Hetero Diels–Alder Reactions of 2-Chloro-1-nitroso-1-phenylethene: Preparation of Novel 4-Chloro-Substituted 1,2-Oxazines and Subsequent Reactions

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Received 25 April 1997; revised 25 June 1997

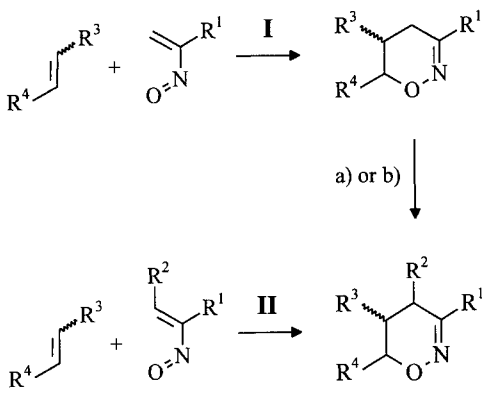
The cycloaddition of 2-chloro-1-nitroso-1-phenylethene (**3**), generated in situ from 2,2-dichloro-1-phenylethan-1-one oxime (**2**) to electron-rich olefins, e.g. silyl enol ethers or alkyl enol ethers, furnished the 4-chloro-substituted 5,6-dihydro-4*H*-1,2-oxazines and 6*H*-1,2-oxazines in moderate to good yields and with good diastereoselectivities. Bromo enol ether **18** led to the unexpected α,α-dichloro oxime derivative **21** as well as the halogenated 6*H*-1,2-oxazines **19** and **20**. Starting from 4-chloro-1,2-oxazines **5** and **17**, 4-azido-, 4-amino-, 4-hydroxy-, and 4-oxo-substituted 1,2-oxazines were prepared. Hydrogenolysis of 5,6-dihydro-4*H*-1,2-oxazine **5** afforded amine **31**.

Considerable attention has been devoted to the preparation and chemistry of 1,2-oxazines, which turned out to be valuable intermediates in organic synthesis.[1–3] Due to the presence of functionalities like C=N, N–O or an additional C=C bond, these heterocycles can be used in the synthesis of biologically active compounds, e.g. pyrroles,[4] γ-lactams,[5] pyridines,[6] proline derivatives[7–9] or indolizidines.[2] Furthermore, 1,2-oxazines have increasing interest for the synthesis of natural products and key intermediates thereof.[2,7,10] The 1,2-oxazine skeleton is also an important subunit of the antitumor antibiotics FR66979 and FR900482, respectively, which are the subject of intensive biological and chemical investigations.[11]

For the preparation of 4-substituted 1,2-oxazines two alternatives starting from in situ generated α-nitrosoalkenes are depicted in Scheme 1. The most frequently used access to these heterocycles is the cycloaddition of terminally unsubstituted α-nitrosoalkenes to suitable dienophiles followed by: a) deprotonation (i.e. with lithium diisopropylamide) and subsequent treatment with electrophiles R^2-X;[9,12] or b) radical bromination reaction with *N*-bromosuccinimide (NBS) in the presence of dibenzoyl peroxide (BzOOBz)[13] (reaction path I). The second route (path II) using α-nitrosoalkenes already bearing a R^2 substituent in the heterodiene has been less thoroughly explored. Only a few examples are described with R^2 = alkyl or halogen to give cycloadducts in mediocre to good yields.[14–16] A further possibility for the preparation of 4-substituted 1,2-oxazines starts with these N,O-heterocycles containing a C-4/C-5 double bond which may be used for addition reactions, such as dihydroxylation[2,7] or epoxidation.[17,18]

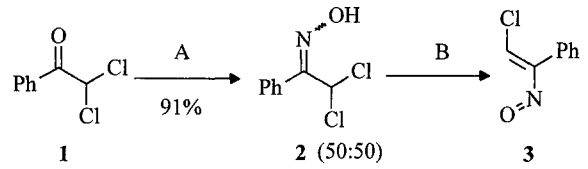
Recently, South and co-workers described the synthesis and reactions of haloazodienes furnishing pyridazine derivatives.[19] These reports prompt us to describe our results on the preparation and reactions of 4-chloro-substituted 1,2-oxazines.

We selected the α,α-dichloroacetophenone oxime **2** as precursor for in situ generation of trisubstituted α-nitrosoethene **3**. Oxime **2** was readily prepared from the commercially available ketone **1** by the typical protocol as described by Korten and Scholl[20] in excellent yield. Treatment of **2** with sodium carbonate produced a blue-green color of the solution which was discharged during the reaction with electron-rich alkenes indicating the existence of the in situ generated chloro-substituted α-nitrosoethene **3**.[21] Ethyl vinyl ether (**4**) underwent a smooth [4+2] cycloaddition with **3** giving 4-chloro-5,6-dihydro-4*H*-1,2-oxazine **5** in 79% yield and with high *cis* selectivity. With silyl enol ether **6**, product **7** was formed as a mixture of *cis*/*trans* diastereomers in 88:12 ratio and 75:25 ratio after purification by chromatography. Interestingly, attempted purification of 1,2-oxazine **7** by prolonged chromatography on neutral alumina led to partial transformation to α,β-unsaturated oxime **8** in up to 19% yield as a 67:33 mixture of oxime isomers. The reaction of the trisubstituted silyl enol ether **9** (*trans*:*cis* = 64:36) with **3** afforded the bicyclic compound **10** in 20% yield as a mixture of four diastereomers (65:28:4:3) of unknown configuration. In the 4,6-disubstituted 5,6-dihydro-4*H*-1,2-oxazines **5** and **7** the 6-alkoxy and 6-siloxy substituents, respectively, hold a pseudo-axial position allowing the N,O-heterocycles to adopt a half-chair conformation.[8] The *cis* configuration of the major isomer of **5** was assigned according to ^{1}H NMR (coupling constants of 4-H and 6-H signals) as already described in ref 8. In addition, the configuration of **5** was confirmed by 2D-COSY and 2D-NOESY NMR experiments. Reactions of intermediate **3** with the easily accessible chiral methyl (*S*)-mandelate enol ether **11**[22] led to a 60:40 mixture of optically active *cis*-configurated 4*H*-1,2-oxazine **12**.[23] The disappointingly low diastereoselectivity (20% de) of this cycloaddition reflects that both diastereotopic faces of enol ether **11** are similarly accessible.



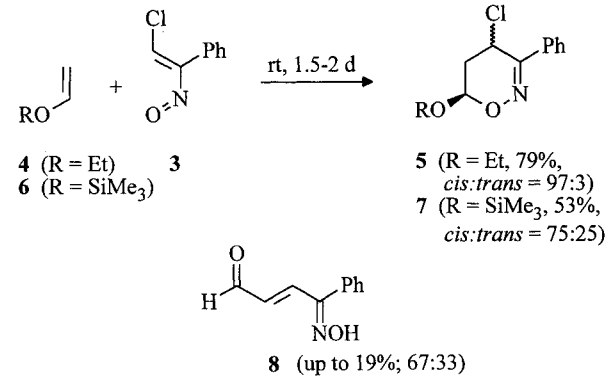
a) 1. LDA, 2. R^2-X; b) NBS. BzOOBz

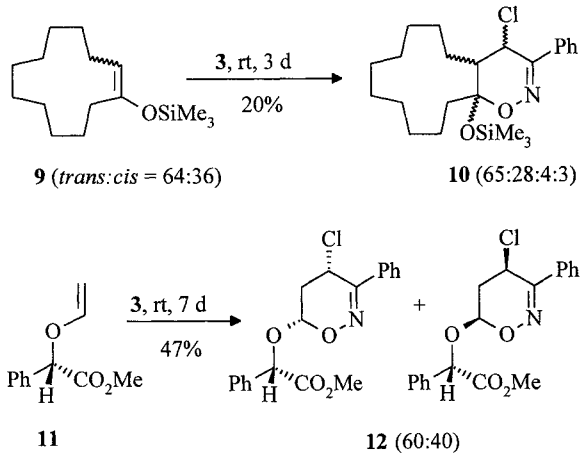
Scheme 1



A: $NH_2OH \cdot HCl$, $MeOH/H_2O$, rt, 20 h; **B:** MeO*t*-Bu, Na_2CO_3

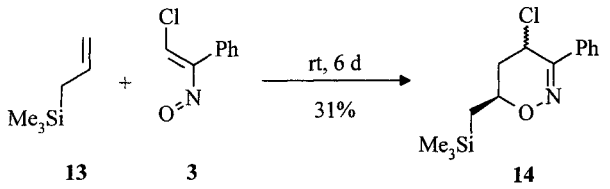
Scheme 2

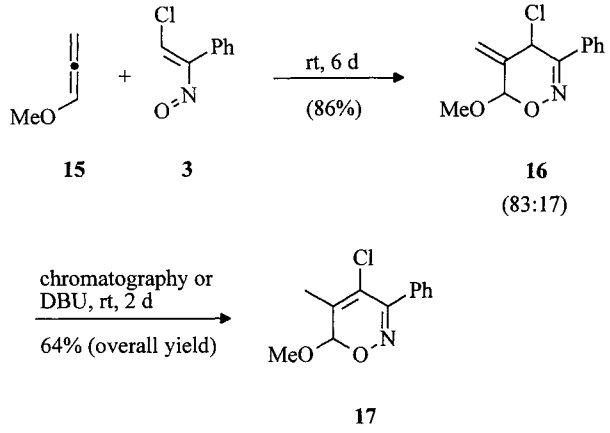




Scheme 3

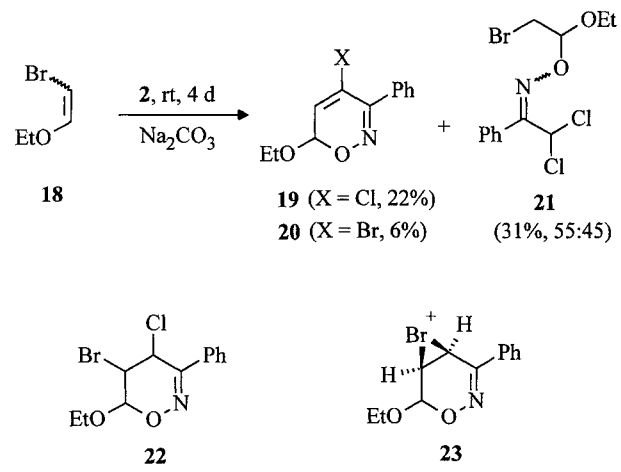
As an example of a less reactive alkene (compared with alkoxy- or siloxyalkenes)[14] allyltrimethylsilane **(13)** led to 6-(trimethylsilylmethyl)-5,6-dihydro-4*H*-1,2-oxazine **14** in 31 % yield, but in this case with moderate predominance of the *trans* isomer (*trans*:*cis* = 67:33). When methoxyallene **(15)**[24] was employed as the alkene which was a very potent dienophile in cycloadditions with other α-nitrosoalkenes,[15] heterodiene **3** provided primary product **16** bearing an exomethylene group as a mixture of diastereomers (83:17) in good yield. No criteria are available to assign the relative configuration in **16**. Subsequent isomerization of the methylene group to a conjugated C=C bond by chromatography of **16** on neutral alumina smoothly afforded 4-chloro-6*H*-1,2-oxazine **17**. This isomerization was also carried out by treatment of cycloadduct **16** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[15] at room temperature, but the yield was lower than in the chromatographic transformation described above.





Scheme 4

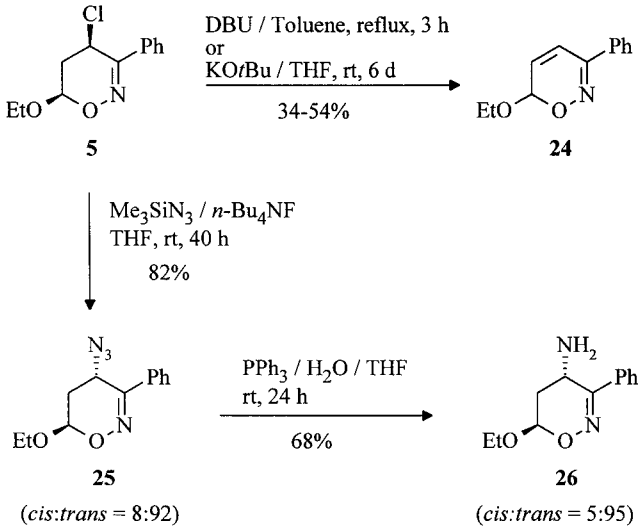
We recently reported the synthesis of dihydroxyprolinols using 6*H*-1,2-oxazines as precursors which were prepared by [4+2] cycloaddition of bromo ether **18** and several α-nitrosoalkenes followed by dehydrobromination under basic conditions.[7] Surprisingly, the reaction of oxime **2** with **18** provided oxime ether **21** as the major product in 31 % yield as an *E*/*Z* mixture (55:45).[25] In addition, we isolated the expected 4-chloro-6*H*-1,2-oxazine **19** together with its known bromo analog **20**.[13] A plausible explanation for the formation of 4-bromo-6*H*-1,2-oxazine **20** is that the 4,5-*trans*-configurated primary cycloadduct **22** suffers a bromine migration via bromonium ion **23** and subsequent abstraction of the 4-H proton to form the C-4/C-5 double bond. However, nucleophilic attack of a bromide ion at C-4 in **22** followed by dehydrobromination to form **20** may also possible.



Scheme 5

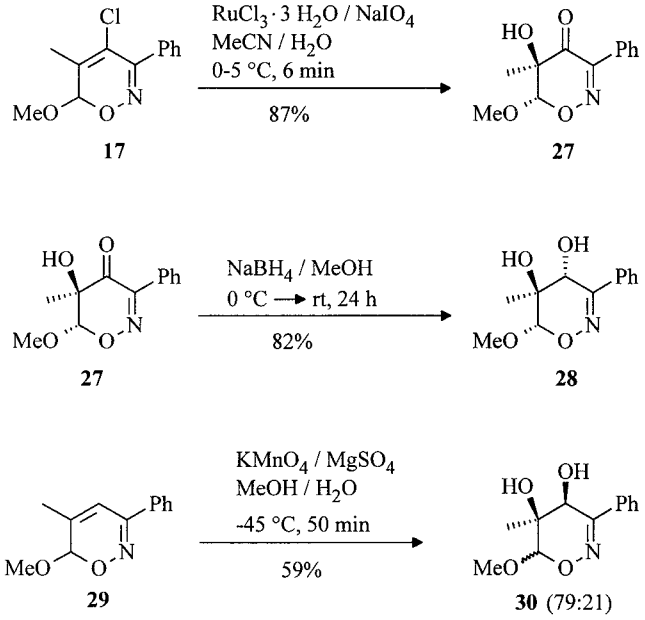
An alternative access to 6*H*-1,2-oxazines was tested from 4-chloro-substituted 5,6-dihydro-4*H*-1,2-oxazines (e.g. **5**). The deyhdrohalogenation of compound **5** required more drastic reaction conditions due to the considerably lower acidity of a 5-H proton compared with a 4-H proton.[12] Thus HCl elimination in **5** is possible with DBU in refluxing toluene as well as with potassium *tert*-butoxide in THF at room temperature to produce the corresponding 6*H*-1,2-oxazine **24**.[7,17] Extension of this elimination to the 6-(trimethylsilylmethyl)-substituted 5,6-dihydro-4*H*-1,2-oxazine **14** failed and we recovered only the *trans*-configurated starting material. Thus, the 6-alkoxy group seems to enhance the acidity of the 5-H proton in **5**.

4-Chloro-substituted 1,2-oxazines offer the possibility of introducing other functional groups at the 4-position. The S_N2 reaction of the 1,2-oxazine **5** with trimethylsilyl azide and tetrabutylammonium fluoride in THF provided the known 4-azido-5,6-dihydro-4*H*-1,2-oxazine **25**[13] (*trans*:*cis* = 92:8) in good yield. Subsequent reduction of the 4-azide group was successfully achieved by treatment with triphenylphosphine and catalytic amounts of water in THF. 4-Amino-5,6-dihydro-4*H*-1,2-oxazine **26** was formed in acceptable yield (68%) and with almost the same *trans*/*cis* ratio (95:5) as **25**.



Scheme 6

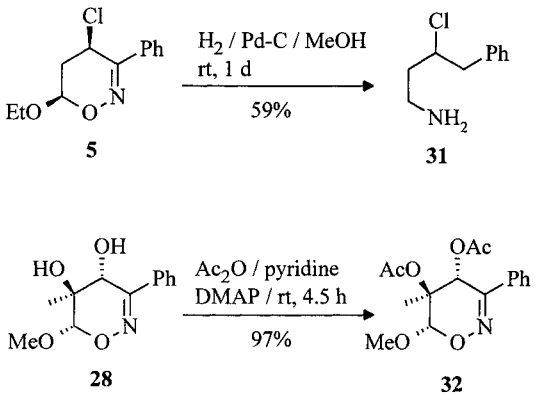
Recently, Shing and co-workers described a new practical and rapid oxidation of C=C bond into *cis* configurated dihydroxy compounds using catalytic amounts of ruthenium(III) chloride and sodium periodate.[26] This experimental protocol was employed for the oxidation of **17**. After 6 min at 0–5 °C **17** was converted into 5-hydroxy-5,6-dihydro-4*H*-1,2-oxazin-4-one **27** as a single isomer in high yield. Similarly to the dihydroxylation of 6*H*-1,2-oxazine **24**[7] we suppose that *trans*-attack with respect to the 6-alkoxy group is favored. Using sodium borohydride in methanol the reduction of the carbonyl unit at C-4 in **27** was smoothly effected and with high diastereoselectivity affording only the 4,5-*trans*-substituted dihydroxy compound **28** in 82% yield. In order to check the *trans* configuration of the 4- and 5-hydroxy group in **28**, we prepared the corresponding *cis*-compound. Thus, 6*H*-1,2-oxazine **29**[15] was *cis*-dihydroxylated by $KMnO_4$ under standard conditions[7,17] to provide the 4,5-dihydroxy-substituted heterocycle **30** as a mixture of two 4,5-*cis*-configurated diastereomers (79:21) in 59% yield whose spectroscopic data were different from those of **28**.



Scheme 7

The transformation of 1,2-oxazines into primary or secondary amines by catalytic hydrogenolysis is well known.[2,7,9,27] When the 4-chloro-substituted compound **5** was used as starting material we obtained 3-chloro-4-phenylbutylamine **(31)** in 59% yield. The γ-chloroamine **31** was too unstable for purification by distillation or chromatography. A plausible mechanism of this multistep hydrogenolysis of 3-phenyl-substituted 1,2-oxazines involving reductive N–O bond opening, formation of a 2-phenyl-substituted pyrrolidine intermediate, and finally cleavage of the benzylic C–N bond has already been discussed.[9,27,28] Acetylation of diol **28** afforded the protected compound **32** which was subjected to hydrogenolysis, but no pyrrole derivatives were formed.[17] Under usual reaction conditions (room temperature, 1 d) only the starting material **32** was reisolated. Further investigations of hydrogenolysis using 4,5-dihydroxylated 5,6-dihydro-4*H*-1,2-oxazines are in progress[29] and will be reported elsewhere.

In the present paper, we have demonstrated a general and convenient route to 4-chloro-substituted 5,6-dihydro-4*H*-1,2-oxazines and 6*H*-1,2-oxazines. The easy access to the halogenated 1,2-oxazines makes it possible to introduce other functionalities, e.g. hydroxy, amino, azido, and carbonyl groups, into these six-membered N,O-heterocycles, thus enhancing the synthetic potential of these compounds.



Scheme 8

All reactions were performed under argon atmosphere 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 spectrometer IR-325 or Nicolet 205. ^{1}H and ^{13}C NMR spectra were recorded with Bruker instruments (AC 200, AC 300 or DRX-500) in $CDCl_3$ solution. The chemical shifts are given relative to TMS from solvent ($CDCl_3$) signal ($\delta_H = 7.27$, $\delta_C = 77.0$). Missing signals of the minor isomer are hidden by signals of the major isomer or they could not be unambiguously identified due to low intensity. Neutral alumina (activity III, Fa. 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 Gallenkamp (MPD 350). Ethyl vinyl ether **(4)**, trimethylsilyl azide, allyltrimethylsilane **(13)**, and dichloro ketone **1** were commercially available and were used as received. Na_2CO_3 was freshly pulverized (electric coffee mill, Braun KSM 1G) before use. Synthesis of starting materials: silyl enol ether **6**[30] and **9**,[31] methyl *O*-vinyl-(*S*)-mandelate **11**,[22] methoxyallene **(15)**,[32] 1-bromo-2-ethoxyethene **(18)**.[33]

2,2-Dichloro-1-phenylethan-1-one Oxime (2):
According to ref. 20 a solution of **1** (31.2 g, 165 mmol) in MeOH (150 mL) was treated with a solution of hydroxylamine hydrochloride (45.9 g, 660 mmol) in H_2O (75 mL). After stirring for 20 h at r.t. the solution was diluted with water and the resulting precipitate was separated by filtration. Recrystallization of the crude product from hexane/cyclohexane gave **2** (30.8 g, 91%, *E*/*Z* isomers = 50:50) as colorless crystals; mp 39–41 °C.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.71$, 8.90 (2 br s, 0.5 H each, NOH), 7.86–7.75, 7.54–7.39 (2 m, 2 H, 3 H, Ph), 6.68, 5.26 (2 s, 0.5 H each, $CHCl_2$).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 155.2$, 154.6 (2 s, C=N), 130.6, 130.1, 130.0, 128.9, 128.3, 128.2, 128.1 (s, 6 d, Ph), 69.7, 59.2 (2 d, $CHCl_2$).

IR ($CHCl_3$): $\nu = 3500–3200$ (O–H), 3050–2900 (=C–H, C–H), 1590 cm^{-1} (C=N).

Anal. calcd for $C_8H_7Cl_2NO$ (204.2): C, 47.05; H, 3.46; N, 6.86; Cl, 34.77. Found: C, 47.39; H, 3.49; N, 6.54; Cl, 36.43.

Synthesis of 1,2-Oxazines; General Procedure:
α-Halo oxime **2** was dissolved in dry MeO*t*Bu (10–20 mL/mmol of oxime) and the corresponding alkene (5–10 equiv) was added. To this solution freshly ground Na_2CO_3 (6–10 mmol/mmol of oxime) was given and the suspension was stirred at r.t. for the indicated time. The progress of the reaction was controlled by TLC. After consumption of oxime **2** the suspension was filtered through a sintered glass plug which contained a pad of Celite. The filtrate was concentrated in vacuo (30–35 °C/100 mbar) and the resulting crude 1,2-oxazine was purified by column chromatography.

(E)-4-(Hydroxyimino)-4-phenylbut-2-enal **(8)**: Pale yellow oil; yield after chromatography of **7** up to 19%, mixture of *Z*/*E* oximes (67:33).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.4$ (br s, 1 H, NOH), 9.76 (d, $J = 7.8$ Hz, 0.33 H, 1-H), 9.64 (d, $J = 7.8$ Hz, 0.67 H, 1-H), 7.95 (d, $J = 16.3$ Hz, 0.33 H, 3-H), 7.52–7.30, 7.36 (m, d, $J = 16.0$ Hz, 5.67 H, Ph, 3-H), 6.34 (dd, $J = 7.8$, 16.3 Hz, 0.33 H, 2-H), 6.09 (dd, $J = 7.8$, 16.0 Hz, 0.67 H, 2-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 194.4$*, 193.7 (2 d, C-1), 157.4, 155.3* (2 s, C-4), 148.9, 137.8*, 136.1*, 134.3 (4 d, C-2, C-3), 133.0, 130.0*, 129.4, 129.1*, 128.8*, 128.5, 128.2 (s, 6 d, Ph). Signals marked with * are due to the minor isomer.

IR (CCl_4): $\nu = 3600–3150$ (O–H), 3090–2860 (=C–H, C–H), 1685 (C=O), 1610 cm^{-1} (C=C, C=N).

Anal. calcd for $C_{10}H_9NO_2$ (175.2): C, 68.56; H, 5.18; N, 7.99. Found: C, 68.00; H, 5.75; N, 7.69.

Table 1. Synthesis of 1,2-Oxazines **5**, **7**, **10**, **12**, **14**, and **16** by Hetero Diels–Alder Reaction

Oxime **2** [g (mmol)]	Dienophile [g (mmol)]	Na_2CO_3 [g (mmol)]	Time (d)	1,2-Oxazine[a] (*cis*:*trans*)	Yield [g (%)]	Solvent for Chromatography	mp (°C) (Solvent)	IR ν (cm^{-1})[b] (C=N)
3.06 (15)	**4** 5.40 (75)	9.54 (90)	1.5	**5** 97:3 (90:10)[c]	2.83 (79)	–	50–53 (hexane/EtOAc)	1585
2.04 (10)	**6** 5.80 (50)	6.36 (60)	2	**7** 75:25 (88:12)[c]	1.49 (53)	hexane/EtOAc (10:1)	41–46	1600
1.38 (6.77)	**9** 0.86 (3.39)[d]	3.50 (33)	3	**10** –[e]	0.279 (20)	hexane/EtOAc (8:1 → 6:1 → 4:1)	resin	1580
0.108 (0.53)	**11** 1.01 (5.25)	0.318 (3)	7	**12** 60:40[f]	0.090 (47)	hexane/EtOAc (3:1)	93–98	1640, 1740 (C=O)
2.04 (10)	**13** 4.71 (41)	6.36 (60)	6	**14** 33:67	0.873 (31)	hexane/EtOAc (10:1)	oil	1600
2.04 (10)	**15** 3.50 (50)	6.36 (60)	6	**16** 83:17[g]	2.15 (86)	–	oil	1600, 1645 (C=C)

[a] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.21, N ± 0.28; exceptions: **7** C + 0.53, H − 0.49; **10** C − 0.78.
[b] Oils as film or in CCl_4, solids as KBr pellets.
[c] *cis*/*trans* Ratio of the crude product.
[d] *trans*:*cis* = 64:36.
[e] Four isomers = 65:28:4:3.
[f] Two *cis* isomers.
[g] Two isomers = 83:17; an elemental analysis was carried out after isomerization to **17**.

Table 2. ^{1}H NMR Data of 1,2-Oxazines **5**, **7**, **10**, **12**, **14**, **16**, **17**, **19**, **24**, **26–28**, **30**, and **32**

Compound	^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ, J (Hz)
cis-**5**[a]	7.79–7.77, 7.15–7.09 (2 m, 2 H, 3 H, Ph), 4.79 (br t, $J \approx 2.8$, 1 H, 6-H), 4.15 (dd, $J = 1.7$, 6.9, 1 H, 4-H), 3.84–3.78, 3.36–3.30 (2 m, 2 H, OCH_2), 2.16 (td, $J = 2$, 15.1, 1 H, 5-H_{eq}), 1.72 (ddd, $J = 3$, 6.9, 15.1, 1 H, 5-H_{ax}), 1.04 (t, $J = 7$, 3 H, Me)
trans-**5**[a,b]	7.76–7.67 (2 m, 2 H, Ph), 5.00 (dd, $J = 1$, 2.5, 1 H, 6-H), 4.46 (t, $J = 5.5$, 1 H, 4-H), 0.99 (t, $J = 7$, 3 H, Me)
cis-**7**	7.83–7.59, 7.55–7.35 (2 m, 2 H, 3 H, Ph), 5.62 (t, $J = 3$, 1 H, 6-H), 4.84 (dd, $J = 2.5$, 6.5, 1 H, 4-H), 2.68–2.38 (m, 2 H, 5-H), 0.22 (s, 9 H, $OSiMe_3$)
trans-**7**[b]	5.57 (dd, $J = 3.5$, 6.5, 1 H, 6-H), 5.04 (t, $J = 5$, 1 H, 4-H), 0.25 (s, 9 H, $OSiMe_3$)
10	7.85–7.75, 7.50–7.37 (2 m, 1.3 H, 3.7 H, Ph), 5.44 (d, $J = 6$, 0.04 H, 4-H), 4.89 (d, $J = 5.5$, 0.65 H, 4-H), 4.65 (d, $J = 5.5$, 0.28 H, 4-H), 4.58 (br s, 0.03 H, 4-H), 2.52–2.30, 2.07–1.07 (2 m, 1 H, 20 H, 4a-H, 5-H to 14-H), 0.17, 0.16, 0.12, 0.11 (4 s, 5.85 H, 0.27 H, 0.36 H, 2.52 H, $OSiMe_3$)
cis-**12** (major)	7.80–7.26 (m, 10 H, 2 Ph), 5.59 (dd, $J = 2.3$, 3.2, 1 H, 6-H), 5.50 (s, 1 H, CH), 4.83 (dd, $J = 1.4$, 7.0, 1 H, 4-H), 3.74 (s, 3 H, OMe), 2.92 (ddd, $J = 1.2$, 2.3, 15.4, 1 H, 5-H_{eq}), 2.63 (ddd, $J = 3.2$, 7.0, 15.4, 1 H, 5-H_{ax})
cis-**12** (minor)[b]	7.80–7.26 (m, 10 H, 2 Ph), 5.31 (s, 1 H, CH), 5.29 (dd, $J = 0.7$, 3.1, 1 H, 6-H), 4.84 (dd, $J = 1.7$, 6.8, 1 H, 4-H), 3.70 (s, 3 H, OMe), 2.76 (ddd, $J = 0.7$, 1.7, 15.4, 1 H, 5-H_{eq}), 2.55 (ddd, $J = 3.1$, 6.8, 15.4, 1 H, 5-H_{ax})
trans-**14**	7.64–7.59, 7.30–7.24 (2 m, 2 H, 3 H, Ph), 4.75 (dd, $J = 2$,4, 1 H, 4-H_{eq}), 4.29–4.12 (m, 1 H, 6-H), 2.25 (td, $J = 2$, 15, 1 H, 5-H_{eq}), 2.02 (ddd, $J = 4$, 11.5, 15, 1 H, 5-H_{ax}), 1.09 (dd, $J = 6.5$, 14.5, 1 H, $SiCH_2$), 0.85 (dd, $J = 8$, 14.5, 1 H, $SiCH_2$), 0.00 (s, 9 H, $SiMe_3$)
cis-**14**[b]	4.87 (dd, $J = 8$, 9.5, 1 H, 4-H_{ax}), 4.00–3.85 (m, 1 H, 6-H), 2.53 (ddd, $J = 2$, 8, 13.5, 1 H, 5-H_{eq}), −0.02 (s, 9 H, $SiMe_3$)
16 (major)	7.78–7.70, 7.45–7.40 (2 m, 2 H, 3 H, Ph), 5.68, 5.65 (2 s, 2 H, $=CH_2$), 5.39, 5.22 (2 s, 2 H, 4-H, 6-H), 3.58 (s, 3 H, OMe)
16 (minor)[b]	5.64, 5.63 (2 s, 2 H, $=CH_2$), 5.57, 5.42 (2 s, 2 H, 4-H, 6-H), 3.64 (s, 3 H, OMe)
17	7.66–7.52, 7.46–7.38 (2 m, 2 H, 3 H, Ph), 5.42 (s, 1 H, 6-H), 3.54 (s, 3 H, OMe), 2.14 (s, 3 H, 5-Me)
19	8.06–8.02, 7.67–7.40 (2 m, 2 H, 3 H, Ph), 6.45 (d, $J = 5.1$, 1 H, 5-H), 5.68 (d, $J = 5.1$, 1 H, 6-H), 4.01–3.88, 3.75–3.61 (2 m, 2 H, OCH_2), 1.22 (t, $J = 7$, 3 H, Me)
24	7.74–7.69, 7.44–7.36 (2 m, 2 H, 3 H, Ph), 6.59 (d, $J = 10$, 1 H, 4-H), 6.41 (dd, $J = 4.5$, 10, 1 H, 5-H), 5.60 (d, $J = 4.5$, 1 H, 6-H), AB part of ABX_3 system ($\delta_A = 3.99$, $\delta_B = 3.69$, $J_{AX} = J_{BX} = 7$, $J_{AB} = 10$, 2 H, OCH_2), 1.22 (t, $J = 7$, 3 H, Me)
trans-**26**	7.65–7.55, 7.50–7.30 (2 m, 2 H, 3 H, Ph), 5.20 (dd, $J = 2.8$, 3.7, 1 H, 6-H), 4.13 (dd, $J = 7.3$, 9.4, 1 H, 4-H), 4.00–3.83, 3.73–3.57 (2 m, 2 H, OCH_2), 2.45–2.28, 1.96 (m, ddd, $J = 2.8$, 9.4, 13.3, 1 H each, 5-H), 1.46 (br s, 2 H, NH_2), 1.23 (t, $J = 7$, 3 H, Me)
cis-**26**[b]	7.71–7.67 (m, 2 H, Ph), 5.31 (t, $J = 2.6$, 1 H, 6-H), 2.45–2.28 (m, 2 H, 5-H), 1.22 (t, $J = 7$, 3 H, Me)
27	7.70–7.61, 7.50–7.34 (2 m, 2 H, 3 H, Ph), 5.10 (s, 1 H, 6-H), 3.70 (s, 3 H, OMe), 3.21 (s, 1 H, 5-OH), 1.45 (s, 3 H, Me)
28	7.92–7.85, 7.45–7.37 (2 m, 2 H, 3 H, Ph), 4.85 (s, 1 H, 6-H), 3.96 (d, $J = 12$, 1 H, 4-H), 3.52 (s, 3 H, OMe), 3.31 (d, $J = 12$, 1 H, 4-OH), 2.36 (br s, 1 H, 5-OH), 1.56 (s, 3 H, 5-Me)[c]
30 (major)	7.71–7.62, 7.45–7.34 (2 m, 2 H, 3 H, Ph), 4.78 (s, 1 H, 6-H), 4.43 (s, 1 H, 4-H), 3.47 (s, 3 H, OMe), 3.30 (br s, 2 H, 2 OH), 1.38 (s, 3 H, 5-Me)
30 (minor)[b]	5.08 (s, 1 H, 6-H), 3.64 (s, 3 H, OMe), 1.41 (s, 3 H, 5-Me)
32	7.60–7.55, 7.43–7.34 (2 m, 2 H, 3 H, Ph), 5.99, 5.73 (2 s, 1 H each, 4-H, 6-H), 3.53 (s, 3 H, OMe), 2.04, 1.99 (2 s, 3 H each, 4-OAc, 5-OAc), 1.59 (s, 3 H, 5-Me)

[a] Recorded on 500 MHz spectrometer in C_6D_6.
[b] Missing signals are hidden by that of the major isomer.
[c] After H/D-exchange with D_2O the doublet at 3.31 ppm and the broad singlet at 2.36 ppm disappeared and the doublet at 3.96 ppm became a singlet.

4-Chloro-6-methoxy-5-methyl-3-phenyl-6*H*-1,2-oxazine (17):
Method A: Chromatography (hexane/EtOAc, 4:1) of **16** (2.15 g, 9.05 mmol) provided **17** (1.53 g, 64% starting from **2**) as a pale yellow oil.

Method B: According to ref. 15 **16** (0.477 g, 2 mmol) and DBU (0.061 g, 0.4 mmol) were dissolved in CH_2Cl_2 (20 mL). After 2 d at r.t. 1 N HCl soln (2 mL) was added, the phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 3 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude residue was purified by chromatography (hexane/EtOAc, 10:1). Yield: 0.262 g (55%) of **17**. The NMR data are given in Tables 2 and 3.

IR (CCl_4): ν = 3180–2760 (=C–H, C–H), 1645 (C=C), 1575 cm^{-1} (C=N).

Anal. calcd for $C_{12}H_{12}ClNO_2$ (237.7): C, 60.64; H, 5.09; N, 5.89; Cl, 14.93. Found: C, 60.20; H, 5.07; N, 5.42; Cl, 14.61.

Reaction of Oxime 2 with Bromo Enol Ether 18:
According to the general procedure, a mixture of **2** (3.06 g, 15 mmol), **18** (11.3 g, 75 mmol), and Na_2CO_3 (9.54 g, 90 mmol) in MeO*t*Bu (250 mL) was stirred for 4 d. Yield after chromatography (hexane/EtOAc, 10:1 → 4:1): 1.65 g (31%) of **21** (two isomers = 55:45) and a mixture of **19** and **20** (0.70 g, 22% **19**, 6% **20**). 4-Chloro-6-ethoxy-3-phenyl-6*H*-1,2-oxazine (**19**): See Tables 2 and 3. 4-Bromo-6-ethoxy-3-phenyl-6*H*-1,2-oxazine (**20**): ^{1}H and ^{13}C NMR data are identical with those reported earlier.[13]

2,2-Dichloro-1-phenylethan-1-one O-(2-Bromo-1-ethoxyethyl)oxime (**21**):

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.80, 7.54–7.38 (2 m, 2 H, 3 H, Ph), 7.35, 6.55* (2 s, 1 H, $CHCl_2$), 5.43, 5.23* (2 t, J = 5.3 and 5.5 Hz, 1 H, C*H*OEt), 3.99–3.41 (m, 4 H, OCH_2, CH_2Br), 1.26, 1.24* (2 t, J = 7 Hz, 3 H, Me). Signals marked with * are due to the minor isomer.

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.6*, 154.4 (2 s, C=N), 130.6, 130.1, 129.8*, 129.1, 128.3*, 128.2, 128.1* (s, 6 d, Ph), 105.6, 105.2* (2 d, *C*HOEt), 70.1*, 59.6 (2 d, $CHCl_2$), 65.6, 65.3* (2 t, OCH_2), 30.8, 30.6* (2 t, CH_2Br), 15.03, 14.98* (2 q, Me). Signals marked with * are due to the minor isomer.

IR (CCl_4): ν = 3100–2840 (=C–H, C–H), 1620 cm^{-1} (C=N).

MS (FI): m/z (%) = 359, 357, 355, 353 (M^+, 13, 43, 100, 56), 153 (21), 152 (52), 151 (27), 150 (33).

Table 3. ^{13}C NMR Data[a] of Prepared 1,2-Oxazines **5**, **7**, **10**, **12**, **14**, **16**, **17**, **19**, **24**, **26–28**, **30**, and **32**

Compound	C-3 (s)	C-4 (d)	C-5 (t)	C-6 (d)	Other signals
cis-**5**	154.0	38.9	32.5	93.6	133.2, 131.0, 128.6, 126.1 (s, 3d, Ph), 63.9 (t, OCH_2), 14.7 (q, Me)
trans-**5**	153.7	44.7	34.0	96.6	132.8, 129.3, 128.5, 126.0 (s, 3d, Ph), 65.0 (t, OCH_2), 14.8 (q, Me)
cis-**7**	153.7	39.3	34.3	89.4	133.5, 129.9, 129.3, 126.4 (s, 3d, Ph), 0.03 (q, $OSiMe_3$)
trans-**7**	152.9	45.4	36.3	92.2	133.0, 129.8, 129.3, 126.3 (s, 3d, Ph), 0.4 (q, $OSiMe_3$)
10[b]	156.0*				134.3*, 133.7#, 129.6, 129.4#, 128.9*, 128.8, 128.3#, 128.0*, 127.8, 127.2,
	151.8#	[c]	[c]	[c]	126.5*, 126.3, 126.0# (2s, 11d, Ph), 104.6, 103.3*, 100.5#, 100.1 (4s, C-14a), 54.8*, 54.1, 45.6, 44.9#, 42.8, 42.1*, 39.5, 36.4# (8d, C-4, C-4a), 36.8*, 35.4#, 32.0, 28.8–20.1 (3t, several t, C-5 to C-14), 1.4#, 1.2, 1.1*, 1.0 (4q, $OSiMe_3$)
cis-**12** (major)	155.0	38.3	32.5	92.32	170.9 (s, CO_2Me), 135.7, 133.3, 130.1–126.5 (2s, several d, 2Ph), 76.7 (d, CH), 52.4 (q, OMe)
cis-**12** (minor)	154.4	38.4	32.3	92.27	170.1 (s, CO_2Me), 135.3, 133.4, 130.1–126.5 (2s, several d, 2Ph), 78.6 (d, CH), 52.3 (q, 5-Me)
trans-**14**	152.0	44.7	36.7	70.4	132.8, 129.1, 128.8, 125.9 (s, 3d, Ph), 22.2 (t, $SiCH_2$), −0.7 (q, $SiMe_3$)
cis-**14**	154.1	46.2	39.1	67.8	132.1, 129.0, 128.6, 126.7 (s, 3d, Ph), 22.7 (t, $SiCH_2$), −0.8 (q, $SiMe_3$)
16 (major)	154.2	42.9	134.5[d] (s)	98.9	132.6,[d] 130.2, 128.7, 126.6 (s, 3d, Ph), 121.3 (t, $=CH_2$), 56.0 (q, OMe)
16 (minor)	156.8	47.6	134.2[d] (s)	99.3	132.3,[d] 129.7, 128.9, 126.5 (s, 3d, Ph), 117.9 (t, $=CH_2$), 56.6 (q, OMe)
17	156.1	[c]	[c]	99.7	134.5, 133.1, 132.2, 129.7, 128.9, 128.1 (3s, 3d, Ph, C-4, C-5), 56.2 (q, OMe), 16.9 (q, 5-Me)
19	155.7	127.8 (s)	123.3 (d)	94.7	131.9, 130.3, 128.8, 128.0 (s, 3d, Ph), 64.3 (t, OCH_2), 14.8 (q, Me)
24	154.1	116.2	126.2[d] (d)	91.8	133.9, 129.9, 128.7, 126.0[d] (s, 3d, Ph), 64.1 (t, OCH_2), 15.0 (q, Me)
trans-**26**	160.9	39.8	33.4	97.1	134.2, 129.7, 129.4, 126.9 (s, 3d, Ph), 64.2 (t, OCH_2), 15.0 (q, Me)
cis-**26**	159.8	37.8	31.3	94.9	134.4, 128.8, 128.6, 126.4 (s, 3d, Ph), 64.0 (t, OCH_2), 15.1 (q, Me)
27	153.7	188.5 (s)	72.4 (s)	107.9	130.8, 129.9, 129.0, 128.4 (d, s, 2d, Ph), 58.0 (q, OMe), 16.5 (q, 5-Me)
28	157.8	65.2	67.4 (s)	102.4	133.8, 130.2, 128.6, 126.6 (s, 3d, Ph), 56.8 (q, OMe), 19.7 (q, 5-Me)
30 (major)	159.6	64.5	67.4 (s)	103.6	133.1, 129.7, 128.3, 127.4 (s, 3d, Ph), 56.7 (q, OMe), 20.6 (q, 5-Me)
30 (minor)	153.8	57.8	72.1 (s)	107.9	130.2, 129.9, 128.6, 125.5 (s, 3d, Ph), 56.6 (q, OMe), 20.9 (q, 5-Me)
32	155.0	62.1	77.8 (s)	97.4	170.3, 169.9 (2s, 2*C*OMe), 132.9, 130.0, 128.5, 126.3 (s, 3d, Ph), 56.8 (q, OMe), 21.8, 20.4 (2q, 2CO*Me*), 15.3 (q, 5-Me)

[a] 75.5 MHz, $CDCl_3$, δ.
[b] Four isomers (65:28:4:3), signals marked with # are due to the major isomer and marked with * are due to the 28%-isomer.
[c] See column "other signals".
[d] Assignment ambiguous; signals are exchangeable with others for this compound.

Anal. calcd for $C_{12}H_{13}BrCl_2NO_2$ (354.1): C, 40.91; H, 3.72; N, 3.98; Br, 22.59; Cl, 20.05. Found: C, 40.82; H, 4.04; N, 4.30; Br, 23.91; Cl, 18.39.

6-Ethoxy-3-phenyl-6*H*-1,2-oxazine (24):
Method A: A solution containing **5** (0.479 g, 2 mmol) and DBU (0.609 g, 4 mmol) in toluene (10 mL) was heated to reflux for 3 h. Then, the resulting mixture was worked-up as described above for the isomerization to **17**. Purification by chromatography (hexane/EtOAc, 6:1) gave 0.138 g (34%) of **24**[17] as a pale yellow oil which slowly crystallized at −20°C; mp 40–41°C.

Method B: To a solution of **5** (0.422 g, 1.76 mmol) in dry THF (10 mL) was added KO*t*Bu (0.351 g, 3.13 mmol). The reaction mixture was stirred for 6 d at r.t., and then filtered through Celite, concentrated and purified by chromatography (hexane/EtOAc, 6:1). Yield: 0.195 g (54%) of **24**. The NMR data are given in Tables 2 and 3.

IR (Nujol): ν = 3090–2800 (=C–H, C–H), 1635 (C=C), 1585 cm^{-1} (C=N).

Anal. calcd for $C_{12}H_{13}NO_2$ (203.2): C, 70.92; H, 6.45; N; 6.89. Found: C, 71.12; H, 6.55; N, 6.61.

4-Azido-6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (25):
To a solution of **5** (0.240 g, 1 mmol) in THF (5 mL) were added successively Me_3SiN_3 (0.173 g, 1.5 mmol) and *n*-$Bu_4NF \cdot 3\ H_2O$ (0.473 g, 1.5 mmol). After 40 h at r.t. the reaction mixture was poured into H_2O (2 mL), and the product was extracted with Et_2O (3 × 5 mL). The organic layers were dried ($MgSO_4$), concentrated, and then chromatographed (hexane/EtOAc, 10:1). Yield: 0.201 g (82%) of **25** (*cis*:*trans* = 8:92) as a yellow oil (ref.[13] mp 56–57°C). ^1H and ^{13}C NMR data are identical with those reported earlier.[13]

4-Amino-6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine (26):
To a solution of **25** (0.100 g, 0.41 mmol) and PPh_3 (0.118 g, 0.45 mmol) in THF (1 mL) were added 2 drops of H_2O. After 24 h at r.t. the mixture was diluted with Et_2O/H_2O (5 mL/1 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and the resulting residue was purified by Kugelrohr distillation (bp 150°C/0.05 mbar). Yield: 0.061 g (68%) of **26** (*cis*:*trans* = 5:95) as a colorless oil. The NMR data are given in Tables 2 and 3.

IR (CCl_4): ν = 3600–3200 (N–H), 3060–2870 (=C–H, C–H), 1620 cm^{-1} (C=N).

Anal. calcd for $C_{12}H_{16}N_2O_2$ (220.3): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.01; H, 7.08; N, 12.30.

5-Hydroxy-6-methoxy-5-methyl-3-phenyl-5,6-dihydro-4*H*-1,2-oxazin-4-one (27):
According to the dihydroxylation protocol as described in ref. 26 (method B) the reaction of **17** (0.940 g, 3.95 mmol), $RuCl_3 \cdot 3\ H_2O$ (58.1 mg, 0.222 mmol), $NaIO_4$ (1.27 g, 5.95 mmol) in $MeCN/H_2O$ (47.5 mL/7.9 mL) (reaction time: 6 min at 0–5°C) provided after purification by chromatography on silica gel (EtOAc/hexane, 3:1 → EtOAc) 0.813 g (87%) of **27**. The NMR data are given in Tables 2 and 3.

IR (CCl_4): ν = 3600–3150 (O–H), 3050–2850 (=C–H, C–H), 1720 (C=O), 1640 cm^{-1} (C=N).

Anal. calcd for $C_{12}H_{13}NO_4$ (235.2): C, 61.27; H, 5.57; N; 5.95. Found: C, 61.00; H, 5.93; N, 5.83.

r-4,t-5-Dihydroxy-c-6-methoxy-c-5-methyl-3-phenyl-5,6-dihydro-4H-1,2-oxazine (28):

27 (0.183 g, 0.775 mmol) was dissolved in dry MeOH (3 mL) and the solution was cooled to 0 °C. Then $NaBH_4$ (0.031 g, 0.8 mmol) was added. After warming up to r.t. the reaction mixture was stirred for 24 h. Then the solution was concentrated and H_2O (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The resulting residue was purified by filtration (EtOAc) to give 0.151 g (82%) of isomerically pure **28** as colorless crystals; mp 104–106 °C. The NMR data are given in Tables 2 and 3.

IR (KBr): ν = 3650–3100 (O–H), 3080–2780 (=C–H, C–H), 1630 cm^{-1} (C=N).

Anal. calcd for $C_{12}H_{15}NO_4$ (237.3): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.44; N, 5.70.

r-4,c-5-Dihydroxy-6-methoxy-t-5-methyl-3-phenyl-5,6-dihydro-4H-1,2-oxazine (30):

To a vigorously stirred solution of **29** (1.02 g, 5 mmol) in MeOH (50 mL) a solution of $KMnO_4$ (0.77 g, 4.87 mmol) and $MgSO_4$ (0.527 g, 4.38 mmol) in H_2O (30 mL) was added within 20 min at −45 °C. The resulting mixture was stirred for further 30 min at this temperature. Then 40% aq $NaHSO_3$ (10 mL) was added and the mixture was allowed to warm up to r.t. After filtration and evaporation of the alcohol the residue was saturated with NaCl. The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$). The evaporation of the solvent under reduced pressure gave **30** (0.703 g, 59%) as a brownish foam (two isomers = 79:21), which was pure according to its ^1H and ^{13}C NMR spectra (see Tables 2 and 3). For full characterization of a subsequent product see ref. 17.

3-Chloro-4-phenylbutylamine (31):

Dry MeOH (30 mL) and 10% Pd/C (0.300 g) were saturated with hydrogen for 1 h at r.t. Then, **5** (0.72 g, 3 mmol) was added and the mixture was stirred under hydrogen at normal pressure for 1 d at r.t. The suspension was filtered through a sintered glass plug which contained a pad of Celite. The filtrate was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL), washed with satd $NaHCO_3$ (5 mL) and dried (Na_2SO_4). Evaporation of the solvent gave 0.646 g (59%) of **31** as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 5H, Ph), 4.11 (m_c, 1H, 3-H), 3.24–3.17, 3.05–2.97 (2m, 1H each, 1-H), 2.24–2.13, 2.03–1.60 (2m, 1H, 5H, 2-H, 4-H, NH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.7, 128.1, 126.6, 126.3 (s, 3d, Ph), 62.4 (d, C-3), 45.8 (t, C-1), 34.1, 25.4 (2t, C-2, C-4).

IR (film): ν = 3600–2800 cm^{-1} (N–H, =C–H, C–H).

A correct elemental analysis of **31** is not given, because the compound is too unstable.

r-4,t-5-Diacetoxy-c-6-methoxy-c-5-methyl-3-phenyl-5,6-dihydro-4H-1,2-oxazine (32):

To a solution of **28** (0.093 g, 0.392 mmol) in dry pyridine (7 mL) DMAP (0.015 g, 0.123 mmol) and Ac_2O (1.5 mL) were added and the solution was stirred at r.t. for 4.5 h. The reaction mixture was concentrated in vacuo, and then chromatographed (hexane/EtOAc, 4:1). Yield: 0.122 g (97%) of **32** as a colorless oil. The NMR data are given in Tables 2 and 3.

IR (film): ν = 3060–2840 (=C–H, C–H), 1750 (C=O), 1580 cm^{-1} (C=N).

Anal. calcd for $C_{16}H_{19}NO_6$ (321.3): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.73; H, 6.36; N, 4.51.

We are most grateful for generous support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. Dr. H.J. Veith and Mr. M. Fischer (Technische Hochschule Darmstadt) for measurements of mass spectra and their interpretation. F.H. thanks the Graduiertenkolleg "Struktur-Eigenschafts-Beziehungen bei Heterocyclen" for a Promotionsstipendium. Furthermore, the authors thank a referee for critical comments.

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