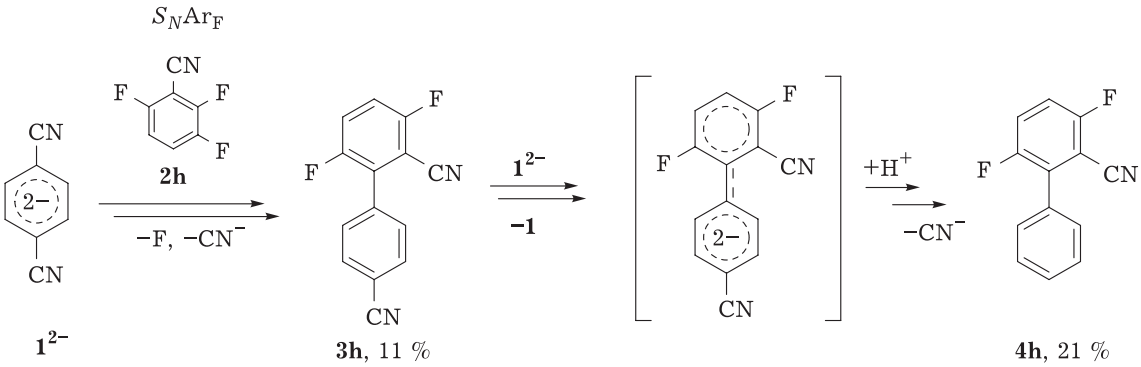
The structure of dicyanophenyls **3a**, **3b**, **3f** corresponds to binding at the *ipso*-position of dianion $\mathbf{1}^{2-}$ and the *para*-position of fluorinated



Scheme 4. *a* – Synthesis, interaction of terephthalonitrile dianion $\mathbf{1}^{2-}$ with difluorobenzonitriles and the yield of reaction products. Reaction conditions: A – liquid NH_3 (40 mL), dinitrile **1** (1.56 mmol), sodium (3.26 mmol), –33 °C, 5 min; B – fluorobenzonitrile **2d–g** (1.80 mmol), 1–1.5 h. *b* – Structure of the single occupied molecular orbital (SOMO) in the anion radical of benzonitrile **2d–g** (DFT B3LYP/6-31+G(d), US GAMESS).

substrate **2d–f**, which was previously observed in the reactions of $\mathbf{1}^{2-}$ with monofluorobenzonitriles **3a–c**. Similar orientation agrees with the structure of the single occupied molecular orbital (SOMO) of anion radicals of these benzonitriles (see Scheme 4). It should be stressed that the orientation of arylation, revealed in the reaction of dianion $\mathbf{1}^{2-}$ and difluorobenzonitrile **2f**, differs from the orientation of arylation of this difluorobenzonitrile by the anion radical of benzonitrile, realized as the substitution of fluorine atom [16]. This direction of arylation is observed in the reaction of $\mathbf{1}^{2-}$ with benzonitrile **2g**, leading to the formation of 2,4′-dicyanobiphenyl **3g**. This direction agrees with the orientation of reactions proceeding according to the $S_{RN}Ar_F$ mechanism, and to a less extent with the structure of anion radical $\mathbf{2g}^{\bullet-}$. For example, amination [19] and aryloxylation [20] of difluorobenzonitrile **2g** are oriented exactly at position 2. In general, the established orientation of cyanophenylation depends on the positions of fluorine atoms in the fluorinated neutral substrate **2** and may be due either to implementation of *ET* mechanism, followed by in-cage recombination of the anion radicals of terephthalonitrile and difluorobenzonitrile, or to the orientation observed in the reactions of fluorinated benzonitriles with carbon-centred and heteroatomic nucleophiles, proceeding according to the $S_{RN}Ar_F$ mechanism [18, 21–26]. This result should be considered as an indication for the dual (reductive and nucleophilic) nature of the reactivity of dianion $\mathbf{1}^{2-}$ with respect to fluorinated benzonitriles.

The interaction of dianion $\mathbf{1}^{2-}$ with trifluorobenzonitriles turned out to be less significant from the viewpoint of synthetic potential. Mainly reaction mixtures containing several products of cyanobiphenyl structure in low yields (10–20 % in total) were obtained. The best result turned out to be that of the reaction of dianion $\mathbf{1}^{2-}$ with 2,3,6-trifluorobenzonitrile **2h**. The major components of the reaction mixture, in addition to initial dinitrile **1** (47 %), are 2-(4-cyanophenyl)-3,6-difluorobenzonitrile (**3h**, 11 %) and 2-phenyl-3,6-difluorobenzonitrile (**4h**, 21 %). The structure of compound **3h** corresponds to the substitution of *ortho*-fluorine atom in nitrile **2h** (a similar orientation was realized in the reaction of dianion $\mathbf{1}^{2-}$ with difluorobenzonitrile **2g**). The appearance of monocyanobiphenyl **4h** may be connected with the reduction of initially formed dicyanobiphenyl **3h** by the dianion and subsequent protonation and decyanation processes (Scheme 5). It cannot be excluded that monocyanobiphenyl **4h** is a



Scheme 5. Interaction of the dianion of terephthalonitrile $\mathbf{1}^{2-}$ with 2,3,6-trifluorobenzonitrile **2h**, probable pathways to the formation of monocyanodiphenyl **4h**. Yields of products **3h** and **4h** according to the data of NMR spectroscopy.

product of the reaction of the anion radical of benzonitrile with trifluorobenzonitrile **2h** [16].

The reason of a decrease in the selectivity of the reactions of dianion $\mathbf{1}^{2-}$ with trifluorobenzonitriles is likely to be an increase in the contribution from the side transformations, competing with nucleophilic substitution of fluorine and hydrogen atoms. The side reactions of this kind may be electron transfer to sufficiently accepting fluorinated reagents and products. It is known that an increase in the number of fluorine atoms in benzonitrile causes an increase in its affinity to electron and decreases the stability of the anion radical formed after electron transfer [27, 28]. Fragmentation of the anion radicals of trifluorobenzonitriles, possible protonation of highly basic dianion with the formation of benzonitrile and further transformations participated by it may give rise to multicomponent mixtures of products in the reactions of dianion $\mathbf{1}^{2-}$ with trifluorinated benzonitriles.

CONCLUSION

The possibility to use terephthalonitrile dianion for *para*-cyanophenylation of 2,3-, 2,4-, 2,6- and 3,4-difluorobenzonitriles with the formation of fluorinated 4,4′- and 2,4′-dicyanobiphenyls is demonstrated. The interaction proceeds through a competition of the mechanisms of aromatic nucleophilic substitution of fluorine atom and electron transfer, followed by recombination of the formed anion radicals. The orientation of substitution of the activated *para*- and *ortho*-fluorine atoms, and *para*-hydrogen atom in benzonitrile by the *para*-cyanophenyl fragment of the dianion is determined by the positions of fluorine atoms in difluorobenzonitrile.

In spite of non-optimized and not very high yields of the target products, the approach to the synthesis involved in the present work may be competitive with the modern methods of catalytic cross-coupling because the former does not require expensive catalytic systems and organoelemental reagents, and exceeds the latter methods substantially in the availability of initial compounds. There are reasons to suppose that variation of the nature of counter-ion metal in the salt of dianion $\mathbf{1}^{2-}$ and reaction temperature affects the competition between nucleophilic and electron donor properties of the dianion. The transition from sodium salts to more nucleophilic potassium salts [29, 30] and a decrease in temperature [31, 32] might lead to an increase in the contribution from the nucleophilic activity and therefore to an increase in the selectivity of transformation in favour of the target products. These studies will be the subject of further work aimed at the development of the proposed approach to the synthesis.

The promising nature of the practical application of the synthesized fluorinated cyanobiphenyls is illustrated, for instance, by the use of difluorodicyanobiphenyl **3f** and its structural analogues in the synthesis of heterocyclic substituted biphenyls for optoelectronic devices [6–8, 33, 34]. In general, fluorinated 4,4′- and 2,4′-dicyanobiphenyls serve as universal precursors in the design of organometallic coordination polymers [35], organic semiconductors [36], biologically active compounds with broad range of action [2, 4, 5, 37, 38] and agricultural chemicals [39].

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