Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 547.368+547.732

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The Synthesis of the Hydrogenated Thiophenes by [3+2] Cycloaddition Reaction of Thiocarbonyl Ylide

Abstract

Aim. To study the use of chloromethyl trimethylsilylmethyl sulfide as a precursor of thiocarbonyl ylide in [3+2] cycloaddition reaction to a number of α,β-unsaturated compounds and to establish the regularities of the reaction course. To develop an effective method for the synthesis of new dihydro- and tetrahydrothiophene derivatives which are convenient for further modification.

Results and discussion. The synthetic approach to tetrahydrothiophenes with substituents in positions 3 and 4 was extended by the [3+2] cycloaddition reaction of thiocarbonyl ylide with a number of compounds containing an activated multiple bond. The stereoselectivity and limitations of this reaction were determined. Further functionalization of the obtained compounds was carried out.

Experimental part. Thiocarbonyl ylide was obtained by fluoride ion-promoted 1,3-desilylation of the known chloromethyl trimethylsilylmethyl sulfide. The synthesis of the target compounds involved the [3+2] cycloaddition of such an ylide to a series of compounds with an activated multiple bond. The stereochemistry of the target compounds was determined by ^{1}H NOESY experiments. Synthetic derivatives of thiolancarboxylic acids, in particular aldehydes, alcohols, amines, amidines, were obtained by functionalization of the [3+2] adducts.

Conclusions. The synthetic approach to functionalized tetrahydrothiophenes by the [3+2] cycloaddition reaction of thiocarbonyl ylide with a number of compounds containing an activated multiple bond has expanded the limits of application of this reaction and allows obtaining the target compounds in multigram quantities. A high stereoselectivity of this reaction was observed. The reaction products are convenient synthetic precursors to the various classes of organic compounds.

Keywords: cycloaddition; thiocarbonyl ylide; dipolarophile; dihydrothiophene; tetrahydrothiophene

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Синтез гідрованих тіофенів реакцією [3+2] циклоприєднання тіокарбонілілідy

Анотація

Мета. Вивчити використання хлорометилтриметилсилілметил сульфіду як попередника тіокарбонілілідy в реакції [3+2] циклоприєднання з рядом α,β-ненасичених сполук та виявити закономірності перебігу цих реакції. Розробити ефективний метод синтезу нових похідних дигідро- та тетрагідротіофенового ряду, які можуть бути зручними для подальшої модифікації.

Результати та їх обговорення. Розширено синтетичний підхід до дигідро- та тетрагідротіофенів із замісниками в 3 та 4 положеннях через реакцію [3+2] циклоприєднання тіокарбонілілідy до ряду сполук з активованим кратним зв'язком. Визначено стереоселективність та межі застосування цієї реакції. Проведено подальшу функціоналізацію отриманих сполук.

Експериментальна частина. Тіокарбонілілід було отримано шляхом промотованого флуорид-йоном 1,3-десилілювання відомого хлорометилтриметилсилілметил сульфіду. Синтез цільових сполук передбачав [3+2]-циклоприєднання такого іліду до ряду сполук з активованими кратними зв'язками. Стереохімію цільових сполук визначено за допомогою ^{1}H NOESY експериментів. Функціоналізацією отриманих сполук одержано синтетичні похідні тіоланкарбонових кислот, зокрема альдегіди, спирти, аміни, амідини.

Висновки. Синтетичний підхід до функціоналізованих дигідро- та тетрагідротіофенів за допомогою реакції [3+2] циклоприєднання тіокарбонілілід з рядом сполук, які містять активований кратний зв'язок, розширив межі застосування цієї реакції і дозволив одержати цільові сполуки у мультиграмових кількостях. Виявлено високу стереоселективність цієї реакції. Продукти реакції є зручними синтетичними попередниками різних класів органічних сполук.
Ключові слова: циклоприєднання; тіокарбонілілід; диполярофіл; дигідротіофен; тетрагідротіофен

Citation: Rudenko, T. V.; Timoshenko, V. M. The Synthesis of the Hydrogenated Thiophenes by [3+2] Cycloaddition Reaction of Thiocarbonyl Ylide. *Journal of Organic and Pharmaceutical Chemistry* **2023**, *21* (2), 53–63.
https://doi.org/10.24959/ophcj.23.283517
Received: *28 April 2023*; **Revised:** *3 June 2023*; **Accepted:** *7 June 2023*

Funding: The authors received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

Among various classes of sulfurorganic compounds, dihydro- and, especially, tetrahydrothiophenes have attracted significant attention due to the widespread occurrence of their ring system in natural and synthetic products with a wide spectrum of biological activity [1–3]. Thus, given the important role in medicinal chemistry of new molecular objects based on dihydro- and tetrahydrothiophenes, the development of convenient preparative methods for their synthesis is relevant [4].

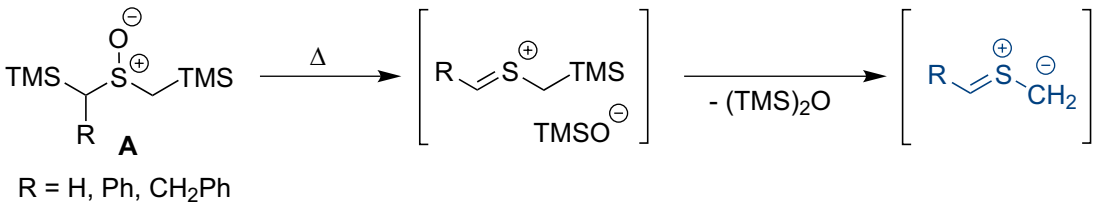
Dipolar cycloaddition of thiocarbonyl ylides (acting as 1,3-dipoles) to compounds with multiple bonds (acting as dipolarophiles) can be an effective method for a one-step diastereoselective construction of five-membered cyclic compounds with ring sulfur atom, in particular hydrogenated thiophenes.

One of the successful methods for obtaining thiocarbonyl ylides by the 1,3-elimination reaction described in literature is the thermal decomposition of organosilicon compounds type **A** by the method similar to the Sila-Pummerer rearrangement [5, 6] (Scheme 1). The [3+2]-cycloaddition of ylides obtained in such a way to a number of acrylates has been described to give cycloadducts in good yields [7], but in harsch reaction conditions using a high pressure (5–14 kbar) and special equipment. At the same time, the thermal decomposition of type **A** compounds at normal pressure provided the same products in only moderate yields [7, 8].

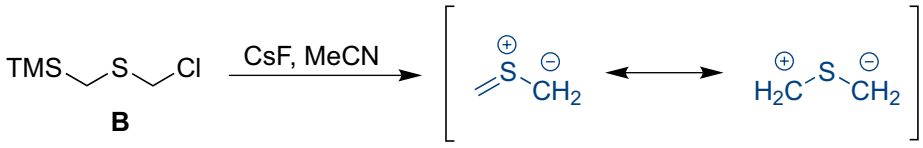
In the course of research aimed at obtaining thia-1,3-dipolar reagents, it was found that chloromethyl trimethylsilylmethyl sulfide (**B**) was a useful precursor of thiocarbonyl ylide (Scheme 2) [9]. The latter was generated under mild conditions using 1,3-elimination (desilylation) reaction promoted by fluoride ion.

Thiocarbonyl ylide generated by this way was reported to be a good partner in 1,3-dipolar [3+2] cycloaddition reactions for: (a) carbonyl compounds (aromatic aldehydes and ketones) [10]; (b) pyridine and other azines [11]; (c) α,β-unsaturated compounds, including ethyl vinyl ketone, acrylates, acetylenedicarboxylate, SF_5-substituted acetylenes [9, 12, 19].

We also previously used this method for generation of thiocarbonyl ylide and found that it readily reacted with polyfluoroalkanethioamides to form new 4-polyfluoroalkyl-1,3-dithiolanes [13]. We also described the cycloaddition of *in situ*

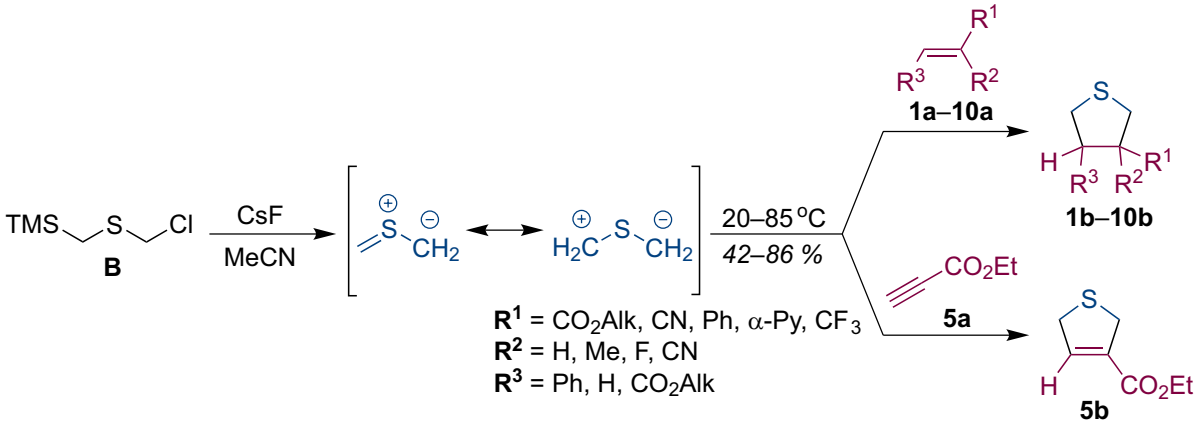


Scheme 1. Generation of thiocarbonyl ylides by the 1,3-elimination reaction



Scheme 2. Chloromethyl trimethylsilylmethyl sulfide as precursor to thiocarbonyl ylide

ISSN 2308-8303 (Print) / 2518-1548 (Online)



Scheme 3. Synthesis of tetrahydro- and 2,5-dihydrothiophenes

generated thiocarbonyl ylide to 3,3,3-trifluoropropene derivatives [14], as well as some its cyclic analogues [15] yielded new 4-(trifluoromethyl)tetrahydrothiophenes with ester, sulfone, sulfoximine, sulfonamide, or phosphonate moiety in the position 3.

Taking into account these successful results of applying reactive thiocarbonyl ylide, in this work we expanded the number of commercially available α,ß-unsaturated compounds as partners in [3+2] cycloaddition reaction with the ylide. The target cycloadducts are perfect objects for further modification and, thus promising for creation of new compounds with useful properties.

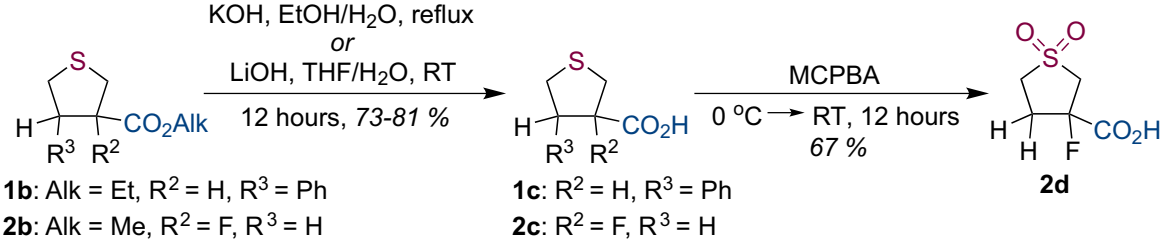
■ Results and discussion

Chloromethyl trimethylsilylmethyl sulfide (**B**) was obtained as described in the literature by the method of chloromethylation of trimethylsilylmethanethiol in 69% yield [12].

As mentioned above, the CsF-catalyzed decomposition of sulfide **B** led to the formation of thiocarbonyl ylide, which reacted *in situ* with a number of dipolarophiles providing the access to substituted dihydro- and tetrahydrothiophenes (Scheme 3, Table 1).

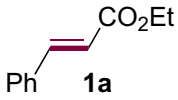
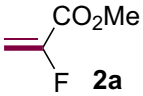
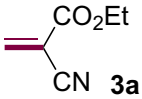
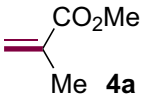
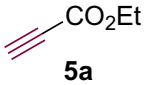
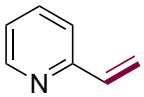
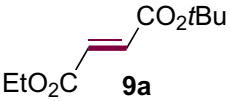
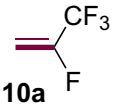
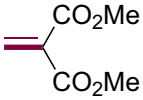
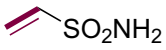
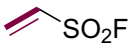
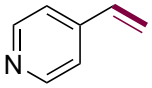
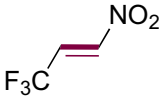
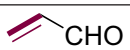
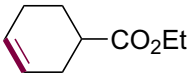
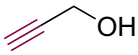
Reactions of **B** with mono- and 1,1-disubstituted electron deficient alkenes – acrylates (**2a**–**4a**), acrylonitrile (**6a**), vinylarenes (**7a**, **8a**) and the fluorinated alkene (**10a**) in the presence of CsF excess easily proceeded at room temperature (heating for **4a**) with the formation of the corresponding tetrahydrothiophenes (**2b**–**4b**, **6b**–**8b**, **10b**) in good yields (Table 1, entries 2–4, 6–8, 10). *E*-1,2-Disubstituted alkenes, namely ethyl cinnamate (**1a**) and ethyl *tert*-butyl fumarate (**9a**), allowed obtaining the corresponding *trans*-3,4-disubstituted tetrahydrothiophenes **1b**, **9b** stereoselectively (entries 1, 9). At the same time, a number of olefins (entries 11–16) occurred to be unsuitable dipolarophiles for obtaining the corresponding thiolane derivatives, they produces polymeric products under the conditions of thiocarbonyl ylide generation. It should be noted that the olefin without an acceptor substituent (entry 17) did not undergo cycloaddition. Alkynes can also be used as dipolarophiles, thus, the corresponding 2,5-dihydrothiophene **5b** was obtained from ethyl acetylenecarboxylate (**5a**, entry 5), but a non-activated triple bond in propargyl alcohol practically did not add thiocarbonyl ylide (entry 18). The results of all transformations studied are presented in Table 1.

We demonstrated that the products of 1,3-dipolar cycloaddition were convenient for further functionalization. In particular, esters **1b**, **2b** were hydrolyzed into acids **1c**, **2c** (basic hydrolysis). Oxidation of **2c** with *m*-chloroperbenzoic acid (MCPBA, 3 equiv) in MTBE at 0 °C gave the corresponding sulfone **2d** with the yield of 67% (Scheme 4). The stereochemistry of compounds **1b** and **1c** was determined according to the literature data [7, 12].



Scheme 4. Hydrolysis and S-oxidation of the representative adducts

Table 1. Reactions of **1** with a range of dipolarophiles

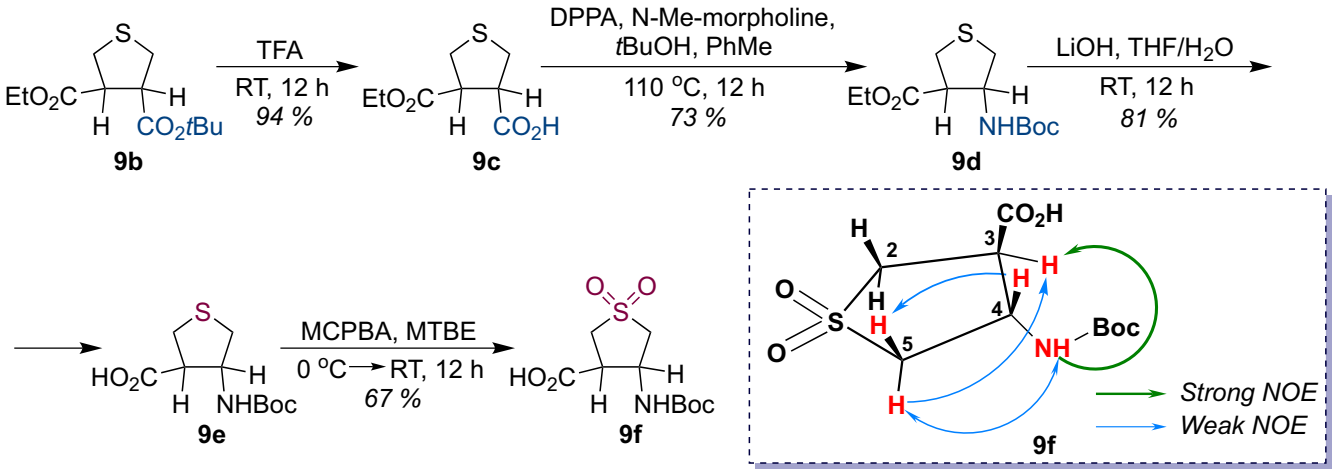
Entry	Alkene/alkyne	Conditions	Yield, %	Product
1	 **1a**	85 °C, 48 h	79	**1b**, R^1 = CO_2Et, R^2 = H, R^3 = Ph
2	 **2a**	r.t., 12 h	83	**2b**, R^1 = CO_2Me, R^2 = F, R^3 = H
3	 **3a**	r.t., 12 h	52	**3b**, R^1 = CO_2Et, R^2 = CN, R^3 = H
4	 **4a**	85°C, 48 h	86	**4b**, R^1 = CO_2Me, R^2 = Me, R^3 = H
5	 **5a**	r.t., 12 h	42	**5b**
6	 **6a**	r.t., 12 h	80	**6b**, R^1 = CN, R^2 = R^3 = H
7	 **7a**	r.t., 12 h	80	**7b**, R^1 = Ph, R^2 = R^3 = H
8	 **8a**	r.t., 12 h	65	**8b**, R^1 = α-Py, R^2 = R^3 = H
9	 **9a**	85 °C, 48 h	70	**9b**, R^1 = CO_2tBu, R^2 = H, R^3 = CO_2Et
10	 **10a**	r.t., 48 h	80	**10b**, R^1 = CF_3, R^2 = F, R^3 = H
11		r.t., 12 h	0[a]	–
12		r.t., 12 h	0[a],[c]	–
13		r.t., 12 h	0[a]	–
14		r.t., 12 h	0[b]	–
15		r.t., 12 h	0[a]	–
16		r.t., 12 h	0[a]	–
17		85 °C, 48 h	0[c]	–
18		85 °C, 48 h	0[c]	–

Notes: [a] Polymeric by-products prevailed; [b] γ-vinylpyridine gave the N-alkylation product; [c] less than 5 % of cycloadduct was detected by NMR and GC

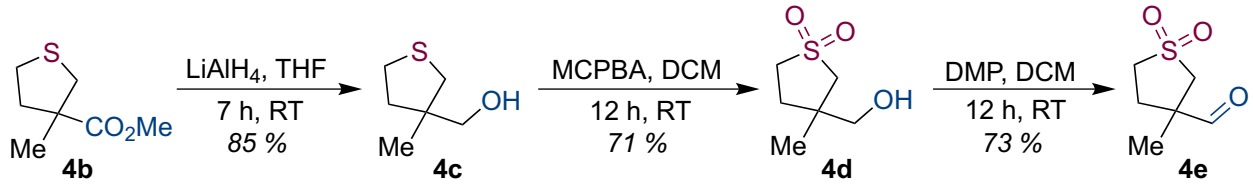
ISSN 2308-8303 (Print) / 2518-1548 (Online)

A similar method was applied to preparation of acid **9c**, which under conditions of the Curtius reaction was converted into Boc-protected amine **9d** through *in situ* formation of the acyl azide. In this way, acid **9c** was converted into Boc-amine **9d** by the treatment with the equivalent amounts of diphenylphosphoryl azide (DPPA), N-methylmorpholine and 3 equiv of *t*BuOH in toluene at reflux for 12 hours. After hydrolysis and oxidation of **9d**, the corresponding sulfone **9f** was obtained (Scheme 5). The determination of the stereochemistry of **9f** was carried out using ^{1}H NOESY experiments.

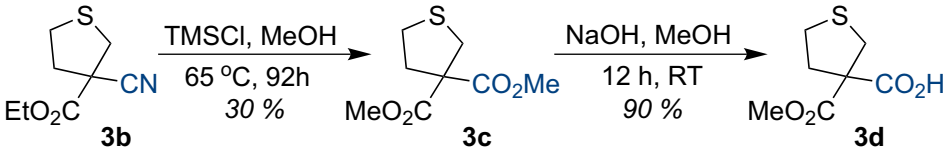
Ester **4b** was reduced to alcohol **4c** with $LiAlH_4$ in THF at room temperature. Oxidation of sulfur using MCPBA in dichloromethane to sulfone



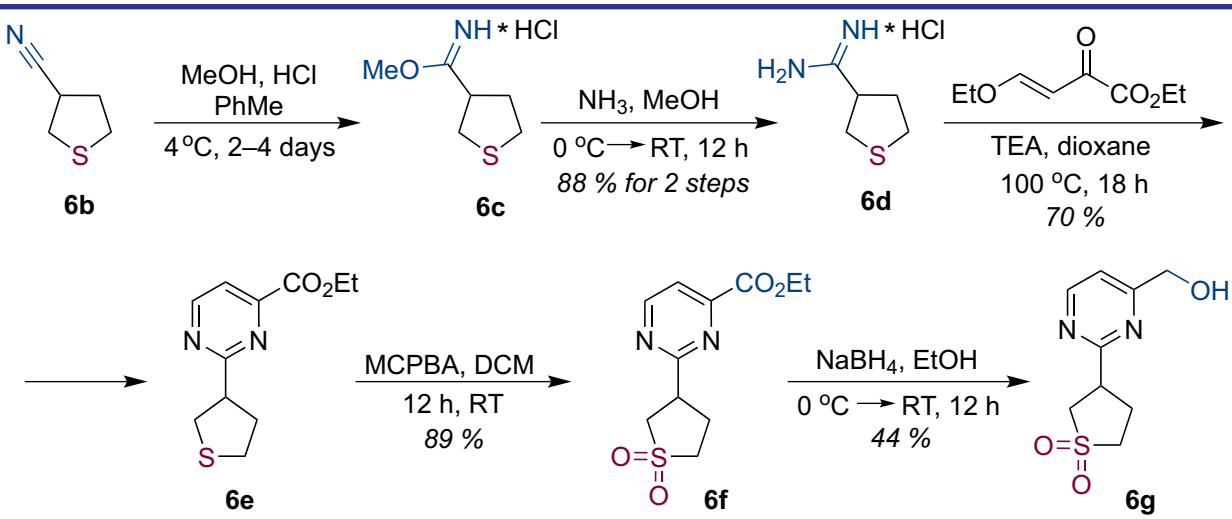
Scheme 5. Transformations of ester **9b** and determination of stereochemistry of the final product



Scheme 6. Modification of ester **4b**



Scheme 7. Stepwise methanolysis and hydrolysis of nitrile **3b**



Scheme 8. Transformations of nitrile **6b**

4d, and the subsequent oxidation of the alcohol group with the Dess-Martin reagent (DMP) at room temperature in dichloromethane gave aldehyde **4e** (Scheme 6).

The treatment of compound **3b** with TMSCl in methanol at 65 °C continued with transesterification and methanolysis to obtain diester **3c**. Further alkaline mono-hydrolysis of the latter gave compound **3d** in a good yield (Scheme 7).

Compound **6b** was successfully transformed into amidine **6d** through the intermediate formation of iminoester **6c**. Pyrimidine **6e** was formed by heterocyclization of amidine with ethyl 4-ethoxy-2-oxobut-3-enoate according to the method described by us earlier [16]. The subsequent oxidation of ring sulfur atom and reduction of the ester group with $NaBH_4$ allowed obtaining alcohol **6g** (Scheme 8).

■ Conclusions

Chloromethyl trimethylsilylmethyl sulfide being a precursor of thiocarbonyl ylide serves as an available and convenient reagent in the 1,3-dipolar cycloaddition to a number of dipolarophiles for the diastereoselective synthesis of substituted hydrogenated thiophenes. Considering mild reaction conditions, this method received wide application scopes. This is confirmed by the synthesis of 28 compounds with various functional groups being reported in the current work. Most of them are previously unknown derivatives of the dihydro- and tetrahydrothiophene series.

It has been shown that the products of 1,3-dipolar [3+2] cycloaddition can be transformed by convenient synthetic methods into other functional derivatives, a significant part of which has not been described in the literature as well. Although some compounds are known, the methods presented in the work is a convenient extention to the existing ones. Noteworthy, in many cases, the methods described here offer shorter synthetic pathways, better yields and start from easily availabile reagents.

■ Experimental part

Melting points were measured on a MPA100 OptiMelt automated melting point system. ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, and 126 MHz for $^{13}C\{^1H\}$ NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR, and 376 MHz for $^{19}F\{^1H\}$ NMR). NMR chemical shifts were reported in ppm (δ scale) upfield from TMS as an internal standard and were referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and $^{13}C\{^1H\}$ in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and $^{13}C\{^1H\}$ in DMSO-d_6. Mass spectra were obtained on an Agilent 1100 LCMSD SL instrument with API-ES ionization, and a Hewlett Packard/Agilent HP 5972 GC/MS instrument with electron impact ionization (EI). IR-spectra were recorded on a Perkin-Elmer BX (film or KBr tablets).

^1H NMR and ^{13}C NMR spectra of known compounds **1b** [7], **1c** [12], **5b** [17], **6b** [18], **7b** [7] were consistent with the literature data.

The general procedure for the synthesis of hydrogenated thiophenes (1b-9b) by 1,3-dipolar [3+2]-cycloaddition

To a stirred solution of chloromethyl trimethylsilylmethyl sulfide (**B**) (1.0–1.5 equiv) and a dipolarophile **1a–9a** (1.0 equiv) in MeCN (5 mL per each mmol of a dipolarophile), CsF (2.5–3.0 equiv) was added under the argon atmosphere. The resulting reaction mixture was stirred under argon at temperatures from 25 to 85 °C until the completion of the reaction (determined by ^1H NMR). The solvent was evaporated, and water (20 mL per each mmol of a dipolarophile) was added to the residue. The aqueous phase was extracted with MTBE (2×20 mL per each mmol of a dipolarophile). The combined organic phase was dried over Na_2SO_4 and concentrated. Purification by flash column chromatography or vacuum distillation (if needed) gave the desired cycloadducts.

***trans*-Ethyl-4-phenyltetrahydrothiophene-3-carboxylate (1b)**

Ethyl cinnamate (**1a**) (2 g, 11 mmol) and compound **B** (2.9 g, 17 mmol) were reacted according to the general procedure. The reaction conditions: 85 °C, 48 h. Purification by vacuum distillation gave compound **1b** as a yellow oil with the yield of 79% (3 g).

B. p. 110 °C (0.2 mm Hg). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.04 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3); 3.02 (1H, m); 3.15–3.23 (4H, m); 3.61 (1H, m); 4.00 (2H, m, $CH_3C\underline{H}_2$); 7.22–7.31 (5H, m, ArH).

Methyl 3-fluorotetrahydrothiophene-3-carboxylate (2b)

Methyl-α-fluoroacrylate (**2a**) (3 g, 29 mmol) and compound **B** (7.3 g, 43 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Purification by vacuum distillation gave compound **2b** as a yellow oil with the yield of 83% (3.9 g).

ISSN 2308-8303 (Print) / 2518-1548 (Online)

B. p. 50°C (0.2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.22–2.39 (1H, m); 2.46–2.54 (1H, m); 2.97–3.10 (2H, m); 3.12–3.21 (1H, m); 3.27–3.40 (1H, m); 3.80 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 29.7; 39.9 (d, $^2J_{CF}$ = 26 Hz); 40.5 (d, $^2J_{CF}$ = 22 Hz); 53.1; 101.8 (d, $^1J_{CF}$ = 193 Hz, C-3); 170.0 (d, $^2J_{CF}$ = 26 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –156.8 (m).

Ethyl 3-cyanotetrahydrothiophene-3-carboxylate (3b)

Ethyl 2-cyanoprop-2-enoate (**3a**) (20 g, 160 mmol) and compound **B** (32.3 g, 192 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Compound **3b** was obtained as a yellow oil with the yield of 52% (15 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.36 (3H, t, $^3J_{HH}$ = 7.3 Hz, CH_3); 2.60 (2H, m); 3.06–3.18 (2H, m); 3.32 (1H, d, $^2J_{HH}$ = 11.3 Hz); 3.41 (1H, d, $^2J_{HH}$ = 11 Hz); 4.33 (2H, q, $^3J_{HH}$ = 7.3 Hz, $CH_3C\underline{H}_2$).

Methyl-3-methyltetrahydrothiophene-3-carboxylate (4b)

Methyl-α-methylacrylate (**4a**) (32 g, 320 mmol) and compound **B** (65 g, 386 mmol) were reacted according to the general procedure. The reaction conditions: 85 °C, 48 h. Purification by vacuum distillation gave compound **4b** as a yellow oil with the yield of 86% (44 g).

B. p. 58 °C (0.2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.31 (3H, s, CH_3); 1.79 (1H, m); 2.39 (1H, m); 2.61 (1H, d, $^2J_{HH}$ = 10.4 Hz); 2.85 (2H, m); 3.22 (1H, d, $^2J_{HH}$ = 10.8 Hz); 3.65 (3H, s, CH_3O).

Ethyl 2,5-dihydrothiophene-3-carboxylate (5b)

Ethyl acetylene carboxylate (**5a**) (3 g, 31 mmol) and compound **B** (5.2 g, 31 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Purification by vacuum distillation gave compound **5b** as a colorless oil with the yield of 42% (2 g).

B. p. 55 °C (0.2 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.26 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3); 3.87 (4H, m); 4.18 (2H, q, $^3J_{HH}$ = 7 Hz, $CH_3C\underline{H}_2$); 6.85 (1H, s, C=CH). ^{1}H NMR (500 MHz, $CDCl_3$-C_6D_6 2:1), δ, ppm: 1.15 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3); 3.67 (2H, m); 3.84 (2H, m); 4.08 (2H, q, $^3J_{HH}$ = 7 Hz, $CH_3C\underline{H}_2$); 6.85 (1H, s, C=CH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 14.2; 37.1; 38.9; 60.8; 135.7; 140.4; 163.8.

Tetrahydrothiophene-3-carbonitrile (6b)

Acrylonitrile (**6a**) (5 g, 94 mmol) and compound **B** (17.5 g, 104 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Purification by vacuum distillation gave compound **6b** as a colorless oil with the yield of 80% (8.5 g).

B. p. 59 °C (0.2 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.26 (2H, m); 2.90 (1H, m); 3.00 (2H, m); 3.06–3.16 (2H, m). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 30.0; 32.9; 34.4; 34.9; 120.1. IR (film), ν_{max}, cm^{-1}: 2943; 2867; 2241; 1439; 1251; 849.

3-Phenyltetrahydrothiophene (7b)

Styrene (**7a**) (5 g, 48 mmol) and compound **B** (9 g, 53 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Purification by vacuum distillation gave compound **7b** as a colorless oil with the yield of 80% (6.2 g).

B. p. 75 °C (0.2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.06 (1H, m); 2.41 (1H, m); 2.93 (1H, m); 2.99 (2H, m); 3.17 (1H, m); 3.33 (1H, m); 7.30 (5H, m, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 31.0; 37.8; 38.1; 49.8; 126.8; 127.1; 128.6; 142.1.

2-(Tetrahydro-3-thienyl)pyridine (8b)

α-Vinylpyridine (**8a**) (5 g, 47 mmol) and compound **B** (9.5 g, 57 mmol) were reacted according to the general procedure. The reaction conditions: 25 °C, 12 h. Purification by vacuum distillation gave compound **8b** as a colorless oil with the yield of 65% (5 g).

B. p. 74 °C (0.2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.22 (1H, m); 2.39 (1H, m); 2.94 (2H, m); 3.11 (2H, m); 3.43 (1H, m); 7.10 (1H, t, $^3J_{HH}$ = 6 Hz, ArH); 7.21 (1H, d, $^3J_{HH}$ = 8 Hz, ArH); 7.58 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH); 8.50 (1H, d, $^3J_{HH}$ = 5.6 Hz, ArH). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 30.9; 36.5; 37.0; 51.5; 121.7; 121.7; 136.4; 149.3; 161.2.

***trans-tert*-Butyl-ethyl-tetrahydrothiophene-3,4-dicarboxylate (9b)**

α-Ethyl *tert*-butyl fumarate (**9a**) (8 g, 40 mmol) and compound **B** (7.4 g, 44 mmol) were reacted according to the general procedure. The reaction conditions: 85 °C, 18 h. Purification by vacuum distillation gave compound **9b** as a colorless oil with the yield of 70% (7.3 g).

B. p. 114 °C (0.2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.22 (3H, t, $^3J_{HH}$ = 6.4 Hz, CH_3); 1.40 (9H, s, *t*Bu); 3.06 (4H, m); 3.33 (2H, m); 4.12 (2H, q, $^3J_{HH}$ = 6.4 Hz, $CH_3C\underline{H}_2$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), δ, ppm: 14.2; 27.9; 33.1; 33.1; 50.7; 51.7; 61.2; 81.5; 171.0; 172.1.

3-Fluoro-3-(trifluoromethyl)tetrahydrothiophene (10b)

Into a dry acetonitrile (10 mL), 2,3,3,3-tetrafluoroprop-1-ene (**10a**) was bubbled through for 5 min. Then to the solution obtained, compound **B**

(0.35 g, 2.1 mmol) followed by cesium fluoride (0.7 g, 4.6 mmol) were added under argon. The reaction mixture was stirred at room temperature for 48 h and diluted with water (20 mL). The aqueous phase was washed with pentane/MTBE mixture (2×30 mL, 9:1). The combined organic phases were dried over Na_2SO_4, and the solvents were distilled off under atmospheric pressure to give 3-fluoro-3-(trifluoromethyl)tetrahydrothiophene (**10b**) as a colorless oil with the yield of 80% (0.37 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.23 (1H, m); 2.55 (1H, m); 3.03 (1H, m); 3.12–3.34 (3H, m). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.9; 35.6 (d, $^2J_{CF}$ = 23 Hz); 36.6 (d, $^2J_{CF}$ = 22 Hz); 102.2 (qd, $^1J_{CF}$ = 192 Hz, $^2J_{CF}$ = 32 Hz, C-3); 123.2 (dq, $^1J_{CF}$ = 282 Hz, $^2J_{CF}$ = 29 Hz, CF_3). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –80.0 (CF_3); –164.4 (CF).

***trans*-4-Phenyltetrahydrothiophene-3-carboxylic acid (1c)**

An aqueous KOH (2.14 g, 38 mmol, 10%) solution was added to the solution of *trans*-ethyl-4-phenyltetrahydrothiophene-3-carboxylate (**1b**) (4.5 g, 19 mmol) in ethanol (50 mL). The reaction mixture was stirred at reflux for 12 h, the organic solvent was distilled off under vacuum, and the remaining aqueous phase was washed with MTBE (15 mL), acidified with concentrated hydrochloric acid to pH 1–2 and extracted with dichloromethane (2×50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (5:95 MeOH/CH_2Cl_2) gave compound **1c** as a white solid with the yield of 73% (2.9 g).

M. p. 89–90 °C. TLC (5% methanol in dichlorometane): R_f = 0.7 (UV). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.04 (1H, m); 3.22-3.27 (4H, m); 3.67 (1H, m); 7.27-7.34 (5H, m); 9.5–12.5 (1H, br. s, COOH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 33.9; 37.9; 52.5; 54.4; 127.2; 127.5; 128.8; 139.8; 178.9. LC-MS (API-ES), *m*/*z*, %: 207.1 [M–H$^-$], 100%.

3-Fluorotetrahydrothiophene-3-carboxylic acid (2c)

An aqueous LiOH solution (1.1 g, 27 mmol of LiOH monohydrate in 80 mL of water) was added to the solution of methyl 3-fluorotetrahydrothiophene-3-carboxylate (**2b**) (3.9 g, 24 mmol) in THF (80 mL). The reaction mixture was stirred for 12 h at room temperature, the organic solvent was distilled off under vacuum, and the remaining aqueous phase was washed with MTBE (20 mL), acidified with $NaHSO_4$, and extracted with dichloromethane (2×50 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Compound **2c** was obtained as a yellow solid with the yield of 81% (2.9 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.30–2.48 (1H, m); 2.55–2.63 (1H, m); 3.04–3.16 (2H, m); 3.20-3.29 (1H, m); 3.37–3.49 (1H, m); 9.73 (s, 1H, COOH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 29.9; 40.0 (d, $^2J_{CF}$ = 25 Hz); 40.7 (d, $^2J_{CF}$ = 22.5 Hz); 101.2 (d, $^1J_{CF}$ = 192.5 Hz, C-3); 175.2 (d, $^2J_{CF}$ = 26.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –157.0.

3-(Methoxycarbonyl)thiolane-3-carboxylic acid (3d)

An aqueous NaOH (1 g, 25 mmol, 20 mL) solution was added dropwise to the solution of dimethyl dihydrothiophene-3,3(2*H*)-dicarboxylate (**3c**) (5.3 g, 26 mmol) in methanol (50 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The organic solvent was distilled off under vacuum, the remaining aqueous phase was washed with MTBE (10 mL), acidified with $NaHSO_4$ (3.45 g, 25 mmol), and extracted with MTBE (2×30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Compound **3d** was obtained as a white solid with the yield of 90% (3.2 g).

^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.58 (2H, m); 2.99 (2H, m); 3.41 (2H, s); 3.81 (3H, s, OCH_3); 7.5–8.75 (1H, br. s, COOH). LC-MS (API-ES), *m*/*z*, %: 191.0, [M+H]$^+$, 100%.

***trans*-4-[(*tert*-Butoxycarbonyl)amino]-tetrahydrothiophene-3-carboxylic acid (9e)**

The compound was obtained from *trans*-ethyl-4-[(*tert*-butoxy-carbonyl)amino]tetrahydrothiophene-3-carboxylate (**9d**) (4 g, 15 mmol) according to the method of hydrolysis of compound **2b**. A white solid (3 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.43 (9H, s, *t*Bu); 2.67–2.70 (1H, m); 3.00–3.24 (4H, m); 4.59 (1H, m); 4.97 (1H, br. s, NH).

***trans*-4-(Ethoxycarbonyl)tetrahydrothiophene-3-carboxylic acid (9c)**

tert-Butyl ethyl *trans*-tetrahydrothiophene-3,4-dicarboxylate (**9b**) (7 g, 27 mmol) was dissolved in trifluoroacetic acid (50 mL), and the resulting solution was stirred for 12 h at room temperature. The solvent was evaporated, and the residue was quenched with an excess of a saturated $NaHCO_3$ solution (50 mL), washed with MTBE (15 mL), the aqueous phase was acidified with $NaHSO_4$ to pH 2–3, and extracted with dichloromethane (2×25 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Compound **9c** was obtained as a colorless oil with the yield of 94% (5.2 g).

ISSN 2308-8303 (Print) / 2518-1548 (Online)

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.27 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3); 3.16 (4H, m); 3.49 (1H, m); 3.56 (1H, m); 4.19 (2H, q, $^3J_{HH}$ = 7 Hz, $CH_3C\underline{H}_2$); 10.8–11.5 (1H, br. s, COOH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 14.0; 32.8; 33.0; 50.3; 50.5; 61.7; 172.0; 178.2.

***trans*-4-[(*tert*-Butoxycarbonyl)amino]-tetrahydrothiophene-3-carboxylic acid 1,1-dioxide (9f)**

MCPBA (6.4 g, 36 mmol) was added portionwise to a stirred solution of *trans*-4-[(*tert*-butoxycarbonyl)amino]tetrahydrothiophene-3-carboxylic acid (**9e**) (3 g, 12 mmol) in MTBE (10 mL) at 0 °C for 30 min. The mixture was stirred for 12 h at room temperature, filtered, the precipitate was washed with MTBE, and air dried to give compound **9f** as a white crystalline solid with the yield of 67% (2.1 g).

M. p. 181 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.37 (9H, s, *t*Bu); 2.94 (1H, m); 3.19 (1H, m); 3.23 (1H, m); 3.51 (1H, m); 3.57 (1H, m); 4.39 (1H, m); 7.40 (1H, br. s, NH); 12.80–13.20 (1H, br. s, COOH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 28.1 (C($\underline{C}H_3)_3$); 45.5 (C-3); 49.5 (C-4); 53.3 (C-2); 55.1 (C-5); 78.6 (O$\underline{C}(CH_3)_3$); 154.7; 171.2. LC-MS (API-ES), *m*/*z*, %: 278.0, $[M–H]^-$, 100%.

3-Fluorotetrahydrothiophene-3-carboxylic acid 1,1-dioxide (2d)

MCPBA (122 g, 707 mmol) was added portionwise to a stirred solution of 3-fluorotetrahydrothiophene-3-carboxylic acid (**2c**) (35 g, 233 mmol) in MTBE (875 mL) at 0 °C for 30 min. The mixture was stirred for 12 h at room temperature, extracted with water (3×500 mL, pH 1–5), water was evaporated, and the residue was dried under reduced pressure. Compound **2d** was obtained as a white crystalline solid with the yield of 67% (30 g, monohydrate).

M. p. 87–115 °C. *x*(H_2O) 49.7 mol% (Fisher analysis). ^{1}H NMR (400 MHz, DMSO-d_6/$CDCl_3$ 1:9), δ, ppm: 2.31–2.51 (2H, m); 2.99–3.08 (2H, m); 3.14–3.28 (1H, m); 3.30–3.41 (1H, m); 6.23 (3H, br. s, COOH+H_2O). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6/$CDCl_3$ 1:9), δ, ppm: 32.3 (d, $^2J_{CF}$ = 24 Hz); 49.8; 59.0 (d, $^2J_{CF}$ = 26 Hz); 95.2 (d, $^1J_{CF}$ = 194 Hz, C-3); 168.9 (d, $^2J_{CF}$ = 25 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6/$CDCl_3$ 1:9), δ, ppm: –154.6. LC-MS (API-ES), *m*/*z*, %: 183.0, $[M+H]^+$, 100%. IR (KBr), ν_{max}, cm^{-1}: 3490 (br., OH); 3404 (br., OH); 3025; 2965; 1994; 1695; 1332; 1310; 1284; 1232; 1151; 1126; 1012; 793; 441.

3-(Hydroxymethyl)-3-methyltetrahydrothiophene 1,1-dioxide (4d)

MCPBA (120.6 g, 699 mmol) was added portionwise to a stirred solution of (3-methyltetrahydrothiophen-3-yl)methanol (**4c**) (30.8 g, 233 mmol) in DCM (700 mL) at 0 °C for 30 min. The mixture was stirred for 12 h at room temperature, filtered, the filtrate was washed with K_2CO_3 (3×250 mL, 5% aqueous), the organic layer was dried and evaporated *in vacuo*. Compound **4d** was obtained as a white crystalline solid with the yield of 71% (27.2 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.21 (3H, s, CH_3); 1.91 (1H, m); 2.23 (1H, m); 2.41 (1H, br. s, OH); 2.80 (1H, d, $^2J_{HH}$ = 13.6 Hz); 3.18 (3H, m); 3.51 (2H, s, C$\underline{H}_2$OH).

Ethyl 2-(1,1-dioxidotetrahydrothiophen-3-yl)pyrimidine-4-carboxylate (6f)

The compound was obtained from ethyl 2-(tetrahydrothiophen-3-yl)pyrimidine-4-carboxylate (**6e**) (63 g, 265 mmol) by the method of oxidation of compound **4c**. A white crystalline solid (63.5 g, 89% yield).

^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.34 (3H, t, $^3J_{HH}$ = 6.9 Hz, CH_3); 2.36 (1H, m); 2.60 (1H, m); 3.26 (2H, m); 3.46 (1H, m); 3.60 (1H, m); 4.03 (1H, m); 4.40 (2H, q, $^3J_{HH}$ = 7.1 Hz, $CH_3C\underline{H}_2$); 7.93 (1H, d, $^3J_{HH}$ = 4.6 Hz, ArH); 9.09 (1H, d, $^3J_{HH}$ = 4.7 Hz, ArH).

Dimethyl dihydrothiophene-3,3(2H)-dicarboxylate (3c)

TMSCl (43.4 g, 400 mmol) was added to the solution of ethyl 3-cyanotetrahydrothiophene-3-carboxylate (**3b**) (7.39 g, 40 mmol) in methanol (90 mL) at room temperature. The reaction mixture was heated at reflux for 92 h, then cooled, and the solvent was evaporated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (0 to 100% gradient MTBE in hexanes) gave compound **3c** as a yellow solid with the yield of 30% (5.3 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.55 (2H, t, $^3J_{HH}$ = 6.9 Hz); 2.96 (2H, t, $^3J_{HH}$ = 6.9 Hz); 3.38 (2H, s); 3.78 (6H, s, OCH_3).

(3-Methyltetrahydrothiophen-3-yl)methanol (4c)

$LiAlH_4$ (7.5 g, 10.03 mmol) was suspended in THF (200 mL), the resulting mixture was cooled to 0 °C, and methyl 3-methyltetrahydrothiophene-3-carboxylate (**4b**) (44 g, 7.17 mmol) in 300 mL THF was added. The reaction mixture was stirred at room temperature for 7 h. The reaction mixture was cooled to 0 °C and quenched with water (10 mL). The solid was filtered, the precipitate was additionally washed with a warm THF. The filtrate was evaporated *in vacuo*, diluted with DCM and washed with water, dried and evaporated under vacuum to obtain compound **4c** with the yield of 85% (30.8 g) as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.13 (3H, s, CH_3); 1.73 (1H, m); 1.78 (1H, br. s, OH); 1.91 (1H, m); 2.53 (1H, d, $^2J_{HH}$ = 10.5 Hz); 2.78 (1H, d, $^2J_{HH}$ = 10.5 Hz); 2.89 (2H, m); 3.55 (2H, s, C$\underline{H_2}$OH).

3-Methyltetrahydrothiophene-3-carbaldehyde 1,1-dioxide (4e)

To the solution of 3-(hydroxymethyl)-3-methyltetrahydrothiophene 1,1-dioxide (**4d**) (12 g, 73 mmol) in 450 mL of CH_2Cl_2, the Dess-Martin reagent (46.5 g, 110 mmol, purity 85%) was added. The resulting mixture was stirred for 12 h at room temperature. Then it was filtered, the precipitate was washed with MTBE, the combined filtrate was dried over sodium sulfate and evaporated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (0 to 100% gradient MTBE in hexanes) gave compound **4e** as white crystals with the yield of 73% (8.5 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.43 (3H, s, CH_3); 2.03 (1H, m); 2.56 (1H, m); 2.87 (1H, d, $^2J_{HH}$ = 13.9 Hz); 3.01 (1H, m); 3.18 (1H, m); 3.63 (1H, d, $^2J_{HH}$ = 13.9 Hz); 9.50 (1H, s, CHO). GC-MS (EI), m/z, %: 133 $[M–CHO]^{\cdot+}$, < 1%.

***trans*-Ethyl-4-[(*tert*-butoxycarbonyl)amino]tetrahydrothiophene-3-carboxylate (9d)**

To the solution of *trans*-4-(ethoxycarbonyl) tetrahydrothiophene-3-carboxylic acid (**9c**) (5.2 g, 25 mmol), dry *t*BuOH (5.7 g, 77 mmol), N-methylmorpholine (3 g, 30 mmol) in toluene (50 mL), DPPA (8.3 g, 30 mmol) was added dropwise at 0 °C under argon. The reaction mixture was heated at reflux for 12 h, then cooled, washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Compound **9d** was obtained as a yellow solid with the yield of 73% (5 g) and was used in the next step without further purification.

M. p. 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.27 (3H, t, $^3J_{HH}$ = 6.5 Hz, CH_3); 1.44 (9H, s, *t*Bu); 2.69–2.77 (1H, m); 3.01–3.23 (4H, m); 4.18 (2H, q, $^3J_{HH}$ = 6.5 Hz, $CH_3C\underline{H_2}$); 4.64 (1H, m); 4.88 (1H, br. s, NH). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), δ, ppm: 14.3; 28.5; 30.5; 36.0; 52.8; 57.4; 61.4; 77.0; 155.0; 171.6.

Tetrahydrothiophene-3-carboximidamide hydrochloride (6d)

To the solution of tetrahydrothiophene-3-carbonitrile (**6b**) (55.0 g, 487 mmol) and a dry methanol (17.9 g, 560 mmol) in toluene (600 mL), dry gaseous HCl (obtained by boiling 36% hydrochloric acid) was bubbled through at 0 °C for 1 h. The flask with the reaction mixture was closed and stored at +4 °C for 2–4 days. The precipitate formed was filtered and dried *in vacuo* to give an intermediate compound – methyl tetrahydrothiophene-3-carbimidate hydrochloride (**6c**). It was dissolved in dry methanol (500 mL) at 0 °C, and gaseous ammonia was bubbled through at 0 °C for 1 h. The resulting reaction mixture was stirred for 12 h at room temperature, and then evaporated *in vacuo*. Compound **6d** was obtained as a white solid with the yield of 88% (71 g) and used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.07 (1H, m); 2.37 (1H, m); 2.83 (1H, m); 2.95 (2H, m); 3.08 (2H, m); 9.0 (4H, br. s, $2NH_2$). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6), δ, ppm: 30.4; 33.7; 34.4; 46.5; 171.1.

Ethyl 2-(tetrahydrothiophen-3-yl)pyrimidine-4-carboxylate (6e)

According to the procedure of pyrimidine carboxylic acid esters synthesis [16], to a stirred solution of ethyl 4-ethoxy-2-oxobut-3-enoate (65.5 g, 381 mmol) and triethylamine (160 mL, 1.15 mol) in 1000 mL of dioxane, tetrahydrothiophene-3-carboximidamide hydrochloride (**6c**) (71.0 g, 426 mmol) was added portionwise at 70 °C. The resulting mixture was stirred at reflux for 18 h, cooled, and the solvent was evaporated. The residue was quenched with water (500 mL) and extracted with MTBE (2×400 mL). The combined extract was washed with water, brine, dried over sodium sulfate, and the solvent was evaporated. Compound **6e** was obtained as a yellow crystalline solid with the yield of 70% (63.5 g).

^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.42 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3); 2.45 (2H, m); 3.00 (2H, m); 3.28 (2H, m); 3.78 (1H, m); 4.47 (2H, q, $^3J_{HH}$ = 7 Hz, $CH_3C\underline{H_2}$); 7.80 (1H, d, $^3J_{HH}$ = 4.8 Hz, ArH); 8.90 (1H, d, $^3J_{HH}$ = 4.8 Hz, ArH). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ, ppm: 14.2; 31.2; 36.1; 36.5; 52.4; 62.6; 118.5; 155.3; 159.2; 164.2; 171.6.

3-(4-(Hydroxymethyl)pyrimidin-2-yl)tetrahydrothiophene 1,1-dioxide (6g)

$NaBH_4$ (4.9 g, 129 mmol) was added to a stirred solution of ethyl 2-(1,1-dioxidotetrahydrothiophen-3-yl)pyrimidine-4-carboxylate (**6f**) (63.5 g, 235 mmol) in 600 mL of absolute ethanol at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then overnight at room temperature. Water (75 mL) was then added, and the reaction mixture was evaporated in vacuo, the residue was dissolved in dichloromethane and dried over sodium sulfate and filtered off. Silica gel (2.5 g) was added to the filtrate, and this mixture was stirred for 15 min, filtered and the filtrate was evaporated *in vacuo*. Compound **6g** was obtained as a colorless crystalline solid with the yield of 44% (23.5 g).

ISSN 2308-8303 (Print) / 2518-1548 (Online)

M. p. 157 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.29 (1H, m); 2.54 (1H, m); 3.17-3.45 (3H, m); 3.54 (1H, m); 3.88 (1H, m); 4.54 (2H, d, $^3J_{HH}$ = 5.8 Hz, C$\underline{H}_2$OH); 5.65 (1H, t, $^3J_{HH}$ = 5.8 Hz, OH); 7.46 (1H, d, $^3J_{HH}$ = 5 Hz, ArH); 8.77 (1H, d, $^3J_{HH}$ = 5 Hz, ArH). LC-MS (API-ES), *m/z*, %: 229.0, $[M+H]^+$, 100%.

■ Acknowledgements

The authors thank Dr. O. O. Stepaniuk for the help with the synthesis, Prof. Dr. A. O. Tolmachev for his encouragement and support, and all the brave defenders of Ukraine for making this publication possible.

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