ISSN 0012-5008, Doklady Chemistry, 2011, Vol. 439, Part 1, pp. 209–212. © Pleiades Publishing, Ltd., 2011.
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CHEMISTRY

3-Trifluoroacetamidobenzoyltrifluoroacetone and Its Europium Complexes

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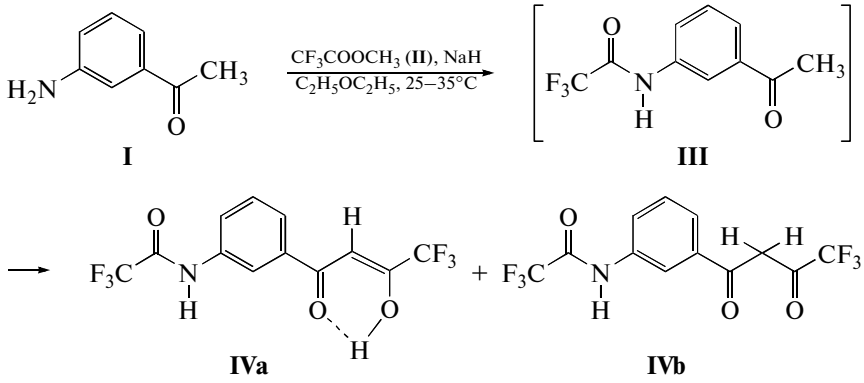
Received February 24, 2011

DOI: 10.1134/S0012500811070111

Europium and terbium complexes with functional ligands are used as luminescent labels in time-resolved fluorescence immunoassay [1–3]. Covalent bonding to the protein molecule of the coordination compound that has a primary amino group at the periphery is carried out with the use of bifunctional glutaraldehyde $H(O)C(CH_2)_3C(O)H$ [4]. Our attempt to obtain a ligand with primary amino group by the reaction of 3-aminoacetophenone (**I**) with excess of methyl trifluoroacetate (**II**) and sodium hydride led to formation of 3-trifluoroacetamidobenzoyltrifluoroacetone (**IVa**, **IVb**) instead of expected 3-aminobenzoyltrifluoroacetone $3\text{-}NH_2\text{–}C_6H_4\text{–}C(O)\text{–}CH_2\text{–}C(O)CF_3$ (Scheme 1).

The intermediate product in this reaction is 3-trifluoroacetamidoacetophenone (**III**). Compound **III** forms quickly and in high yield in the reaction of **I** with **II** in the absence of sodium hydride.

Compound **IV** exists in acetone-d_6 and chloroform-d_3 solutions as a mixture of enol and ketone forms in the 15 : 1 ratio. The presence of enol **IVa** is confirmed by the signal at 6.91 ppm (C–H), while the existence of diketone **IVb** follows from the singlet signal of two protons of the CH_2 group at 4.81 ppm. The mass spectrum of compound **IV** shows maximum intensity peaks for fragment ions with m/z 69.6, 216.2, 240.4, 258.3, and 307.1. The peak of the molecular ion with m/z 327.0 is of low intensity. The presence of the peaks with m/z 69.6, 258.3, and 307.1 indicates that the fragmentation of the molecule of β-diketone **IV** begins with abstraction of HF (m/z 20) and the CF_3 radical (m/z 69.3).



Scheme 1.

It is known that the protection of the primary amino group is accomplished by its transformation into amide one [5]. The trifluoroacetamide protective group $CF_3C(O)NHR$ is considered to be the most convenient because its deprotection (by the treatment of amide with an alcoholic solution of alkali or potassium carbonate) is carried out under milder conditions as compared with a nonfluorinated analogue $CH_3C(O)NHR$.

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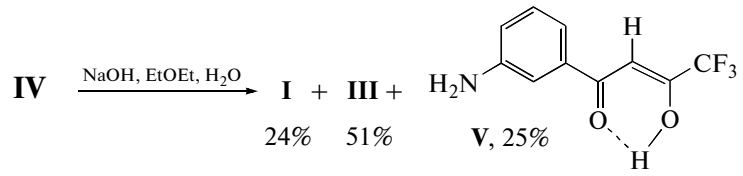
$$RNH_2 \xrightarrow[[CF_3C(O)]_2O]{CF_3COOCH_3} RNHC(O)CF_3$$
$$\xrightarrow{NaOH,\ CH_3OH,\ H_2O} RNH_2.$$

Our attempt to prepare 3-aminobenzoyltrifluoroacetone (**V**) in this manner led to formation (according to ^{1}H NMR, IR, HPLC, and GC-MS) of the target compound in only 25% yield. The treatment of a solution of compound **IV** in diethyl ether with sodium hydroxide resulted in competitive cleavage of the β-diketone to compounds **I** and **III** (Scheme 2).



Scheme 2.

The ^{1}H NMR spectrum of the reaction mixture shows the appearance of two singlet signals from the protons of the methyl groups in compounds **I** (2.47 ppm) and **III** (2.59 ppm), and the IR spectrum exhibits two bands of the N–H stretching vibrations in the primary amino group at 3370 and 3466 cm^{-1}.

Europium(III) tris(3-trifluoroacetamidobenzoyltrifluoroacetonate) trihydrate $EuL_3 \cdot 3H_2O$ (**VI**) was obtained from compound **IV**, NaOH, and europium chloride in an aqueous alcohol medium (L is the anion of 3-trifluoroacetamidobenzoyltrifluoroacetone). This compound is a fine orange powder.

Figure 1 shows the electronic absorption spectra of ligand **IV** and complex **VI**. The spectra of these compounds are alike and composed of two absorption bands with maxima at 242 and 324 nm. The large similarity is due to the existence of both the ligand and the complex as chelates. In the enol form of the ligand (**IVa**), the proton bound to the oxygen atom of the carbonyl group by intramolecular hydrogen bond plays a role of a metal cation.

The preparation of europium(III) tris(3-aminobenzoyltrifluoroacetonate) trihydrate **VII** containing amino group was carried out by the elimination of the protective group under conditions similar to those used for the reaction of ligand **IV** with NaOH. Complex **VI** proved to be moderately stable toward the alkaline reagent. The appearance of the amino group in the reaction product is clearly detected by IR spectroscopy. Figure 2 shows a spectral region within 4000–3000 cm^{-1} for initial compound **VI** and the product of its reaction with NaOH (**VII**). The disappearance of ν(NH) absorption band of the amide group at 3300 cm^{-1} and the emergence of two bands at 3364 and 3455 cm^{-1} of the primary amino group are observed.

Compounds **VI** and **VII** exhibit strong red–orange photoluminescence (PL) in dilute acetonitrile solutions ($c = 10^{-3}$–10^{-6} M) (Fig. 3). Emission spectra are identical on the whole, whereas photoluminescence excitation (PLE) spectra are different. When detected at wavelength of Eu^{3+} cation emission at 615 nm, the PLE spectra show single bands at 370 nm for com-

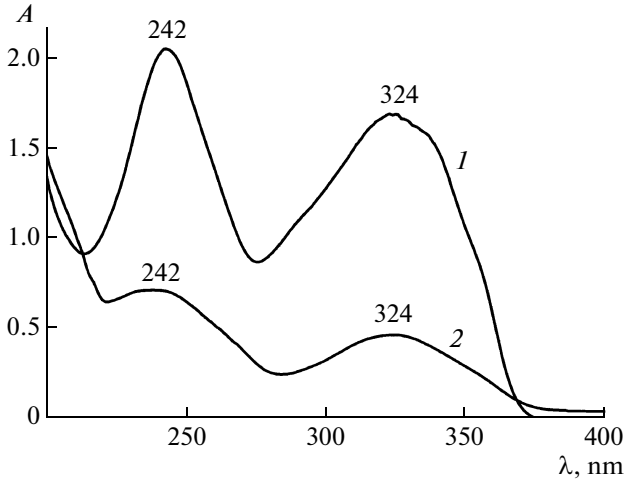


Fig. 1. Electronic absorption spectra of acetonitrile solutions of ligand **IV** ($c = 1.8 \times 10^{-4}$ M) (*1*) and complex **VI** ($c = 6.8 \times 10^{-6}$ M) (*2*).

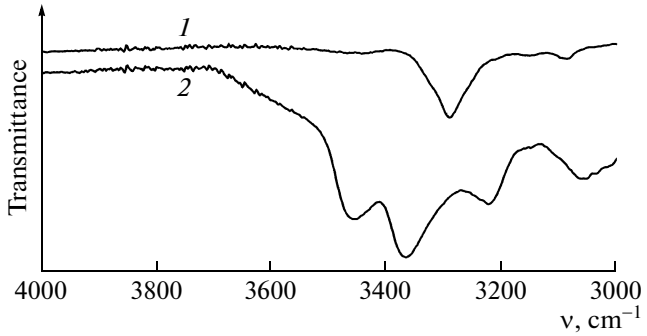


Fig. 2. IR spectra of compounds **VI** (*1*) and **VII** (*2*) in the region of N–H stretching vibrations.

pound **VI** and at 405 nm for compound **VII**. The PL spectra in both cases contain the strongest band of the $^5D_0 \rightarrow {}^7F_2$ transition in Eu^{3+} cation with λ_{max} 615 nm.

Thus, our study revealed that the reaction of 3-aminoacetophenone with methyl trifluoroacetate proceeds in two stages and leads to formation of 3-trifluoroacetamidobenzoyltrifluoroacetone instead of expected 3-aminobenzoyltrifluoroacetone. The reason consists in the ease of the reaction of CF_3COOCH_3 with the amino group of starting 3-aminoacetophenone and the initial formation of 3-trifluoroacetamidoacetophenone. Luminescent europium β-diketonate containing primary amino group at the periphery was obtained by the treatment of the amide derivative with an alkali solution.

EXPERIMENTAL

IR spectra were recorded as thin films between KBr plates or as Nujol mulls on an FSM 1201 Fourier-transform IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-200 spectrometer (operating at 200 MHz) at 25°C with TMS as an internal reference. Fluorescence and fluorescence excitation spectra were measured with a PerkinElmer LS-55 spectrofluorimeter in acetonitrile solutions. Electronic absorption spectra were recorded on a PerkinElmer Lambda 25 spectrophotometer.

GC-MS analysis was performed with a Polaris Q/Trace GC Ultra chromatograph–mass spectrometer using a TR-5MS capillary column 60 m long and 0.25 mm in diameter. The flow rate of the carrier gas (helium of M 60 grade) was 1.2 mL/min, the column temperature was programmed from 40 to 200°C at a rate of 10 K/min. Mass spectra were detected at an ionizing voltage of 70 eV in the range of 40–400 daltons. NIST 2005 library was used for the identification of detected substances.

The analysis of products for the reaction of compound **IV** with NaOH was accomplished with a Knauer liquid chromatograph equipped with an UV detector using a 6 × 100 mm column with a Separon Si C18 sorbent (5 μm) and 60% aqueous acetonitrile as the eluent.

Sodium hydride was used as a 60% suspension in a mineral oil (Acros). Methyl trifluoroacetate (PIM Invest) and 3-aminoacetophenone (Acros) were used without preliminary purification.

3-Trifluoroacetamidoacetophenone (III) was obtained by the reaction of equimolar amounts of compounds **I** and **II** in ether. Yield, 87%.

IR (ν, cm^{-1}): 3300 (NH), 1716 (amide I), 1614, 1550 (C=O), 1590 (amide II), 1489, 1458, 1282, 1221, 1188, 1150, 1120 (CF_3), 788.

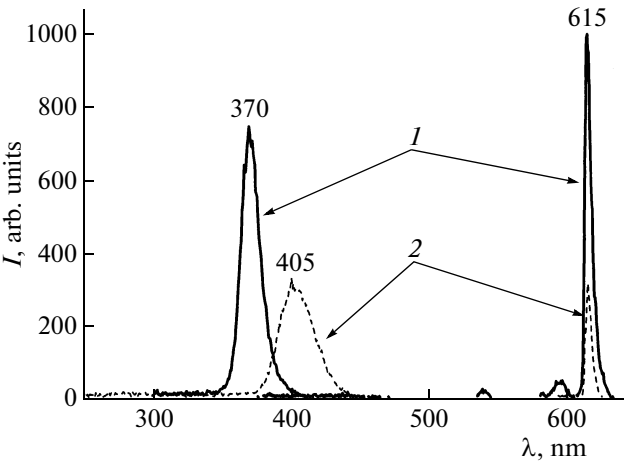


Fig. 3. Fluorescence excitation spectra (λ_{reg} = 615 nm) and fluorescence spectra of complexes (*1*) **VI** (λ_{ex} = 340 nm, $c = 6.8 \times 10^{-6}$ M) and (*2*) **VII** (λ_{ex} = 440 nm, $c = 3 \times 10^{-3}$ M) in an acetonitrile solution.

^{1}H NMR ($(CD_3)_2CO$, δ, ppm, *J*, Hz): 2.60 (s, 3H, $C\underline{H}_3C(O)$–), 7.57–7.61 (t, 1H, arom., *J* = 8.03), 7.7–7.89 (d, 1H, arom.), 8.00–8.02 (d, 1H, arom.), 8.33 (s, 1H, arom.), 10.44 (s, 1H, NH).

For $C_{10}H_8F_3NO_2$ anal. calcd. (wt %): C, 51.95; H, 3.49. Found (wt %): C, 51.06; H, 3.07.

3-Trifluoroacetamidobenzoyltrifluoroacetone (IV). A three-necked flask equipped with s stirrer, a dropping funnel, and a reflux condenser was heated to 100°C in an argon flow, the flask was charged with a solution of 3.0 g (0.075 mol) of NaH in 100 mL of anhydrous diethyl ether, and 19.2 g (0.15 mol) of methyl trifluoroacetate was added dropwise with stirring. Then, a solution of 5.0 g (0.037 mol) of 3-aminoacetophenone in 20 mL of anhydrous diethyl ether was added, stirred for 3 h, and a 10% solution of H_2SO_4 was added to neutral reaction. The ether layer was separated from the aqueous solution and dried with Na_2SO_4, and the diketone was recrystallized from the diethyl ether–hexane mixture. The compound was finally purified by vacuum sublimation to give 9.4 g (78%) of diketone **IV**.

IR (ν, cm^{-1}): 3300 (NH), 3087 (C=C–H), 1716 (amide I), 1614, 1550 (C=O), 1590 (amide II), 1489, 1458, 1282, 1221, 1188, 1150, 1120 (CF_3), 788.

^{1}H NMR ($(CD_3)_2CO$, δ, ppm, *J*, Hz): 4.81 (s, 2H, $C\underline{H}_2$ in diketone), 6.91 (s, 1H, $C\underline{H}$ in enol), 7.64–7.68 (t, 1H, arom., *J* = 8.03), 8.02–8.04 (d, 1H, arom.), 8.08–8.1 (d, 1H, arom.), 8.44 (s, 1H, arom.), 10.49 (s, NH).

For $C_{12}H_7F_6NO_3$ anal. calcd. (wt %): C, 44.03; H, 2.16. Found (wt %): C, 43.20; H, 2.15.

Europium(III) tris(3-trifluoroacetamidobenzoyltrifluoroacetonate) trihydrate (VI). Compound **IV** (0.98 g, 3 mmol) was dissolved in 15 mL of 95% ethanol. Then, 3 mL of 1 N NaOH and 5 mL of 0.2 M aqueous solution of europium chloride (1 mmol) was added with vigorous stirring. To this mixture, 100 mL of water was added, and the mix was heated to 60°C and cooled. The resulting orange precipitate of compound **VI** was purified by recrystallization from a dichloromethane–hexane mixture. Yield, 0.5 g (43%).

IR (ν, cm^{-1}): 3300 (NH), 3087 (C=C–H), 1716 (amide I), 1614 (C=O), 1590 (amide II), 1560, 1533, 1489, 1465, 1299, 1225, 1188, 1150, 1120 (CF_3), 788.

^1H NMR ($(CD_3)_2CO$, δ, ppm, *J*, Hz): 6.57 (s, 1H, C<u>H</u>), 6.92–7.00 (t, 1H, arom., $J = 8.03$), 7.15–7.18 (d, 1H, arom.), 7.26–7.30 (d, 1H, arom.), 10.02 (s, 1H, arom.).

For $C_{36}H_{24}EuF_{18}N_3O_{12}$ anal. calcd. (wt %): C, 36.46; H, 2.04. Found (wt %): C, 37.40; H, 2.15.

Europium(III) tris(3-aminobenzoyltrifluoroacetonate) trihydrate (VII). To a magnetically stirred solution of 0.5 g (0.42 mmol) of compound **VI** in 20 mL of ethanol, 2 mL of 1 N NaOH was added dropwise. The mixture was stirred for 7 h at 25°C. Excess alkali was neutralized with acid. The solvent and water were removed in vacuum. The solid residue was dissolved in dichloromethane and washed two times with water. The organic layer was separated from the aqueous solution and dried with Na_2SO_4. The solvent was removed in vacuum to give 0.25 g (70%) of compound **VII** as a yellow powder.

IR (ν, cm^{-1}): 3364, 3455 (NH_2), 3060 (C=C–H), 1719, 1682 (C=O), 1614, 1580, 1529, 1492, 1316, 1292, 1259, 1191, 1137 (CF_3), 798.

For $C_{30}H_{27}EuF_9N_3O_9$ anal. calcd. (wt %): C, 40.13; H, 3.03. Found (wt %): C, 41.06; H, 2.83.

Analyses were performed in the Analytical Center, Razuvaev Institute of Organometallic Chemistry, Russian Academy of Sciences.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (project nos. 08–03–00771 and 10–03–90006-Bel), the Ministry of Education and Science (State contract no. 16.740.11.0015), and the Presidium of the Russian Academy of Sciences (program "Directed Synthesis of Substances with Prescribed Properties and Design of Functional Materials Based Thereof").

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