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INVESTIGATION OF PATHS FOR THE SYNTHESIS OF 5,5-DIALKYL-3-PERFLUOROALKYL-5,6-DIHYDRO-1,2,4-TRIAZOLO[3,4-*a*]ISOQUINOLINES

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Substituted 3-trifluoromethyl-5,6-dihydro-1,2,4-triazolo[3,4-a]isoquinolines were obtained by the reaction of substituted 1-methylthio-3,4-dihydroisoquinolines with hydrazine hydrate and trifluoroacetic acid. The corresponding 3-perfluoroalkyl derivatives are formed in the course of dehydration of 2-(3,3-dimethyl-3,4-dihydro-1-isoquinolyl)hydrazides of perfluorocarboxylic acids.

Keywords: hydrazides, hydrazones, isoquinoline, 1,2,4-triazolo[3,4-*a*]isoquinoline, perfluorocarboxylic acids, perfluorocarboxylic esters.

The condensed derivatives of quinoline and isoquinoline substituted by perfluoroalkyl groups are extremely promising for the creation of new biologically active compounds [1, 2]. Earlier we described a method for the synthesis of 3-methyl- and 3-aryl-1,2,4-triazolo[3,4-*a*]isoquinolines [3]. In the present paper we consider methods for the production of triazolo[3,4-*a*]isoquinolines (**1a-e**) containing perfluoroalkyl group $CF_3(CF_2)_n$, where n = 0, 1, or 2, at position 3. The compounds are of interest as they are isosteres of 1,2,4-triazolo[3,4-*a*]-phthalazines – well-known agonists of benzodiazepine receptors [4]. To compare the physicochemical characteristics we also synthesized triazolo[3,4-*a*]isoquinolines (**1f,g**) unsubstituted at position 3 and also the 3-alkyl-substituted derivatives (**1h,i**) (Scheme).

The reaction of heterylhydrazines with carboxylic acids or their derivatives is a classical method for the production of condensed triazoloheteroarenes [5]. Heating of amidrazones in carboxylic acids (method A) leads smoothly to triazolo[3,4-*a*]isoquinolines for acetic, propionic, and trifluoroacetic acids (see Table 1; compound **1h** was described earlier [3]). Since thioethers **2a,b** are known to react readily with amines in acetic acid [6], we also developed an one-pot method for the production of compounds **1a,b,h** by the direct reaction of thioethers **1a,b**, hydrazine hydrate, and the respective acid with boiling (method B); compounds **1a,b,h** are obtained here in a fairly pure state but with smaller yields (Table 1).

It could be expected that the reaction of amidrazones **3a,b** with formic acid would take place smoothly and lead to compounds **1f,g**. However, the reaction of 99% formic acid with compound **3a** both at room temperature and with boiling (1-5 h) leads to oligomeric products and to the previously described [7] azine of 3,3-dimethyl-3,4-dihydroisocarbostyril (**4**). In this case heterylhydrazone clearly disproportionates to azine and hydrazine hydrate under the influence of formic acid, as is possible for this type of compounds [5]. We tried to produce compound **1f** through thioether **1a** and formylhydrazine, but the reaction of these substances in boiling methanol again gives mainly azine **4**, while increase in temperature (reaction in boiling *o*-dichlorobenzene) leads as could be expected to self-condensation of formylhydrazine and gives a moderate yield (30%) of compound **4a**. The latter was obtained by an alternative method with a yield of 90% by boiling thio ether **1a** and 4-amino-1,2,4-triazole for 2 h in glacial acetic acid.

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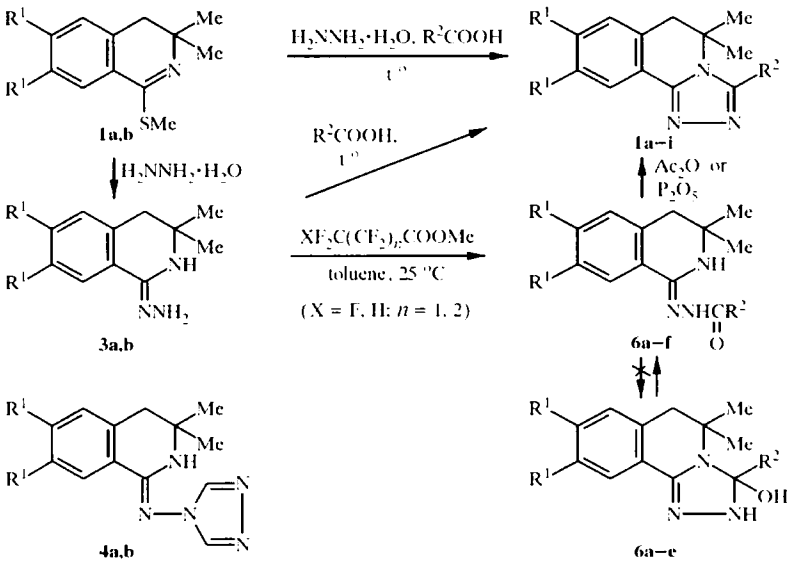
Scheme



1 a R^1 = H, R^2 = CF_3; **b** R^1 = OMe, R^2 = CF_3; **c** R^1 = H, R^2 = C_2F_5; **d** R^1 = OMe, R^2 = C_2F_5; **e** R^1 = H, R^2 = C_3F_7; **f** R^1 = H, R^2 = H; **g** R^1 = OMe, R^2 = H; **h** R^1 = H, R^2 = Me; **i** R^1 = H, R^2 = Et; **2-4 a** R^1 = H; **b** R^1 = OMe; **6 a** R^1 = H, R^2 = Et; **b** R^1 = H, R^2 = C_2F_5; **c** R^1 = OMe, R^2 = C_2F_5; **d** R^1 = H, R^2 = C_3F_7; **e** R^1 = OMe, R^2 = C_3F_7; **f** R^1 = H, R^2 = CF_2CF_2H

An attempt to bring formic acid into the reaction under the conditions of method A led to a mixture of polymeric and oligomeric products, compound **1f**, and the corresponding dimer bis-1,4-(3,3-dimethyl-3,4-dihydro-1-isoquinolyl)-1,2,4,5-tetrahydrotetrazine (**5**), which could not be isolated in the pure form. The dimer **5** was identified by its mass spectrum (M^+ 398) as an impurity in insufficiently purified samples of compound **1f**. The formation of such a dimer was described earlier for the reaction of orthoformic ester with phenylhydrazine hydrochloride [8]. The reason for the anomalous behavior of formic acid with amidrazones **3a,b** is evidently connected, on the one hand, with its increased acidity (compared with acetic acid) and, on the other, with the bifunctionality and dual reactivity.

Unlike formic acid itself its derivatives react with amidrazones **3a,b** without anomalies. Thus, the boiling of amidrazones **3a,b** for 1-2 h in an excess of ethyl orthoformate (method C) leads to triazolo[3,4-*a*]isoquinolines (**1f,g**) not substituted at C-3 (Table 1). The exothermic reaction of amidrazone **3a** with the mixed anhydride of formic and acetic acids according to the method [3] leads to the same result.

An attempt to extend method B to perfluoropropionic acid gave a mixture of hydrazides **6b,c** and the target triazolo[3,4-*a*]isoquinolines **1b,c** in a ratio of ~2:1 (according to the ^{1}H NMR spectra). To obtain compounds **6b,c** in the pure form we used the reaction of hydrazones **2a,b** with methyl esters of perfluorocarboxylic acids, since the latter is known to react readily with amines even at room temperature [9]. In fact, the reaction of methyl perfluoropropionate with amidrazones **3a,b** (toluene, 20°C, 12 h) gives pure hydrazides **6b,c**, which undergo cyclization to compounds **1c,d** when boiled in acetic anhydride (method D).

Methyl perfluorobutyrate reacts with amidrazones **3a,b** in a similar way, but the further dehydration of the obtained hydrazides **6d,e** by the action of acetic anhydride is no longer possible and only takes place with phosphorus pentoxide (method E). Published data [10] indicate that with increase in the size of the perfluoroalkyl radical to C_3F_7 or larger radicals compounds **6d,e** can exist in the cyclic form (see the Scheme). The IR and NMR spectra of compounds **6a-f** were recorded in order to investigate this question.

TABLE 1. The Physicochemical Characteristics of Compounds **1, 4, 6**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (crystallization solvent)	Yield, % (method)
		C	H	N		
1a	$C_{13}H_{12}F_3N_3$	58.39 / 58.42	4.65 / 4.53	15.69 / 15.72	175-177 (ethanol)	54 (A) 82 (B)
1b	$C_{15}H_{10}F_3N_3O_2$	63.40 / 63.15	5.78 / 5.65	14.48 / 14.73	209-210 (ethanol)	35 (A) 79 (B)
1c	$C_{14}H_{12}F_6N_3$	53.32 / 53.00	3.96 / 3.81	13.28 / 13.24	178-181 (ethanol + H_2O)	80 (A) 75 (D)
1d	$C_{16}H_{10}F_6N_3O_2$	50.82 / 50.93	4.55 / 4.27	11.17 / 11.14	193-196 (ethanol)	75 (A) 77 (D)
1e	$C_{15}H_{12}F_5N_3$	40.25 / 40.06	3.46 / 3.29	11.58 / 11.44	171-175 (hexane CH_2Cl_2)	32 (E)
1f	$C_{12}H_{13}N_3$	72.58 / 72.34	7.01 / 6.57	20.98 / 21.09	115-117 (ethyl acetate hexane)	60 (C)
1g	$C_{14}H_{17}N_3O$	65.03 / 64.85	6.56 / 6.61	16.37 / 16.20	191-193 (dioxane hexane)	64 (C)
1i	$C_{14}H_{17}N_3$	74.11 / 73.97	7.78 / 7.54	18.68 / 18.47	155-157 (ethyl acetate hexane)	44 (A)
4a	$C_{14}H_{15}N_5$	64.82 / 64.71	6.09 / 6.27	29.26 / 29.02	270-274 (ethanol)	90
4b	$C_{15}H_{19}N_5O_3$	59.58 / 59.79	6.21 / 6.35	23.10 / 23.24	277-279 ($CHCl_3$ 2-propanol)	66
6a	$C_{14}H_{19}N_3O$	68.34 / 68.54	8.10 / 7.81	17.11 / 17.13	169-171 (dioxane 2-propanol)	85
6b	$C_{13}H_{14}F_3N_3O$	51.84 / 51.70	4.20 / 4.34	12.73 / 12.92	162-164 (toluene)	77
6c	$C_{16}H_{18}F_3N_3O_3$	48.49 / 48.61	4.50 / 4.59	10.52 / 10.63	143-145 (benzene)	84
6d	$C_{15}H_{14}F_5N_3O$	46.74 / 46.76	3.89 / 3.66	11.17 / 10.91	155-157 (ethanol)	55
6e	$C_{17}H_{18}F_5N_3O_3$	46.02 / 45.85	4.42 / 4.07	9.28 / 9.44	209-210 (benzol)	74
6f	$C_{14}H_{16}F_4N_3O$	53.38 / 53.35	4.66 / 4.79	13.41 / 13.33	177-179 (toluene)	68

In the IR spectra of triazolo[3,4-*a*]isoquinolines **1f,g** not substituted at position 3 there are bands for the stretching vibrations of the (=C–H) groups at 3090-3130 cm^{-1}.

In the IR spectra of hydrazides **6a-f**, recorded in vaseline oil, the NH groups appear in the form of broad bands at 3260-3080 cm^{-1}; in chloroform solution for compound **6d** there are two bands at 3350 and 3310 cm^{-1}. The absorption bands of the carbonyl groups at 1650-1660 cm^{-1} have low intensity as a result of the formation of intermolecular hydrogen bonds.

In the ^1H NMR spectra of hydrazides **6a-f** the signals of the 2-NH group are at 6.36-7.40 ppm in chloroform and at 7.01-7.33 ppm in DMSO-d_6 (Table 2), i.e., they are in the region of the resonance of the aromatic protons, and this makes it difficult to assign them. The same can be said of the signals of the α-NH groups: greatly broadened singlets at 7.29-9.61 ppm in chloroform and singlets at 7.38-7.60 ppm in DMSO-d_6. It is known from published data that the signals of the OH groups for the cyclic forms of perfluoro-substituted hydrazides of type **6** appear also in the region of 7.0-7.3 ppm [11]. The only argument from the ^1H NMR data in favor of the acyclic form of **6d,e** is the absence of a downfield shift of the signal for the *gem*-dimethyl groups by 0.2-0.4 ppm, which is observed in all triazoles containing perfluoroalkyl radical – 1.54-1.58 ppm in compounds **1a-e** against 1.13-1.37 ppm in **6a-f**. The same downfield shift (to 1.52 ppm) is also observed in the ^1H NMR spectrum of triazole containing ethyl group **1i**, indicating the general character of the descreening of the *gem*-dimethyl groups by alkyl or perfluoroalkyl radical at position 3 of triazolo[3,4-*a*]isoquinoline.

TABLE 2. The Spectral Characteristics of Compounds **1, 4, 6**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm				
		$(Me)_2$	CH_2, s	8(10)-H	5,6,7(7,8,9)-H	Other protons
1	2	3	4	5	6	7
1a	1605, 1580, 1535, 1490, 1335, 1295, 1265, 1240, 1215, 1190, 1175, 1150, 1125, 1090, 1050, 1030, 980, 960	1.54	3.08	8.11 m	7.15-7.42 (3H, m)	
1b	1600, 1595, 1530, 1330, 1265, 1255, 1235, 1225, 1180, 1125, 1075, 1045, 1000, 980, 955, 940, 925	1.55	3.00	7.65 s	6.64	3.89 (3H, s, OMe); 3.91 (3H, s, OMe)
		1.58*	3.15*	7.55* s	6.95* (1H, s, 7-H)	3.88* (3H, s, OMe); 3.90* (3H, s, OMe)
1c	1575, 1535, 1260, 1230, 1180, 1140, 1100, 1060, 1005, 955, 780 (w), 760, 740, 660, 635, 560	1.57	3.09	8.00 m	7.16-7.32 (3H, m)	
1d	1605, 1540, 1310, 1280, 1270, 1235 (s), 1180, 1125, 1065, 1020, 955, 875, 825	1.56	3.01	7.64 s	6.71 (1H, s, 7-H)	3.88 (3H, s, OMe); 3.90 (3H, s, OMe)
1e	1600, 1530, 1275, 1250, 1225, 1175, 1120, 1050, 990, 975, 960, 885, 860	1.57	3.08	8.17 m	7.21-7.44 (3H, m)	—
1f	3110, 3090, 1600, 1570, 1535, 1490, 1315, 1270, 1225, 1210, 1200, 1190, 1170, 1155, 1135, 1105, 1060, 1030, 1000, 960	1.46	2.95	8.06 m	7.23-7.35 (3H, m)	8.24 (1H, s, -CH=)
1g	3130, 1605, 1580, 1540, 1480, 1275, 1250, 1230, 1215, 1190, 1165, 1140, 1120, 1050, 1000, 975	1.48	2.91	7.60 s	6.69 (1H, s, 7-H)	3.86 (3H, s, OMe); 3.90 (3H, s, OMe); 8.17 (1H, s, -CH=)
1i	1630, 1610, 1520, 1310, 1280, 1240, 1215, 1170, 1160, 1125, 1095, 1075, 1060, 1040, 975, 765, 735, 565	1.52	2.97	8.07 m	7.26-7.34 (3H, m)	1.42 (1H, t, CH_3); 2.89 (2H, q, CH_2)

TABLE 2 (continued)

1	2	3	4	5	6	7
4a	3160-3200 (br), 3100, 1620, 1595, 1565, 1500, 1305, 1250, 1200, 1175, 1065, 980, 950, 975	1.13	2.83	8.02 d	7.27-7.47 (3H, m)	7.03 (1H, s, NH); 8.02 (2H, s, –CH=)
4b	3200 (br), 1660, 1600, 1515, 1260, 1225, 1190, 1165, 1145, 1085 (s), 1040, 1005, 965, 880, 840, 825, 805	1.25	2.78	7.52	6.60 (1H, s, 5-H)	3.85 (6H, s, OMe); 7.10 (1H, s, NH); 8.08 (2H, s, CH=)
6a	3230-3270 (br), 1650, 1605, 1280, 1250, 1235, 1170, 1150, 1080, 1035	1.13	2.72	7.93 m	6.98-7.31 (3H, m)	1.07 (3H, t, Me); 2.13 (2H, q, CH_2); 6.36 (1H, br. s, 2-NH); 9.61 (1H, br. s, α-NH)
6b	3180-3110 (br), 1660, 1615, 1595, 1535, 1335, 1310, 1255, 1230, 1180, 1140, 1000, 950, 900	1.26	2.82	8.20 m	7.01-7.28 (4H, m, 5,6,7-H + α-NH)	6.45 (1H, br. s, 2-NH)
6c	3200-3110 (br), 1660, 1605, 1540, 1310, 1265, 1235, 1180, 1130, 1115, 1070, 1025, 955, 875	1.31	2.95	7.62 s	6.68 s (1H, 5-H)	3.90 (6H, s, OMe); 7.08 (1H, s, 2-NH); 8.80 (1H, br. s, α-NH)
6d	3200-3100 (br), 1655 (w), 1600, 1535, 1280, 1255, 1225 (s), 1175, 1135, 1120, 1050, 995, 980, 960, 885, 865, 840	1.37*	3.00*	8.15*	7.32-7.60* (5H, m, 5,6,7-H + 2NH)	
6e	3340, 3345 (sh), 1650 (w), 1600, 1550, 1520, 1230, 1210, 1170, 1140, 1110, 1050, 1010, 980, 870	1.32	2.81	7.38	6.64 (1H, s, 5-H)	3.86 (3H, s, OMe); 3.89 (3H, s, OMe); 7.01 (1H, br. s, 2-NH); 7.29 (1H, s, α-NH);
		1.37*	3.00*	8.15 d	6.90 (1H, s, 5-H)	3.88* (6H, s, OMe); 7.33* and 7.38* (two NH)
6f	3260-3080 (br), 1660, 1600, 1530, 1325, 1300, 1240, 1220, 1165, 1115, 1100, 1075, 1040, 980, 965, 920, 900, 840, 800, 780, 725	1.32	2.87	7.95	7.20-7.61 (4H, m, 5,6,7-H + 2-NH)	5.47; 6.14 and 6.81 (1H, three t, $CF_2\underline{H}$)

* The spectrum was recorded in DMSO-d_6.

In our opinion the IR and ^{1}H NMR spectra of compounds **6d,e** do not offer possibility to make an unequivocal choice between the cyclic and acyclic forms of these compounds. In order to resolve this question hydrazone **3a** was reacted with methyl 2,2,3,3-tetrafluoropropionate, and the ^{1}H NMR spectrum of the obtained compound **6a** was recorded. Splitting of the triplets of the terminal proton, due to the presence of the two enantiomers of the cyclic form of compound **6f**, should be observed in the case of the cyclic form. However, since such splitting was not observed in the ^{1}H NMR spectrum of compound **6f** (at 80 MHz), we assigned the acyclic form to hydrazides **6d,e,f**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Tesla BS-587A (80 MHz) and Bruker WM-250 (250 MHz) instruments (compounds **2f, 6d,e**) with HMDS as internal standard. The IR spectra were recorded on a UR-20 instrument in vaseline oil. The mass spectra of compounds **1a,f,g, 4a, 6d** were obtained on a Hitachi M-80 instrument with direct injection of the sample into the ion source at 70 eV. The reactions were monitored by TLC on Silufol plates in 9:1 chloroform–acetone with development in 2% solution of chloranil in toluene (compounds **1f,g, 2, 3, 4, 6a**) or in concentrated sulfuric acid (compounds **1a-e,h,i, 6b-f**).

5,5-Dimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (1f). C. Hydrazone **3a** [3] (2.0 g, 10.6 mmol) was boiled in orthoformic ester (3.2 ml, 19 mmol) for 3 h under argon. The reaction mixture was diluted with hexane (1.5 ml), the precipitate washed with hexane, and crystallized. Mass spectrum, *m/z* (I_{rel}, %): M^+ 199 (5); [M-CH_3] 184 (100); 171 (5); 158 (9); 142 (15); 128 (19); 116 (25); 103 (10); 90 (16). Compound **1g** was obtained similarly. Mass spectrum: M^+ 259 (100); [M-CH_3] 244 (54); 228 (25); 216 (15); 199 (18); 184 (20); 171 (15); 160 (15); 149 (16); 136 (18); 123 (23); 111 (32).

3-Ethyl-5,5-dimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (1i). D. Hydrazide **6a** (1 g, 4.1 mmol) was boiled with acetic anhydride (5 ml) for 2 h. The mixture was cooled, poured into water (40 ml), and neutralized to pH ~7 with sodium bicarbonate. The product was extracted with chloroform (3 × 10 ml) and dried with sodium sulfate. The solvent was distilled off, the residue was crystallized, and 0.41 g (44%) of compound **1i** were obtained. Compounds **1c,d** were obtained similarly by method D from hydrazides **6b,c**.

5,5-Dimethyl-3-trifluoromethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (1a). A. Hydrazone **3a** (1.93 g, 10 mmol) was boiled in trifluoroacetic acid (5 ml) for 1 h. The mixture was cooled, and water (30 ml) and sodium bicarbonate were added to pH ~7. The formed precipitate was separated, dried, and crystallized. Mass spectrum, *m/z* (I_{rel}, %): M^+ 266 (100); [M^+-1] 265 (40); 250 (50); 230 (15).

B. To thio ether **2a** (2.08 g, 10 mmol) hydrazine hydrate (0.55 ml, 10 mmol) and dropwise trifluoroacetic acid (3 ml) were added. After the vigorous release of methyl hydrosulfide (!) the mixture was boiled for 1 h and cooled, and the product was isolated as in method A. Compound **1b** was obtained similarly.

5,5-Dimethyl-3-perfluoropropionyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (1c). A. Hydrazone **3a** (1 g, 5.3 mmol) was boiled in perfluoropropionic acid (1.5 ml) for 2 h, cooled, and poured into water (25 ml). Sodium bicarbonate was added to pH 7, the mixture was extracted with chloroform, and the extract was dried with magnesium sulfate. The residue after distillation of the solvent was crystallized from aqueous ethanol, and 1.35 g (80%) of compound **1c** were obtained; mp 178-181°C. Compound **1d** was obtained similarly.

3,3-Dimethyl-1-propionylhydrazono-1,2,3,4-tetrahydroisoquinoline (6a). The compound was obtained by the acylation (0-5°C) of hydrazone **3a** (1 g, 5.3 mmol) dissolved in pyridine (5 ml) with propionyl chloride (0.93 g, 0.87 ml, 10 mmol) in ether (20 ml). After 12 h the precipitate was filtered off, washed with water, dried, and crystallized.

3,3-Dimethyl-1-perfluorobutyrylhydrazono-1,2,3,4-tetrahydroisoquinoline (6d). Hydrazone **3a** (1.93 g, 10 mmol) was mixed with methyl perfluorobutyrate (1.6 ml, 10 mmol) in toluene (8 ml). After 12 h the precipitate was filtered off and recrystallized. Mass spectrum: M^+ 385 (29); [M^+-CH_3] 370 (31); 216 (77); 188 (95); 173 (53); 169 (80); 158 (64); 14 (90); 143 (45); 130 (35); 117 (42); 116 (100); 115 (68); 89 (62); 69 (98). Compounds **6b,c,e,f** were obtained similarly.

5,5-Dimethyl-3-perfluorobutyryl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinoline (1e). E. Hydrazide **6d** (0.39 g, 1 mmol) was boiled in methylene chloride (15 ml) over phosphorus pentoxide (2.5 g) for 0.5 h and decanted. The solvent was distilled off, and the residue was treated with water and sodium bicarbonate. The product was filtered off, dried, and recrystallized. Compound **1e** (0.12 g, 32%) was obtained.

3,3-Dimethyl-1-(1,2,4-triazol-4-ylamino)-3,4-dihydroisoquinoline (4a). Thio ether **2a** (2.08 g, 10 mmol) was boiled with formylhydrazine (1.20 g, 20 mmol) in *o*-dichlorobenzene (5 ml) for 4 h. The solvent was distilled off, and the residue was treated with benzene (2 ml), the product was filtered off and crystallized, and 0.72 g (30%) of compound **4a** were obtained. Mass spectrum: M+ 241 (43); 226 (8); 171 (32); 158 (11); 144 (100); 130 (12); 116 (48); 103 (8); 90 (15).

Thio ether **2a** (2.08 g, 10 mmol) was boiled with 4-amino-1,2,4-triazole (0.84 g, 10 ml) in glacial acetic acid (20 ml) for 2 h. The mixture was cooled and poured into water, and sodium bicarbonate was added to pH ~7. The precipitate was separated and crystallized. Compound **4a** (2.16 g, 90%) was obtained. Compound **4b** was obtained similarly from thio ether **2b**.

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