A New Access to Pyrrolizidine Derivatives: Ring Contraction of Methyl (E)-[1,2-Oxazin-3-yl]propenoates

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Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

Abstract: Nitrosoalkene 2 generated in situ from oxime 3 underwent smooth hetero Diels–Alder reaction with enol ethers 1 to afford 1,2-oxazine derivatives 4 bearing an exocyclic C=C bond. Methoxyllalene 8 and 2 provided 6H-1,2-oxazine 10 in good overall yield. The exocyclic double bond of this type of 1,2-oxazines can be employed for addition reactions as demonstrated by dihydroxylation of 4a with potassium permanganate, smoothly delivering 1,2-diol 11. A reductive cascade reaction involving ring cleavage at the N-O bond followed by cyclization steps furnished pyrrolizidinone derivatives 12 in good yields. In the case of 12b this transformation proceeded with excellent stereoselectivity. Finally, the lactam moiety of 12 could be reduced with borane to provide the corresponding pyrrolizidine derivatives 19 in good yield.

Key words: 1,2-oxazines, pyrrolizidines, hydrogenation, lactams, pyrroles, hetero Diels–Alder reaction

A common strategy for the construction of functionalized heterocyclic compounds involves ring contraction of easily available precursor heterocycles. For this purpose, a moiety allowing smooth ring opening is required, a property which is given with the relatively weak N–O bond. The compound class of 1,2-oxazines fulfills this prerequisite and hence it is frequently employed in organic synthesis. Ring cleavages and ring transformations could be exploited for the synthesis of a variety of nitrogen-containing heterocycles such as pyrroles, proline derivatives, pyrrolidines, cyclic five-membered nitrones, aziridines, γ-lactams, pyridines, and indolizidines. To date, not much is known about the preparation of pyrrolidizines starting from 1,2-oxazine derivatives. The pyrrolidizine core is found in many alkaloids including examples with interesting pharmacological activity. Polyhydroxyalated pyrrolidizidine alkaloids are of particular importance as inhibitors of glycosidases and glycosyltransferases. The present report deals with the preparation of methyl (E)-3-[1,2-oxazin-3-yl]propenoates and their simple transformation into pyrrolizidinone and pyrrolizidine derivatives.

1,2-Oxazines 4 with an exocyclic C=C bond at position 3 can easily be prepared by hetero Diels–Alder reaction of electron-rich olefins 1 and nitrosoalkene 2, which are generated in situ from the corresponding α-bromooxime 3 by treatment with a base such as sodium carbonate (Scheme 1). Cycloadducts 4 were generally obtained in moderate to excellent yields. Dienophile 1c was used as an E/Z mixture of isomers (60:40), however, only the more reactive E-isomer underwent cycloaddition with 2 providing 4c in good yield and with trans-orientated trimethylsiloxy groups. The high kinetic preference for E-configured dienophiles is a common feature of nitrosoalkene cycloadditions.

Scheme 1 Hetero Diels–Alder reactions of enol ethers 1 with nitrosoalkene 2

Allyltrimethylsilane (5) is also a suitable dienophile for hetero Diels–Alder reactions with nitrosoalkenes, although the reactivity of 5 is lower in comparison with olefins 1. The cycloaddition of 2 and 5 under standard conditions (see Scheme 1) gave the 1,2-oxazine 6 only in

Equation 1 Hetero Diels–Alder reaction of allyltrimethylsilane with nitrosoalkene 2
low yield (4–30%). However, the yield of 6 could be improved when the reaction was performed at 60 °C in an ACE pressure tube (Equation 1). The reaction time was dramatically decreased under these conditions, but the expected product 6 was accompanied by bicyclic nitrone 7, which was obtained as a mixture of two diastereomers (ca. 1:1). The formation of nitrone 7 can be explained by a subsequent [3+2] cycloaddition of the primary adduct 6 with nitrosoalkene 2. It cannot be ruled out that 2 and 6 first undergo a [4+2] cycloaddition and the primary 2:1 adduct then rearranges to nitrone 7. This type of transformation of 1,2-oxazines into nitrones was reported earlier.

Donor-substituted allenes, in particular alkoxyallenes, are synthetically very useful dienophiles in [4+2] cycloadditions with nitrosoalkenes. Gratifyingly, the hetero Diels–Alder reaction of nitrosoalkene 2 with methoxynitrene (8) led to 5-methylene-5,6-dihydro-4H-1,2-oxazine 9 in excellent yield. Primary adduct 9 was smoothly converted into the 6H-1,2-oxazine 10 containing two C=C bonds on treatment with DBU at room temperature (Scheme 2).

The C=C bonds of 1,2-oxazines such as 4 or 10 can be used to add new substituents or functional groups to the heterocycle. This option is demonstrated in the dihydroxylation of 1,2-oxazine 4a with potassium permanganate as the oxidizing reagent in the presence of magnesium sulfate. The expected 1,2-diol 11 was obtained in good yield and with surprisingly high diastereoselectivity (Equation 2). Although we could not determine the relative configuration of the obtained diastereomers, the high stereoselection exhibited by the axial 6-ethoxy group is quite remarkable. The asymmetric induction operates in a 1,5/1,6 fashion with respect to the dihydroxylated C=C bond.

Having attained a good access to heterocyclic precursors 4a, 10, and 11, we turned our attention to their conversion into pyrrolizidinones. The hydrogenolysis of these 1,2-oxazines furnished pyrrolizidinones 12a-c in good yields (Scheme 3). We applied palladium on charcoal as catalyst for this multi-step reaction. Interestingly, the diastereoselectivity in the case of 7-methyl-substituted pyrrolizidinone 12b is excellent, whereas the reduction and lactamization of 11 afforded the dihydroxylated pyrrolizidine 12c as a 60:40 mixture of isomers. This strongly differing stereoselectivity can be explained by the sequence of steps during this reductive ring contraction cascade (see below).

A plausible mechanism for the formation of pyrrolizidine 12b from 1,2-oxazine 10 is illustrated in Scheme 4. The first step probably involves reduction of both C=C bonds. Intermediate 13 is very likely generated with the relative configuration as depicted, since the axial 6-methoxy group of 10 should lead to a high induction for the reduction of the 4,5-double bond. The subsequent reduction of the C=N bond of 13 is strongly influenced by the two existing stereogenic centers to preferentially form intermediate 14 with all-cis configuration as shown. This step determines the high diastereoselectivity of the overall process. Reductive cleavage of the N–O bond, ring closure, and water elimination to give cyclic imine 16 followed by a reduction of the C=N bond and finally lactamization of intermediate 17 furnishes pyrrolizidine 12b. This sequence of reduction steps explains the observed relative configuration, whereas the mechanism as proposed in earlier examples should lead to lower diastereoselectivity.

Since 1,2-oxazine 11 bears no substituent at C-5, but only the more flexible stereogenic centers at the side chain, no comparable stereoselectivity of the C=N reduction occurs and 12c is generated as a 60:40 mixture of diastereomers. We also attempted to prepare pyrrolizidinones by microwave-assisted transfer hydrogenolysis, but failed. Treatment of 1,2-oxazine 4a with ammonium formate in the presence of palladium on charcoal furnished pyrrole de...

Scheme 2 Preparation of 6H-1,2-oxazine 10: Reagents and conditions: a) 2, Na2CO3, t-BuOMe, r.t., 6 d; b) DBU, CH2Cl2, r.t., 6 h.

Scheme 3 Reductive ring contraction and lactamization of 1,2-oxazines leading to pyrrolizidinones 12

Equation 2 Dihydroxylation of 4H-1,2-oxazine 4a
All reactions were performed under argon in flame-dried flasks, and the components were added by means of syringes. All solvents were dried by standard methods. IR spectra were measured with a Perkin-Elmer IR-325 or Nicolet 205 spectrometer. 1H and 13C NMR spectra were recorded on Bruker instruments (AC 200 or AC 300) in CDCl3 solution. The chemical shifts are given relative to the TMS or CDCl3 signals (δH = 7.27, δC = 77.03). Missing signals of the minor isomer are either hidden by signals of the major isomer or they could not be unambiguously identified due to low intensity. Neutral alumina (activity III, Merck) was used for column chromatography. Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohr oven. Melting points (uncorrected) were measured with an apparatus from Rapido (Boëtius). Na2CO3 was freshly pulverized (electric coffee mill, Braun KSM 1G) before use. All solvents were dried by standard methods.

Syntheses of starting materials were done according to literature: silyl enol ethers 1b,d27 and 1c,28 oxime 3,15 and methoxyallenyl (8).29

4H-1,2-Oxazines; General Procedure 1

Freshly ground Na2CO3 (6 equiv) was added to a solution of the corresponding olefin (10 equiv) and α-bromoketoxime 3 (1 equiv) in t-BuOMe (12–16 mL/mmol of oxime 3). After stirring at r.t. for the time indicated in the individual reaction, the suspension was filtered through a pad of Celite to remove inorganic salts. The resulting filtrate was concentrated in vacuo and the excess of olefin was distilled off by Kugelrohr distillation. The residue was purified by chromatography (alumina, elution with hexane–EtOAc; 4:1 or 9:1) to furnish the 4H-1,2-oxazine 4a.

Methyl (E)-3-(6′-Ethoxy-5′,6′-dihydro-4′H-1′,2′-oxazin-3′-yl)propenolate (4a)

According to general procedure 1, a mixture of 1a (26.0 g, 360 mmol), oxime 3 (7.99 g, 36.0 mmol), and Na2CO3 (22.9 g, 216 mmol) in t-BuOMe (400 mL) was stirred for 5 d at r.t. The resulting crude product was purified by column chromatography (hexane–EtOAc; 4:1) to give 1,2-oxazine 4a (7.16 g, 93%) as colorless crystals; mp 52–53 °C.

IR (KBr): 3450–2800 (–CH, –OH), 1760, 1730 cm–1 (C=O), 1640 cm–1 (C=C).

1H NMR (CDCl3, 200 MHz): δ = 7.34, 6.17 (2 d, J = 16 Hz, 1 H each, 3-H, 2-H), 5.16 (t, J = 2.5 Hz, 1 H, 6-H), 3.85, 3.62 (2 qd, J = 7, 10 Hz, 1 H each, OCH2CH3), 3.79 (s, 3 H, CO2CH3), 2.45 (ddd, J = 7.5, 12.5, 17.5 Hz, 1 H, 4′-H), 2.26 (ddd, J = 2.5, 6.5, 17.5 Hz, 1 H, 3′-H).

Hz. 1 H, 4°-H), 2.06 (dd, J = 2.5, 7.5, 13.5 Hz, 1 H, 5°-H), 1.91 (dd, J = 2.5, 6.5, 12.5, 13.5 Hz, 1 H, 5°-H), 1.19 (t, J = 7 Hz, 3 H, OCH₂CH₃). ¹³C NMR (CDCl₃, 50.3 MHz): δ = 166.4, 51.8 (s, q, CO₂CH₃), 155.4 (s, C-3°), 141.6 (d, C-3), 121.5 (d, C-2), 95.7 (d, C-6°), 63.8, 14.9 (t, q, OCH₂CH₃), 22.0 (t, C-5°), 151.1 (t, C-4°).

Anal. Calcd for C₉H₁₀NO₄Si: C, 56.54; H, 7.43; N, 6.56.

Methyl (E)-3-[5°'-6'-Dihydro-6'-(trimethylsilyl)-4'-H-1,2-oxazin-3'-y1-propenoate (4b)]
According to general procedure 1, a mixture of 1b (2.88 g, 24.8 mmol), oxime 3 (1.10 g, 4.96 mmol), and Na₂CO₃ (3.07 g, 29.8 mmol) in tBuOMe (50 mL) was stirred for 5 d at rt. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to give 1,2-oxazine 4b (0.317 g, 25%) as colorless crystals; mp 97–98 °C.

IR (KBr): 3060–2850 (=C–H, C–H), 1715 (C=O), 1635 (C=C), 1560 cm⁻¹ (C=N).

Found: C, 51.45; H, 7.58; N, 5.46.

Methyl (E)-3-[5°'-6'-Dihydro-6'-bis(trimethylsilyl)-4'-H-1,2-oxazin-3'-y1-propenoate (4c)]
According to general procedure 1, a mixture of 1c (1.14 g, 10.0 mmol), oxime 3 (0.111 g, 0.50 mmol), and Na₂CO₃ (0.318 g, 6.00 mmol) in CH₂Cl₂ (20 mL) was stirred for 20 h at 60 °C in an ACE pressure tube. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to provide 3 fractions: fraction 1, 1,2-oxazine 6b (0.025 g, 41%) as colorless crystals; fraction 2, a 1:2 mixture of 6 and 7 (0.029 g); and fraction 3, product 7 (0.009 g, 5%) as a colorless oil.

Compound 6
Mp 79–81 °C.

IR (KBr): 3080–2800 (=C–H, C–H), 1710 (C=O), 1635 (C=C), 1560 cm⁻¹ (C=N).

Found: C, 58.09; H, 8.65; N, 4.39.

Methyl (E)-3-[5°'-6'-Dihydro-6'-(tributylstannyl)methyl]-3'-H-1,2-oxazin-3'-yl-propenoate (6) and (E,E)-5,6,7,7a-Tetrahydro-2,7-bis-[2-methoxybenzyl]thienyl-1-oxo-5-[trialkylstannyl]methyl]-3'H-4-oxa-1,3 diazaindole (7)
Analogous to general procedure 1, a mixture of 5 (1.44 g, 10.0 mmol), oxime 3 (0.111 g, 0.50 mmol), and Na₂CO₃ (0.318 g, 6.00 mmol) in CH₂Cl₂ (20 mL) was stirred for 20 h at 60 °C in an ACE pressure tube. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to provide 3 fractions: fraction 1, 1,2-oxazine 6 (0.025 g, 41%) as colorless crystals; fraction 2, a 1:2 mixture of 6 and 7 (0.029 g); and fraction 3, product 7 (0.009 g, 5%) as a colorless oil.

Compound 7
Mixture of two diastereomers, 56:44.

IR (KBr): 3050–2800 (=C–H, C–H), 1720 (C=O), 1635 (C=C), 1560 cm⁻¹ (C=N).

Found: C, 47.98; H, 7.78; N, 4.01.

Methyl (E)-3-[5°'-6'-Hexahydro-5',6',7',8',8'a-Heptyhoxazole-8'-y1-[(trimethylsilyl)-4'-H-1,2-benzoxazin-3'-y1-propenoate (4d)]
According to general procedure 1, a mixture of 1d (1.36 g, 8.00 mmol), oxime 3 (0.222 g, 1.00 mmol), and Na₂CO₃ (0.318 g, 6.00 mmol) in tBuOMe (10 mL) was stirred for 6 d at rt. The resulting crude product was purified by column chromatography (hexane–EtOAc, 9:1) to give 1,2-oxazine 4d (0.130 g, 42%) as colorless crystals; mp 117–118 °C.

IR (KBr): 3080–2800 (=C–H, C–H), 1715 (C=O), 1640 (C=C), 1580 cm⁻¹ (C=N).
MS (FD): m/z (%) = 398 (14, [M + 2]+), 397 (40, [M + 1]+), 396 (100, M-1), 321 (33).
Anal. Calcld for C18H28N2O6Si (396.5): C, 54.52; H, 7.12; N, 7.06.

According to general procedure 1, a mixture of methoxylallene (8; 4.20 g, 60.0 mmol), oxime 3 (2.70 g, 12.2 mmol), and Na2CO3 (3.88 g, 73.2 mmol) in r-ButOMe (180 mL) was stirred for 7 d at r.t. The resulting crude product (2.40 g, 93%) was used in the next step without further purification.

Hydrogenolysis of 1,2-Oxazines; General Procedure 2
A suspension of 10% Pd/C in MeOH (8–20 mL/mmol substrate) was saturated with H2. The corresponding 1,2-oxazine dissolved in MeOH (25 mL/mmol substrate) was added, and the mixture was stirred under H2 at atmospheric pressure and r.t. for the time indicated in the individual experiment. The suspension was then filtered through Celite, eluting with MeOH. The resulting filtrate was concentrated in vacuo and the crude product was purified as described.

Methyl-2,3-dihydroxy-3'-6'-methoxy-5'-methylene)-4'H-1,2'-oxazin-3'-ylpropenecarboxylic (11)
To a vigorously stirred solution of 6H-1,2-oxazine 4a (2.00 g, 9.38 mmol) in EtOH (200 mL) was added over a period of 20 min at 45°C a solution of KMnO4 (2.21 g, 14.0 mmol) and MgSO4 (1.70 g, 14.2 mmol) dissolved in H2O (100 mL). The resulting mixture was stirred for further 30 min at this temperature. Then 40% aq NaHSO3 (30 mL) was added, and the mixture was allowed to warm up to r.t. After filtration of the suspension and evaporation of the alcohol, the residue was saturated with NaCl. The resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (MgSO4). Evaporation of the solvent under reduced pressure gave the 2,3-dihydroxylated compound 11 (1.73 g, 75%) as a mixture of two diastereomers (82:18), which was NMR spectroscopically pure.

Hydrogenolysis of 1,2-Oxazines; General Procedure 2
A suspension of 10% Pd/C in MeOH (8–20 mL/mmol substrate) was saturated with H2. The corresponding 1,2-oxazine dissolved in MeOH (25 mL/mmol substrate) was added, and the mixture was stirred under H2 at atmospheric pressure and r.t. for the time indicated in the individual experiment. The suspension was then filtered through Celite, eluting with MeOH. The resulting filtrate was concentrated in vacuo and the crude product was purified as described.

1,2,5,6,7,8-Hexahydro-3H-pyrrolizin-3-one (12a)
According to general procedure 2, a mixture of 1,2-oxazine 4a (0.426 g, 2.00 mmol) and 10% Pd/C (0.200 g) in MeOH (20 mL) was stirred for 2 d at r.t. The resulting crude product was purified by Kugelrohr distillation (70°C/0.03 mbar) to give 1,2-oxazine 12a (0.176 g, 70%) as a colorless oil.

Hydrogenolysis of 1,2-Oxazines; General Procedure 2
A suspension of 10% Pd/C in MeOH (8–20 mL/mmol substrate) was saturated with H2. The corresponding 1,2-oxazine dissolved in MeOH (25 mL/mmol substrate) was added, and the mixture was stirred under H2 at atmospheric pressure and r.t. for the time indicated in the individual experiment. The suspension was then filtered through Celite, eluting with MeOH. The resulting filtrate was concentrated in vacuo and the crude product was purified as described.

6-Methyl-1,2,5,6,7,8-hexahydro-3H-pyrrolizin-3-one (12b)
According to general procedure 2, a mixture of 1,2-oxazine 10 (0.130 g, 0.62 mmol) and 10% Pd/C (0.150 g) in MeOH (15 mL) was stirred for 3 d at r.t. The resulting crude product was purified by column chromatography (alumina, hexane–EtOAc, 2:1 to 1:3) to give 1,2-oxazine 12b (0.044 g, 51%; mixture of two diastereomers, 96:4) as a colorless oil.

H NMR (CDCl 3, 300 MHz):  δ = 3.68 (m, 1 H, 8-H), 3.24, 2.88 (2
td, J = 6.5, 11.5 Hz, 2 H each, 3-H, 5-H), 2.17 (ddd, J = 6.5, 7, 12.5 Hz,
2 H, 1-H, 7-H), 1.98 (m, 2 H, 2-H, 6-H), 1.90 (m, 2 H, 2-H,
6-H), 1.57 (ddd, J = 6, 6.5, 12.5 Hz, 2 H, 1-H, 7-H).
13C NMR (CDCl 3, 75.5 MHz):  δ = 73.3 (d, C-8), 63.5 (t, C-3, C-5),
32.0 (t, C-1, C-7), 25.3 (t, C-2, C-6).

The NMR data of 19a are in agreement with those given in ref.33

2-Methyl-2,3,5,6,7,8-hexahydro-1H-pyrrolizidine (19b)25
According to general procedure 3, a mixture of pyrrolizidinone 12b
(0.065 g, 0.467 mmol) and BH 3·SMe2 (0.45 mL, 4.68 mmol) in THF
(6 mL) was stirred for 16 h at r.t. The resulting crude product was
purified by Kugelrohr distillation (65 °C/0.02 mbar) to give pyrro-
лизинidine 19b (0.045 g, 77%, mixture of two diastereomers, 94:6)
as a colorless oil.

H NMR (CDCl 3, 300 MHz):  δ = 3.79–3.71 (m, 1 H, 8-H), 3.43–
3.38, 3.15–3.03, 2.90–2.93, 2.59 (3 m, m, 1 H each, 3-H, 5-H),
2.34–2.23, 2.13–2.03, 2.00–1.80, 1.66–1.47 (4 m, 2 H, 1 H, 2 H, 1
H, 1-H, 2-H, 6-H, 7-H), 1.11 (dt, J = 10, 12 Hz, 1 H, 1-H), 1.01 (d,
J = 6.5 Hz, 3 H, CH3);  δ (additional signals assigned to minor
isomer) = 1.04 (d, J = 6.5 Hz, 3 H, CH3).

13C NMR (CDCl 3, 75.5 MHz):  δ = 74.1 (d, C-8),
70.7, 64.4 (2 t, C-3, C-5), 42.1, 31.4, 24.0 (3 t, C-1, C-6, C-7),
33.2 (d, C-2), 16.3 (q, CH3);  δ (minor isomer) = 73.8 (d, C-8), 39.5, 33.7,
25.2 (3 t, C-1, C-6, C-7), 16.1 (q, CH3).

The NMR data of 19b are in agreement with those given in ref.25

trans-1,2-Dihydroxy-2,3,5,6,7,8-hexahydro-1H-pyrrolizidine (19c)24,32a,b,34
According to general procedure 3, a mixture of pyrrolizidinone 12c
(0.134 g, 0.852 mmol) and BH 3·SMe2 (0.45 mL, 4.68 mmol) in THF
(10 mL) was stirred for 2 d at r.t. to give the spectroscopi-
cally pure pyrrolizidine 19c (0.114 g, 93%,
two diastereomers, 68:32) as a colorless resin.

Major Isomer
IR (KBr): 3620–3180 (O–H), 3030–2850 (C–H), 1760 cm–1 (C=O).

1H NMR (CDCl 3, 300 MHz):  δ = 4.30–4.15, 3.85–3.77, 3.70–3.51,
3.45–3.35 (4 m, 1 H, 1 H, 2 H, 1 H, 2-H, 8-H, OH), 3.30–3.04,
3.02–2.80 (2 m, 2 H each, 3-H, 5-H), 2.20–1.70 (m, 4 H, 4-H, 6-H, 7-H).

13C NMR (CDCl 3, 75.5 MHz):  δ = 82.0, 77.8, 77.7 (3 d, C-1, C-2,
C-8), 66.0, 65.1 (2 t, C-3, C-5), 30.0, 24.5 (2 t, C-6, C-7).

Additional Signals Assigned to the Minor Isomer
H NMR (CDCl 3, 300 MHz):  δ = 4.50–4.38, 4.00–3.92 (2 m, 1 H, 1

13C NMR (CDCl 3, 75.5 MHz):  δ = 77.9, 75.9, 75.2 (3 d, C-1, C-2,
C-8), 66.7, 65.6 (2 t, C-3, C-5), 26.2, 24.8 (2 t, C-6, C-7).

HRMS: m/z calcd for C19H16NO3: 143.0946; found: 143.0959.

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