Tandem of nucleophilic substitution of hydrogen and cyclocondensation with participation of nitro group in the synthesis of fluorine-containing 3-amino-1,2,4-benzotriazines

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Reactions of 3-fluoro-1-nitrobenzenes with guanidine hydrochloride in THF in the presence of Bu^{t}OK gave isomeric 5- and 7-fluoro-containing 3-amino-1,2,4-benzotriazines.

Key words: nucleophilic substitution of hydrogen, *ipso*-substitution of fluorine, 3,4-difluoro-1-nitrobenzene, 4-R-3-fluoro-1-nitrobenzenes, fluorine-containing 3-amino-1,2,4-benzotriazines.

In the last two decades, the methodology of nucleophilic substitution of hydrogen (S_NH) have become an increasingly significant tool for the synthesis and functionalization of arenes and hetarenes.[1—4] The role of S_NH-reactions is especially important when the hydrogen atom (atoms) is (are) displaced by nucleophiles from the ring containing good leaving groups: this increases the functionalization index and provides prerequisites for design of fused structures.

In the present work, we present an application of S_NH-methodology to the synthesis of fluorinated 1,2,4-benzotriazines. Fused 1,2,4-triazines belong to an important class of biologically active compounds.[5] 3-Amino-1,2,4-benzotriazine 1,4-dioxide ("tirapazamine") is an efficient antitumor drug,[6] 3-amino-7-chloro-1,2,4-benzotriazine 1-oxide exhibits antimalaria properties,[7] and 3-dimethylamino-4*H*-[1,2,4]triazino[5,6-*b*]indazole shows a herbicidal activity.[8] 6,8-Dimethylpyrimido[5,4-*e*][1,2,4]-triazine-5,7(6*H*,8*H*)-dione ("fervenulin") is known to be a broad-spectrum antibiotic.[9] In recent years, fluoro-containing azaheterocycles are of particular interest because of close similarities in the electronic characteristics of fluoroarene and hydroxypyrimidine molecules (*e.g.*, 2,4-difluorotoluene and thymine) and of the tendency of fluorine atoms toward hydrogen bonding.[10] It suffices to be noted that some of the earlier obtained fluorinated 3-phenyl-1,2,4-benzotriazines exhibit a high antiviral activity.[11]

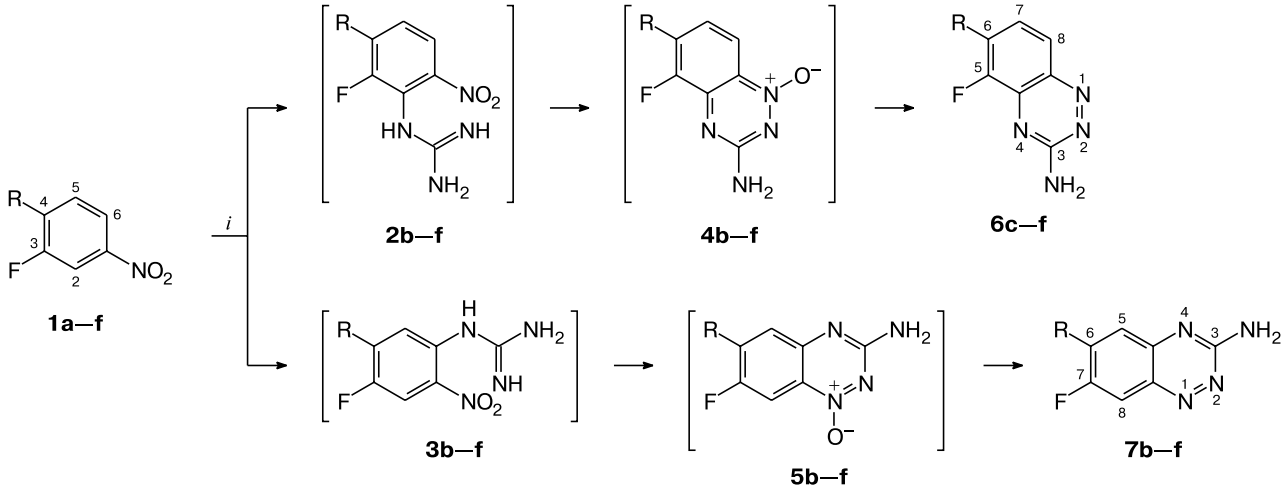
Methods for the synthesis of fused 1,2,4-triazines are usually complicated and include many steps and synthetic strategies vary with the starting reagents.[12] For instance, we have obtained fluorine-containing 3-phenyl-1,2,4-benzotriazines by intramolecular cyclization of 1-(3,4-difluorophenyl)-3,5-diphenylformazans synthesized, in turn, by diazotization of 3,4-difluoroaniline followed by azo coupling with benzaldehyde phenylhydrazone.[11]

3-Amino-1,2,4-benzotriazines have been reported[13] to be obtained by reactions of *o*-fluoronitrobenzenes with guanidine; the closure of the 1,2,4-triazine ring involves *ipso*-substitution of guanidine for the F atom and cyclocondensation *via* the nitro group. The use of S_NH-reactions with activated arenes for the synthesis of fused heterocycles has been recently elucidated in a review:[3] it follows therefrom that data on the synthesis of annulated 1,2,4-triazines by S_NH-reactions are very limited.[14—16] Fused 1,2,4-triazines can be obtained by S_NH-reactions of nitronaphthalenes and nitroquinolines followed by cyclocondensation with guanidines and amidines in the presence of Bu^{t}OLi (see Ref. 14). 3-Aryl-1,2,4-triazino[6,5-*f*]quinolines have been synthesized from nitroquinolines and arenecarbaldehyde hydrazones *via* nucleophilic substitution of the hydrazone residue for hydrogen followed by cyclocondensation.[15,16]

No route to fluorinated 3-amino-1,2,4-benzotriazines has been reported hitherto. Here we present a method for the synthesis of fluoro-containing 3-amino-1,2,4-benzotriazines by S_NH-reactions of fluoronitroarenes **1a—f** (Scheme 1). We used 3,4-difluoro-1-nitrobenzene (**1a**) and 4-R-3-fluoro-1-nitrobenzenes (**1b—f**) containing alcohol and cycloalkylimine residues as the starting reagents. 3,4-Difluoro-1-nitrobenzene (**1a**) was prepared

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1196—1200, July, 2006.

Scheme 1



R = F (**1a**), OMe (**1b**, **7b**), OPr^i (**1c**, **6c**, **7c**), OBu^t (**1d**, **6d**, **7d**), —N⟨⟩O (**1e**, **6e**, **7e**), —N⟨⟩ (**1f**, **6f**, **7f**)

i. $H_2NC(=NH)NH_2$, HCl, Bu^{t}OK, THF.

by nitration of *o*-difluorobenzene[17] and 4-R-3-fluoro-1-nitrobenzenes (**1b—f**) were synthesized by reactions of compound **1a** with appropriate alcohols in the presence of NaOH or with morpholine and pyrrolidine in DMSO. The structures of nitroarenes **1b—f** were confirmed by elemental analysis and ^{1}H NMR spectroscopy (Table 1).

A reaction of 3,4-difluoro-1-nitrobenzene (**1a**) with guanidine hydrochloride in dry THF in the presence of an excess of Bu^{t}OK at 60—62 °C for 6 h gave a mixture of 5- and 7-fluoro-substituted 3-amino-6-*tert*-butoxy-1,2,4-benzotriazines **6d** and **7d** in the ratio 3 : 1 (Table 2). On dilution of the mixture with water, triazine **6d** was isolated in 51% yield (Table 3). The minor product (triazine **7d**) was not isolated in the individual state. The structure of compound **7d** was determined from the ^{1}H NMR spectrum of the mixture containing, along with the characteristic signals for triazine **6d**, two doublets for the H(5) and H(8) protons with the *meta*- and *ortho*-constants at the F atom (see Table 2). A reaction of 4-*tert*-butoxy-3-fluoro-

Table 1. Yields, melting points, elemental analysis data, and ^{1}H NMR spectra (DMSO-d_6) of fluoro-containing nitroarenes **1b—f**

Compound	Yield (%)	M.p. /°C	Found (%) / Calculated			Molecular formula	^{1}H NMR δ (*J*/Hz)
			C	H	N		
1b	55	111—112	48.92 49.12	3.54 3.50	8.10 8.19	$C_7H_6FNO_3$	4.00 (s, 3 H, MeO); 7.35 (dd, 1 H, H(5), J = 8.9, $^4J_{H,F}$ = 8.5); 8.00 (dd, 1 H, H(6), J = 8.9, $^4J_{H,F}$ = 8.3); 8.09 (dd, 1 H, H(2), J = 7.6, $^3J_{H,F}$ = 10.7)
1c	70	32—33	54.30 54.27	5.07 5.03	7.04 7.04	$C_9H_{10}FNO_3$	1.38, 1.42 (both s, 3 H each, $\underline{Me}_2CHO$); 4.85 (m, 1 H, $Me_2C\underline{H}O$); 7.34 (dd, 1 H, H(5), J = 8.6, $^4J_{H,F}$ = 8.6); 7.98 (dd, 1 H, H(6), J = 8.5, J = 6.6); 8.02 (dd, 1 H, H(2), J = 7.6, $^3J_{H,F}$ = 10.5)
1d	21	Oil	56.11 56.33	5.71 5.63	6.62 6.57	$C_{10}H_{12}FNO_3$	1.43 (s, 9 H, Me_3CO); 7.47 (dd, 1 H, H(5), J = 8.7, $^4J_{H,F}$ = 8.6); 8.04 (dd, 1 H, H(6), J = 9.3, J = 8.6); 8.12 (dd, 1 H, H(2), J = 7.47, $^3J_{H,F}$ = 10.1)
1e	55	108—109	53.50 53.10	5.49 4.87	12.54 12.10	$C_{10}H_{11}FN_2O_3$	3.26 (m, 4 H, $N(CH_2)_2$); 3.76 (m, 4 H, $O(CH_2)_2$); 7.14 (dd, 1 H, H(5), J = 9.3, $^4J_{H,F}$ = 8.2); 7.94 (dd, 1 H, H(6), J = 11.1, J = 8.2); 7.98 (dd, 1 H, H(2), J = 8.8, $^3J_{H,F}$ = 11.4)
1f	60	137—138	58.11 57.14	5.10 5.24	13.39 13.33	$C_{10}H_{11}FN_2O_2$	1.99, 3.50 (both m, 4 H each, $(CH_2)_2$); 6.70 (dd, 1 H, H(5), J = 9.3, $^4J_{H,F}$ = 8.8); 7.83 (dd, 1 H, H(6), J = 9.5, J = 7.8); 7.88 (dd, 1 H, H(2), J = 9.1, $^3J_{H,F}$ = 11.9)

Table 2. Yields and ^{1}H NMR spectra (DMSO-d_6) of a mixture of isomeric 5- and 7-fluoro-containing 3-amino-1,2,4-triazines **6c—f** and **7c—f**

Compound	Product*	Yield (%)	^{1}H NMR, δ (*J*/Hz)	
			Triazines **6c—f** (5-F)	Triazines **7c—f** (7-F)
1a	**6d+7d** (3 : 1)	15	1.45 (s, 9 H, Me_3CO); 7.25 (dd, 1 H, H(7), J = 9.2, $^4J_{H,F}$ = 7.3); 7.40 (br.s, 2 H, NH_2); 7.95 (dd, 1 H, H(8), J = 9.2, $^5J_{H,F}$ = 1.5)	1.57 (s, 9 H, Me_3CO); 7.05 (d, 1 H, H(5), $^4J_{H,F}$ = 8.2); 7.35 (br.s, 2 H, NH_2); 7.85 (d, 1 H, H(8), $^3J_{H,F}$ = 10.1)
1c	**6c+7c** (2 : 1)	41	1.38 (s, 6 H, Me_2); 4.98 (m, 1 H, CHO); 6.95 (dd, 1 H, H(7), J = 9.6, $^4J_{H,F}$ = 7.4); 7.25 (br.s, 2 H, NH_2); 7.52 (dd, 1 H, H(8), J = 9.2, $^5J_{H,F}$ = 1.8)	1.33 (s, 6 H, Me_2); 4.98 (m, 1 H, CHO); 6.52 (d, 1 H, H(5), $^4J_{H,F}$ = 8.1); 6.82 (br.s, 2 H, NH_2),; 7.42 (d, 1 H, H(8), $^3J_{H,F}$ = 11.0)
1e	**6e+7e** (1 : 1)	36	3.65—3.90 (m, 8 H, $N(CH_2)_4O$); 7.18 (dd, 1 H, H(7), J = 9.5, $^4J_{H,F}$ = 8.2); 7.38 (br.s, 2 H, NH_2); 7.84 (dd, 1 H, H(8), J = 9.4, $^5J_{H,F}$ = 1.4)	3.25 (m, 4 H, $N(CH_2)_2$); 3.42 (m, 4 H, $O(CH_2)_2$); 6.78 (dd, 1 H, H(5), $^4J_{H,F}$ = 8.4); 7.40 (br.s, 2 H, NH_2); 7.64 (d, 1 H, H(8), $^3J_{H,F}$ = 13.2)
1f	**6f+7f** (3 : 1)	60	2.00 (m, 4 H, $(CH_2)_2$); 3.59 (m, 4 H, $(CH_2)_2$); 6.68 (dd, 1 H, H(7), J = 9.2, $^4J_{H,F}$ = 8.8); 7.85 (dd, 1 H, H(8), J = 9.4, $^5J_{H,F}$ = 1.4)	2.04 (m, 4 H, $(CH_2)_2$); 3.55 (m, 4 H, $(CH_2)_2$); 6.33 (d, 1 H, H(5), $^4J_{H,F}$ = 8.1); 7.15 (br.s, 2 H, NH_2), 7.85 (d, 1 H, H(8), $^3J_{H,F}$ = 9.6)

* Reaction conditions: 60—62 °C, 6 (**1a,c**) and 12 h (**1e,f**). The molar ratio of the products is given in parentheses.

Table 3. Reaction conditions and the yields, melting points, elemental analysis data, mass spectra, and ^{1}H NMR spectra (DMSO-d_6) of fluoro-containing 3-amino-1,2,4-benzotriazines **6d,e** and **7b**

Compound	*T*/°C (τ/h)*	Yield (%)	M.p./°C (R_f)**	Found / Calculated (%)			Molecular formula (*M*)	MS, *m*/*z* (I_{rel} (%))	^{1}H NMR, δ (*J*/Hz)
				C	H	N			
6d	60—62 (6)	51	232—233 (0.85)	55.71 55.92	5.56 5.50	23.66 23.70	$C_{11}H_{13}FN_4O$ (236.24)	236 $[M]^+$ (6), 221 $[M]^+$ (14), 180 $[M]^+$ (5), 152 $[M]^+$ (100)	1.41 (s, 9 H, Me_3CO); 7.30 (dd, 1 H, H(7), J = 9.2, $^4J_{H,F}$ = 7.5); 7.85 (br.s, 2 H, NH_2); 7.98 (dd, 1 H, H(8), J = 9.2, $^5J_{H,F}$ = 1.7)
6e	60—62 (12)	51	234—235 (0.87)	52.38 53.01	4.87 4.81	27.62 28.11	$C_{11}H_{12}FN_5O$ (249.1)	249 $[M+1]^+$ (100), 221 $[M]^+$ (84), 183 $[M]^+$ (2), 163 $[M]^+$ (38)	3.31 (m, 4 H, $N(CH_2)_2$); 3.82 (m, 4 H, $O(CH_2)_2$); 6.61 (dd, 1 H, H(7), J = 9.6, $^4J_{H,F}$ = 8.1); 7.81 (dd, 1 H, H(8), J = 9.6, $^5J_{H,F}$ = 1.8); 13.2 (br.s, 2 H, NH_2)
7b	25 (24)	29	198—200 (0.88)	49.82 49.48	3.72 3.60	29.02 28.85	$C_8H_7FN_4O$ (194.15)	194 $[M]^+$ (2), 180 $[M]^+$ (44), 152 $[M]^+$ (100)	4.08 (s, 3 H, MeO); 6.98 (d, 1 H, H(5), $^4J_{H,F}$ = 8.2); 7.13 (br.s, 2 H, NH_2); 7.76 (d, 1 H, H(8), $^3J_{H,F}$ = 10.5)

* Reaction conditions.
** Dichloromethane—ethanol (8 : 1) as an eluent.

1-nitrobenzene (**1d**) with guanidine under analogous conditions afforded triazine **6d** in 53% yield.

The results obtained suggest that the reaction of 3,4-difluoro-1-nitrobenzene (**1a**) involves *ipso*-substitution of the F atom that is *para* to the nitro group. The following competitive S_N^H-processes at positions 2 and 6 give guanidinonitrobenzenes **2d** and **3d**. Atmospheric oxygen acts as an oxidant in this reaction, because an analogous reaction does not occur under argon. Then, an intramolecular nucleophilic attack on the nitro group gives rise to 1,2,4-triazine *N*-oxides **4d** and **5d** whose reduction finally yields 3-amino-1,2,4-benzotriazines **6d** and **7d**.

It should be noted that the reaction of 3-fluoro-4-methoxynitrobenzene (**1b**) with guanidine under analogous conditions is accompanied by resinification of the reaction mixture. This reaction under milder conditions (25 °C, 24 h) mainly gave triazine **7b** isolated in 29% yield by precipitation with water. The minor compound (triazine **6d**) was isolated in 23% yield by extraction with CH_2Cl_2. This is the product of transalkoxylation by

Bu^{t}OK, which was confirmed by ^{1}H NMR, MS, and TLC data (see Table 3). In a reaction of 3-fluoro-4-isopropoxynitrobenzene (**1c**) with guanidine under analogous conditions at room temperature, the starting compound was recovered. The reaction at 60—62 °C for 6 h gave an oily mixture inseparable by column chromatography. Triazines **6c** and **7c** (R = OPr^i) obtained in the ratio 2 : 1 were identified from the ^{1}H NMR spectra (see Table 2).

A reaction of 3-fluoro-4-morpholino-1-nitrobenzene (**1e**) with guanidine (60—62 °C, 6 h) yielded a 1 : 1 mixture of triazines **6e** and **7e**; after a 12-h reaction under the same conditions, 3-amino-5-fluoro-6-morpholino-1,2,4-benzotriazine (**6e**) was isolated in 51% yield by precipitation with water from a 2 : 1 mixture of the isomers. Triazines **6f** and **7f** obtained in the ratio 3 : 1 from 3-fluoro-1-nitro-4-pyrrolidinobenzene (**1f**) were identified from the ^{1}H NMR spectrum of the mixture (see Table 2).

The structures of triazines **6c—f** and **7b—f** were determined from elemental analysis, ^{1}H NMR, and MS data. Signals for the F atoms in the products were assigned from the coupling constants $^nJ_{F,H}$. The ^{1}H NMR spectra of compounds **6c—f** show a signal for the H(7) proton at δ 6.61—7.31 as a characteristic doublet of doublets and a signal for the H(8) proton at δ 7.52—8.20 with the vicinal constant $^3J_{H(7),H(8)}$ and the constants $^4J_{H(7),F(5)}$ and $^5J_{H(8),F(5)}$ at the F atom. In contrast, in the spectra of triazines **7b—f**, a signal for the H(5) proton appears as a doublet at δ 6.30—7.05, while a signal for the H(8) proton appears as a doublet at δ 7.42—7.85, both having only the coupling constants $^4J_{H(5),F(7)}$ and $^3J_{H(8),F(7)}$ at the F atom (see Tables 2 and 3).

The assumption of the formation of the 1,2,4-triazine ring through the corresponding *N*-oxides is based on MS data. The mass spectra of a mixture of morpholino-1,2,4-benzotriazines **6e** and **7e** contain the molecular ion peaks $[M]^+$ of *N*-oxides **4e** and **5e** with *m/z* 265 (I_{rel} = 7%). For a mixture of pyrrolidino-1,2,4-benzotriazines **6f** and **7f**, the molecular ion peaks $[M]^+$ of *N*-oxides **4f** and **5f** appear with *m/z* 249 (I_{rel} = 6%). We failed to isolate the 1,2,4-triazine *N*-oxides since the *N*-oxide bond undergoes easy *in situ* reduction by an excess of Bu^{t}OK.

Reactions with nitroarenes containing fragments of primary amines (methylamine, ethylamine, cyclohexylamine, and monoethanolamine) did not give the corresponding 3-amino-1,2,4-benzotriazines. Apparently, this is due to the insufficient electrophilicities of fluoro-containing nitrobenzenes, which hinders the nucleophilic substitution of the guanidino group for hydrogen.

Thus, we carried out for the first time a tandem of S_N^H-reactions and cyclocondensation with the participation of nitro group for fluoro-containing nitroarenes as a route to novel 5- and 7-fluoro-containing 3-aminobenzo-1,2,4-triazines. Competitive S_N^H-processes in 4-R-3-fluoro-1-nitrobenzenes afford 5-fluoro- or 7-fluoro-1,2,4-triazine as the major product, depending on the substituent R and the reaction conditions.

Experimental

^{1}H NMR spectra were recorded on Bruker WP-250 (250.13 MHz) and Bruker DRX-400 spectrometers (400.13 MHz) with Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT-311A spectrometer (accelerating voltage 3 kV, ionizing electron energy 70 eV, direct inlet probe). The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in $CHCl_3$—ethanol (4 : 1) and CH_2Cl_2—ethanol (8 : 1). The characteristics of the compounds obtained are summarized in Tables 1—3.

3,4-Difluoro-1-nitrobenzene (1a). *o*-Difluorobenzene (172 g, 1.5 mol) was added dropwise to a stirred, ice-cooled nitrating mixture (prepared from HNO_3 (d = 1.36, 195 mL) and H_2SO_4 (d = 1.84, 225 mL)) so that the reaction temperature was no higher than 60—70 °C. The reaction mixture was stirred at 60—70 °C for 6 h, cooled to 25 °C, and poured onto finely crushed ice and water (350 mL). The organic layer was separated, the product from the mother liquor was extracted with $CHCl_3$ (2×50 mL), and the extract was washed with water (100 mL), 10% Na_2CO_3, and again with water to pH 7. The extracts in chloroform were combined with the organic layer, dried over $CaCl_2$, and concentrated in a rotary evaporator to an oily yellow residue. The yield of compound **1a** was 217 g (91%), n_D^{20} = 1.5088.

Synthesis of substituted 3-fluoro-1-nitrobenzenes 1b—d (general procedure). Finely divided NaOH (48 mmol) was dissolved with heating in stirred DMSO (100 mL). An appropriate alcohol (13 mmol) in DMSO (10 mL) and then 3,4-difluoro-1-nitrobenzene (**1a**) (13 mmol) were added with cooling and stirring. The reaction mixture was stirred at 25 °C for 1 h, poured into ice water (70 mL), and acidified with 10% HCl to pH 3—4. The precipitate that formed was filtered off and recrystallized from ethanol.

Synthesis of substituted 3-fluoro-1-nitrobenzenes 1e,f (general procedure). An appropriate amine (2.1 mmol) in DMSO (2 mL) was added in portions to a stirred solution of 3,4-difluoro-1-nitrobenzene (**1a**) (2 mmol) in DMSO (2 mL). The reaction mixture was heated on a water bath with stirring for 2 h and then cooled. Ice water (70 mL) was added and the precipitate was filtered off and recrystallized from ethanol.

3-Amino-6-*tert*-butoxy-5-fluoro-1,2,4-benzotriazine (6d). ***A.*** Potassium *tert*-butoxide (1.88 g, 17 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.38 g, 4 mmol) was added. After 10 min, a solution of compound **1a** (0.3 g, 2 mmol) in dry THF (10 mL) was added to the resulting suspension. The reaction mixture was stirred at 60—62 °C for 6 h, cooled, and poured into ice water (100 mL). The yellow precipitate that formed was filtered off, dried, and recrystallized from ethanol. The yield of triazine **6d** was 0.23 g (51%).

B. Potassium *tert*-butoxide (1.34 g, 12 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.27 g, 2.8 mmol) was added. After 10 min, a solution of 4-*tert*-butoxy-3-fluoro-1-nitrobenzene (**1d**) (0.3 g, 1.4 mmol) in THF (10 mL) was added to the resulting suspen-

sion. The reaction mixture was stirred at 60—62 °C for 6 h. Triazine **6d** was isolated analogously. The yield was 0.18 g (53%).

3-Amino-7-fluoro-6-methoxy-1,2,4-benzotriazine (7b). Potassium *tert*-butoxide (0.8 g, 7.3 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.16 g, 1.7 mmol) was added. After 10 min, a solution of 3-fluoro-4-methoxynitrobenzene (**1b**) (0.15 g, 0.9 mmol) in dry THF (15 mL) was added to the resulting suspension. The reaction mixture was stirred at 25 °C for 24 h and poured into water (100 mL). The dark yellow precipitate of triazine **7b** that formed was filtered off, dried, and recrystallized from ethanol. Organic material from the filtrate was extracted with CH_2Cl_2 and the extract was dried over $CaCl_2$ and concentrated. The yield of 3-amino-6-*tert*-butoxy-5-fluoro-1,2,4-benzotriazine (**6d**) was 0.05 g (29%).

3-Amino-5-fluoro-6-isopropoxy-1,2,4-benzotriazine (6c) and 3-amino-7-fluoro-6-isopropoxy-1,2,4-benzotriazine (7c). Potassium *tert*-butoxide (0.90 g, 8 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.20 g, 2.1 mmol) was added. After 10 min, a solution of 3-fluoro-4-isopropoxynitrobenzene (**1c**) (0.22 g, 1.1 mmol) in dry THF (10 mL) was added to the resulting suspension. The reaction mixture was heated at 60—62 °C for 6 h, cooled, and poured into ice water (100 mL). The product was extracted with CH_2Cl_2 and the extract was dried over $CaCl_2$ and concentrated to an oily, dark yellow residue. This was a mixture of triazines **6c** and **7c**, which were not separated off by column chromatography. The total yield of the isomers was 0.1 g (41%).

3-Amino-5-fluoro-6-morpholino-1,2,4-benzotriazine (6e). Potassium *tert*-butoxide (1.12 g, 10 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.24 g, 2.5 mmol) was added. After 10 min, a solution of 3-fluoro-4-morpholino-1-nitrobenzene (**1e**) (0.3 g, 1.3 mmol) in THF (10 mL) was added to the resulting suspension. The reaction mixture was stirred at 60—62 °C for 12 h. Ice water (100 mL) was added and the dark brown precipitate that formed was filtered off, dried, and recrystallized from ethanol. The yield of triazine **6e** was 0.17 g (51%).

3-Amino-5-fluoro-6-pyrrolidino-1,2,4-benzotriazine (6f) and 3-amino-7-fluoro-6-pyrrolidino-1,2,4-benzotriazine (7f). Potassium *tert*-butoxide (2.5 g, 10 mmol) was dissolved in dry THF (15 mL) by stirring at 25 °C for 30 min. Guanidine hydrochloride (0.47 g, 4.9 mmol) was added. After 10 min, a solution of 3-fluoro-1-nitro-4-pyrrolidinobenzene (**1f**) (0.5 g, 2.5 mmol) in dry THF (10 mL) was added to the resulting suspension. The reaction mixture was stirred at 60—62 °C for 12 h. Ice water (100 mL) was added and the dark brown precipitate that formed was filtered off and dried. Recrystallization from ethanol gave a mixture of triazines **6f** and **7f**, which were not separated off by column chromatography. The total yield of the isomers was 0.33 g (60%).

This work was financially supported by the Russian Foundation for Basic Research (Project Nos. 05-03-33112a and 05-03-32792a) and the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools, Grant NSh-9178.2006.3).

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Received February 27, 2006;
in revised form July 1, 2006