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Behavior of Benzoins and Hydroxy ketones in Acid Media: I. Reaction of 1-Aryl-2-(2,5-dimethylthiophen-3-yl)-2-hydroxyethanones with Thiols in Trifluoroacetic Acid

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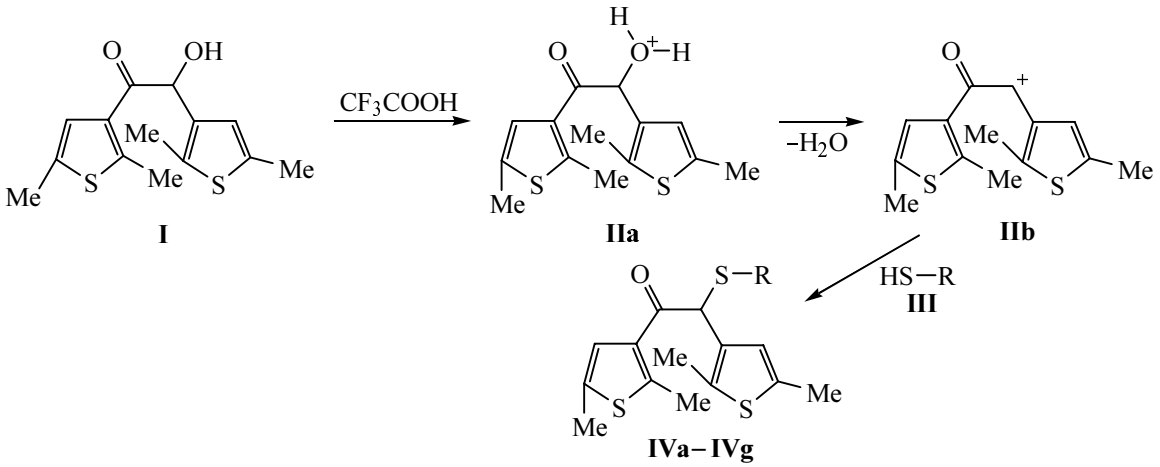
Abstract—Reactions of 1-aryl-2-(2,5-dimethylthiophen-3-yl)-2-hydroxyethanones with thiols in trifluoroacetic acid lead to formation of substituted 1-aryl-2-(2,5-dimethylthiophen-3-yl)-2-sulfanylethanones.

Chemistry of functionally substituted 1,2-dithienylethane derivatives attracts considerable interest, taking into account their wide application in the synthesis of photochromes [1, 2]. We previously used 2-hydroxy-1,2-bis(2,5-dimethylthiophen-3-yl)ethanone (**I**) and its analog to obtain a wide series of photochromic 1,2-dihetarylethenes [3–5]. The present communication reports on the behavior of these hydroxy-containing compounds in trifluoroacetic acid in the presence of various sulfur-containing nucleophiles, such as aromatic and heteroaromatic thiols and methyl sulfanylacetate (Scheme 1), synthesis of β-keto sulfides, and their subsequent transformation into substituted ethanones.

We have found that hydroxy ketone **I** reacts with thiols **III** in trifluoroacetic acid even at room temperature through intermediate conjugate acid **IIa** and dehydrated species **IIb**. As a result, the corresponding β-keto sulfides **IVa**–**IVg** are formed in good yields. The reaction of **I** with methyl sulfanylacetate in trifluoroacetic acid is the most vigorous: the process is complete within a few minutes, and the yield of compound **IVg** is almost quantitative. However, in order to obtain sulfide **IVg** in a high yield, it is necessary to use 5 equiv of methyl sulfanylacetate with respect to hydroxy ketone **I**. The order of mixing of the reactants is also important: hydroxy ketone **I** should be added to a solution of methyl

Scheme 1.



III, **IV**, R = 4-FC_6H_4 (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 5-amino-1,3,4-thiadiazol-2-yl (**d**), 1-methylimidazol-2-yl (**e**), 5-(4-methoxyphenyl)-1,2,4-triazin-3-yl (**f**), $MeOCOCH_2$ (**g**).

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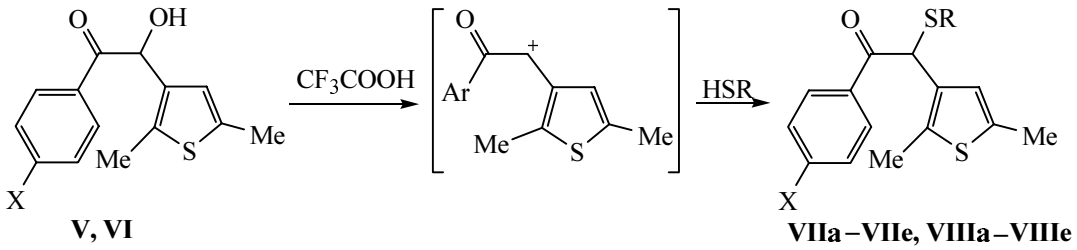
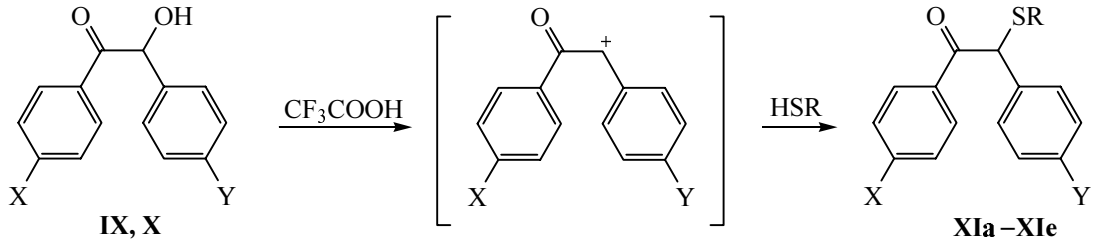
Scheme 2.



VII, **VIII**, R = 4-FC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 5-amino-1,3,4-thiadiazol-2-yl (**c**), 1-methylimidazol-2-yl (**d**), $MeOCOCH_2$ (**e**).

Scheme 3.



XI, R = 4-FC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 5-amino-1,3,4-thiadiazol-2-yl (**c**), 1-methylimidazol-2-yl (**d**), $MeOCOCH_2$ (**e**); **IX**, X = Y = H; **X**, **XI**, X = Cl, Y = MeO.

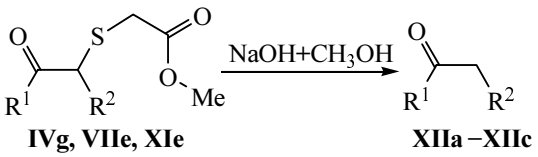
sulfanylacetate, otherwise decomposition of compound **I** occurs. No reaction was observed in weaker acids, such as acetic and formic; here, the initial reactants were recovered from the reaction mixture.

Replacement of the dimethylthienyl substituent at the carbonyl group by phenyl or *p*-fluorophenyl group in hydroxy ketone **I** had no effect on the reaction course: hydroxy ketones **V** and **VI** smoothly reacted with thiols **III**, though at a lower rate (Scheme 2). It should be noted that unsubstituted benzoin (**IX**) failed to react with the above thiols: all attempts to involve it in reactions with HSR nucleophiles resulted in recovery of the initial compounds. On the other hand, unlike benzoin **IX**, compound **X** having an electron-donor *p*-methoxyphenyl group reacted with various thiols to give derivatives **XI** (Scheme 3). Presumably, the reaction mechanism includes protonation of the initial hydroxy ketone, elimination of water with formation of carbocation, and addition of thiol, as shown in Scheme 1. The cationic species are stabilized due to effect of electron-rich dimethylthiophene or electron-donor *p*-methoxyphenyl substituent (Schemes 1, 3). Analogous stabilization is impossible in the cation derived from unsubstituted benzoin (**IX**), and the reaction does not occur.

We can conclude that the observed reaction of 2-hydroxyethanones with sulfur-containing nucleophiles in trifluoroacetic acid provides a convenient procedure for the synthesis of aromatic and heterocyclic β-keto sulfides. The known method for the preparation of structurally related sulfides, which is based on the reaction of chloroketones with aromatic or heteroaromatic thiols, requires more severe conditions [6].

The obtained sulfides are readily converted into the corresponding substituted ethanones which are key intermediate products in the synthesis of photochromic dihetarylethenes. By analogy with published data [7, 8], compounds **IVg**, **VIIe**, and **XIe** were reduced to ketones **XIIa**–**XIIc** by heating in aqueous–alcoholic alkali (Scheme 4). The synthesis of sulfides and their reduction

Scheme 4.



R^1, R^2 = Ar, Het.

to ketones can be combined into a one-pot process. We succeeded in excluding the stage of isolation of sulfides **IVg**, **VIIe**, and **XIe**, and the corresponding ketones were thus obtained in 82–95% yield.

Thus the proposed combination of the addition and reductive cleavage can be regarded as a convenient method for the transformation of hydroxyethanones into ethanones.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) and Bruker WM-250 (250 MHz) spectrometers using DMSO-d_6 or $CDCl_3$ as solvent. The melting points were determined on a Boetius device and were not corrected. The reaction mixtures were analyzed, and the purity of products was checked, by TLC on Silica gel 60 F_{254} plates (Merck); eluent hexane–ethyl acetate.

1,2-Bis(2,5-dimethylthiophen-3-yl)-2-(4-fluorophenylsulfanyl)ethanone (IVa). Hydroxy ketone **I**, 0.1 g (0.36 mmol), was added to a solution of 0.2 g (1.2 mmol) of 4-fluorobenzenethiol in 2 ml of trifluoroacetic acid. The mixture was kept for 15 min at room temperature, diluted with diethyl ether, neutralized with an aqueous solution of sodium hydroxide, and extracted with diethyl ether. The extract was washed with water, 20% aqueous sodium hydroxide, and water again, dried over $MgSO_4$, and evaporated. The residue was recrystallized from methanol. Yield 0.1 g (76%), mp 67–69°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.95 s (3H, CH_3), 2.30 s (3H, CH_3), 2.40 s (3H, CH_3), 2.70 s (3H, CH_3), 5.40 s (1H, CH), 6.65 s (1H, thienyl), 6.70 s (1H, thienyl), 6.90–7.00 m (2H, H_{arom}), 7.20–7.30 m (2H, H_{arom}). Found, %: C 61.40; H 4.96; F 4.74. $C_{20}H_{19}FOS_3$. Calculated, %: C 61.51; H 4.90; F 4.86.

Compounds **IVb**–**IVf** were synthesized in a similar way.

1,2-Bis(2,5-dimethylthiophen-3-yl)-2-phenylsulfanylethanone (IVb). Yield 0.1 g (85%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.05 s (3H, CH_3), 2.30 s (3H, CH_3), 2.45 s (3H, CH_3), 2.70 s (3H, CH_3), 5.50 s (1H, CH), 6.70 s (1H, thienyl), 6.80 s (1H, thienyl), 7.20–7.40 m (5H, H_{arom}). Found, %: C 64.27; H 5.45; S 25.68. $C_{20}H_{20}OS_3$. Calculated, %: C 64.48; H 5.41; S 25.82.

2-(4-Chlorophenylsulfanyl)-1,2-bis(2,5-dimethylthiophen-3-yl)ethanone (IVc). Yield 78%, mp 105–107°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (3H, CH_3), 2.30 s (3H, CH_3), 2.40 s (3H, CH_3), 2.65 s (3H, CH_3), 5.40 s (1H, CH), 6.65 s (1H, thienyl), 6.70 s (1H, thienyl), 7.15 d (2H, H_{arom}, J = 7.0 Hz), 7.30 d (2H, H_{arom}, J = 7.0 Hz). Found, %: C 58.85; H 4.75; Cl 8.65; S 23.48. $C_{20}H_{19}ClOS_3$. Calculated, %: C 59.02; H 4.71; Cl 8.71; S 23.63.

2-(5-Amino-1,3,4-thiadiazol-2-ylsulfanyl)-1,2-bis(2,5-dimethylthiophen-3-yl)ethanone (IVd). Yield 73%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 s (9H, CH_3), 2.65 s (3H, CH_3), 5.60 s (2H, NH_2), 6.10 s (1H, CH), 6.60 s (1H, thienyl), 6.80 s (1H, thienyl). Found, %: C 48.35; H 4.37; N 10.48; S 32.48. $C_{16}H_{17}N_3OS_4$. Calculated, %: C 48.58; H 4.33; N 10.62; S 32.42.

1,2-Bis(2,5-dimethylthiophen-3-yl)-2-(1-methyl-1*H*-imidazol-2-ylsulfanyl)ethanone (IVe). Yield 71%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (3H, CH_3), 2.35 s (6H, CH_3), 2.65 s (3H, CH_3), 3.25 s (3H, NCH_3), 5.80 s (1H, CH), 6.60 s (1H), 6.70 s (1H), 6.90 s (1H), 7.10 s (1H). Found, %: C 57.55; H 5.44; N 7.38; S 25.64. $C_{18}H_{20}N_2OS_3$. Calculated, %: C 57.41; H 5.35; N 7.44; S 25.54.

1,2-Bis(2,5-dimethylthiophen-3-yl)-2-[5-(4-methoxyphenyl)-1,2,4-triazin-3-ylsulfanyl]ethanone (IVf). Yield 63%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3), 2.40 s (3H, CH_3), 2.50 s (6H, CH_3), 3.85 s (3H, OCH_3), 6.50 s (1H, CH), 6.60 s (1H), 6.95 d (2H, H_{arom}, J = 7.0 Hz), 7.30 s (1H), 8.05 d (2H, H_{arom}, J = 7.0 Hz), 9.70 s (1H). Found, %: C 59.73; H 4.70; N 8.91; S 19.84. $C_{24}H_{23}N_3O_2S_3$. Calculated, %: C 59.85; H 4.81; N 8.72; S 19.97.

Methyl [1,2-bis(2,5-dimethylthiophen-3-yl)-2-oxoethylsulfanyl]acetate (IVg). Hydroxy ketone **I**, 0.2 g (0.7 mmol), was added to a solution of 0.4 g (3.8 mmol) of methyl sulfanylacetate in 2 ml of trifluoroacetic acid. The mixture was kept for 5 min, diluted with diethyl ether, treated with a solution of 2 g of NaOH in 5 ml of water, and extracted with three portions of diethyl ether. The combined extracts were washed with water, 20% aqueous alkali, and water again, dried over $MgSO_4$, and evaporated. Yield 0.23 g (90%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3), 2.40 s (3H, CH_3), 2.45 s (3H, CH_3), 2.65 s (3H, CH_3), 3.10 d (1H, CH_2, J = 18.0 Hz), 3.20 d (1H, CH_2, J = 18.0 Hz), 3.70 s (3H, OCH_3), 5.65 s (1H, CH), 6.65 s (1H, thienyl), 6.90 s (1H, thienyl). Found, %: C 55.51; H 5.34; S 26.15. $C_{17}H_{20}O_3S_3$. Calculated, %: C 55.41; H 5.47; S 26.10.

Methyl [1-(2,5-dimethylthiophen-3-yl)-2-oxo-2-phenylethylsulfanyl]acetate (VIIe). Hydroxy ketone

V, 2.46 g (10.0 mmol), was added to a solution of 5.6 g (52.8 mmol) of methyl sulfanylacetate in 15 ml of trifluoroacetic acid. The mixture was kept for 1 h, diluted with diethyl ether, treated with a solution of 10.1 g of NaOH in 35 ml of water, and extracted with three portions of diethyl ether. The combined extracts were washed with water, 20% aqueous alkali, and water again, dried over $MgSO_4$, and evaporated. Yield 2.97 g (89%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3), 2.50 s (3H, CH_3), 3.10 d (1H, CH_2, J = 18.0 Hz), 3.25 d (1H, CH_2, J = 18.0 Hz), 3.70 s (3H, CH_3), 6.00 s (1H, CH), 6.65 s (1H, thienyl), 7.40–7.60 m (3H, H_{arom}), 7.90–8.00 m (2H, H_{arom}). Found, %: C 60.87; H 5.44; S 19.01. $C_{17}H_{18}O_3S_2$. Calculated, %: C 61.05; H 5.42; S 19.17.

Compounds **VIIa** and **VIIIa** were synthesized in a similar way.

2-(2,5-Dimethylthiophen-3-yl)-2-(4-fluorophenylsulfanyl)-1-phenylethanone (VIIa). Yield 74%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.05 s (3H, CH_3), 2.25 s (3H, CH_3), 6.25 s (1H, CH), 6.50 s (1H, thienyl), 7.10 m (2H, H_{arom}), 7.35 m (2H, H_{arom}), 7.45 m (2H, H_{arom}), 7.55 m (1H, H_{arom}), 7.90 m (2H, H_{arom}). Found, %: C 67.37; H 4.77; F 5.38. $C_{20}H_{17}FOS_2$. Calculated, %: C 67.39; H 4.81; F 5.33.

2-(2,5-Dimethylthiophen-3-yl)-1-(4-fluorophenyl)-2-(4-fluorophenylsulfanyl)ethanone (VIIIa). Yield 63%, mp 75–77°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.05 s (3H, CH_3), 2.25 s (3H, CH_3), 6.30 s (1H, CH), 6.50 s (1H, thienyl), 7.15 m (2H, H_{arom}), 7.30 m (4H, H_{arom}), 8.00 m (2H, H_{arom}). Found, %: C 64.27; H 4.27; F 10.28. $C_{20}H_{16}F_2OS_2$. Calculated, %: C 64.15; H 4.31; F 10.15.

1,2-Bis(2,5-dimethylthiophen-3-yl)ethanone (XIIa). Hydroxy ketone I, 0.2 g (0.7 mmol), was added to a solution of 0.4 g (3.8 mmol) of methyl sulfanylacetate in 2 ml of trifluoroacetic acid. The mixture was kept for 5 min at room temperature, and 20 ml of a 15% solution of sodium hydroxide in a 1 : 1 (by volume) methanol–water mixture was added. The mixture was heated for 1 h under reflux and diluted with cold water, and the precipitate was filtered off and washed with a 50% solution of alcohol. Yield 0.17 g (92%), mp 44–46°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3), 2.35 s (3H, CH_3), 2.45 s (3H, CH_3), 2.7 s (3H, CH_3), 4.20 s (2H, CH_2), 6.50 s (1H, thienyl), 7.10 s (1H, thienyl). Found, %: C 63.48; H 6.18; S 24.11. $C_{14}H_{16}OS_2$. Calculated, %: C 63.60; H 6.10; S 24.25.

Compounds **XIIb** and **XIIc** were synthesized in a similar way.

2-(2,5-Dimethylthiophen-3-yl)-1-phenylethanone (XIIb). Yield 89%, mp 55–57°C; published data [10]: mp 56–57°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 s (3H, CH_3), 2.40 s (3H, CH_3), 4.20 s (2H, CH_2), 6.50 s (1H, thenoyl), 7.20–7.50 m (3H, H_{arom}), 7.95–8.05 m (2H, H_{arom}).

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-ethanone (XIIc). Yield 91%, mp 108–110°C; published data [11]: mp 111°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.70 s (3H, OCH_3), 4.30 s (2H, CH_2), 6.90 d (2H, H_{arom}, J = 7.5 Hz), 7.20 d (2H, H_{arom}, J = 7.5 Hz), 7.50 d (2H, H_{arom}, J = 7.5 Hz), 8.05 d (2H, H_{arom}, J = 7.5 Hz).

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