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Behavior of Benzoins and Hydroxy Ketones in Acid Medium: II.* Reactions of 1,2-Bis(2,5-dimethyl-3-thienyl)-2-hydroxyethan-1-one with N,S-Binucleophiles in Trifluoroacetic Acid

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Abstract—1,2-Bis(2,5-dimethyl-3-thienyl)-2-hydroxyethan-1-one reacts with thioamides, thiosemicarbazides, and methyl hydrazinecarbodithioate in trifluoroacetic acid to give the corresponding thiazole, thiadiazine, and pyrazole derivatives, respectively.

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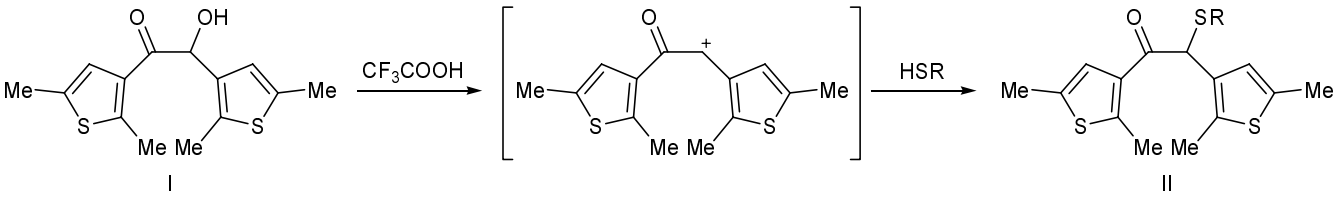
We previously showed that 1,2-bis(2,5-dimethyl-3-thienyl)-2-hydroxyethan-1-one (**I**) smoothly reacts with sulfur-centered nucleophiles in trifluoroacetic acid to give ketones **II** (Scheme 1) [1]. In the present study we tried to extend this reaction to difunctional N,S-nucleophiles. For this purpose, we examined reactions of thenoin **I** with thioamides, thiosemicarbazides, and methyl hydrazinecarbodithioate in trifluoroacetic acid with a view to obtain dithienylethene derivatives in which the thiophene rings are linked to thiazole, thiadiazine, and pyrazole fragments.

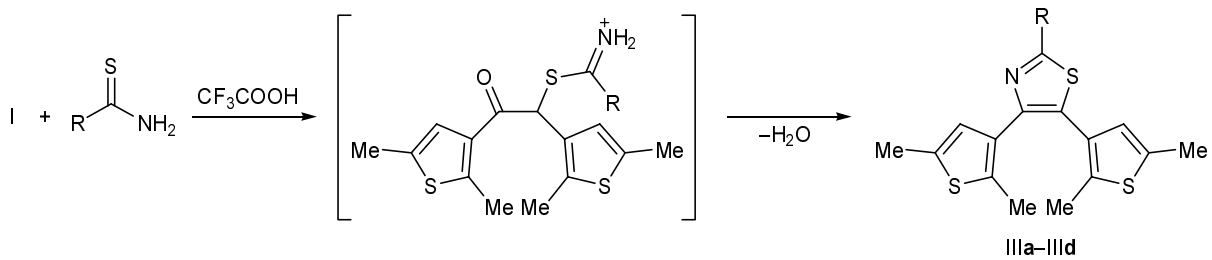
The reaction of ketone **I** with primary carbothioamides in trifluoroacetic acid at room temperature was complete in 24 h, and the products were the corresponding thiazole derivatives **IIIa**–**IIId** which were formed in quantitative yield (Scheme 2). Thiazole **IIIb** was synthesized by us previously by condensation of thiourea with 2-chloro-1,2-bis(2,5-dimethyl-3-thienyl)-

Scheme 1.



I II

Scheme 2.

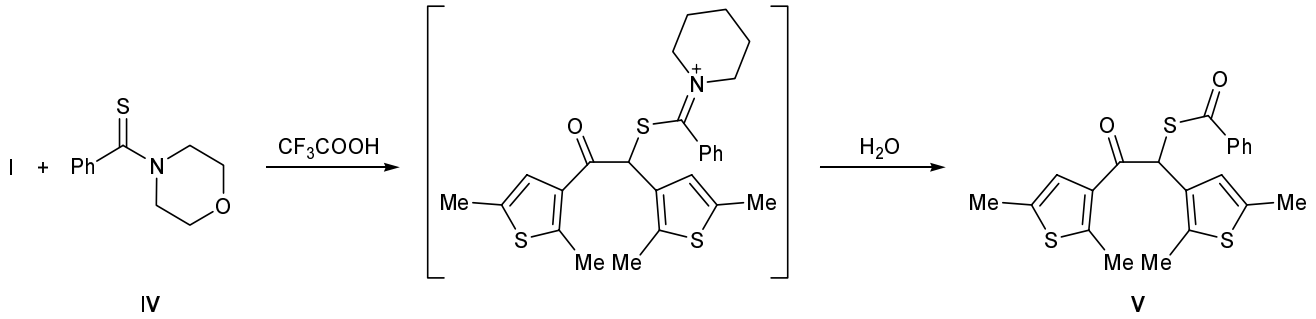


IIIa–IIId

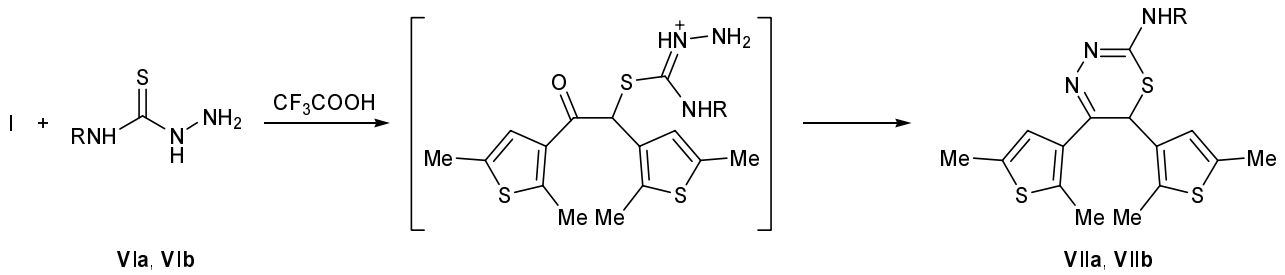
R = Me (**a**), NH_2 (**b**), Ph (**c**), $NCCH_2$ (**d**).

* For communication I, see [1].

Scheme 3.



Scheme 4.



R = H (**a**), Ph (**b**).

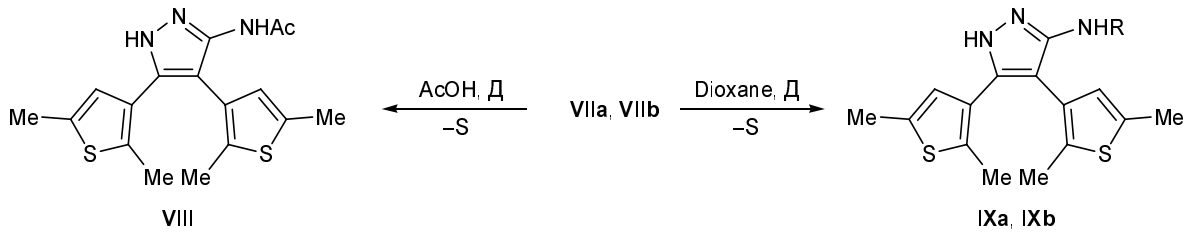
ethanone [2]. The reaction described in the present article is general; the proposed procedure requires no preliminary preparation of the corresponding α-chloro ketone, thus making photochromic compounds **IIIa**–**IIId** more accessible. By reaction of ketone **I** with morpholide **IV** we obtained benzothioic acid *S*-ester **V** in a good yield (Scheme 3), in keeping with our previous results [1].

Using thiosemicarbazides **VIa** and **VIb** as nucleophiles, we succeeded in synthesizing dithienylethenes having a thiadiazine bridging fragment (Scheme 4). The reactions were carried at room temperature (reaction time 24 h), and thiadiazines **VIIa** and **VIIb** were isolated in 75% yield. In both cases, the order of mixing of the reactants was important: initially, thiosemicarbazide should be dissolved in trifluoroacetic acid, and only then thenoin **I** should be added. Simultaneous addition of the reactants to trifluoroacetic acid or addition of thiosemicarbazide **VI** to a solution of ketone **I** in trifluoroacetic acid led to considerably reduced yields of the products owing to decomposition of initial compound **I**.

1,3,4-Thiadiazines **VII** turned out to readily undergo transformation into the corresponding pyrazoles (Scheme 5). By prolonged heating of thiadiazine **VIIa** in boiling acetic acid we obtained pyrazole derivative **VIII**, while pyrazoles **IXa** and **IXb** were formed when compounds **VIIa** and **VIIb**, respectively, were heated in dioxane for a long time. It should be noted that the transformation of 1,3,4-thiadiazines into pyrazoles is a characteristic reaction of these heterocycles [3].

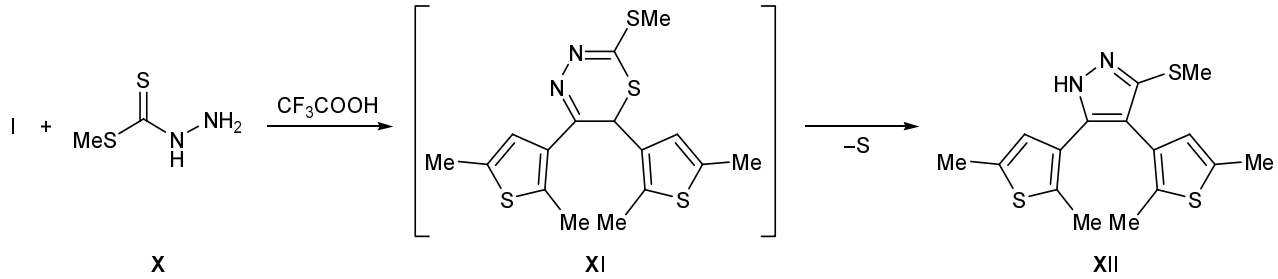
Presumably, the reaction of thenoin **I** with methyl hydrazinecarbodithioate (**X**) in trifluoroacetic acid follows an a analogous scheme (Scheme 6), but in this case extrusion of sulfur from intermediate thiadiazine **XI** occurs much more readily. Therefore, we failed to

Scheme 5.



R = H (**a**), Ph (**b**).

Scheme 6.



X XI XII

isolate compound **XI** from the reaction mixture, and the product was pyrazole **XII**.

We examined photochemical behavior of compounds **IIIa**–**IIId**, **IXa**, and **XII** in acetonitrile under UV irradiation. The spectral parameters of open-chain and (**A**) and cyclic forms (**B**) of compounds **IIIa**–**IIId** in acetonitrile are given below.

Compound no.	**IIIa**	**IIIb**	**IIIc**	**IIId**
Absorption maximum of form **A**, λ_A, nm	~288	295	327	290
Molar absorption coefficient ε_A, l mol^{-1} cm^{-1}	6400	6000	10 700	6600
Irradiation time, min	3	4	2	12
Absorption maximum of form **B**, λ_B, nm	515	486	549	523
Molar absorption coefficient ε_B, l mol^{-1} cm^{-1}	700	1000	1200	6200

These data show that thiazole derivatives **IIIa**–**IIId** exhibit photochromic properties (Scheme 7). Irradiation with UV light of their solutions in acetonitrile gives rise to an additional broad absorption band in the visible region (λ_{max} 486–549 nm; halfwidth 100 nm), which indicates formation of closed structure **B** [4–6]. The absorption curves plotted during the irradiation process were characterized by isosbestic points ($\lambda \approx$ 250–260 nm); this means that the transformation of **A** into **B** is reversible. However, compounds **IIIa**–**IIId** turned out to be insufficiently stable under UV irradiation; therefore, a more detailed study of their photochromic and optical properties seems to be unreasonable. Unlike thiazole derivatives **III**, pyrazoles **IXa** and **XII** showed no photochromic properties upon UV irradiation at λ 313 nm (4 min) or additional direct irradiation with unfiltered light (1 min).

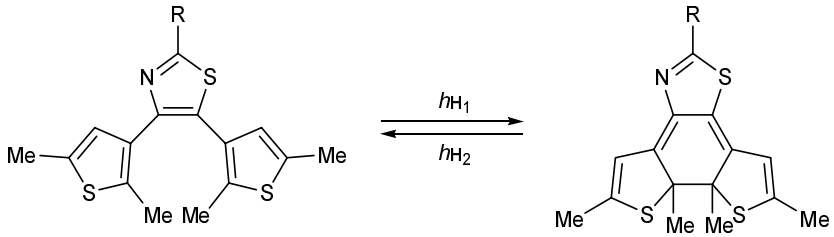
EXPERIMENTAL

The electronic absorption spectra were recorded on a Varian Cary 50 Bio spectrophotometer from solutions in acetonitrile (ultrapure grade) with a concentration of 10^{-4} M using 10-mm quartz cells. An OI-18A illuminator equipped with a DRK-120 mercury lamp (λ 313 nm) was used in irradiation experiments. The ^{1}H NMR spectra were measured on Bruker AM-30 (300 MHz) and Bruker WM-250 spectrometers (250 MHz). The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS-30 mass spectrometer with direct sample admission into the ion source. The melting points were determined on a Boetius melting point apparatus; uncorrected values are given. The reaction mixtures and the products were analyzed by TLC on Silufol UV-254 plates using ethyl acetate–hexane as eluent.

S-1,2-Bis(2,5-dimethyl-3-thienyl)-2-oxoethyl benzothioate (**V**) was isolated by column chromatography on silica gel (grade 22, 60–200 mesh; Aldrich) using hexane–ethyl acetate (6:1) as eluent.

4,5-Bis(2,5-dimethyl-3-thienyl)-2-methyl-1,3-thiazole (IIIa). Compound **I**, 0.10 g (0.36 mmol), was

Scheme 7.



A IIIa–IIId B

added to a solution of 0.10 g (1.33 mmol) of thioacetamide in 1.50 g of trifluoroacetic acid, and the mixture was kept for 24 h at room temperature, diluted with diethyl ether, and neutralized with an aqueous solution of sodium hydroxide. The aqueous phase was extracted with diethyl ether, the extracts were washed in succession with water, a 20% solution of sodium hydroxide, and water again, dried over $MgSO_4$, and evaporated. Yield 0.11 g (92%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.05 s (6H, CH_3), 2.35 s (6H, CH_3), 2.70 s (3H, CH_3), 6.50 s (1H, 4-H, thienyl), 6.65 s (1H, 4'-H, thienyl). Found, %: C 60.25; H 5.30; N 4.40; S 30.18. $C_{16}H_{17}NS_3$. Calculated, %: C 60.15; H 5.36; N 4.38; S 30.11.

4,5-Bis(2,5-dimethyl-3-thienyl)-1,3-thiazol-2-amine (IIIb). Yield 0.11 g (94%), mp 171–173°C; published data [2]: mp 173–175°C.

4,5-Bis(2,5-dimethyl-3-thienyl)-2-phenyl-1,3-thiazole (IIIc). Yield 0.16 g (95%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 s (3H, CH_3), 2.20 s (3H, CH_3), 2.40 s (3H, CH_3), 2.45 s (3H, CH_3), 6.55 s (1H, 4-H, thienyl), 6.65 s (1H, 4'-H, thienyl), 7.40–7.50 m (3H, H_{arom}), 8.00–8.10 m (2H, H_{arom}). Found, %: C 66.24; H 5.09; N 3.70; S 25.18. $C_{21}H_{19}NS_3$. Calculated, %: C 66.10; H 5.02; N 3.67; S 25.21.

2-[4,5-Bis(2,5-dimethyl-3-thienyl)-1,3-thiazol-2-yl]acetonitrile (IIId). Yield 0.15 g (90%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.05 s (3H, CH_3), 2.10 s (3H, CH_3), 2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 4.10 s (2H, CH_2), 6.45 s (1H, 4-H, thienyl), 6.55 s (1H, 4'-H, thienyl). Found, %: C 59.20; H 4.70; N 8.10; S 27.88. $C_{17}H_{16}N_2S_3$. Calculated, %: C 59.27; H 4.68; N 8.13; S 27.92.

***S*-[1,2-Bis(2,5-dimethyl-3-thienyl)-2-oxoethyl]-benzothioate (V).** Compound **I**, 0.28 g (0.10 mmol), was added to a solution of 0.24 g (1.10 mmol) of morpholide **IV** in 1 g of trifluoroacetic acid. The mixture was kept for 24 h at room temperature, diluted with diethyl ether, and neutralized with aqueous sodium hydroxide. The aqueous phase was extracted with diethyl ether, the extract was washed in succession with water, a 20% solution of sodium hydroxide, and water again, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography on silica gel using hexane–ethyl acetate (6:1) as eluent. Yield 0.30 g (75%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 2.50 s (3H, CH_3), 2.70 s (3H, CH_3), 6.25 s (1H, CH), 6.65 s (1H, 4-H, thienyl), 7.10 s (1H, 4-H, thienyl), 7.35–7.45 m (2H, H_{arom}), 7.55–7.60 m (1H, H_{arom}), 7.90–8.00 m (2H, H_{arom}). Found, %: C 62.93; H 4.96; S 24.16. $C_{21}H_{20}O_2S_3$. Calculated, %: C 62.97; H 5.03; S 24.01.

5,6-Bis(2,5-dimethyl-3-thienyl)-6*H*-1,3,4-thiadiazin-2-amine (VIIa). Compound **I**, 0.20 g (0.72 mmol), was added to a solution of 0.25 g (2.74 mmol) of thiosemicarbazide in 3 g of trifluoroacetic acid. The mixture was kept for 24 h at room temperature, diluted with diethyl ether, and neutralized with aqueous sodium hydroxide. The aqueous phase was extracted with diethyl ether, the extract was washed in succession with water, a 20% solution of sodium hydroxide, and water again, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from ethanol. Yield 0.18 g (75%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.25 s (3H, CH_3), 2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 2.50 s (3H, CH_3), 5.20 s (1H, CH), 6.15 s (1H, 4-H, thienyl), 6.80 s (1H, 4'-H, thienyl) 6.65 s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 335 $[M]^+$ (100). Found, %: C 53.75; H 5.15; N 12.55; S 28.52. $C_{15}H_{17}N_3S_3$. Calculated, %: C 53.70; H 5.11; N 12.52; S 28.67.

5,6-Bis(2,5-dimethyl-3-thienyl)-*N*-phenyl-6*H*-1,3,4-thiadiazin-2-amine (VIIb). Yield 0.40 g (75%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (6H, CH_3), 2.40 s (3H, CH_3), 2.50 s (3H, CH_3), 5.45 s (1H, CH), 6.25 s (1H, 4-H, thienyl), 6.85 s (1H, 4'-H, thienyl), 7.10–7.35 m (5H, H_{arom}), 12.25 s (1H, NH). Found, %: C 61.24; H 5.11; N 10.25; S 23.32. $C_{21}H_{21}N_3S_3$. Calculated, %: C 61.28; H 5.14; N 10.21; S 23.37.

***N*-[4,5-Bis(2,5-dimethyl-3-thienyl)-1*H*-pyrazol-3-yl]acetamide (VIII).** A mixture of 0.34 g (1.0 mmol) of compound **VIIa** and 3 ml of acetic acid was heated for 5 h at the boiling point. The mixture was then cooled, diluted with water, and extracted with diethyl ether. The extract was washed in succession with water, a solution of $NaHCO_3$, and water again, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from ethanol. Yield 0.305 g (88%), mp 212–214°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (3H, CH_3), 2.20 s (6H, CH_3), 2.35 s (3H, CH_3), 2.45 s (3H, CH_3), 6.45 s (2H, 4-H, thienyl). Found, %: C 59.15; H 5.55; N 12.13; S 18.52. $C_{17}H_{19}N_3OS_2$. Calculated, %: C 59.10; H 5.54; N 12.16; S 18.56.

4,5-Bis(2,5-dimethyl-3-thienyl)-1*H*-pyrazol-3-amine (IXa). A mixture of 0.34 g (1.0 mmol) of compound **VIIa** and 3 ml of 1,3-dioxane was heated for 5 h at the boiling point. The mixture was cooled and filtered, and the filtrate was evaporated. Yield 0.27 g (90%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.95 s (3H, CH_3), 2.05 s (3H, CH_3), 2.35 s (3H, CH_3), 2.40 s

(3H, CH_3), 4.85 br.s (2H, NH_2), 6.50 s (2H, 4-H, thienyl). Mass spectrum, *m*/*z* (I_{rel}, %): 303 $[M]^+$ (100). Found, %: C 59.32; H 5.61; N 13.82; S 21.14. $C_{15}H_{17}N_3S_2$. Calculated, %: C 59.37; H 5.65; N 13.85; S 21.13.

4,5-Bis(2,5-dimethyl-3-thienyl)-*N*-phenyl-1*H*-pyrazol-3-amine (IXb). A mixture of 0.38 g (1.0 mmol) of compound **VIIb** and 3 ml of 1,3-dioxane was heated for 5 h at the boiling point. The mixture was cooled and filtered, the filtrate was evaporated, and the residue was recrystallized from ethanol. Yield 0.318 g (83%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.95 s (3H, CH_3), 2.00 s (3H, CH_3), 2.30 s (3H, CH_3), 2.35 s (3H, CH_3), 6.45 s (1H, 4-H, thienyl), 6.55 s (1H, 4'-H, thienyl), 7.05–7.35 m (5H, H_{arom}), 12.25 s (1H, NH). Found, %: C 66.42; H 5.61; N 11.02; S 16.91. $C_{21}H_{21}N_3S_2$. Calculated, %: C 66.46; H 5.58; N 11.07; S 16.90.

4,5-Bis(2,5-dimethyl-3-thienyl)-3-methylsulfanyl-1*H*-pyrazole (XII). Compound **I**, 0.20 g (0.72 mmol), was added to a solution of 0.35 g (2.88 mmol) of methyl hydrazinecarbodithioate in 3 g of trifluoroacetic acid. The mixture was kept for 24 h at room temperature, diluted with diethyl ether, and neutralized with aqueous sodium hydroxide. The aqueous phase was extracted with diethyl ether, the extract was washed in succession with water, a 20% solution of sodium hydroxide, and water again, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from ethanol. Yield 0.18 g (74%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.90 s (3H, CH_3), 2.00 s (3H, CH_3), 2.25 s (3H, CH_3), 2.35 s (3H, CH_3), 2.45 s (3H, CH_3), 6.50 s (2H, 4-H, thienyl), 13.00 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 334 $[M]^+$ (100). Found, %: C 57.55; H 5.45; N 8.40; S 28.72. $C_{16}H_{18}N_2S_3$. Calculated, %: C 57.45; H 5.42; N 8.37; S 28.75.

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