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Svetlana V. Amosova[a]; Galina M. Gavrilova[a]; Alexander I. Albanov[a]
[a] A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk, Russia

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RESEARCH ARTICLE

Reactions of 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene with thiosemicarbazide and thiourea

SVETLANA V. AMOSOVA*, GALINA M. GAVRILOVA and ALEXANDER I. ALBANOV

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russia

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3,6-Bis(2-thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene has been prepared in up to 77% yield by reacting 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene with thiosemicarbazide (ratio 1:2) in ethanol or in DMF (20°C). Unexpectedly, with a four-fold amount of thiosemicarbazide at 70–80°C (DMF), the reaction afforded a fluorinated nitrogen- and sulfur-containing fused heterocycle, 2-amino-8,9-difluoro-10-(2-thiosemicarbazidoethylsulfonyl)-5,6-dihydrobenzo[*h,i*]-1,4-thiazino[4,3-*d*]-1,3,4-thiadiazin-7,7-dioxide (54% yield). The use of tributylamine produced this heterocycle from 3,6-bis(2-thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene in 80% yield along with 2-amino-8,9-difluoro-5,6-dihydrobenzo[*h,i*]-1,4-thiazino[4,3-*d*]-1,3,4-thiadiazine-7,7-dioxide (18% yield).

Keywords: Vinylsulfonylfluorobenzene; Thiosemicarbazide; Nucleophilic addition; Intramolecular substitution

1. Introduction

Recently we have found that vinylsulfonyl groups of 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene (**1**) exhibit high activity in both radical [1–3] and nucleophilic addition reactions. Contrary to literature data [4, 5], compounds containing an SH group add to activated double bonds of vinylsulfonylfluorobenzene **1** without a base catalysts [6]. In reactions with 2-aminoethanol [7] and allylamine [8], amino groups participate in both nucleophilic addition and substitution of fluorine atoms in the ortho-position of the benzene ring, giving new heterocyclic systems.

* Corresponding author. E-mail: amosova@irioch.irk.ru

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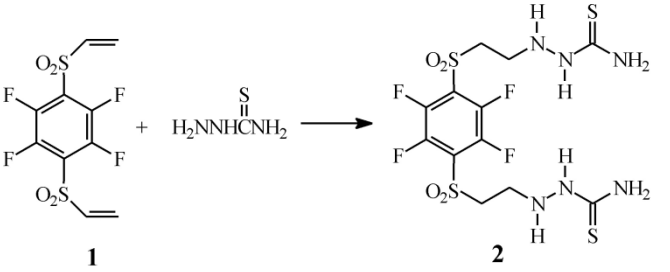


SCHEME 1

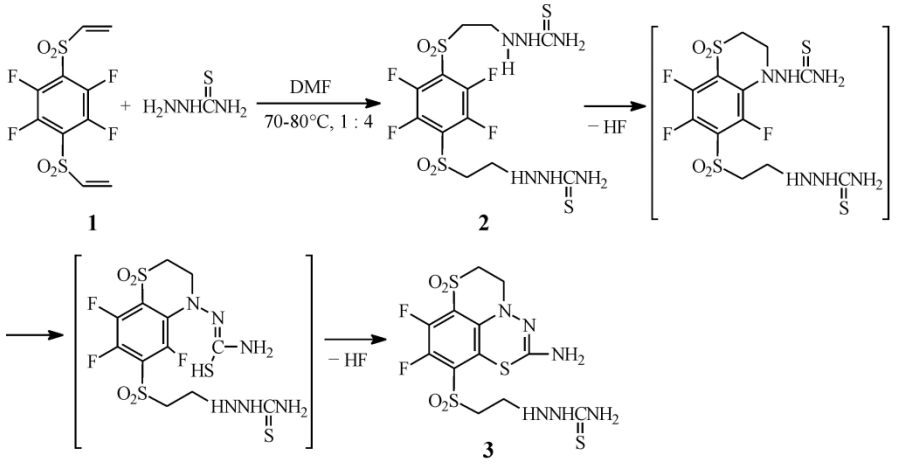
2. Results and discussion

In continuation of investigations focused on the reactivity of vinylsulfonylfluorobenzene **1**, we have studied its interaction with thiosemicarbazide and thiourea. Since the latter compounds possess two nucleophilic centers located at sulfur and nitrogen atoms (in the case of thiosemicarbazide, the nitrogen center is the 1-NH_2 group, which is more nucleophilic than the 4-NH_2 group [8, 9]), one might expect that both centers will be involved in the addition reactions with **1**. We did not rule out possible nucleophilic substitution of fluorine in the benzene ring of **1** as well.

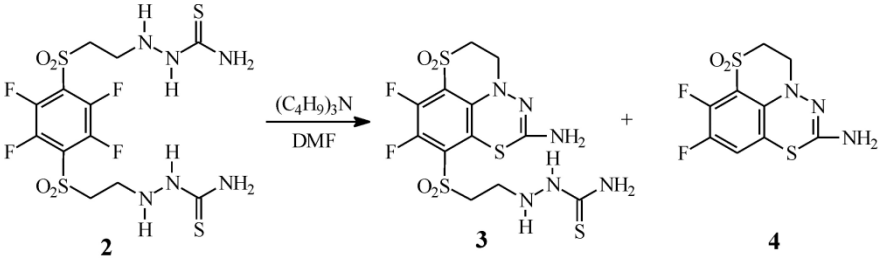
The reaction of **1** with thiosemicarbazide was carried out in DMF and ethanol at 20°C and 75–80°C using 1:2 and 1:4 reactant ratios. At 20°C with a two-fold molar excess of thiosemicarbazide, both in DMF and ethanol, a diadduct, 3,6-bis(2-thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene (**2**) is formed in 70% and 77% yield, respectively (scheme 1).

Increasing the reaction temperature to 70–80°C in DMF lowered the yield of **2** (53%). Under these conditions, along with the nucleophilic addition, competing nucleophilic substitution of fluorine atoms in the benzene ring may well occur, thus lowering the yield of the adduct **2**. Carrying out the reaction with a four-fold excess of thiosemicarbazide (which makes the reaction medium more basic) at 70–80°C led to an interesting result: a new fluorinated nitrogen- and sulfur-containing fused heterocycle, 2-amino-8,9-difluoro-10-(2-thiosemicarbazidoethylsulfonyl)-5,6-dihydrobenzo[*h, i*]-1,4-thiazino[4,3-*d*]-1,3,4-thiadiazine-7,7-dioxide (**3**) was obtained in 54% yield (scheme 2). Compound **3** is a high-melting brown powder, soluble in DMF and DMSO.

The formation of heterocycle **3** can be explained by the initial addition of the 1-NH_2 group of thiosemicarbazide to both activated double bonds of vinylsulfonylfluorobenzene **1** to afford



SCHEME 2



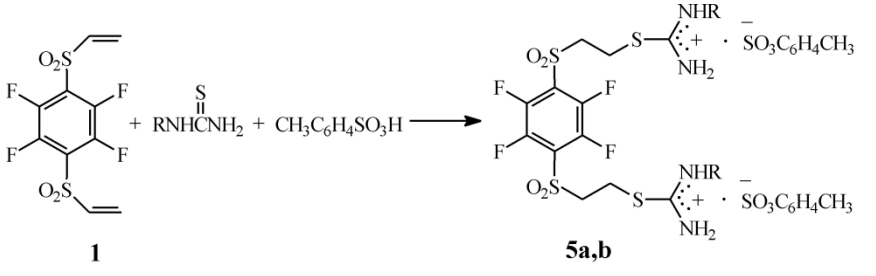
SCHEME 3

the diadduct **2** with subsequent intramolecular substitution of fluorine atoms in the *o*-position by the NH group, and in the *m*-position by the second nucleophilic center of thiosemicarbazide, the sulfur atom. Increasing the reaction temperature (70–80°C) and medium basicity facilitates nucleophilic substitution of fluorine atoms in the benzene ring, affording the product **3** (scheme 2). One of 2-thiosemicarbazidoethylsulfonyl groups of **2** participates in the intramolecular nucleophilic substitution. We have experimentally confirmed that heating the diadduct **2** in DMF at 70–80°C for 12 h results in the heterocyclic compound **3** in up to 40% yield.

Examples of simultaneous nucleophilic addition to the vinylsulfonyl group and substitution of fluorine atom in the *o*-position of the benzene ring in 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene by an amino group of amines have been described by us earlier [6, 7].

From the results obtained it follows that the realization of intramolecular nucleophilic substitution reactions requires sufficient basicity of the medium (excess of thiosemicarbazide) and higher reaction temperatures. In fact, heating compound **2** in DMF at 70–80°C in the presence of a 3-fold excess of a stronger base, tributylamine, gives tricyclic compound **3** in 81% yield, evidently as a result of intramolecular substitution reactions with participation of one of two 2-thiosemicarbazidoethylsulfonyl groups (scheme 3). Under these conditions there also occurs a side reaction that gives a new heterocycle, 2-amino-8,9-difluoro-5,6-dihydrobenzo [*h, i*]-1,4-thiazino[4,3-*d*]-1,3,4-thiadiazin-7,7-dioxide (**4**) in 18% yield. The mode of formation of **4** is unclear.

In the presence of *p*-toluenesulfonic acid in ethanol at 75°C, both thiosemicarbazide and thiourea add to double bonds of **1**, now employing their second nucleophilic center, the sulfur atom, to form 3,6-bis[(2-*S*-aminoisothiuronium ethylsulfonyl)-*p*-toluenesulfonate]-1,2,4,5-tetrafluorobenzene (**5a**) and 3,6-bis[(2-*S*-isothiuronium ethylsulfonyl)-*p*-toluenesulfonate]-1,2,4,5-tetrafluorobenzene (**5b**) in 20 and 80% yields, respectively (scheme 4). Compounds



5a, R = NH_2
5b, R = H

SCHEME 4

5a,**b** are attractive as building blocks for assembling new heterocyclic systems *via* corresponding dithiols.

The structures of the new compounds **2**–**5a**,**b** were confirmed by IR and ^{1}H, ^{13}C, ^{19}F, and ^{15}N NMR spectroscopy.

In conclusion, vinylsulfonylfluorobenzene **1** represents a reactive system for the design of various polyfunctional compounds, including heterocycles through nucleophilic addition and substitution reactions.

3. Experimental

IR spectra were recorded on a Bruker IFS 25 instrument in KBr pellets. ^{1}H, ^{13}C, ^{19}F and ^{15}N NMR spectra were run on a Bruker DPX 400 spectrometer. Internal standards used were HMDS for ^{1}H and ^{13}C, $CFCl_3$ for ^{19}F, and CH_3NO_2 for ^{15}N NMR spectra. The ^{15}N NMR spectrum obtained by DEPT technique with the coupling constant $^{15}N–H = 90$ Hz contained only signals of nitrogen atoms directly bound to protons.

3.1 *3,6-bis(2-Thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene (2)*

3,6-Bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene (0.5 g, 1.5 mmol) and thiosemicarbazide (0.28 g, 3 mmol) were dissolved in ethanol (30 ml). The reaction mixture was then stirred for 2 days at room temperature to give a precipitate (0.68 g), which was filtered off and washed with chloroform and diethyl ether. Reprecipitation from DMSO into ethanol gave 0.6 g (77%) of the compound **2** as a light-yellow powder. Mp 205°C (decomp.); IR (KBr) ν (cm^{-1}): 1142 and 1327 (SO_2), 1485 (C_{Ar}-F), 3186, 3216, 3340, 3457 (NH). ^{1}H NMR (DMSO-d_6), δ, (ppm): 3.12 (m, 4H, $2CH_2SO_2$), 3.72 (m, 4H, $2CH_2NH$), 5.40 (m, 2H, $2NHCH_2$), 7.23 and 7.82 (d, 4H, $2NH_2C{=}S$), 8.82 (br. s., 2H, 2NHC=S). ^{13}C NMR, δ (ppm): 43.72 (CH_2NH), 55.19 (CH_2SO_2), 123.07 (C_i-SO_2), 144.5 (dd, C_{Ar}-F), ^{1}J (F-C_{aryl}) = 260.78; ^{2}J (C_{aryl}-F) = 23.3 Hz. ^{19}F NMR, δ (ppm): −134.8 s. Found, (%): C 27.57; H 3.31; F 14,38; N 16.71; S 25.49. $C_{12}H_{16}F_4N_6O_4S_4$. Calcd. (%): C 28.12; H 3.15; F 14.83; N 16.40; S 25.02.

3.2 *2-Amino-8,9-difluoro-10-(2-thiosemicarbazidoethylsulfonyl)-5,6-dihydrobenzo[h,i]-1,4-thiazino[4,3-**d**]-1,3,4-thiadiazin-7,7-dioxide (3)*

To a stirred solution of thiosemicarbazide (0.84 g, 9.6 mmol) in DMF (20 ml) heated to 75°C was added 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene (0.8 g, 2.4 mmol) in DMF (5 ml). The reaction was carried out for 12 h at 75–80°C. The resulting reaction mixture was poured into water, and the so-formed precipitate was filtered off and then washed with ethanol, chloroform and diethyl ether to give 0.6 g (54.5%) of **3**, a dark-brown powder. Mp 235°C (decomp.); IR, ν (cm^{-1}): 1134 and 1326 (SO_2), 3314 (NH), 3454 (NH_2). ^{1}H NMR (DMF-d_7), δ (ppm) (J, Hz): 3.33 (m, 2H, CH_2SO_2), 3.85 [m, 2H, CH_2SO_2 (ring)], 3.89 (m, 2H, CH_2N), 4.15 [m, 2H, CH_2N (ring)], 5.40 (br. s., 1H, CH_2NH), 6.77 (br. s., 2H, $NH_2C{=}N$), 7.81, 7.50 (br. s., 2H, $NH_2C{=}S$), 8.85 (s, H, NHC=S). ^{13}C NMR, δ (ppm) (J, Hz): 43.84 (CH_2NH), 47.75 [CH_2N (ring)], 49.38 [CH_2SO_2 (ring)], 53.05 (CH_2SO_2), 119.90 [d, $C^4_{aryl.}$, ^{2}J (C_{aryl}-F_8) = 12.93], 122.23 (C^6_{aryl}), 128.45 [d, C^1_{aryl}, ^{2}J($C^{1-}F^9$) = 10.78], 138.87 (C^5_{aryl}), 143.51 [dd C^2_{aryl}, ^{1}J (C^2_{aryl}-F^9) = 260, ^{2}J (C^2_{aryl}-F^8) = 17.7], 146.74 [dd C^3_{aryl}, ^{1}J (C^3_{aryl}-F^8) = 256, ^{2}J (C^3_{aryl}-.F^9) = 16], 148.62 (C=N), 181.33 (C=S). ^{19}F NMR, δ (ppm) (J, Hz): −138.63 [d, 1F, F^9, ^{3}J (F^9, F^8) = 23.5], −142.75 [d, 1F, F^8, ^{3}J(F^8, F^9) = 23.5]. ^{15}N NMR, δ (ppm): −308.8 ($NH_2C{=}N$), −307.44 (NHNHC=S), −276.33 ($NH_2C{=}S$), −243.78 (NHC=S). Found, (%): C 29.89; H 3.12; F 8.52; N 17.08; S 27.13. $C_{12}H_{14}F_2N_6O_4S_4$. Calcd. (%): C 30.50; H 2.99; F 8.04; N 17.78; S 27.14.

3.3 *2-Amino-8,9-difluoro-5,6-dihydrobenzo[h,i]-1,4-thiazino[4,3-*d*]-1,3,4-thiadiazin-7,7-dioxide (4)*

To a solution of 3,6-bis(2-thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene in DMF (8 ml) was added tributylamine (1 g, 5.4 mmol) in DMF (3 ml). The reaction mixture was then stirred at 75–80°C for 16 h. DMF was removed under vacuum and the residue was precipitated into water. The precipitate formed was filtered off and washed with water, ethanol and diethyl ether to give 0.65 g (81%) of compound **3**, a brown powder. Aqueous ethanol was evaporated to give an orange powder, which was then washed with diethyl ether to give 0.1 g (18%) of **4**. Mp 165°C (decomp.). IR (KBr) ν (cm^{-1}): 1135 and 1317 (SO_2), 3305 and 3410 (NH_2). ^{1}H NMR (DMSO-d_6), δ (ppm) (*J*, Hz): 3.79 (m, 2H, CH_2SO_2), 3.99 (m, 2H, CH_2N), 6.65 (s, 2H, NH_2), 7.75 [dd $H_{aromatic}$ ^3J (H, F^9) = 10.0, ^4J (H, F^8) = 8.2]. ^{13}C NMR, δ (ppm) (*J*, Hz): 48.89 (CH_2N), 49.66 (CH_2SO_2), 115.79 [d, C^6, ^2J(C^6-F^8) = 13.79], 120.34 [d, C^3_{aryl}, ^2J (C^3_{aryl}-F^9) = 21.12], 117.74 (C^4_{aryl}), 138.67 (C^5_{aryl}), 144.00 [ddd, C^2_{aryl}, ^1J (C^2-F^9) = 244.53, ^2J (C^2_{aryl}-F^8) = 12.93; ^2J (C^2_{aryl}, H) = 6.47], 146.07 [ddd, C^1_{aryl}, ^1J (C^1, F^8) = 254.31, ^2J (C^1_{aryl}, F^9) = 15.52; ^3J (C^1_{aryl},.C^3,H) = 8.19]. ^{19}F NMR, δ (ppm) (*J*, Hz): −140.6 [dd, F^8, ^3J (F^8, F^9) = 23.2, ^4J (F^8 - CCCH) = 8.2] and −145.3 [dd, F^9, ^3J(F^9F^8) = 23.2, ^3J (HCC-F^9) = 10.0].

3.4 *3,6-bis[(2-S-Isothiuroniumethylsulfonyl)-p-toluenesulfonate]-1,2,4,5-tetrafluorobenzene (5b)*

3,6-Bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene (1 g, 3 mmol), thiourea (0.45 g, 6 mmol) and *p*-toluenesulfonic acid (1 g, 6 mmol) were dissolved in ethanol (20 ml) and heated upon stirring at 75°C for 5 h. The precipitate formed was filtered off and washed with chloroform and diethyl ether to give 1.6 g of compound **5b**. Removal of ethanol from the mother liquor followed by washing the precipitate with chloroform and diethyl ether afforded an additional 0.8 g of the compound **5b**, total yield 80%. Mp 249°C (decomp.); IR (KBr) ν (cm^{-1}): 1150 and 1340 (SO_2), 3016-3336 br. s. (NH_3^+). ^{1}H NMR (DMF-d_7), δ (ppm): 2.30 (s, 6H, $2CH_3$), 3.80 (t, 4H, $2CH_2SO_2$), 4.20 (t, 4H, $2CH_2S$), 7.16 and 7.61 (dd, 8H, 2 C_6H_4), 9.48 and 9.71 (d, 8H, $4NH_2$). Found, (%): C 37.58; H 3.72; F 9.67; N 6.69 S 23.68. $C_{26}H_{30}F_4N_4O_{10}S_6$. Calcd. (%): C 37.76; H 3.66; F 9.19; N 6.77; S 23.26.

3.5 *3,6-bis[(2-S-Aminoisothiuroniumethylsulfonyl)-p-toluenesulfonate]-1,2,4,5-tetrafluorobenzene (5a)*

This was obtained analogously in 20% yield. Mp 160°C; ^{1}H NMR (DMF-d_7), δ (ppm): 2.30 (s, 6H, $2CH_3$), 3.65 (m, 4H, $2CH_2SO_2$), 4.11 (m, 4H, $2CH_2S$), 7.17, 7.64 (dd, 8H, $2C_6H_4$), 5.46 (br. s., 8H, $4NH_2$). Found, (%): C 36.02; H 3.56; F 9.20; N 9.54; S 22.68. $C_{26}H_{32}F_4N_6O_{10}S_6$. Calcd. (%): C 36.44; H 3.76; F 8.87; N 9.81; S 22.45.

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