**Computational Insights into Cycloadditions of Thioisomünchnones with Acetylenes: How Does Sulfur Escape from Cycloadducts?**

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The spontaneous loss of sulfur or isocyanate from transient 7-thia-2-azabicyclo[2.2.1]hept-5-en-3-ones, which are initially formed by 1,3-dipolar cycloadditions of thioisomünchnones with acetylenic dipolarophiles, is the key step in the chemoselective syntheses of pyridin-2-ones or thiophenes. The way by which sulfur is released has been the subject of previous studies pointing to a concerted retro-cheletropic mechanism as a more favorable route than the alternative stepwise pathway. The latter however, is apparently prevalent for elimination of isocyanate. Working with a conformationally-restricted bicyclic thioisomünchnone that undergoes facile cycloaddition with acetylenes, sulfur elimination has now been interrogated by experiment and theoretical calculations at the M06-2X and M11 methods in combination with the 6-311++G(d,p) basis set, which unveil rather a sigmatropic shift via the intermediacy of thiirane species. These results provide new vistas and synthetic opportunities in mesoionic cycloadditions.

**Keywords**

Mesoionic.

Cycloaddition.

Thiazolopyridone.

Thiirane.

Sigmatropic rearrangement.

**Introduction**

Construction of densely functionalized heterocycles, and especially natural products and their analogs, by means of dipolar cycloadditions has been a fruitful area of research in recent decades.1 Like the search for Dielsalderases, the chase of natural 1,3-dipolar cycloadditions has remained elusive until the recent finding that a prenylated flavin cofactor adopts an azomethine ylide form and plays a key role in ubiquinone biosynthesis and detoxification processes.2,3

Structurally exotic on their own,4 mesoionic heterocycles, yet displaying significant aromaticity,5 behave as masked dipoles and undergo thermal cycloadditions with a variety of dipolarophiles.6 Thioisomünchnones (thiazol-4-ium-3-olates) emerged as a versatile family that can be harnessed in catalytic and non-catalytic routes toward numerous naturally-occurring systems.7 Further decoration of such mesoionic rings by dialkylamino substituents gives rise to a subclass of reactive dipoles and enables the access to heterocycles not easily foreseen in cycloaddition chemistry.8 Thioisomünchnones often react with dipolarophiles via one-step procedures which involve actually domino reactions from the non-isolated cycloadducts. A salient postcycloaddition modification is the spontaneous sulfur extrusion that removes this element and renders up sulfur-free heterocycles, which are more suitable as drug-like candidates for in vivo studies.9 Herein we revisit postcycloaddition through a new bicyclic thioisomünchnone that leads to novel dihydrothialozo ring-fused pyrid-2-ones.

A few years ago we reported in detail the cycloaddition of 1,3-thiazolium-4-olates with acetylenes to give pyrid-2-ones. Based on mechanistic considerations, the intermediate bicycles would have extruded sulfur by two possible routes: either a concerted retro-cheletropic process (path a) or a stepwise pathway (b) (Scheme 1).10



**Scheme 1.** Proposed concerted (a) and stepwise (b) mechanisms for the extrusion of sulfur from 7-thia-2-azabicyclo[2.2.1]hept-5-en-3-ones.

The concerted 1,4-retrocycloaddition has been largely invoked as the most plausible route for the extrusion of sulfur, while the stepwise mechanism is supported by the isolation of carbonothioate derivatives in the reaction of thioisomünchnones with azodipolarophiles,11 as well as by the thionation reaction of these mesoionic dipoles with isothiocyanates (which should most likely be occurring by a stepwise pathway too).8b-d In this work we investigate thoroughly the loss of sulfur from 1:1 initial cycloadducts. Our results suggest that sulfur elimination takes place by a sigmatropic-type sulfur displacement followed by a 1,2-elimination from the thiirane intermediate, which has never been taken into account as working hypothesis. The computational study unravels how this elimination takes place and does proceed with high levels of selectivity, thus shedding light into an overlooked mechanistic pathway.

**Results and discussion**

Dihydrothiazolo[3,2-a]pyrid-2-one rings are privileged scaffolds that can be obtained by thioisomünchnone cycloadditions with triple bonds so long as the masked dipoles are built on a cyclic dithiocarbamate like thiazolidine-2-thione (**1**). The latter was then subjected to the well-established condensation with an α-haloacid [i.e. α-bromophenylacetic acid (**2**)], in basic medium, followed by cyclodehydration with Ac2O/NEt3 (1:3 ratio) (Scheme 2).12 Thus, the transient thioglycolic acid derivative (**3**) evolved into a new thioisomünchnone (**4**), obtained as an orange solid.



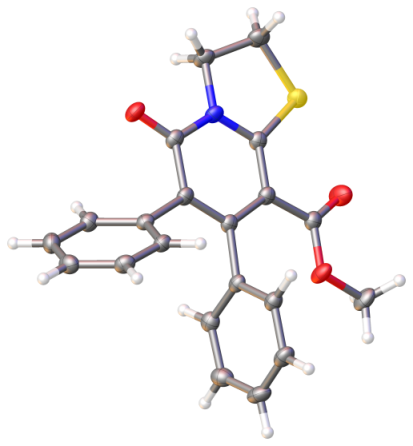
**Scheme 2.** Synthesis of 2-phenyl-5,6-dihydrothiazolo[2,3-b]thiazol-4-ium-3-olate (**4**) from thiazolidine-2-thione (**1**).

Reactions of **4** with acetylenic dipolarophiles **5**-**9** were carried out in toluene at reflux using an excess (25%) of dipolarophile. That the reaction goes to completion could be easily monitored by observing the gradual disappearance of the orange color. The solvent was removed under reduced pressure, the corresponding residues treated with diethyl ether and then recrystallized from alcohols (EtOH or MeOH), which afforded essentially pure 5-oxo-6-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyridines (**15**-**19**) from the intermediate cycloadducts **10**-**14** in good overall yields (~70%).

This synthesis of thiazolopyrid-5-ones in a regiospecific fashion suggests that cycloaddition of **4** with asymmetrically-substituted dipolarophiles (**6**-**9**) leads exclusively to the corresponding cycloadducts **11**-**14**, which yield spontaneously compounds **16**-**19** after sulfur extrusion (Scheme 3). The solid-state structure of **18** could be unambiguously elucidated by single-crystal X-ray diffraction (Figure 1),13 whereas the structure of **19** was assigned by comparison of its NMR data with those of **18**. 13C NMR data of **19** do not show any significant difference with respect to **18**, with the sole exception of an additional signal resonating at 60.8 ppm (attributed to the methylene carbon of the ethyl carboxylate group). Also, the structure of **17** was established on the basis of NOE enhancements that revealed the spatial proximity of H-7 (8.00 ppm) to the *ortho* hydrogens of phenyl group on C-6 resonating at 7.70 ppm (see Supplementary Material). The structure of **16** was elucidated by comparing its NMR data with those of **17**. 13C NMR spectra of **16** and **17** were quite similar differing only by the presence of the methylene signal at 61.2 ppm in the spectrum of **17**.



**Scheme 3.** Reaction of thioisomünchnone **4** with acetylenic dipolarophiles **5**-**9** leading to thiazolo[3,2-a]pyridine-5-ones **15**-**19**.



**Figure 1**. Solid-state structure of compound **18**. Crystal data were collected at 100(2) K; triclinic crystal system (P-1 space group). Ellipsoids are drawn at 50% probability.

To shed light into the reactivity of **4** against asymmetrically-substituted acetylenic dipolarophiles, we performed a computational study of the cycloaddition of **4** with methyl propiolate (**6**) using the Gaussian09 package.14 The M06-2X15 density functional method in conjunction with the 6-311++G(d,p) basis set16 was selected for all the geometry optimizations and frequency analysis. Ground and transition states were characterized by none and one imaginary frequency, respectively. Solvent effects (in toluene) were included in all geometry optimizations using the SMD method.17 To further corroborate the validity of results, all stationary points of the alternative reaction pathways were also completely re-optimized using the M11 functional plus the 6-311++G(d,p) basis set as above. Relative to other DFT methods, the accuracy of the M11 functional is particularly suitable for estimating alkyl bond dissociation energies, barrier heights, and noncovalent interaction energies18.

The reaction of **4** with methyl propiolate (**6**) may in principle generate two regioisomeric cycloadducts (**11** and **20**), whose subsequent evolution would afford thiazolo[3,2-*a*]pyridine-5-ones (**16** and **21**) by sulfur extrusion and/or thiophenes (**22** and **23**) through an isocyanate retrocycloaddition (Scheme 4).



**Scheme 4.** Hypothetical conversion of cycloadducts **11** and **20** into pyridones **16** and **21** and/or thiophenes **22** and **23**, respectively.

Figure 2 shows the reaction pathways leading to cycloadducts **11** and **20**. It should be noted that the energy barriers for either concerted (red line) or stepwise (black line) mechanisms differ by more than 3 kcal mol-1, thus pointing to a regioselective transformation that agrees with the experimental results (see below). The free energy difference that separates **TS111** from **TS211** (ΔΔ*G*‡ = -0.79 kcal mol-1) is very small and lies within the error range of DFT methods, which does not allow us to ensure that the second stage is actually the rate-determining step. This surmise was confirmed by conducting the optimization of **TS111** and **TS211** at the same level in dichloromethane and at the M06-2X/6-31+G(d) level. In addition, the geometric and energetic likeness of **TS111**, **I11** and **TS211** does not exclude the possibility that the allegedly stepwise mechanism takes place in a concerted manner as evidenced by further optimization performed at the MP2/6-311++G(d,p) level (Table 1).



**Figure 2**. Reaction pathways leading to regioisomeric cycloadducts **11** and **20**, and subsequent conversion of **11** into pyridone **16** and thiophene **22**. (ΔG values are given in kcal mol-1)

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| **Table 1**. Bond lenghts (Å) and free energy differencesa (kcal mol-1) found for saddle points **TS111** and **TS211** at several levels of theory. | | | | |
| **Level** | **Structure** | **C6-C7** | **C8-C8a** | **ΔΔ*G* ‡** |
| M06-2X/6-311++G(d,p) in toluene (SMD) | **TS111** | 1.97 | 3.10 | -0.79 |
| **TS211** | 1.62 | 2.79 |
| M06-2X/6-311++G(d,p) in dichloromethane (SMD) | **TS111** | 1.99 | 3.16 | -0.51 |
| **TS211** | 1.62 | 2.74 |
| M06-2X/6-31+G(d) in toluene (SMD) | **TS111** | 1.98 | 3.12 | 0.31 |
| **TS211** | 1.62 | 2.78 |
| MP2/6-311++G(d,p) in toluene (SMD) | **TS111** | 2.14 | 2.31 | ----- |
| aΔ*G* (**TS111**) - Δ*G* (**TS211**). | | | | |

It is also worth noting that while C6-C7 and C8-C8a bond lengths in **TS111** are 1.97 Å and 3.10 Å, respectively [at the M06-2X/6-311++G(d,p) level in toluene], consistent with a stepwise mechanism in which the C6-C7 bond is initially formed, the lengths of those bonds (2.46 Å and 2.11 Å, respectively) in **TS20** leading to cycloadduct **20** unveil its concerted and asynchronous nature. The same conclusion can be attained by estimating the bond orders for intermediates and transition structures involved in the formation of **11** and **20** (Table 2).

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| **Table 2**. Selected Mulliken bond orders (BO) for both intermediates and transition structures involved in the formation of **11** and **20**. | | |
| **Structure** | **BO(C6-C7)** | **BO(C8-C8a)** |
| **TS111** | 0.44 | 0.05 |
| **I11** | 0.91 | 0.03 |
| **TS211** | 0.82 | 0.12 |
| **11** | 0.99 | 0.95 |
| **TS20** | 0.22 | 0.38 |
| **20** | 0.96 | 0.98 |

Figure 3 and Table S1 show the energy barriers for all stationary points across the reaction pathways leading to regioisomeric thiazolopyridones **16** and **21** and thiophenes **22** and **23**, which would have arisen from cycloadducts **11** and **20**. Results show that, in all cases, the rate-determining step is the initial 1,3-dipolar cycloaddition (see Figure 2 for monitoring the formation and evolution of cycloadducts **11** and **20**). The fast evolution of **11** and **20** proceeds through energy barriers that do not exceed 20 kcal mol-1 to give **16** and **21**, respectively. Both ΔΔ*G*‡ [Δ*G*(**TS20**) - Δ*G*(**TS211**) > 3 kcal mol-1] and ΔΔ*G* [Δ*G*(**21**) - Δ*G*(**16**) ~ 6 kcal mol-1] values indicate that the formation of **16** is a kinetically and thermodynamically controlled process.



**Figure 3.** Reaction pathways leading to regioisomeric thiazolopyridones **16** and **21**,and thiophenes **22** and **23** (ΔG values are given in kcal mol-1).

In order to clarify how sulfur escapes from the initial cycloadducts **11** and **20** to give the corresponding pyrid-2-ones **16** and **21**, we tried to optimize and characterize all the stationary points involved in both mechanistic pathways, i.e. the retro-cheletropic reaction (Scheme 1a) and the stepwise process (Scheme 1b). However, we were unable to locate the transition structure corresponding to the former. Initially we assumed that the transition structure found actually (**TS16**, Figure 3) would lead to a zwitterionic intermediate, although a further IRC analysis showed its direct conversion into thiirane **I16** (Figure 4). So, sulfur removal appears to be consistent with an initial sulfur sigmatropic rearrangement leading to a three-membered cyclic intermediate, which has not yet been considered as mechanistic hypothesis.

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**Figure 4.** IRC of **TS16** and M06-2X/6-311++G(d,p)/(SMD)-optimized structures for saddle point **TS16**, thiirane **I16**, and cycloadduct **11**.

It is fair to say that thiiranes are not new kids in scenarios involving sulfur elimination. Their formation and further evolution to alkenes have been postulated in previous theoretical studies19 and explored experimentally too.20 This suggest that the intermediate thiiranes **I16** and **I21**would evolve into the corresponding alkenes (namely thiazolopyridones **16** and **21**) and S8, formed by oligomerization of S2, S3 and S4 species, as evidenced by previous studies19.

It is well known that ring-fused thioisomünchnones do not give rise to thiophenes by reaction with acetylenes. Figure 3 shows that the energy gap [Δ*G*(**TS22**) - Δ*G*(**TS16**)] for the intramolecular retrocycloaddition of isocyanate is 14.33 kcal mol-1 higher than the alternative sulfur sigmatropic rearrangement leading to the exclusive formation of **16**. Likewise, the chemoselective transformation of cycloadduct **20** into pyridone **21** has an energy barrier 17.17 kcal mol-1 lower than that affording thiophene **23**. Clearly, the sulfur sigmatropic rearrangement is kinetically favored with respect to the retro-cycloaddition of isocyanate. Figure 3 and Table S2 show the relative energies of all stationary points leading to thiophene **22** and **23** from cycloadducts **11** and **20**, respectively. Selected bond lengths and bond orders in transition states **TS22** and **TS23** point to concerted, yet asynchronous, retrocycloaddition processes (Table S3).

Table 3 collects the relative electronic energies, enthalpies, and free energies of all stationary points located for the alternative reaction pathways of **4** and **6** optimized at the M11/6-311++G(d,p) level. These results almost mirror those previously obtained using the M06-2X functional, even although the latter magnifies the energy barriers leading to thiophene derivatives by ~1 kcal mol-1 and reduces on the contrary those leading to 5-oxothiazolo[3,2-a]pyridines by <2 kcal mol-1.

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| **Table 3.** Relative electronic energy (Δ*E*), enthalpy (Δ*H*), and free energy (Δ*G*) (in kcal mol-1)a of all stationary states involved in the reactions of **4** and **6** leading to 5-oxothiazolo[3,2-*a*]pyridines **16** and **21** and thiophenes **22** and **23**. | | | |
| **Structure** | **Δ*E*** | **Δ*H*** | **Δ*G*** |
| **TS111** | 9.54 | 9.95 | 24.12 |
| **I11** | 5.02 | 6.54 | 22.22 |
| **TS211** | 7.51 | 8.38 | 24.01 |
| **11** | -40.62 | -37.74 | -22.48 |
| **TS16** | -20.34 | -18.32 | -3.14 |
| **I16** | -62.76 | -59.38 | -44.25 |
| **16** + 1/8 **S8** | -83.38 | -79.97 | -67.57 |
| **TS20** | 11.62 | 12.09 | 27.44 |
| **20** | -46.09 | -43.39 | -28.46 |
| **TS21** | -26.63 | -24.65 | -9.42 |
| **I21** | -66.01 | -62.92 | -48.57 |
| **21** + 1/8 **S8** | -76.98 | -73.85 | -61.52 |
| **TS22** | -7.74 | -6.76 | 8.53 |
| **22** | -63.24 | -60.32 | -49.64 |
| **TS23** | -9.59 | -8.64 | 6.00 |
| **23** | -60.85 | -58.14 | -49.33 |
| a Related to the electronic energy (Δ*E*), enthalpy (Δ*H*), and free energy (Δ*G*) of **4** + **6**. | | | |

In order to evaluate the influence of the dipolarophile size on the dipolar cycloaddition, the condensations of **4** with acetylene derivatives **5** and **8** have also been explored, in following the same methodology as dipolarophile **6** (Tables S4 and S5). Given the symmetrical substitution pattern of **5**, its reaction with **4** afforded only pyridone **15** (Figure S1). On the other hand, in the 1,3-dipolar cycloaddition of **4** with methyl phenylpropiolate (**8**), the formation of regioisomeric pyridones **18** and **24** should be taken into account (Figure S2). Computation at the M06-2X/6-311++G(d,p) level shows that molecular size is indeed a critical factor as the energy barriers to be overcome in the reactions with dipolarophiles **5** (Δ*G*15 = 29.28 kcal mol-1) and **8** (Δ*G*18 = 26.93 kcal mol-1; Δ*G*24 = 28.08 kcal mol-1) are slightly higher than that of methyl propiolate (**6**) (see Supplementary Material).



**Conclusions**

A structurally rigid 1,3-thiazolium-4-olate (**4**) can be conveniently prepared from 1,3-thiazolidine-2-thione by standard protocols of condensation with an α-haloacid and further cyclodehydration. Thermal [3+2]-cycloadditions of **4** with acetylenic dipolarophiles produce thiazolo[3,2-a]pyridones in good yields without isolation of the corresponding cycloadducts. The use of asymmetrically-substituted acetylenes unravels a complete regioselection where the alkoxycarbonyl group is attached to the C-8 atom of the six-membered ring. This selectivity is supported by DFT calculations [at the M06-2X and M11 methods in combination with the 6-311++G(d,p) basis set] with inclusion of solvent effects (SMD method), which prove that the isolated regioisomers are both kinetically and thermodynamically-controlled products. Sulfur extrusion en route to pyridones does not occur through a retro-cheletropic process as usually thought, but rather by two consecutive steps, namely (a) 1,3-sigmatropic rearrangement of the sulfur atom leading to a thiirane intermediate, and (b) thermal fragmentation of the latter affording an alkene (double bond of the heterocyclic moiety). The theoretical analysis also indicates that the rate-limiting step is invariably the initial formation of cycloadducts, regardless of formation of either pyridones or thiophenes. Moreover, the six-membered heterocycle is kinetically favored relative to the intramolecular retro-cycloaddition of isocyanate that leads to thiophenes.

**Experimental section.**

**General Methods.**

Solvents and reagents were purchased from commercial suppliers and used without further purification. The identity of all compounds was confirmed by their elemental analyses, high-resolution mass spectra, mp’s and NMR data (see Supplementary Material).

**Computational details**

All of the calculations reported in this work were carried out using the Gaussian09 package.14 The M06-2X15 and M1118 density functional methods in conjunction with the 6-311++G(d,p)16 basis set were selected for all the geometry optimizations and frequency analysis. The geometries were optimized including solvation effects in toluene, which have been estimated by the density-based self-consistent reaction field theory of bulk electrostatic, i. e. the the well-known solvation model density (SMD)17 method that takes into account different contributions such as long-range electrostatic polarization (bulk solvent effect),21 as well as short-range effects due to cavitation, dispersion, and solvent’s structure.22 Frequency calculations at 298.15 K on all the stationary points were carried out at the same level of theory as the geometry optimizations to ascertain the nature of the stationary points. Ground and transition states were characterized by none and one imaginary frequency, respectively. All of the relative energies shown are free energies calculated at 298.15 K with respect to the reactants. It was found that each saddle point belonged to the reaction path by the corresponding IRC analysis (intrinsic reaction coordinate).

**2-Phenyl-5,6-dihydrothiazolo[2,3-b]thiazol-4-ium-3-olate (4)**. A mixture of thazolidine-2-thione (**1**) (17 mmol), 2-bromo-2-phenylacetic acid (**2**) (17 mmol), triethylamine (17 mmol), and benzene (100 mL) was stirred at room temperature for 72 h. Then, the resulting triethylammonium bromide was filtered off. In order to remove dissolved salts, the solution was also passed through a silica gel [Merck® 60 (400-230 mesh)] column using ethyl acetate as eluent. The solvent was evaporated to dryness to give an oily residue (3.11 g), which contained the intermediate product **3**. To this oil a mixture of acetic anhydride and triethylamine (1:3, 25 mL) was added. The mixture was softly heated for a few minutes, yielding the title compound as orange crystals, which were collected by filtration and washed with ethyl ether (1.8 g, 68%). Mp: 193-194 ºC. FT-IR (KBr) νmax 1579, 1493, 1431, 1364, 1139, 752, 691 cm-1. 1H NMR (500 MHz, CDCl3, 25 ºC) δ 7.71 (dd, 2H, *J* = 7 Hz; *J* = 1.5 Hz), 7.29-7.25 (m, 2H), 7.05-7.03 (m, 1H), 4.45 (t, 2H, *J* = 7.5 Hz), 3.98 (t, 2H, *J* = 8 Hz) ppm. 13C NMR (125 MHz, CDCl3, 25 ºC) δ 156.1 (C), 152.1 (C), 134.2 (C), 128.6 (CH), 124.2 (CH), 122.8 (CH), 97.9 (C), 49.3 (CH2), 36.6 (CH2) ppm. Anal. Calcd for C11H9NOS2: C, 56.17; H, 3.85; N, 5.95; S, 27.25. Found: C, 56.15; H, 3.98; N, 5.94; S, 27.03.

**General Procedure for the Cycloadditions of 4 with Acetylenic Dipolarophiles (5-9)**. A mixture of **4** (2.1 mmol), the dipolarophile (2.7 mmol), and toluene (25 mL) was heated at reflux until disappearance of the orange color (TLC analysis: ethyl acetate:hexane 1:1 v/v). The solvent was evaporated to dryness and the resulting residue was suspended in ethyl ether to yield the corresponding pyridones (**15**-**19**), which were further recrystallized from methanol or ethanol.

**Dimethyl 5-oxo-6-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-7,8-dicarboxylate (15)**. Following the general procedure, compound **15** was obtained from **4** and **5** after 2 h. Recrystallized from methanol (0.47 g, 66%) showed mp 163-166 ºC. FT-IR (KBr) νmax 2958, 2941, 1742, 1698, 1642, 1509, 1434, 1360, 1314, 1215, 984, 699 cm-1. 1H NMR (400 MHz, CDCl3, 25 ºC) δ 7.37-7.28 (m, 5H), 4.58 (t, 2H, *J* = 10 Hz), 3.83 (s, 3H), 3.58 (s, 3H), 3.37 (t, 2H, *J* = 10 Hz). 13C NMR (100 MHz, CDCl3, 25 ºC) δ 166.6 (C), 164.1 (C), 160.5 (C), 157.7 (C), 142.6 (C), 132.9 (C), 129.7 (CH), 128.3 (CH), 128.0 (CH), 125.0 (C), 101.4 (C), 52.5 (CH3), 52.2 (CH3), 51.6 (CH2), 27.6 (CH2) ppm. Anal. Calcd for C17H15NO5S: C, 59.13, H, 4.36, N, 4.05, S, 9.27. Found: C, 58.75, H, 4.15, N, 4.21, S, 9.31.

**Methyl 5-oxo-6-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-8-carboxylate (16)**. Following the general procedure, compound **16** was obtained from **4** and **6** after 2 h. Recrystallized from methanol (0.42 g, 70%) showed mp 153-154 ºC. FT-IR (KBr) νmax 3051, 3013, 2948, 2900, 1685, 1621, 1523, 1429, 1294, 1247, 1107, 789, 777, 693 cm-1. 1H NMR (400 MHz, CDCl3, 25 ºC) δ 8.00 (s, 1H), 7.68 (d, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 8 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 4.59 (t, 2H, *J* = 8 Hz), 3.90 (s, 3H), 3.40 (t, 2H, *J* = 8.4 Hz). 13C NMR (100 MHz, CDCl3, 25 ºC) δ 165.2 (C), 160.9 (C), 156.1 (C), 137.3 (CH), 135.6 (C), 128.4 (CH), 128.3 (CH), 127. 8 (CH), 125. 6 (C), 104.4 (C), 52.2 (CH3), 51.2 (CH2), 27.8 (CH2) ppm. Anal. Calcd for C15H13NO3S: C, 62.71, H, 4.53, N, 4.87, S, 11.15. Found: C, 62.46, H, 4.77, N, 4.69, S, 11.24.

**Ethyl 5-oxo-6-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-8-carboxylate (17)**. Following the general procedure, compound **17** was obtained from **4** and **7** after 2 h. Recrystallized from ethanol (0,46 g, 72%) showed mp 132-133 ºC. FT-IR (KBr) νmax 3051, 3011, 2976, 2896, 1633, 1689, 1525, 1447, 1373, 1297, 1245, 1198, 1105, 1034, 788, 695 cm-1. 1H NMR (400 MHz, CDCl3, 25 ºC) δ 8.00 (s, 1H), 7.67-7.31 (m, 5H), 4.59 (t, 2H, *J* = 8 Hz), 4.35 (q, 2H, *J* = 6.8 Hz), 3.39 (t, 2H, *J* = 8 Hz), 1.37 (t, 3H, *J* = 7.2 Hz). 13C NMR (100 MHz, CDCl3, 25 ºC) δ 164.8 (C), 160.9 (C), 155.8 (C), 137.4 (CH), 135.7 (C), 128.4 (CH), 128.2 (CH), 127.7 (CH), 125.6 (C), 104.7 (C), 61.2 (CH2), 51.2 (CH2), 27.8 (CH2), 14.4 (CH3). HRMS (M + Na)+ Calcd for C16H15O3NNaS: 324.0655. Found: 324.0665

**Methyl 5-oxo-6,7-diphenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-8-carboxylate (18).** Following the general procedure, compound **18** was obtained from **4** and **8** after 24 h. Recrystallized from methanol (0,47 g, 61%) showed mp 177-178 ºC. FT-IR (KBr) νmax 3052, 3003, 2950, 1682, 1604, 1506, 1431, 1310, 1227, 704, 606 cm-1. 1H NMR (500 MHz, CDCl3, 25 ºC) δ 7.13-7.07 (m, 6H), 6.96-6.90 (m, 4H), 4.62 (t, 2H, *J* = 7.5 Hz), 3.36 (t, 2H, *J* = 7.5 Hz), 3.37 (s, 3H). 13C NMR (125 MHz, CDCl3, 25 ºC) δ 166.6 (C), 160.7 (C), 155.4 (C), 150.4 (C), 138.5 (C), 134.7 (C), 130.8 (CH), 128.4 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 106.2 (C), 51.7 (CH2), 51.6 (CH3), 27.7 (CH2). HRMS (M + Na)+ Calcd for C21H17O3NNaS: 386.0808. Found: 386.0821.

**Ethyl 5-oxo-6,7-diphenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-8-carboxylate (19).** Following the general procedure, compound **19** was obtained from **4** and **9** after 24 h. Recrystallized from ethanol (0,44 g, 55%) showed mp 171-175 ºC. FT-IR (KBr) νmax 3059, 2978, 2934, 1884, 1606, 1558, 1503, 1393, 1250, 1222, 714, 605 cm-1. 1H NMR (500 MHz, CDCl3, 25 ºC) δ 7.13-7.07 (m, 6H), 6.97-6.92 (m, 4H), 4.62 (t, 2H, *J* = 8 Hz), 3.87 (q, 2H, *J* = 7 Hz), 3.70 (t, 2H, *J* = 8 Hz), 0.70 (t, 3H, *J* = 7 Hz). 13C NMR (125 MHz, CDCl3, 25 ºC) δ 166.3 (C), 160.8 (C), 155.4 (C), 150.5 (C), 138.8 (C), 134.8 (C), 130.8 (CH), 128.5 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 106.4 (C), 60.8 (CH2), 51.6 (CH2), 27.7 (CH2), 13.2 (CH3). Anal. Calcd for C22H19NO3S: C, 70.02, H, 5.04, N, 3.71, S, 8.48. Found: C, 69.85, H, 5.15, N, 3.91, S, 8.86.

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