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Synthesis of ethyl 4,5-disubstituted 2-azido-3-thiophenecarboxylates and use in the synthesis of thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones

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ABSTRACT

New heterocyclic azides, ethyl 2-azido-4-R^1-5-R^2-3-thiophenecarboxylates, were synthesized by diazotization of 2-aminothiophenes and subsequent treatment with sodium azide. The reactions of these heterocyclic azides with β-ketoesters and activated acetonitriles were studied. The derivatives of thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine, a new ring system, were prepared in high yields via an anionic hetero-domino reaction.

1. Introduction

In our preceding article,[1] the synthesis of tetrazole derivatives from available Gewald 2-aminothiophenes was reported. It was shown that such compounds have unexpected chemical properties including cleavage of the tetrazole ring in the reaction with hydrazine. As a result, 2,3-diaminopyrimidines, which are not easily available, were prepared. Such a transformation allows us to continue an investigation of the amino group modifications in alkyl 2-aminothiophene-3-carboxylates. Moreover, the 1,2,3-triazole ring has some similar properties to the tetrazole ring due to the isostructural fragment (N_3), close geometry and the character of the aromatic ring.[2] From a practical point of view, triazole derivatives exhibit diverse biological activity[3] and their application in industry and technology is being developed.[4]

In addition, it is of note that 1,2,3-triazoles are synthesized from organic azides in most cases.[5] Heterocyclic aromatic azides with electron-deficient aromatic rings are most widely studied, since such azides are synthesized by nucleophilic substitution of halogen or another similar group by the azide ion. An electron-rich aromatic ring is not suitable for such a reaction. Hence, diazotization of amino derivatives and their conversion into azides by the reaction with sodium azide are the main methods for the synthesis of such heteroazides. Unfortunately, the difficulty in diazonium salts' preparation in some aminoheterocycles leads to certain restrictions with this method.[6]

2. Results and discussion

In the present work, we describe diazotization of alkyl 2-aminothiophene-3-carboxylates and their conversion into the corresponding azides. Previously, diazotization of Gewald 2-aminothiophenes was performed in concentrated hydrochloric[7–9] and sulfuric acids.[10] In one paper,[11] different conditions of diazotization were discussed and the advantages of the use of sulfuric acid were shown. The analysis of the articles cited above leads to the conclusion that due to the high reactivity and instability of thiophene diazonium salts certain complications with the synthesis of azides may appear. Taking into account this premise we prepared ethyl 2-azido-5-R^2-4-R^1-3-thiophenecarboxylates from the corresponding 2-amino derivatives under various reaction conditions.

Diazotization of 4,5-disubstituted alkyl 2-aminothiophene-3-carboxylates **1** in concentrated hydrochloric acid did not lead to the formation of stable diazonium salts. Independent of the temperature (from −30 °C to 5 °C), there was a rapid cleavage of the diazonium salts or in some cases compounds **1** remained unreacted after diazotization. Azide synthesis under such reaction conditions and its extraction from the products of the cleavage were not

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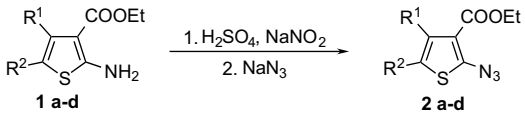
possible. Instead, we prepared azides **2a–d** in sulfuric acid. We dissolved alkyl 2-aminothiophene-3-carboxylates **1a–d** in concentrated sulfuric acid and added ice up to 40% acid solution. We succeeded to get stable diazonium salts by further treatment of the obtained solution with sodium nitrite. Their reaction with sodium azide yielded the corresponding 2-azidothiophenes **2a–d** (Scheme 1, Table 1).

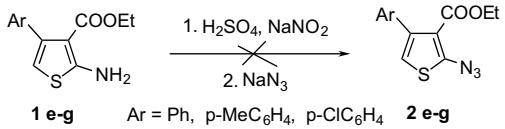


Scheme 1.

Table 1
Azides **2a–d**

2	R^1	R^2	Yield, %
a	Me	Me	65
b	$-(CH_2)_4-$		74
c	Me	Ac	78
d	Me	CO_2Et	75

However, in the case of 4-arylthiophenes **1e–g**, stable diazonium salts did not form under any of the tested reaction conditions (Scheme 2).



Scheme 2.

The attempts to separate diazonium salts from the reaction mixture and transform them into azides did not give a positive result. In fact, the process of diazotization completes with the precipitation of a black solid. We filtered the solid and found by TLC that the precipitate was a mixture of more then five components. It can be explained by appropriate competitive reactions. The free 5-position in the thiophene ring was ready for attack by electrophiles, such as diazonium or nitrous ions. Subsequently, compounds of type **I** or **II** could be formed (Fig. 1). Similar behaviour of some 2-aminothiophenes during the reaction of diazotization was mentioned in a number of articles.[7,10]

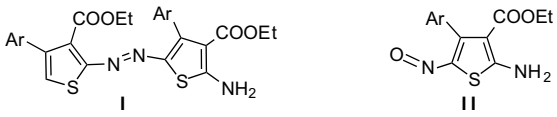


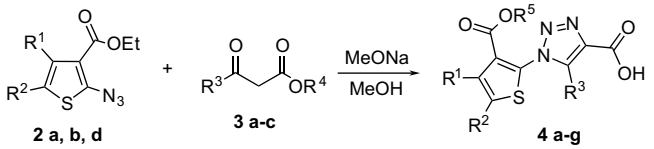
Figure 1.

2-Azidothiophenes **2a–d** were separated and identified. They were used in the reaction immediately after their formation because of their instability. Compounds **2a–d** were cleaved after a few hours at room temperature. It is also possible to assume that the electron-rich thiophene ring decreases the stability of diazonium salt and azide.

Similar 2-azidothiophene was previously described only in a patent[12] and was prepared by nucleophilic substitution of the methanesulfonyl group in methyl 3-aryl-4-cyano-5-methanesulfonylthiophene-2-carboxylate. However, the reactions of such azides have not been studied previously.

It is well known that organic azides undergo base-catalyzed condensation reactions with activated methylenic compounds.[5] Generally, 1,2,3-triazoles form in such reactions except for some cases when the reduction of azides to amines takes place.

We used commercially available alkyl β-oxopropanoates **3a–c** as reaction partners of ethyl 2-azido-3-thiophenecarboxylates **2a**,**b**,**d** (Scheme 3, Table 2).



Scheme 3.

Table 2
1-(3-Carboxythienyl-2)-1*H*-1,2,3-triazole-4-carboxylic acid **4a–g**

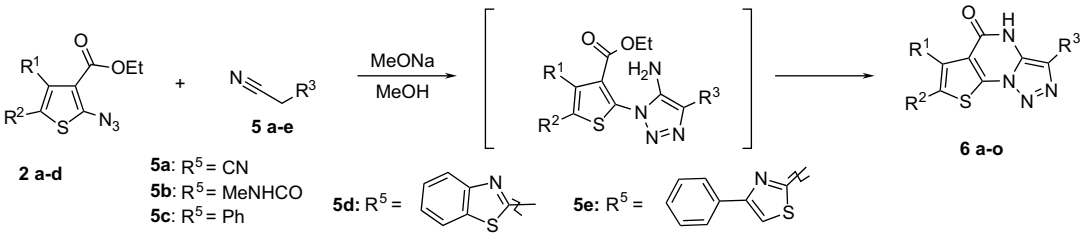
4	R^1	R^2	R^3	R^5	Yield, %
a	Me	Me	Me	Me	65
b	$-(CH_2)_4-$		Me	H	72
c	Me	COOH	Me	H	75
d	Me	Me	*i*-Pr	H	81
e	$-(CH_2)_4-$		*i*-Pr	H	83
f	Me	Me	Ph	H	77
g	$-(CH_2)_4-$		Ph	H	85

When the solution of azides **2** was allowed to react with ethyl acetoacetate or benzoylacetate in sodium methoxide the corresponding 1,2,3-triazoles **4a–c**,**f**,**g** precipitated in good yields from the reaction medium. Reactions with methyl 4-methyl-3-oxopentanoate resulted in the formation of triazoles **4d**,**e**, which were soluble in the reaction medium. For the reaction completion and full hydrolysis of ester groups the reaction was heated under reflux for 1 h; 2 equiv of base in water was needed for homogenization of the reaction mixture. Afterwards, the mixture was boiled for one more hour.

It is important to emphasize that compound **4a** was isolated as its monomethyl ester. Hydrolysis of the ester group in the triazole ring occurred faster than in the thiophene one due to electron-deficient character of the triazole ring. Therefore, different reactivity of ester groups gives the opportunity to modify them separately.

Aromatic azides, containing a neighbouring carboxylic or nitrile group, were studied as reagents in domino reactions for construction of [1,2,3]triazolo[1,5-*a*]pyrimidine system.[5] Although this type of reaction was well described for the aromatic series, it was applied to heterocycles only in a few cases. On the other hand, it is a versatile entry to annelated [1,2,3]triazolo[1,5-*a*]pyrimidines, some of which are new heteropolycyclic systems with unstudied properties. It makes such reactions promising for the synthesis of new pharmaceutical substances. For instance, azides on pyrrole,[13] indole,[14] pyrazole,[15] imidazole[16] and 1,2,3-triazole[17] series were used for this type of domino reaction. Moreover, most of the articles cited above reported interesting biological activity of annelated [1,2,3]triazolo[1,5-*a*]pyrimidines. In addition, one example of use of the thiophene derivatives in [1,2,3]triazolo[1,5-*a*]pyrimidine synthesis was given.[18] In the reaction of 3-azido-2-thiophenecarbaldehyde dimethyl acetal with substituted acetonitriles, the derivatives of the thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5(4*H*)-one ring system were obtained. These compounds are isomers of thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones discussed in the current work.

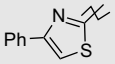
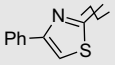
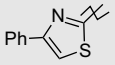
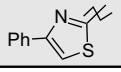
We found out that 2-azidothiophenes **2a–d** reacted with acetonitriles **5a–e** in sodium methoxide methanol solution



Scheme 4.

(Scheme 4). The reaction was carried out using 1 equiv of sodium methoxylate: it exhibited an appreciable exothermal effect and was completed within 1–2 min. In general, the product of the reaction formed immediately after mixing the reagents except for phenylacetonitrile, which reacted slower. The polycyclic compounds **6a–o** were isolated in good yields (73–94%) (Table 3).

Table 3
Thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **6a–o**

6	R^1	R^2	R^3	Yield, %
a	Me	Me	CN	83
b	Me	Me	MeNHCO	88
c	Me	Me	Ph	75
d	Me	Me	Bth[a]	91
e	Me	Me		94
f	$-(CH_2)_4-$		C(=NH)OMe	84
g	$-(CH_2)_4-$		MeNHCO	93
h	$-(CH_2)_4-$		Ph	73
i	$-(CH_2)_4-$		Bth	92
j	$-(CH_2)_4-$			90
k	Me	Ac	CN	86
l	Me	Ac		95
m	Me	COOEt	CN	89
n	Me	COOEt	MeNHCO	82
o	Me	COOEt		94

[a] Bth—1,3-benzothiazol-2-yl.

The mechanism of such reactions includes two stages. The azido group is supposed to attack the dipolarophile in the same way the anion of methylene active acetonitrile does. The intermediate triazole, obtained from 1,3-dipolar cycloaddition reactions, contained amino group, which has a tendency to further react with the carboxylate function to provide the formation of the pyrimidine ring (compounds **6a–o**).

In order to obtain thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **6** from azides **2**, 1,3-benzothiazol-2-yl- and (4-phenyl-1,3-thiazol-2-yl)-acetonitrile **5d,e** were chosen as reactive methylenic partners. Thus, they exhibited high reactivity, as methylenic compounds for such anion domino reactions, for the construction of [1,2,3]triazolo[1,5-*a*]pyrimidines system with heterocyclic substituents.

The structure of the polycyclic ring system was determined from the NMR spectroscopic data. The range of carbon characteristic signals in the heterocyclic skeleton of compounds **6** is shown in Figure 2.

It was also found that in the case of the reaction of azide **2b** with malononitrile **5a**, compound **6f** was isolated as a product of the reaction and its structure was determined by mass and NMR spectra (Scheme 5). Such a result is the consequence of the parallel addition reaction of the nitrile group, activated by the electron-deficient triazole ring, and methoxide anion.

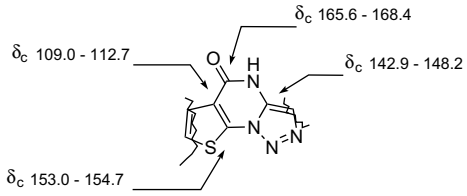
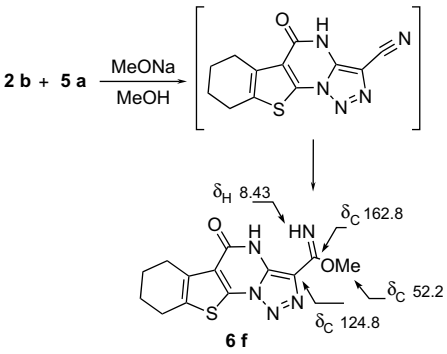


Figure 2. Characteristic values of ^{13}C NMR spectroscopic signals of thieno[3,2-*e*]-[1,2,3]triazolo [1,5-*a*]pyrimidin-5(4*H*)-ones **6a–o**.



Scheme 5. Synthesis and values of some NMR spectroscopic signals of compound **6f**.

As is obvious from the results, due to slight variations of the experimental conditions, the method can be generally applied for the synthesis of substituted thiophenes. In addition, it is important to note that substituted thienopyrimidines are well known for their diverse biological activity.[19] Thus, our findings reveal a useful synthetic approach giving access to new derivatives of this class to be tested for biological activity.

3. Conclusion

Base-catalyzed cycloaddition reactions of new heterocyclic azides with activated methylene compounds were studied. It was shown that 1,2,3-triazole derivatives could be obtained by this method. The application of 2-azidothiophenes in domino reactions for the synthesis of the new ring system of thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-5-ones was also reported.

4. Experimental

4.1. General

^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^1H, 125 MHz for ^{13}C). The ^1H

and ^{13}C chemical shifts were reported in parts per million relative to tetramethylsilane or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Starting Gewald 2-aminothiophenes **1a–d**,[20] (1,3-benzothiazol-2-yl)-acetonitrile **5d**[21] and (4-phenyl-1,3-thiazol-2-yl)-acetonitrile **5e**[22] were prepared according to the procedures described in the literature. We used such abbreviations in NMR spectra presentation: Tr=triazole, Th=thiophene and Tz=thiazole.

4.2. General procedure for the synthesis of alkyl 2-azidothiophene-3-carboxylates 2a–d

Appropriate 2-aminothiophene **1** (0.02 mol) was dissolved in concentrated sulfuric acid (5 mL) and ice (15 g) was added. When the mixture was cooled to 0 °C, saturated sodium nitrite (1.73 g; 0.025 mol) aqueous solution was added keeping the temperature below 5 °C. After 10 min, resinous sediment (in case it was formed) should be filtered. To the filtrate solution of the diazonium salt sodium azide (1.3 g; 0.02 mol) in 5 mL of water was added dropwise. The solution was left for 15 min at room temperature and azide was extracted by diethyl ether (3×10 mL). Ether was evaporated in vacuo. Azides were used without subsequent cleaning: **2a**, yield 2.92 g, 65%; dark red oil; MS (*m*/*z*): 226 (M^++1); **2b**, yield 3.71 g, 74%; dark red oil; MS (*m*/*z*): 252 (M^++1); **2c**, yield 4.71 g, 78%; brown solid, mp: 61–62 °C; MS (*m*/*z*): 284 (M^++1); **2d**, yield 3.81 g, 75%; dark pink solid, mp: 34–35 °C; MS (*m*/*z*): 254 (M^++1). Identification of azides **2a–d** was performed by chromatography–mass spectrometry since they decomposed slowly during the preparation of the analyzed samples.

4.3. General procedure for the synthesis of 1-(3-carboxythienyl-2)-1*H*-1,2,3-triazole-4-carboxylic acids 4a–g

Sodium (0.23 g, 0.01 mol) was added to 20 mL of absolute methanol. β-Ketoester **3** (0.01 mol) and the appropriate azide **2** (0.01 mol) were slowly added (cooling by ice water) to the obtained sodium methylate solution. The mixture was kept in ice water bath for 30 min and then slowly heated under reflux for 1 h. The solid sedimented. Hot water was added to dissolve the sediment (50 mL), if necessary the solution of sodium hydroxide can be added to pH 11–12 and heated under reflux for 1 h. Hot solution was poured to a 10 mL of concentrated HCl and left to be crystallized. The obtained solid was filtered, washed with water twice and crystallized from ethanol.

4.3.1. 1-[3-(Methoxycarbonyl)-4,5-dimethyl-2-thienyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid ***4a***

Yield 1.92 g, 65%; white solid; mp: 110–111 °C; IR (KBr) ν_{max} 1717 (s, C=O), 1705 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (3H, s, Me), 2.40 (3H, s, Me), 2.45 (3H, s, Me), 3.58 (3H, s, MeO); ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.0 (Me_{Tr}), 13.6 (Me_{Th}), 14.0 (Me_{Th}), 52.8 (OMe), 130.9 (C), 133.6 (C), 134.0 (C), 135.9 (C), 136.5 (C), 142.6 (C), 162.4 (CO), 162.9 (CO); MS (*m*/*z*): 296 (M^++1). Anal. Calcd for $C_{12}H_{13}N_3O_4S$: C 48.80, H 4.44, N 14.23; found: C 48.61, H 4.57, N 14.16.

4.3.2. 1-(3-Carboxy-4,5,6,7-tetrahydro-1-benzothien-2-yl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid ***4b***

Yield 2.21 g, 72%; white solid; mp: 147–148 °C; IR (KBr) ν_{max} 1715 (s, C=O), 1681 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–1.92 (4H, m, CH_2), 2.41 (3H, s, Me), 2.78–2.87 (4H, m, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.0 (Me), 22.4 (CH_2), 22.9 (CH_2), 25.1 (CH_2), 26.3 (CH_2), 130.4 (C), 134.7 (C), 135.8 (C), 136.4 (C), 138.1 (C), 142.7 (C), 163.0 (CO), 163.3 (CO); MS (*m*/*z*): 308 (M^++1). Anal. Calcd for $C_{13}H_{13}N_3O_4S$: C 50.81, H 4.26, N 13.67; found: C 50.97, H 4.34, N 13.48.

4.3.3. 5-(4-Carboxy-5-methyl-1H-1,2,3-triazol-1-yl)-3-methyl-2,4-thiophenedicarboxylic acid ***4c***

Yield 2.33 g, 75%; white solid; mp: 204–205 °C; IR (KBr) ν_{max} 1702 (s, C=O), 1693 (s, C=O), 1660 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.45(3H, s, Me), 2.72 (3H, s, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.1 (Me_{Tr}), 15.3 (Me_{Th}), 128.8 (C), 133.1 (C), 137.5 (C), 140.7 (C), 142.8 (C), 144.5 (C), 159.2 (CO), 162.9 (CO), 163.3 (CO); MS (*m*/*z*): 312 (M^++1). Anal. Calcd for $C_{11}H_9N_3O_6S$: C 42.44, H 2.91, N 13.50; found: C 42.32, H 2.79, N 13.37.

4.3.4. 1-(3-Carboxy-4,5-dimethyl-2-thienyl)-5-isopropyl-1H-1,2,3-triazole-4-carboxylic acid ***4d***

Yield 2.50 g, 81%; white solid; mp: 191–192 °C; IR (KBr) ν_{max} 1718 (s, C=O), 1687 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.16 (6H, d, *J* 6.8 Hz, 2 Me), 2.22 (3H, s, Me), 2.23 (3H, s, Me), 2.98–3.03 (1H, m, $CHMe_2$), 12.60 (1H, s, COOH), 12.72 (1H, br s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.6 (Me_{Th}), 14.6 (Me_{Th}), 18.9 (2 $Me_{i\text{-}Pr}$), 37.0 ($CHMe_2$), 114.8 (C), 123.7 (C), 123.7 (C), 130.0 (C), 144.5 (C), 158.6 (C), 166.0 (CO), 196.6 (CO); MS (*m*/*z*): 310 (M^++1). Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C 50.47, H 4.89, N 13.58; found: C 50.62, H 4.70, N 13.34.

4.3.5. 1-(3-Carboxy-4,5,6,7-tetrahydro-1-benzothien-2-yl)-5-isopropyl-1H-1,2,3-triazole-4-carboxylic acid ***4e***

Yield 2.78 g, 83%; white solid; mp: 193–194 °C; IR (KBr) ν_{max} 1714 (s, C=O), 1691 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.16 (6H, d, *J* 6.8 Hz, 2Me), 1.72–1.82 (4H, m, CH_2), 2.59–2.64 (2H, m, CH_2), 2.73–2.78 (2H, m, CH_2), 2.98–3.03 (1H, m, $CHMe_2$); 12.61 (1H, s, COOH), 12.63 (1H, br s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.9 (2 Me), 22.9 (CH_2), 23.2 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 37.0 ($CHMe_2$), 113.6 (C), 126.8 (C), 126.9 (C), 131.9 (C), 145.3 (C), 158.6 (C), 165.9 (CO), 196.6 (CO); MS (*m*/*z*): 336 (M^++1). Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C 53.72, H 5.11, N 12.53; found: C 53.51, H 5.27, N 12.44.

4.3.6. 1-(3-Carboxy-4,5-dimethyl-2-thienyl)-5-phenyl-1H-1,2,3-triazole-4-carboxylic acid ***4f***

Yield 2.64 g, 77%; white solid; mp: 112–113 °C; IR (KBr) ν_{max} 1703 (s, C=O), 1686 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.22 (3H, s, Me), 2.33 (3H, s, Me), 7.32–7.42 (5H, m, Ph); 12.80 (1H, br s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4 (Me_{Th}), 13.9 (Me_{Th}), 126.2 (C), 128.4 (CH), 128.7 (C), 129.6 (CH), 130.5 (CH), 132.8 (C), 133.3 (C), 135.1 (C), 137.1 (C), 143.5 (C), 163.0 (CO), 163.7 (CO); MS (*m*/*z*): 344 (M^++1). Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C 55.97, H 3.82, N 12.24; found: C 55.79, H 3.94, N 12.38.

4.3.7. 1-(3-Carboxy-4,5,6,7-tetrahydro-1-benzothien-2-yl)-5-phenyl-1H-1,2,3-triazole-4-carboxylic acid ***4g***

Yield 3.14 g, 85%; as a white solid; mp: 124–125 °C; IR (KBr) ν_{max} 1701 (s, C=O), 1680 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.72–1.84 (4H, m, CH_2), 2.68–2.76 (4H, m, CH_2), 7.32–7.42 (5H, m, Ph); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.4 (CH_2), 22.9 (CH_2), 25.1 (CH_2), 26.2 (CH_2), 126.7 (C), 128.4 (CH), 129.7 (CH), 130.2 (C), 130.5 (CH), 132.5 (C), 132.8 (C), 135.5 (C), 137.3 (C), 143.5 (C), 163.0 (CO), 163.1 (CO); MS (*m*/*z*): 370 (M^++1). Anal. Calcd for $C_{18}H_{15}N_3O_4S$: C 58.53, H 4.09, N 11.38; found: C 55.41, H 3.97, N 11.31.

4.4. General procedure for the synthesis of thieno[3,2-*e*]-[1,2,3]triazolo[1,5-*a*]pyrimidines 6a–o

To the solution of sodium methoxide (540 mg, 10.0 mmol) in dry methanol (20 mL) substituted acetonitrile **5** (10.0 mmol) was

added. To this solution 2-azidothiophene **2** (10.0 mmol) in dry methanol (2 mL) was added dropwise and the solid started to precipitate. The mixture was stirred for 24 h. The resulting suspension was filtered and the solid product was washed with water and methanol to give the corresponding thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **6a–o**.

4.4.1. 6,7-Dimethyl-5-oxo-4,5-dihydrothieno[3,2-e][1,2,3]triazolo-[1,5-a]pyrimidine-3-carbonitrile **6a**

Yield 2.03 g, 83%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3325 (s, NH), 2214 (s, CN), 1650 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.30 (3H, s, Me), 2.43 (3H, s, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4 (Me), 14.1 (Me), 103.2 (3-C), 111.8 (5a-C), 115.5 (CN), 122.7 (6-C or 7-C), 127.9 (6-C or 7-C), 148.2 (3a-C), 153.2 (8a-C), 166.2 (CO); MS (*m*/*z*): 246 (M^++1). Anal. Calcd for $C_{10}H_7N_5OS$: C 48.97, H 2.88, N 28.55; found: C 49.05, H 2.74, N 28.45.

4.4.2. N,6,7-Trimethyl-5-oxo-4,5-dihydrothieno[3,2-e][1,2,3]-triazolo[1,5-a]pyrimidine-3-carboxamide **6b**

Yield 2.44 g, 88%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3320 and 3170 (s, 2NH), 1687 (s, C=O), 1661 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.30 (3H, s, Me), 2.44 (3H, s, Me), 2.96 (3H, d, ^3J 4.8, Me), 8.00 (1H, q, ^3J 4.8, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4 (Me), 14.2 (Me), 26.0 (NHMe), 111.1 (5a-C), 121.7 (6-C or 7-C), 125.2 (3-C), 129.0 (6-C or 7-C), 144.9 (3a-C), 153.5 (8a-C), 162.3 (CO), 165.6 (CO); MS (*m*/*z*): 278 (M^++1). Anal. Calcd for $C_{11}H_{11}N_5O_2S$: C 47.64, H 4.00, N 25.26; found: C 47.54, H 4.13, N 25.32.

4.4.3. 6,7-Dimethyl-3-phenylthieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one **6c**

Yield 2.22 g, 75%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3305 (s, NH), 1658 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.31 (3H, s, Me), 2.48 (3H, s, Me), 7.13 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.36 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 8.35 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.2 (Me), 14.0 (Me), 109.9 (5a-C), 120.8 (6-C or 7-C), 124.2 (CH), 125.5 (CH), 127.3 (3-C), 128.0 (6-C or 7-C), 128.8 (CH), 133.8 (C_{Ph}), 142.9 (3a-C), 153.7 (8a-C), 165.6 (CO); MS (*m*/*z*): 297 (M^++1). Anal. Calcd for $C_{15}H_{12}N_4OS$: C 60.79, H 4.08, N 18.91; found: C 60.49, H 4.20, N 18.82.

4.4.4. 3-(1,3-Benzothiazol-2-yl)-6,7-dimethylthieno[3,2-e][1,2,3]-triazolo[1,5-a]pyrimidin-5(4H)-one **6d**

Yield 3.21 g, 91%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3390 (s, NH), 1677 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (3H, s, Me), 2.48 (3H, s, Me), 7.28 (1H, t, ^3J 7.8, 5-H_{Btz}), 7.41 (1H, t, ^3J 7.8, 6-H_{Btz}), 7.93 (2H, d, ^3J 7.8, 7-H_{Btz}), 7.97 (2H, d, ^3J 7.8, 4-H_{Btz}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4 (Me), 14.2 (Me), 111.7 (5a-C), 122.2 (6-C or 7-C), 122.2 (CH), 122.4 (CH), 124.5 (CH), 125.4 (3-C), 126.6 (CH), 127.9 (6-C or 7-C), 134.0 (7a-C_{Bth}), 143.9 (3a-C), 153.4 (8a-C), 154.5(3a-C_{Bth}), 160.2 (2-C_{Bth}), 165.6 (CO); MS (*m*/*z*): 354 (M^++1). Anal. Calcd for $C_{16}H_{11}N_5OS_2$: C 54.37, H 3.14, N 19.82; found: C 54.46, H 3.01, N 19.99.

4.4.5. 6,7-Dimethyl-3-(4-phenyl-1,3-thiazol-2-yl)thieno[3,2-e]-[1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one **6e**

Yield 3.56 g, 94%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3384 (s, NH), 1680 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (3H, s, Me), 2.48 (3H, s, Me), 7.29 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.42 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 7.72 (1H, s, H_{Tz}), 8.04 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.5 (Me), 14.2 (Me), 111.1 (5a-C), 112.1 (CH), 121.7 (6-C or 7-C), 125.4 (3-C), 126.8 (CH), 127.9 (6-C or 7-C), 129.4 (CH), 129.4 (C_{Ph}), 134.0 (4-C_{Tz}), 143.6 (3a-C), 153.4 (8a-C), 154.5 (5-C_{Tz}), 159.7 (2-C_{Tz}), 166.0 (CO); MS (*m*/*z*): 380 (M^++1). Anal. Calcd for $C_{18}H_{13}N_5OS_2$: C 56.97, H 3.45, N 18.46; found: C 56.82, H 3.29, N 18.31.

4.4.6. Methyl 5-oxo-4,5,6,7,8,9-hexahydro[1]benzothieno[3,2-e]-[1,2,3]triazolo[1,5-a]pyrimidine-3-carboximidoate **6f**

Yield 2.54 g, 84%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3321 and 3225 (s, 2NH), 1653 (s, C=O), 1629 (s, C=NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–1.92 (4H, m, CH_2), 2.64–2.70 (2H, m, CH_2), 2.94–3.00 (2H, m, CH_2), 3.84 (3H, s, OMe), 8.43 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.8 (CH_2), 23.4 (CH_2), 25.4 (CH_2), 26.5 (CH_2), 52.2 (MeO), 110.2 (5a-C), 121.6 (5b-C or 9a-C), 124.8 (3-C), 130.2 (5b-C or 9a-C), 145.6 (3a-C), 153.3 (10a-C), 162.8 (CNH), 165.6 (CO); MS (*m*/*z*): 304 (M^++1). Anal. Calcd for $C_{13}H_{13}N_5O_2S$: C 51.47, H 4.32, N 23.09; found: C 51.60, H 4.21, N 23.17.

4.4.7. N-Methyl-5-oxo-4,5,6,7,8,9-hexahydro[1]benzothieno-[3,2-e][1,2,3]triazolo[1,5-a]pyrimidine-3-carboxamide **6g**

Yield 2.82 g, 93%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3356 and 3126 (s, 2NH), 1662 (s, C=O), 1637 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.78–1.90 (4H, m, CH_2), 2.63–2.69 (2H, m, CH_2), 2.96 (3H, d, ^3J 4.9, CH_3), 3.16–3.20 (2H, m, CH_2), 8.01 (1H, q, ^3J 4.9, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6 (CH_2), 23.2 (CH_2), 25.1 (Me), 25.8 (CH_2), 26.3 (CH_2), 110.0 (5a-C), 124.2 (5b-C or 9a-C), 124.7 (5b-C or 9a-C), 130.0 (3-C), 144.8 (3a-C), 153.0 (10a-C), 162.3 (CO), 166.0 (CO); MS (*m*/*z*): 304 (M^++1). Anal. Calcd for $C_{13}H_{13}N_5O_2S$: C 51.47, H 4.32, N 23.09; found: C 51.35, H 4.19, N 22.93.

4.4.8. 3-Phenyl-6,7,8,9-tetrahydro[1]benzothieno[3,2-e]-[1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one **6h**

Yield 2.35 g, 73%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3310 (s, NH), 1650 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.80–1.93 (4H, m, CH_2), 2.62–2.71 (2H, m, CH_2), 2.97–3.03 (2H, m, CH_2), 7.13 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.37 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 8.36 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.9 (CH_2), 23.5 (CH_2), 25.4 (CH_2), 26.6 (CH_2), 109.0 (5a-C), 123.9 (5b-C or 9a-C), 124.4 (CH), 125.7 (CH), 128.1 (5b-C or 9a-C), 129.0 (CH), 130.0 (3-C), 134.1 (C_{Ph}), 143.2 (3a-C), 153.6 (10a-C), 166.1 (CO); MS (*m*/*z*): 323 (M^++1). Anal. Calcd for $C_{17}H_{14}N_4OS$: C 63.33, H 4.38, N 17.38; found: C 63.45, H 4.27, N 17.51.

4.4.9. 3-(1,3-Benzothiazol-2-yl)-6,7,8,9-tetrahydro[1]benzothieno-[3,2-e][1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one **6i**

Yield 3.49 g, 92%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3352 (s, NH), 1678 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.79–1.93 (4H, m, CH_2), 2.66–2.73 (2H, m, CH_2), 2.97–3.04 (2H, m, CH_2), 7.29 (1H, t, ^3J 7.8, 5-H_{Bth}), 7.41 (1H, t, ^3J 7.8, 6-H_{Bth}), 7.94 (1H, d, ^3J 7.8, 7-H_{Bth}), 7.97 (1H, d, ^3J 7.8, 4-H_{Bth}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6 (CH_2), 23.3 (CH_2), 25.2 (CH_2), 26.3 (CH_2), 110.5 (5a-C), 122.1 (CH), 122.2 (5b-C or 9a-C), 124.3 (CH), 125.3 (3-C), 125.4 (CH), 126.3 (CH), 130.0 (5b-C or 9a-C), 134.0 (7a-C_{Bth}), 143.7 (3a-C), 153.1 (10a-C), 154.3 (3a-C_{Bth}), 160.1 (2-C_{Bth}), 166.6 (CO); MS (*m*/*z*): 380 (M^++1). Anal. Calcd for $C_{18}H_{13}N_5OS_2$: C 56.97, H 3.45, N 18.46; found: C 57.22, H 3.15, N 18.67.

4.4.10. 3-(4-Phenyl-1,3-thiazol-2-yl)-6,7,8,9-tetrahydro[1]-benzothieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one **6j**

Yield 3.64 g, 90%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3381 (s, NH), 1646 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.82–1.94 (4H, m, CH_2), 2.67–2.74 (2H, m, CH_2), 2.98–3.05 (2H, m, CH_2), 7.30 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.43 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 7.72 (1H, s, H_{Tz}), 8.06 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6 (CH_2), 23.3 (CH_2), 25.2 (CH_2), 26.3 (CH_2), 111.0 (5a-C), 111.9 (CH), 124.8 (5b-C or 9a-C), 125.7 (3-C), 126.6 (CH), 128.2 (5b-C or 9a-C), 129.1 (CH), 130.0 (C_{Ph}), 135.1 (4-C_{Tz}), 143.4 (3a-C), 153.2 (10a-C), 154.4 (5-C_{Tz}), 159.6 (2-C_{Tz}), 166.4 (CO); MS (*m*/*z*): 406 (M^++1). Anal. Calcd for $C_{20}H_{15}N_5OS_2$: C 59.24, H 3.73, N 17.27; found: C 59.43, H 3.70, N 17.42.

4.4.11. 7-Acetyl-6-methyl-5-oxo-4,5-dihydrothieno[3,2-e][1,2,3]-triazolo[1,5-a]pyrimidine-3-carbonitrile ***6k***

Yield 2.35 g, 86%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3312 (s, NH), 2220 (s, CN), 1705 (s, C=O), 1635 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.46 (3H, s, Me), 2.92 (3H, s, Ac); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.2 (Me), 30.7 (MeCO), 104.0 (3-C), 112.8 (5a-C), 114.7 (CN), 127.7 (6-C), 143.2 (3a-C), 149.4 (7-C), 154.0 (8a-C), 168.6 (CO), 191.3 (CO_{Ac}); MS (*m*/*z*): 274 (M^++1). Anal. Calcd for $C_{11}H_7N_5O_2S$: C 48.35, H 2.58, N 25.63; found: C 48.17, H 2.40, N 25.78.

4.4.12. 7-Acetyl-6-methyl-3-(4-phenyl-1,3-thiazol-2-yl)thieno-[3,2-e][1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-one ***6l***

Yield 3.87 g, 95%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3338 (s, NH), 1718 (s, C=O), 1631 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.48 (3H, s, Me), 2.97 (3H, s, Ac), 7.30 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.43 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 7.76 (1H, s, H_{Tz}), 8.06 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.2 (Me), 30.7 (MeCO), 112.2 (5a-C), 112.5 (CH), 126.2 (3-C), 126.6 (CH), 126.8 (6-C), 128.3 (C_{Ph}), 129.2 (CH), 135.0 (4-C_{Tz}), 143.8 (3a-C), 144.2 (7-C), 154.6 (8a-C), 154.6 (5-C_{Tz}), 159.1 (2-C_{Tz}), 168.0 (CO), 191.2 (CO_{Ac}); MS (*m*/*z*): 408 (M^++1). Anal. Calcd for $C_{19}H_{13}N_5O_2S_2$: C 56.00, H 3.22, N 17.19; found: C 56.09, H 3.07, N 17.11.

4.4.13. Ethyl 3-cyano-6-methyl-5-oxo-4,5-dihydrothieno[3,2-e]-[1,2,3]triazolo[1,5-a]pyrimidine-7-carboxylate ***6m***

Yield 2.70 g, 89%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3303 (s, NH), 2225 (s, CN), 1720 (s, C=O), 1672 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.35 (3H, t, ^3J 7.2, Me), 2.88 (3H, s, Me), 4.26 (2H, q, ^3J 7.2, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.7 (Me), 15.7 (Me), 60.9 (CH_2), 103.9 (3-C), 112.4 (5a-C), 114.7 (CN), 115.2 (6-C), 145.1 (3a-C), 149.4 (7-C), 153.6 (8a-C), 162.7 (CO), 168.4 (CO); MS (*m*/*z*): 304 (M^++1). Anal. Calcd for $C_{12}H_9N_5O_3S$: C 47.52, H 2.99, N 23.09; found: C 47.33, H 2.84, N 23.00.

4.4.14. Ethyl 6-methyl-3-[(methylamino)carbonyl]-5-oxo-4,5-dihydrothieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidine-7-carboxylate ***6n***

Yield 2.75 g, 82%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3320 and 3117 (s, 2NH), 1730 (s, C=O), 1690 (s, C=O), 1639 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.35 (3H, t, ^3J 7.2, Me), 2.89 (3H, s, Me), 2.94 (3H, d, ^3J 4.8, MeN), 4.26 (2H, q, ^3J 7.2, CH_2), 7.99 (1H, q, ^3J 4.8, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.0 (Me), 16.1 (Me), 26.1 (MeN), 61.0 (CH_2), 112.0 (5a-C), 114.5 (6-C), 125.0 (3-C), 145.6 (3a-C), 145.8 (7-C), 154.2 (8a-C), 162.3 (CO), 162.7 (CO), 167.9 (CO); MS (*m*/*z*): 336 (M^++1). Anal. Calcd for $C_{13}H_{13}N_5O_4S$: C 46.56, H 3.91, N 20.88; found: C 46.70, H 3.79, N 20.75.

4.4.15. Ethyl 6-methyl-5-oxo-3-(4-phenyl-1,3-thiazol-2-yl)-4,5-dihydrothieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidine-7-carboxylate ***6o***

Yield 4.11 g, 94%; white solid; mp: >300 °C; IR (KBr) ν_{max} 3344 (s, NH), 1720 (s, C=O), 1651 (s, C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.37 (3H, t, ^3J 7.2, Me), 2.94 (3H, s, Me), 4.27 (2H, q, ^3J 7.2, CH_2), 7.30 (1H, t, ^3J 7.8, 4-H_{Ph}), 7.43 (2H, t, ^3J 7.8, 3,5-H_{Ph}), 7.76 (1H, s, H_{Tz}), 8.06 (2H, d, ^3J 7.8, 2,6-H_{Ph}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.0 (Me), 16.2 (Me), 61.0 (CH_2), 112.0 (CH), 112.7 (5a-C), 114.3 (6-C), 126.3 (3-C), 126.8 (CH), 128.3 (C_{Ph}), 129.4 (CH), 135.2 (4-C_{Tz}), 144.4 (3a-C), 145.8 (7-C), 154.3 (8a-C), 154.7 (5-C_{Tz}), 159.3 (2-C_{Tz}), 163.2 (CO), 167.9 (CO); MS (*m*/*z*): 438 (M^++1). Anal. Calcd for $C_{20}H_{15}N_5O_3S_2$: C 54.91, H 3.46, N 16.01; found: C 54.95, H 3.32, N 16.15.

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