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Synthesis of Thieno[3,2-*b*]thiophenes from 2,5-Dicarbonyl 3-Nitrothiophenes via Nucleophilic Aromatic Substitution of the Nitro Group with Thiolates

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Abstract: In this study, we developed an efficient strategy for constructing thieno[3,2-*b*]thiophene molecules from 3-nitrothiophenes, containing carbonyl fragments at the C-2 and C-5 atoms, by nucleophilic aromatic substitution of the nitro group in these substrates. It was shown that the reaction of 3-nitrothiophene-2,5-dicarboxylates with thiophenols, thioglycolates and 2-mercaptoacetone in the presence of K_2CO_3 proceeds rapidly via nucleophilic displacement of the nitro group with the formation of 3-sulfenylthiophene-2,5-dicarboxylates. Further treatment of the resulting thiophene-2,5-dicarboxylates, which have -SCH_2CO_2Alk or -SCH_2COMe moiety at C-3 atom, with sodium alcoholates afford obtaining 2,3,5-trisubstituted thieno[3,2-*b*]thiophene derivatives according to the Dieckman condensation. In turn, the reaction of methyl 5-formyl-4-nitrothiophene-2-carboxylate with methyl thioglycolate or 2-mercaptoacetone in the presence of K_2CO_3 proceeds to directly form 2,5-disubstituted thieno[3,2-*b*]thiophenes.

Keywords: 3-nitrothiophenes; leaving nitro group; thiols; thieno[3,2-*b*]thiohenes; nucleophilic aromatic substitution

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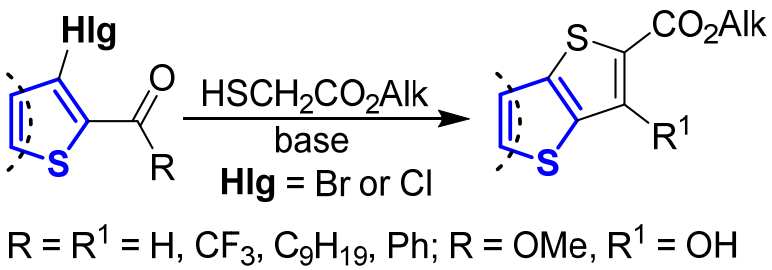
1. Introduction

Thieno[3,2-*b*]thiophene (TT) is a simple bicyclic ring system based on two fused thiophene units, whose scaffold has attracted considerable attention of researchers due to its wide application for the development of photo- and electroactive compounds, including π-conjugated small molecules, oligomers and polymers [1,2]. Thus, a rigid and planar TT framework, having capabilities of end-to-end π conjugation and intermolecular S···S contacts [2], was used to design organic semiconductor materials for organic light-emitting diodes [3–5] and organic field-effect transistors [6–10], polymer [11–17] and small-molecule [18–23] materials for organic solar cells, and hole transport materials for perovskite solar cells [24–26]. In addition, TT derivatives have been shown to be applicable to the development of biologically active compounds [27]. Among them, there are TT-glycine-linked cephalosporin derivatives as a potential antibiotic agent [28], and TT-2-sulfonamides as carbonic anhydrase inhibitors [29]. It should also be mentioned that TT-linked distamycin A analog is a DNA binding ligand to treat drug-resistant bacteria [30] as well as 3,5-disubstituted TT-2-carboxylic acids as G protein-coupled receptor 35 agonists [31]. From these data, it is clear that TT derivatives are high in demand due to their practical application, and the TT molecule is an important objective for organic synthesis. In regard to synthetic routes for TT scaffold, the main strategy for its construction is based on annulation reactions of a second thiophene unit onto a single-ring thiophene substrate. Indeed, the halogen-to-sulfur exchange of 3-chloro- and 3-bromo-substituted thiophene compounds is a more often used reaction for the synthesis of TT derivatives [2]. Among these approaches, there are main group of methods based on nucleophilic aromatic substitution (S_NAr) of the activated halogen atom at C-3 of thiophene substrates, bearing

electron-withdrawing group at its C-2 position, with *S*-nucleophiles, such as thioglycolic acid esters in the present of bases, followed by base-promoted cyclization to form TT molecules (Scheme 1) [32–40]. In addition, several protocols for the synthesis of TTs based on cyclization of 3-alkylthio-substituted thiophenes should also be mentioned, which, in turn, were formed by the treatment of thiophen-3-yl lithium intermediates with elemental sulfur and alkylating agents [41–45] or dialkyl disulfides [46,47].



Scheme 1. Basic strategy for the synthesis of thieno[3,2-*b*]thiophenes.

At the same time, it is a well-known fact that the aromatic nitro group is a good leaving group in various S_NAr reactions [48]. Indeed, nucleophilic displacement of the nitro group in a number of nitroaromatic substrates with nucleophiles, including thiolates, was reported in the literature, and these reactions were used for the synthesis of different functionalized aromatic compounds [49,50]. Moreover, several effective protocols based on the aromatic nitro group substitution reaction were previously suggested for the synthesis of benzo[*b*]thiophenes starting from 2-nitrobenzhaldehydes [51–53], 2-nitrobenzoates [54], and 2-nitrobenzonitriles [55–57] by their reaction with thioglycolates in the presence of bases. Given these data, it is very surprising that 3-nitro-substituted thiophenes have not been previously used for the synthesis of thieno[3,2-*b*]thiophenes. Nitro-substituted thiophenes are accessible substrates, since the electron-rich character of the thiophene ring is favorable to proceeding with its nitration process, even for those derivatives that already contain electron-deficient substituents due to the high electrophilic activity of nitronium ion.

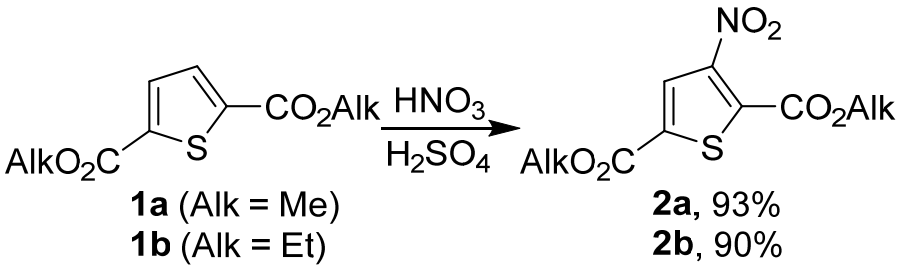
Herein, we wish to report the results of our study on the nucleophilic displacement of the nitro group to thiolates in 3-nitro-substituted thiophenes, bearing electron-withdrawing groups at C-2 and C-5 atoms, and the application of this reaction to construct thieno[3,2-*b*]thiophene molecules.

2. Results and Discussion

3-Nitrothiophene-2,5-dicarboxylic acid esters **2a**,**b** were selected as accessible substrates to study their reactions with thiols for implementing our research plan. To this end, these compounds were prepared in multigram-scale quantities from corresponding esters **1a**,**b** by their nitration with a mixture of concentrated nitric and sulfuric acids (Scheme 2). It should be noted that dimethyl 3-nitrothiophene-2,5-dicarboxylate (**2a**) was first described in 2015 [58]. However, there are only two reactions for this compound in the literature, namely its acidic hydrolysis to form 3-nitrothiophene-2,5-dicarboxylic acid [58], and its nitro group reduction with hydrogen on Pd catalyst to form methyl 3-aminothiophene-2,5-dicarboxylate [59].

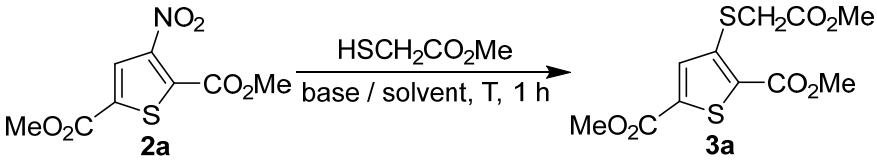
To find optimal reaction conditions for the nucleophilic substitution of the nitro group in the thiophene ring, we performed several experiments on the treatment of ester **2a** with methyl thioglycolate using various bases and solvents (Table 1). In all these cases, we observed a rapid color change of a reaction mixture from colorless to deep red after its heating began, and subsequent weakening of the red color to pale pink during the progress of the reaction. Compound **3a** was isolated in 25–30% yield when KOH or LiOH was used as a base for the reaction (Table 1, entries 1–3), and we suggest that there was occurred partial saponification of ester groups leading to low product yield in these cases. In contrast

to this, the yield of product **3a** turned out to be significantly higher using alkali metal carbonates, and the best result was obtained using acetone as a solvent and K_2CO_3 as a base (Table 1, entry 6). It is important to note that we failed to obtain compound **3a** using alcohols, such as methanol, ethanol or isopropanol, as solvents for this reaction. Thus, it can be stated that polar aprotic solvents and moderate bases are suitable for this reaction.



Scheme 2. The synthesis of 3-nitrothiophene-2,5-dicarboxylate **2a**,**b**.

Table 1. Optimization of reaction conditions for the synthesis of **3a**.



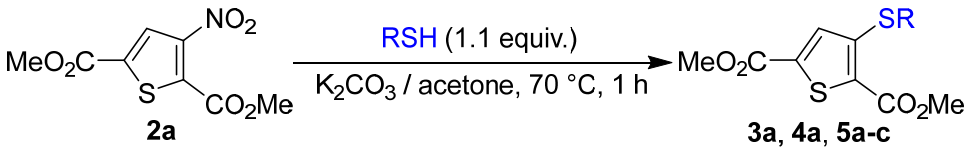
Entry	Solvent	Base	T, °C	Yield 3a, % [a]
1	MeCN	KOH	90	25
2	MeCN	LiOH	90	30
3	DMF	LiOH	100	29
4	MeCN	K_2CO_3	90	88
5	DMF	K_2CO_3	100	83
6	acetone	K_2CO_3	70	93
7	acetone	Na_2CO_3	70	90

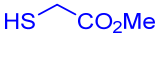
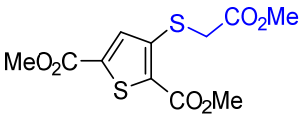
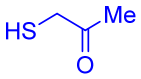
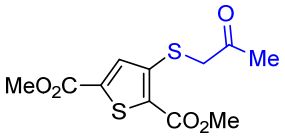
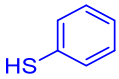
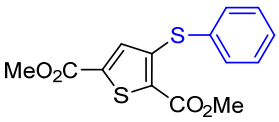
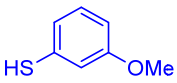
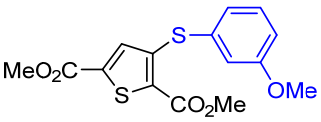
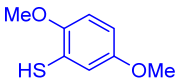
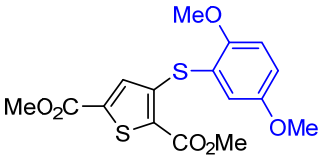
[a] Ester **2a** (245 mg, 1 mmol), $HSCH_2CO_2Me$ (0.10 mL, 1.1 mmol), base (2 mmol), and solvent (10 mL) were used in these experiments.

In a similar manner, we were also able to perform the nucleophilic substitution of the nitro group in substrate **2a** with some other thiols, such as 2-mercaptoacetone, using its commercially available dimer-2,5-dimethyl-2,5-dihydroxy-1,4-dithiane, as well as thiophenols, to obtain product **4a** in an 89% yield and products **5a-c** in a yield ranging from 78 to 90% (Scheme 3).

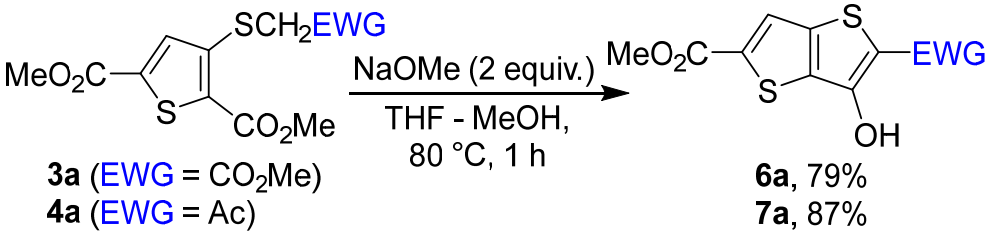
At the same time, a reaction of ester **2a** with benzyl mercaptan or isopropyl mercaptan under the same conditions has afforded a complex mixture of compounds in both these cases, while the desired 3-alkylthio-substituted derivatives were only detected in trace amounts. We suggest that treatment of substrate **2a** with these mercaptans in the presence of K_2CO_3 causes a reduction in its nitro group since the corresponding disulfides and small amounts of methyl 3-aminothiophene-2,5-dicarboxylate were also detected in the reaction mixtures.

In the next part of our study, we carried out the construction of thieno [3,2-*b*]thiophene molecules using NO_2/thiolate displacement in esters **2a**,**b**. To this end, we initially explored the cyclization ability of substrates **3a** and **4a** according to Dieckman condensation and found that treatment of these compounds with NaOMe and subsequent acidic workup of a reaction mixture readily afforded 2,3,5-trisubstituted TT derivatives **6a** and **7a** in 79% and 87% yields, respectively (Scheme 4).



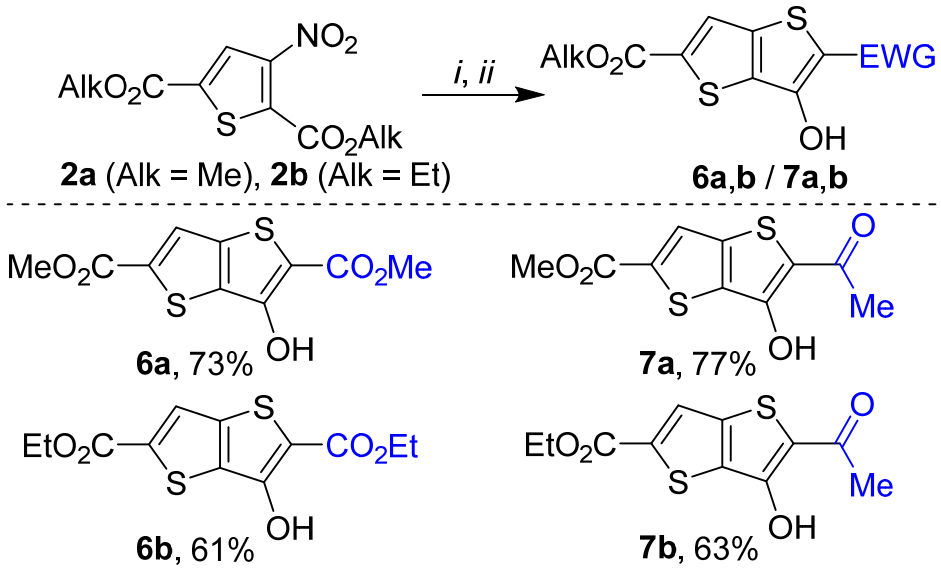
Entry	Thiol (RSH)	Product (yield)
1		 **3a** (93%)
2		 **4a** (89%)
3		 **5a** (88%)
4		 **5b** (90%)
5		 **5c** (78%)

Scheme 3. A reaction of ester **2a** with thiols, scope and yield products.



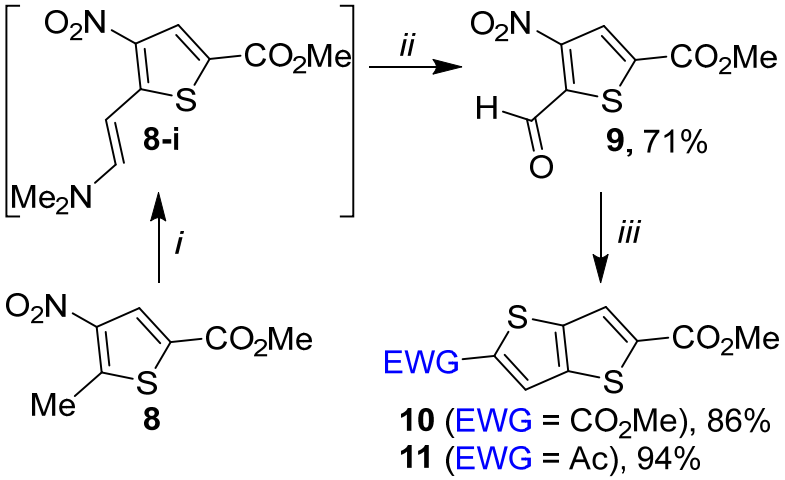
Scheme 4. The Dieckman condensation of substrates **3a** and **4a**.

Compounds **6a** and **7a** were also prepared directly from ester **2a** without purification of substrates **3a** and **4a**. In this case, acetone solutions of these compounds, obtained after treatment of ester **2a** with methyl thioglycolate or 2-mercaptoacetone, were concentrated under reduced pressure; the residues were dissolved in dry THF and then treated with NaOMe in methanol to afford products **6a** and **7a** in 73% and 77% yields based on ester **2a** (Scheme 5). In the same manner, TT derivatives **6b** and **7b** were synthesized in 61% and 63% yields based on ester **2b** by its reaction with ethyl thioglycolate or 2-mercaptoacetone in the presence of K_2CO_3 followed by treatment of the formed intermediates with NaOEt. It should be noted that the present protocol is suitable for the gram-scale synthesis of TT compounds due to the availability of the starting materials and easy-to-perform procedures. For instance, compound **6a** was readily produced in a quantity of almost 20 g from 0.1 mol of ester **2a**.



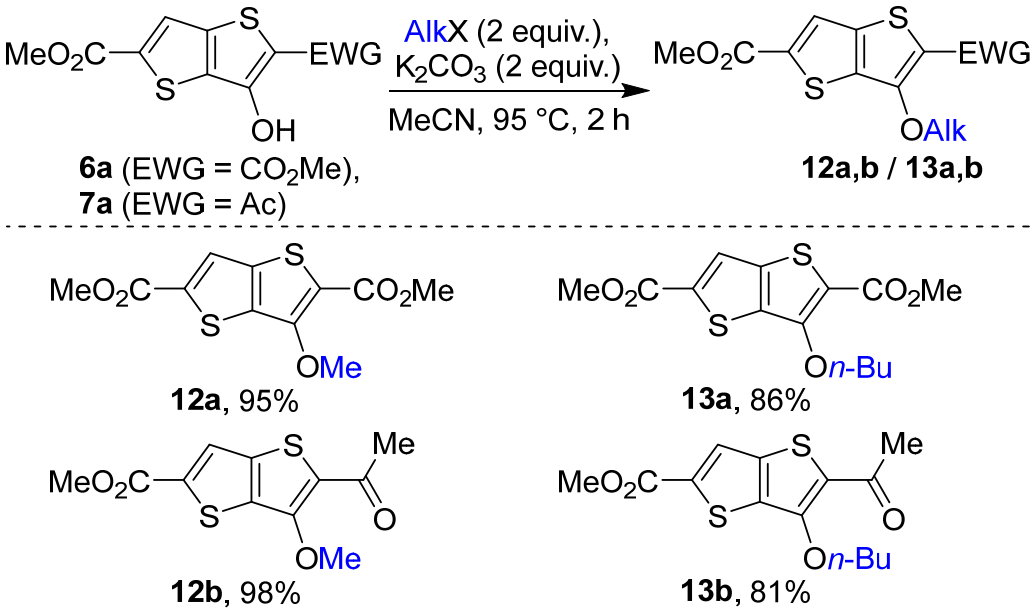
Scheme 5. The synthesis of 2,3,5-trisubstituted TT derivatives **6a**,**b** and **7a**,**b**.

We are also able to apply our approach for the synthesis of the 2,5-disubstituted TTs (Scheme 6). To this end, nitro-thienaldehyde **9** was prepared in 71% yield from methyl 5-methyl-4-nitrothiophene-2-carboxylate (**8**) [60] by its condensation with dimethylformamide dimethyl acetal (DMF-DMA) and oxidative cleavage of the enaminic C=C double bond in intermediate **8-i** with $NaIO_4$. We found that substrate **9** reacted with methyl thioglycolate and 2-mercaptoacetone in the presence of K_2CO_3 afforded directly to form 2,5-disubstituted TT compounds **10** and **11**. This can be explained by the formyl group of thienaldehyde **9** being more electrophilic compared to the CO_2Me group of ester **2a**, which increases the rate of initial nucleophilic substitution of the nitro group in substrate **9** with thiolates and facilitates the process of intramolecular cyclization in the formed intermediates to the TT scaffolds. Indeed, both these reactions proceeded efficiently under mild conditions, and products **10** and **11** were obtained in 86% and 94% yields, respectively, without any purification procedures after dilution of the reaction mixtures with water.



Scheme 6. The synthesis of 2,5-disubstituted TT derivatives **10** and **11**.

In addition, we performed alkylation of the hydroxy group in TTs **6a** and **7a** to show the next modification of these molecules. Thus, methoxy- and butoxy-substituted TT derivatives **12a**,**b** and **13a**,**b** were synthesized by treatment of substrates **6a** and **7a** with dimethyl sulfate or 1-bromobutane and K_2CO_3 in a solution of acetonitrile in yields of 81–98% (Scheme 7).



Scheme 7. The O-alkylation of TT compounds **6a** and **7a**.

3. Conclusions

To sum up, we have demonstrated for the first time that 3-nitrothiophenes with electron-deficient groups at C-2 and C-5 atoms are convenient and accessible substrates for the synthesis of TTs as an alternative to the similar 3-chloro- and 3-bromothiophenes that were previously used to construct TT compounds. We investigated the reaction of 3-nitro-substituted thiophene-2,5-dicarboxylates with thiols in the presence of bases and found that nucleophilic aromatic substitution of the nitro group to thiolate proceeded under mild reaction conditions to afford 3-sulfenyl-substituted derivatives. This process was used by us for constructing TT molecules bearing hydroxy, alkoxycarbonyl and acetyl groups. In turn, the prepared compounds, due to the presence of different functional groups in their structures, are of interest as building blocks for the next design of more complex molecules with TT scaffolds.

4. Materials and Methods

Analytical studies were carried out using equipment of the Center for Joint Use "Spectroscopy and Analysis of Organic Compounds" at the Postovsky Institute of Organic Synthesis of the Russian Academy of Sciences (Ural Division). Elemental analysis was carried out using an automated CHNS Euro EA 3000 analyzer (Eurovector Instruments, Pavia, Italy). NMR measurements were performed on NMR spectrometers DRX-400 and AVANCE 500 (Bruker BioSpin, Ettlingen, Germany) in $CDCl_3$ or DMSO-d_6 with $SiMe_4$ as an internal standard for ^1H and ^{13}C spectra (see Supplementary Materials to obtain the copies of NMR spectra of compounds). Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Melting points were determined on combined heating stages and were uncorrected. 3-Nitrothiophene-2,5-dicarboxylates **2a**,**b** were synthesized from dialkyl thiophene-2,5-dicarboxylates **1a**,**b** using a slightly modified procedure for the preparation of ester **2a** described in the literature [58].

Procedure for nitration of thiophene-2,5-dicarboxylates **1a**,**b**

Dimethyl thiophene-2,5-dicarboxylate (**1a**) (56 g, 0.28 mmol) was added portion-wise to a stirred sulfuric acid (400 mL, 98% wt.) at 0 °C. Nitric acid (17.6 mL, 97% wt.) was added dropwise to this solution at the same temperature. A mixture was stirred at ambient temperature for 1 h, and then poured into water and crushed ice (1 L/500 g) with continuous stirring for 0.5 h. The formed precipitate was filtered, washed with water (10 × 100 mL) and dried under vacuum at ambient temperature to give ester **2a** in a yield of 93%. Nitration of diethyl thiophene-2,5-dicarboxylate (**1b**) (18.6 g, 81.5 mmol) with H_2SO_4 (140 mL, 98% wt.) and HNO_3 (5 mL, 97% wt.) using the same procedure afforded to obtain ester **2b** in a yield of 90%.

Dimethyl 3-nitrothiophene-2,5-dicarboxylate (**2a**)

White solid, yield 64 g (93%), m.p. 89–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 3.90 (s, 6H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H).

Compound **2a** was previously described in the literature and its analytical data are identical to the reported data [58].

Diethyl 3-nitrothiophene-2,5-dicarboxylate (**2b**)

White solid, yield 20 g (90%), m.p. 56–57 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 4.67–4.05 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.4, 158.1, 146.9, 135.6, 132.7, 127.9, 63.0, 62.4, 13.8, 13.5. Anal. Calcd for $C_{10}H_{11}NO_6S$: C, 43.95; H, 4.06; N, 5.13; S, 11.73. Found: C, 43.93; H, 4.13; N, 5.20; S, 11.63. HRMS (ESI) calcd for $C_{10}H_{12}NO_6S$ m/z 274.0380 $[M + H]^+$, found m/z 274.0379 $[M + H]^+$.

General procedure for the synthesis of thiophene-2,5-dicarboxylates **3a**, **4a** and **5a**–**c**

K_2CO_3 powder (1.66 g, 12 mmol) was added in one portion to a stirred solution of ester **2a** (1.47 g, 6 mmol) and an appropriate thiol (6.6 mmol) in acetone (30 mL), and the suspension was stirred and heated at reflux (70 °C) for 1 h. The color of the liquid phase first changes from colorless to deep red, and then toward the end of the reaction to pale pink. A reaction mixture was cooled to ambient temperature, diluted with water (45 mL) and stirred for 30 min. The formed precipitate was filtered, washed with water (3 × 15 mL), and dried at 80 °C. The crude substance was crystallized from ethanol to give an analytically pure form of the desired product.

Dimethyl 3-[(2-methoxy-2-oxoethyl)thio]thiophene-2,5-dicarboxylate (**3a**)

White needles, yield 1.70 g (93%), m.p. 101–102 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77 (s, 1H), 4.17 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.6, 161.2, 160.9, 143.2, 136.3, 131.8, 125.6, 53.0, 52.6, 52.5, 33.8. Anal. Calcd for $C_{11}H_{12}O_6S_2$: C, 43.41; H, 3.97; S, 21.07. Found: C, 43.42; H, 3.94; S, 20.71. HRMS (ESI) calcd for $C_{11}H_{13}O_6S_2$ m/z 305.0148 $[M + H]^+$, found m/z 305.0149 $[M + H]^+$.

Dimethyl 3-[(2-oxopropyl)thio]thiophene-2,5-dicarboxylate (**4a**)

White crystals, yield 1.54 g (89%), m.p. 118–119 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (s, 1H), 4.29 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 202.9, 161.2, 160.9, 143.6, 136.3, 131.9, 125.4, 52.9, 52.6, 42.8, 28.6. Anal. Calcd for $C_{11}H_{12}O_5S_2$: C, 45.82; H, 4.20; S, 22.24. Found: C, 45.66; H, 4.13; S, 22.21. HRMS (ESI) calcd for $C_{11}H_{13}O_5S_2$ m/z 289.0199 $[M + H]^+$, found m/z 289.0201 $[M + H]^+$.

Dimethyl 3-(phenylthio)thiophene-2,5-dicarboxylate (**5a**)

White crystals, yield 1.63 g (88%), m.p. 158–159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68–7.50 (m, 5H), 6.77 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 161.5, 145.3, 136.4, 134.8, 132.5, 131.6, 129.8, 129.6, 125.9, 52.6, 52.4. Anal. Calcd for $C_{14}H_{12}O_4S_2$: C, 54.53; H, 3.92; S, 20.79. Found: C, 54.36; H, 3.83; S, 20.69. HRMS (ESI) calcd for $C_{14}H_{13}O_4S_2$ m/z 309.0250 $[M + H]^+$, found m/z 309.0245 $[M + H]^+$.

Dimethyl 3-[(3-methoxyphenyl)thio]thiophene-2,5-dicarboxylate (**5b**)

White crystals, yield 1.83 g (90%), m.p. 106–107 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54–7.39 (m, 1H), 7.22–7.18 (m, 2H), 7.15–7.11 (m, 1H), 6.84 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 161.6, 160.3, 145.2, 136.5, 132.7, 132.5, 130.6, 127.0, 125.9, 119.8, 115.7, 55.4, 52.6, 52.4. Anal. Calcd for $C_{15}H_{14}O_5S_2$: C, 53.24; H, 4.17; S, 18.95. Found: C, 53.18; H, 3.93; S, 19.86. HRMS (ESI) calcd for $C_{15}H_{15}O_5S_2$ m/z 339.0355 $[M + H]^+$, found m/z 339.0354 $[M + H]^+$.

Dimethyl 3-[(2,5-dimethoxyphenyl)thio]thiophene-2,5-dicarboxylate (**5c**)

Yellowish crystals, yield 1.73 g (78%), m.p. 123–124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24–7.07 (m, 3H), 6.74 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 161.7, 154.0, 153.7, 144.6, 136.0, 132.8, 125.9, 121.5, 119.7, 117.1, 112.8, 56.5, 55.8, 52.5, 52.4. Anal. Calcd for $C_{16}H_{16}O_6S_2$: C, 52.16; H, 4.38; S, 17.40. Found: C, 52.06; H, 4.16; S, 17.30. HRMS (ESI) calcd for $C_{16}H_{17}O_6S_2$ m/z 369.0461 $[M + H]^+$, found m/z 369.0457 $[M + H]^+$.

CCDC 2378472 (**5c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures/Search?ccdc=2378472, accessed on 15 October 2024.

General procedure for the synthesis of TT compounds **6a**,**b** and **7a**,**b** from esters **2a**,**b**

Ester **2a** (4.90 g, 20 mmol) or ester **2b** (5.47 g, 20 mmol) as well as alkyl thioglycolate (22 mmol) or 2-mercaptoacetone, used its dimer-2,5-dimethyl-2,5-dihydroxy-1,4-dithiane, (2.0 g, 11 mmol) were dissolved in acetone (90 mL). A powdered K_2CO_3 (5.52 g, 40 mmol) was added in one portion to this solution, and the suspension was stirred and heated at reflux (70 °C) for 1 h. The solid was filtered and washed on a filter with warm acetone (3 × 25 mL). The combined filtrates were concentrated under reduced pressure, and the formed semi-solid residue of a crude 3-substituted thiophene-2,5-dicarboxylate was dissolved in dry THF (30 mL). This solution was dropped rapidly to a solution of NaOMe (40 mmol) in MeOH (20 mL), in the case of using **2a**, or NaOEt (40 mmol) in EtOH (20 mL), in the case of using **2b**. A reaction mixture was stirred and heated at reflux (80 °C) for 1 h to form a yellowish suspension. It was diluted with water (100 mL), neutralized with AcOH (5 mL), and stirred for 30 min. The formed precipitate was filtered, washed with water (5 × 20 mL), and dried at 80 °C. The crude substance was purified by the crystallization from *i*-PrOH to give an analytically pure form of the desired product. The solutions of sodium alcoholates for these experiments were prepared by dissolving Na metal (0.92 g, 40 mmol) in MeOH or EtOH, respectively.

Dimethyl 3-hydroxythieno [3,2-*b*]thiophene-2,5-dicarboxylate (**6a**)

White powder, yield 4.0 g (73%), m.p. 208–209 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.17 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.8, 161.8, 152.9, 138.6, 137.4, 133.6, 127.6, 109.7, 52.8, 51.9. Anal. Calcd for $C_{10}H_8O_5S_2$: C, 44.11; H, 2.96; S, 23.55. Found: C, 44.07; H, 2.71; S, 23.36. HRMS (ESI) calcd for $C_{10}H_9O_5S_2$ m/z 272.9886 $[M + H]^+$, found m/z 272.9885 $[M + H]^+$.

Diethyl 3-hydroxythieno [3,2-*b*]thiophene-2,5-dicarboxylate (**6b**)

White crystals, yield 3.67 g (61%), m.p. 111–112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.14 (s, 1H), 4.34 (q, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 4H), 1.30 (t, J = 7.1 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.5, 161.3, 153.1, 138.5, 137.8, 133.5, 127.3, 109.6, 61.6, 60.6, 14.2, 14.1. Anal. Calcd for $C_{12}H_{12}O_5S_2$: C, 47.99; H, 4.03; S, 21.35. Found: C, 47.88; H, 4.06; S, 21.20. HRMS (ESI) calcd for $C_{12}H_{13}O_5S_2$ m/z 301.0199 $[M + H]^+$, found m/z 301.0197 $[M + H]^+$.

Methyl 5-acetyl-6-hydroxythieno [3,2-*b*]thiophene-2-carboxylate (**7a**)

Yellowish needles, yield 3.95 g (77%), m.p. 144–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.13 (s, 1H), 3.88 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 191.1,

161.8, 152.3, 140.0, 138.0, 133.6, 127.4, 123.7, 52.7, 28.7. Anal. Calcd for $C_{10}H_8O_4S_2$: C, 46.86; H, 3.15; S, 25.02. Found: C, 46.97; H, 3.00; S, 25.10. HRMS (ESI) calcd for $C_{10}H_9O_4S_2$ m/z 256.9937 $[M + H]^+$, found m/z 256.9932 $[M + H]^+$.

Ethyl 5-acetyl-6-hydroxythieno [3,2-*b*]thiophene-2-carboxylate (**7b**)

Yellow crystals, yield 3.41 g (63%), m.p. 176–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.12 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.54 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 191.1, 161.3, 152.3, 140.0, 138.4, 133.5, 127.2, 123.6, 61.6, 28.7, 14.1. Anal. Calcd for $C_{11}H_{10}O_4S_2$: C, 48.88; H, 3.73; S, 23.72. Found: C, 48.73; H, 3.73; S, 23.82. HRMS (ESI) calcd for $C_{11}H_{11}O_4S_2$ m/z 271.0093 $[M + H]^+$, found m/z 271.0092 $[M + H]^+$.

Procedure for the synthesis of thienaldehyde **9**

Dimethylformamide dimethyl acetal (9 mL, 67.7 mmol) was added in one portion to a solution of 5-methyl-4-nitrothiophene-2-carboxylate **8** (10.75 g, 53.4 mmol) in dry THF (50 mL). A reaction mixture was stirred and heated at reflux (80 °C) for 3 h under an argon atmosphere. The formed dark-red solution of intermediate **8-i** was cooled to ambient temperature and added to a stirred solution of $NaIO_4$ (34.27 g, 160.2 mmol) in water (300 mL) at 5 °C. A reaction mixture was stirred for 12 h at ambient temperature and filtered to remove the precipitate of inorganic salts. The filtrate was extracted with EtOAc (2 × 100 mL, 2 × 50 mL), and the combined extracts were washed with water (100 mL) and brine (2 × 50 mL) and dried with $CaCl_2$. The solvent was evaporated under reduced pressure, and the residue was dissolved in Et_2O (100 mL). This solution was passed through a silica gel layer (5 cm × 5 cm) on a filter, and the filtrate was concentrated under reduced pressure to give compound **9** as a brown oil. The oil substance crystallized completely in the air within a few days.

Methyl 5-formyl-4-nitrothiophene-2-carboxylate (**9**)

Dark-orange needles, yield 8.62 g (75%), m.p. 49–50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.26 (s, 1H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.4, 160.2, 147.2, 144.3, 138.1, 129.2, 53.4. Anal. Calcd for $C_7H_5NO_5S$: C, 39.07; H, 2.34; N, 6.51; S, 14.90. Found: C, 38.86; H, 2.55; N, 6.32; S, 15.02. HRMS (ESI) calcd for $C_7H_6NO_5S$ m/z 215.9961 $[M + H]^+$, found m/z 215.9959 $[M + H]^+$.

General procedure for the synthesis of TT compounds **10**, **11**

K_2CO_3 powder (1.28 g, 9.30 mmol) was added in one portion to a stirred solution of thienaldehyde **9** (1.0 g, 4.65 mmol) and methyl thioglycolate (0.46 mL, 5.12 mmol) or 2-mercaptoacetone, used its dimer-2,5-dimethyl-2,5-dihydroxy-1,4-dithiane, (0.46 g, 2.55 mmol) in acetone (25 mL). The obtained suspension was stirred and heated to reflux (70 °C) for 0.5 h and then cooled to ambient temperature. A reaction mixture was diluted with water (25 mL) and stirred for 0.5 h. The formed precipitate was filtered and washed with *i*-PrOH (3 × 5 mL) and water (5 × 10 mL) and dried at 110 °C to obtain an analytically pure form of the desired product.

Dimethyl thieno [3,2-*b*]thiophene-2,5-dicarboxylate (**10**)

White powder, yield 1.02 g (86%), m.p. 231–232 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.9, 142.4, 137.6, 126.9, 52.7. Anal. Calcd for $C_{10}H_8O_4S_2$: C, 46.86; H, 3.15; S, 25.02. Found: C, 46.72; H, 3.02; S, 25.12. HRMS (ESI) calcd for $C_{10}H_9O_4S_2$ m/z 256.9937 $[M + H]^+$, found m/z 256.9933 $[M + H]^+$.

Methyl 5-acetylthieno [3,2-*b*]thiophene-2-carboxylate (**11**)

Cream crystals, yield 1.05 g (94%), m.p. 203–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.27 (s, 1H), 3.88 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 191.7, 161.8, 148.8, 143.0, 142.6, 137.9, 127.1, 127.1, 52.7, 26.5. Anal. Calcd for $C_{10}H_8O_3S_2$: C, 49.99; H, 3.36; S, 26.68. Found: C, 50.05; H, 3.15; S, 26.72. HRMS (ESI) calcd for $C_{10}H_9O_3S_2$ m/z 240.9988 $[M + H]^+$, found m/z 240.9989 $[M + H]^+$.

General procedure for the O-alkylation of TT compounds **6a** and **7a**

K_2CO_3 powder (0.69 g, 5 mmol) was added in one portion to a stirred solution of substrate **6a** (0.68 g, 2.5 mmol) or 7a (0.64 g, 2.5 mmol) in MeCN (20 mL). The suspension was stirred for 0.5 h at ambient temperature, and then treated with Me_2SO_4 (0.48 mL, 5 mmol) or *n*-BuBr (0.54 mL, 5 mmol). A reaction mixture was stirred and heated to reflux (95 °C) for 2 h, and then diluted with ice water (40 mL). The formed precipitate was filtered, washed with water (3 × 10 mL) and dried in air. The crude substance was crystallized from EtOH to obtain an analytically pure form of the desired product.

Dimethyl 3-methoxythieno [3,2-*b*]thiophene-2,5-dicarboxylate (**12a**)

White crystals, yield 0.68 g (95%), m.p. 170–171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 4.23 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 161.9, 154.5, 139.6, 138.4, 132.7, 126.1, 115.2, 60.0, 52.6, 52.0. Anal. Calcd for $C_{11}H_{10}O_5S_2$: C, 46.15; H, 3.52; S, 22.39. Found: C, 46.09; H, 3.31; S, 22.21. HRMS (ESI) calcd for $C_{11}H_{11}O_5S_2$ *m*/*z* 287.0042 $[M + H]^+$, found *m*/*z* 287.0041 $[M + H]^+$.

Methyl 5-acetyl-6-methoxythieno [3,2-*b*]thiophene-2-carboxylate (**12b**)

Yellowish crystals, yield 0.66 g (98%), m.p. 162–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 4.33 (s, 3H), 3.94 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.2, 161.9, 153.1, 141.2, 138.8, 131.6, 128.2, 126.3, 59.4, 52.6, 29.2. Anal. Calcd for $C_{11}H_{10}O_4S_2$: C, 48.88; H, 3.73; S, 23.72. Found: C, 49.07; H, 3.71; S, 23.66. HRMS (ESI) calcd for $C_{11}H_{11}O_4S_2$ *m*/*z* 271.0093 $[M + H]^+$, found *m*/*z* 271.0094 $[M + H]^+$.

Dimethyl 3-butoxythieno [3,2-*b*]thiophene-2,5-dicarboxylate (**13a**)

White crystals, yield 0.71 g (86%), m.p. 85–86 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 4.46 (t, *J* = 6.3 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 1.77–1.68 (m, 2H), 1.55–1.44 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.5, 161.2, 153.2, 139.3, 137.4, 132.7, 127.3, 115.6, 72.5, 52.7, 51.9, 31.4, 18.4, 13.5. Anal. Calcd for $C_{14}H_{16}O_5S_2$: C, 51.20; H, 4.91; S, 19.53. Found: C, 51.17; H, 5.04; S, 19.27. HRMS (ESI) calcd for $C_{14}H_{17}O_5S_2$ *m*/*z* 329.0512 $[M + H]^+$, found *m*/*z* 329.0512 $[M + H]^+$.

Methyl 5-acetyl-6-butoxythieno [3,2-*b*]thiophene-2-carboxylate (**13b**)

Yellowish crystals, yield 0.63 g (81%), m.p. 103–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 4.56 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 2.60 (s, 3H), 1.92–1.83 (m, 2H), 1.64–1.48 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.3, 162.0, 152.7, 141.3, 138.7, 131.8, 128.3, 126.4, 72.3, 52.6, 31.8, 29.3, 19.0, 13.6. Anal. Calcd for $C_{14}H_{16}O_4S_2$: C, 53.83; H, 5.16; S, 20.53. Found: C, 53.88; H, 5.24; S, 20.82. HRMS (ESI) calcd for $C_{14}H_{17}O_4S_2$ *m*/*z* 313.0563 $[M + H]^+$, found *m*/*z* 313.0566 $[M + H]^+$.

Supplementary Materials: The following supplementary information can be downloaded at: https://www.mdpi.com/article/10.3390/org5040027/s1, Copies of ^{1}H and ^{13}C NMR spectra of compounds.

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