Alkylidene[1,3]dithiolane-1,3-dioxides as Potent Michael-Type Acceptors

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Received 3 May 2006

Dedicated to Hansgeorg Schnöckel on the occasion of his 65th birthday

Abstract: Nucleophilic additions of enolates, piperidine and methanol to easily prepared alkylidene[1,3]dithiolane-1,3-dioxides afforded the respective adducts with good yields. Selectivities were strongly dependant from the steric hindrance of the substrate and reached 92:8 to ≥ 98:2 in additions to the phenyl-substituted bissulfoxide product.

Key words: nucleophilic additions, sulfoxides, thioacetals, Umpolung, stereoelectronic effects

Alkylidenebissulfoxides[1] have repeatedly been used in organic synthesis due to their electron-deficient double bond.[2] Since unsymmetrically substituted sulfoxides are chiral, these reactions can be led diastereoselectively. Aggarwal and co-workers used very successfully dithiane- and dithiolane-derived bissulfoxides of type **2** and **3** in epoxidations, cyclopropanations and cycloadditions (Figure 1).[3] The cleavage of the auxiliary liberating a carbonyl compound is achieved, for example, by Pummerer reaction.[3b,4] Malacria, Fensterbank et al. used bis(tolylsulfinyl)alkenes of type **1** in Michael-type additions and achieved excellent selectivities in the addition of enolates, cuprates and amines.[5] The stereoselectivities were explained in accordance to an X-ray crystallographic analysis of **1** (R = Ph) showing a π-stacking of the toluene moieties leaving only one side of the molecule free for an attack of the nucleophiles. Recently, we presented dithiane-derived bissulfoxides **2** as acceptors for nucleophilic additions and found high selectivities in the addition of enolates thought steric hindrance (X-ray crystallographic analysis of **2**, R = Ph) should be negligible.[6] We think that stereoelectronic effects have a significant influence and should be particularly considered in explanations of selectivities. The method presented by us has been used in an umpoled reaction for the synthesis of 1,4-dicarbonyl compounds.

In this letter we wish to report on the utilization of dithiolane-derived substrates **3** as strong Michael-type acceptors.

Cycloadditions with the parent methylene[1,3]dithiolane-1,3-dioxide **3a** (R = H) have been thoroughly investigated by Aggarwal et al.[3a,b,7] and the methyl derivative **3c** (R = Me) has been proposed as an intermediate once.[8] Nevertheless, a synthesis for substituted substrates which

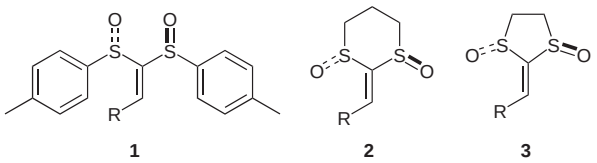
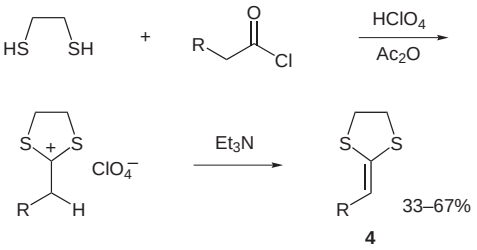


Figure 1

were mandatory for our investigations had not been published before our work.

We found that the previously used synthetic protocol[6,7] established for the dithiane-derived substrates **2** (Peterson olefination of dithiane and subsequent stereoselective oxidation of the sulfide moieties) is not applicable here. Deprotonation of dithiolane would induce a cycloreversion giving rise to the formation of ethene and dithioformate.[9] Consequently, we tested a method introduced by Okuyama et al. starting with ethane-1,2-dithiol and an acyl chloride.[9] Though yields were in the range of only 33–67%, this method could be used for the convenient and cheap synthesis of ample amounts of alkylidenedithiolanes **4** (Scheme 1).

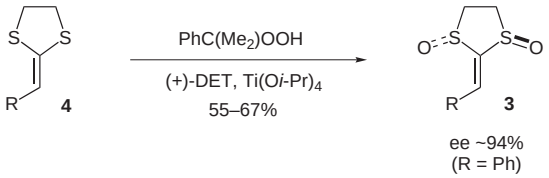


Scheme 1

Stereoselective oxidation of the sulfide moieties was achieved by slight modification of the protocol presented previously[6,10] avoiding basic conditions during the work-up process (Scheme 2, Table 1). Enantio- and diastereoselective oxidation with cumene hydroperoxide, diethyl tartrate (DET) and tetraisopropoxy titanate yielded the respective bissulfoxides in yields of 55–67%. The enantiomeric excess was determined for the phenyl-substituted bissulfoxide by means of a chiral shift reagent (α-methoxyphenylacetic acid, MPA)[11] to be 94%. The purity could be improved to ≥ 98% ee by a single recrystallization.

The dithiolane-derived alkylidenebissulfoxides turned out to be much more reactive than the respective dithiane-

SYNLETT 2006, No. 13, pp 2043–2046
Advanced online publication: 09.08.2006
DOI: 10.1055/s-2006-948202; Art ID: G16006ST



Scheme 2

Table 1 Synthesis of Dithiolane-Derived Bissulfoxides **3**

Entry	Compd	R	Yield (%)
1	**3b**	Ph	55[a]
2	**3c**	Me	67[b]
3	**3d**	Et	66[c]
4	**3e**	*i*-Pr	65
5	**3f**	*t*-Bu	63

[a] 94% ee; ≥98% ee after a single recrystallization.
[b] Formation of the methanol adduct (33%, 85:15).[12]
[c] Formation of the methanol adduct (16%, 88:12) and of 2-propen-1-yl[1,3]dithiolan-1,3-dioxide (14%).[12]

derived substrates what caused some problems already during the work-up process. Chromatography with dichloromethane and methanol on silica gel led to a significant addition of methanol to the electron-deficient double bond. The methanol adducts to **3c** and **3d** were isolated with 33% and 16% yield, respectively. The selectivity in these additions was about 85:15.

The structure of the methyl derivative **3c** could be revealed by X-ray crystallographic analysis of a co-crystal formed with its methanol adduct **7c** (major isomer, Figure 2).[13] In this view nucleophilic attack to **3c** should be possible preferentially from top left or bottom right (no oxygen prevents attack of the nucleophile) where an attack from the left should be less likely, especially for substituents bulkier than the methyl group.

We tested addition of the acetophenone enolate prepared from acetophenone and sodium hexamethyldisilazide (NaHMDS) and found that in fact best results were obtained with the bulky phenyl-substituted substrate **3b** leading to only one diastereomer (≥98:2, Scheme 3, Table 2, entry 1). Selectivities dropped with smaller substituents and – not astonishingly – almost vanished with a small methyl group present (55:45, entry 5). Here the nucleophile has to discriminate between a hydrogen atom and a marginally bulkier methyl group. Nevertheless, approach is preferred from the bottom (orientation as seen in Figure 2) which could be proven by X-ray crystallographic analyses of the enolate adduct **5b** (Figure 3) and the methanol adduct **7c** (Figure 2).[13]

The further-tested piperidine and malonate anion added to the bissulfoxide **3b** with high yields and selectivities (entries 6 and 7). This finding again proved the high reactiv-

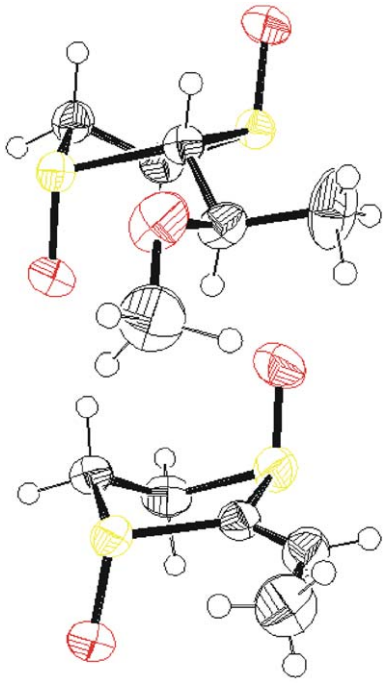
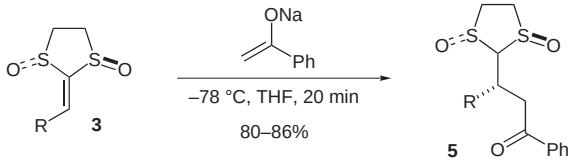


Figure 2 Structure of **3c** (bottom) and its methanol adduct (**7c**, major isomer) as formed during chromatography of **3c** with MeOH (co-crystal)[13]



Scheme 3

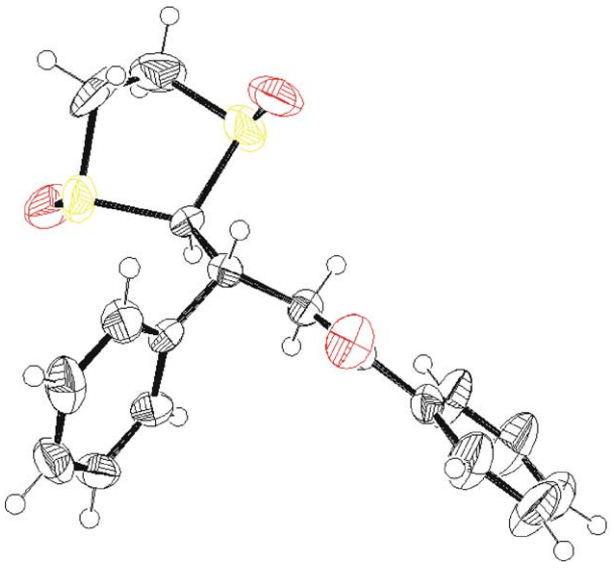


Figure 3 Structure of acetophenone adduct **5b** in the crystal[13]

Table 2 Addition of Nucleophiles to Bissulfoxides **3**

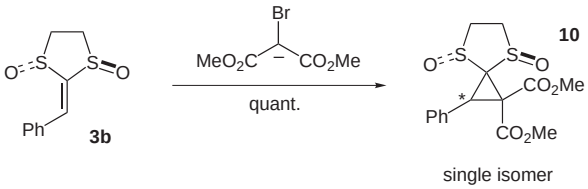
Entry	Educt	Nu	Product	Yield (%)	dr
1	**3b**, R = Ph		**5b**	80	≥98:2
2	**3f**, R = *t*-Bu		**5f**	86	92:8
3	**3e**, R = *i*-Pr		**5e**	82	71:29
4	**3d**, R = Et		**5d**	81	67:33
5	**3c**, R = Me		**5c**	85	55:45
6	**3b**, R = Ph		**6**	Quant.	92:8
7	**3b**, R = Ph	MeOH[a]	**7b**	Quant.	90:10
8	**3b**, R = Ph		**8**	92	94:6
9	**3b**, R = Ph	Bu_2CuLi	**9**	9	[b]

[a] Alox, pH 9, MeOH, r.t., 2 h.
[b] Only a single isomer was detected.

ity of the herein presented substrates. While the dithiane-derived compound **2** (R = Ph) gave only a poor 20% yield when reacted for 48 hours in piperidine as the solvent, bissulfoxide **3b** cleanly gave the adduct **6** with only two equivalents piperidine at –78 °C for 30 minutes (Table 2, entry 6). We think that this astonishingly high reactivity is due to an especially favorable stereoelectronic stabilization of the intermediate carbanion by the two axial S=O bonds (n → S–O-σ*).[14,15] Investigations and calculations on the influence of stereoelectronic effects in this and similar substrates are now under investigation and will be published elsewhere.

The unintended formation of methanol adducts during chromatography of **3c** and **3d** prompted us to test this addition with better defined reaction conditions. While the reaction of **3b** with sodium methanolate was very sluggish below –20 °C and led to decomposition of the substrate above that temperature, we achieved a quantitative addition of methanol to the bissulfoxide **3b** in the presence of basic alumina within two hours (→ **7b**, dr 90:10, entry 7). Only a poor 9% yield was obtained in the addition of a butyl cuprate, however with high selectivity, a single isomer **9** was detected in the product fraction (entry 9).

The initially formed anion in the addition of nucleophiles could be trapped when a leaving group was present in the molecule (Scheme 4).[16] Spiro compound **10** was formed as a single diastereoisomer with quantitative yield.



Scheme 4

The high reactivity of these alkylidenebissulfoxides derived from dithiolanes opens new possibilities for the addition of poor nucleophiles. Investigations in this direction are now on the way in our laboratories.

General Procedure for the Preparation of Alkylidenedithiolanes

Ethane-1,2-dithiol (2.83 g, 30 mmol, 1 equiv) was added dropwise at 0 °C to the respective acid chloride (1 equiv) and stirring was continued for 30 min at this temperature. Then, $HClO_4$ (70%, 3.1 mL, 36 mmol, 1.2 equiv) was carefully added dropwise. An exothermic reaction started after 0.5–5 min. The mixture was stirred for 30 min at r.t., cooled to 0 °C and freshly distilled Ac_2O (15 mL) was carefully added dropwise. The dithiolanylium salt was precipitated with anhyd Et_2O (50 mL) and filtrated under argon. The red needles were washed with Et_2O (3 × 20 mL) and dissolved in anhyd MeCN (30 mL). Afterwards, Et_3N was added until the red color disappeared and the solvents were removed at reduced pressure. The resulting oil was dissolved in sat. aq NH_4Cl solution (40 mL) and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4 and K_2CO_3), the solvents were removed and the residue was distilled by bulb-to-bulb distillation.

2-Benzyliden[1,3]dithiolane (4b)[9]

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.31–3.36 (m, 2 H), 3.52–3.56 (m, 2 H), 6.65 (s, 1 H, C=C*H*Ph), 7.12–7.19, 7.30–7.43 (2 m, 5 H, Ph).

General Procedure for the Preparation of Alkylidenedithiolane Dioxides

(+)-Diethyl tartrate (2 equiv, traces of H_2O removed by azeotropic distillation with toluene) and freshly distilled Ti(O*i*-Pr)$_4$ (0.5 equiv) were dissolved at r.t. under argon in anhyd CH_2Cl_2 (5 mL/mmol) and stirred for 30 min. The alkylidenedithiolane (1 equiv) in CH_2Cl_2 (1 mL/mmol) was added, the mixture was cooled to –40 °C and stirred for 2 h. Cumene hydroperoxide (technical grade, 80%, 4 equiv; diluted with CH_2Cl_2 to twice the volume) was added within 1 h. The solution was warmed to –20 °C and stored for 15 h in a freezer (lower than –20 °C). H_2O (20 equiv) was added and the mixture was stirred vigorously for 1 h at r.t. The slurry was kept for 1 h in an ultrasonication bath and the resulting suspension was filtered through a sinter glass (G2) covered with a Celite® pad (1.5 cm). The filter cake was washed repeatedly with small amounts of CH_2Cl_2. The solvents were removed and the pure bissulfoxide was obtained by chromatography on SiO_2 (CH_2Cl_2–acetone, 2:1).

(1*R*,3*R*)-2-Benzylidene[1,3]dithiolane-1,3-dioxide (3b)

Colorless crystals, mp 146–148 °C (CH_2Cl_2–hexane); R_f = 0.32 (CH_2Cl_2–acetone, 2:1); $[\alpha]_D^{20}$ –676 (*c* 1.0, $CHCl_3$). IR (DRIFT): 2986 (m), 2934 (m), 2044 (m), 1883 (m), 1599 (m), 1494 (m), 1447 (m), 1404 (m), 1395 (m), 1207 (m), 1094 (m), 1026 (s, S=O) cm^{-1}. UV (EtOH): λ_{max} (ε) = 200 (22600), 290 nm (20100). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62–3.67 (m, 1 H), 3.76–3.93 (m, 3 H), 7.50–7.57, 7.81–7.84 (2 m, 5 H, Ph), 8.10 (s, 1 H, C=C*H*Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.5 (t), 52.1, (t), 129.3 (d), 130.6 (d), 132.2 (d), 132.8 (s), 150.7 (d), 153.5 (s). MS (EI, 70 eV, 70 °C): *m/z*

(%) = 226 (8) [M^+], 198 (17), 150 (17), 134 (100) [$M^+ - C_7H_8$], 118 (31), 114 (20), 102 (34), 96 (23), 88 (62), 77 (40). HRMS (EI): *m/z* calcd for $C_{10}H_{10}O_2{}^{32}S_2$: 226.0122; found: 226.0119. Anal. Calcd for $C_{10}H_{10}O_2S_2$ (226.32): C, 53.07; H, 4.45. Found: C, 52.87; H, 4.69.

General Procedure for the Addition of Acetophenone Enolate to Alkylidenedithiolane Dioxides

To a solution of acetophenone (1.4 equiv) in THF (10 mL/mmol) was added at –78 °C NaHMDS (1.2 equiv, 2 M in hexane). The solution was transferred via a cannula after 45 min at –78 °C to a precooled (–78 °C) solution of the bissulfoxide (1.0 equiv in THF, 15 mL/mmol). After 10 min, an excess MeOH (ca .0.5 mL) was added, the solution was poured into sat. NH_4Cl solution (20 mL/mmol), extracted with EtOAc (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), and dried (Na_2SO_4, K_2CO_3). The solvents were removed and the selectivity was determined by ^1H NMR or ^{13}C NMR of the crude product (integration of the acetal proton). The residue was purified by chromatography on SiO_2.

(3*R*,1′*R*,3′*R*)-3-{1,3-Dioxo[1,3]dithiolan-2-yl}-1,3-diphenyl-propan-1-one (5b)

Selectivity ≥ 98:2; colorless crystals; mp 184 °C (CH_2Cl_2–acetone); R_f = 0.19 (CH_2Cl_2–acetone, 2:1); $[\alpha]_D^{20}$ +88.3 (*c* 0.8, $CHCl_3$). IR (DRIFT): 2978 (m), 1680 (s, C=O), 1596 (m), 1452 (m), 1412 (m), 1377 (w), 1301 (w), 1229 (m), 1027 (s, S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.53–3.56 (m, 1 H), 3.66–3.74 (m, 3 H), 3.79–3.90 (m, 2 H), 3.98–4.04 (m, 1 H, H-3), 4.44 (dd, 1 H, *J* = 11.8, 1.1 Hz, H-2′), 7.25–7.45, 7.51–7.55, 7.85–7.87 (3 m, 10 H, 2 Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.8 (d), 43.6 (t), 50.7 (t), 52.1 (t), 97.4 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.1 (d), 133.4 (d), 136.4 (s), 139.5 (s), 196.6 (s). MS (EI, 70 eV, 190 °C): *m/z* (%) = 346 (11) [M^+], 221 (22), 210 (31), 107 (14), 105 (100) [$C_7H_5O^+$], 77 (28). HRMS (EI): *m/z* calcd for $C_{18}H_{18}O_3{}^{32}S_2$: 346.0697; found: 346.0695. Anal. Calcd for $C_{18}H_{18}O_3S_2$ (226.32): C, 62.40; H, 5.24. Found: C, 62.13; H, 5.47.

Acknowledgment

We are deeply indebted to Dr. Wolfgang U. Frey (University of Stuttgart) for the X-ray crystal structure analyses. We thank Prof. Dr. W. Klopper (University of Karlsruhe) and Prof. Dr. E. Juaristi (Mexico) for inspiring discussions.

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(13) CCDC 603241 (co-crystal of **3c** and **7c**) and CCDC 603242 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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