3-Oxo-1,3\(\lambda^6\),4-oxathiazines: A Novel Class of Heterocyclic S,O-Acetals

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Dedicated to Prof. D. Enders on the occasion of his 70th birthday

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Abstract In this study, two synthetic methods for the synthesis of a hitherto unknown class of heterocyclic diastereo- and enantiopure S,O-acetals are described. Method A involves a chemoselective monohalogenation of sulfoximines and method B a stereoselective ring opening of sulfonimidates with a carbenoid as the key step, both followed by a base-induced cyclization of the S-(halomethyl)sulfoximine intermediates. The absolute configuration of the resulting 3-oxo-1,3\(\lambda^6\),4-oxathiazines has been confirmed by X-ray structural analysis. Furthermore, the first experiments exploring the reactivity of the new compounds are described.

Key words sulfoximines, sulfonimidates, oxathiazines, carbenoids, umpolung

Chiral, non-racemic 2-alkenyl sulfoximines have proven to be valuable and versatile solutions for asymmetric d\(^3\)-synthons.\(^1\)\(^,\)\(^2\) The enantiomerically pure allylic sulfoximines required were prepared either by reacting the corresponding allyllithium or Grignard compounds with cyclic sulfonimidates such as 1 (Scheme 1) or by a procedure employing a cycloalkanone and an S-methylsulfoximine like 9.\(^1\)\(^,\)\(^b\)\(^,\)\(^f\) The sulfonimidates were prepared from sulfinic acid amides of O-silylated amino alcohols.\(^2\) Deprotonation of the 2-alkenyl sulfoximines with n-BuLi followed by transmetalation to the corresponding titanium complex furnished a chiral carbon nucleophile that can be \(\gamma\)-hydroxalkylated in a highly diastereoselective manner.\(^1\)\(^b\)\(^,\)\(^g\) When amino aldehydes were used for this process, then the resulting vinyl sulfoximines can undergo a cyclizing Michael-type addition with the nitrogen as the nucleophile.\(^1\)\(^e\) This sequence finally delivers diastereo- and enantiomerically pure highly substituted (poly)heterocyclic compounds as illustrated by structure 2 (Scheme 1).\(^1\)\(^b\)\(^,\)\(^e\)

As is often the case with auxiliary-based asymmetric syntheses, its removal frequently poses problems. Although we found some solutions delivering either an angular methyl\(^1\)\(^b\) or a vinyl group,\(^1\)\(^e\) there is still room for improvement. Stimulated by the discovery that the sterically highly congested \(\alpha\)-deprotonated sulfoximine 2 is a rather unreactive species that only reacts with small and highly reactive electrophiles like carbenoids, we thought about the possibility to introduce oxygen substitution in such a way that sulfimamide extrusion may become possible furnishing a valuable formyl group in 6 instead of the olefin 4. After some unsuccessful experimentation with oxene precursors like lithiated

![Scheme 1](image-url)
tert-butyl hydroperoxide, the idea was born to use the oxygen atom of the auxiliary itself that would lead to a special kind of an O,S-acetal like 5, which in turn should easily be hydrolyzed to form the desired aldehyde 6.

The precursor of 5 would be the α-oxygenated 2-alkenyl sulfoximine 7 which may be synthesized starting from hitherto unknown oxathiazine oxides 8. Interestingly, this heterocyclic ring system has never been described before, for which reason we had to find a method to prepare these compounds in an enantiomerically pure state. One obvious way to reach this goal is to cyclize S-(halomethyl)sulfoximines, which should be accessible by halogenation of known S-methylsulfoximines like 9a (Scheme 2).3c In a first attempt we tried a ‘one-pot’ procedure combining the α-halogenation with the cyclization. Double deprotonation of 9a, followed by bromination was hoped to deliver the alkoide 10a, which should cyclize to the desired oxathiazine 8a.

Unfortunately, this does not happen. After aqueous workup only the hydrolysis product of the intermediate, the S-(bromomethyl)sulfoximine 11a was isolated in a low yield. Moreover, unexpectedly, this compound does not cyclize under basic conditions.

A possible explanation for these disappointing results may be the increased acidity of the α-position caused by the bromination, leading to a proton exchange within 10a yielding a carbanionic species that cannot cyclize. Therefore, we next aimed at the synthesis of O-silylated S-(halomethyl)sulfoximines that may undergo a fluoride ion induced cyclization (Scheme 3).

To avoid lengthy procedures involving triethylalanes,4 we envisioned the application of less basic zincates to avoid deprotonation of the halogenated product. In the event, we lithiated the TBS-protected S-methylsulfoximine 12a,1f transmetalated to the organozinc species 13a, which undergoes clean reactions with bromine (69% yield) and especially with iodine to deliver the desired S-(iodomethyl)sulfoximine 15a in 90% yield. To our delight the latter compound indeed cyclizes under the influence of tetrabutylammonium fluoride as the desilylating reagent, delivering the target oxathiazine S-oxide 8a in 82% yield.

The new compound is a white crystalline solid and we managed to obtain single crystals suited for X-ray structural analysis.5 From the crystal structure the expected absolute configuration R,R,S was confirmed.6 The six-membered ring adopts a chair conformation with the aryl group in an equatorial and the isopropyl group in an axial position. Despite this successful preparation, we began to think about the possibilities to shorten the route to the oxathiazines. In particular, we looked for alternatives avoiding the protection/deprotection steps associated with the described silyl ether chemistry.

As early as 1986 Matteson showed that in situ generated chloromethylthioliium obtained by reaction of n-butyl-lithium or methylthioliium with chloroiodomethane can be used to prepare chlorohydrins or epoxides from aldehydes.7 Based on these observations we wondered whether it would be possible to use the diastereomeric sulfonimidates 1a and 1b as electrophiles in Barbier-type reactions with the dihalomethane and n-BuLi (Scheme 4).

To our delight this turned out to be a feasible route to the S-(chloromethyl)sulfoximines 16a and 16b. The moderate yields are due to instabilities of the products towards the workup conditions and column chromatography. After protection of the alcohol ent-16a as its TBS ether, it was
possible to isolate the corresponding S-(chloromethyl)sulf oximine in 78% yield (not shown). To be sure that the reaction with the carbendol occurs with inversion of the sulfur configuration, we conducted an X-ray structural analysis of 16b derived from the sulfonimidate 1b. In accordance with the stereochemical course of reactions of the sulfonimidates with other carbon nucleophiles used so far, inversion of the sulfur configuration was observed, thus confirming the configurations given for 16a and 16b in Scheme 4. Their conversion into the target oxathiazines 8a and 8b proceeded smoothly by refluxing the precursors in the presence of potassium hydride in THF. Their relative and absolute configurations were also verified by crystal structural analyses. Finally, we found that a one-pot procedure, avoiding the yield losses due to the already mentioned work-up problems with the intermediates 16, was the superior variant maximizing yield and minimizing the number of steps (Scheme 4).

With the new compounds at hand, we next explored the possibility to deprotonate the α-position and the reactivity of the potential carbon nucleophile towards electrophilic substitution (Scheme 5). Furthermore, the anticipated ring cleavage under acidic conditions was of interest. As hoped, it was possible to lithiate 8a with n-BuLi in THF at low temperatures and to deuterate the resulting carbanionic species with methanol-d4. Interestingly, not only was it possible to isolate the deuterated compound 17 in a reasonable yield of 59%, but it turned out that this deuteration was quite stereoselective. The ratio of the two diastereomers 17 and epi-17 was around 10:1 (judged by 2H NMR spectroscopy of the mixture) in favor of an isomer with unknown configuration at the new stereogenic center. It should be noted that the crude reaction mixture contains a second (non-deuterated) compound of unknown structure, which surprisingly was not the expected hydrolysis product (the sulfinic acid amide of valinol; checked by comparison with an authentic sample) of the oxathiazine. Treatment of 8a with concentrated acetic acid leads, presumably via the oxonium ion 8a-H, to the transacetalization product 18, thus proving the expected hydrolyzability of the S,0-acetal-like moiety in the oxathiazine S-oxide. Finally, it should be noted that the new heterocyclic compounds are not stable at room temperature on the month timescale. Even in the solid state they are prone to decomposition, forming complex mixtures containing N-sulfinylated oxazolidines like 19, probably again via the ring-opened intermediate 8a-H.

In conclusion, we developed methods for the synthesis of S-(bromomethyl)- and S-(iodomethyl)sulfloximines like 14a and 15a, starting from the corresponding S-methylsulfoximine 12a in good yields without resorting to aluminates. Furthermore, a direct asymmetric synthesis of S-(chloromethyl)sulfloximines 16 by reaction of sulfonimidates 1 with chloromethyl lithium has been developed. These reactions, whose stereochemical course was secured by X-ray structural analyses, are the first instances of carbenoid reactions leading to sulfloximines. The resulting S-(halomethyl)sulfloximines were cyclized to hitherto unknown 3-oxo-, 1,3x4-4-oxathiazines 8; the potential of these compounds as solutions for asymmetric d1 and d2-synthons will be explored in the future.

All solvents used were dried with appropriate drying agents and distilled under an argon atmosphere prior to use. Moisture sensitive steps were carried out under an argon atmosphere, using flame-dried glassware and syringe/Schlenk techniques. Unless otherwise stated, sat. aq NaHCO3 and sat. aq Na2S2O3 solutions were used. TLC was performed on SilG/UV254 (Macherey Nagel & Co.). Chromatographic separations were carried out on Merck silica gel (60 (15–40 μm) at 2–3 bar. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Specific optical rotations were determined on a Perkin-Elmer Polarimeter 241 with Haake D8 thermostat in 1-dm cuvettes. NMR spectra were measured on Bruker AC 300 or DRX 500 spectrometers using TMS as internal reference. Mass spectra were run on a Bruker-Franzen Esquire LC mass spectrometer (MS (ESI)) and on a double-focusing spectrometer MAT 95 (EI-MS). Elemental analyses were performed on a Vario EL by Elementar. The crystallographic data were collected at r.t. on an Enraf-Nonius CAD-4 diffractometer with CuKα radiation (λ = 1.54180 Å). The atom numbering in the experimental used for the assignment of the NMR spectra differs from IUPAC conventions and is shown in Figure 1.

(RF)-S-(Bromomethyl)-N-[[15]-[(tert-butyldimethylsiloxy)meth yl]-2-methylpropyl]-S-p-tolysulfoximine (14a)

To a stirred solution of S-methylsulfoximine 12a [539 mg, 1.46 mmol, 1 equiv] in THF (2 ml) and Et2O (10 ml), 2.5 M n-BuLi in hexane (0.63 mL, 100 mg, 1.55 mmol, 1.0 equiv) was added dropwise by syringe at −78 °C and the mixture was stirred for 30 min. After warming the mixture to 0 °C anhyd ZnBr2 (478 mg, 2.12 mmol, 1.5 equiv) was added. The resulting suspension was stirred for 1 h at 0 °C. Then the resulting solution was added dropwise to a well-stirred solution/emulsion of Br2 (256 mg, 1.60 mmol, 1.1 equiv) in Et2O (5 ml) over 30 min at 0 °C. The resulting mixture was stirred for a further 15 min at 0 °C and then warmed to r.t. After the addition of Et2O (20 ml), the mixture was washed with Na2S2O3 solution (30 ml). The layers were separated and the aqueous phase was extracted with Et2O (3 x 20 mL). The combined organic layers were dried (Na2SO4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexane/Et2O, 10:1) furnishing 14a (448 mg, 69%) as a colorless oil; Rf = 0.41 (hexane/Et2O, 5:1); [α]D20 = −26.7 (c 1.05, CH2Cl2).
IR (film): 3026.6, 2955.6, 2928.5, 2857.0, 1596.0, 1471.1, 1386.3, 1362.4, 1305.0, 1256.5, 1102.6, 837.0, 813.9, 775.8, 524.3 cm⁻¹.

1H NMR (500 MHz, CDCl₃, 300 K): δ = 0.009 [s, br, 6 H, 2 × Si(CH₃)₃], 0.867 [s, 9 H, Si(CH₃)₃], 0.945 (d, 3 H, 4-H), 1.035 (d, 3 H, 4'-H), 2.034 (dqq, 1 H, 3-H), 2.447 (s, 3 H, 9-H), 3.23 (dd, 1 H, 2-H), 3.572 (d, 2 H, 1-H), 4.46 (d, 1 H, 10-H), 4.678 (d, 1 H, 10'-H), 7.326 (d, 2 H, 7-H), 7.891 (d, 2 H, 6-H); J₁₁ = 6.6 Hz, J₁₂ = 3.4 Hz, J₂₃ = 6.8 Hz, J₃₄ = 6.9 Hz, J₄₅ = 8.3 Hz, J₅₆ = 11.2 Hz.

13C NMR (125 MHz, CDCl₃, 300 K): δ = –5.29, –5.13 [2 × Si(CH₃)₃], 16.78 (C-4), 18.38 (C-10), 18.52 (Si(CH₃)₃), 20.59 (C-4'), 21.71 (C-9), 26.14 (Si(CH₃)₃), 30.30 (C-3), 62.17 (C-2), 66.00 (C-1), 129.66 (C-7), 129.99 (C-14), 134.22 (C-5), 143.33 (C-8).

MS (ESI) (MeOH): m/z (%) = 488.2 (100, [M + H⁺]), 472.2 (95, [M + H + 2H⁺]), 470.2 (60, [M + Na⁺]), 472.2 (70, [M + Na + 2H⁺]).


(R,R)-(N-{[15S]-1-[(tert-Butyldimethylsilyloxy)methyl]-2-methylpropyl}-S-(iodomethyl)-S-p-tolylsulfoximine (15a)

To a stirred solution of sulfonimidate 12a [(18.011 g, 48.73 mmol, 1.0 equiv) in THF (30 ml) and Et₂O (150 ml), 2.5 M n-But Li in hexane (19.51 ml, 3.121 g, 48.73 mmol, 1.0 equiv) was added dropwise by syringe at –78 °C and the mixture was stirred for 30 min. After the addition of anhyd ZnBr₂ (13.168 g, 58.47 mmol, 1.2 equiv) the mixture was warmed to 0 °C within 1.5 h. Then the resulting solution was added dropwise at 0 °C to a well-stirred solution of I₂ (13.604 g, 53.60 mmol, 1.1 equiv) in THF (30 ml) and Et₂O (150 ml) within 30 min. The resulting mixture was stirred for a further 15 min at 0 °C and then warmed to r.t. After the addition of Et₂O (150 ml), the mixture was washed with Na₂SO₄ solution (100 ml). The layers were separated and the aqeous phase was extracted with Et₂O (3 × 40 ml). The combined organic layers were dried (Na₂SO₄) and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (hexane/Et₂O, 20:1, 10:1, 1:3) furnishing 15a (21.706 g, 90%) as a colorless oil; Rf = 0.25 (hexane/Et₂O, 5:1); [α]₂³⁰ = –11.31 (c 1.2, CHCl₃).

(R,R)-S-(Chloromethyl)-N-[15S]-1-[(hydroxymethyl)-2-methylpropyl]-S-p-tolylsulfoximine (16a); Typical Procedure

To a stirred solution of sulfonimide 1a (4.048 g, 16.91 mmol, 1 equiv) and CICH₃ (6.1 ml, 83.57 mmol, 5 equiv) in THF (70 ml, 4 ml/mmol), 2.5 M n-But Li in hexane (33.24 ml, 5.533 g, 83.57 mmol, 5 equiv) was added dropwise via syringe over 50 min at –78 °C. The resulting mixture was stirred for 1 h at –78 °C, and then quenched by the addition of NaHCO₃ solution (6 ml/mmol) under vigorous stirring at –78 °C. After warming to r.t. with stirring, the layers were separated and the aqueous phase was extracted with Et₂O (3 × 100 ml). Then the combined organic extracts were dried (Na₂SO₄) and then the solvents were removed under reduced pressure. The residue was purified by flash chromatography (hexane/Et₂O, 1:1, 1:2) furnishing S-(chloromethyl)sulfoximine 16a (2.338 g, 48%) as a colorless oil; Rf = 0.09 (hexane/Et₂O, 1:1); [α]₂³⁰ = –24 (c 1, CHCl₃).

IR (film): 3491.9, 2960.0, 2873.9, 1597.4, 1492.4, 1467.0, 1263.5, 1135.3, 1082.8, 1081.5, 880.7, 711.4, 628.8, 526.8 cm⁻¹.

1H NMR (500 MHz, CDCl₃, 300 K): δ = 1.022 (d, 3 H, 4-H), 1.041 (d, 3 H, 4'-H), 1.881 (dqq, 1 H, 3-H), 2.459 (s, 3 H, 9-H), 3.016 (s, br, 1 H, OH), 3.234 (dd, 1 H, 2-H), 3.592 (dd, 1 H, 1-H), 4.558 (d, 1 H, 10-H), 4.805 (d, 1 H, 10'-H), 7.370 (d, 2 H, 7-H), 7.938 (d, 2 H, 6-H); J₁₁ = 11.2 Hz, J₁₂ = 8.3 Hz, J₂₃ = 2.1 Hz, J₃₄ = 5.2 Hz, J₄₅ = 6.8 Hz, J₅₆ = 6.9 Hz, J₆₇ = 8.4 Hz, J₇₈ = 12.3 Hz.

13C NMR (125 MHz, CDCl₃, 300 K): δ = 18.72 (C-4), 20.19 (C-4'), 21.72 (C-9), 32.06 (C-3), 64.39 (C-2), 65.52 (C-1), 56.21 (C-10), 129.85 (C-7), 129.95 (C-6), 132.99 (C-5), 144.93 (C-8).

MS (ESI) (CHCl₃, MeOH): m/z (%) = 312.1 (100, [M + Na⁺]), 313.1 (15, [M + Na⁺ + 1⁺]), 314.1 (38, [M + Na + 2⁺]).

HRMS (EI): m/z [M + H⁺] calcd for C₁₃H₁₂ClNO₅S: 290.0977; found: 290.0976; Δ = ±0.003.

(S,S)-S-(Chloromethyl)-N-[15S]-1-[(hydroxymethyl)-2-methylpropyl]-S-p-tolylsulfoximine (16b)

Analogous to the typical procedure for 16a, the diastereomer 16b was prepared from sulfonimide 1b (10.416 g, 43.52 mmol, 1 equiv). CICH₃ (8.6 ml, 117.51 mmol, 2.7 equiv), and 2.5 M n-But Li in hexane (43.91 ml, 7.025 g, 109.67 mmol, 2.5 equiv). Flash chromatography (hexane/Et₂O, 1:2, 1:3) gave S-(chloromethyl)sulfoximine 16b (3.811 g, 30%) as colorless crystals; Rf = 0.30 (hexane/Et₂O, 1:3); mp 91 °C; [α]₂³⁰ = –51.9 (c 1, CHCl₃).

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To a stirred solution of 3-oxo-oxathiazine 3a (121 mg, 0.42 mmol, 1 equiv) in THF (3 mL) was added K2CO3 (18 mg, 0.45 mmol, 1 equiv) in THF (3 mL), 1 M TBAF in THF (87.5 mL) was added KH (18 mg, 0.45 mmol, 1 equiv) at 0 °C. Then cooling to r.t. and addition of Et2O (60 mL), NaHCO3 solution (150 mL) was added. The layers were separated and the aqueous phase was extracted with Et2O (3×100 mL). The combined organic layers were dried (Na2SO4) and the solvents were removed under reduced pressure. The residue was recrystallized (t-BuOMe) at 4 °C furnishing 3a (47.1 g, 66%) as a crystalline solid.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3λ4,4-oxathiazine (8a) by One-Pot Procedure from Sulfonimidate 1a

To a stirred solution of sulfonimidate 1a (6.779 g, 28.32 mmol, 1 equiv) and CICH2I (5.2 mL, 70.81 mmol, 2.5 equiv) in THF (90 mL), 2.5 M n-BuLi in hexane (28.35 mL, 4536.70 mL, 2.5 equiv) was added dropwise by syringe over 50 min at −78 °C. The resulting mixture was stirred for 1 h at −78 °C, and then quenched by the addition of NaHCO3 solution (150 mL) under vigorous stirring at −78 °C. After warming to r.t., the mixture was separated, and the aqueous phase was extracted with Et2O (3×150 mL) and the combined organic layers were dried (Na2SO4). All volatiles were removed under reduced pressure delivering the crude S-(chloromethyl)sulfoximine as a yellow oil.

To a stirred solution of the crude S-(chloromethyl)sulfoximine in THF (200 mL) was added KH (1.200 g, 29.92 mmol, 1.1 equiv) at 0 °C. Then the mixture was refluxed until complete consumption of the S-(chloromethyl)sulfoximine (TLC monitoring: hexane/ Et2O, 1:1) furnishing 8a (2.251 g, 70%, [M + Na]+). After cooling to r.t. and addition of Et2O (90 mL), NaHCO3 solution (150 mL) was added. The layers were separated and the aqueous phase was extracted with Et2O (3×100 mL). The combined organic layers were dried (Na2SO4) and the solvents were removed under reduced pressure. The residue was recrystallized (t-BuOMe) at 4 °C furnishing 8a (47.1 g, 66%) as a crystalline solid.
1H NMR (500 MHz, CDCl3, 300 K): δ = 0.989 (d, 3 H, 4-H), 0.994 (d, 3 H, 4-H′), 1.978 (m, 1 H, 3-H), 2.067 (s, 3 H, 12-H), 2.408 (s, 3 H, 9-H), 3.257 (m, 1 H, 2-H), 3.729 (dd, 1 H, 1-H), 3.877 (dd, 1 H, 1-H′), 4.227 (d, 1 H, NH), 5.179 (d, 1 H, 10-H), 5.244 (dd, 1 H, 10-H′), 7.295 (d, 2 H, 7-H), 7.607 (d, 2 H, 6-H); J1,1′ = 9.9 Hz, J1,2 = 4.7 Hz, J1′,2′ = 4.1 Hz, J1,4 = 6.8 Hz, J1′,4′ = 6.8 Hz, J8,9 = 8.2 Hz, J10,10′ = 6.2 Hz.

13C NMR (125 MHz, CDCl3, 300 K): δ = 12.135 (C-6), 129.55 (C-7), 141.37 (C-8), 142.91 (C-5), 170.52 (C-11), 21.39 (C-9), 29.93 (C-3), 60.80 (C-2), 71.16 (C-1), 89.07 (C-10), 101.45, 94.51, 81.23 cm−1.

IR (film): 3213.5, 2962.0, 2931.0, 2879.3, 1744.6, 1596.5, 1491.8, 1272.9, 1193.2, 1151.5, 1104.5, 1033.2, 965.8, 759.7, 745.9, 687.8 cm−1.

HRMS (ESI) (MeOH): m/z (%) = 336.2 (100, [M + Na]+).

HRMS (EI): m/z [M]+ calcd for C15H23NO4S: 313.1348; found: 313.1348; ± 0.002.

Anal. Calcd for C15H23NO4S (313.41): C, 57.48; H, 7.40; N, 4.47. Found: C, 57.38; H, 7.44; N, 4.45.

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Supporting Information

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Primary Data

Primary data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000085 and can be cited using the following DOI: 10.4125/pd0085th.

References


(5) CCDC 617316 (8a), CCDC 617318 (8b) and CCDC 617319 (16b) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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