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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.

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]

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 $K_3[Fe(CN)_6]$.[10d]

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

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[10d] 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[14] such as DMSO-P_2O_5, DMSO-acetic anhydride, DMSO-DCC, and DMSO-$BF_3{\cdot}OEt_2$. 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[15] or thiazolidine[16] rings in the thiazolopyrimidine scaffold.

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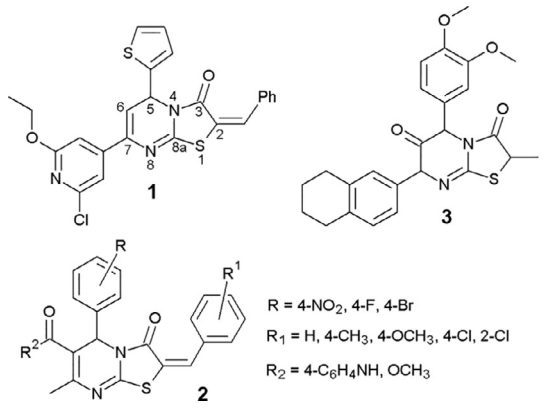


Fig. 1. Selected derivatives of thiazolo[3,2-*a*]pyrimidin-3(2*H*)-ones showing antiparkinsonian (**1**), anti-inflammatory (**2**) and antiviral (**3**) activities.

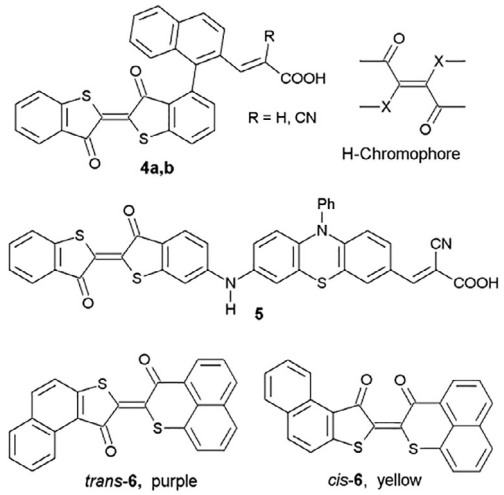
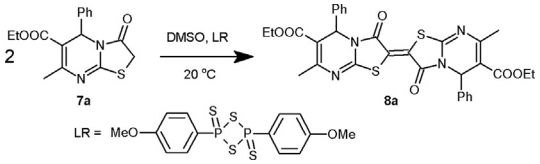


Fig. 2. H-Chromophore and thioindigo derivatives applicable for solar cells (**4**, **5**) and imaging or data storage (**6**).

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.[17] 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.

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,[18] 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

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



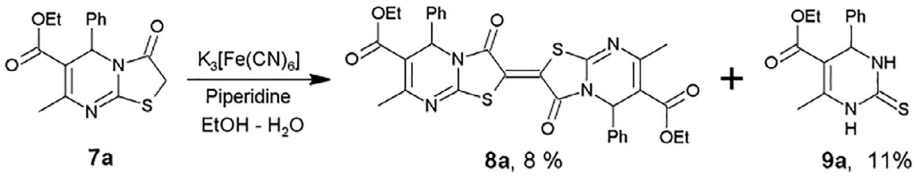
Entry[a]	**7a**: DMSO: LR	Solvent	Time (h)	Yield **8a** (%)[b]
1	1:1:1	CH_2Cl_2	10	12
2	1:2:1	CH_2Cl_2	10	18
3	1:5:1.5	CH_2Cl_2	10	37
4	1:5:1.5	$CHCl_3$	10	35
5	1:7:1.5	CH_2Cl_2	10	41
6	1:7:1.5	CH_2Cl_2	20	35
7	1:7:1.2	CH_2Cl_2	10	40
8	1:7:1.5	Toluene	10	23
9	1:70:1.5	DMSO	10	20
10	1:7:1.5	CH_2Cl_2	5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

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

to the corresponding thiones under similar conditions.[19] 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.[20] It is known that LR reacts with DMSO at elevated temperatures to yield dimethyl sulfide and dimethyl disulfide.[21] 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[22] as a key step (Scheme 2).

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.



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.