Synthesis and Characterization *via* Molecular Quantum Parameters of 2*H*-Thiazolo[3,2-*a*]pyrimidine-3,5,7(6*H*)-trione

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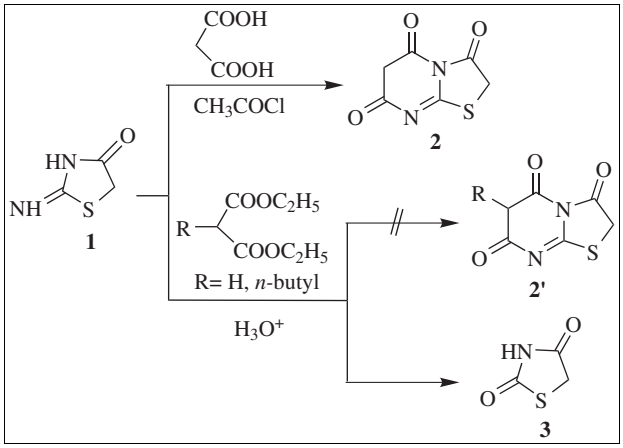

2*H*-Thiazolo[3,2-*a*]pyrimidine-3,5,7(6*H*)-trione (**2**) was synthesized and characterized *via* molecular quantum parameters using the PM3-semiempirical MO method. This is considered the only route not previously reported in the literature to synthesize compound **2** from 2-imino-4-thiazolidinone (**1**).

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INTRODUCTION

Biological activities of compounds containing uracil moiety incorporated other heterocycles have been reported [1,2]. Considering these reports, the development of new and simple synthetic method for the efficient preparation of heterocycles containing uracil ring fragment is therefore an interesting challenge. The thiazolidinone ring system has been widely used in the investigation of pharmacologically active heterocyclic compounds [3–9], perhaps most notably as a common structural motif in the Rosiglitazone class of PPAR-8 agonists [10,11], anti-inflammatory Darbufelone [12,13], and antiviral activities [14], have been found.

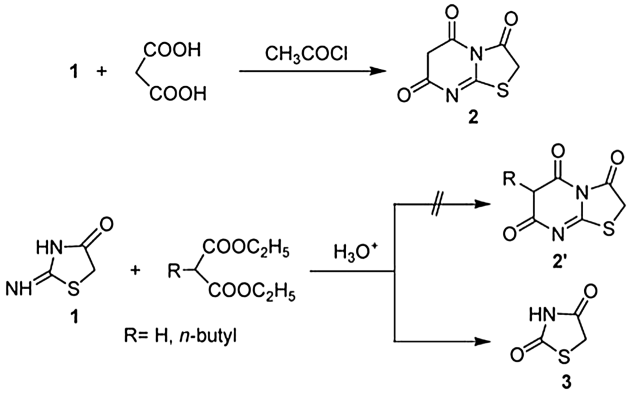
Few methods have been reported for the preparation of thiazolo[3,2-*a*]pyrimidines, and the existed methodologies required prolonged reaction times and strict reaction conditions in organic solvents [15,16]. The preparation of thiazolo [3,2-*a*]pyrimidines have been occurred by the reaction of enones with 2-aminothiazole in ethanol [15], 2-thioxo-1,2,3,4-tetrahydropyrimidines with phenacyl bromide in glacial acetic acid [16], dihydropyrimidine-2-thiones with α-bromophenylacetaldehyde in acetonitrile [17] and 4-phenyl-3,4-dihydropyrimidine(1*H*)-2-thione with chloroacetic acid in DMF [18] to afford thiazolo[3,2-*a*]pyrimidines has also been reported.

RESULTS AND DISCUSSION

The therapeutic importance of uracil nucleus condensed with other heterocycles [1,2], enthused us to develop selective procedures to synthesize a number of condensed heterocycles. Therefore, compound **1** as acetate salt was reacted with an equimolar amount of the diesters namely; diethyl malonate or diethyl *n*-butyl malonate in ethanol containing few drops of H_2O (least required amount to dissolve the salt) to give 2*H*-thiazolo[3,2-*a*]pyrimidine-3,5,7 (6*H*)-trione (**2′**) was unsuccessful, but the thiazolidine-2,4-dione (**3**) was obtained instead of the expected compound **2′**. The structure of **3** was identical with that reported in literature [19,20] (Scheme 1).

In addition, trials to obtain **2** by reaction of **1** with diethylmalonate in the presence of the following media (i) diphenyl ether, (ii) glacial acetic acid, (iii) triethylamine/butanol, nitrobenzene or dry xylene, (iv) sodium ethoxide/ethanol, or (v) diethylmalonate as solvent, were failed. Accordingly, we used malonic acid catalyzed by acetyl chloride at 60°C whereby, 2*H*-thiazolo[3,2-*a*]-pyrimidine-3,5,7(6*H*)-trione (**2**) was formed through bifunctional attack of the reagent to the *exo*-cyclic imino and *endo*-cyclicamido group of **1**. The probable mechanism for construction of **2** may be through the formation

Scheme 1



of protonated malonyl diacetate intermediate (**A**) followed by its conversion to malonyl chloride *via* the chloride ion attack to the intermediate (**A**), and subsequent condensation with the thiazolidinone derivative **1**. The condition of formation of compound **2** was in line with the condition reported in literature [21].

The structure **2** was established on the basis of its analytical and spectral data. Thus, the ^{1}H NMR spectrum of **2** displays two singlet signals at δ 4.38 and δ 4.69 ppm due to (CH_2CO) and (S-CH_2) protons, respectively. Its mass spectrum added further support to the assigned structure and showed the molecular ion peak at *m/z* 184 (M^+, 8%; Fig. 1).

The reaction between thiazolidinone and diethyl malonate showed that, the bidentate addition of diethyl malonate to the thiazolidinone ring is not possible, and the formation of compound **2** was unsuccessful. The electronic interaction behavior between the two molecules was investigated using the PM3-semiempirical MO method. Once, the two molecules approaching each other till a certain distance, an interaction is generated between H-atom attached to N_3 with oxygen atom of carbonyl ($C_{3'}$= O) group. Consequently, geometry optimization

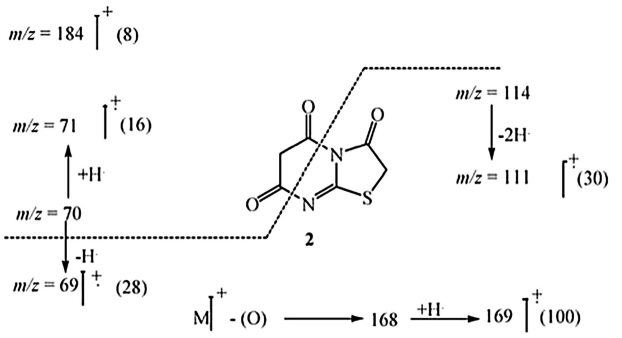


Figure 1. Fragmentation pattern of 2*H*-thiazolo[3,2-*a*]pyrimidine-3,5,7 (6H)-trione (**2**).

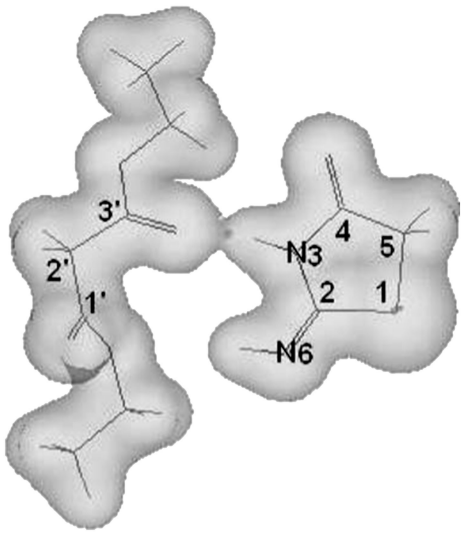


Figure 2. 3D-isosurface map at the total charge density contour value 0.02 of compound **1** with diethyl malonate.

process of this intermediate state did not lead to any additional interaction between hydrogen atom attached to N_6 with the oxygen atom of ($C_{1'}$= O), or any other kind of bidentate interaction, which lead to ring nitrogen juncture and the formation of compound **2** (Fig. 2).

The molecular quantum parameters and the electronic structure of diethylmalonate and compound **1** when interacted with each other were calculated. The resulted data indicated that no bidentate addition is possible. Thus, we used malonic acid in the presence of acetyl chloride instead of diethyl malonate to produce the active malonyl chloride reagent (Fig. 3). The MO calculations indicated that, the bidentate addition of malonyl chloride to the thiazolidinone ring is a possible process to be occurred as the two molecules approach to each other as shown in Table 1.

Once the two molecules approaching each other till a certain distance, a strong interaction, raised between Cl atoms of the malonyl chloride with H atoms of the thiazolidinone ring. The 3D-isosurface was mapped at the total charge density contour value of 0.02 and presented in Figure 4. The molecular quantum parameters and the electronic structure of malonyl chloride with compound **1** were calculated and the quantum parameters are shown in Table 2.

The distance between O— ($C—'_3$) and H— (N_{-3}) was calculated to be 1.878 Å. This value is lower than the sum of the van der Waal's radii of the two atoms (3.0 Å); this indicates the strong H-bonding between the two atoms prevent any interaction, that may occur between the carbon atom of the carbonyl group of malonic acid with *exo*-cyclic imino group. The same behavior was observed with the *endo*-cyclic amido group H— (N_{-6}) with O— ($C_{-1'}$).

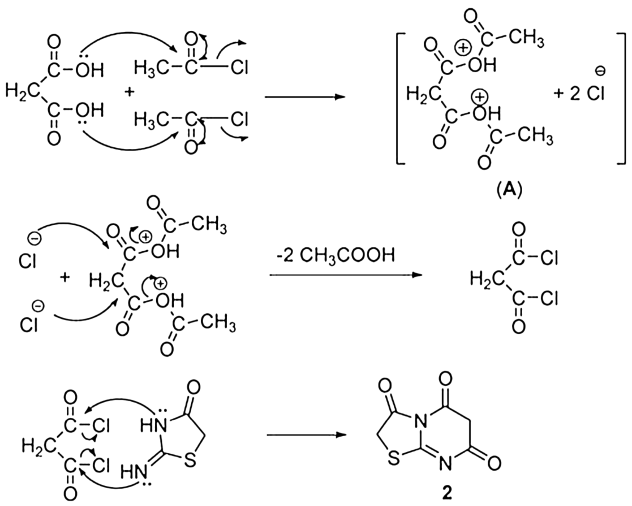


Figure 3. Mechanism of formation of 2*H*-thiazolo[3,2-*a*]pyrimidine-3,5,7(6H)-trione (**2**).

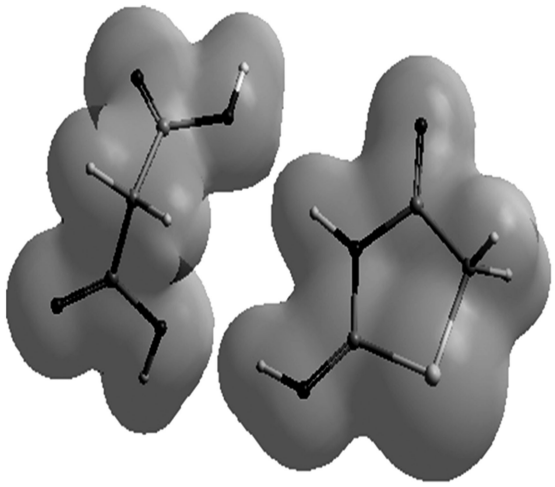


Figure 4. 3D-isosurface map at the total charge density contour value 0.02 of compound **1** with malonic acid.

However, in case of malonyl chloride, the distance between the Cl— (C'_{-3}) and H— (N_{-3}) was calculated to be 2.58 Å, which is lower than the sum of van der Waal's radii of the two atoms (3.0 Å). This indicates the strong interaction between H (N_{-3}) and Cl ($C_{-3'}$) and the possibility of the elimination of HCl molecule, whereas, the bond between H— (N_{-6}) (of *exo*-cyclic imino group) and Cl— ($C_{-1'}$) is stronger than the H —(N_{-3}) (of *endo*-cyclic amido group of thiazolidinone **1**) and Cl ($C_{-3'}$) as indicated from the shorter distance between H— (N_{-6})….Cl— ($C_{-1'}$). These parameters give us an indication that the *exo*-cyclic imino group of thiazolidinone **1** is more active for the annulations process than that of *endo*-cyclic amido group. The molecular quantum parameters and the electronic structure of malonyl chloride with compound **1** were calculated and illustrated in Table 2 and Figure 5.

This is the only route to synthesize compound **2** until now from 2-imino-4-thiazolidinone (**1**) as Fedorova *et al*. [22], tried to obtain compound **2** starting from thiobarbituric acid by alkylation with ethyl bromoacetate in ethanol in the presence of alkali, she obtained undesired 5-(2-oxo-2,5-dihydro-1,3-thiazol-4-y1)-2-thiobarbituric acid (**4**) (Fig. 6). The two molecules were allowed to approach each other and reorientate themselves according to their electrostatic potential behavior.

This 3D-mapped isosurface of the molecule was calculated for the optimized geometry of the two molecules (each under the field-effect of the other) using the PM3-semiempirical MO method. This display is a surface drawn with values of total electron density and according to values of the electrostatic potential. Accordingly, in Fedorova *et al*. reaction [22], there is a possibility for interaction of the bromine atom with the *S*-atom as shown in Figure 7. But there is no chance for the additional interaction between the carbon atom of acetate molecule with the nitrogen atom of the *endo*-cyclic amido group of thiobarbituric acid molecule, which may lead to cyclization. This is attributed to the steric hindrance as well as the unsuitable charges and electrostatic potential at these concerned sites. The important quantum chemical parameters for the effective atoms and distances are depicted in Table 3.

EXPERIMENTAL

All melting points were determined on a Gallenkamp electric melting point apparatus are uncorrected. Elemental microanalyses were carried out at Microanalytical Unit (Faculty of Science,

Table 1

Important quantum chemical parameters for the effective atoms and bonds in compound **1** and diethyl malonate when interacted with each other (Fig. 2).

Atom	Charge	Bond	Bond length (Å)	Bond order
O= ($C_{1'}$)	(−0.270)	O= $C_{1'}$	1.213	1.841
O= ($C_{3'}$)	(−0.263)	O= $C_{3'}$	1.219	1.76
H— ($N_{6'}$)	(+0.089)	N_6— H	0.988	0.993
O— ($C_{-3'}$)	(+0.155)	N_3— H	0.998	0.004
N_6	(−0.095)	N_6 H…O= $C_{1'}$	4.03	—
N_3	(−0.051)	N_3 H…O= $C_{3'}$	1.82	—
		N_6 …$C_{1'}$	4.61	—
		N_3 …$C_{3'}$	3.86	—

Table 2

Important quantum chemical parameters for the effective atoms and bonds in compound **1** and malonyl chloride.

Atom	Charge	Bond	Bond length (Å)	Bond order
Cl— ($C_{1'}$)	(−0.058)	Cl— ($C_{1'}$)	1.765	0.890
Cl— ($C_{3'}$)	(−0.031)	Cl— ($C_{3'}$)	1.780	0.908
H— (N_6)	(0.109)	N_6 H	1.000	0.000
H— (N_3)	(0.079)	N_3 H	0.991	0.000
C_1	(0.260)	Cl….H— N_6	2.580	0.008
C_3	(0.270)	Cl….H— N_3	2.520	0.005

Cairo University). IR spectra were recorded using KBr discs with a Mattson 5000 FTIR spectrometer, Faculty of Science, Cairo University. ^{1}H NMR data were measured in $CDCl_3$ or DMSO-d_6 on a Varian XL 200, 300 MHz instruments using TMS as an internal standard. Chemical shifts were reported in ppm (δ) downfield from that of TMS and coupling constants are expressed in hertz. The mass spectra were recorded on GC-MS QP-1000 EX. Shimadzu Instrument (Faculty of Science, Cairo University). Reactions were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp. Molecular orbital calculations and the quantum chemical parameters were determined using the PM3-Semiempirical MO method using evaluation copy of HyperChem.ver 7.5 (www.hyper.com). Package accommodated on PIV-2.8-MHz computer system.

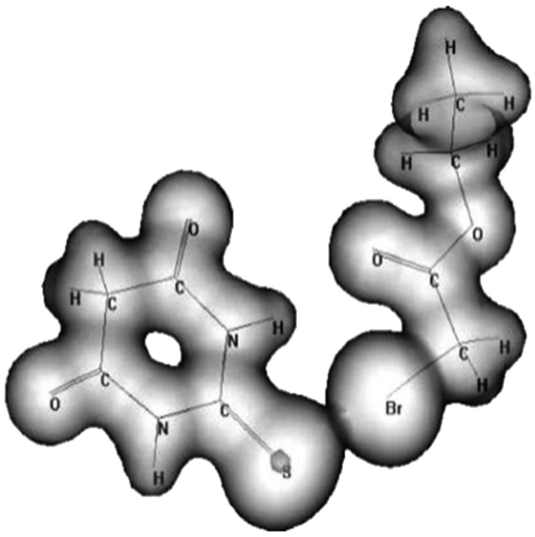


Figure 7. 3D-isosurface map at the total charge density contour value of 0.02 of thiobarbituric acid with ethyl bromoacetate.

2H-Thiazolo[3,2-*a*]pyrimidine-3,5,7(6H)-trione (2). To the solution of 2-iminothiazolidin-4-one (**1**) (1 g, 8.6 mmol) in acetyl chloride (10 mL), malonic acid (0.9 g, 8.6 mmol) was added, and then the reaction mixture was heated for 3 h at 50–55°C. The reaction mixture poured onto ice temperature The precipitate formed was collected by filtration and recrystallized from

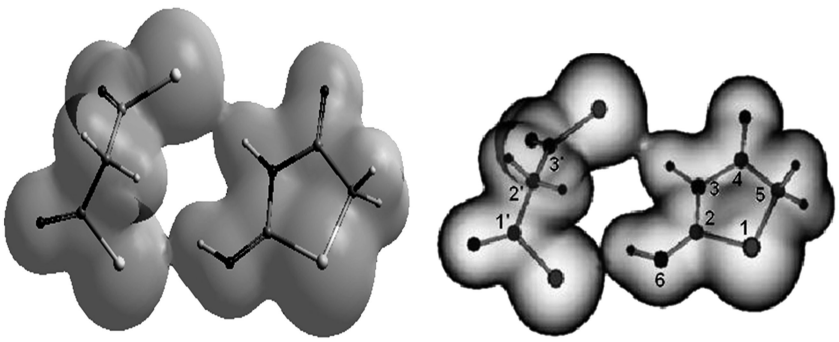


Figure 5. 3D-isosurface map at the total charge density contour value 0.02 of compound **1** with malonylchloride.

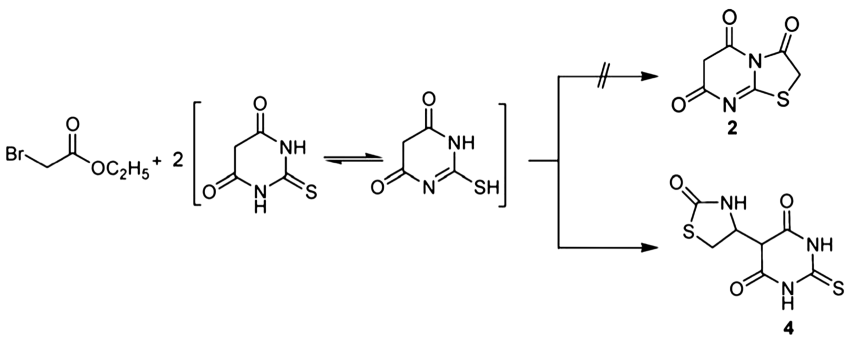


Figure 6. Synthesis of 5-(2-oxo-2,5-dihydro-1,3-thiazol-4-y1)-2-thiobarbituric acid (**4**).

Table 3

Important quantum chemical parameters for the effective atoms and bonds in thiobarbituric acid and ethyl bromoacetate.

Atom	Charge	Bond	Bond length (Å)
S	−0.208	Br-S	2.261
Br	0.029		
N(thiobarbituric acid)	0.057	NH(thiobarbituric acid) —O= C (acet)	3.8374
H— (N thiobarbituric acid)	0.153		
C(C= O acet)	0.379	NH(thiobarbituric acid)— O(acet)	2.7243
O(C= O acet)	−0.379		
O(OC_2H_5 acet)	−0.270		

MeOH/DMF to afford (0.76 g, 48%) of **2**; mp >300°C; brown crystals; R_f = 0.68 [pet. ether (40–60)/ethyl acetate, (1:4)]; IR (KBr) ύ (cm^{-1}), 2936, 2862, 1674, 1562, 1266, 1188, 768; ^{1}H NMR (200 MHz, DMSO-d_6): 4.38 (s, 2H, CH_2), 4.69 (s, 2H, CH_2); MS: (*m*/*z*, %): 185 (M^++1, 8), 184 (M^+, 8), 168 (14), 169 (100), 111 (30), 71 (16), 69 (28). *Anal*. Calcd. for $C_6H_4N_2O_3S$ (184.17): C, 39.13; H, 2.19; N, 15.21. Found: C, 38.76; H, 2.07; N, 15.16.

Thiazolidine-2,4-dione (3). Acetate salt of 2-imino-4-thiazolidinone (**1**) (0.33 g, 2.8 mmol) was refluxed in aqueous/ethanol (distilled water, 10 mL) for 2 h and left to cool. The formed precipitate was collected by filtration and recrystallized from ethanol to afford (0.14 g, 44%) of **3**; mp 122-123°C [Lit [20] mp 123°C]; R_f = 0.65 [pet. ether (40–60)/ethyl acetate, (1:3)]; IR (KBr) ύ (cm^{-1}), 2936, 2862, 1674, 1562, 1266, 1188, 768; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (s, 2H, CH_2), 11.9 (s, 1H, NH exchangeable with D_2O); ms: (*m*/*z*, %): 117 (M^+, 95), 52 (100).

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