Preparation of Halogenated Derivatives of Thiazolo[5,4-*d*]thiazole *via* Direct Electrophilic Aromatic Substitution

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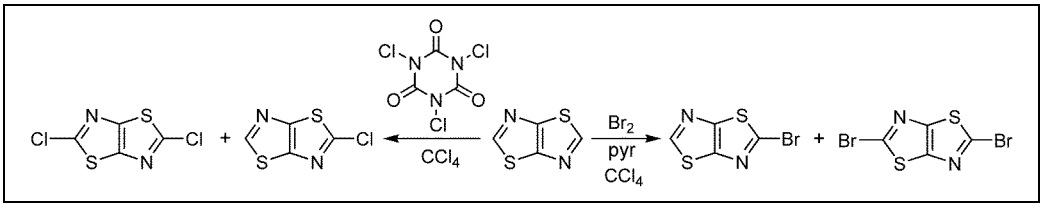
Received September 11, 2007



Chlorination and bromination reactions of thiazolo[5,4-*d*]thiazole led to the generation of its mono- and dihalogenated derivatives. These are the first instances of successful direct electrophilic aromatic substitution in the thiazolo[5,4-*d*]thiazole ring system. X-ray analysis demonstrates that both 2-bromothiazolo[5,4-*d*]-thiazole and 2,5-dibromothiazolo[5,4-*d*]thiazole are planar structures, with strongly manifested π-stacking in the solid state. Theoretical analysis of the pyridine-catalyzed halogenation (*MP2/6-31+G(d)* and *B3LYP/6-31+G(d)* calculations) reveals that introduction of one halogen actually leads to a slightly enhanced reactivity towards further halogenation. Several halogenation mechanisms have been investigated: 1) The direct C-halogenation with N-halopyridine as electrophile; 2) C-halogenation *via* intermediate N-halogenation, and 3) C-halogenation following an addition – elimination pathway, with intermediate formation of a cyclic halonium ion. The theoretical studies suggest that the direct C-halogenation is the favored mechanism.

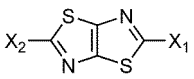
J. Heterocyclic Chem., **45**, 811 (2008).

INTRODUCTION

High-carrier mobility organic molecules and polymers are essential for the preparation of efficient flexible solar cells, flexible light-emitting displays and related microelectronic devices. The majority of available polymeric materials with potential use in such devices are of the p-type, generating considerable interest in the design and synthesis of materials with enhanced electron-accepting properties and enhanced charge carrier mobilities. One such compound is thiazolo[5,4-*d*]thiazole **1** (TTZ), a heterocyclic, electron-deficient molecule. TTZ derivatives have been reported recently in works focused on the preparation of soluble electron-transporting copolymers for organic light-emitting diodes (OLED)[1] as well as works on *n*-type semiconductors for organic field-effect transistors (OFET).[2-4] The incorporation of the TTZ unit has been found advantageous from several different perspectives: 1) X-ray analysis of several derivatives of TTZ demonstrated that these structures tend to stack well, leading to tightly packed arrangements in the solid state and short inter-molecular distances.[2,3,5-7] This should lead to enhanced charge mobility; 2) In addition to π-stacking, the lack of peripheral H-atoms in 2,5-disubstituted TTZ derivatives may very well lead to closer lateral interactions, further improving charge mobility; 3) The tight packing in the solid state should be beneficial for the chemical stability of TTZ-based materials, since it would diminish physical contact between any aggressive reagents and the molecules of the material in the solid state. The absence of H-atoms in the core should enhance stability as well; 4) TTZ and its conjugated derivatives have been shown to exhibit planar or nearly planar geometry[2,3], which would correspond to smaller reorganization energy upon ionization, a fact that would also lead to enhanced charge mobility.

The electron-accepting ability of thiazolo[5,4-*d*]thiazole is predicted to dramatically increase upon direct linkage of several TTZ units, according to B3LYP calculations.[8] In light of this, we were interested in the preparation of TTZ oligomers. Our investigation necessitated the synthesis of some mono- and dihalogenated derivatives of thiazolo[5,4-*d*]thiazole (Compounds **2a,b** and **3a,b**), which are the first examples of direct electrophilic aromatic substitution in the thiazolo[5,4-*d*]thiazole ring system. The current report describes the synthetic methodology for chlorination and bromination of **1**, theoretical mechanistic investigation of these processes, and X-ray analysis of some of the halogenated derivatives.

RESULTS AND DISCUSSION



1: $X_1 = X_2 = H$
2a: $X_1 = Cl$, $X_2 = H$; **2b**: $X_1 = Br$, $X_2 = H$
3a: $X_1 = X_2 = Cl$; **3b**: $X_1 = X_2 = Br$

A. Synthesis. The parent thiazolo[5,4-*d*]thiazole **1** was used as a starting material in the preparation of the halogenated derivatives. The synthesis of **1** was optimized by significantly modifying the original procedure of Ketcham *et al.*[9], to avoid the use of large amounts of pyridine and facilitate the workup process (Scheme 1). Accordingly, pyridine was completely eliminated as a solvent, replaced by a 1:1 mixture of *t*-BuOH and water, in the presence of phase-transfer catalyst (*Aliquat 336*). The major difficulty in the isolation of the diacid **5** stems from the poor water solubility of its dipotassium salt, which is therefore not in solution but mixed with the MnO_2 precipitation. Preparations in the past have coped with this issue by repeated extraction of the precipitate with large volumes of boiling water, solubilizing eventually the dipotassium salt.[9] We have replaced this lengthy protocol with a suspension of the oxidation precipitate in an aqueous solution of $NaHSO_3$, leading to reduction and dissolution of the Mn-containing species. The dipotassium salt is then simply filtered, suspended in water and the mixture acidified with HCl to yield the diacid **5**. The latter is subjected to thermal decarboxylation to yield thiazolo[5,4-*d*]thiazole **1**.

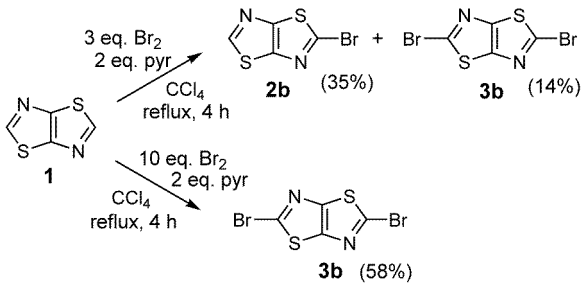
The thiazolo[5,4-*d*]thiazole ring system is electron deficient and inert towards electrophiles. In fact earlier studies had concluded that direct electrophilic aromatic substitution reactions, such as halogenation, nitration and sulfonation, were impossible.[9] There is a note in the work of Ketcham *et al.* on the preparation of 2-bromo-thiazolo[5,4-*d*]thiazole (**2b**) and 2,5-dibromo thiazolo[5,4-*d*]thiazole (**3b**) in low yields, based on the Hunsdiecker reaction, but the details of the syntheses have never been published.[9] Our original attempts were focused on indirect introduction of halogen, through the TTZ carbanion. Thus, the preparation of the bromide **2b** was attempted by treatment of **1** with *n*-BuLi, followed by reaction with CBr_4, as described in the literature for several related heterocyclic structures, including benzothiazole and thiazole.[10] The process yielded only trace amounts of compounds **2b** and **3b**. The results did not improve by the use of alternative bases, such as *t*-BuLi or LDA.

Further experiments and parallel theoretical studies[11] both suggested that the thiazolo[5,4-*d*]thiazole carbanion was most likely a highly unstable species that readily undergoes ring opening, analogous to the recently reported for the anions of oxazole and benzoxazole.[12] Hence, we decided to seek routes avoiding the use of strongly basic conditions. Following a recommended protocol for highly deactivated substrates, we attempted bromination with NBS in 100% H_2SO_4, which led however to quantitative isolation of unreacted starting material.[13] Also unsuccessful was the attempted chlorination with trichloroisocyanuric acid (TCICA) in 100% H_2SO_4. A plausible explanation for these failures could be based on the protonation of TTZ in the strongly acidic conditions, which would further diminish its reactivity in electrophilic aromatic substitution reactions.

Thus, after several initial attempts, the only viable strategy that remained was to avoid both strongly acidic and strongly basic conditions. Successful bromination was eventually carried out with elemental bromine, in the presence of pyridine (Scheme 2). Both bromide **2b** and dibromide **3b** were prepared utilizing the same approach, with variation of the relative quantity of bromine and reaction time. Best yields of **2b** were obtained using moderate excess of Br_2 and termination of the reaction prior to complete consumption of the starting material **1**. Extended reaction times or larger excess of Br_2 drive the process to complete dibromination. Dibromide **3b** was obtained in good yield upon reaction with large excess of bromine/pyridine, in refluxing CCl_4.

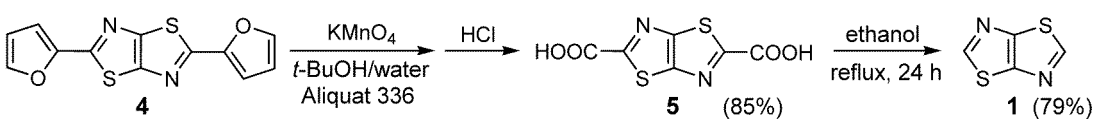
Successful mono- and dichlorination of thiazolo[5,4-*d*]-thiazole was accomplished using excess TCICA, in refluxing CCl_4 (Scheme 3). Just as in the case of bromination, described above, it is not possible to selectively monochlorinate thiazolo[5,4-*d*]thiazole in these conditions. Prior to consumption of the starting material, the monochlorinated product **2a** starts to undergo further chlorination, yielding **3a**, even when the reaction was conducted with one equivalent of TCICA. In the latter case,

Scheme 2



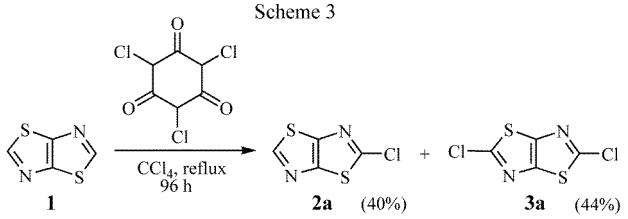
after 24 h at reflux, the reaction mixture consisted of approximately 75% TTZ and 25% of **2a** (GC – MS results). However, after 48 h the mixture showed approximate

Scheme 1



composition of 60% TTZ, 35% of **2a** and 5% of **3a** (GC – MS), and the quantity of the latter continued to grow with prolonged reaction time. However, the reaction could not be brought to completion under these conditions, most likely due to thermal degradation of TCICA over a long period of time at the reflux temperature.

Scheme 3



B. X-ray Structural Studies. X-ray crystallographic analysis was carried out on compounds **2b** and **3b** and ORTEP plots are shown in Figure 1. In the case of **2b** there are two molecules per asymmetric unit and no smaller cell could be found. The dibromide **3b** is a highly symmetric structure with an inversion center at the middle point of the C(2) – C(2i) bond. Selected structural parameters for both molecules are shown in Table 1, and are compared to the values for thiazolo[5,4-*d*]thiazole (**1**).[14] In structure **2b** the asymmetrical substitution at the 2- and 5-positions causes slight differences in the corresponding bond distances and bond angles in the two fused thiazole rings. Similar to other TTZ derivatives, there are differences in the lengths of the two formally single C – S bonds in each of the thiazole rings, e.g. C(1) – S(1) vs. C(2) – S(1).[6,14] Such difference, combined with the fact that the central C(2) – C(3) bond is longer than a typical C = C bond, has been explained on the basis of resonance delocalization.[6,14] Structures **2b** and **3b** are essentially planar, as evidenced by the values of the dihedral angles in the fused ring system.

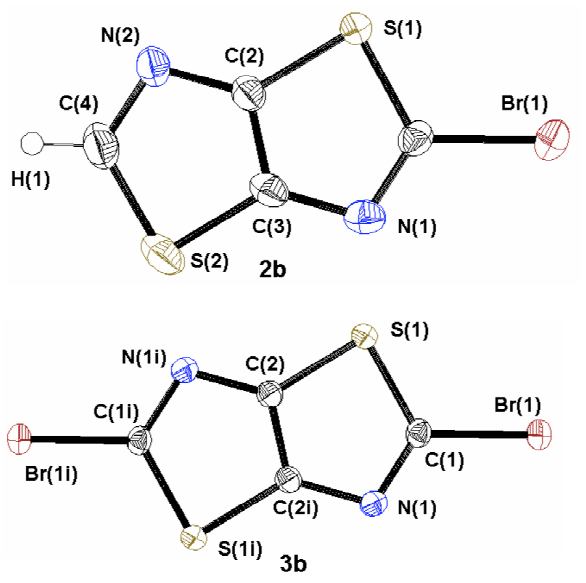


Figure 1. *ORTEP* drawings of 2-bromothiazolo[5,4-*d*]thiazole (**2b**) and 2,5-dibromothiazolo[5,4-*d*]thiazole (**3b**). The thermal ellipsoids are drawn at 50% probability. Hydrogen atom is given an arbitrary radius.

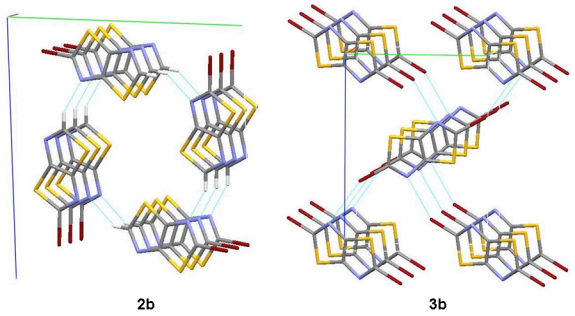


Figure 2. Matrix packing plots for 2-bromothiazolo[5,4-*d*]thiazole (**2b**) and 2,5-dibromothiazolo[5,4-*d*]thiazole (**3b**), looking down the *a*-axis. Dashed blue lines show close contacts.

Table 1 also lists calculated structural parameters, obtained from *B3LYP/6-31+G(d)* optimizations. Overall, the theoretical values are in good to excellent agreement with the experimental results.

Plots of the crystal packing for **2b** and **3b**, along the *a*-axis, are shown in Figure 2. The individual molecules are arranged in columnar structures, with strongly manifested π-stacking. The distance between the π-stacked molecules in a column is about 3.90 Å in **2b** and 3.96 Å in **3b**. The stacking is not perfect, neighboring molecules being offset by approximately 0.90 Å in **2b** and 1.44 Å in **3b**. In the crystal structure of compound **2b** there are several short lateral contacts with distances less than the sum of the van der Waals radii: S -- N (2.95 Å), N -- H (2.52 Å), N -- N (3.07 Å), C -- N (3.24 Å) and Br -- Br (3.62 Å). In the crystal structure of **3b** there is a lateral contact Br -- N with a value of 3.09 Å

C. Mechanism of pyridine-catalyzed halogenation of thiazolo[5,4-d]thiazole – a theoretical investigation. Experimental studies on both chlorination and bromination showed that the process cannot be stopped at the monohalogenated derivative, even though thiazolo[5,4-*d*]-thiazole is very deactivated towards S_EAr reactions. TLC and GC-MS analysis demonstrated that generation of some quantity of the monohalogenated derivative is associated with subsequent appearance of the dihalogenated material, the latter steadily increasing in quantity over time, prior to consumption of the parent thiazolo[5,4-*d*]thiazole. This result seems to suggest that the reactivity of the parent structure is not reduced upon monohalogenation, a somewhat counterintuitive notion. We decided, therefore, to investigate the halogenation process theoretically. All calculations were performed using the *Gaussian03/GaussView* software package[15], employing both second-order perturbation theory (*MP2/6-31+G(d)*)

Table 1

Selected experimental (X-ray analysis, regular text) and theoretical (italicized text) bond lengths (Å), angles (deg) and dihedral angles (deg) for 2-bromothiazolo[5,4-*d*]thiazole **2b**, 2,5-dibromothiazolo[5,4-*d*]thiazole **3b** and thiazolo[5,4-*d*]thiazole (**1**). Theoretical values from *B3LYP/6-31+G(d)* calculations.

Parameter [a]	**2b**			**3b**		**1** [b]	
	Experimental Molecule 1	Experimental Molecule 2	B3LYP	Experimental	B3LYP	Experimental	B3LYP
C(1) – S(1)	1.740(3)	1.737(3)	*1.769*	1.738(2)	*1.769*	1.736(2)	*1.764*
C(2) – S(1)	1.735(3)	1.732(3)	*1.746*	1.730(2)	*1.746*	1.719(2)	*1.742*
C(1) – N(1)	1.297(3)	1.297(4)	*1.297*	1.304(3)	*1.298*	1.296(3)	*1.306*
C(3) – N(1)	1.376(4)	1.376(3)	*1.365*	1.377(3)	*1.364*	1.368(2)	*1.363*
C(3) – S(2)	1.722(3)	1.723(3)	*1.741*	1.730(2)	*1.746*	1.719(2)	*1.742*
C(4) – S(2)	1.729(3)	1.735(3)	*1.764*	1.738(2)	*1.770*	1.736(2)	*1.764*
C(2) – N(2)	1.366(4)	1.372(3)	*1.361*	1.377(3)	*1.364*	1.368(2)	*1.363*
C(4) – N(2)	1.317(4)	1.304(4)	*1.306*	1.304(3)	*1.298*	1.296(3)	*1.306*
C(1) – Br(1)	1.876(3)	1.880(3)	*1.878*	1.870(2)	*1.877*	-	
C(4) – H(1)	0.9500	0.9500	*1.084*	-	-	0.95(3)	*1.084*
C(2) – C(3)	1.366(4)	1.366(4)	*1.386*	1.364(4)	*1.383*	1.372(3)	*1.388*
C(2) – S(1) – C(1)	86.97(13)	86.87(13)	*87.18*	87.23 (11)	*87.12*	87.7(1)	*87.66*
C(1) – N(1) – C(3)	106.6(2)	106.4(2)	*108.19*	106.7(2)	*108.18*	108.0(2)	*108.55*
N(1) – C(3) – C(2) – N(2)	179.7(2)	179.6(2)	*180.00*	180.00	*180.00*	180.00	*180.00*
S(1) – C(2) – C(3) – S(2)	179.66(14)	179.83(13)	*179.99*	180.00	*180.00*	180.00	*180.00*

[a] Atom labels in accordance with the crystallographic designation for compound **2b**. [b] Values from Ref. [14]

[16-19] and DFT (*B3LYP/6-31+G(d)*).[20-22] Minima and transition state structures were validated by subsequent frequency calculations at the same level of theory. All minimum structures had sets of only positive second derivatives, while transition state structures all had one imaginary frequency. ZPE corrections were not scaled. In some cases, the relationship of minima and connecting transition states was further verified by *IRC* calculations. [23,24] Transition state searches were conducted employing the Transit-Guided Quasi-Newton method (STQN, opt = qst2), or the Berny algorithm (opt = TS). [25,26] Calculations were conducted with Halogen = Cl.

Previous studies on the mechanism of pyridine-catalyzed halogentation reactions have revealed certain complexity of the process and the involvement of more than one active species[27], one of them being the N-halopyridinium ion[28,29], which we used as the actual electrophilic agent in our theoretical analysis. Three

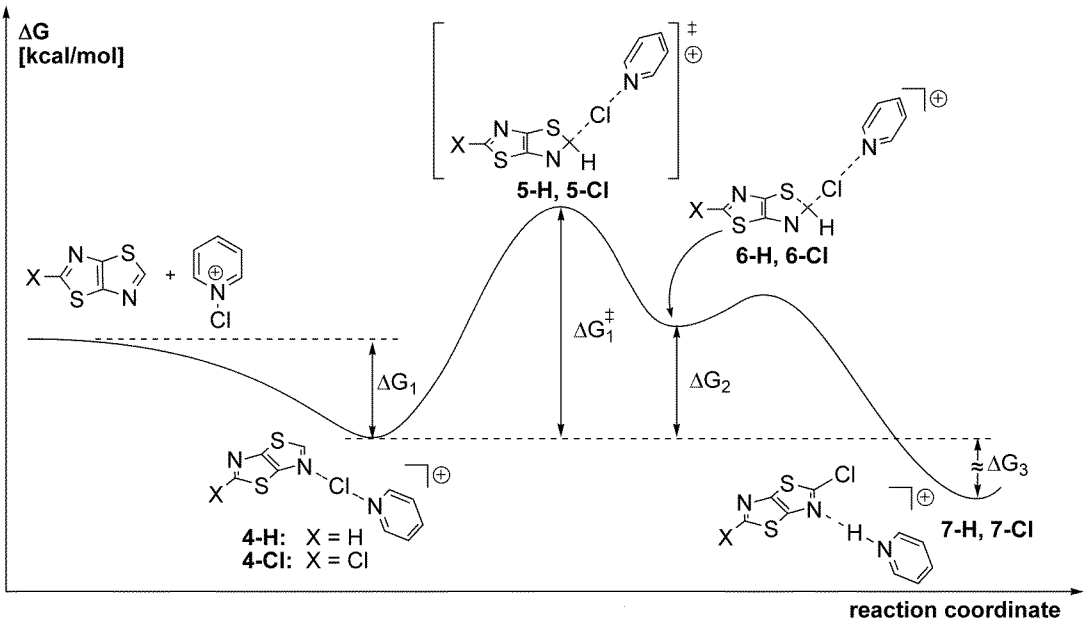


Figure 3. Calculated Gibbs free energy profile for the pyridine-catalyzed chlorination of thiazolo[5,4-*d*]thiazole **1** (X = H) or 2-chlorothiazolo[5,4-*d*]thiazole **2a** (X = Cl), following a mechanism for direct C-chlorination. The *B3LYP/6-31+G(d)* and *MP2/6-31+G(d)* profiles contain equal in number and structurally similar stationary points.

different mechanisms were investigated: 1) A direct C-chlorination mechanism with N-chloropyridinium ion as the electrophile; 2) C-chlorination *via* intermediate N-chlorination, and 3) C-chlorination following an addition – elimination mechanism, with a cyclic chloronium ion as the key intermediate. Calculated results for the direct C-chlorination mechanism are shown in Figure 3 (Gibbs free energy profile), Figure 4 (Optimized structures of the stationary points from the *B3LYP/6-31+G(d)* calculations), and Table 2 (relative Gibbs free energy values for the stationary points).

The direct C-chlorination mechanism involves the formation of an initial association complex of pyridine and compound **1** (or **2a**), in which the nitrogen centers are both coordinated to chlorine (Structure **4-H** or **4-Cl**, Figure 4). This initial complex is converted to a classical σ-complex (**6-H** or **6-Cl**) *via* transition state **5**, in the rate-determining step. The step involves a concerted shift of the N-chloropyridinium unit and its coordination to the carbon center of the TTZ ring. Deprotonation of the σ-complex leads to the chlorinated product **7-H** or **7-Cl**, with a pyridinium ion coordinated to one of the nitrogen centers.

The relative Gibbs free energy values are listed in Table 2. It is clearly seen that the *B3LYP/6-31+G(d)* calculations provide unrealistically low values, which would correspond to exceedingly fast conversion rates. Activation barriers are about two times larger at the *MP2/6-31+G(d)* level. DFT and MP2 predict comparable relative stabilities of the initial complexes **4-H** (**4-Cl**), but the values for the barrier of the subsequent rate-determining step are considerably higher at the MP2 level. According to both the MP2 and DFT calculations the reactions have considerable negative Gibbs free energy values.

Values in Table 2 also demonstrate that the introduction of one chlorine does not affect adversely the reactivity of the thiazolo[5,4-*d*]thiazole ring. On the contrary, according to the calculations the rate-determining step for chlorination of **2a**, compared to chlorination of **1**, has an activation barrier that is 1.6 kcal/mol or 2.8 kcal/mol lower, at the *B3LYP/6-31+G(d)* or *MP2/6-31+G(d)* levels respectively. A rationale for these results can be presented, in terms of simple resonance structures, as shown in Figure 5. Some stabilization of the σ-complex **6** and the transition state **5** can be derived by the presence of chlorine in the molecule and can be pictured in terms of conjugation of a lone pair at the chlorine center with the ring π-system. In support of that notion, the calculated C – Cl distances in **6-Cl** and **5-Cl** are 1.68 Å and 1.70 Å respectively, compared to 1.73 Å in **2a**, *i.e.* some shortening of the C – Cl bond is indeed observed.

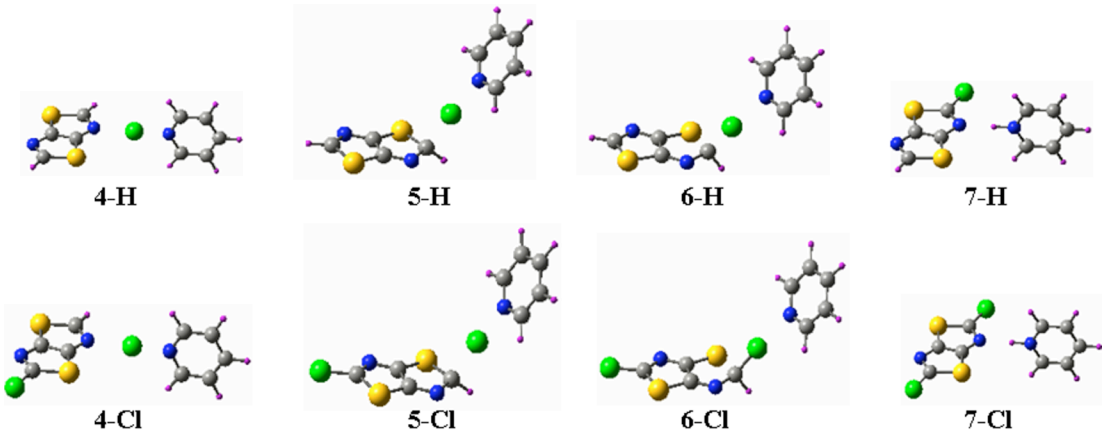


Figure 4. Optimized structures of stationary points for the pyridine-catalyzed chlorination of thiazolo[5,4-*d*]thiazole **1** and 2-chloro-thiazolo[5,4-*d*]thiazole **2a**, according to the direct C-chlorination mechanism. Structures shown in the figure are from *B3LYP/6-31+G(d)* optimizations.

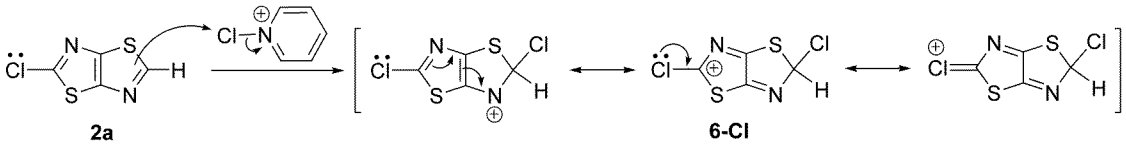


Figure 5. Resonance stabilization of σ-complex **6-Cl** by the chlorine center.

For some N-containing heterocycles, such as imidazoles, an alternative pathway for C-halogenation, involving an intermediate N-halogenation, has been suggested in certain cases.[30] Such pathway was identified for **1** and **2a** and the results from *B3LYP/6-31+G(d)* calculations are presented in Figure 6. N-chlorination of the thiazolo[5,4-*d*]thiazole ring by the full transfer of Cl to the N-atom of **1** or **2a**, leads to conversion of complex **4-H** (**4-Cl**) to the local minimum structure **9-H** (**9-Cl**), which is about 20 kcal/mol higher in energy. A [1,2]-shift of Cl from nitrogen to the adjacent carbon center, *via* transition state **10-H (10-Cl)**, generates the σ-complex **11-H (11-Cl)**, in a process with an activation barrier of about 30 kcal/mol. Complex **11** undergoes deprotonation to yield the chlorinated product **7-H** (**7-Cl**). The results, however, clearly indicate that such route for C-chlorination, *via* intermediate N-chlorination, is a much higher energy pathway for both thiazolo[5,4-*d*]thiazoles.

An addition – elimination mechanism was investigated as a third plausible pathway. A key intermediate, if such mechanism is followed, is the corresponding cyclic chloronium ion. However, our calculations demonstrated that such species could not be identified as a distinct minimum structure, at either the *B3LYP/6-31+G(d)* or the *MP2/6-31+G(d)* level.

CONCLUSIONS

The goal of this research project was the preparation and characterization of several halogenated derivatives of thiazolo[5,4-*d*]thiazole. Our investigation has led to the development of a more efficient and environmentally sound methodology for the generation of thiazolo[5,4-*d*]-thiazoledicarboxylic acid **5** and thiazolo[5,4-*d*]thiazole **1**. In addition, we have successfully conducted the first electrophilic aromatic substitution reactions of thiazolo[5,4-*d*]thiazole, resulting in the generation of mono- and dihalogenated derivatives **2a,b** and **3a,b**.

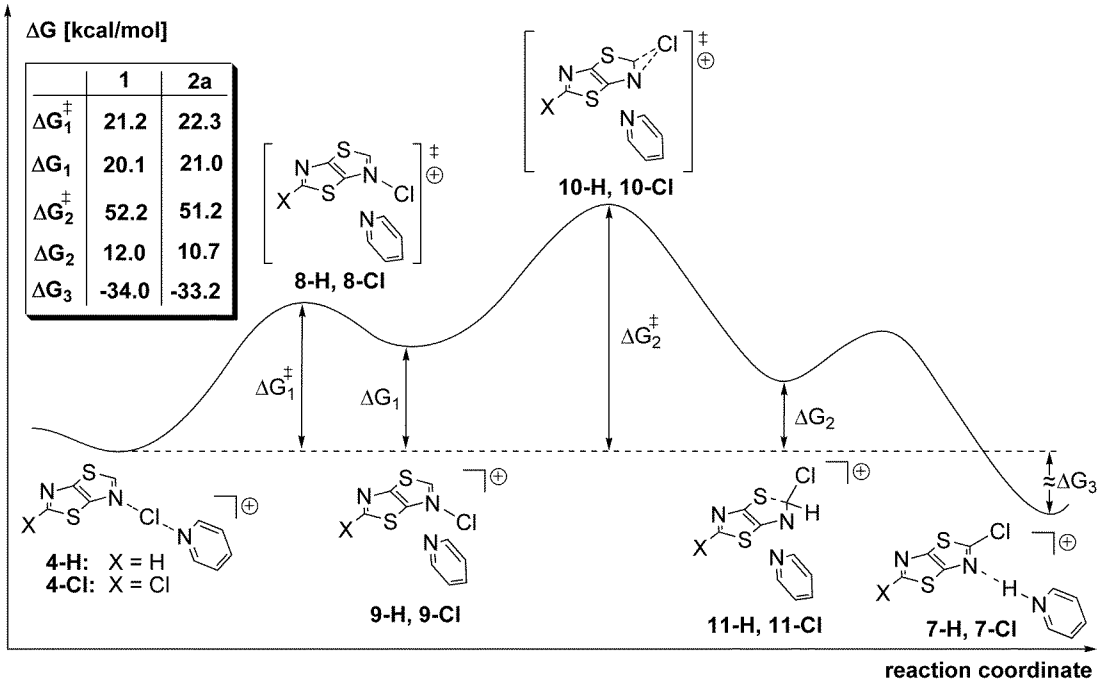


Figure 6. Calculated Gibbs free energy profiles for the pyridine-catalyzed chlorination of thiazolo[5,4-*d*]thiazole **1** (X = H) and 2-chlorothiazolo[5,4-*d*]thiazole **2a** (X = Cl), following a mechanism for C-chlorination *via* intermediate N-chlorination. Gibbs free energy differences in [kcal/mol]. Data from *B3LYP/6-31+G(d)* calculations.

Table 2

Relative Gibbs free energies, in kcal/mol, of the stationary points on the direct C-chlorination pathway (see Figure 3), calculated at the *MP2/6-31+G(d)* (**bold text**) or *B3LYP/6-31+G(d)* (regular text) levels of theory.

Structure	ΔG_1		$\Delta G_1^{\neq}$		ΔG_2		ΔG_3	
	MP2	B3LYP	**MP2**	B3LYP	**MP2**	B3LYP	**MP2**	B3LYP
1	**-7.7**	-5.1	**+25.6**	+14.2	**+23.1**	+12.6	**-38.2**	-34.0
2a	**-6.3**	-4.1	**+22.8**	+12.6	**+19.8**	+10.1	**-38.1**	-33.2

High-quality X-ray structures of 2-bromothiazolo[5,4-*d*]thiazole (**2b**) and 2,5-dibromothiazolo[5,4-*d*]thiazole (**3b**) have shown both of them to be planar structures, with π-stacking in the solid phase.

Theoretical analysis of the pyridine-catalyzed chlorination (*MP2/6-31+G(d)* and *B3LYP/6-31+G(d)* calculations) has revealed two distinct pathways: 1) A direct C-chlorination, with an N-chloropyridinium cation as the electrophile, and 2) A C-chlorination through intermediate N-chlorination. Calculations indicate that pathway (2) is a much higher energy route. The calculations have demonstrated that introduction of one chlorine actually leads to a slightly enhanced reactivity of the ring system.

EXPERIMENTAL

^{1}H and ^{13}C spectra were recorded at 300 MHz and 75 MHz respectively and referenced to the solvent ($CDCl_3$: 7.27 ppm and 77.0 ppm; DMSO-d_6: 2.49 ppm and 39.5 ppm). Mass spectrometry measurements were performed on a Hewlett-Packard 5890 instrument. Elemental analysis was provided by Atlantic Microlab, Norcross, GA. X-ray data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, S146 Kolthoff Hall, Department of Chemistry, University of Minnesota. X-ray structures were obtained on a Siemens SMART Platform CCD diffractometer with graphite monochromatic MoK_α radiation.[31] All quantum mechanical calculations were performed utilizing the Gaussian03-Linda/GaussView software package[15] on a Linux-operated cluster (QuantumCube QS4-2400C by Parallel Quantum Solutions, Fayetteville, AR). The preparation of compounds **1** and **5**, although previously reported[9], is described in detail, since the synthetic protocol is substantially different from the one in the literature. Ketcham *et al.* have mentioned the preparation of both **2b** and **3b**, in low yields, utilizing the Hunsdiecker reaction[9], but the experimental details have never been published and there aren't any literature data available on either the mono- or dibromide. The preparation of 2,5-dichlorothiazolo[5,4-*d*]thiazole **3a** has been reported before, following a completely different method, form acyclic precursors.[32,33] We report its preparation by direct chlorination of **1**, together with previously unavailable NMR and MS data.

X-ray crystallography of 2-bromothiazolo[5,4-*d*]thiazole (2b). A crystal with approximate dimensions 0.20 x 0.20 x 0.10 mm^3 was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Siemens SMART Platform CCD diffractometer for a data collection at 173(2) K.[31] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 55 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 30 seconds and a detector distance of 4.954 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.80 Å. Four major sections of frames were collected with 0.50° steps in ω at four different φ settings and a detector position of -28° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[34] Final cell constants were calculated from the xyz centroids of 2266 strong reflections from the actual data collection after integration (SAINT).[35] The structure was solved using SIR97[36] and refined using SHELXL-97.[37] The space group *P*-1 was determined based on the lack of systematic absences and intensity statistics and had the following dimensions: a = 3.9026(8) Å, b = 12.389(3) Å, c = 13.827(3) Å, α = 86.769(2)°, β = 83.580(2)°, γ = 87.185(2)°, V = 662.7(3) Å^3. For Z = 4 and F.W. = 221.10, the calculated density is 2.216 g/cm^3. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares/difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1$ = 0.0311 and $wR2$ = 0.0591 (F^2, all data).

X-ray crystallography of 2,5-dibromothiazolo[5,4-*d*]-thiazole (3b). A crystal with approximate dimensions 0.40 x 0.09 x 0.04 mm^3 was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Siemens SMART Platform CCD diffractometer for a data collection at 173(2) K.[31] A preliminary set of cell constants was calculated from reflections harvested from four sets of 30 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 140 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 45 seconds and a detector distance of 4.914 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.77 Å. Three major sections of frames were collected with 0.50° steps in ω at three different φ settings and a detector position of -28° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[34] Final cell constants were calculated from the xyz centroids of 2265 strong reflections from the actual data collection after integration (SAINT).[35] The structure was solved using SHELXS-97 and refined using SHELXL-97.[37] The space group $P2_1/n$ was determined based on systematic absences and intensity statistics and had the following dimensions: a = 3.8749(7) Å, b = 8.3961(14) Å, c = 11.3208(19) Å, α = 90°, β = 94.353(2)°, γ = 90°, V = 367.25(11) Å^3. For Z = 2 and F.W. = 300.00, the calculated density is 2.713 g/cm^3. A Patterson map solution was calculated which provided the positions of the Br and S atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. The final full matrix least squares refinement converged to $R1$ = 0.0214 and $wR2$ = 0.0434 (F^2, all data).

2,5-Thiazolo[5,4-*d*]thiazoledicarboxylic acid (5). 2,5-Bis(2-furyl)thiazolo[5,4-*d*]thiazole **4** (3.30 g, 12.03 mmol) was suspended in *t*-butyl alcohol (130 mL) and the mixture heated to reflux. Heating was removed and water (30 mL) was added to the rapidly stirred mixture. Aliquat 336 (1.5 mL) was added followed by a portionwise addition of $KMnO_4$ (21.78 g, 137.82 mmol) at a rate such as to maintain a temperature of ~ 70 °C, accompanied by addition of water to a total amount of 100 mL.

Stirring was continued for 18 h at ambient temperature, the resultant brown solid was filtered through a fine fritted funnel and the filter cake suspended in an aqueous solution of $NaHSO_3$. The resultant mixture was stirred for 0.5 h, filtered and the white solid washed with water, followed by THF. The solid was then suspended in water (200 mL), the suspension cooled in an ice – water bath while conc. HCl was added to a *pH* of 0 – 1. The mixture was left standing for 0.5 h, filtered, the white solid washed with small amount of cold water and air-dried for 12 h to yield 2.73 g (85%) of 2,5-thiazolo[5,4-*d*]thiazoledicarboxylic acid **5**. Mp 208 – 209 °C (Lit. 212 °C).[9]

Thiazolo[5,4-*d*]thiazole (1). 2,5-Thiazolo[5,4-*d*]thiazole dicarboxylic acid **5** (2.73 g, 10.26 mmol) was suspended in 96% ethanol (200 mL) and the resultant mixture stirred at reflux for 24 h. The solution was cooled to ambient temperature and the solvent removed under reduced pressure. The solid residue was dissolved in small amount of CH_2Cl_2 and passed through a short silica gel column (Eluent CH_2Cl_2). The solvent was removed under reduced pressure to yield 1.16 g (79%) of thiazolo[5,4-*d*]-thiazole **1** as a white solid. Mp 149 – 150 °C (Lit. 150 – 151 °C).[9] ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 2H).

Chlorination of thiazolo[5,4-*d*]thiazole. Thiazolo[5,4-*d*]-thiazole **1** (0.20 g, 1.41 mmol) was dissolved in CCl_4 (15 mL). Trichloroisocyanuric acid, TCICA (3.27 g, 14.08 mmol) was added in one portion and the resultant mixture stirred at reflux for 7 days. TLC indicated complete conversion of the starting material. The mixture was vacuum filtered and the solid washed with CCl_4 (15 mL). The filtrate was concentrated under reduced pressure, the residue was re-dissolved in a small amount of hexane/CH_2Cl_2 mixture (3:1), and placed on a short silica gel column. The column was successively eluted with hexane, hexane:CH_2Cl_2 = 1:1 (collection of **3a**) and CH_2Cl_2 (collection of **2a**). Products were isolated after removal of the solvents under reduced pressure.

2-Chlorothiazolo[5,4-*d*]thiazole (2a). Isolated as a white solid (0.10 g, 40% yield). Further purification *via* recrystallization from methanol at – 30 °C yields colorless needles. Mp 57 – 59 °C. ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 150.4, 153.3, 154.0; MS *m/e* 178 ([M+2]$^+$, 30), 176 (M$^+$, 90), 115 (35), 88 (100), 70 (50). Anal. Calcd. for $C_4HClN_2S_2$: C, 27.20; H, 0.57; N, 15.86. Found: C, 27.50; H, 0.52; N, 15.81.

2,5-Dichlorothiazolo[5,4-*d*]thiazole (3a). Isolated as a white solid (0.13 g, 44% yield). Further purification *via* recrystallization from toluene at – 30 °C yields colorless needles. Mp 175 – 177 °C (Lit. 171 – 172 °C)[33]. ^{13}C NMR ($CDCl_3$) δ 145.3, 151.8; MS *m/e* 214 ([M+4]$^+$, 15), 212 ([M+2]$^+$, 65), 210 (M$^+$, 85), 88 (100), 70 (80). Anal. Calcd. for $C_4Cl_2N_2S_2$: C, 22.76; N, 13.27. Found: C, 22.98; N, 13.02.

Bromination of thiazolo[5,4-*d*]thiazole. Thiazolo[5,4-*d*]-thiazole **1** (0.65 g, 4.58 mmol) was dissolved in CCl_4 (30 mL). Pyridine (0.54 g, 6.87 mmol, 0.56 mL) was added, followed by bromine (1.10 g, 6.87 mmol, 0.35 mL). The resultant solution was stirred at reflux for 2 h, followed by addition of more pyridine (0.18 g, 2.29 mmol, 0.19 mL) and bromine (1.10 g, 6.87 mmol, 0.35 mL), and the stirring was continued at reflux for additional 2 h. The resultant mixture was poured into aq. $NaHSO_3$ to quench the excess bromine, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was separated on a silica gel column (Eluent CH_2Cl_2) with four major fractions collected. Fraction #1: 2,5-dibromothiazolo-[5,4-*d*]thiazole **3b**; Fraction #2: 3,5-dibromopyridine, identified by comparison with literature NMR data; Fraction #3: 2-bromothiazolo[5,4-*d*]thiazole **2b**; Fraction #4: thiazolo[5,4-*d*]-thiazole **1**, identified by TLC analysis and comparison with authentic NMR data. Substances were isolated after removal of the solvents under reduced pressure.

2-Bromothiazolo[5,4-*d*]thiazole (2b). Isolated as a colorless solid (0.35 g, 35% yield). Further purification *via* recrystallization from methanol at – 30 °C yields colorless needles. Mp 52 – 53 °C. ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 137.9, 147.7, 152.1, 154.2; MS *m/e* 222 ([M+2]$^+$, 48), 220 (M$^+$, 40), 88 (100), 70 (85). Anal. Calcd. for $C_4HBrN_2S_2$: C, 21.73; H, 0.46; N, 12.67. Found: C, 21.94; H, 0.47; N, 12.58.

2,5-Dibromothiazolo[5,4-*d*]thiazole (3b). Isolated as a bluish solid (0.19 g, 14% yield). Further purification *via* recrystallization from toluene at – 30 °C yields bluish needles. Mp 153 – 154 °C. ^{13}C NMR ($CDCl_3$) δ 137.7, 149.1; MS *m/e* 302 ([M+4]$^+$, 30), 300 ([M+2]$^+$, 48), 298 (M$^+$, 26), 88 (80), 70 (100). Anal. Calcd. for $C_4Br_2N_2S_2$: C, 16.01; N, 9.34. Found: C, 16.24; N, 9.31.

Dibromination of thiazolo[5,4-*d*]thiazole. Thiazolo[5,4-*d*]-thiazole **1** (0.46 g, 3.24 mmol) was dissolved in CCl_4 (20 mL). Pyridine (0.51 g, 6.48 mmol, 0.52 mL) was added, followed by bromine (5.18 g, 32.40 mmol, 1.66 mL). The resultant solution was stirred at reflux for 4 h and TLC analysis indicated complete consumption of the starting material. The mixture was poured into aq. $NaHSO_3$ and stirred until all excess bromine was reacted. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was separated on a silica gel column (Eluent CH_2Cl_2) to yield 0.56 g (58%) of **3b** as a bluish solid. Physical and spectral characteristics matched those of the sample obtained in the previous experiment.

Acknowledgements. We gratefully acknowledge the DoD High Performance Computing office for a grant of computer time and resources, for some of the computational results reported herein. Funding for V. Benin was provided by the American Society for Engineering Education, as part of the Air Force Summer Faculty Fellowship program (Summer 2006).

Supporting Information Available. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers **CCDC 625746** and **625747.** Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44–(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Calculated energies and thermodynamic parameters of optimized global minimum structures of compounds **2a,b** and **3a,b** are summarized in Table S1. Calculated energies and thermodynamic parameters of stationary points for the processes of pyridine-catalyzed chlorination of compounds **1** and **2a** are summarized in Tables S2 and S3.

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