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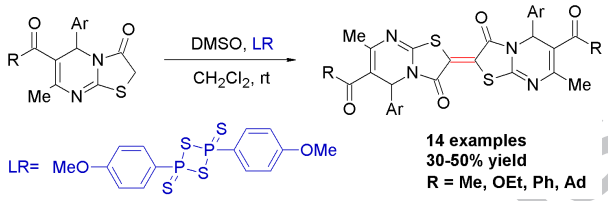

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Oxidation of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones with DMSO and Lawesson's reagent

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ABSTRACT

2,2'-Dimers with a central double bond were prepared by the oxidation of 5,6-disubstituted 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones with DMSO and Lawesson's reagent at room temperature. The role of DMSO as an oxidizing reagent was confirmed by NMR spectroscopy. The *E*-configuration of the central C=C bond for the two diastereomers of compound **8m** was proven by single crystal X-ray data. The dimeric thiazolopyrimidines were orange or red colored and absorption bands at 283-330 and 459-476 nm were observed in the UV spectra.

1. Introduction

Thiazolo[3,2-*a*]pyrimidines are readily available structures, and their derivatives show antimicrobial, antiparkinsonian, antiviral, anticancer, anti-inflammatory, antioxidant and other activities (Fig. 1).[1, 2d] Thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones are typically synthesized[2] by the reaction of 2-halogenocarboxylic acids or their derivatives with 2-thioxo-1,2,3,4-tetrahydropyrimidines prepared by one of the variants[3] of the Biginelli reaction. Thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones possess an active methylene group at C-2, and this feature has been used for the preparation of 2-benzylidene[4] (**1**, **2**, Fig. 1), 2-hydrazono,[5] and 2-oxyimino[6] derivatives.

Until now, oxidation of the thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one scaffold has not been reported, despite it being a simplified analogue of thioindigo. First synthesized by Friedländer in 1906,[7] novel derivatives have recently been used as sensitizers in solar cells,[8] for imaging and data storage[9] (Fig. 2), and as molecular switches.[10] The spectral and stability properties of thioindigo have been studied by experimental and theoretical methods,[11] and the H-shaped chromophore identified (Fig. 2).

The hemithioindigo scaffold, whose structure is similar to thiazolo[3,2-*a*]pyrimidine 2-benzylidene derivatives **1**, **2** (Fig. 1), has been used for the preparation of photoswitchable molecules.[10d]

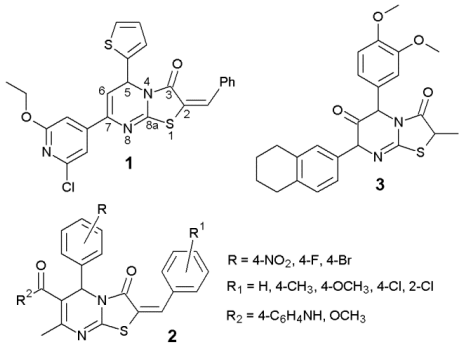

Figure 1. Selected derivatives of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones showing antiparkinsonian (**1**), anti-inflammatory (**2**) and antiviral (**3**) activities.

The synthesis of thioindigo derivatives and analogs[12] includes oxidation of the active methylene group with $K_3[Fe(CN)_6]$, air, selenium dioxide, or various condensation reactions. Recently a Ley-oxidation[13] with TPAP-NMO was employed for the dimerization of 3-*R*-4-oxotetrahydrothiophene-3-carboxylic acid, and this reagent gave slightly lower yields in comparison with $K_3[Fe(CN)_6]$.[14]

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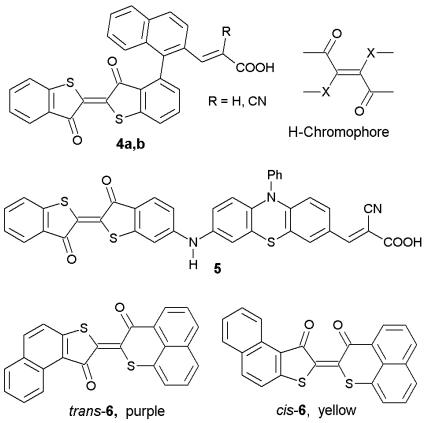
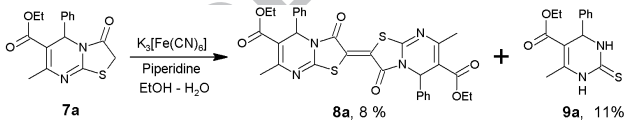


Figure 2. H-Chromophore and thioindigo derivatives applicable for solar cells (**4**, **5**) and imaging or data storage (**6**).

Herein, we report the synthesis of dimeric thioindigo-like molecules by the oxidation of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones.

2. Results and Discussion

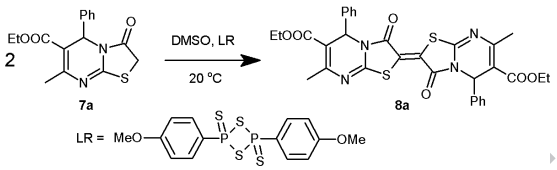
The oxidation of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one **7a** with $K_3[Fe(CN)_6]$ in the presence of piperidine[14] gave the dimeric product **8a** and 2-thioxo-1,2,3,4-tetrahydropyrimidine **9a** in low yields (Scheme 1). To avoid hydrolysis of the thiazolidine ring in water/ethanol, the oxidation reaction was examined with DMSO. Thiazolopyrimidine **7a** was stable in hot DMSO and did not react with well-known DMSO reagents[15] such as DMSO-P_2O_5, DMSO-acetic anhydride, DMSO-DCC, and DMSO-BF_3•OEt_2. Fortunately, the addition of P_4S_{10} gave product **8a** in low yield (14%). The reaction with excess DMSO and the more soluble Lawesson's reagent (LR) in CH_2Cl_2 at room temperature, afforded **8a** in 40% yield. Changing the solvent, temperature and excess of reagent did not improve the yield (Table 1), probably, due to possible cleavage of the dihydropyrimidine[16] or thiazolidine[17] rings in the thiazolopyrimidine scaffold.



Scheme 1. Oxidation of thiazolopyrimidine with $K_3[Fe(CN)_6]$. Reagents and conditions: **7a** (0.8 mmol), $K_3[Fe(CN)_6]$ (3.2 mmol), piperidine (3.2 mmol), EtOH (3 mL), H_2O (2 mL), 0.5 h at 60 °C then 0.5 h at 25 °C.

Using the optimal conditions (Entry 7), a number of thiazolopyrimidine thioindigo analogs **8a-n** were synthesized (Table 2). In all cases, thionation products or tetrahydropyrimidine-2-thiones were not isolated or detected by TLC. Recently, the oxidation of active methylene compounds with DMSO in the presence of a base has been developed.[18] However, the authors noted this procedure was not applicable to methylene groups neighboring a heteroatom as is the case in the thiazolo[3,2-*a*]pyrimidine-3(2*H*)-one (7**a**) structure.

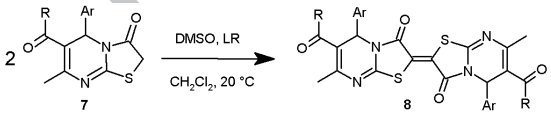
Table 1. Synthesis of dimeric thiazolo[3,2-*a*]pyrimidine **8a**



Entry[a]	**7a** : DMSO : LR	Solvent	Time (h)	Yield **8a** (%)[b]
1	1 : 1 : 1	CH_2Cl_2	10	12
2	1 : 2 : 1	CH_2Cl_2	10	18
3	1 : 5 : 1.5	CH_2Cl_2	10	37
4	1 : 5 : 1.5	$CHCl_3$	10	35
5	1 : 7 : 1.5	CH_2Cl_2	10	41
6	1 : 7 : 1.5	CH_2Cl_2	20	35
7	1 : 7 : 1.2	CH_2Cl_2	10	40
8	1 : 7 : 1.5	toluene	10	23
9	1 : 70 : 1.5	DMSO	10	20
10	1 : 7 : 1.5	CH_2Cl_2	5	29

[a] Reagents and conditions: **7a** (1 mmol), solvent (5 mL). [b] Isolated yield.

Table 2. Synthesis of dimeric thiazolo[3,2-*a*]pyrimidines[a]

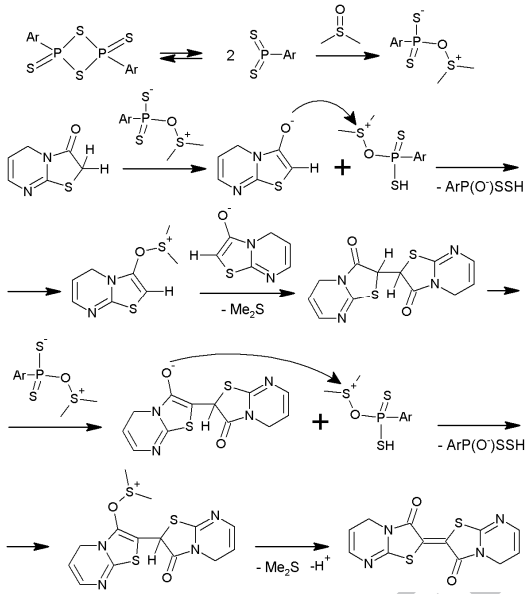


Product	R	Ar	Time (h)	Yield **8**[b] (%)
8a	OEt	Ph	10	40
8b	OEt	4-$MeOC_6H_4$	10	48
8c	OEt	2-$MeOC_6H_4$	16	32
8d	OEt	3,4-$(MeO)_2C_6H_3$	10	48
8e	OEt	4-(HO)-3-$(MeO)C_6H_3$	16	38
8f	OEt	2-ClC_6H_4	14	46
8g	Me	Ph	14	46
8h	Me	4-$MeOC_6H_4$	16	34
8i	Me	2-$MeOC_6H_4$	16	48
8j	Me	3,4-$(MeO)_2C_6H_3$	20	36
8k	Me	4-ClC_6H_4	16	36
8l	Me	2-ClC_6H_4	16	50
8m	Ph	Ph	16	36
8n	Ad[c]	Ph	24	30

[a] Reagents and conditions: **7** (1 mmol), LR (1.2 mmol), DMSO (7 mmol), CH_2Cl_2 (5 mL). [b] Isolated yield. [c] 1-Adamantyl.

No reaction of the thiazolopyrimidine-3(2*H*)-ones **7a-n** was observed with either LR or DMSO separately. Typically, LR transforms carbonyl compounds to thiocarbonyl ones,[19] but thionation products were not detected in this reaction. Also, heating a mixture of thiazolopyrimidine **7a** and LR in toluene did not give thiocarbonyl derivatives, whereas thiazolidine-4-ones were transformed to the corresponding thiones under similar conditions.[20] A dimeric product was isolated from the reaction of 3-(prop-2-en-1-yl)-2-thioxo-1,3-thiazolidin-4-one with LR in toluene at reflux, however, the dimer was fully thionated.[21] It is known that LR reacts with DMSO at elevated temperatures to yield dimethyl sulfide and dimethyl disulfide.[22] The reaction of LR with DMSO did not proceed in CH_2Cl_2 at rt without thiazolopyrimidine **7**. The reaction only started when all three components were mixed together; the solution became light red immediately, and the color became dark red after several hours.

Running the reaction of thiazolopyrimidine **7a** in an NMR tube with DMSO-d_6 as a reagent and $CDCl_3$ as a solvent, was then investigated. After preparing the reaction mixture, the doublet of one thiazole methylene proton was shifted to the low field (from 3.78 to 3.93 ppm), the singlet of the benzyl proton at C-5 was shifted to the high field (from 6.03 to 5.82 ppm), and a signal of the neighboring carbonyl carbon was slightly shifted to the high field (see ESI). These data confirm the formation of a complex due to the reaction of LR and DMSO with the thiazolopyrimidine. After 10 h the dimethyl sulfide septet signal at 17.1 ppm was observed in the ^{13}C NMR spectrum, which proves that DMSO is the oxidizing agent in the examined reaction. The proposed mechanism of the dimeric structures formation, probably, includes nucleophilic substitution at the sulfur atom[23] as a key step (Scheme 2).



Scheme 2. Proposed mechanism of thiazolopyrimidine oxidation with DMSO-LR (substituents at the pyrimidine ring are omitted for clarity).

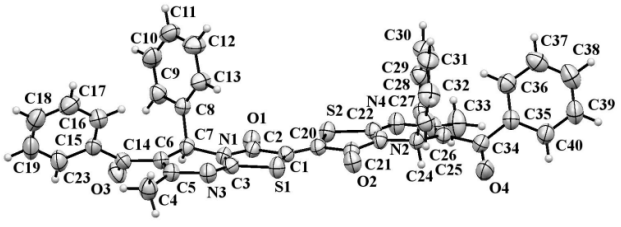


Figure 3. ORTEP drawing of *bis*-thiazolopyrimidine *RR*/*SS*-**8m** (50% probability level, *RR*-enantiomer is shown). Selected bond lengths (Å) and angles (°): C1-C20 (central C=C bond) 1.318, C5-C6-C14-O3 131.38.

Presumably, dimers **8a-n** are formed as mixtures of diastereomers, but in the NMR spectra only one set of signals was found for each compound. To confirm the dimeric structure, compound **8m** was crystallized from DMF for single crystal X-ray analysis. Fortunately, two types of crystals were found in the course of crystal selection for analysis. Single crystal X-ray analysis of two selected crystals showed that one is formed by the racemic *RR*/*SS* form and the other is formed by the *RS* *meso*-form (Fig. 3 and 4). Both isomers are crystallized as solvates with DMF and have an *E*-configuration of the central double bond. The *bis*-heterocyclic moieties of both molecules are planar in the limits 0.2 Å for *RR*/*SS*-**8m** (maximum deviation from the plane for the C_{sp3}-atoms) and 0.13 Å for *RS*-**8m** (maximum deviation from the plane for S-atoms).

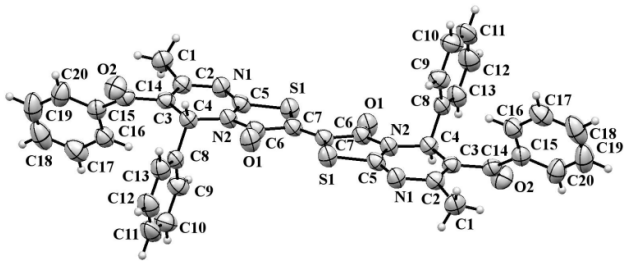
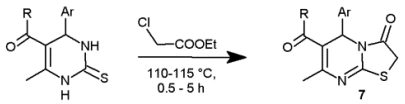


Figure 4. ORTEP drawing of *bis*-thiazolopyrimidine *RS*-**8m** (50% probability level)**.** Selected bond lengths (Å) and angles (°): C7-C7 (central C=C bond) 1.343, C2-C3-C14-O2 129.57.

Compounds **8a-n** are orange to red colored, and their UV spectra showed two absorption bands at 283-330 and 459-476 nm. TD-DFT calculations[11b] of the exited states using the PBE0 hybrid functional and the 6-311G+(2d,p) basis set gave an accurate prediction of the λ_{max} in the visible spectra for thioindigo derivatives. The calculations confirmed the larger λ_{max} values for the *trans*-isomers (519-591 nm) in comparison with the *cis*-isomers (467-515 nm). Diapason of λ_{max} for the *trans*-thiazolopyrimidine dimers **8a-n** matches the corresponding diapason for thioindigo *cis*-isomers (Fig. 3, 4). The pyrimidine ring in **8a-n** is not aromatic which causes the shift of the absorbtion band to shorter wavelengths.

The starting thiazolopyrimidines **7a-n** were prepared[2] by heating the corresponding 2-thioxo-1,2,3,4-tetrahydropyrimidine[3] (1 mmol) with ethyl chloroacetate (9.3 mmol) at 110-115 ºC for 0.5-5 h (see ESI and Table 3).

Table 3. Synthesis of thiazolo[3,2-*a*]pyrimidines



Compound	R	Ar	Time (h)	Yield **7** (%)[a]
7a	OEt	Ph	0.5	67
7b	OEt	4-$MeOC_6H_4$	0.5	65
7c	OEt	2-$MeOC_6H_4$	0.5	82
7d	OEt	3,4-$(MeO)_2C_6H_3$	0.5	62
7e	OEt	4-(HO)-3-(MeO)C_6H_3	0.5	54
7f	OEt	2-ClC_6H_4	0.5	61
7g	Me	Ph	0.5	52
7h	Me	4-$MeOC_6H_4$	0.5	42
7i	Me	2-$MeOC_6H_4$	0.5	51
7j	Me	3,4-$(MeO)_2C_6H_3$	0.5	47
7k	Me	4-ClC_6H_4	0.5	55
7l	Me	2-ClC_6H_4	0.5	40
7m	Ph	Ph	0.5	74
8n	Ad[b]	Ph	5	18

[a] Isolated yield. [b] 1-Adamantyl.

3. Conclusion

In summary, a new method was developed for the oxidative dimerization of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones using DMSO and Lawesson's reagent at rt. The dimers were prepared as a mixture of diastereomers with an *E*-configuration of the central double bond, and can possibly be used for the development of pigments, sensitizers in solar cells and molecular switches.

Acknowledgments

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Supplementary Material

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Highlights

- The oxidation of the thiazolo[3,2-a]pyrimidin-3(2H)-ones was studied for the first time.
- DMSO with Lawesson's reagent was employed as an oxidant for the first time.
- The reaction proceeds at room temperature selectively at C2 position.
- Novel thioindigo-like compounds were obtained.