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LETTERS TO THE EDITOR

Synthesis of Perfluoroalkyl[1,2,4]triazolo[1,3]thiazinones

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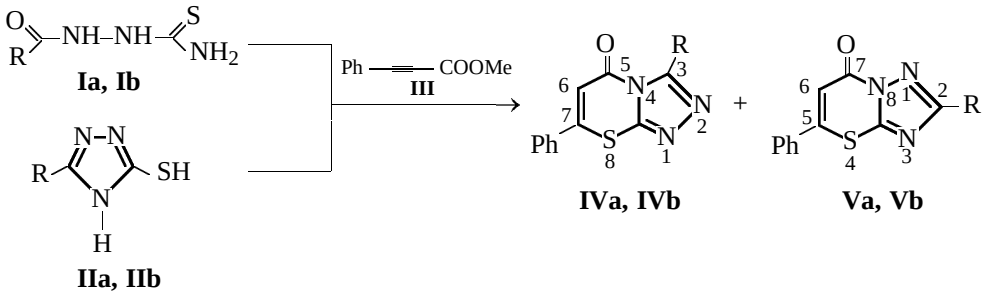
It is known that 1,3-thiazines are most commonly synthesized by reactions of thioamides, thioureas inclusive, with acetylenecarboxylic acid derivatives that play the role of a three-carbon bulding block for constructing the thiazine ring [1–4]. According to [5], *N*-aminothiourea (thiosemicarbazide) reacts with methyl propynoate in methanol to give methyl 3-thiosemicarbazonopropanoate. We found [6] that in boiling ethanol thiosemicarbazide reacts with methyl phenylpropynoate, forming initially methyl 3-phenyl-3-thiosemicarbazonopropanoate whose subsequent heterocyclization provides a monocyclic 1,3-thiazinone, methyl 3-[(4-oxo-6-phenyl-4*H*-1,3-thiazin-2-yl)-hydrazono]-3-phenylpropanoate. Since thiosemicarbazide is easily acetylated in acetic acid, nucleophilic addition to its triple bond of 3-phenylpropynoate gets impossible and the reaction goes through the thioamide group, yielding the bicyclic 3-methyl-7-phenyl-5*H*-[1,2,4]triazolo[3,4-b][1,3]thiazin-5-one [6]. Therefore, proceeding with searching for synthetic approaches to potentially biologically active 1,3-thioazinones and their fusion products, we turned to reactions of 1-(perfluoroacyl)thiosemicarbazides **Ia**, **Ib** and 5-(perfluoroalkyl)triazole-3-thiols **IIa**, **IIb** with methyl phenylpropynoate (**III**) in view of the increasing interest heterocyclic systems with perfluoroalkyl substituents have attracted over the past years [7]. This interest is explained by changes in chemical properties and biological activity produced by perfluoroalkyl substituents.



R = C_6F_{13} (**a**), CF_3 (**b**).

1-(Perfluoroheptanoyl)semicarbazide (**Ia**) and 5-(perfluorohexyl)triazole-3-thiol (**IIa**) reacts with methyl phenylpropynoate (**III**) in boiling acetic acid or in boiling ethanol to form a mixture of the isomers 3-(perfluorohexyl)-7-phenyl-5*H*-[1,2,4]triazolo[3,4-*b*]-[1,3]thiazin-5-one (**IVa**) and 2-(perfluorohexyl)-5-phenyl-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one (**Va**) in a total yield of 70–80% and a 10 : 1 ratio. Therewith, the structures of the prevailing isomer formed from thiosemicarbazide **Ia** and sulfanyltriazole **IIa** are the same. This is evidenced by the full coincidence of the NMR and IR spectra, the same chromatographic mobility (TLC), and lack of melting point depression of the mixed sample.

1-(Trifluoroacetyl)thiosemicarbazide (**Ib**) in acetic acid and 5-(trifluoromethyl)triazole-3-thiol (**IIb**) in alcohol react with methyl phenylpropynoate, forming mixtures of isomeric (trifluoromethyl)phenyltriazolothiazinones **IVb**, **Vb** with a roughly the same yield as in the case of compounds **IVa**, **Va**. However, the structures of the prevailing isomers in the mixtures of

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IVb and **Vb** are different. Therewith, melting point depression of the mixed sample is observed, and the chemical shifts of the thiazine C_6H proton signals differ by 0.20 ppm.

The fact that compounds **IV** and **V** contain a triazole ring is obvious, since, as already noted, the mixtures of products of the reactions of thiosemicarbazides **I** and sulfanyltriazoles **II** with methyl phenylpropyoate have identical spectral characteristics. Evidence for the presence of a 1,3-thiazine ring comes from the observation of a molecular ion peak at *m/z* 547 in the mass spectra of the condensation product of perfluorohexyltriazole **IIa** and thiosemicarbazide **Ia**; the presence in the ^1H and ^{13}C NMR spectra of solutions of compounds **IV** and **V** of signals characteristic of the "aromatic" carbon atom (C^6H) of the thiazine ring (δ 7.20–7.50 and 114.0–115.0 ppm, respectively), four downfield singlets of triazole and thiazine ring carbons (δ_C 148.0–162.0 ppm), and benzene ring multiplets (δ 7.46–7.85 and 127.9–133.6 ppm). In addition, the ^1H and ^{13}C NMR spectra lack signals of the $COOCH_3$ methoxy group at δ 2.5–3.5 and 50.0 ppm, respectively, as well as downfield NH or OH proton signals and signals of *sp*-hybridized carbon atoms near 60–90 ppm in the ^{13}C NMR spectra.

Unfortunately, isomers **IV** and **V** cannot be firmly distinguished on the basis of IR, NMR, and mass spectra. Therefore, the names of the isomers in the present communication should be considered arbitrary until X-ray diffraction data are obtained.

3-(Perfluorohexyl)-7-phenyl-5*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazin-5-one (IVa). *a*. A solution of 0.437 g of 1-(perfluoroheptanoyl)thiosemicarbazide (**Ia**) [8] and 0.160 g of methyl phenylpropynoate (**III**) in 10 ml of glacial acetic acid was refluxed for 5 h, cooled, and poured into water (70 ml). A precipitate formed within 20 h and was filtered off, washed with water and 5 ml of ethanol, and recrystallized from butan-1-ol. Yield 68%, mp 121–124°C, R_f 0.44 (hexane–acetone, 2 : 1).

b. A solution of 0.419 g of 5-(perfluorohexyl)triazole-3-thiol (**IIa**) [8] and 0.160 g of ester **II** in 10 ml of glacial acetic acid was refluxed for 5 h and treated according to procedure *a*. Yield 72%, mp 121–124°C, R_f 0.44 (hexane–acetone, 2 : 1).

c. Ester **III**, 0.160 g, was added to a suspension of 0.437 g of 1-(perfluoroheptanoyl)thiosemicarbazide (**Ia**) in 10 ml of ethanol. The mixture was refluxed for 5 h and then concentrated by 4/5 in a vacuum (20 mm), the precipitate was filtered off, washed with 5 ml of ethanol, and recrystallized from butan-1-ol. Yield 60%, mp 121–124°C, R_f 0.44 (hexane–acetone, 2 : 1).

d. A solution of 0.419 g of 5-(perfluorohexyl)-1,2,4-triazole-3-thiol (**IIa**) and 0.160 g of ester **III** in 10 ml of ethanol was refluxed for 5 h and then concentrated by 4/5 in a vacuum (20 mm), and the precipitate was filtered off and recrystallized from butan-1-ol. Yield 65%, mp 121–124°C, R_f 0.44 (hexane–acetone, 2 : 1). IR spectrum, δ, cm^{-1}: 3115, 3075, 2720, 1710, 1560, 1500, 1250, 1200, 1145. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.48 s (1H, CH), 7.77 m (5H, H arom.). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 105.0–120.0 m (6C, C_6F_{13}), 114.81, 127.04, 129.72, 132.30, 133.23, 150.33, 151.20 t, 154.11, 155.00. Mass spectrum, *m/z*: 547 $[M]^{+\cdot}$, 528 $[M - F]^+$, 278 $[M - F - C_5F_{10}]^+$, 250 $[M - F - C_5F_{10} - CO]^+$, 209 $[M - F - C_5F_{10} - CO - MeCN]^+$, 169 $[M - F - C_5F_{10} - CO - MeCN - CN_2]^+$, 181 $[M - F - C_5F_{10} - CO - MeCN - N_2]$. Found, %: C 39.3; H 1.4; N 7.2; S 5.9. $C_{17}H_6F_{13}N_3OS$. Calculated, %: C 37.3; H 1.1; N 7.7; S 5.5.

7-Phenyl-3-(trifluoromethyl)-5*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazin-5-one (IVb). A solution of 0.169 g of trifluoromethyltriazole **IIb** [8] and 0.160 g of ester **III** in 10 ml of ethanol was refluxed for 5 h, the solvent was removed in a vacuum (20 mm), and the residue was recrystallized from heptane. Yield 61%, mp 140–142°C, R_f 0.57 (hexane–acetone, 4 : 1). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.47 s (1H, CH), 7.75 m (5H, H arom.). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 118.25 q, 114.75, 127.02, 129.70, 132.30, 133.20, 150.36, 151.60 q, 154.16, 155.00. Found, %: C 48.1; H 2.7; N 13.7; S 11.8. $C_{12}H_6F_3N_3OS$. Calculated, %: C 48.5; H 2.0; N 14.1; S 10.8.

5-Phenyl-2-(trifluoromethyl)-7*H*-[1,2,4]triazolo-[5,1-*b*][1,3]thiazin-7-one (Vb). A solution of 0.187 g of (trifluoroacetyl)thiosemicarbazide (**Ib**) [8] and 0.160 g of ester **III** in 10 ml of glacial acetic acid was refluxed for 5 h, cooled, and poured into water (70 ml). A precipitate formed within 20 h and was filtered off, washed with water and 5 ml of ethanol, and recrystallized from propan-2-ol. Yield 59%, mp 140– 142°C, R_f 0.57 (hexane–acetone, 4 : 1). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.27 s (1H, CH), 7.71 m (5H, H arom.). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 114.92, 118.0 q, 127.55, 129.91, 132.88, 133.91, 151.26, 153.80 q, 154.20, 155.27. Found, %: C 48.0; H 2.0; N 14.9; S 11.1. $C_{12}H_6F_3N_3OS$. Calculated, %: C 48.5; H 2.0; N 14.1; S 10.8.

The IR spectra were recorded on an IKS-29 spectrophotometer for suspensions in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively, for solutions in DMSO-d_6 relative to TMS.

The mass spectra were obtained on an MX-1321 instrument with direct inlet (140–300°C), ionizing energy 70 eV. The reaction progress and the purity of products was follwed by TLC on Sorbfil plates.

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