Synthesis of ethyl 3-(3-hydroxy-2-thienyl)-3-oxopropanoates

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An approach to the synthesis of substituted ethyl 3-(3-hydroxy-2-thienyl)-3-oxopropanoates was developed based on the reaction of ethyl cyanoacetate, carbon disulfide, and ethyl 4-chloroacetoacetate. The reaction regioselectively involved the ester group, rather than the nitrile one like in the case when malononitrile or cyanacetamide were used.

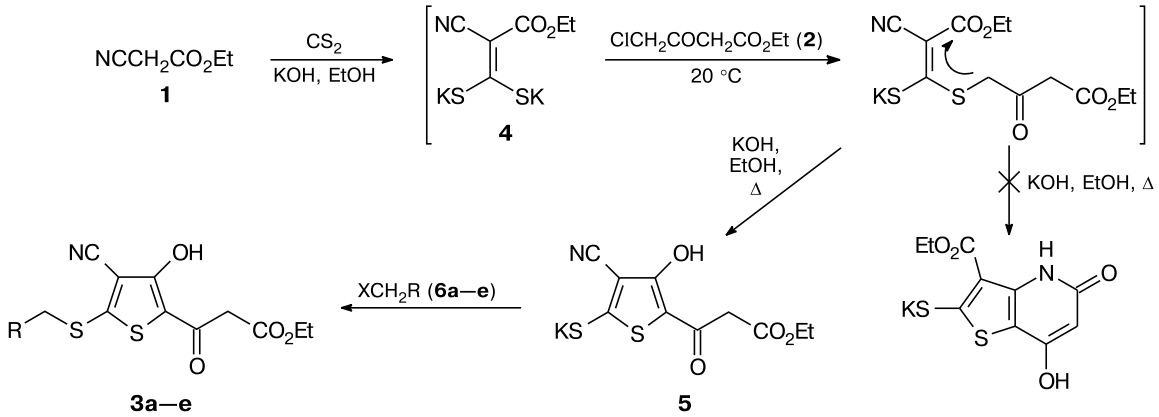
Key words: 3-oxythiophenes, ethyl cyanoacetate, ethyl 4-chloroacetoacetate, Dieckmann reaction.

Earlier, we have developed an approach to the synthesis of thieno[3,2-*b*]pyridines based on malononitrile, cyanacetamide, and ethyl 4-chloroacetoacetate[1] by the domino-type reaction: S_N2 reaction → Thorpe—Ziegler reaction → Thorpe—Guareshi reaction. In this case, the alkylation of the pre-prepared dipotassium salt of dimercaptomethylenemalononitrile or cyanacetamide is followed by the reaction of the nitrile and the active methylene groups (the Thorpe—Ziegler reaction) with the 3-aminothiophene ring closure. Then, the amino group formed was involved in the pyridine ring closure. It is of significant interest to use in such a synthesis of other bifunctional compounds, for example, ethyl cyanoacetate. The literature data[2] show that the outcome of the reaction of ethyl cyanoacetate with carbon disulfide and ethyl 4-bromoacetoacetate depends on the order in which the reagents are mixed and leads either to the substituted 2-methylidene-1,3-dithiolane, or to the intermediate 3-aminothiophene of our interest. However, no pyridine ring closure with the formation of thieno[3,2-*b*]pyridine occurred under the mild conditions used (NaH, tetrahydrofuran, 0 °C).[2]

In this connection, the purpose of the present work was to study the reaction of ethyl cyanoacetate (**1**), carbon disulfide, and ethyl 4-chloroacetoacetate (**2**) under conditions, which were used earlier in the reactions of malononitrile and cyanacetamide.[1]

The synthesis was carried out under conditions described for malononitrile.[1] The reaction led to the formation of 3-hydroxythiophenes **3a**—**e**. Thus, the *in situ* pre-prepared dipotassium salt **4** was alkylated by ester **2** with subsequent cyclization at the ester group, rather than at the nitrile one (Scheme 1).

Scheme 1



Compounds	**3a**, **6a**	**3b**, **6b**	**3c**, **6c**	**3d**, **6d**	**3e**, **6e**
R	PhCO	Ph	4-MeC_6H_4	EtOOC	MeCO

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Since the structure of the intermediately formed salt **5** does not have an amino group, the reaction stops at the step of the thiophene ring closure and in contrast to the reaction with malononitrile is not followed by the intramolecular cyclization. Salt **5** is a convenient building block and can be converted without isolation to the target compounds **3a**—**e** by alkylation with halides **6a**—**e**.

The structure of thiophenes **3a**—**e** was confirmed by ^{1}H NMR and IR spectroscopy and high resolution mass spectrometry. The IR spectra of compounds **3** exhibit absorption bands of the carbonyl and ester groups of the oxopropanoate fragment and the absorption band of the nitrile group at 2220—2230 cm^{-1}.

In the ^{1}H NMR spectra, the signals for the protons of the ethyl group of one of the ester fragment are found at δ 1.16—1.17 and 4.08—4.09, and the signal for the two protons of the methylene group is found as a singlet at δ 3.85—3.87.

In conclusion, we found that the reaction of ethyl cyanoacetate (**2**), carbon disulfide, and ethyl 4-chloroacetoacetate selectively led to the formation of 3-(3-hydroxy-2-thienyl)-3-oxopropanoates **3a**—**e**. After alkylation of the intermediately formed dipotassium salt, the product gives the Dieckmann reaction involving the ester group, rather than the Thorpe—Ziegler cyclization.

Experimental

Melting points were determined on a Kofler heating stand. IR spectra were recorded on a Bruker Alpha spectrophotometer in KBr pellets, ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer (300.13 MHz) in solutions in DMSO-d_6, using the residual signal of the solvent (δ_H = 2.5) as a reference. High resolution mass spectra were obtained on a Bruker micrOTOF instrument.

Synthesis of substituted thiophenes 3a—e (general procedure). Ethyl cyanoacetate (**1**) (2.82 g, 25 mmol) was added to a solution of KOH (1.4 g, 25 mmol) in EtOH (50 mL) at 10 °C, and the mixture was stirred for 30 s, followed by a sequential addition of CS_2 (1.5 mL, 25 mmol) and KOH (1.4 g, 25 mmol) in EtOH (50 mL). The reaction mixture was stirred for 60 min, diluted with H_2O (40 mL) until a precipitate formed was dissolved. Ester **2** (3.4 mL, 25 mmol) was added dropwise to the solution obtained over 30 min. After stirring for 10 min, a solution of KOH (1.4 g, 25 mmol) in EtOH (50 mL) was added, and the mixture was refluxed for 2 h. Then, the solution was cooled, followed by the addition of concentrated HBr (2.8 mL, 25 mmol) and stirring for 30 min. The thus obtained solution of salt **5** was poured into five flasks (5 mmol of salt **5** each), added the corresponding alkyl halide **6a**—**e** (5 mmol), heated to reflux, and cooled. A precipitate formed was filtered off to obtain thiophenes **3a**—**e** in 52—58% yields.

Ethyl 3-{4-cyano-3-hydroxy-5-[(2-oxo-2-phenylethyl)sulfanyl]-2-thienyl}-3-oxopropanoate (3a). The yield was 55%, m.p. 154—156 °C. IR, ν/cm^{-1}: 3435 (OH), 2221 (CN), 1742 (CO_2Et), 1677 (CO). ^{1}H NMR, δ: 1.17 (t, 3 H, CH_3, J = 7.1 Hz); 3.86 (s, 2 H, $COCH_2CO$); 4.09 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.1 Hz); 5.17 (s, 2 H, SCH_2); 7.58 (m, 2 H, C_6H_5); 7.72 (t, 1 H, C_6H_5, J = 7.3 Hz); 8.06 (d, 2 H, C_6H_5, J = 7.4 Hz). The signal for the OH group was not found, probably, because of the exchange processes with the solvent. MS ESI, found: m/z 390.0464 $[M + H]^+$; $C_{18}H_{16}NO_5S_2$; calculated: m/z 390.0470.

Ethyl 3-[5-(benzylsulfanyl)-4-cyano-3-hydroxy-2-thienyl]-3-oxopropanoate (3b). The yield was 52%, m.p. 73—75 °C. IR, ν/cm^{-1}: 3430 (OH), 2226 (CN), 1720 (CO_2Et), 1686 (CO). ^{1}H NMR, δ: 1.16 (t, 3 H, CH_3, J = 7.1 Hz); 3.85 (s, 2 H, $COCH_2CO$); 4.08 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.1 Hz); 4.50 (s, 2 H, SCH_2); 7.25—7.50 (m, 5 H, C_6H_5), 8.09 (br.s, 1 H, OH). MS ESI, found: m/z 362.0515 $[M + H]^+$; $C_{17}H_{16}NO_4S_2$; calculated: m/z 362.0521.

Ethyl 3-(4-cyano-3-hydroxy-5-{[(4-methylphenyl)methyl]sulfanyl}-2-thienyl)-3-oxopropanoate (3c). The yield was 56%, m.p. 80—82 °C. IR, ν/cm^{-1}: 3422 (OH), 2228 (CN), 1717 (CO_2Et), 1681 (CO). ^{1}H NMR, δ: 1.17 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.1 Hz); 2.28 (s, 3 H, CH_3); 3.85 (s, 2 H, $COCH_2CO$); 4.08 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.1 Hz); 4.46 (s, 2 H, SCH_2); 7.16 (d, 2 H, C_6H_4, J = 7.7 Hz); 7.32 (d, 2 H, C_6H_4, J = 7.7 Hz); 8.12 (br.s, 1 H, OH). MS ESI, found: m/z 376.0672 $[M + H]^+$; $C_{18}H_{18}NO_4S_2$; calculated: m/z 376.0677.

Ethyl 3-{4-cyano-3-hydroxy-5-[(2-ethoxy-2-oxoethyl)sulfanyl]-2-thienyl}-3-oxopropanoate (3d). The yield was 58%, m.p. 82—84 °C. IR, ν/cm^{-1}: 3438 (OH), 2228 (CN), 1725 (CO_2Et), 1691 (CO). ^{1}H NMR, δ: 1.10—1.25 (m, 6 H, 2 CH_3); 3.87 (s, 2 H, $COCH_2CO$); 4.05—4.20 (m, 4 H, 2 $\underline{CH_2}CH_3$); 4.24 (s, 2 H, SCH_2); 7.30 (br.s, 1 H, OH). MS ESI, found: m/z 358.0414 $[M + H]^+$, $C_{14}H_{16}NO_6S_2$; calculated: m/z 358.0419.

Ethyl 3-{4-cyano-5-[(2-oxopropyl)sulfanyl]-3-hydroxy-2-thienyl}-3-oxopropanoate (3e). The yield was 53%, m.p. 97—99 °C. IR, ν/cm^{-1}: 3432 (OH), 2229 (CN), 1722 (CO_2Et), 1686 (CO). ^{1}H NMR, δ: 1.17 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.1 Hz); 2.27 (s, 3 H, CH_3CO); 3.86 (s, 2 H, $COCH_2CO$); 4.09 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.1 Hz); 4.47 (s, 2 H, SCH_2); 6.91 (br.s, 1 H, OH). MS ESI, found: m/z 328.0308 $[M + H]^+$, $C_{13}H_{14}NO_5S_2$; calculated: m/z 328.0313.

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