Reaction of *N*,*N*-Dioxyenamines with Anhydrides of Carboxylic and Sulfonic Acids; A New Method for the Synthesis of α-Hydroxyoxime Derivatives

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Abstract: The reactions of *N*,*N*-dioxyenamines with carboxylic and sulfonic acid anhydrides were investigated. A new method for the synthesis of α-hydroxyoxime derivatives via the reaction of *N*,*N*-dioxyenamines with trifluoroacetic anhydride is described.

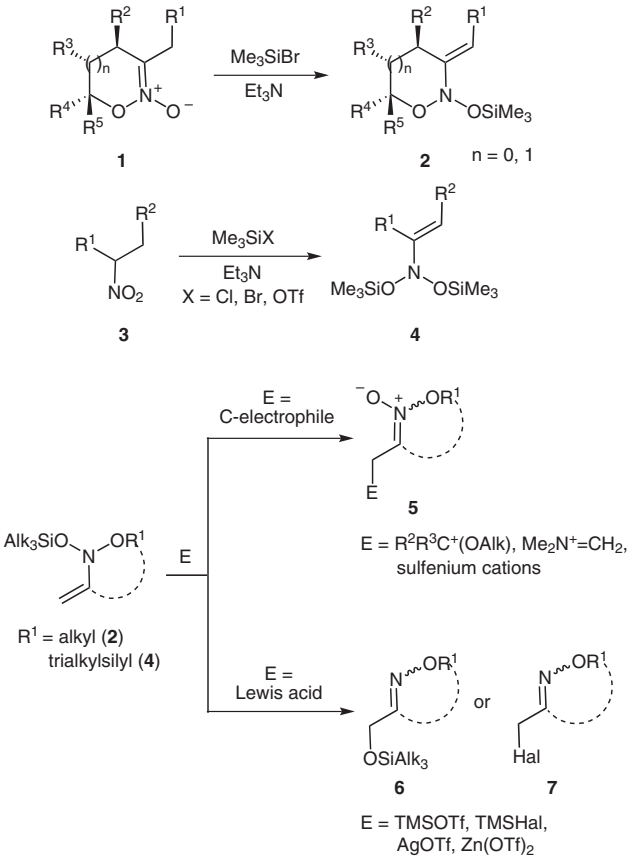
Key words: 1,2-oxazine, trifluoroacetic anhydride, hydroxyoxime, enamine, rearrangement

N,*N*-Dioxyenamines, cyclic *N*-alkoxy-*N*-siloxyenamines **2** and *N*,*N*-bis(siloxy)enamines **4**, are convenient agents in organic synthesis (Scheme 1). They are easily accessible via silylation of the corresponding nitronates[1] **1** and nitro compounds[2] **3**. The chemical properties of *N*,*N*-dioxyenamines significantly differ from 'classical' enamines. They can react not only with electrophiles (carboxonium cations,[1,3] iminium cations,[1] diarylcarbocations,[4] bromine,[5] sulfenyl chlorides, and episulfonium cations[6]), but also with nucleophiles (silyl-nitronates,[7] nitrogen-containing heterocycles and amines,[1,8] TMSCN,[9] dimethyl malonate,[10] and $TMSN_3$[11]) and sulfonyl or carboxy-stabilized radicals.[12]

Reaction of *N*,*N*-dioxyenamines **2** and **4** with electrophiles proceeds through several reaction routes to give various types of products. In the case of stabilized carbocations, nitronates **5** are formed as *N*,*N*-dioxyenamines are regarded as weak enamines.[13] In the case of Lewis acids [TMSOTf, TMSHal, $Zn(OTf)_2$, AgOTf], α-hydroxy-[14] or α-halogen-substituted[15] oxime derivatives **6** and **7**, respectively, are formed (Scheme 1).

Since acid anhydrides are strong carbon electrophiles, their reaction with *N*,*N*-dioxyenamines **2** and **4** a priori could yield nitronates **5** or oxime derivatives **6**. Herein we report our investigations on this reaction.

N,*N*-Dioxyenamine **2a** was chosen as the model substrate owing to its relative stability. It was treated with various anhydrides leading to the formation of a mixture of cyclic oxime ethers **6**–**9** in moderate yields (Scheme 2, Table 1). No traces of alkylnitronates **5** expected to be formed in the case of C-attack could be detected in the reaction mixture. The most improved result was obtained in case of reaction with trifluoroacetic anhydride (Table 1, entry 2). Unfortunately, we could not isolate trifluoroacetates like **9a**, although some of them (**9a**–**c**) were characterized by NMR spectra in the reaction mixture (see experimental part). Attempts to obtain analogous tosylate or mesylate derivatives failed (Table 1, entries 6–12).



Scheme 1 Synthesis and properties of *N*,*N*-dioxyenamines **2** and **4**

We have clearly demonstrated that treatment of *N*,*N*-dioxyenamines with trifluoroacetic anhydride represents a universal method for the synthesis of α-hydroxyoxime derivatives (Scheme 3, Table 2). Methanol workup of the reaction mixture with potassium carbonate or sodium hydroxide followed by ethyl acetate extraction gave practically pure derivatives **10** or **11** in good yields. All new compounds were characterized, see experimental part and Figure 1 for NMR numbering.

Previously reported methods for the synthesis of derivatives **10** and **11** from **2** and **4**, respectively, include rearrangement and subsequent hydrolysis of *N*,*N*-dioxyenamines (Scheme 4).[14,16]

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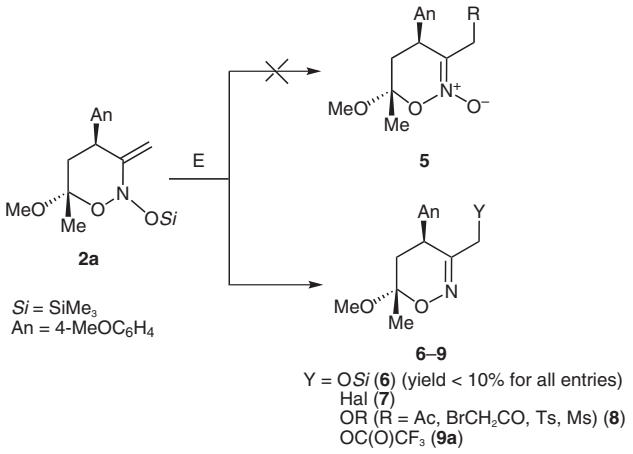
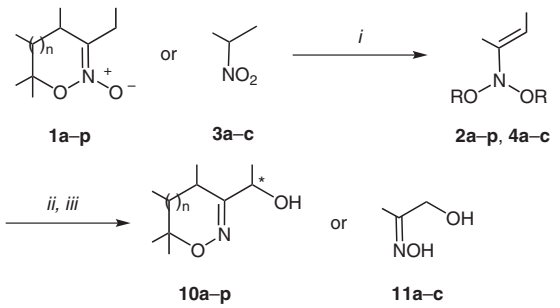
Table 1 Reaction of *N*,*N*-Dioxyenamine **2a** with Various Anhydrides

Entry	E, Conditions	Yield[a] (%)		Conversion[a] (%) of **2a**
		7	**8**	
1	AcBr (2 equiv), 1 h	<5	<5	100
2	TFAA (1.1 equiv), 1 h	–	69 (**9a**)	100
3	Ac_2O (1 equiv), 1 d	<5	<5	<5
4	$BrCH_2COBr$ (1 equiv), 2 h	<5	<5	100
5	AcCl (1 equiv), 2 h	20	<5	40
6	TsCl (1 equiv), 2 d	<5	10	36
7	MsCl (1 equiv), 1 d	<5	39	100
8	TsCl (1.5 equiv), MeOH (0.1 equiv), 7 d	15	25	84
9	TsCl (1.5 equiv), $TsOH·H_2O$ (0.01 equiv), 2 d	<5	16	35
10	TsCl (1.5 equiv), MeOH (1 equiv), 7 d	39	23	100
11	TsCl (1.5 equiv), MeOH (1 equiv), $CHCl_3$, reflux, 8 h	23	20	100
12	TsCl (1.5 equiv), H_2O (0.5 equiv), 2 d	17	19	58

[a] According to NMR with internal standard ($PhNO_2$).

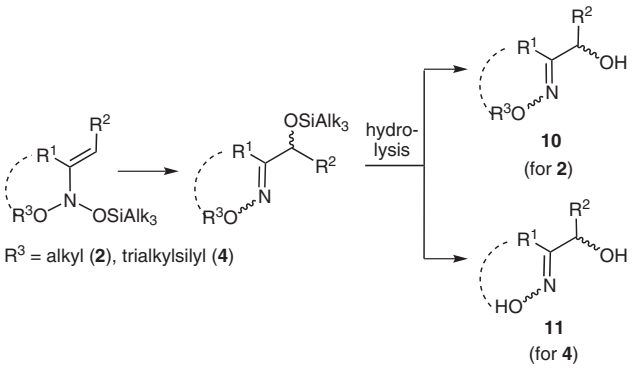


Scheme 2 Reaction of the model enamine **2a** with various anhydrides



Scheme 3 Synthesis of α-hydroxyoxime derivatives **10** and **11**. *Reaction conditions*: (*i*) TMSBr, Et_3N, CH_2Cl_2, –78 °C to r.t., 1–3 d; (*ii*) TFAA, CH_2Cl_2, –78 °C to r.t., 20 min to 1 h; (*iii*) K_2CO_3 or NaOH, MeOH, r.t., 1–3 h.

It was found that structure of the substrate has a significant effect on the reaction conditions and product yields. *N*,*N*-Bis(siloxy)enamines underwent rearrangement in good yields by treatment with zinc triflate,[14a] six-membered cyclic *N*-alkoxy-*N*-siloxyenamines by exposure to wet chloroform;[16] five-membered cyclic *N*-alkoxy-*N*-siloxyenamines did not gave satisfactory results under either conditions mentioned.[17] Thus, there was no common preparative method.



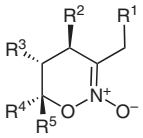
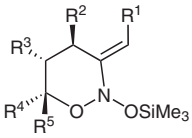
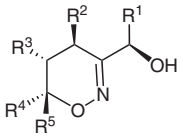
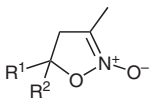
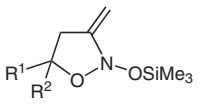
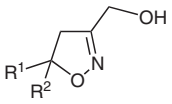
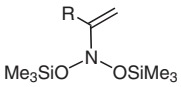
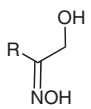
Scheme 4 Rearrangement of *N*,*N*-dioxyenamines

The reaction of six-membered cyclic *N*-alkoxy-*N*-siloxyenamines bearing an exocyclic internal double bond (Table 2, entries 7–13) with trifluoroacetic anhydride gave significantly higher yields of the target products than those reported for the known procedure (~20% on average). The method has proven to be effective for *N*,*N*-dioxyenamines that could not be subjected to the rearrangement process with reasonable yields: *N*,*N*-dioxyenamines with a terminal double bond (Table 2, en-

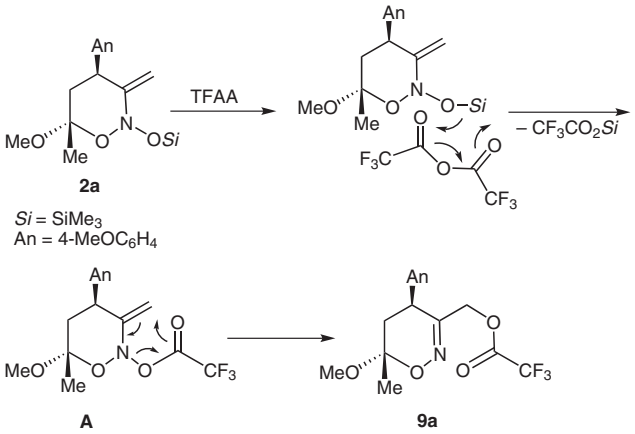
tries 1–6) and five-membered cyclic *N*-alkoxy-*N*-siloxyenamines (Table 2, entries 14–16).

We suggest that reaction of *N*,*N*-dioxyenamines with trifluoroacetic anhydride proceeds via formation of trifluoroacetoxyenamine **A**,[18] that subsequently undergoes [3,3]-sigmatropic rearrangement (Scheme 5). The high diastereoselectivity of the reaction can be explained by the preference for only one of the conformations of enamine **A** during the reaction course.[19]

Table 2 Synthesis of a-Hydroxyoxime Derivatives **10**, **11** via *N*,*N*-Dioxyenamines **2**, **4**

Entry	Starting compound	Enamine		Product			Yield (%) from **2**	de (%)	Total yield (%)
									
	1a–m	**2a–m**		**10a–m**					
	R^1	R^2	R^3	R^4	R^5				
1	H	4-$MeOC_6H_4$	H	OMe	Me	**10a**	60[a]	–	59
2	H	Ph	H	OMe	Me	**10b**	50[a]	–	49
3	H	Ph	H	Me	Me	**10c**	64[a]	–	61
4	H	4-$MeOC_6H_4$	H	Me	Me	**10d**	63[a]	–	49
5	H	4-ClC_6H_4	H	Me	Me	**10e**	76[a]	–	74
6	H	4-$MeOC_6H_4$	H	OEt	H	**10f**	50[a]	–	49
7	Me	4-$MeOC_6H_4$	H	OMe	Me	**10g**	99[b]	>95	95
8	Me	4-$MeOC_6H_4$	H	OEt	H	**10h**	75[b]	50	74
9	Me	4-$MeOC_6H_4$	$(CH_2)_4$		H	**10i**	74[b]	>95	65
10	Me	4-ClC_6H_4	H	OMe	Me	**10j**	97[b]	>95	91
11	Et	4-$MeOC_6H_4$	H	OMe	Me	**10k**	97[b]	>95	95
12	CH_2CO_2Me	4-$MeOC_6H_4$	H	OMe	Me	**10l**	86[b]	>95	80
13	Me	2-$MeOC_6H_4$	H	OMe	Me	**10m**	98[b]	83	88
									
	1n–p	**2n–p**		**10n–p**					
	R^1		R^2						
14	Ph		H			**10n**	97[b]	–	72
15	CO_2Me		H			**10o**	59[a]	–	41
16	CO_2Me		Me			**10p**	70[a]	–	50
									
	3a–c	**4a–c**		**11a–c**					
	R								
17	$(CH_2)_2CO_2Me$					**11a**	74[b]	–	67
18	Ph					**11b**	84[b]	–	74
19	Bn					**11c**	88[b]	–	77

[a] Product was purified by column chromatography if crude product was not spectroscopically pure (NMR).
[b] According to NMR with internal standard ($CHCl=CCl_2$) if crude product was spectroscopically pure (NMR).



Scheme 5 Possible mechanism for the reaction of *N*,*N*-dioxyenamines (e.g., **2a**) with trifluoroacetic anhydride

α-Hydroxyoximes and their derivatives are widely used in the synthesis of natural compounds, e.g. alkaloids,[20] 1,2-amino alcohols,[21] hydroxyamino acids.[22] Thus, we recognize that the reduction of the oxazine fragment in products **10a–m** into amino alcohols or the pyrrolidine group[23] is an important synthetic task. Moreover, since the initial nitronates **1** are available in enantiopure form, the rearrangement of *N*,*N*-dioxyenamines can also be used in the enantioselective synthesis of substituted prolinols **12** (Scheme 6).

Scheme 6 Possible route for the reduction of derivatives **10**

In summary the reaction of various *N*,*N*-dioxyenamines with acid anhydrides was investigated. A simple and universal method for the synthesis of α-hydroxyoxime derivatives **10** and **11** from available *N*,*N*-dioxyenamines **2** and **4** via trifluoroacetic anhydride mediated rearrangement was developed.

All reactions were performed in oven-dried (150 °C) glassware under an argon atmosphere. Melting points were determined on a Koffler melting point apparatus and are uncorrected. Chromatographic separations were performed on silica gel (Merck Kieselgel 230–400 mesh) with analytical grade solvents, driven by a positive pressure of air. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or anisaldehyde. NMR spectra were recorded on NMR spectrometers Bruker AM-300 (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz, ^{29}Si: 59.63 MHz) and Bruker WM-250 (^{1}H: 250 MHz, ^{13}C: 62.9 MHz,) for $CDCl_3$ solns with residual solvent peak as an internal standard.[24] The INEPT pulse sequence was used for ^{29}Si signal observation. Atom-numbering of selected compounds is shown in Figure 1. Elemental analyses were performed by the analytical centre of the N. D. Zelinsky Institute of Organic Chemistry.

Hexane, EtOAc, and MeOH were distilled without drying agents. The following reaction solvents and reagents were distilled from the indicated drying agents: CH_2Cl_2 (CaH_2), $CHCl_3$ (CaH_2), Et_3N (CaH_2), TFAA (P_2O_5), and AcBr (CaH_2). TsCl was purified by the literature procedure.[25] The following chemicals were purchased from the indicated sources: TMSBr (Acros), Ac_2O (Acros), $BrCH_2COBr$ (Acros), AcCl (Acros), MsCl (Acros), K_2CO_3 (Acros), NaOH (Lancaster), $TsOH·H_2O$ (Fluka).

Enamines 2a–m, 4a–c

Enamines **2a–c**,**f**,[1] **2e**,**i–m**,[16] **2g**,[15] **4a**,[2a] **4b**,[4] and **4c**[11] were prepared by the indicated procedures. Enamine **2d** was prepared by the procedure used for the synthesis of **2c**,[1] enamine **2h** by the procedure used for the synthesis of **2f**.[1] All enamines were used further without additional purification.

4-(4-Methoxyphenyl)-6,6-dimethyl-3-methylene-2-(trimethylsiloxy)-1,2-oxazinane (2d)

Oil; yield: 78%.

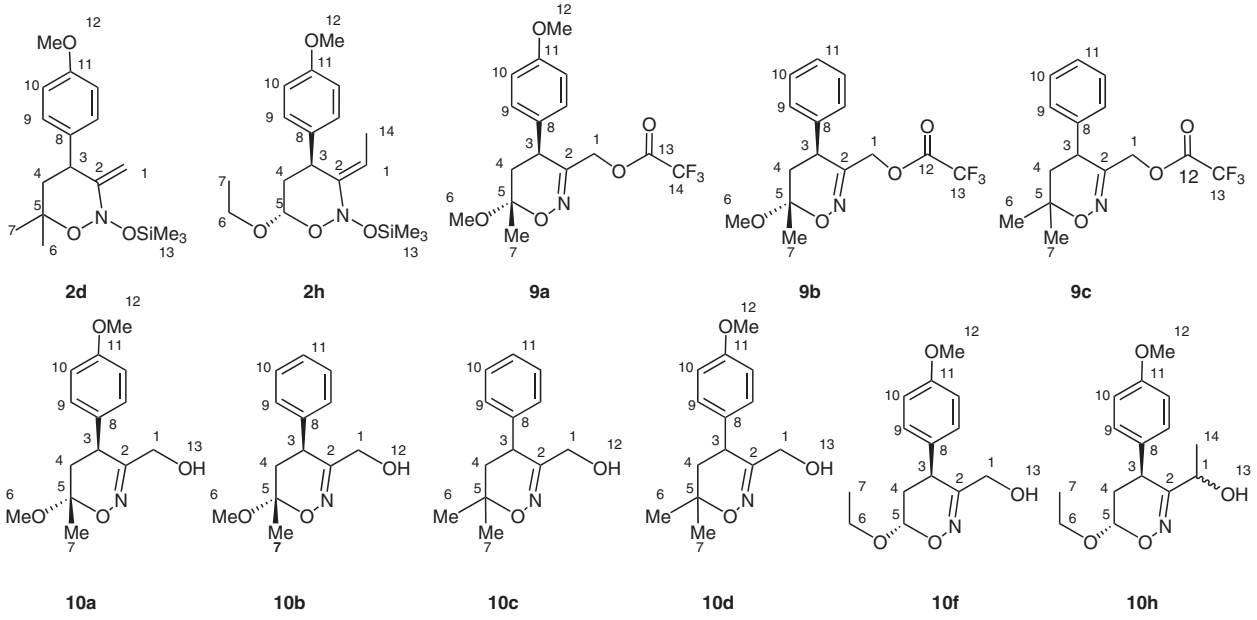


Figure 1 Structures of compounds **2d**,**h**, **9a–c**, **10a–d**,**f**,**h**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 (s, 9 H, 13-CH_3), 1.31 (s, 3 H, 6-CH_3), 1.50 (br s, 3 H, 7-CH_3), 1.73 (dd, *J* = 12.9, 4.8 Hz, 1 H, 4-C*H*$_a$), 1.98 (t, *J* = 12.9 Hz, 1 H, 4-C*H*$_b$), 3.75 (br d, *J* = 11.0 Hz, 1 H, 3-CH), 3.80 (s, 3 H, 12-CH_3), 3.93 (br s, 1 H, 1-C*H*$_a$), 4.98 (br s, 1 H, 1-C*H*$_b$), 6.87 (d, *J* = 8.8 Hz, 2 H, 10-CH), 7.19 (d, *J* = 8.8 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.7 (13-CH_3), 28.9 and 31.5 (6-CH_3, 7-CH_3), 42.0 and 43.7 (3-CH, 4-CH_2), 55.2 (12-CH_3), 76.8 (5-C), 96.9 (1-CH_2), 113.8 (10-CH), 129.7 (9-CH), 158.4 (11-C). Signals of 8-C and 2-C could not be unambiguously identified due to low intensity and broadening because of dynamic processes.[1]

***rel*-(4*S*,6*S*)-(*E*)-6-Ethoxy-3-ethylidene-4-(4-methoxyphenyl)-2-(trimethylsiloxy)-1,2-oxazinane (2h)**

Oil; yield: 98%. Mixture of two conformers in a 3:1 ratio (NMR).

Major Conformer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.27 (s, 9 H, 13-CH_3), 1.17 (t, *J* = 6.8 Hz, 3 H, 7-CH_3), 1.35 (d, *J* = 7.2 Hz, 3 H, 14-CH_3), 2.09–2.21 (m, 1 H, 4-C*H*$_a$), 2.31 (ddd, *J* = 13.1, 8.5, 5.3 Hz, 1 H, 4-C*H*$_b$), 3.35 (dq, *J* = 9.2, 7.2 Hz, 1 H, 6-C*H*$_a$), 3.78 (s, 3 H, 12-CH_3), 3.90 (dq, *J* = 9.2, 7.2 Hz, 1 H, 6-C*H*$_b$), 4.05 (br s, 1 H, 3-CH), 4.61 (dd, *J* = 8.2, 6.2 Hz, 1 H, 5-CH), 5.51 (q, *J* = 7.2 Hz, 1 H, 1-CH), 6.81 (d, *J* = 8.8 Hz, 2 H, 10-CH), 7.33 (d, *J* = 8.8 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.1 (13-CH_3), 11.9 (14-CH_3), 14.8 (7-CH_3), 34.0 (4-CH_2), 38.3 (3-CH), 55.1 (12-CH_3), 63.4 (6-CH_2), 99.7 (5-CH), 108.3 (1-CH), 113.6 (10-CH), 129.1 (9-CH), 134.6 (8-C), 148.7 (2-C), 157.9 (11-C).

^{29}Si NMR (60 MHz, $CDCl_3$): δ = 23.8.

Minor Conformer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 (s, 9 H, 13-CH_3), 1.17 (t, *J* = 6.8 Hz, 3 H, 7-CH_3), 1.55 (d, *J* = 7.2 Hz, 3 H, 14-CH_3), 2.09–2.20 (m, 2 H, 4-CH_2), 3.44–3.54 (m, 1 H, 6-C*H*$_a$), 3.78 (s, 3 H, 12-CH_3), 3.90 (dq, *J* = 9.2, 7.2 Hz, 1 H, 6-C*H*$_b$), 4.16 (br s, 1 H, 3-CH), 4.95 (br t, *J* = 5.5 Hz, 1 H, 5-CH), 5.80 (q, *J* = 7.2 Hz, 1 H, 1-CH), 6.85 (d, *J* = 8.6 Hz, 2 H, 10-CH), 7.27 (d, *J* = 8.6 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.8 (13-CH_3), 11.8 (14-CH_3), 14.0 (7-CH_3), 35.9 (4-CH_2), 36.3 (3-CH), 55.1 (12-CH_3), 64.3 (6-CH_2), 98.2 (5-CH), 110.5 (1-CH), 113.5 (10-CH), 128.6 (9-CH), 134.6 (8-C), 148.7 (2-C), 157.9 (11-C).

^{29}Si NMR (60 MHz, $CDCl_3$): δ = 23.8.

Enamines 2n–p; General Procedure

Nitronates **1n**,**o** were prepared by the literature procedure.[26] **1p** was synthesized by a procedure analogous to that described for **1o**.[26] (Yield: 74%, spectroscopic data are identical to those previously reported.[27])

Et_3N (0.50 mL, 3.6 mmol, 1.2 equiv) was added to stirred soln of nitronate **1** (3 mmol) in CH_2Cl_2 (6 mL) at –78 °C. Then TMSBr (0.44 mL, 1.1 equiv, 3.3 mmol) was added. The mixture was maintained at the same temperature for 24 h, diluted with hexane (15 mL) and poured into a mixture of hexane (30 mL) and aq $NaHSO_4$ soln (0.5 g in 30 mL of H_2O). The organic layer was washed with H_2O (30 mL) and brine (2 × 30 mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give enamines **2n**–**p** as colorless oils, which were used in the next step without additional purification. Yields of crude products: **2n**: 74%, **2o**: 69%, **2p**: 71%.

Trifluoroacetates 9a–c; General Procedure

Soln of enamine **2** (0.3 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirring soln of TFAA (50 μL, 0.35 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C under an argon atmosphere. The mixture was stirred for 30 min and the solvent was removed in vacuo to give a brown oil.

***rel*-[(4*S*,6*S*)-6-Methoxy-4-(4-methoxyphenyl)-6-methyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl 2,2,2-Trifluoroacetate (9a)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H, 7-CH_3), 1.96 (t, *J* = 13.0 Hz, 1 H, 4-C*H*$_{ax}$), 2.32 (dd, *J* = 13.0, 7.7 Hz, 1 H, 4-C*H*$_{eq}$), 3.32 (s, 3 H, 6-CH_3), 3.73 (dd, *J* = 13.0, 7.7 Hz, 1 H, 3-CH), 3.80 (s, 3 H, 12-CH_3), 4.64–4.73 (m, 2 H, 1-CH_2), 6.89 (d, *J* = 8.4 Hz, 2 H, 10-CH), 7.11 (d, *J* = 8.4 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (7-CH_3), 36.3 and 38.1 (3-CH, 4-CH_2), 49.5 (6-CH_3), 55.2 (12-CH_3), 66.2 (1-CH_2), 98.7 (5-C), 114.8 (10-CH), 129.4 (9-CH), 129.5 (8-C), 155.4 (2-C), 159.3 (11-C).

***rel*-[(4*S*,6*S*)-6-Methoxy-6-methyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl 2,2,2-Trifluoroacetate (9b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H, 7-CH_3), 1.98 (t, *J* = 13.0 Hz, 1 H, 4-C*H*$_{ax}$), 2.35 (dd, *J* = 13.0, 7.7 Hz, 1 H, 4-C*H*$_{eq}$), 3.32 (s, 3 H, 6-CH_3), 3.77 (dd, *J* = 13.0, 7.7 Hz, 1 H, 3-CH), 4.64–4.73 (m, 2 H, 1-CH_2), 7.18–7.38 (m, 5 H, 9-CH, 10-CH, 11-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (7-CH_3), 37.1 and 38.0 (3-CH, 4-CH_2), 49.5 (6-CH_3), 66.2 (1-CH_2), 98.5 (5-C), 128.0 (11-CH), 128.3 and 129.3 (9-CH, 10-CH), 137.8 (8-C), 154.9 (2-C).

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl 2,2,2-Trifluoroacetate (9c)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 and 1.41 (both s, both 3 H, 6-CH_3, 7-CH_3), 1.96 (dd, *J* = 13.7, 11.7 Hz, 1 H, 4-C*H*$_{ax}$), 2.15 (dd, *J* = 13.7, 7.7 Hz, 1 H, 4-C*H*$_{eq}$), 3.55 (dd, *J* = 11.7, 7.7 Hz, 1 H, 3-CH), 4.64–4.75 (m, 2 H, 1-CH_2), 7.17–7.38 (m, 5 H, 9-CH, 10-CH, 11-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 and 28.1 (6-CH_3, 7-CH_3), 37.8 and 39.4 (3-CH, 4-CH_2), 66.6 (1-CH_2), 76.1 (5-C), 128.0 (11-CH), 128.1 and 129.4 (9-CH, 10-CH), 138.0 (8-C), 152.5 (2-C).

Oxazines 10a–f and Isoxazoles 10o,p; General Procedure

A soln of enamine **2** (2 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a stirred soln of TFAA (0.31 mL, 2.2 mmol) in CH_2Cl_2 (4 mL) at –78 °C under an argon atmosphere. The mixture was stirred for 1 h and then allowed to warm to r.t. Then MeOH (4 mL) and K_2CO_3 (0.5 g) were added and the mixture was stirred for 1 h and poured into a mixture of EtOAc (70 mL) and brine (50 mL). The organic layer was washed with brine (50 mL) [for **10o** additional extraction from the aqueous layer with EtOAc (50 mL) and addition of solid NaCl was needed] and dried (Na_2SO_4). The solvents were removed in vacuo. The residue was subjected to column chromatography (hexane–EtOAc, 5:1, 1:1, 1:2) to give target derivatives **10** as colorless oils. For yields see Table 2.

***rel*-[(4*S*,6*S*)-6-Methoxy-4-(4-methoxyphenyl)-6-methyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methanol (10a)**

Mp 100–101 °C (EtOAc); R_f = 0.25 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H, 7-CH_3), 1.93 (dd, *J* = 13.5, 12.5 Hz, 1 H, 4-C*H*$_{ax}$), 2.26 (dd, *J* = 13.5, 7.7 Hz, 1 H, 4-C*H*$_{eq}$), 2.75 (br s, 1 H, 13-OH), 3.31 (s, 3 H, 6-CH_3), 3.63 (dd, *J* = 12.5, 7.7 Hz, 1 H, 3-CH), 3.80 (s, 3 H, 12-CH_3), 3.94 (s, 2 H, 1-CH_2), 6.87 (d, *J* = 8.4 Hz, 2 H, 10-CH), 7.11 (d, *J* = 8.4 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (7-CH_3), 35.9 (3-CH), 38.4 (4-CH_2), 49.3 (6-CH_3), 55.1 (12-CH_3), 62.1 (1-CH_2), 97.8 (5-C), 114.3 (10-CH), 129.2 (9-CH), 130.6 (8-C), 158.8 (2-C), 159.2 (11-C).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.53; H, 7.40; N, 5.14.

***rel*-[(4*S*,6*S*)-6-Methoxy-6-methyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methanol (10b)**

Mp 75–80 °C; R_f = 0.30 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H, 7-CH_3), 1.96 (t, J = 12.8 Hz, 1 H, 4-CHH_{ax}), 2.29 (dd, J = 12.8, 7.7 Hz, 1 H, 4-CHH_{eq}), 2.70 (br s, 1 H, 13-OH), 3.32 (s, 3 H, 6-CH_3), 3.68 (dd, J = 12.8, 7.7 Hz, 1 H, 3-CH), 3.95 (br s, 2 H, 1-CH_2), 7.18 (d, J = 7.3 Hz, 2 H, 9-CH), 7.27–7.36 (m, 3 H, 10-CH, 11-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (7-CH_3), 36.7 (3-CH), 38.5 (4-CH_2), 49.3 (6-CH_3), 62.1 (1-CH_2), 97.7 (5-C), 127.4 (11-CH), 128.2 and 128.9 (9-CH, 10-CH), 138.9 (8-C), 158.9 (2-C).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.11; N, 6.14.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methanol (10c)

R_f = 0.34 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 and 1.37 (both s, both 3 H, 6-CH_3, 7-CH_3), 1.92 (dd, J = 13.3, 12.2 Hz, 1 H, 4-CHH_{ax}), 2.07 (dd, J = 13.3, 8.1 Hz, 1 H, 4-CHH_{eq}), 2.90 (br s, 1 H, 12-OH), 3.49 (dd, J = 12.2, 8.1 Hz, 1 H, 3-CH), 3.94 (br s, 2 H, 1-CH_2), 7.17 (d, J = 7.2 Hz, 2 H, 9-CH), 7.24–7.36 (m, 3 H, 10-CH, 11-CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.8 and 28.5 (6-CH_3, 7-CH_3), 37.7 and 40.4 (3-CH, 4-CH_2), 62.4 (1-CH_2), 75.0 (5-C), 127.6 (11-CH), 128.3 and 129.2 (9-CH, 10-CH), 139.5 (8-C), 156.7 (2-C).

[4-(4-Methoxyphenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methanol (10d)

R_f = 0.26 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 and 1.37 (both s, both 3 H, 6-CH_3, 7-CH_3), 1.90 (dd, J = 13.3, 12.0 Hz, 1 H, 4-CHH_{ax}), 2.04 (dd, J = 13.3, 7.7 Hz, 1 H, 4-CHH_{eq}), 2.72 (br s, 1 H, 13-OH), 3.43 (dd, J = 12.0, 7.7 Hz, 1 H, 3-CH), 3.79 (s, 3 H, 12-CH_3), 3.94 (br s, 2 H, 1-CH_2), 6.87 (d, J = 8.6 Hz, 2 H, 10-CH), 7.09 (d, J = 8.6 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 and 28.4 (6-CH_3, 7-CH_3), 36.9 and 40.3 (3-CH, 4-CH_2), 55.3 (12-CH_3), 62.4 (1-CH_2), 75.0 (5-C), 114.5 (10-CH), 129.2 (9-CH), 131.1 (8-C), 156.7 (2-C), 158.9 (11-C).

[4-(4-Chlorophenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methanol (10e)

Spectroscopic data is identical to that previously reported.[16]

***rel*-[(4*S*,6*S*)-6-Ethoxy-4-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methanol (10f)**

Mp 61–62 °C; R_f = 0.33 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.0 Hz, 3 H, 7-CH_3), 2.09 (td, J = 11.0, 2.6 Hz, 1 H, 4-CHH_{ax}), 2.21 (ddd, J = 11.0, 7.5, 2.3 Hz, 1 H, 4-CHH_{eq}), 2.88 (br s, 1 H, 13-OH), 3.58–3.67 (m, 2 H, 6-CH_2), 3.78 (s, 3 H, 12-CH_3), 3.89 (dd, J = 11.0, 7.5 Hz, 1 H, 3-CH), 3.93 (br s, 2 H, 1-CH_2), 5.17 (t, J = 2.3 Hz, 1 H, 5-CH), 6.87 (d, J = 8.5 Hz, 2 H, 10-CH), 7.11 (d, J = 8.5 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (7-CH_3), 32.5 (4-CH_2), 33.9 (3-CH), 55.1 (12-CH_3), 62.4 and 63.8 (1-CH_2 and 6-CH_2), 95.9 (5-CH), 114.4 (10-CH), 129.2 (9-CH), 130.7 (8-C), 158.8 and 159.1 (2-C and 11-C).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.30; H, 7.31; N, 5.30.

Methyl 3-(Hydroxymethyl)-4,5-dihydroisoxazole-5-carboxylate (10o)

R_f = 0.19 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.26–3.40 (m, 3 H, CH_2, OH), 3.78 (s, 3 H, OCH_3), 4.41 (s, 2 H, CH_2OH), 5.05 (dd, J = 11.0, 7.3 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.1 (CH_2), 52.8 (OCH_3), 57.3 (CH_2OH), 77.3 (CH), 158.5 (C=N), 170.8 (CO_2Me).

Methyl 3-(Hydroxymethyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (10p)

R_f = 0.23 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, CH_3), 2.93 (d, J = 17.4 Hz, 1 H, CHH_a), 3.29 (br s, 1 H, OH), 3.52 (d, J = 17.4 Hz, 1 H, CHH_b), 3.77 (s, 3 H, OCH_3), 4.36 (s, 2 H, CH_2OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_3), 44.8 (CH_2), 52.9 (OCH_3), 57.4 (CH_2OH), 85.5 (C), 158.9 (C=N), 172.5 (CO_2Me).

Oxazines 10g–m and Isoxazole 10n; General Procedure

TFAA (0.31 mL, 2.2 mmol) was added dropwise to a stirred soln of enamine **2** (2 mmol) in CH_2Cl_2 (4 mL) at –78 °C under an argon atmosphere and the mixture was stirred for 20 min at the same temperature. Then MeOH (4 mL) was added dropwise and the mixture was stirred for 1 h. K_2CO_3 (0.5 g) was added and the mixture was allowed to warm to r.t., stirred for 3 h, and poured into a mixture of EtOAc (70 mL) and brine (50 mL). The organic layer was washed with brine (50 mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give target oxime derivatives **10**. For yields see Table 2.

For derivatives **10g**,**i**–**m** spectroscopic data are identical to those previously reported.[16]

***rel*-1-[(4*S*,6*S*)-6-Ethoxy-4-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazin-3-yl]ethanol (10h)**

Mixture of isomers, ratio 3:1; R_f = 0.42 (hexane–EtOAc, 1:1, UV).

Major Isomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.26 (m, 6 H, 7-CH_3, 14-CH_3), 2.11 (ddd, J = 13.5, 12.1, 2.6 Hz, 1 H, 4-CHH_a), 2.23 (ddd, J = 13.5, 7.9, 3.3 Hz, 1 H, 4-CHH_e), 3.56–3.68 (m, 2 H, 6-CHH_a, 13-OH), 3.76–3.83 (m, 1 H, 3-CH), 3.80 (s, 3 H, 12-CH_3), 3.89 (dq, J = 9.8, 7.2 Hz, 1 H, 6-CHH_b), 4.15 (m, J = 6.6 Hz, 1 H, 1-CH), 5.13 (dd, J = 3.3, 2.6 Hz, 1 H, 5-CH), 6.87 (d, J = 8.5 Hz, 2 H, 10-CH), 7.15 (d, J = 8.5 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (7-CH_3), 21.0 (14-CH_3), 33.4 (4-CH_2), 34.1 (3-CH), 55.3 (12-CH_3), 63.9 (6-CH_2), 68.0 (1-CH), 95.9 (5-CH), 114.5 (10-CH), 129.6 (9-CH), 131.7 (8-C), 158.6 (11-C), 162.7 (2-C).

Minor Isomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.26 (m, 6 H, 7-CH_3, 14-CH_3), 2.04 (ddd, J = 13.5, 12.1, 2.6 Hz, 1 H, 4-CHH_a), 2.23 (ddd, J = 13.5, 7.6, 2.6 Hz, 1 H, 4-CHH_e), 3.55–3.69 (m, 3 H, 3-CH, 6-CHH_a, 13-OH), 3.80 (s, 3 H, 12-CH_3), 3.87 (dq, J = 9.8, 7.2 Hz, 1 H, 6-CHH_b), 4.09 (m, J = 6.6 Hz, 1 H, 1-CH), 5.16 (t, J = 2.6 Hz, 1 H, 5-CH), 6.87 (d, J = 8.5 Hz, 2 H, 10-CH), 7.11 (d, J = 8.5 Hz, 2 H, 9-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (7-CH_3), 21.9 (14-CH_3), 33.5 (3-CH), 33.8 (4-CH_2), 55.3 (12-CH_3), 63.7 (6-CH_2), 66.7 (1-CH), 95.9 (5-CH), 114.6 (10-CH), 129.5 (9-CH), 131.3 (8-C), 159.0 (11-C), 162.0 (2-C).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.71; H, 7.66; N, 4.95.

(5-Phenyl-4,5-dihydroisoxazol-3-yl)methanol (10n)
Slightly yellow solid; mp 59–63 °C; R_f = 0.31 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (dd, *J* = 17.3, 8.4 Hz, 1 H, 4-CH_a), 3.41 (br s, 1 H, OH), 3.46 (dd, *J* = 17.3, 11.0 Hz, 1 H, 4-CH_b), 4.40 (s, 2 H, CH_2OH), 5.57 (dd, *J* = 11.0, 8.5 Hz, 1 H, CH), 7.27–7.38 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.9 (4-CH_2), 57.7 (CH_2OH), 82.1 (5-CH), 125.7 and 128.6 (*o*-CH_{Ar} and *m*-CH_{Ar}), 128.1 (*p*-CH_{Ar}), 140.5 (C_{Ar}), 158.5 (C=N).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.51; H, 6.52; N, 7.68.

Hydroxyoximes 11a–c; General Procedure
Soln of enamine **4** (2 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred soln of TFAA (0.60 mL, 4.2 mmol) in CH_2Cl_2 (8 mL) at –78 °C under an argon atmosphere; the mixture was stirred for 1 h. Then MeOH (2 mL) was added and the mixture was allowed to warm to r.t. over 1 h and a soln of NaOH (0.34 g, 8.4 mmol) in MeOH (4 mL) was added and the mixture was stirred for an additional 1.5 h. Then the mixture was poured into a mixture of EtOAc (70 mL) and brine (20 mL). The organic layer was washed with brine (20 mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give target oxime derivatives **11a–c**. For yields see Table 2. Spectroscopic data of **11a–c** are identical to those previously reported.[14a]

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