3-Oxo-1,3λ6,4-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-1,3λ6,4-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 d3-synthons.1,2 The enantiomerically pure allylic sulfoximines required were prepared either by reacting the corresponding allylithium or Grignard compounds with cyclic sulfonimidates such as 1 (Scheme 1) or by a procedure employing a cycloalkanone and an S-methylsulfoximine like 9.3,4 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 γ-hydroxyalkylated in a highly diastereoselective manner.3,4,5 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.6 This sequence finally delivers diastereo- and enantiomerically pure highly substituted (poly)heterocyclic compounds as illustrated by structure 2 (Scheme 1).3,4

As is often the case with auxiliary-based asymmetric syntheses, its removal frequently poses problems. Although we found some solutions delivering either an angular methyl1 or a vinyl group,1,6 there is still room for improvement. Stimulated by the discovery that the sterically highly congested α-deprotonated sulfoxime 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 sulfonamide 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 Olefinating desulfuration and hypothetical formylative desulfuration of sulfonimidoylmethyl-substituted polyheterocyclic compounds prepared from amino aldehydes and allylic sulfoximines
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). 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 S-silylated S-(halomethyl)sulfoximines that may undergo a fluoride ion induced cyclization (Scheme 3).

To avoid lengthy procedures involving triethylalananates,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,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 chloromethylthyllium obtained by reaction of n-butyl-lithium or methylthyllithium 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 16a as its TBS ether, it was
possible to isolate the corresponding S-(chloromethyl)sulfoximine in 78% yield (not shown). To be sure that the reaction with the carbeneon occurs with inversion of the sulfur configuration, we conducted an X-ray structural analysis of 16b derived from the sulfonimide 1b. In accordance with the stereochemical course of reactions of the sulfonimides 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 carbaniopics 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 the superior variant maximizing yield and minimizing the number of steps (Scheme 4).

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 Na2S2O8 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.

Scheme 5 Selective deuteration and transacetalization of 8a

(R′)-S-(Bromomethyl)-N-[(15)-1-[(tert-butyldimethylsiloxy)methyl]-2-methylpropyl]-S-p-tolylsulfoximine (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 B2 (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 Na2S2O8 solution (30 mL). The layers were separated and the aqueous phase was extracted with Et2O (3 × 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; [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 (dq, 1 H, 3-H), 2.447 (s, 3 H, 9-H), 3.232 (ddd, 1 H, 2-H), 3.572 (d, 2 H, 1-H), 4.466 (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): J₁ = 6.6 Hz, J₂ = 3.4 Hz, J₃ = 6.8 Hz, J₄ = 6.9 Hz, J₅ = 8.3 Hz, J₀.₀１₀⁻ = 1.2 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), 129.84 (C-6), 134.60 (C-5), 144.23 (C-8).

MS (EI): m/z (%) = 188.9 (100), 496.0 (3, [M + H]+), 518.0 (26, [M + Na]+), 534.0 (5, [M + K]+).

Analog calc. for C₁₀H₁₄INO₃S: 495.53: C, 66.05; H, 6.29; N, 2.83. Found: C, 66.22; H, 6.94; N, 2.83.

(R₆)-S-(Chloromethyl)-N-[15]-1-(hydroxymethyl)-2-methylpropyl]-S-p-tolylsulfoximine (16a); Typical Procedure

To a stirred solution of sulfonimidate 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-BuLi in hexane (33.24 mL, 5.535 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 rt. 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/EtO, 1:1) to furnish 16a (2.338 g, 48%) as a colorless oil; R₆ = 0.09 (hexane/EtO, 1:1); [α]₂⁰ = −34 (c 1, CH₂Cl₂).

IR (film): 3491.9, 2960.0, 2873.9, 1597.4, 1492.4, 1467.0, 1263.5, 1135.3, 1082.8, 1081.5, 808.7, 711.4, 628.8, 526.8 cm⁻¹.

1H NMR (500 MHz, CDCl₃, 300 K): δ = 0.102 (d, 3 H, 4-H), 1.041 (d, 3 H, 4’-H), 1.881 (dq, 1 H, 3-H), 2.459 (s, 3 H, 9-H), 3.016 (s, br, 1 H, OH), 3.234 (ddd, 1 H, 2-H), 3.572 (d, 1 H, 1-H), 3.662 (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): J₁ = 11.2 Hz, J₂ = 8.3 Hz, J₃ = 2.1 Hz, J₄ = 5.2 Hz, J₅ = 6.8 Hz, J₆ = 6.9 Hz, J₀.₀₁₀⁻ = 8.4 Hz, J₀.₀₁₅⁻ = 12.3 Hz.

13C NMR (125 MHz, CDCl₃, 300 K): δ = 18.72 (C-2), 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).


HRMS (EI): m/z [M + H+] calcd for C₁₁H₁₃INO₃S: 290.0977; found: 290.0976; ± 0.003.

(S₆)-S-(Chloromethyl)-N-[15]-1-(hydroxymethyl)-2-methylpropyl]-S-p-tolylsulfoximine (16b)

Analogous to the typical procedure for 16a, the diastereomer 16b was prepared from sulfonimidate 1b (10.416 g, 43.52 mmol, 1 equiv). CICH₃ (8.6 mL, 117.51 mmol, 2.7 equiv), and 2.5 M n-BuLi in hexane (43.91 mL, 7.025 g, 109.67 mmol, 2.5 equiv). Flash chromatography (hexane/EtO, 1:2, 1:3) gave 16b (3.811 g, 30%) as colorless crystals; R₆ = 0.30 (hexane/EtO, 1:3); mp 91 °C; [α]₂⁰ = −51.9 (c 1, CH₂Cl₂).

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IR (KBr): 3497.4, 3066.7, 3014.1, 2965.3, 2930.0, 2870.7, 1596.4, 1488.6, 1465.3, 1385.3, 1258.9, 1236.4, 1153.0, 1123.4, 1090.1, 1051.8, 981.4, 962.0, 953.1, 864.4, 807.8, 714.2, 629.0, 534.6 cm⁻¹.

1H NMR (500 MHz, CDCl₃, 300 K): δ = 0.950 (d, 3 H, 3-H, 4-H), 0.968 (d, 3 H, 4-H), 1.797 (dq, 1 H, 1-H), 2.454 (s, 3 H, 9-H), 2.767 (dd, 1 H, 1-H), 3.033 (dd, 1 H, 2-H), 3.527 (dd, 1 H, 1-H), 3.614 (dd, 1 H, 1-H), 4.622 (d, 1 H, 10-H), 4.700 (d, 1 H, 10-H), 7.368 (d, 2 H, 7-H), 8.285 (d, 2 H, 6-H); 1051.8, 981.4, 962.0, 953.1, 864.4, 807.8, 714.2, 629.0, 534.6 cm⁻¹.

13C NMR (125 MHz, CDCl₃, 300 K): δ = 19.98 (C-13), 21.69 (C-13', 21.69 (C-13); 19.81 (C-4'), 21.69 (C-4), 59.61 (C-10), 63.72 (C-2), 65.45 (C-1), 129.91 (C-6), 130.02 (C-5), 144.77 (C-8), 31.92 (C-3), 59.61 (C-10), 63.72 (C-2), 65.45 (C-1), 129.91 (C-6), 130.02 (C-5), 144.77 (C-8), 31.92 (C-3), 59.61 (C-10), 63.72 (C-2), 65.45 (C-1), 129.91 (C-6), 130.02 (C-5), 144.77 (C-8).

MS (ESI) [CHCl₃, MeOH]: m/z (%) = 312.1 (100, [M + Na⁺]), 313.1 (18, [M + Na + 1⁺]), 314.1 (41, [M + Na + 2⁺]).

Analytical Calcd for C₁₃H₁₉NO₂S: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.60; H, 7.61; N, 5.43.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3,4-oxathiazine (8a) from S-(iodomethyl)sulfoximine 15a

To a stirred solution of S-(iodomethyl)sulfoximine 15a (2.251 g, 70%) as colorless crystals; λmax (CH2Cl2) = 128.57 (C-8), 129.92 (C-9), 136.40 (C-7), 144.93 (C-10). Anal. Calcd for C₁₃H₁₅NO₂S: C, 61.63; H, 7.61; N, 5.43.

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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), 3.807 (dd, 1 H, 1'-H), 4.227 (d, 1 H, NH), 5.179 (d, 1 H, 10-H), 5.244 (d, 1 H, 10'-H), 7.295 (d, 2 H, 7-H). 13C NMR (125 MHz, CDCl3, 300 K): δ = 18.75 (C-4), 19.28 (C-4'), 21.04 (C-12), 21.39 (C-9), 29.93 (C-3), 60.80 (C-2), 71.16 (C-1), 89.07 (C-10), 125.49 (C-6), 129.55 (C-7), 141.37 (C-8), 142.91 (C-5), 170.52 (C-11). MS (ESI) (MeOH): m/z (%) = 336.2 (100, [M + Na]+).

1H NMR (500 MHz, CDCl3, 300 K): δ = 0.894 (d, 3 H, 4-H), 0.994 (d, 3 H, 9-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), 3.807 (dd, 1 H, 1'-H), 4.227 (d, 1 H, NH), 5.179 (d, 1 H, 10-H), 5.244 (d, 1 H, 10'-H), 7.295 (d, 2 H, 7-H). 13C NMR (125 MHz, CDCl3, 300 K): δ = 18.75 (C-4), 19.28 (C-4'), 21.04 (C-12), 21.39 (C-9), 29.93 (C-3), 60.80 (C-2), 71.16 (C-1), 89.07 (C-10), 125.49 (C-6), 129.55 (C-7), 141.37 (C-8), 142.91 (C-5), 170.52 (C-11). MS (ESI) (MeOH): m/z (%) = 336.2 (100, [M + Na]+).

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

1H NMR (500 MHz, CDCl3, 300 K): δ = 1.978 (m, 1 H, 3-H), 2.067 (s, 3 H, 12-H), 2.408 (s, 3 H, 9-H), 3.379 (dd, 1 H, 1-H), 3.807 (dd, 1 H, 1'-H). 13C NMR (125 MHz, CDCl3, 300 K): δ = 18.75 (C-4), 19.28 (C-4'), 21.39 (C-9), 29.93 (C-3), 60.80 (C-2), 71.16 (C-1), 89.07 (C-10), 125.49 (C-6), 129.55 (C-7), 141.37 (C-8), 142.91 (C-5), 170.52 (C-11). MS (ESI): 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.

References
13. (a) CCDC 617316 (8a), CCDC 617318 (8b) and CCDC 617316 (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.