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Synthesis of 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate

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Abstract. 2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate has been synthesized by the reaction of ethyl (E)-2-((5-(4-methoxyphenyl)-2-oxofuran-3(2H)-ylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate or 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate with potassium tert-butoxide.

INTRODUCTION

One of the main tasks in organic chemistry is the synthesis of new compounds that have practical applications. Due to the presence of several reaction centers in the molecules of 3-imino-3H-furan-2-ones, these type of compounds make it possible to obtain various structures of acyclic and heterocyclic frameworks [1-5]. These reactions often proceed with the preservation of a fragment of 2,4-dioxobutanoic acids, the compounds which currently remains at a high level of interest in the field of medical chemistry [6-15].

![Chemical structures](image.png)

**FIGURE 1.** Biologically active compounds obtained based on 2,4-dioxobutanoic acid

At the same time, the introduction of an additional biologically active fragment, such as 2-aminothiophenes Gewald, into the structure of 3-imino-3H-furan-2-ones allows one to expect the appearance of new biologically active
properties [16-20]. In addition, we previously studied the chemical transformations of 3-imino-3H-furan-2-ones containing the aminothiophenes Gewald fragment partially [21-25].

**EXPERIMENTAL**

**General Methods**

Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra.

$^1$H and $^{13}$C NMR spectra were recorded at 400 MHz for $^1$H and 100 MHz for $^{13}$C NMR at room temperature; the chemical shifts (δ) were measured in ppm with respect to the solvent (CDCl$_3$, DMSO$_{60}$). $^1$H: δ = 7.26 ppm, $^{13}$C: δ = 77.16 ppm. Coupling constants (J) are given in Hertz. Splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), dd (doublet of doublets) and br (broadened). Melting points were determined with a «Stuart SMP 30» and the values are uncorrected. Flash chromatography was performed on silica gel Macherey Nagel (40-63 μm).

Reaction progress was monitored by thin-layer chromatography (TLC) on aluminum backed plates with Merck Kiesel 60 F254 silica gel. The TLC plates were visualized either by UV radiation at a wavelength of 254 nm or stained by exposure to a Dragendorff’s reagent or aqueous potassium permanganate solution. All the reactions were carried out using dried and freshly distilled solvent.

**General method for synthesis of compound 3**

Synthesis of 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid 3: A solution of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 2 (0.01 mol) in ethanol (20 mL) was added to a solution of 2-hydroxy-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid 1 (0.01 mol) in ethanol (20 mL). The mixture was allowed to stand at room temperature for 24 h. and cooled to 0 °C, filtered off the precipitate formed and recrystallized from acetonitrile. Compound 3 is a red solid, obtained in 86% yield, readily soluble in chloroform and DMSO, soluble in toluene and ethanol when heated, and insoluble in water and alkanes.

**General method for synthesis of compound 4**

Synthesis of ethyl (E)-2-((5-(4-methoxyphenyl)-2-oxofuran-3(2H)-ylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 4: A mixture of 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid 3 (0.01 mol) and propenoic anhydride (4 mL) was stirred for 2 h. at 140 °C, then cooled to 0 °C. A precipitate formed was filtered off (Fig. 3). Compound 4 is a dark red solid, obtained in 92% yield, soluble in chloroform and DMSO, soluble in toluene and ethanol when heated, and insoluble in water and alkanes.
General method for synthesis of compound 5

Synthesis of potassium 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate 5: Method A. Potassium tert-butoxide (0.01 mol) was added to Ethyl (E)-2-((5-(4-methoxyphenyl)-2-oxofuran-3(2H)-ylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 4 (0.01 mol) in dioxane (20 mL). The solution was stirred at room temperature for 24 hours and then cooled to 0 °C. A precipitate formed was filtered off (Fig. 5). Compounds 5 is a yellow solid, obtained in 90% yield, soluble in DMSO and water.

Method B. Potassium tert-butoxide (0.01 mol) was added to 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid 3 (0.01 mol) in dioxane (20 mL) and the resulting solution was stirred at room temperature for 24 hours, then cooled to 0 °C. A precipitate formed was filtered off (Fig. 5). Compounds 5 is a yellow solid, obtained in 96% yield, soluble in DMSO and water.

Characterization of the products

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid (3). Red solid (yield 86 %), m.p. 186-187 °C. IR (nujol) v: 1712, 3412. $^1$H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.40 (t, $J$ 7.1 Hz, 3H), 1.82 (m, 2H), 1.87 (m, 2H), 2.75 (m, 2H), 2.79 (m, 2H), 3.90 (s, 3H), 4.38 (q, $J$ 7.1 Hz, 2H), 7.01 (m, 2H), 7.08 (s, 1H), 8.03 (m, 2H), 12.19 (s, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (ppm): 14.2, 22.4, 22.7, 24.9, 26.5, 55.7, 61.3, 96.5, 114.3, 117.6, 128.7, 129.6, 131.2, 134.6, 145.5, 162.4, 164.3, 187.7 [26].

Ethyl (E)-2-((5-(4-methoxyphenyl)-2-oxofuran-3(2H)-ylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4). Dark red solid (yield 92 %), m.p. 146-147 °C. IR (nujol) v: 1610, 1797. $^1$H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.40 (t, $J$ 7.1 Hz, 3H), 1.82 (m, 2H), 1.87 (m, 2H), 2.75 (m, 2H), 2.79 (m, 2H), 3.90 (s, 3H), 4.38 (q, $J$ 7.1
Hz, 2H), 6.77 (s, 1H), 7.00 (m, 2H), 7.80 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (ppm): 14.3, 22.3, 22.9, 25.2, 25.7, 55.9, 61.2, 96.4, 114.8, 119.5, 128.7, 131.6, 136.0, 136.2, 146.2, 149.7, 161.3, 163.6, 164.1, 166.5 [27].

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate (5). Yellow solid (yield Method A 90%, Method B 96%). m.p. 303–305 °C. IR (nujol) ν: 1705, 3412. 1H NMR (DMSOd$_6$, 400 MHz) δ (ppm): 1.35 (t, J 7.1 Hz, 3H), 1.72 (m, 4H), 2.53 (m, 2H), 2.69 (m, 2H), 3.83 (s, 3H), 4.34 (q, J 7.1 Hz, 2H), 5.87 (s, 1H), 7.01 (m, 2H), 7.86 (m, 2H), 13.35 (s, 1H). Anal. Calcd for C$_{22}$H$_{22}$KNO$_6$S: C 56.51, H 4.74, N 3.00, S 6.86. Found: C 56.55, H 4.72, N 3.03, S 6.89.

CONCLUSIONS

We have synthesized new 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate compounds in two different methods from ethyl (E)-2-((5-(4-methoxyphenyl)-2-oxofuran-3(2H)-ylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate and 2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate.

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