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New macrocyclic bistriazolophanes with thioindigo chromophore

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ABSTRACT

Bi(4-methoxycarbonyl-3-oxothiolan-2-ylidene) derivatives are prepared by oxidative dimerization of 4-oxotetrahydrothiophene-3-carboxylates with either TPAP–NMO or $K_3[Fe(CN)_6]$. The products are obtained as mixtures of four diastereoisomers due to (*E*)- or (*Z*)-configuration of the C–C double bond and relative *syn*- or *anti*-configuration of two stereocenters. The red compounds contain the prototype of the thioindigo chromophore. Their double bond configuration can be switched from (*E*) to (*Z*) by visible light. Two propargyl-functionalized thiolane monomers were clicked together by *para*-bis(azidoalkyl)benzene derivatives with $[Cu(\mu\text{-}OH)(tmeda)]_2Cl_2$ as the catalyst, thus, the subsequent oxidative dimerization yielded macrocyclic triazolophane products with the bi(thiolan-2-ylidene) unit only in relative *syn*-configuration.

1. Introduction

Thioindigo and its derivatives[1] are interesting materials, whose photochromic properties can be attributed to light-induced (*E*/*Z*)-isomerization.[2] Interestingly, the double benzo-annulation is not necessarily required in order to achieve colored compounds. For example, if only one benzothiophene ring is retained, so called hemithioindigo compounds are obtained, which are also interesting and well investigated photoswitchable dyes.[3] Moreover, compounds without any benzene ring, e.g., the bi(3-oxo-2-ylidene) motif itself, define a red chromophore with absorption maxima dependent on the double bond configuration.[1d,4]

Since the discovery of copper(I)-catalysis[5] of the Huisgen 1,3-dipolar cycloaddition of azides with alkynes,[6] this so called 'Click reaction'[7] has found widespread applications also for the formations of macrocyclic compounds. Since the 1,2,3-triazole moiety can be regarded as a steric and electronic mimic of a peptide bond,[8] it has, for example, been used for the preparation of macrocyclic peptidomimetics.[9] Triazoles have also been incorporated into macrocyclic oligosaccharides[10] or macrocyclic drugs like epothilone[11] and other macrocyclic 'drug-like' structures.[12] Apart from potentially biologically active compounds, triazole containing macrocycles have also found applications in several functional materials, like cation[13] or anion[14] receptors or materials for optoelectronic applications.[15]

In the course of our investigations on 3-oxotetrahydrothiophenecarboxylates as starting materials for the preparation of tetrahydro-1,4-thiazocin-3-ones[16] we have observed the formation of colored, dimeric oxidation products with the thioindigo chromophore, which were usually formed as mixtures of several diastereoisomers. In order to reduce the number of possible stereoisomers, we have formed macrocycles by applying the copper-catalyzed Huisgen 1,3-dipolar cycloaddition. In view of the recent focus[17] of triazolophanes as functional materials, as outlined above, we wish to report herein on our recent results and experiences with this class of hetero-macrocyclic compounds.

2. Results and discussion

Since quite a while we are interested in the enantioselective formation of quaternary stereocenters by conjugate addition reactions.[18] During these studies we have prepared racemic compound **2a** by iron-catalyzed reaction[19] of β-oxoester **1**[20] with methyl vinyl ketone (Scheme 1, Table 1). Since product **2a** gave no sufficient baseline resolution upon GLC on a chiral phase, we were looking for a fast and reliable derivatization of this compound for analytical purposes, which could be the oxidation of the cyclic thioether moiety to a sulfoxide or sulfone. After some experimentation with hydrogen peroxide and *m*CPBA, we have chosen the Ley-oxidation with TPAP–NMO[21] and isolated dimerization product **3a** in 39% yield as a red material. Compound **3a** was obtained as a mixture of

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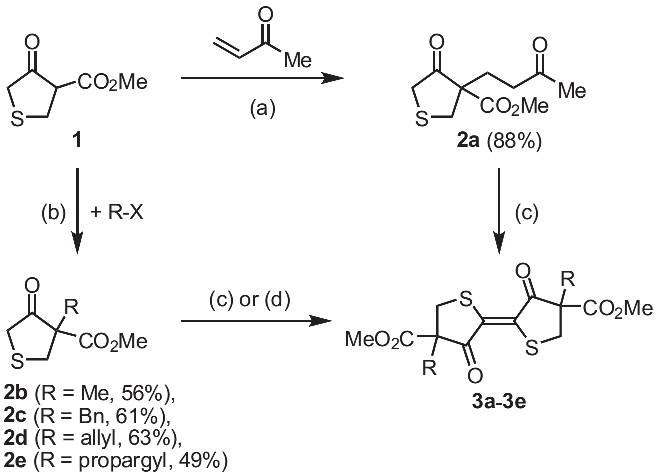
four unseparable diastereoisomers (dr 2.5:2.5:1:1) originating from three stereogenic elements: one C–C double bond being (*E*)- or (*Z*)-configurated [in Scheme 1 only the (*E*)-isomer is shown for simplicity] and two stereocenters being either in relative *meso*- or *rac*-configuration. The *meso*-diastereoisomer is the *anti*-compound with the (*E*)-double bond and the *syn*-isomer with the (*Z*)-configuration. The racemic diastereoisomers are *syn* for the (*E*)-double bond and *anti* for the (*Z*)-configuration. The two major diastereoisomers were assigned (vide infra) to be the (*E*)-configurated *meso*- and *rac*-compounds (dr 2.5:2.5), whereas the two minor isomers have the double bond in (*Z*)-configuration (*meso*/*rac* 1:1).



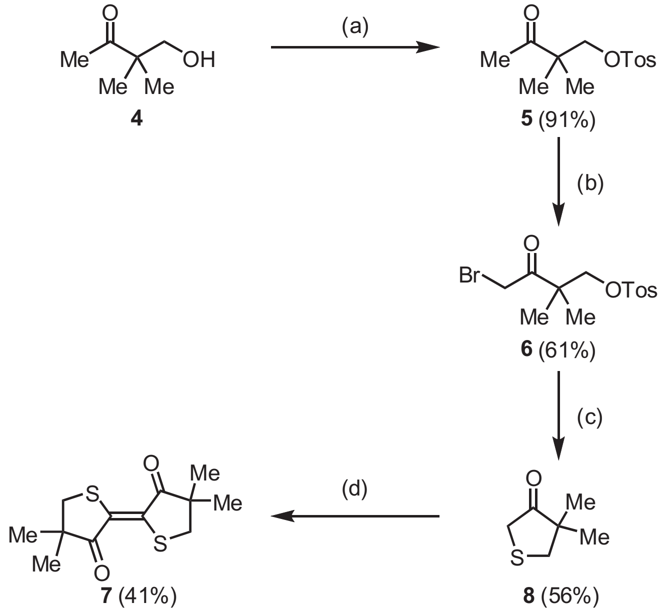
Scheme 1. Preparation of racemic starting materials **2** and dimers **3**. For compounds **3** only the (*E*)-isomers are shown for simplicity. For yields and residues R of products **3** see Table 1. Reagents and conditions: (a) 0.1 equiv $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, 23 °C, 2 d; (b) 2 equiv MeI (for **2b**) or 1.1 equiv RBr (for **2c**–**2e**), 2 equiv K_2CO_3, acetone, reflux, 1 h; (c) 3 equiv NMO, 0.05 equiv TPAP, mol. sieves 4 Å, MeCN, 16 h, 40 °C; (d) 4 equiv $K_3[Fe(CN)_6]$, 4 equiv piperidine, EtOH–H_2O, 60 °C, 0.5 h, then 23 °C, 0.5 h.

Despite the large number of investigations on the thioindigo chromophore[1d,4] no compounds like **3a** with two β-oxoester motifs were reported so far. Since we found switching the double bond configuration by visible light being an interesting issue, we have prepared four more congeners by alkylation of oxoester **1** with the respective halides. All compounds **2a**–**2e** have, by the way, been reported in the literature before,[22] but without full characterization data. Dimerization of compounds **2b**–**2e** was again achieved using TPAP–NMO (Table 1), but it turned out that application of $K_3[Fe(CN)_6]$ and piperidine, as originally suggested by Lüttke and co-workers,[4b] was much more efficient and often gave superior yields. Products **3b**–**3e** are again obtained as four diastereoisomers with (*E*)- and (*Z*)-ratios as given in Table 1 and with equal amounts of *rac*- and *meso*-isomers, respectively. An exception is compound **3e**, which is obtained with dr=13:6:2:1 [(*E*), (*E*), (*Z*), (*Z*)].

For comparison and assignment of (*E*)- and (*Z*)-isomers, we have prepared tetramethyl-derivative **7**, which was so far the standard compound in investigations of the thioindigo chromophore,[4] in four steps following a strategy suggested by Lüttke[23] and De Kimpe[24] (Scheme 2). The alcohol-function of aldol-compound **4** was activated with TosCl and the intermediate product **5** then α-brominated to give the 1,4-dielectrophile **6**, which was subsequently cyclized with Na_2S to give oxotetrahydrothiophene **8**. Oxidative dimerization to thioindigo-analog **7** was again achieved with $K_3[Fe(CN)_6]$ [41% yield, (*E*/*Z*)=2.2:1]. The UV/vis-spectrum of compound **7** showed a dominant absorption at 457 nm (see Table 2), which was assigned in agreement with the literature[4c] to be the (*E*)-isomer and a shoulder, which originated from the (*Z*)-isomer. Exposure to sunlight for six days shifted the (*E*/*Z*)-ratio to 1:7.2, which was followed by ^{13}C NMR (C_6D_6) and UV/vis (CH_2Cl_2).

Table 1
Oxidative dimerization of compound **2**. Conditions and yields

Product	R	Yield (*E*/*Z*) (TPAP–NMO)	Yield (*E*/*Z*) ($K_3[Fe(CN)_6]$)
3a	CH_2CH_2COMe	40% (2.5:1)	18% (20:1)
3b	Me	13% (2.1:1)	25% (5:1)
3c	Bn	26% (9.5:1)	46% (8:1)
3d	Allyl	31% (2.5:1)	31% (5.9:1)
3e	Propargyl	30% (5.7:1)	59% (6.3:1)



Scheme 2. Preparation of tetramethyl congener **7** [(*E*/*Z*)=2.2:1, only the (*E*)-isomer is shown for simplicity]. Reagents, conditions, and yields: (a) 1.2 equiv TosCl, pyridine, 23 °C, 16 h, 91%; (b) 1 equiv Br_2, $CHCl_3$, 61 °C, 1 h, 61%; (c) 2 equiv Na_2S aq, DMF, 80 °C, 1 h, 56%; (d) 4 equiv $K_3[Fe(CN)_6]$, 4 equiv piperidine, EtOH–H_2O, 60 °C, 0.5 h, then 23 °C, 0.5 h, 41%.

The same spectroscopic features were observed for compounds **3a**–**3e** (Table 2). The spectra are dominated by an absorption between 460 and 480 nm, respectively, which can be assigned to the major (*E*)-isomer, and a shoulder between 414 and 434 nm attributed to the (*Z*)-isomer. Exposure to sunlight for six days led to equilibrium mixtures, e.g., with (*E*/*Z*)=1:1.7 (for **3b**), (*E*/*Z*)=1:1.3 (for **3c**), or (*E*/*Z*)=1:1 (for **3e**), respectively. This equilibration was again followed by ^{13}C NMR (C_6D_6) and UV/vis (CH_2Cl_2). Each (*E*)- and (*Z*)-isomer showed a double signal set with dr 1:1 in the ^{13}C NMR spectra, which did not change upon irradiation and can therefore be attributed to the *rac*- and *meso*-diastereoisomers.

Table 2
Spectroscopic properties of compounds **3a**–**3e**, **7**, **11a**, and **11b** (CH_2Cl_2)

Compound (*E*/*Z*)	λ_{max}/nm (*E*)	λ_{max}/nm (*Z*)	log (ε/dm^3 mol^{-1} cm^{-1})	λ_{em}/nm (λ_{ex}/nm)	Φ
3a	464	414	3.47	533 (414), 543 (464)	0.001
3b	465	414	3.89	536 (414 or 465)	[a]
3c	475	434	3.88	558 (434 or 475)	[a]
3d	468	425	3.85	546 (425), 539 (468)	0.001
3e	479	439	3.87	541 (439 or 479)	[a]
7	457 (458)[b]	400 (408)[b]	3.81 (4.07)[b]	534 (400 or 457)	0.003
11a	479	440	3.89	542 (440 or 479)	0.001
11b	479	440	3.91	543 (440 or 479)	0.001

[a] Not determined.
[b] Literature value[4c] ($CHCl_3$).