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SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences A.I. Konovalov on the 70th Anniversary of His Birth

Synthesis of Naphtho[2,3-*b*]furan-4,9-diones Having a Trifluoromethyl Group under Conditions of Phase-Transfer Catalysis

D. V. Davydov and I. P. Beletskaya

Faculty of Chemistry, Lomonosov Moscow State University, Vorob'evy Gory, Moscow, 119992 Russia
e-mail: dvdav@elorg.chem.msu.ru

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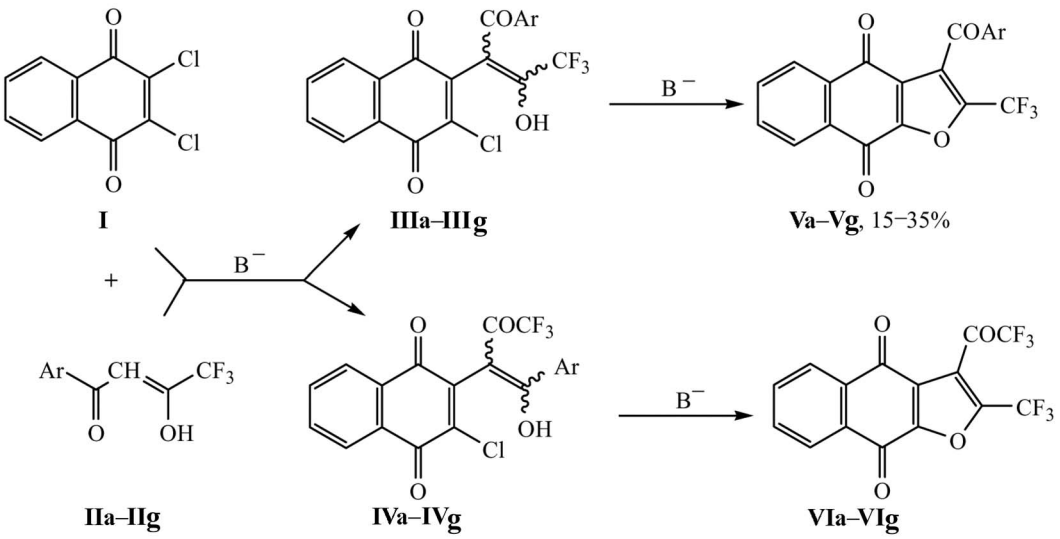
Naphtho[2,3-*b*]furan-4,9-diones are fairly widely spread in nature [1], and they exhibit versatile biological activity [2–6]. Introduction of fluorine-containing substituents, e.g., CF_3 group, into molecules of a biologically active compound usually improves its properties, specifically enhances its lipophilicity and volatility [7]. A simplest version of the synthesis of naphtho[2,3-*b*]furan-4,9-dione having a trifluoromethyl group may be condensation of a 2,3-disubstituted 1,4-naphthoquinone with a 4,4,4-trifluoro-1,3-dicarbonyl compound. While studying the reactivity of enolates derived from 1,3-diketones in nucleophilic substitution at an sp^2-hybridized carbon atom, we examined the possibility of synthesizing 3-aroyl-2-trifluoromethyl-naphtho[2,3-*b*]furan-4,9-diones **Va**–**Vg** by reaction of 2,3-dichloronaphthoquinone (**I**) with the corresponding 4,4,4-trifluoro-1-phenyl-1,3-butanediones **IIa**–**IIg** (Scheme 1). It should be noted that we previously observed formation of benzofurans in analogous processes with participation of nonfluorinated 1,3-dicarbonyl compounds [8–10] and that strongly acidic 4,4,4-trifluoro-1,3-dicarbonyl compounds (pK_a = 5.4–6.0) [11] failed to react under similar conditions [9].

Several general procedures for the synthesis of naphtho[2,3-*b*]furan-4,9-diones from 2,3-dichloronaphthoquinone (**I**) and fluorine-free 1,3-dicarbonyl compounds have been reported [12]. These procedures are based on condensation of the reactants in alcohol in the presence of an organic base [13, 14] or in DMF in the presence of KF [15]. Optimization of the reaction conditions with commercially available 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**Ia**) as an example showed that none of the classical procedures for the preparation of naphtho[2,3-*b*]furan-4,9-diones ensures formation of the expected condensation product, **Va** or **VIa**. Our attempts to obtain the target products under conditions of phase-transfer catalysis using the system benzene–50% NaOH–Bu_4NBr [16] or toluene–K_2CO_3–$Me_3(C_{16}H_{33})NBr$ on heating were also unsuccessful. On the other hand, replacement of toluene in the latter system by *o*-xylene allowed us to isolate the condensation products in 15–35% yield.

These findings indicated that, in the initial stage of the process, substrate **I** is attacked (at least partially) by the nucleophilic carbon center of the ambident anion derived from diketone **II** to give two possible substitution products, **III** and **IV**. We believe that this reaction is the first example of substitution at an sp^2-hybridized carbon atom involving a soft nucleophilic carbon center in strongly acidic enolates derived from 1,3-dicarbonyl compounds [11]. In the second stage of the process, intermediate enolates **III** or **IV** are capable of undergoing intramolecular cyclization to isomeric naphthofurandiones **V** or **VI** with participation of the hard oxygen center [8, 9]. The choice between the isomeric condensation products (structures **V** and **VI**) was made on the basis of the ^{13}C NMR data. The ^{13}C NMR spectra of naphtho[2,3-*b*]furan-4,9-diones **V** should contain three singlets from three nonequivalent carbonyl carbon atoms. Isomers **VI** should give rise to two singlets from the carbonyl groups in the naphthoquinone fragment and one quartet from the trifluoroacetyl group due to coupling with fluorine nuclei. In the ^{13}C NMR spectra of the condensation products obtained from diketones **IIa**, **IIb**, and **IId** we observed only three singlets in the δ_C region from 165 to 200 ppm. These data unambiguously indicated that the

Scheme 1.



II–VI, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 3,4-$(MeO)_2C_6H_3$ (**e**), 3,4,5-$(MeO)_3C_6H_2$ (**f**), 2-thienyl (**g**).

condensation products have the structure of 3-aroyl-2-trifluoromethylnaphtho[2,3-*b*]furan-4,9-dione **V**. Although the yields of compounds **Va**–**Vg** did not exceed 35%, the products can readily be detected in the reaction mixture by TLC on Silufol UV-254 plates (under UV irradiation at л 365 nm) and isolated by flash chromatography.

The NMR spectra were recorded on a Varian VXR-400 spectrometer. The mass spectra were measured on a Finnigan MAT-113 instrument with direct sample admission into the ion source. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil.

Condensation of 2,3-dichloro-1,4-naphthoquinone (I) with 4,4,4-trifluoro-1-aryl-1,3-butanediones IIa–IIh (*general procedure*). A mixture of 1.135 g (5 mmol) of naphthoquinone **I**, 0.14 g (11 mmol) of K_2CO_3, and 0.091 g (5 mol %) of cetyltrimethyl-ammonium bromide in 100 ml of *o*-xylene was heated to the boiling point, and 0.01 mol of the corresponding 4,4,4-trifluoro-1-aryl-1,3-butanedione **II** was added in small portions over a period of 1 h under vigorous stirring. The mixture was heated with stirring until initial naphthoquinone disappeared (TLC, eluent $CHCl_3$) and was then passed through a layer of silica gel which was washed with excess xylene. The product was washed off with chloroform. The solution was evaporated, and the residue was recrystallized from chloroform.

3-Benzoyl-2-trifluoromethylnaphtho[2,3-*b*]furan-4,9-dione (Va). Yield 35%. Colorless crystals, mp 192–194°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.50–7.86 m (5H, Ph), 7.88–7.93 m (2H, 6-H, 7-H), 8.08–8.12 m and 8.26–8.30 m (1H each, 5-H, 8-H). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): d_F: –64.5 ppm, s (3F, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %) : 370 (25) M^+, 342 (20) $[M–CO]^+$, 322 (30) $[M–CO–HF]^+$, 293 (25) $[M–Ph]^+$. IR spectrum: n 1690 cm^{-1}, br (C=O). Found, %: C 64.80; H 2.40; F 15.24. $C_{20}H_9F_3O_4$. Calculated, %: C 64.87; H 2.45; F 15.39.

3-(4-Fluorobenzoyl)-2-trifluoromethyl-naphtho-[2,3-*b*]furan-4,9-dione (Vb). Yield 30%. Colorless crystals, mp 160–162°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 7.30–7.36 m (2H, H_{arom}), 7.88–7.98 m (2H, 6-H, 7-H), 8.04–8.08 m and 8.23-8.27 m (1H each, 5-H, 8-H), 8.11–8.17 m (2H, H_{arom}). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6), δ_F, ppm: –62.00 s (3F, CF_3), –102.61 s (1F, C_6H_4F). Mass spectrum, *m*/*z* (I_{rel}, %): 388 (35) M^+, 360 (10) $[M – CO]^+$, 340 (30) $[M–CO–HF]^+$, 293 (25) $[M–C_6H_4F]^+$. IR spectrum: ν 1690 cm^{-1}, br (C=O). Found, %: C 61.77; H 2.00; F 19.45. $C_{20}H_8F_4O_4$. Calculated, %: C 61.87; H 2.08; F 19.57.

3-(4-Bromobenzoyl)-2-trifluoromethylnaphtho-[2,3-*b*]furan-4,9-dione (Vc). Yield 30%. Colorless crystals, mp 164–166°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 7.75–7.7.79 m (2H, H_{arom}), 7.89–7.96 m (2H, 6-H, 7-H), 7.96–7.80 (2H, H_{arom}), 8.04–8.07 m and 8.23–8.26 m (1H each, 5-H, 8-H). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): δ_F –62.05 ppm, s (3F, CF_3). Mass

spectrum, *m*/*z* (I_{rel}, %): 450 (40) and 448 (40) [M^+ H]$^+$, 422 (10) and 420 (10) [M^+H–CO]$^+$, 402 (30) and 400 (30) [M^+ H–CO–HF]$^+$, 293 (25) [M^+H–C_6H_4Br]$^+$. IR spectrum: ν 1690 cm^{-1}, br (C=O). Found, %: C 53.35; H 1.65; F 12.60. $C_{20}H_8F_3O_4$. Calculated, %: C 53.48; H 1.80; F 12.69.

3-(4-Methoxybenzoyl)-2-trifluoromethylnaphtho[2,3-*b*]furan-4,9-dione (Vd). Yield 30%. Colorless crystals, mp 153–155°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 3.45 s (3H, CH_3O), 6.58 d (2H, H_{arom}, J = 9.00 Hz), 7.42–7.50 m (2H, 6-H, 7-H), 7.52 d (2H, H_{arom}, J = 9.00 Hz), 7.57–7.60 m and 7.76–7.79 m (1H each, 5-H, 8-H). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): δ_F –61.90 ppm, s (3F, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 400 (75) M^+, 372 (5) [M–CO]$^+$, 352 (20) [M–CO–HF]$^+$, 293 (8) [M–$C_6H_4OCH_3$]$^+$. IR spectrum: ν 1680 cm^{-1}, br (C=O). Found, %: C 62.90; H 2.70; F 14.19. $C_{21}H_{11}F_3O_5$. Calculated, %: C 63.01; H 2.77; F 14.24.

3-(3,4-Dimethoxybenzoyl)-2-trifluoromethylnaphtho[2,3-*b*]furan-4,9-dione (Ve). Yield 30%. Colorless crystals, mp 210–212°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 3.85 s (3H, CH_3O), 3.90 s (3H, CH_3O), 6.83 d (1H, H_{arom}, J = 8.25 Hz), 7.25 d.d (1H, H_{arom}, J_1 = 8.25, J_2 = 2.05 Hz), 7.63 d (1H, H_{arom}, J = 2.05 Hz), 7.74–7.82 m (2H, 6-H, 7-H), 8.06–8.08 m and 8.20–8.22 m (1H each, 5-H, 8-H). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): δ_F –61.90 ppm, s (3F, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 430 (100) M^+, 412 (5) [M–CO]$^+$, 392 (5) [M–CO–HF]$^+$, 293 (40) [M–$C_6H_3(OCH_3)_2$]$^+$. IR spectrum, ν, cm^{-1}: 1670 br (C=O), 1690 br (C=O). Found, %: C 61.35; H 3.00; F 13.20. $C_{22}H_{13}F_3O_6$. Calculated, %: C 61.40; H 3.04; F 13.24.

2-Trifluoromethyl-3-(3,4,5-trimethoxybenzoyl)naphtho[2,3-*b*]furan-4,9-dione (Vf). Yield 30%, colorless crystals, mp 178–180°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 3.85 s (6H, CH_3O), 3.96 s (3H, CH_3O), 7.16 s (2H, H_{arom}), 7.80–7.88 m (2H, 6-H, 7-H), 8.12–8.16 m and 8.28–8.32 m (1H each, 5-H, 8-H). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): δ_F –61.70 ppm, s (3F, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %) : 460 (100) M^+, 432 (5) [M–CO]$^+$, 422 (5) [M–CO–HF]$^+$, 293 (60) [M–$C_6H_2(OCH_3)_3$]$^+$. IR spectrum, ν, cm^{-1}: 1680 br (C=O), 1690 br (C=O). Found, %: C 61.00; H 3.25; F 12.29. $C_{23}H_{15}F_3O_7$. Calculated, %: C 61.01; H 3.28; F 12.38.

3-(2-Thenoyl)-2-(trifluoromethyl)naphtho[2,3-*b*]furan-4,9-dione (Vg). Yield 35%. Colorless crystals, mp 208–210°C (from $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 7.24 d.d (1H, thienyl, J_1 = 4.91, J_2 = 3.95 Hz), 7.84 d.d (1H, thienyl, J_1 = 1.12, J_2 = 2.75 Hz), 7.90–7.8 m (2H, 6-H, 7-H), 8.08–8.12 m and 8.22–8.25 m (1H each, 5-H, 8-H), 8.18 d.d (1H, thienyl, J_1 = 1.12, J_2 = 2.75 Hz). ^{19}F NMR spectrum ($CDCl_3$, C_6F_6): δ_F –64.5 ppm, s (3F, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %) : 376 (30) M^+, 348 (5) [M–CO]$^+$, 322 (5) [M–CO HF]$^+$, 293 (10) [M–C_4H_3S]$^+$. IR spectrum: 1680 cm^{-1}, br (C=O). Found, %: C 57.40; H 1.80; F 15.09. $C_{18}H_7F_3O_4$. Calculated, %: C 57.45; H 1.87; F 15.15.

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