ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 4, pp. 500–503. © Pleiades Publishing, Ltd., 2011.
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Synthesis of 4-Formylphenyl 7-Acetyl-8-oxononylcarbamate and Europium Complex Based Thereon

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Received June 22, 2010

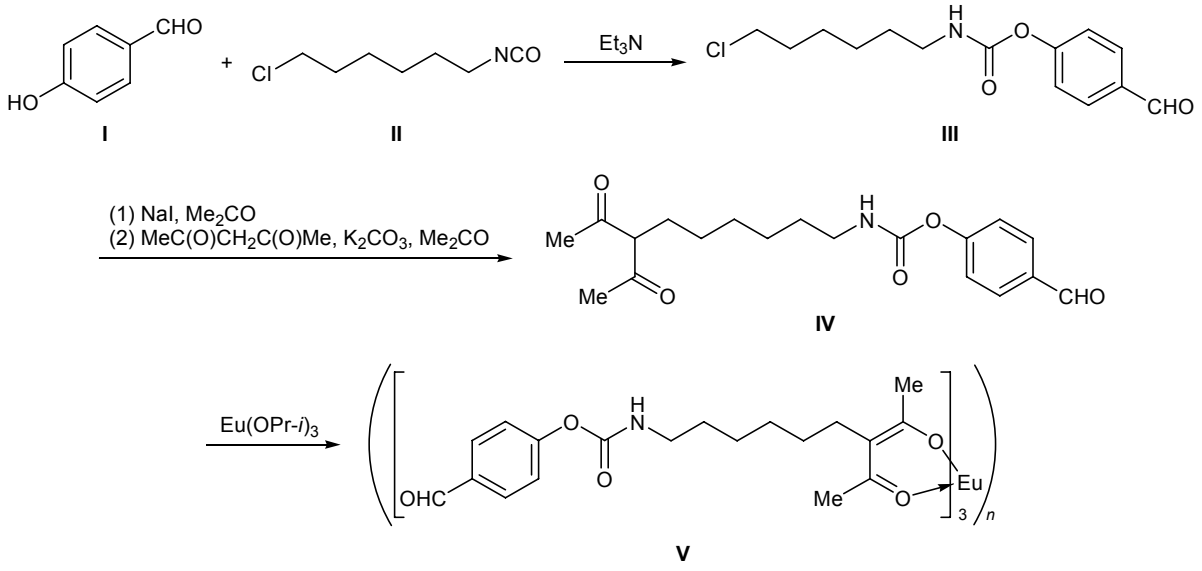
Abstract—A new chelating ligand, 4-formylphenyl 7-acetyl-8-oxononylcarbamate, was synthesized starting from 4-hydroxybenzaldehyde and 6-chlorohexyl isocyanate. The reaction of this ligand with europium triisopropoxide gave the corresponding europium(III) complex.

DOI: 10.1134/S1070428011040051

β-Diketones are universal chelating ligands that are used in the synthesis of coordination compounds of non-transition, transition, and rare-earth metals [1–4]. Such ligands endow the corresponding complexes with such properties as volatility, solubility, and resistance to oxygen and moisture. Modern technologies imply the necessity of synthesizing complexes with functionalized organic ligands to ensure their application in heterogeneous catalysis, medicine, and optics.

Coordination compounds of rare-earth metals are used as luminescent labels in medical diagnostics [5–7]. Europium and terbium complexes are used more frequently than complexes of other metals due to photoluminescence in the red (Eu^{3+}) or green (Tb^{3+}) region of the spectrum. The problem related to chemical binding of a biomarker to proteins is solved by introduction of an organic group capable of reacting with fragments of polypeptide chain. The choice of appropriate groups is strongly limited. A few known examples include isothiocyanate [8] and sulfonyl chloride derivatives [9]. A complex having a primary amino group in the ligand can be linked to protein through glutaraldehyde which readily reacts with amino groups in both protein and the complex [10].

Scheme 1.

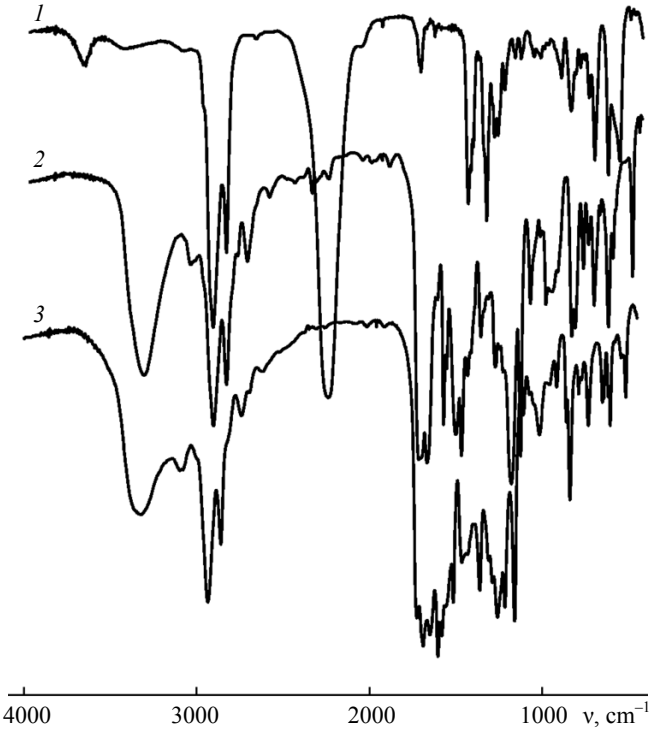


An aldehyde group present in the ligand molecule should ensure direct binding of luminescent label to biomolecule. In the present work we tried to implement the above approach with the use of acetylacetone as most popular and accessible representative of pentane-2,4-diones [11].

As starting compounds for functionalization of acetylacetone we selected 4-hydroxybenzaldehyde (**I**) and 6-chlorohexyl isocyanate (**II**). Compound **I** was the source of aldehyde group, and isocyanate **II** was used as spacer providing the possibility for introduction of an aldehyde group into β-diketone molecule. It is known [12] that alcohols and phenols readily react with isocyanates to give carbamic acid esters (urethanes). Organic substituent can be introduced into the methylene group of β-diketone via reaction of halogen derivatives with CH acid in the presence of hydrogen halide acceptor, e.g., primary amine or alkali metal carbonate. The reaction sequence leading to the target ligand, 4-formylphenyl 7-acetyl-8-oxononylcarbamate (**IV**), is shown in Scheme 1. 4-Hydroxybenzaldehyde (**I**) reacted with 6-chlorohexyl isocyanate to give 4-formylphenyl 6-chlorohexylcarbamate (**III**). Taking into account that nucleophilic substitution in iodoalkanes occurs more readily than in chloro analogs, compound **III** was initially converted into iodo derivative. The subsequent reaction with acetylacetone was carried out in the presence of potassium carbonate which ensured better results as compared to triethylamine.

Compound **III** was isolated as a white powder, and compound **IV** was a colored viscous liquid. Our attempts to purify these compounds by vacuum sublimation were unsuccessful: decomposition occurred with formation of non-volatile tarry products. The progress of the reaction of aldehyde **I** with isocyanate **II** can be readily monitored by IR spectroscopy, following disappearance of the characteristic NCO absorption band at 2271 cm^{-1}. Figure shows the IR spectra of isocyanate **II** and addition product **III**. The IR spectrum of the latter contained absorption bands due to stretching vibrations of the amide N–H group at 3337 cm^{-1}, aromatic C–H bonds at 3065 cm^{-1}, and aldehyde C–H bond at 2738 cm^{-1}. A number of strong absorption bands in the region 1800–1500 cm^{-1} were assigned to vibrations of the carbamate and aldehyde fragments [1740 (C=O, aldehyde), 1698 (amide I), 1531 cm^{-1} (amide **II**)], as well as of aromatic C=C bonds (1600, 1498 cm^{-1}). The presence of a hydrocarbon chain consisting of six methylene units is confirmed by absorption at 1465, 1385, and 730 cm^{-1}. A strong band at 1212 cm^{-1} corresponds to C–O–C stretching vibrations of the ester group. Compound **II** displayed in the ^{1}H NMR spectrum two triplets, two quintets, and one multiplet with an intensity ratio of 1 : 1 : 1 : 1 : 2. Two downfield triplets at δ 3.53 and 3.30 ppm belong to protons in the terminal CH_2 groups which are linked to electronegative substituents (Cl, σ_I = 0.43; NCO, σ_I = 0.38) [13]; the neighboring methylene protons resonated as two quintets at δ 1.74 and 1.62 ppm, and the multiplet signal at δ 1.36–1.49 ppm corresponds to two central methylene units in the six-membered chain. Addition of 4-hydroxybenzaldehyde slightly affects the position of the above signals, but four downfield signals appear due to protons in the NH (δ 7.00 ppm), *p*-phenylene (δ 7.32–7.36, 7.91–7.95 ppm), and aldehyde groups (δ 9.99 ppm).

Comparison of the IR spectra of **III** and **IV** (see figure) shows complication of the spectral pattern in the range from 1700 to 1500 cm^{-1} in going from **III** to **IV**, which may be due to the presence of two carbonyl groups in the acetylacetone fragment. The spectral pattern in the regions 3500–2700 and 1500–500 cm^{-1} changes less significantly. The ^{1}H NMR spectrum of **IV** contained two singlets from methyl protons in the



IR spectra of (*1*) 6-chlorohexyl isocyanate (**II**), (*2*) 4-formylphenyl 6-chlorohexylcarbamate (**III**), and (*3*) 4-formylphenyl 7-acetyl-8-oxononylcarbamate (**IV**).

β-diketone fragment at δ 2.12 (ketone) and 2.21 ppm (enol), a signal from the CH proton at δ 5.46 ppm (diketone tautomer), and a signal from the enolic hydroxy proton at δ 15.30 ppm.

Functionalized β-diketon (**IV**) rapidly reacted with europium triisopropoxide in THF to give insoluble β-diketonate **V**. Poor solubility of the product suggests that the complex exists as coordination polymer. Analogous pattern was observed for anhydrous tris(acetylacetonato)europium(III) [14]. We succeeded in converting compound **V** into a soluble state only by heating with excess tributylphosphine oxide (but not with phenanhtroline) in acetone. A solution of **V** in $Bu_3P{=}O$ showed a very weak cationic luminescence which considerably increased upon addition of an equimolar amount of phenanthroline. The photoluminescence spectrum contained four emission bands due to europium cation with their maxima at 537 ($^5D_1 \rightarrow {}^7F_1$), 557 ($^5D_1 \rightarrow {}^7F_2$), 594 ($^5D_0 \rightarrow {}^7F_1$), and 616 nm ($^5D_0 \rightarrow {}^7F_2$), the latter being the most intense. Fluorescence of the ligand was observed as a broad band centered at λ 475 nm.

Thus we have demonstrated the possibility for synthesizing luminescent europium(III) coordination compound in which the ligand possesses an aldehyde group capable of reacting with polypeptide chain.

EXPERIMENTAL

The IR spectra were recorded from films between KBr plates or dispersions in mineral oil on an FSM 1201 spectrometer with Fourier transform. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX-200 instrument (200 MHz) at 25°C using tetramethylsilane as internal reference. The fluorescence and fluorescence excitation spectra of compound **V** were measured on a Perkin–Elmer LS-55 spectrofluorimeter from a solution in $Bu_3P{=}O$–acetone (1:5 by volume) in the presence of an equimolar amount of phenanthroline. 4-Hydroxybenzaldehyde, 6-chlorohexyl isocyanate, and acetylacetone were analyzed on a Tsvet-800 gas chromatograph equipped with a thermal conductivity detector and a 0.3×300-cm column packed with 5% of SE-30 on Inerton-AW; carrier gas helium. Europium triisopropoxide was synthesized from anhydrous $EuCl_3$ and NaOPr-*i* according to the procedure described in [15]. 4-Hydroxybenzaldehyde was sublimed under reduced pressure, and acetylacetone was distilled prior to use.

4-Formylphenyl 6-chlorohexylcarbamate (III). 4-Hydroxybenzaldehyde (**I**), 13.92 g (114 mmol), was dissolved in 50 ml of tetrahydrofuran, 27.62 g (171 mmol) of 6-chlorohexyl isocyanate (**II**) and 0.10 g (1 mmol) of triethylamine were added, the mixture was heated for 20 h at 90°C, and the solvent was distilled off under reduced pressure. The residue was a viscous liquid which was washed first with toluene and then with hexane. The solvent was removed under reduced pressure. Yield 25.03 g (77%), white powder, mp 43°C. IR spectrum, ν, cm^{-1}: 3336 (N–H); 3063 (C–H_{arom}); 2936, 2859 (C–H_{aliph}); 2735 (C–H_{ald}); 1737 (C=O, aldehyde); 1697 (C=O, amide I); 1598 (C=C_{arom}); 1534 (δNH, amide II). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.41–1.49 m (4H, CH_2CH_2), 1.53–1.65 m (2H, C**H**$_2$$CH_2$NH), 1.72–1.82 m (2H, C**H**$_2$$CH_2$Cl), 3.18–3.28 q (2H, C**H**$_2$NH, J = 6.3 Hz), 3.57–3.64 t (2H, CH_2Cl, J = 6.8 Hz), 7.00 s (1H, NH), 7.32–7.36 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.91–7.95 d (2H, 2′-H, 6′-H, J = 8.53 Hz), 9.99 s (1H, CHO). Found, %: C 59.16; H 6.33; Cl 12.00. $C_{14}H_{18}ClNO_3$. Calculated, %: C 59.26; H 6.35; Cl 12.52.

4-Formylphenyl 7-acetyl-8-oxononylcarbamate (IV). A solution of 23.25 g (82 mmol) of compound **III** in 30 ml of acetone was added to a solution of 13.70 g (91 mmol) of sodium iodide in 80 ml of acetone. The mixture was stirred for 6 h at 80°C, the precipitate of sodium chloride was filtered off, and 8.00 g (0.80 mmol) of acetylacetone and 12.30 g (89 mmol) of potassium carbonate were added. The mixture was stirred for 7 h at 80°C and filtered, and the solvent and volatile products were distilled off from the filtrate under reduced pressure at 50°C. Yield 16.60 g (59%), viscous yellow–green liquid. IR spectrum, ν, cm^{-1}: 3333 (N–H); 3086 (C–H_{arom}); 2936, 2863 (C–H_{aliph}); 2743 (C–H_{ald}); 1724 (C=O); 1687 (C=O, amide I); 1647, 1601, 1577, 1510 (δNH, amide II). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.06–1.13 m (4H, CH_2CH_2), 1.27–1.58 m (2H, C**H**$_2$$CH_2$NH), 1.68–1.87 m (2H, C**H**$_2$$CH_2$CH), 2.12 s and 2.21 s (3H each, CH_3), 3.15–3.25 m (2H, C**H**$_2$NH), 3.34–3.44 m (2H, C**H**$_2$CH), 5.46 s (1H, CH), 6.98–7.02 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.36 s (1H, NH), 7.76–7.80 d (2H, 2′-H, 6′-H, J = 8.5 Hz), 9.83 s (1H, CHO), 15.30 s (1H, OH, enol). Found, %: C 64.56; H 7.03; N 3.87. $C_{19}H_{25}NO_5$. Calculated, %: C 65.67; H 7.26; N 4.03.

Tris(4-formylphenyl 7-acetyl-8-oxononylcarbamato)europium(III) (V). An ampule was charged with a solution of 2.65 g (8 mmol) of compound **IV** in 5 ml of THF, a solution of 0.84 g (2.5 mmol) of Eu(OPr-*i*)$_3$ in 5 ml of THF was added, and the ampule was evacuated, sealed, and heated for 3 h at 80°C. After cooling, the ampule was opened, and the precip-

itate was separated by centrifugation, washed with THF, toluene, and diethyl ether, and dried under reduced pressure. Yield 1.50 g (47%), yellow powder insoluble in THF, toluene, diethyl ether, methylene chloride, and acetonitrile and soluble in tributylphosphine oxide. IR spectrum, ν, cm^{-1}: 3333, 1015, 917, 836, 765, 650. Luminescence spectrum (λ_{excit} 340 nm), λ, nm: 475 (ligand), 537 (Eu $^5D_1 \rightarrow {}^7F_1$), 557 (Eu $^5D_1 \rightarrow {}^7F_2$), 594 (Eu $^5D_0 \rightarrow {}^7F_1$), 616 (Eu $^5D_0 \rightarrow {}^7F_2$). Found, %: C 56.86; H 6.73; Eu 12.31. $C_{57}H_{75}N_3O_{15}Eu$. Calculated, %: C 57.33; H 6.33; Eu 12.73.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 08-03-00771, 10-03-90006Bel), by the Ministry of Education and Science of the Russian Federation (project no. GK 16.740.11.0015), and by the Presidium of the Russian Academy of Sciences (program "Target-Oriented Synthesis of Substances with Specified Properties and Design of Functional Materials Based Thereon").

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