Utility Of 2-Amino-4,5,6,7-Tetrahydrobenzo[b]Thiophene-3-Carboxylic Acid In The Synthesis Of Novel Thieno[2,3-b][1,2,4]Triazepinones And Thieno[2,3-d][1,3,4]Thiadiazolo[2,3-b]Pyrimidinones

Sobhi M. Gomha¹ and Hassan M. Abdel-Aziz²
¹Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt
²Department of Chemistry, Faculty of Science, Bani Suef University, Bani Suef, Egypt

Abstract
A new series of thienothiadiazolopyrimidinone 4 was prepared via the reaction of hydrazonoyl chlorides 2 with 2-amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid 1 followed by cyclization with 1,1'-carbonyldiimidazole. Furthermore, benzothienothiadiazolo pyrimidinone derivatives 11a-c were prepared. The structure of the newly synthesized compounds were established on the basis of spectral data (Mass, IR, ¹H and ¹³C NMR) and elemental analyses.

Key words: Hydrazonoyl halides, 2-amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid, thienothiadiazolo-pyrimidinone, thienothiadiazolopyrimidinone.

I. Introduction
Hydrazonoyl halides have been widely employed in the synthesis of heterocyclic derivatives.¹⁻⁵ Condensed thienopyrimidines exhibit interesting biological activities like antibacterial,⁶ antihistaminic,⁷ analgesic and anti-inflammatory⁸⁻¹⁰ and antimalarial.¹¹ Various condensed thienopyrimidine systems were studied for their biological activities.¹²⁻¹⁶ All the above findings encouraged us to synthesize a new series of tetrahydrobenzothienothiadiazolopyrimidinone 4 via the reaction of hydrazonoyl chlorides 2 with 2-amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid 1.

II. Results and discussion
Reaction of 2-Amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid 1 with hydrazonoyl halides 2 in the presence of TEA under heating resulted in the formation of the respective amidrazone derivatives 3a-i (Scheme 1). The structure of compounds 3a-i was evidenced by its microanalysis and spectral data (mass, IR, ¹H NMR) (see Experimental).
Treatment of the latter products, 3a,b,f,g with 1,1’-carbonyldiimidazole in dioxane yielded the corresponding triazepinone derivatives 4a,b,f,g rather than the pyrimidinone derivatives 5a,b,f,g (Scheme 1).

The actual structures of these products were assigned 4 rather than 5 based on their $^{1}$H NMR spectra which showed characteristic singlet signals at $\delta$8.64-8.73 ppm assigned for the triazepinone-NH of compounds 4 rather than the aniline-NH for compound 5. The formation of the triazepinones in the line with previous reports. Attempted X-ray of the products are failed.
Diazodization of 1 in the presence of hydrochloric acid in acetic acid solution afforded diazonium chloride 6 that readily coupled with active chloromethylene compounds 7a,b to yield the corresponding hydrazonoyl chlorides 8a,b. Reacting 8a,b with potassium thiocyanate gave the respective thiaziazoloopyrimidinone derivatives 11a,b. It is assumed that compound 11 is formed via initial nucleophilic displacement of halide with thiocyanate group forming the non-isolable products 9a,b which undergo in situ nucleophilic addition of hydrazone-NH into the thiocyanate group to give the iminothia diazoine derivatives 10a,b followed by elimination of water molecule to give the final isolable products 11a,b.  

Similarly, coupling of phenacyl thiocyanate 12 with diazonium chloride 6 gives the non-isolable acid 9c which undergoes cyclization via dehydration to give compound 11c.

III. Experimental
Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in a Pye-Unicam SP300 instrument in potassium bromide discs. 1H NMR and 13C NMR spectra were recorded in a Varian Mercury VX-300 spectrometer 300 MHz in CHCl₃ and the chemical shifts were related to TMS as standard solvent. Mass spectra were recorded in a GCMS-QP 1000 EX Shimadzu spectrometer, the ionizing voltage was 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt. 2-Amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid 17 and hydrazonoyl halides 2 21, 22 were prepared and were reported in the literature.

Reaction of 2-amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid (1) with hydrazonoyl halides (2). A mixture of 2-amino-tetrahydrobenzo[b]thiophene-3-carboxylic acid 1 (0.394 g, 2 mmol) and hydrazonoyl halides 2 (2 mmol) in dioxane (20 mL) in the presence of TEA (0.3 mL) was stirred at room temperature till complete reaction (4 h, monitored by TLC). The mixture was evaporated under reduced pressure and the residue was collected by filtration and purified by crystallization from the proper solvent to give pure 3a-i.

2-(2-Oxo-N'-phenylpropy1hydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3a).
Yield 82%; yellow solid; mp 216 °C (from ethanol); 1H NMR (CDCl₃): δ 1.37 (m, 4H), 2.50 (m, 4H), 2.61 (s, 3H, COCH₃), 7.21-7.37 (m, 5H, Ar-H), 8.24 (s, 1H, NH), 9.09 (s, 1H, NH), 12.35 (s, 1H, OH) ppm; IR (KBr): v_max 3447-3149 (2NH, OH), 1708, 1674 (2C=O) cm⁻¹; MS, m/z (%) 357 (M⁺, 100), 339 (50), 179 (25), 77 (80). Anal. Calcd. for C₁₈H₁₄N₃O₃S (357.43): C, 60.49; H, 5.36; N, 11.76. Found: C, 60.25; H, 5.29; N, 11.48%.

2-(2-Oxo-N'-p-tolylpropy1hydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3b).
Yield 78%; yellow solid; mp 136 °C (from ethanol); 1H NMR (CDCl₃, 300 MHz): δ 1.32 (m, 4H), 2.40 (s, 3H, Ar-CH₃), 2.52 (m, 4H), 2.68 (s, 3H, COCH₃), 7.13-7.27 (m, 4H, Ar-H), 8.25 (s, 1H, NH), 9.04 (s, 1H, NH), 12.24 (s, 1H, OH) ppm; IR (KBr): v_max 3448-3242 (2NH, OH), 1706, 1662 (2C=O) cm⁻¹; MS, m/z (%) 371 (M⁺, 28), 353 (30), 248 (23), 179 (25), 106 (100), 91 (70). Anal. Calcd. for C₁₉H₁₄N₃O₃S (371.33): C, 61.44; H, 5.70; N, 11.31. Found: C, 61.37; H, 5.74; N, 11.22%.

2-(N'-(4-Chlorophenyl)-2-oxopropylhydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3e).
Yield 84%; yellow solid; mp 146 °C (from dioxane); 1H NMR (CDCl₃, 300 MHz): δ 1.36 (m, 4H), 2.53 (m, 4H), 2.71 (s, 3H, COCH₃), 7.23-7.31 (m, 4H, Ar-H), 8.21 (s, 1H, NH), 9.12 (s, 1H, NH), 12.29 (s, 1H, OH) ppm; IR (KBr): v_max 3486-3244 (2NH, OH), 1743, 1665 (2C=O) cm⁻¹; MS, m/z (%) 393 (M⁺, 2), 391 (M⁺, 25), 373 (38), 302 (23), 247 (58), 179 (70), 99 (87), 63 (100). Anal. Calcd. for C₁₉H₁₇ClN₃O₃S (391.08): C, 55.17; H, 4.63; N, 10.72. Found: C, 55.09; H, 4.69; N, 10.48%.

2-(N'-(4-Nitrophenyl)-2-oxopropylhydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3d).
Yield 86%; yellow solid; mp 187 °C (from dioxane); 1H NMR (CDCl₃, 300 MHz): δ 1.40 (m, 4H), 2.41 (m, 4H), 2.83 (s, 3H, COCH₃), 7.26-8.27 (m, 4H, Ar-H), 8.61 (s, 1H, NH), 9.32 (s, 1H, NH), 12.19 (s, 1H, NH) ppm; IR (KBr): v_max 3446-3175 (2NH, OH), 1699, 1653 (2C=O) cm⁻¹; MS, m/z (%) 402 (M⁺, 50), 384 (65), 204 (48), 179 (48), 122 (50), 64 (100). Anal. Calcd. for C₁₉H₁₈N₃O₃S (402.10): C, 53.72; H, 4.51; N, 13.92. Found: C, 53.56; H, 4.43; N, 13.77%.

2-(N'-(4-Methoxyphenyl)-2-oxopropylhydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3e).
Yield 80%; dark yellow solid; mp 132 °C (from ethanol); 1H NMR (CDCl₃, 300 MHz): δ 1.36 (m, 4H), 2.50 (s, 3H, Ar-OCH₃), 2.58 (m, 4H), 2.76 (s, 3H, COCH₃), 6.89-7.27 (m, 4H, Ar-H), 8.15 (s, 1H, NH), 9.01 (s, 1H, NH), 12.20 (s, 1H, OH) ppm; IR (KBr): v_max 3446-3146 (2NH, OH), 1739, 1655 (2C=O) cm⁻¹; MS, m/z (%) 387 (M⁺, 25), 369 (5), 304 (7) 179 (25), 122 (100), 65 (32). Anal. Calcd. for C₁₉H₁₇N₃O₃S (387.13): C, 58.90; H, 5.46; N, 10.85. Found: C, 58.67; H, 5.46; N, 10.69%.

2-(2-Ethoxy-2-oxo-N'-phenylvacetohydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3f).
Yield 82%; yellow solid; mp 128 °C (from ethanol); 1H NMR (CDCl₃, 300 MHz): δ 1.38 (t, 3H, CH₃), 1.85 (m, 4H), 2.70 (m, 4H), 4.31 (q, 2H, CH₂), 7.27-7.36 (m, 5H, Ar-H), 11.00 (s, 1H, NH), 11.24 (s, 1H, NH), 12.16 (s, 1H, OH) ppm; IR (KBr): v_max 3484-3238 (2NH, OH), 1707, 1652 (2C=O) cm⁻¹; MS, m/z (%) 387 (M⁺, 21), 369 (35), 296 (29), 204 (18), 105 (20), 65 (100). Anal. Calcd. for C₁₉H₁₂N₂O₃S (387.13): C, 58.90; H, 5.46; N, 10.85. Found: C, 58.76; H, 5.34; N, 10.76%.

2-(2-Ethoxy-2-oxo-N'-p-tolylacetohydrazonamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3g).
Yield 78%; yellow solid; mp 120 °C (from ethanol); 1H NMR (CDCl₃, 300 MHz): δ 1.36 (t, 3H, CH₃), 1.77...
2-(N’-(4-Chlorophenyl)-2-ethoxy-2-oxoacetohydrazono-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3h). Yield 82%; yellow solid; mp 174 °C (from dioxane); 1H NMR (CDCl3, 300 MHz): δ 1.36 (t, 3H, CH3), 1.81 (m, 4H), 2.69 (m, 4H) 4.33 (q, 2H, CH2), 7.16 (d, 2H, Ar-H) 7.29 (d, 2H, Ar-H), 10.98 (s, 1H, NH), 11.28 (s, 1H, NH), 12.29 (s, 1H, OH) ppm; IR (KBr): vmax 3447-3184 (2NH, OH), 1707, 1650 (2C=O) cm⁻¹; MS, m/z (%) 423 (M⁺+2, 10), 421 (M⁺, 25), 403 (30), 330 (44), 205 (24), 179 (41), 99 (100), 63 (53). Anal. Caled. For C19H14ClN3O6S (421.09): C, 54.09; H, 3.34; N, 10.68. Found: C, 54.06; H, 3.36; N, 10.73.

2-(2-Ethoxy-N’-(4-nitrophenyl)-2-oxoacetohydrazono-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (3i). Yield 80%; dark yellow solid; mp 174 °C (from ethanol); 1H NMR (CDCl3, 300 MHz): δ 1.36 (t, 3H, CH3), 1.81 (m, 4H), 2.69 (m, 4H) 4.33 (q, 2H, CH2), 7.16 (d, 2H, Ar-H) 7.29 (d, 2H, Ar-H), 10.98 (s, 1H, NH), 11.28 (s, 1H, NH), 12.16 (s, 1H, OH) ppm; IR (KBr): vmax 3447-3184 (2NH, OH), 1701, 1680 (2C=O) cm⁻¹; MS, m/z (%) 434 (M⁺+2, 10), 432 (M⁺, 25), 403 (30), 111 (100). Anal. Caled. For C19H14ClN3O6S (432.11): C, 52.77; H, 4.66; N, 12.96. Found: C, 52.63; H, 4.43; N, 12.76.

Cyclization of 3a,b,f,g

A mixture of 3a,b,f,g (1 mmol) and 1,1’-carbonyldimidazole (0.2g) in dioxane (10 mL) was refluxed for 2h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice, acidified with dilute hydrochloric acid. The precipitate so obtained was filtered, washed with water, dried and recrystallized from the proper solvent to give 4a,b,f,g.

2-Acetyl-4-(p-tolyl)-6,7,8,9-tetrahydro-1H-benzo[4,5]thieno[2,3-e][1,2,4]triazepin-5(4H)-one (4a). Yield 80%; yellow solid; mp 186 °C (from ethanol); 1H NMR (CDCl3, 300 MHz): δ 1.37 (m, 4H), 2.51 (m, 4H), 2.61 (s, 3H, CH3), 3.13-7.27 (m, 5H, Ar-H), 9.12 (s, 1H, NH) ppm; 13C NMR (CDCl3, 75 MHz): δ 18.5, 19.6, 20.1, 20.8, 22.3 101.5, 113.2, 116.0, 120.8, 124.6, 131.0, 138.3, 141.8, 147.6, 168.2, 185.6 ppm; IR (KBr): vmax 3323 (NH), 1702, 1652 (2C=O) cm⁻¹; MS, m/z (%) 339 (M⁺, 24), 179 (25), 93 (43), 77 (86), 65 (100). Anal. Caled. For C19H14N3O6S (339.10): C, 56.70; H, 5.05; N, 12.38. Found: C, 56.35; H, 5.12; N, 12.23.

2-Acetyl-4-(p-tolyl)-6,7,8,9-tetrahydro-1H-benzo[4,5]thieno[2,3-e][1,2,4]triazepin-5(4H)-one (4b). Yield 77%; yellow solid; mp 177 °C (from ethanol); 1H NMR (CDCl3, 300 MHz): δ 1.32 (m, 4H), 2.40 (s, 3H, Ar-CH3), 2.52 (m, 4H), 2.61 (s, 3H, COCH3), 17.7-7.43 (m, 4H, Ar-H), 9.13 (s, 1H, NH) ppm; IR (KBr): vmax 3273 (NH), 1703, 1663 (2C=O) cm⁻¹; MS, m/z (%) 353 (19), 179 (16), 106 (100), 77 (60). Anal. Caled. For C19H14N3O6S (353.12): C, 56.74; H, 5.42; N, 11.89. Found: C, 56.35; H, 5.48; N, 11.77%.

Sobhi M. Gomha et al. Int. Journal of Engineering Research and Application

www.ijera.com

IV. General procedures for preparation of compounds 8a,b and 11c

A solution of 1 (0.394g, 2 mmol) in acetic acid (8 mL), was treated with concentrated hydrochloric acid (6 mL) and sodium nitrite (0.69 g, 2 mmol) at 0 °C. This mixture was added gradually with stirring, to a cooled solution of free chloromethylene compounds 7a,b or phenacyl thio carbamoyl 12 (2 mmol) in ethanol (10 mL) and sodium acetate (1.0 g). After complete addition, the reaction mixture was kept at room temperature for one hour. The solid product, so formed, was collected by filtration.

2-(2-(1-Chloro-2-oxo-propylidene)hydrazinyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (8a). Yield 74%; yellow solid; mp 143 °C (from ethanol); 1H NMR (CDCl3, 300 MHz): δ 1.85 (m, 4H), 2.31 (t, 3H, CH3), 2.70 (m, 4H), 11.00 (s, 1H, NH), 12.03 (s, 1H, OH)
ppm; IR (KBr): \( \nu_{\text{max}} \) 3482 - 3341 (NH, OH), 1718, 1703 (C=O) cm\(^{-1}\); MS, \( m/z \) (%): 300 (M\(^+\), 100), 197(50), 105 (20), 53 (73). Anal. Calcd. For \( \text{C}_16\text{H}_2\text{ClN}_2\text{O}_3\text{S} \) (300.03): C, 47.92; H, 4.36; N, 9.31. Found: C, 47.75; H, 4.47; N, 9.12%.

2-(2-(1-Chloro-2-ethoxy-2-oxoethylidene)hydrazinyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylic acid (8b). Yield 82%; yellow solid; mp 135 °C (dioxane); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 1.33 (t, 3H, CH\(_3\)), 1.82 (m, 4H), 2.73 (m, 4H), 4.21 (q, 2H, CH\(_2\)), 11.04 (s, 1H, NH), 11.83 (s, 1H, OH) ppm; IR (KBr): \( \nu_{\text{max}} \) 3479 - 3338 (NH, OH), 1712, 1698 (C=O) cm\(^{-1}\); MS, \( m/z \) (%): 330 (M\(^+\)), 100, 197 (42), 105 (43), 53 (67). Anal. Calcd. For \( \text{C}_16\text{H}_1\text{ClN}_2\text{O}_3\text{S} \) (300.04): C, 50.13; H, 3.91; N, 12.53. Found: C, 50.10; H, 3.76; N, 12.36%.

References


**Graphical Abstract**
Utility of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid in the synthesis of novel thieno[2,3-b][1,2,4]triazepinones and thieno[2,3-d] [1,3,4]thiadiazolo[2,3-b]pyrimidinones

Sobhi M. Gomha¹ and Hassan M. Abdel-aziz²*