DOI 10.1007/s10593-015-1647-z
Chemistry of Heterocyclic Compounds, Vol. 50, No. 12, March, 2015 (Russian Original Vol. 50, No. 12, December, 2014)

ETHYL 2-AMINOTHIOPHENE-3-CARBOXYLATES IN THE SYNTHESIS OF ISOMERIC THIENOPYRIDINES

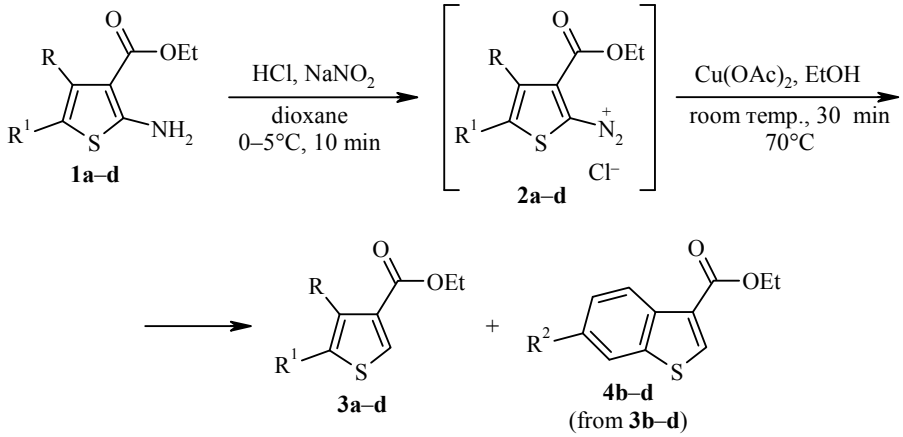
N. T. Pokhodylo[1]*, O. Ya. Shyyka[1], and N. D. Obushak[1]

A convenient method for the synthesis of thieno[3,2-c]pyridinones was developed. A number of thiophene derivatives was prepared, and the possibility of using thiophene desamino derivatives for the design of potentially biologically active molecules was demonstrated.

Keywords: aminothiophenes, thienopyridinones, thiophene-3-carboxylic acids, Curtius rearrangement, electrophilic cyclization.

The high biological activity of thiophene-based fused heterocyclic system derivatives (thieno[2,3-*b*]-pyridinones, thieno[2,3-*c*]pyridines, thieno[2,3-*d*]pyrimidines, thieno[2,3-*b*][1,5]benzodiazepines, and others) [1-6] stimulated the search of new convenient methods for their synthesis [7]. In this paper, we explore the use of desaminated aminothiophenes as precursors for thiophene derivatives with an annelated pyridinone cycle.

2-aminothiophenes **1** obtained by Gewald's reaction as described in the literature [8] were used as starting reagents in this study. Through subsequent diazotization and desamination reactions, 2-amino-thiophenes were converted into compounds **3**, which were isolated in satisfactory yields. In this reaction, ethanol was used as the reducing agent [8, 9].



1-3 a R = R^1 = Me, **b** R+R^1 = $(CH_2)_4$, **c** R+R^1 = $CH_2CH_2CH(Me)CH_2$, **d** R+R^1 = $CH_2CH_2CH(t\text{-Bu})CH_2$;
4 b R^2 = H, **c** R^2 = Me, **d** R^2 = *t*-Bu

*To whom correspondence should be addressed, e-mail: pokhodylo@gmail.com.

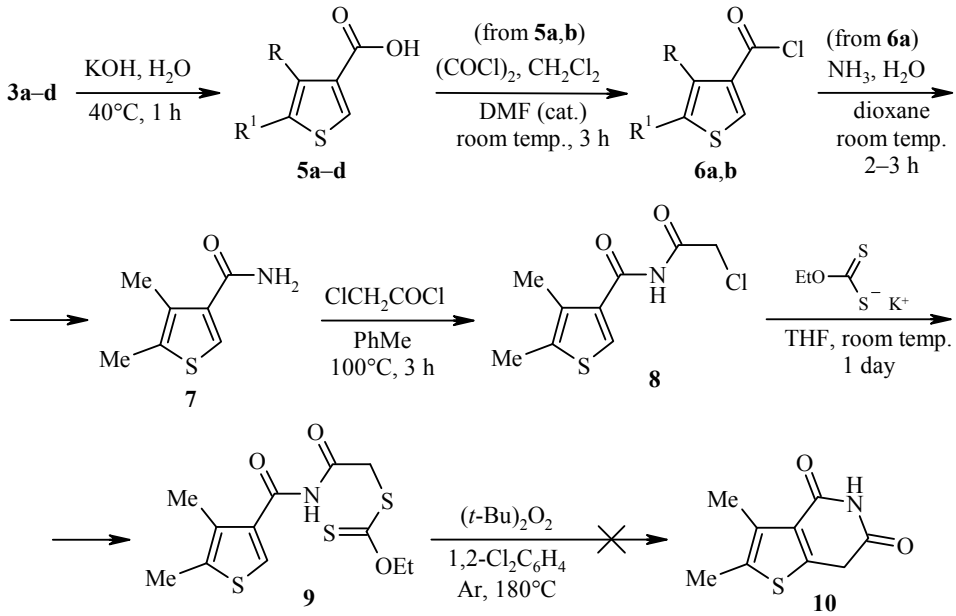
[1]Ivan Franko National University of Lviv, 6 Kyryla and Mefodiya St., Lviv 79005, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1900-1907, December, 2014. Original article submitted August 31, 2014; revision submitted September 6, 2014.

It should be noted that despite moderate product yields this approach offers the advantage over the prior known multistep thiophene-3-carboxylic acid ester synthesis methods [10-13] of affording various thiophene derivatives in two synthetic steps from simple and available reagents.

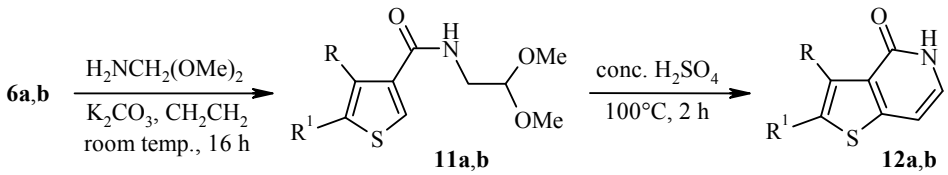
Interestingly, when 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **1b-d** were used in this reaction, compounds **4b-d**, by-products stemming from cyclohexane fragment dehydrogenation, were isolated from the reaction mixture together with the main desamination products **3b-d**. The formation of by-products **4b-d** in 4-7% yields was confirmed by ^{1}H NMR spectroscopy and chromato-mass spectrometry analysis of the reaction mixture. Individual substances were isolated by vacuum distillation and chromatography.

A further stage of our work was the study of the intramolecular cyclization of thiophene-3-carboxylic acid derivatives occurring at position 2 of the heterocyclic ring. For this purpose, esters **3a-d** were converted into thiophene carboxylic acids **5a-d** in quantitative yields; acyl chlorides **6a**,**b** were prepared from acids **5a**,**b**. Acyl chloride **6a** was consecutively transformed into amide **7** and chloroacetylamide **8**, from which a previously unknown xanthate derivative **9** was synthesized. Regrettably, heating the latter with a considerable excess of di-*tert*-butyl peroxide under an argon atmosphere [14] resulted in a complex mixture of products from which the cyclic thieno[3,2-*c*]pyridinedione **10** could not be isolated.



5, 6 a R = R^1 = Me, **b** R+R^1 = $(CH_2)_4$, **c** R+R^1 = $CH_2CH_2CH(Me)CH_2$, **d** R+R^1 = $CH_2CH_2CH(t\text{-}Bu)CH_2$

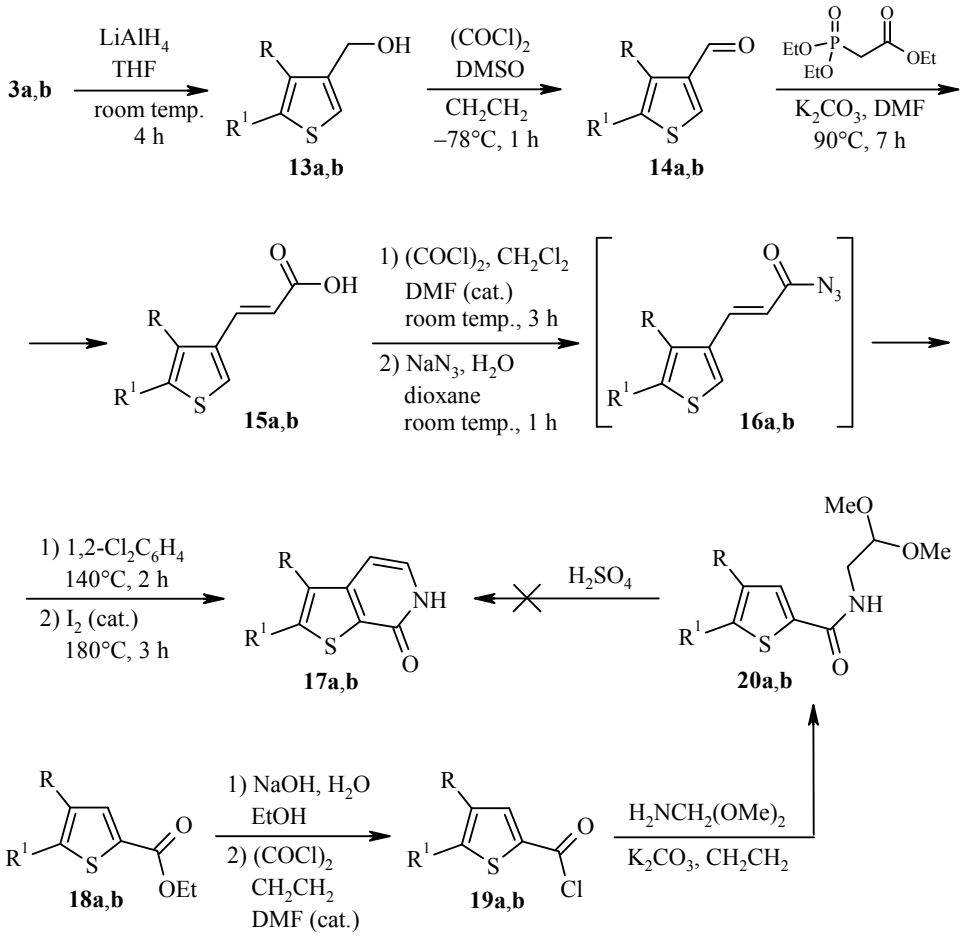
Meanwhile, employing thiophene carboxylic acid chlorides **6a**,**b** in a reaction with 1,1-dimethoxymethanamine in the presence of a base yielded derivatives **11a**,**b**, which, when heated in concentrated sulfuric acid, undergo cyclization to thieno[3,2-*c*]pyridinone derivatives **12a**,**b**.



a R = R^1 = Me, **b** R+R^1 = $(CH_2)_4$

A different synthetic approach was utilized for the synthesis of the isomeric thieno[2,3-*c*]pyridinone system, based on Curtius rearrangement for the synthesis of cyclic pyridinone derivatives [15].

Thienylacrylic acids **15a**,**b** were used as the key starting materials, which in turn were synthesized in three steps from compounds **3a**,**b**. Esters **3a**,**b** were reduced with lithium aluminum hydride to the corresponding alcohols **13a**,**b**. The resulting alcohols were oxidized to aldehydes **14a**,**b** by the Swern method. The Horner–Wadsworth–Emmons reaction of aldehydes **14a**,**b** with ethyl 2-(diethoxyphosphoryl)acetate and subsequent hydrolysis of the reaction mixture afforded thienylacrylic acids **15a**,**b**, which were then converted to azides **16a**,**b**. The latter formed thienopyridinones **17a**,**b** *via* the Curtius rearrangement and subsequent cyclization. An alternative method for the synthesis of compounds **17a,b** using esters **18a**,**b** [16] did not lead to the desired products. Amides **20a**,**b** did not enter into the cyclization reaction, presumably due to a different electron density distribution in the thiophene ring in comparison to azides **16a**,**b**.



a R = R^1 = Me, **b** R+R^1 = $(CH_2)_4$

As a result of this study, convenient methods for the synthesis of new thiophene derivatives and thienopyridinones were found that could afford compounds with potentially useful biological properties.

EXPERIMENTAL

^{1}H NMR spectra were acquired on Varian VXR-300 (300 MHz, compounds **12a**,**b**) and Varian Mercury (400 MHz, remaining compounds) spectrometers in DMSO-d_6, with TMS as internal standard. Mass spectra

were recorded on an Agilent 1100 LC/MSD LC-MS system, atmospheric-pressure CI. Merck Grade 9385, 60 Å, 230-400 silica gel was used for column chromatography.

Preparation of Thiophene-3-carboxylic Acid Esters 3a-d (General Method). Conc. HCl (57 ml) was added to a solution of aminothiophene **1a-d** (75.0 mmol) in dioxane (70 ml) with cooling and stirring. Then a solution of $NaNO_2$ (5.18 g, 75.0 mmol) in H_2O (6 ml) was added dropwise with vigorous stirring and cooling to 0-5°C. When the addition of $NaNO_2$ was complete, the solution was kept for 10 min and then allowed to gradually warm up to room temperature. The obtained mixture was filtered if needed. The filtrate was added dropwise to $Cu(OAc)_2$ (0.50 g, 2.8 mmol) in EtOH (150 ml). The solution was kept at room temperature for 30 min, then heated to 70°C, after 1 h at this temperature, cooled, diluted with three volumes of H_2O, and extracted three times with three volumes of CH_2Cl_2. The solvent was evaporated, and the obtained ester **3a-d** was distilled under vacuum. In the case of esters **3b-d**, the product was purified by column chromatography after distillation to remove impurity **4b-d**.

Ethyl 4,5-Dimethylthiophene-3-carboxylate (3a). Yield 43%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.86 (1H, s, H-2); 4.22 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 2.35 (3H, s, CH$_3$); 2.29 (3H, s, CH$_3$); 1.34 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$). Mass spectrum, *m*/*z*: 185 $[M+H]^+$. Found, %: C 58.79; H 6.68. $C_9H_{12}O_2S$. Calculated, %: C 58.67; H 6.56. All characteristics conform to literature data [17].

Ethyl 4,5,6,7-Tetrahydrobenzo[*b*]thiophene-3-carboxylate (3b). Yield 57%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.89 (1H, s, H-2); 4.22 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 2.82-2.72 (4H, m, 2CH$_2$); 1.84-1.73 (4H, m, 2CH$_2$); 1.32 (3H, t, *J* = 7.1, OC$\underline{H}_2$CH$_3$). Mass spectrum, *m*/*z*: 211 $[M+H]^+$. Found, %: C 62.91; H 6.80. $C_{11}H_{14}O_2S$. Calculated, %: C 62.83; H 6.71.

Ethyl 6-Methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (3c). Yield 63%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.89 (1H, s, H-2); 4.22 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 3.01-2.97 (1H, m, CH); 2.84-2.79 (1H, m, CH); 2.71-2.62 (1H, m, CH); 2.36-2.27 (1H, m, CH); 1.89-1.86 (2H, m, CH$_2$); 1.43-1.36 (1H, m, CH); 1.33 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$); 1.07 (3H, d, *J* = 7.1, 6-CH$_3$). Mass spectrum, *m*/*z*: 225 $[M+H]^+$. Found, %: C 64.32; H 7.28. $C_{12}H_{16}O_2S$. Calculated, %: C 64.25; H 7.19.

Ethyl 6-(*tert*-Butyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (3d). Yield 59%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.88 (1H, s, H-2); 4.23 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 3.15-3.12 (1H, m, CH); 2.83-2.78 (1H, m, CH); 2.61-2.54 (1H, m, CH); 2.05-2.01 (1H, m, CH); 1.52-1.43 (1H, m, CH); 1.39 (1H, s, CH); 1.33 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$); 1.29-1.22 (1H, m, CH); 0.95 (9H, s, C(CH$_3$)$_3$). Mass spectrum, *m*/*z*: 267 $[M+H]^+$. Found, %: C 67.72; H 8.41. $C_{15}H_{22}O_2S$. Calculated, %: C 67.63; H 8.32.

Ethyl Benzo[*b*]thiophene-3-carboxylate (4b). Yield 4%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.51 (1H, s, H-2); 7.38-7.48 (4H, m, H Ar); 4.36 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 1.42 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$). Mass spectrum, *m*/*z*: 207 $[M+H]^+$. Found, %: C 64.21; H 4.99. $C_{11}H_{10}O_2S$. Calculated, %: C 64.05; H 4.89. All characteristics conform to published data [18].

Ethyl 6-Methylbenzo[*b*]thiophene-3-carboxylate (4c). Yield 5%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.51 (1H, s, H-2); 8.39 (1H, s, H Ar); 8.35 (1H, d, *J* = 8.2, H Ar); 7.27 (1H, d, *J* = 8.2, H Ar); 4.36 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 2.48 (3H, s, 6-CH$_3$); 1.43 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$). Mass spectrum, *m*/*z*: 221 $[M+H]^+$. Found, %: C 65.51; H 5.67. $C_{12}H_{12}O_2S$. Calculated, %: C 65.43; H 5.49.

Ethyl 6-(*tert*-Butyl)benzo[*b*]thiophene-3-carboxylate (4d). Yield 7%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, s, H-2); 8.38 (2H, d, *J* = 8.7, H Ar); 7.54-7.49 (1H, m, H Ar); 4.37 (2H, q, *J* = 7.1, OC$\underline{H}_2$CH$_3$); 1.42 (3H, t, *J* = 7.1, OCH$_2$C$\underline{H}_3$); 1.40 (9H, s, C(CH$_3$)$_3$). Mass spectrum, *m*/*z*: 263 $[M+H]^+$. Found, %: C 68.85; H 7.07. $C_{15}H_{18}O_2S$. Calculated, %: C 68.67; H 6.92.

Preparation of Thiophene-3-carboxylic Acids 5a-d (General Method). KOH (1.7 g, 30 mmol) was added to an emulsion of ester **3a-d** (30 mmol) in H_2O (20 ml). The mixture was heated with vigorous stirring until a clear solution was obtained (1 h) and then for further 30 min. The solution was cooled, washed with PhMe; the aqueous layer was separated and acidified with HCl to pH 4. The precipitate was filtered off and recrystallized from EtOH–DMF.

4,5-Dimethylthiophene-3-carboxylic Acid (5a). Yield 95%, white powder, mp 145-146°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.14 (1H, br. s, COOH); 7.83 (1H, s, H-2); 2.35 (3H, s, CH_3); 2.29 (3H, s, CH_3). Mass spectrum, *m*/*z*: 157 $[M+H]^+$. Found, %: C 53.90; H 5.23. $C_7H_8O_2S$. Calculated, %: C 53.83; H 5.16. All characteristics conform to literature data [12].

4,5,6,7-Tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (5b). Yield 96%, white powder, mp 182-183°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.15 (1H, s, COOH); 8.09 (1H, s, H-2); 2.82 (2H, t, *J* = 5.9, CH_2); 2.74 (2H, t, *J* = 5.9, CH_2); 1.92-1.69 (4H, m, $2CH_2$). Mass spectrum, *m*/*z*: 183 $[M+H]^+$. Found, %: C 59.43; H 5.61. $C_9H_{10}O_2S$. Calculated, %: C 59.32; H 5.53. All characteristics conform to literature data [19].

6-Methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (5c). Yield 96%, white powder, mp 181-182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.16 (1H, s, COOH); 7.85 (1H, s, H-2); 3.07-2.99 (1H, m, CH); 2.89-2.83 (1H, m, CH); 2.72-2.64 (1H, m, CH); 2.39-2.27 (1H, m, CH); 1.89-1.86 (2H, m, CH_2); 1.43-1.29 (1H, m, CH); 1.07 (3H, d, *J* = 7.1, CH_3). Mass spectrum, *m*/*z*: 197 $[M+H]^+$. Found, %: C 61.30; H 6.22. $C_{10}H_{12}O_2S$. Calculated, %: C 61.20; H 6.16.

6-(*tert*-Butyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (5d). Yield 97%, white powder, mp 178-179°C. ^{1}H NMR spectrum, δ, ppm: 12.19 (1H, br. s, COOH); 7.88 (1H, s, H-2); 3.15-3.10 (1H, m, CH); 2.82-2.77 (1H, m, CH); 2.59-2.54 (1H, m, CH); 2.05-1.98 (1H, m, CH); 1.52-1.45 (1H, m, CH); 1.39 (1H, s, CH); 1.32-1.22 (1H, m, CH); 0.95 (9H, s, $C(CH_3)_3$). Mass spectrum, *m*/*z*: 239 $[M+H]^+$. Found, %: C 65.63; H 7.72. $C_{13}H_{18}O_2S$. Calculated, %: C 65.51; H 7.61.

Preparation of Acyl Chlorides of Thiophene-3-carboxylic Acids 6a,b (General Method). Oxalyl chloride (10 ml) and DMF (1 drop) were added dropwise with vigorous stirring to a solution of acid **5a**,**b** (50 mmol) in CH_2Cl_2 (100 ml). The solution was stirred at room temperature until evolution of gases ceased (3 h). The solvent and excess of oxalyl chloride were removed under reduced pressure to afford pure acyl chlorides **6a**,**b**.

4,5-Dimethylthiophene-3-carboxamide (7). A solution of chloride **6a** (0.5 g, 2.9 mmol) in dry dioxane (10 ml) was added dropwise to conc. aqueous NH_3 (5 ml). After several hours at room temperature, the mixture was poured into ice water (20 ml), acidified with diluted HCl to pH 3. The formed precipitate was filtered off and washed with water until neutral pH. The reaction product was recrystallized from EtOH. Yield 88%, white powder, mp 138-139°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.61 (1H, s, H-2); 7.10 (2H, d, *J* = 9.8, NH_2); 2.32 (3H, s, CH_3); 2.23 (3H, s, CH_3). Mass spectrum, *m*/*z*: 156 $[M+H]^+$. Found, %: C 54.27; H 5.89; N 9.18. C_7H_9NOS. Calculated, %: C 54.17; H 5.84; N 9.02.

***N*-(2-Chloroacetyl)-4,5-dimethylthiophene-3-carboxamide (8)**. Chloroacetyl chloride (0.3 ml, 3.75 mmol) was added dropwise to a solution of amide **7** (0.39 g, 2.50 mmol) in PhMe (5 ml). The mixture was heated at 100°C for 3 h and cooled to room temperature. The precipitate was filtered off and washed with a small amount of hexane. Yield 78%, white powder, mp 178-179°C. ^{1}H NMR spectrum, δ, ppm: 11.13 (1H, s, NH); 8.12 (1H, s, H-2); 4.67 (2H, s, CH_2); 2.36 (3H, s, CH_3); 2.25 (3H, s, CH_3). Mass spectrum, *m*/*z*: 232 $[M+H]^+$. Found, %: C 46.73; H 4.48; N 6.17. $C_9H_{10}ClNO_2S$. Calculated, %: C 46.65; H 4.35; N 6.05.

***S*-[2-(4,5-Dimethylthiophene-3-carboxamido)-2-oxoethyl]-*O*-ethylcarbonodithioate (9)**. Potassium ethyl xanthate (0.24 g, 1.4 mmol) was added to a solution of *N*-(2-chloroacetyl)amide **8** (0.30 g, 1.3 mmol) in THF (20 ml). The mixture was stirred at room temperature for 1 day. The excess solvent was evaporated under reduced pressure. The residue was washed with a small amount of water and dried. Yield 80%, light-yellow powder, mp 143-144°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.12 (1H, s, NH); 8.10 (1H, s, H-2); 4.63 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 4.46 (2H, s, $COCH_2S$); 2.35 (3H, s, CH_3); 2.26 (3H, s, CH_3); 1.42 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$). Mass spectrum, *m*/*z*: 318 $[M+H]^+$. Found, %: C 45.49; H 4.82; N 4.53. $C_{12}H_{15}NO_3S_3$. Calculated, %: C 45.40; H 4.76; N 4.41.

***N*-(2,2-Dimethoxyethyl)thiophene-3-carboxamides 11a,b (General Method)**. Acyl chloride **6a**,**b** (2.5 mmol) was added with vigorous stirring to a suspension of K_2CO_3 (1.0 g, 7.2 mmol) and 1,1-dimethoxymethanamine (0.3 ml, 2.5 mmol) in CH_2Cl_2 (10 ml), and the mixture was left at room temperature overnight.

The mixture was then washed with water, and the solvent removed under reduced pressure to yield pure amides **11a**,**b**.

***N*-(2,2-Dimethoxyethyl)-4,5-dimethylthiophene-3-carboxamide (11a)**. Yield 76%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.97 (1H, s, NH); 7.55 (1H, s, H-2); 4.45 (1H, t, *J* = 5.5, C<u>H</u>(OMe)$_2$); 3.32 (6H, s, 2OCH$_3$); 3.27 (2H, d, *J* = 5.5, CH$_2$); 2.33 (3H, s, CH$_3$); 2.21 (3H, s, CH$_3$). Mass spectrum, *m*/*z*: 244 [M+H]$^+$. Found, %: C 54.43; H 7.25; N 5.93. $C_{11}H_{17}NO_3S$. Calculated, %: C 54.30; H 7.04; N 5.76.

***N*-(2,2-Dimethoxyethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (11b)**. Yield 74%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.15 (1H, s, NH); 7.37 (1H, s, H-2); 4.44 (1H, t, *J* = 5.1, C<u>H</u>(OMe)$_2$); 3.32 (6H, s, 2OCH$_3$); 3.28 (2H, d, *J* = 5.1, C<u>H</u>$_2$CH(OMe)$_2$); 2.75 (2H, br. s, CH$_2$); 2.59 (2H, br. s, CH$_2$); 1.81 (4H, br. s, 2CH$_2$). Mass spectrum, *m*/*z*: 270 [M+H]$^+$. Found, %: C 58.11; H 7.26; N 5.43. $C_{13}H_{19}NO_3S$. Calculated, %: C 57.97; H 7.11; N 5.20.

Preparation of Thieno[3,2-*c*]pyridinones 12a,b (General Method). A solution of amide **11a**,**b** (2.5 mmol) in conc. H_2SO_4 (5 ml) was heated at 100°C for 2 h. The mixture was consecutively cooled to room temperature, and 6 M solution of NaOH was added carefully to pH 10. The aqueous solution was extracted with EtOAc (5×15 ml), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

2,3-Dimethylthieno[3,2-*c*]pyridin-4(5*H*)-one (12a). Yield 65%, white powder, mp 220-221°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.09 (1H, s, NH); 7.01 (1H, d, *J* = 6.9) and 6.51 (1H, d, *J* = 6.9, H-6,7); 2.45 (3H, s, CH$_3$); 2.37 (3H, s, CH$_3$). Mass spectrum, *m*/*z*: 180 [M+H]$^+$. Found, %: C 60.44; H 5.20; N 7.92. C_9H_9NOS. Calculated, %: C 60.31; H 5.06; N 7.81.

6,7,8,9-Tetrahydrobenzo[4,5]thieno[3,2-*c*]pyridin-1(2*H*)-one (12b). Yield 63%, white powder, mp 200-201°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.23 (1H, s, NH); 7.12 (1H, d, *J* = 6.9) and 6.69 (1H, d, *J* = 6.9, H-3,4); 2.95 (2H, br. s, CH$_2$); 2.74 (2H, br. s, CH$_2$); 1.76 (4H, br. s, 2CH$_2$). Mass spectrum, *m/z*: 206 [M+H]$^+$. Found, %: C 64.44; H 5.53; N 6.99. $C_{11}H_{11}NOS$. Calculated, %: C 64.36; H 5.40; N 6.82.

Preparation of (Thiophen-3-yl)methanols 13a,b (General Method). $LiAlH_4$ (2 g, 53 mmol) was added with vigorous stirring to a cooled (0°C) solution of ester **3a**,**b** (50 mmol) in dry THF (100 ml). The mixture was kept for 4 h. Then it was cooled and quenched by dropwise adding H_2O (2 ml), 10% aqueous NaOH (4 ml), and H_2O (2 ml). The formed mixture was stirred at room temperature for 15 min, filtered, and the filtrate evaporated under reduced pressure. Yield of alcohols **13a**,**b** was quantitative, the obtained compounds could be used without additional purification. Characteristics of (4,5-dimethylthiophen-3-yl)-methanol **13a** and (4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)methanol **13b** correspond to literature data [20, 21].

Preparation of Thiophene-3-carbaldehydes 14a,b (General Method). Oxalyl chloride (4.0 ml, 5.7 g, 45.2 mmol) and DMSO (5.3 ml, 5.8 g, 75.3 mmol) were added to CH_2Cl_2 (400 ml) cooled to -78°C. The reaction mixture was stirred at -78°C for 15 min, then a solution of alcohol **13a**,**b** (20 mmol) in CH_2Cl_2 (50 ml) was added, and stirring continued at -78°C for 1 h. Next, Et_3N (21.0 ml, 150.7 mmol) was added, and the reaction mixture allowed to reach room temperature. H_2O (100 ml) was added, the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent removed. The obtained aldehydes **14a**,**b** were additionally purified by vacuum distillation. Yields of compounds **14a** and **14b** were 63 and 75%, respectively. Characteristics of 4,5-dimethylthiophene-3-carbaldehyde (**14a**) and 4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbaldehyde (**14b**) conform to literature data [21, 22].

Preparation of (Thiophen-3-yl)acrylic Acids 15a,b (General Method). Ethyl 2-(diethoxyphosphoryl)-acetate (10 ml, 50 mmol) and K_2CO_3 (10 g, 72 mmol) were added to a solution of aldehyde **14a**,**b** (39 mmol) in DMF (20 ml). The reaction mixture was stirred at 90°C for 7 h, cooled, diluted with water to a volume of 35 ml, and extracted with CH_2Cl_2 (2×50 ml). After removal of solvent, EtOH (50 ml) and a solution of NaOH (3.2 g, 80 mmol) in H_2O (50 ml) were added to the residue. The mixture was heated under reflux for 1 h, EtOH was removed under reduced pressure, the residual aqueous solution was washed with CH_2Cl_2 and acidified by addition of HCl. The formed precipitate was filtered off and purified by recrystallization from EtOH.

(*E*)-(4,5-Dimethylthiophen-3-yl)acrylic acid (15a). Yield 89%, white powder, mp 159-161°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.84 (1H, br. s, COOH); 7.98 (1H, d, *J* = 16.0) and 6.54 (1H, d, *J* = 16.0, C<u>H</u>=C<u>H</u>COOH); 7.79 (1H, s, H-2); 2.34 (3H, s, CH_3); 2.27 (3H, s, CH_3). Mass spectrum, *m*/*z*: 183 $[M+H]^+$. Found, %: C 59.43; H 5.60. $C_9H_{10}O_2S$. Calculated, %: C 59.32; H 5.53.

(*E*)-(4,5,6,7-Tetrahydrobenzo[*b*]thiophen-3-yl)acrylic Acid (15b). Yield 93%, white powder, mp 169-171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.80 (1H, br. s, COOH); 8.02 (1H, d, *J* = 16.2) and 6.63 (1H, d, *J* = 16.2, C<u>H</u>=C<u>H</u>COOH); 7.91 (1H, s, H-2); 2.89-2.71 (4H, m, $2CH_2$); 1.93-1.67 (4H, m, $2CH_2$). Mass spectrum, *m/z*: 209 $[M+H]^+$. Found, %: C 63.40; H 5.93. $C_{11}H_{12}O_2S$. Calculated, %: C 63.43; H. 5.81.

Preparation of Thieno[2,3-*c*]pyridinones 17a,b (General Method). Oxalyl chloride (10 ml) and DMF (1 drop) were added dropwise with vigorous stirring to a solution of acid **15a**,**b** (25 mmol) in CH_2Cl_2 (50 ml). The solution was stirred at room temperature until evolution of gases ceased (3 h). The solvent and excess oxalyl chloride were evaporated under reduced pressure. The obtained acyl chloride was dissolved in dioxane (20 ml), and this solution was added dropwise to a solution of NaN_3 (3.2 g, 50 mmol) in a mixture of water (7 ml) and dioxane (20 ml) at 0°C. The reaction mixture was kept at room temperature for 1 h, then H_2O (50 ml) was added, and extracted with 1,2-dichlorobenzene (70 ml). The organic extract was washed with H_2O (2×30 ml) and dried over $CaCl_2$. Residual dioxane and water were removed by distillation under reduced pressure. The obtained solution of the intermediate azide **16a**,**b** was diluted with 1,2-dichlorobenzene to a 110-ml volume, and added dropwise to 1,2-dichlorobenzene (10 ml) heated to 140°C. The mixture was kept at this temperature until evolution of nitrogen stoped (2 h), then a crystal of iodine was added, the temperature of the mixture was increased to 180°C, and the mixture was kept at this temperature for 3 h. Consequently, the reaction mixture was concentrated to a 20-ml volume by distillation under reduced pressure and cooled to room temperature. The formed precipitate was filtered off, washed with hexane, and dried under reduced pressure. The obtained thieno[2,3-*c*]pyridinones **17a**,**b** were purified by column chromatography (eluent MeOH–$CHCl_3$, 2:1).

2,3-Dimethylthieno[2,3-*c*]pyridin-7(6*H*)-one (17a). Yield 13%, white powder, mp 208-210°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.17 (1H, s, NH); 7.08 (1H, d, *J* = 7.2) and 6.47 (1H, d, *J* = 7.2, H-4,5); 2.53 (3H, s, CH_3); 2.29 (3H, s, CH_3). Mass spectrum, *m*/*z*: 180 $[M+H]^+$. Found, %: C 60.31; H 5.28; N 7.84. C_9H_9NOS. Calculated, %: C 60.31; H 5.06; N 7.81.

5,6,7,8-Tetrahydro[1]benzothieno[2,3-*c*]pyridin-1(2*H*)-one (17b). Yield 19%, white powder, mp 219-221°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.31 (1H, s, NH); 7.24 (1H, d, *J* = 7.0) and 6.58 (1H, d, *J* = 7.0, H-3,4); 2.96 (2H, br. s, CH_2); 2.70 (2H, br. s, CH_2); 1.92-1.66 (4H, m, $2CH_2$). Mass spectrum, *m*/*z*: 206 $[M+H]^+$. Found, %: C 64.40; H 5.31; N 6.74. $C_{11}H_{11}NOS$. Calculated, %: C 64.36; H 5.40; N 6.82.

REFERENCES

1. Y. Huang and A. Doemling, *Mol. Diversity*, **15**, 3 (2011).
2. S. A. Al-Trawneh, M. M. El-Abadelah, J. A. Zahra, S. A. Al-Taweel, F. Zani, M. Incerti, A. Cavazzoni, and P. Vicini, *Bioorg. Med. Chem.*, **19**, 2541 (2011).
3. N. I. Sweidan, M. Z. Nazer, M. M. El-Abadelah, and W. Voelter, *Lett. Org. Chem.*, **7**, 79 (2010).
4. D. S. Dhanoa, O. Becker, S. Noiman, P. Mohanty, D. Chen, M. Lobera, L. Wu, Y. Marantz, B. Inbal, A. Heifetz, S. Bar-Haim, and S. Shacham, US Pat. Appl. 7982040.
5. J. W. Scott, B. J. W. van Denderen, S. B. Jorgensen, J. E. Honeyman, G. R. Steinberg, J. S. Oakhill, T. J. Iseli, A. Koay, P. R. Gooley, D. Stapleton, and B. E. Kemp, *Chem. Biol.*, **15**, 1220 (2008).
6. G. Gentile, G. Bernasconi, A. Pozzan, G. Merlo, P. Marzorati, P. Bamborough, B. Bax, A. Bridges, C. Brough, P. Carter, G. Cutler, M. Neu, and M. Takada, *Bioorg. Med. Chem. Lett.*, **15**, 4823 (2011).
7. J. Sircar, K. C. Sunil Kumar, T. J. Davis, and W. Ying, US Pat. Appl. 7365200.
8. K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).

9. V. I. Shvedov, V. K. Ryzhkova, and A. N. Grinev, *Chem. Heterocycl. Compd.*, **3**, 789 (1967). [*Khim. Geterotsikl. Soedin.*, 1010 (1967).]
10. J. Sice, *J. Org. Chem.*, **19**, 70 (1954).
11. F. Bohlmann and E. Bresinsky, *Chem. Ber.*, **97**, 2109 (1964).
12. T. L. Fevig, W. G. Phillips, and P. H. Lau, *J. Org. Chem.*, **66**, 2493 (2001).
13. T. L. Fevig, P. H. Lau, and W. G. Phillips, EP Pat. Appl. 1023283.
14. N. Charrier, Z. Liu, and S. Z. Zard, *Org. Lett.*, **14**, 2018 (2012).
15. N. Briet, M. H. Brookes, R. J. Davenport, F. C. A. Galvin, P. J. Gilbert, S. R. Mack, and V. Sabin, *Tetrahedron*, **58**, 29, 5761 (2002).
16. A. T. Mavrova, D. Wesselinova, Y. A. Tsenov, and P. Denkova, *Eur. J. Med. Chem.*, **44**, 63 (2009).
17. T. Kohara, H. Tanaka, K. Kimura, H. Horiuchi, K. Seio, M. Arita, T. Fujimoto, and I. Yamamoto, *J. Heterocycl. Chem.*, **39**, 163 (2002).
18. D. Melandri, P. C. Montevecchi, and M. L. Navacchia, *Tetrahedron*, **55**, 12227 (1999).
19. M. Susumu, T. Tatsuo, H. Tsunetoshi, H. Yoshiharu, O. Toshihiko, H. Hiroshi, K. Shiro, I. Masanao, A. Akinori, Y. Kiyoshi, and A. Fujio, *J. Med. Chem.*, **46**, 2446 (2003).
20. A. Schöning and W. Friedrichsen, *Liebigs Ann. Chem.*, 405 (1989).
21. M. S. Chambers, N. R. Curtis, A. M. MacLeod, R. J. Maxey, and H. J. Szekeres, US Pat. Appl. 2005101586 (2005).
22. A. Wiersema and S. Gronowitz, *Acta Chem. Scand.*, **24**, 2593 (1970).