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**Full Paper**

# Synthesis of 6-Ethoxy-6*H*-1,2-oxazines by Hetero Diels-Alder Reaction of 1-Bromo-2-ethoxyethene with α-Nitroso Alkenes

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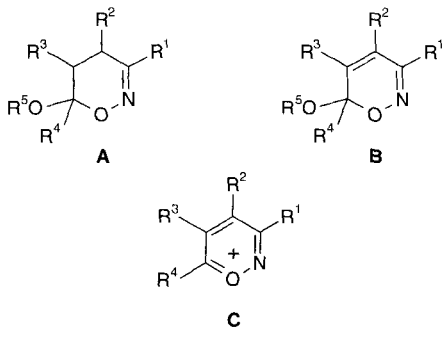
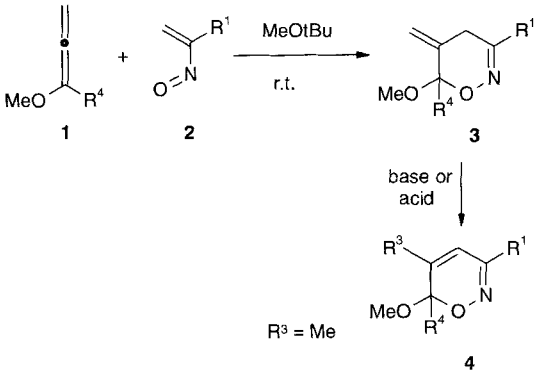
*Dedicated to Professor Ernst Schmitz on the Occasion of his 70th Birthday*

**Abstract.** A variety of 6*H*-1,2-oxazines **10** could efficiently be prepared by hetero Diels–Alder reaction of α-nitroso alkenes **2** with 1-bromo-2-ethoxyethene (**8**) and consecutive elimination of HBr by DBU. Heterodienes **2** were generated *in situ* from α-halogen oximes **6**. Primary cycloadducts **9** were isolated in singular cases, however, an attempt to substitute bromide in **9e** by an azido group gave the desired compound **11** only as minor component together with elimination product **10e**. 6*H*-1,2-oxazines **10** are valuable precursors for addition reactions which open new synthetic possibilities.

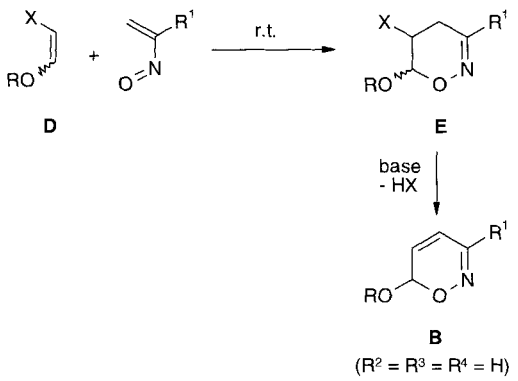
5,6-Dihydro-4*H*-1,2-oxazines **A** are very versatile building blocks for organic synthesis since their ring cleavages or ring transformations lead to a variety of interesting compounds [3]. Their preparation usually involves hetero Diels–Alder reaction of an electron-rich olefin with an α-nitroso alkene which is generated in situ from α-halogen oximes [4]. For several examples introduction of a substituent $R^2$ at C-4 was possible either by deprotonation and reaction with electrophiles [5] or by substitution of halogen by suitable nucleophiles [6]. Although many 1,2-oxazines **A** could be prepared with these methods we were looking for more flexible alternatives. Therefore, syntheses of 6-alkoxy-6*H*-1,2-oxazines with general formula **B** were new targets, since many new 5,6-dihydro-4*H*-1,2-oxazines **A** with previously unaccessible substitution pattern should be approachable by addition of various components to the C-4/C-5 double bond of **B** [7]. An additional option of 6*H*-1,2-oxazines **B** in synthesis involves their Lewis-acid promoted dissociation into azapyrylium ions **C** and subsequent reaction with nucleophiles [8].



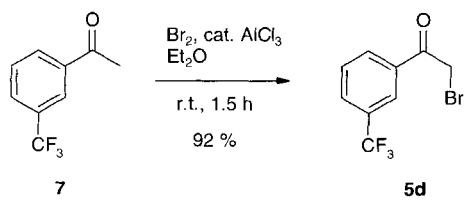

The first approach to examples of **B** involved methoxyallene derivatives **1** [9] which smoothly reacted with several α-nitroso alkenes **2** giving 5-methylene-5,6-dihydro-4*H*-1,2-oxazines **3** in generally excellent yields. These cycloadducts were efficiently transformed into the corresponding conjugated 5-methyl substituted 6*H*-1,2-oxazines **4** by base or acid catalysis [10], which could be further substituted by deprotonation and reactions with electrophiles [11].

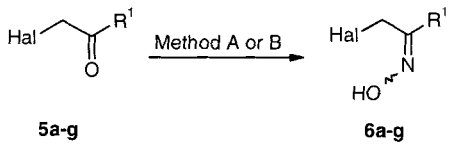



Since the methoxyallene route notoriously gives 6*H*-1,2-oxazines **B** with substituent $R^3$ = Me we were searching for a second approach leading to **B** with $R^3 = R^2 = H$ [7]. Again a hetero Diels–Alder reaction [12] with inverse electron demand of an $\alpha$-nitroso alkene was anticipated to be the crucial step, however, the electron-rich dienophile **D** should be equipped with a potential leaving group which would allow elimination to the desired 6*H*-1,2-oxazine **B** ($R^2$, $R^3$, $R^4$ = H).

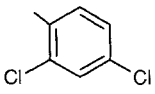
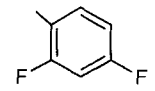
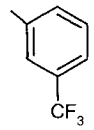
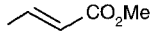



The resulting new 6*H*-1,2-oxazines were also of interest as compounds with potential biological activity [13] and hence we extended the range of substituents $R^1$ at C-3 to new entities. For this reason several new $\alpha$-halogen oximes **6** were synthesized, which were accessible by treatment of the corresponding ketones **5** with hydroxylamine hydrochloride (Scheme 1) [14–16]. The *Z*:*E* ratio of the oxime seems to be rather unpredictable, however, this was of no importance for the subsequent cycloaddition step.



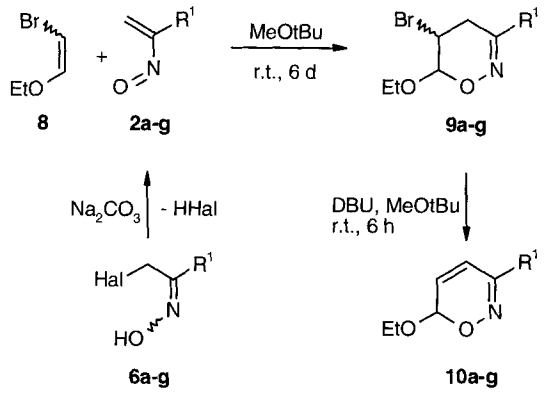

Method A: $NH_2OH \cdot HCl$, MeOH, $H_2O$, r.t.
Method B: $NH_2OH \cdot HCl$, $CHCl_3$, $H_2O$, reflux

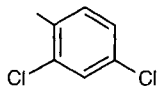
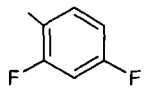
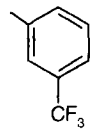
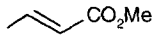
| $R^1$ | Hal | 6 | Method | Yield | *Z* : *E* |
|---|---|---|---|---|---|
| Ph | Cl | **a** | A | [14] | >97 : 3 |
|  | Cl | **b** | A | 61 % | >97 : 3 |
|  | Cl | **c** | A | 41 % | 75 : 25 |
|  | Br | **d** | A | 80 % | 84 : 16 |
| $CO_2Et$ | Br | **e** | B | [15] | 83 : 17 |
|  | Br | **f** | B | [16] | 92 : 8 |
| $CF_3$ | Br | **g** | B | 61 % | 47 : 53 |

**Scheme 1**

$\alpha$-Bromoketone **5d** was prepared for the first time by $AlCl_3$-catalyzed bromination [17] of *m*-trifluoromethylacetophenone (**7**) [18] in excellent yield.

As a synthetic equivalent to dienophile **D** we planned to employ the easily available 1-bromo-2-ethoxyethene (**8**) [19]. It was not evident whether **8** would be a suitable component since the bromine substituent is rather bulky and its electronic effect should also hamper cycloaddition with $\alpha$-nitroso alkenes **2**. Fortunately, our doubts were unfounded since treatment of $\alpha$-halogen oximes **6a–g** with sodium carbonate in the presence of **8** smoothly provided primary cycloadducts **9a–g** with good efficiency (Scheme 2). However, we had to use a much higher excess (10 equivalents) of dienophile **8** for trapping of $\alpha$-nitroso alkenes **2a–g** to obtain similar yields as with simple enol ethers [4]. Thus, **8** seems to be considerably less reactive towards **2** than other electron-rich dienophiles. In general, the *cis*/*trans*-mixture of primary cycloadducts **9** was not purified but directly converted into the desired products **10** by elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature. Now most of the excess of **8** could be recovered by kugelrohr distillation. The overall efficiency of this two-step protocol is good to excellent and makes 6*H*-1,2-oxazines **10a–g** available in reasonable quantities.

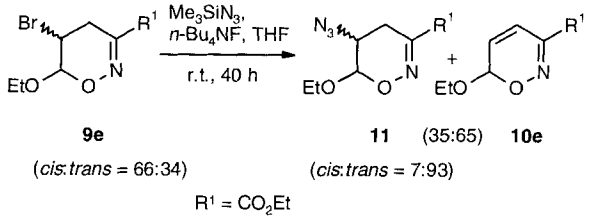



| | | 10 | Yield |
|---|---|---|---|
| $R^1$ = | Ph | a | 81 % |
| |  | b | 72 % |
| |  | c | 59 % |
| |  | d | 73 % |
| | $CO_2Et$ | e | 96 % |
| |  | f | 98 % |
| | $CF_3$ | g | 67 % |

**Scheme 2**

Most characteristic in the $^1H$ NMR spectra of 6*H*-1,2-oxazines **10** are the olefinic protons at C-4 and C-5 which generally couple with approximately 10 Hz. The vicinal coupling of 5-H to 6-H is in the range of 4.5 Hz and indicates a pseudoaxial position of the 6-ethoxy group. The chemical shifts of 4-H and 5-H as well as that of C-4 and C-5 reflect the weak electron-withdrawing effect of the oxime ether functionality incorporated in **10**.

5-Bromo-4,5-dihydro-4*H*-1,2-oxazines **9** are highly prone to elimination, but in the case of **9e–g** we were able to isolate and characterize these intermediates spectroscopically. An attempt to substitute the 5-bromo substituent of **9e** by azide using azidotrimethylsilane in the presence of fluoride [20] led to formation of the corresponding 5-azido compound **11**, but mainly to 6*H*-1,2-oxazine **10e**.




This result underscores the ease of HBr elimination and illustrates that intermediates **9** are only of limited use for direct transformations at C-5. Thus, introduction of substituents at this position and at C-4 is better achieved at the stage of 6*H*-1,2-oxazines **10**. Our results concerning these efforts will be reported in due course [7, 21]. With the efficient and highly flexible preparation of 6*H*-1,2-oxazines **10** by the two step procedure described in this report we have established the basis for these investigations.

Support of this work by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg "Struktur-Eigenschafts-Beziehungen bei Heterocyclen") and the Fonds der Chemischen Industrie is most gratefully acknowlegded. We also thank Frau Ute Hain for experimental help.

## Experimental

IR spectra were measured with a Perkin Elmer spectrometer IR-325 or Nicolet 205. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 200, Bruker AC 300 or Bruker DRX-500 in $CDCl_3$ solution. The chemical shifts are given in relative to TMS from solvent ($CDCl_3$) signal ($\delta_H = 7.27$, $\delta_C = 77.0$). Missing signals of the minor isomers are hidden by signals of the major isomers 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). $Na_2CO_3$ was freshly pulverized (electric coffee mill, Braun KSM 1G) before used.

All solvents were dried by standard methods. The experiments were carried out under exclusion of moisture. Synthesis of starting materials: **6a** [14], **6e** [15], **6f** [16] and **8** [19].

### Synthesis of α-Haloketoximes (General Procedure)

*Method A*: A solution of α-haloketone **5** (1 equivalent) in methanol (4–5 ml/mmol ketone) was treated with a solution of hydroxylamine hydrochloride (1.5–3 equivalents) in water (1 ml/mmol ketone). The mixture was then stirred at room temp. for 1 d. The two liquid phases were separated, and the aqueous layer was extracted with chloroform (3 × 1 ml/mmol ketone). The combined organic phases were dried over $Na_2SO_4$ and concentrated. The residue was purified by distillation or recrystallization.

*Method B*: Similar procedure as described above, but the reaction mixture was refluxed in chloroform/water over night.

*2,2',4'-Trichloro-acetophenonoxime* (**6b**)

11.2 g (50.0 mmol) of 2,2',4'-trichloro-acetophenone (**5b**) and 10.5 g (150 mmol) of hydroxylamine hydrochloride were treated according to the general procedure (method A). Recrystallization (*n*-hexane/cyclohexane) afforded 7.30 g (61%) of *Z*-configurated oxime **6b** as pale yellow crystals (*m.p.* 86–87 °C). – $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$/ppm = 9.55 (s, 1H, NOH), 7.45, 7.33 (2 $m_c$, 1H, 2H, $C_6H_3Cl_2$), 4.60 (s, 2H, $CH_2Cl$). – $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$/ppm = 154.5 (s, C=N), 136.3, 133.7, 131.6 (3 s, C-1', C-2', C-4'), 132.3, 129.8, 127.4 (3 d, C-3', C-5', C-6'), 35.1 (t, $CH_2Cl$). – IR (KBr): $\nu$/cm$^{-1}$ = 3450 (br, O-H), 3170–2800 (=C-H, C-H), 1590 (C=N).

| | | | | | |
|---|---|---|---|---|---|
| $C_8H_6Cl_3NO$ | Calcd.: | C 40.26 | H 2.54 | N 5.87 | Cl 44.63 |
| (238.6) | Found: | C 40.38 | H 2.51 | N 5.77 | Cl 44.86. |

*2-Chloro-2',4'-difluoro-acetophenonoxime* (**6c**)

15.0 g (78.7 mmol) of 2-chloro-2',4'-difluoro-acetophenone (**5c**) and 16.1 g (230 mmol) of hydroxylamine hydrochloride were treated according to the general procedure (method A). Recrystallization (*n*-pentane) afforded 6.58 g (41%) of oxime **6c** (*Z*:*E* = 75:25) as colourless crystals (*m.p.* 47–51 °C). – $^1$H NMR ($CDCl_3$, 200 MHz): Z-Isomer: $\delta$/ppm = 9.40 (br s, 1H, NOH), 7.58–7.35, 7.05–6.80 (2 m, 1H, 2H, $C_6H_3F_2$), 4.62 (s, 2H, $CH_2$). – *E*-Isomer: $\delta$/ppm = 4.42 (s, 2H, $CH_2$); missing signals are hidden by signals of the *Z*-isomer. – $^{13}$C NMR ($CDCl_3$, 50.3 MHz): *Z*-isomer: $\delta$/ppm = 164.0 (dd, $^{1,3}J_{CF}$ = 253, 12 Hz, =CF), 160.8 (dd, $^{1,3}J_{CF}$ = 253, 12 Hz, =CF), 152.0 (d, $^3J_{CF}$ = 2.6 Hz, C=N), 131.3 (*ddd*, $^{3,3}J_{CF}$ = 9.9, 4.6 Hz, =CH), 117.9 (dd, $^{2,4}J_{CF}$ = 13, 4.0 Hz, *i*-C), 112.0 (ddd, $^{2,4}J_{CF}$ = 22, 3.6 Hz, =CH), 104.7 (td, $^{2,2}J_{CF}$ = 26 Hz, =CH), 34.3 (dt, $^4J_{CF}$ = 4.8 Hz, $CH_2Cl$). – *E*-Isomer: $\delta$/ppm = 163.9 (dd, $^{1,3}J_{CF}$ = 252, 12 Hz, =CF), 159.6 (dd, $^{1,3}J_{CF}$ = 252, 12 Hz, =CF), 149.9 (d, $^3J_{CF}$ = 2.3 Hz, C=N), 131.3 (ddd, $^{3,3}J_{CF}$ = 9.9, 4.6 Hz, =CH), 114.6 (dd, $^{2,4}J_{CF}$ = 17, 4 Hz, *i*-C), 111.6 (ddd, $^{2,4}J_{CF}$ = 22, 3.6 Hz, =CH), 104.4 (td, $^{2,2}J_{CF}$ = 26 Hz, =CH), 44.4 (dt, $^4J_{CF}$ = 2.8 Hz, $CH_2Cl$). – IR (KBr): $\nu$/cm$^{-1}$ = 3450 (br, O-H), 2780 (=C-H, C-H), 1615 (C=N), 1150, 1110 (C–F).

| | | | | | |
|---|---|---|---|---|---|
| $C_8H_6ClF_2NO$ | Calcd.: | C 46.74 | H 2.94 | N 6.81 | Cl 17.27 |
| (205.6) | Found: | C 46.75 | H 2.98 | N 6.69 | Cl 17.96. |

*2-Bromo-3'-trifluoromethyl-acetophenone* (**5d**)

To a solution of 5.64 g (30.0 mmol) of 3'-trifluoromethyl-acetophenone (**7**) in 50 ml of dry diethyl ether 0.150 g (1.12 mmol) of aluminiumtrichloride and 4.80 g (30.0 mmol) of bromine were added (in 3 portions within 30 min). After stirring for 1 h at room temp. the solvent was removed *in vacuo*, and the residue was dissolved in pentane/water (25 ml each). The separated aqueous layer was extracted with pentane and the combined organic phases were dried over $Na_2SO_4$. Removal of the solvent and drying *in vacuo* (0.05 mbar) afforded 7.77 g (92%) of 2-bromo-3'-trifluoro-methyl-acetophenone (**5d**) as light yellow oil (*m.p.* 3–5 °C). – $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$/ppm = 8.25 (s, 1H, 2'-H), 8.18, 7.87 (2 d, *J* = 7.8 Hz each, 2H, 4'-H, 6'-H), 7.66 (t, *J* = 7.8 Hz, 1H, 5'-H), 4.48 (s, 2H, $CH_2$). – $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$/ppm = 190.1 (s, C=O), 134.4 (s, C-1'), 132.0, 129.5 (2 d, C-5', C-6'), 131.4 (q, $^2J_{CF}$ = 33 Hz, C-3'), 130.2, 125.7 (2 dq, $^3J_{CF}$ = 4 Hz each, C-2', C-4'), 123.5 (q, $^1J_{CF}$ = 272 Hz, $CF_3$), 30.2 (t, $CH_2$). – IR (neat): $\nu$/cm$^{-1}$ = 3150–2975 (=C-H, C-H), 1690 (C=O), 1180, 1125 (C–F).

| | | | | | |
|---|---|---|---|---|---|
| $C_9H_6BrF_3O$ | Calcd.: | C 40.46 | H 2.27 | Br 29.95 | |
| (267.1) | Found: | C 40.47 | H 2.25 | Br 31.00. | |

*2-Bromo-3'-trifluoromethyl-acetophenonoxime* (**6d**)

6.68 g (25.0 mmol) of 2-bromo-3'-trifluoromethyl-acetophenone (**5d**) and 5.21 g (75.0 mmol) of hydroxylamine hydrochloride were treated according to the general procedure (method A). Recrystallization (*i*-propanol) afforded 5.60 g (80%) of oxime **6d** (*Z*:*E* = 84:16) as colourless crystals (*m.p.* 37–41 °C). – $^1$H NMR ($CDCl_3$, 300 MHz): *Z*-isomer: $\delta$/ppm = 9.13 (br s, 1H, NOH), 7.95 (s, 1H, 2'-H), 7.87, 7.69 (2 d, *J* = 7.8 Hz each, 2H, 4'-H, 6'-H), 7.55 (t, *J* = 7.8 Hz, 1H, 5'-H), 4.63 (s, 2H, $CH_2$). – *E*-isomer: $\delta$/ppm = 4.43 (s, 2H, $CH_2$); missing signals are hidden by signals of the *Z*-isomer. – $^{13}$C NMR ($CDCl_3$, 75.5 MHz): *Z*-isomer: $\delta$/ppm = 153.35 (s, C=N), 134.1 (s, C-1'), 131.4 (q, $^2J_{CF}$ = 48 Hz, C-3'), 129.5, 129.3 (2 d, C-5', C-6'), 126.5, 123.1 (2 dq, $^3J_{CF}$ = 4 Hz each, C-2', C-4'), 123.8 (q, $^1J_{CF}$ = 272 Hz, $CF_3$), 44.4 (t, $CH_2$). – *E*-isomer: $\delta$/ppm = 153.42 (s, C=N), 134.2 (s, C-1'), 129.1, 129.0 (2 d, C-5', C-6'), 125.4, 125.0 (2 dq, $^3J_{CF}$ = 3.5 Hz each, C-2', C-4'), 31.9 (t, $CH_2$). -- IR (KBr): $\nu$/cm$^{-1}$ = 3280 (br, O-H), 3090–2930 (=C-H, C-H), 1600 (C=N), 1170, 1130 (C–F).

| | | | | | |
|---|---|---|---|---|---|
| $C_9H_7BrF_3NO$ | Calcd.: | C 38.30 | H 2.51 | N 4.96 | |
| (282.2) | Found: | C 39.38 | H 2.91 | N 5.54. | |

*1-Bromo-3,3,3-trifluoroacetonoxime* (**6g**)

25.0 g (131 mmol) of 1-bromo-3,3,3-trifluoroacetone (**5g**) and 13.9 g (200 mmol) of hydroxylamine hydrochloride were treated according the general procedure (method B). Distillation by kugelrohr oven afforded 16.4 g (61%) of oxime **6g** (*Z*:*E* = 53:47) as colourless oil (*b.p.* 70–90 °C/130 mbar); ref. [3m]: 51% yield. The full characterization of compound **6g** is given in ref. [3m].

## Synthesis of 6*H*-1,2-Oxazines 10 (General Procedure)

Freshly grounded sodium carbonate (6 equivalents) was added to a solution of olefin **8** (10 equivalents; *Z*-**8**:*E*-**8** ≈ 6:1) and the corresponding $\alpha$-haloketoxime (1 equivalent) in *tert*-butyl methyl ether (12–16 ml/mmol oxime). After stirring at room temp. for 6 d the suspension was filtered through a pad of Celite to remove inorganic salts. The resulting filtrate was treated with DBU (1.5 equivalents), and the mixture was stirred for 6 h at room temp. The solution was then washed with water (3 × 1 ml/mmol oxime) and dried over $Na_2SO_4$. The solvent was removed *in vacuo*, and the excess of **8** was distilled off by kugelrohr distillation (20–60 °C/20 mbar). The residue was purified by filtration through alumina (elution with *n*-hexane/ethyl acetate = 4:1) to furnish the 6*H*-1,2-oxazine **10**.

*Workup for 6H-1,2-oxazine* **10g** [22]:

The cycloaddition and elimination were performed in dichloromethane instead of MeO*t*-Bu. After the removal of the solvent the remaining residue was added to a mixture of

THF/2N aqueous HCl solution (100 ml each). After hydrolysis of the unconsumed bromo enol ether **8** (7 h at r.t.) the solution was neutralized by 2N aqueous NaOH solution. Then the mixture was extracted with dichloromethane (3 × 60 ml) and the combined organic phases were dried with $Na_2SO_4$. The solvent was removed *in vacuo* and the crude product was purified by kugelrohr distillation (70–85 °C/6–10 mbar).

For analytical and NMR data of **10a–g** see tables 1–4.

*NMR data of the 5-bromo intermediates* **9e–g**

**Table 1** Synthesis of 6*H*-1,2-Oxazines **10a–g**

| Oxime | Amount of **6** [g (mmol)] | Amount of **8** [g (mmol)] | Product | Yield [g (%)] |
|---|---|---|---|---|
| **6a** | 8.50 (50.1) | 75.5 (500) | **10a** | 8.28 (81) |
| **6b** | 1.19 (5.00) | 7.55 (50.0) | **10b** | 0.978 (72) |
| **6c** | 0.620 (3.00) | 2.26 (15.0) | **10c** | 0.425 (59) |
| **6d** | 0.863 (3.06) | 15.1 (100) | **10d** | 0.607 (73) |
| **6e** | 1.68 (8.00) | 15.1 (100) | **10e** | 1.53 (96) |
| **6f** | 2.91 (10.1) | 15.3 (101) | **10f** | 2.08 (98) |
| **6g** | 2.06 (10.0) | 15.1 (100) | **10g** | 1.30 (67) |

*5-Bromo-5,6-dihydro-6-ethoxy-3-ethoxycarbonyl-4H-1,2-oxazine* (**9e**)

*cis*:*trans* = 66:34. – $^1$H NMR ($CDCl_3$, 200 MHz): *cis*-isomer: $\delta$//ppm = 5.23 (d, $J$ = 2.5 Hz, 1H, 6-H), 4.40 [q, $J$ = 7 Hz, 2H, $OCH_2$ (ester)], 4.31–4.09 (m, 1H, 5-H), 4.00–3.85, 3.77–3.21 (2 m, 2H, $OCH_2$), 3.21–2.83 (m, 2H, 4-H), 1.37, 1.25 (t, $J$ = 7 Hz each, 3H each, $2CH_3$). – *trans*-isomer: $\delta$/ppm = 5.21 (d, $J$ = 2.5 Hz, 1H, 6-H); missing signals are hidden by signals of the *cis*-isomer. – $^{13}$C NMR ($CDCl_3$, 50.3 MHz): *cis*-isomer: $\delta$//ppm = 162.0 (s, C=O), 149.7 (s, C-3), 96.5 (d, C-6), 65.1, 62.3 (2 t, $2OCH_2$), 38.3 (d, C-5), 27.3 (t, C-4), 14.5, 14.0 (2 q, $2CH_3$). – *trans*-isomer: $\delta$/ppm = 149.7 (s, C-3), 94.4 (d, C-6), 64.9, 62.2 (2 t, $2OCH_2$), 36.2 (d, C-5), 25.6 (t, C-4), 14.8, 14.0 (2 q, $2CH_3$).

*Methyl (E)-3-[(5-bromo-5,6-dihydro-6-ethoxy)-4H-1,2-oxazin-1-yl]propenoate* (**9f**)

*cis*:*trans* = 85:15. – $^1$H NMR ($CDCl_3$, 300 MHz): *cis*-isomer: $\delta$//ppm = 7.24 (d, $J$ = 16.5 Hz, 1H, 3-H), 6.11 (d, $J$ = 16.5 Hz, 1H, 2-H), 5.13 (d, $J$ = 2.5 Hz, 1H, 6'-H), 4.16 (ddd, $J$ = 2.5, 7, 11.5 Hz, 1H, 5'-H), AB part of $ABX_3$ system ($\delta_A$ = 3.81, $\delta_B$ = 3.65, $J_{AX}$ = $J_{BX}$ = 7 Hz, $J_{AB}$ = 10 Hz, 2H, $OCH_2$), 3.73 (s, 3H, $CO_2CH_3$), 2.84 (dd, $J$ = 11.5, 17.5 Hz, 1H, 4'-$H_a$), 2.74 (dd, $J$ = 7, 17.5 Hz, 1H, 4'-$H_e$), 1.19 (t, $J$ = 7 Hz, 3H, $CH_3$). – *trans*-isomer: $\delta$/ppm = 7.33, 6.27 (2 d, $J$ = 16.5 Hz each, 2H, HC=CH), 5.53 (d, $J$ = 4 Hz, 1H, 6'-H), 3.74 (s, 3H, $OCH_3$), 1.17 (t, $J$ = 7 Hz, 3H, $CH_3$). – $^{13}$C NMR ($CDCl_3$, 75.5 MHz): *cis*-isomer: $\delta$/ppm = 166.0 (s, C-1), 154.4 (s, C-3'), 139.8, 122.8 (2 d, C-2, C-3), 96.7 (d, C-6'), 65.0 (t, $OCH_2$), 52.0 (q, $OCH_3$), 38.9 (d, C-5'), 29.7 (t, C-4'), 14.6 (q, $CH_3$). – *trans*-isomer: $\delta$/ppm = 139.9 (s, C-3), 29.6 (t, C-4'), 14.0 (q, $CH_3$); missing signals are hidden by signals of the *cis*-isomer.

*5-Bromo-5,6-dihydro-6-ethoxy-3-(trifluoromethyl)-4H-1,2-oxazine* (**9g**)

*cis*:*trans* = 55:45. – $^1$H NMR ($CDCl_3$, 300 MHz): *cis*-isomer: $\delta$/ppm = 5.24 (d, $J$ = 2.5 Hz, 1H, 6-H), 4.17 (ddd, $J$ = 2.5, 7, 12 Hz, 1H, 5-$H_a$), 3.73 ($m_c$, 2H, $OCH_2$), 2.92 (dd, $J$ = 12, 18 Hz, 1H, 4-$H_a$), 2.83 (dd, $J$ = 7, 18 Hz, 1H, 4-$H_e$), 1.26 (t, $J$ = 7 Hz, 3H, $CH_3$). – *trans*-isomer: $\delta$/ppm = 5.20 (d, $J$ = 2.5 Hz, 1H, 6-H), 4.23 (ddd, $J$ = 2, 2.5, 5.5 Hz, 1H, 5-$H_e$), 3.92 ($m_c$, 2H, $OCH_2$), 3.17 (dd, signal with fine structure, $J$ = 5.5, 19 Hz, 1H, 4-$H_a$), 2.66 (dd, $J$ = 2, 19 Hz, 1H, 4-$H_e$), 1.26 (t, $J$ = 7 Hz, 3H, $CH_3$). – $^{13}$C NMR ($CDCl_3$, 75.5 MHz): *cis*-isomer: $\delta$/ppm = 147.5 (q, $^2J_{CF}$ = 31 Hz, C-3), 119.8 (q, $^1J_{CF}$ = 275 Hz, $CF_3$), 96.6 (d, C-6), 65.2 (t, $OCH_2$), 36.8 (d, C-5), 25.1 (t, C-4), 14.9 (q, $CH_3$). – *trans*-isomer: $\delta$/ppm = 145.0 (q, $^2J_{CF}$ = 34 Hz, C-3), 119.4 (q, $^1J_{CF}$ = 276 Hz, $CF_3$), 96.6 (d, C-6), 65.0 (t, $OCH_2$), 34.6 (d, C-5), 23.8 (t, C-4), 14.6 (q, $CH_3$). – IR (neat): $\nu$/cm$^{-1}$ = 2990, 2940 (C-H), 1630 (C=N), 1195, 1140 ($CF_3$).

*5-Azido-5,6-dihydro-6-ethoxy-3-ethoxycarbonyl-4H-1,2-oxazine* (**11**)

To a solution of 0.560 g (2.00 mmol) of 5-bromo-4*H*-1,2-oxazine **9e** (*cis*:*trans* = 66:34) in 8 ml of dry THF was added under an argon atmosphere 0.364 g (3.00 mmol) of trimethylsilyl azide and 0.946 g (3.00 mmol) of tetra-*n*-butylammonium fluoride trihydrate. After stirring at room temp. for 38 h the solvent was removed *in vacuo*. Purification of the residue by column chromatography on neutral alumina (activity III, *n*-

**Table 2** Analytical Data of 6*H*-1,2-Oxazines **10a–g**

| Compound | *F* (°C) | IR (cm$^{-1}$) (C=C, C=N) | Formula (m.w.) | % C (calcd./found) | % H | % N |
|---|---|---|---|---|---|---|
| **10a** | 40–41 [a] | 1635, 1585 | $C_{12}H_{13}NO_2$ (203.2) | 70.92 71.12 | 6.45 6.55 | 6.89 6.61 |
| **10b** | 34–37 | 1620, 1590 | $C_{12}H_{11}Cl_2NO_2$ [b] (272.2) | 52.94 53.29 | 4.08 4.20 | 5.14 5.13 |
| **10c** | 48–52 | 1620, 1595 | $C_{12}H_{11}F_2NO_2$ (239.2) | 60.25 60.25 | 4.64 4.50 | 5.86 5.80 |
| **10d** | Oil | 1610, 1540 1170, 1130 ($CF_3$) | $C_{13}H_{12}F_3NO_2$ (271.2) | 57.57 56.36 [c] | 4.46 4.37 | 5.16 5.07 |
| **10e** | Oil | 1745 (C=O) 1645, 1535 | $C_9H_{13}NO_4$ (199.2) | 54.27 54.64 | 6.58 6.86 | 7.03 6.76 |
| **10f** | 107–108 | 1720 (C=O) 1670, 1645, 1620 | $C_{10}H_{13}NO_4$ (211.2) | 56.87 56.78 | 6.20 6.10 | 6.63 6.55 |
| **10g** | Oil | 1635, 1190, 1135 ($CF_3$) | $C_7H_8F_3NO_2$ (195.1) | 43.09 42.55 | 4.13 4.62 | 7.18 7.11 |

[a] Compound crystallized at –20 °C [b] Cl: calcd.: 26.08, found: 26.02 [c] No correct C value available in this case

**Table 3** $^1$H NMR Data of 6*H*-1,2-Oxazines **10a–g**

| Compound | $\delta$ values in ppm, measured in $CDCl_3$ (assignment) |
|---|---|
| **10a** | 7.74–7.69, 7.44–7.36 (2 m, 2H, 3H, Ph), 6.59 (d, $J$ = 10 Hz, 1H, 4-H), 6.41(dd, $J$ = 4.5, 10 Hz, 1H, 5-H), 5.60 (d, $J$ = 4.5 Hz, 1H 6-H), AB part of $ABX_3$ system ($\delta_A$ = 3.99, $\delta_B$ = 3.69, $J_{AX}$ = $J_{BX}$ = 7 Hz, $J_{AB}$ = 10 Hz, 2H, $OCH_2$), 1.22 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10b** | 7.40–7.15 (m, 3H, $C_6H_3Cl_2$), 6.37 (d, $J$ = 9.7 Hz, 1H, 4-H), 6.30 (dd, $J$ = 4.2, 9.7 Hz, 1 H, 5-H), 5.63 (d, $J$ = 4.2 Hz, 1 H, 6-H), 4.08–3.92, 3.79–3.64 (2 m, 2H, $OCH_2$), 1.15 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10c** | 7.74–7.65, 6.99–6.70 (2 m, 1H, 2H, $C_6H_3F_2$), 6.50 (dd, $J_{HF}$ = 3 Hz, $J_{HH}$ = 10 Hz, 1H, 4-H), 6.33 (dd, $J$ = 4.5, 10 Hz, 1H, 5-H), 5.61 (d, $J$ = 4.5 Hz, 1H, 6-H), 4.10–3.92, 3.81–3.64 (2 m, 2H, $OCH_2$), 1.24 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10d** | 8.01 (s, 1 H, 2'-H), 7.91, 7.68 (2 d, $J$ = 7.7 Hz each, 2H, 4'-H, 6'-H), 7.55 (t, $J$ = 7.7 Hz, 1H, 5'-H), 6.60 (d, $J$ = 10 Hz, 1H, 4-H), 6.45 (dd, $J$ = 4.4, 10 Hz, 1H, 5-H), 5.64 (d, $J$ = 4.4 Hz, 1H, 6-H), 4.09–3.93, 3.79–3.64 (2m, 2H, $OCH_2$), 1.23 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10e** | 6.71 (d, $J$ = 10 Hz, 1 H, 4-H), 6.30 (dd, $J$ = 4.5, 10 Hz, 1 H, 5-H), 5.67 (d, $J$ = 4.5 Hz, 1 H, 6-H), 4.39 (q, $J$ = 7 Hz, 2H, $CO_2CH_2$), AB part of $ABX_3$ system ($\delta_A$ = 4.00, $\delta_B$ = 3.70, $J_{AX}$ = $J_{BX}$ = 7 Hz, $J_{AB}$ = 9.5 Hz, 2H, $OCH_2$), 1.39 (t, $J$ = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.22 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10f** | 7.39 (d, $J$ = 16 Hz, 1H, 3-H), 6.43 (d, $J$ = 10 Hz, 1H, 4'-H), 6.37 ($m_c$, 1H, 5'-H), 6.35 (d, $J$ = 16 Hz, 1H, 2-H), 5.61 (d, $J$ = 4 Hz, 1 H, 6'-H), AB part of $ABX_3$ system ($\delta_A$ = 3.96, $\delta_B$ = 3.68, $J_{AX}$ = $J_{BX}$ = 7 Hz, $J_{AB}$ = 9.5 Hz, 2H, $OCH_2$), 3.80 (s, 3H, $CO_2CH_3$), 1.21 (t, $J$ = 7 Hz, 3H, $CH_3$) |
| **10g** | 6.38 (dd, $J$ = 4, 10 Hz, 1H, 5-H), 6.31 (d, $J$ = 10 Hz, 1H, 4-H), 5.67 (d, $J$ = 4 Hz, 1H, 6-H), AB part of $ABX_3$ system ($\delta_A$ = 3.99, $\delta_B$ = 3.71, $J_{AX}$ = $J_{BX}$ = 7 Hz, $J_{AB}$ = 9.5 Hz, 2H, $OCH_2$), 1.23 (t, $J$ = 7 Hz, 3H, $CH_3$) |

**Table 4** $^{13}$C NMR Data of 6*H*-1,2-Oxazines **10a–g**

| Compound | $\delta$ values in ppm, measured in $CDCl_3$ (assignment) |
|---|---|
| **10a** | 154.1 (s, C-3), 133.9, 129.9, 128.7, 126.2, 126.0 (s, 4 d, Ph, C-5), 116.2 (d, C-4), 91.8 (d, C-6), 64.1 (t, $OCH_2$), 15.0 (q, $CH_3$) |
| **10b** | 154.3 (s, C-3), 136.1, 133.5, 132.3 (3 s, C-1', C-2', C-4'), 131.5, 129.9, 127.4, 124.3 (4 d, C-3', C-5', C-6', C-5), 118.3 (d, C-4), 91.9 (d, C-6), 64.0 (t, $OCH_2$), 15.0 (q, $CH_3$) |
| **10c** | 164.0 (dd, $^{1,3}J_{CF}$ = 264, 12 Hz, =C-F), 159.1 (dd, $^{1,3}J_{CF}$ = 253, 12 Hz, =C-F), 151.5 (d, $^3J_{CF}$ = 2 Hz, C-3), 130.7 (ddd, $^{3,3}J_{CF}$ = 10, 4.5 Hz, =C-H), 125.0 (d, C-5), 118.6 (dd, $^{2,4}J_{CF}$ = 12, 4 Hz, i-C), 117.9 (dd, $^4J_{CF}$ = 6.5 Hz, C-4), 111.9 (ddd, $^{2,4}J_{CF}$ = 21.5, 3.5 Hz, =C-H), 104.5 (td, $^{2,2}J_{CF}$ = 26 Hz, =C-H), 92.0 (d, C-6), 64.1 (t, $OCH_2$), 15.0 (q, $CH_3$) |
| **10d** | 153.0 (s, C-3), 134.8 (s, C-1'), 131.3 (q, $^2J_{CF}$ = 33 Hz, C-3'), 129.2 (d, C-6'), 129.1 (dq, $^4J_{CF}$ = 1 Hz, C-5'), 126.6 (d, C-5), 126.3, 122.9 (2 dq, $^3J_{CF}$ = 4 Hz each, C-2', C-4'), 123.8 (q, $^1J_{CF}$ = 273 Hz, $CF_3$), 115.5 (d, C-4), 92.0 (d, C-6), 64.2 (t, $OCH_2$), 14.9 (q, $CH_3$) |
| **10e** | 162.2 (s, $COOC_2H_5$), 148.3 (s, C-3), 124.8 (d, C-5), 114.9 (d, C-4), 92.7 (d, C-6), 64.5, 62.3 (2 t, 2 $OCH_2$), 15.0, 14.2 (2 q, 2 $CH_3$) |
| **10f** | 165.9 (s, C-1), 152.2 (s, C-3'), 138.4 (d, C-3), 125.7, 122.4 (2 d, C-2, C-5'), 113.8 (d, C-4'), 92.4 (d, C-6'), 64.1 (t, $OCH_2$), 51.8 (t, $CO_2CH_3$), 14.7 (q, $CH_3$) |
| **10g** | 147.4 (q, $^2J_{CF}$ = 34 Hz, C-3), 126.3 (d, C-5), 120.2 (q, $^1J_{CF}$ = 274 Hz, $CF_3$), 111.9 (d, C-4), 92.6 (d, C-6), 64.5 (t, $OCH_2$), 14.7 (q, $CH_3$) |

hexane:ethyl acetate = 9:1) provided 0.326 g of a 35:65 mixture of **11** (27%, *cis*:*trans* = 7:93) and 6*H*-1,2-oxazine **10e** (50%) which could not completely separa-ted. NMR data of **11:** $^1$H NMR ($CDCl_3$, 200 MHz): *trans*–isomer: $\delta$/ppm = 5.06 (d, $J$ = 2.9 Hz, 1H, 6-H), 4.44–4.28 [m, 2H, $OCH_2$ (ester)], 4.05–3.85, 3.77–3.21 (2 m, 2H, 1H, 5-H, $OCH_2$), 2.69–2.64 (m, 2H, 4-H), 1.38, 1.21 (t, $J$ = 7 Hz each, 3H each, $2CH_3$). – *cis*-isomer: $\delta$/ppm = 5.10 (d, $J$ = 3 Hz, 1H, 6-H), 2.76 ($m_c$, 2H, 4-H); missing signals are hidden by signals of the *trans*-isomer. – $^{13}$C NMR ($CDCl_3$, 50.3 MHz): *trans*-isomer: $\delta$/ppm = 162.6 (s, C=O), 148.8 (s, C-3), 95.7 (d, C-6), 64.8, 62.2 (2 t, 2 $OCH_2$), 51.2 (d, C-5), 22.0 (t, C-4), 14.7, 13.5 (2 q, 2 $CH_3$). – *cis*-isomer: $\delta$/ppm = 96.2 (d, C-6), 65.0, 62.3 (2 t, $2OCH_2$), 51.0 (d, C-5), 21.8 (t, C-4), 14.1, 13.5 (2 q, $2CH_3$); missing signals are hidden by signals of the *trans*-isomer.

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[22] Due to the low boiling point of **10g** separation from **8** by distillation was not possible. Therefore an alternative workup procedure involving hydrolysis of the excess of **8** was developed.

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