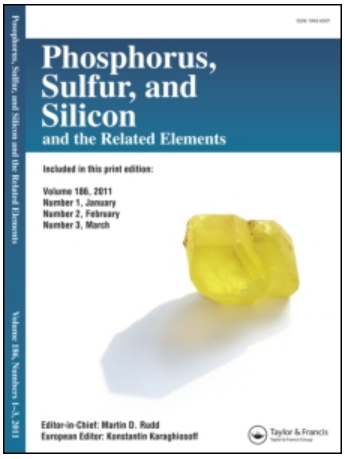

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THE PECULIAR α-AMIDOALKYLATION OF VINYLTRIMETHYLSILANE

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α-Amidoalkylation of allyltrimethylsilane with methyl-2-chloro-2-(p-chlorobenzoylamino)-ethanoate **1** gave in the presence of Lewis acid racemic methyl-2-(p-chlorobenzoylamino)-4-pentenoate **2**. Under the same conditions, vinlytrimethylsilane afforded (±)-*trans*-2-(p-chlorophenyl)-5,6-dihydro-4-methoxycarbonyl-6-trimethylsilyl-4H-1, 3-oxazine 4 as the major, by n.m.r. data and x-ray crystallography established product.

Key words: α-Amidoalkylation; unsaturated α-amino acids; allylglycine derivative; (4 + 2)-cycloaddition of vinyltrimethylsilane; diastereoisomeric 1,3-oxazines; regioisomeric 1,3-oxazines.

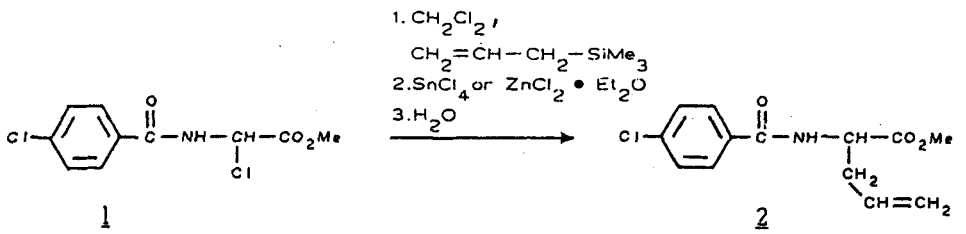
INTRODUCTION

Unsaturated α-amino acids have been of interest recently[1] because of their ability of act as suicide inhibitors of pyridoxal-linked enzyme systems[2] and their use as intermediates in organic synthesis.[3]

In the course of our studies on electrophilic α-amidoalkylation reactions, we became interested in the preparation of allyl- and vinyl-glycine derivatives using olefinic silanes as nucleophiles. Following the recently published survey[4] on the electrophilic substitution of allyl- and vinylsilanes, we wish to report our investigations on the use of allyl- and vinyltrimethylsilane in the preparation of some amino acid derivatives. The unusual behaviour of the latter silane is highlighted in particular.

RESULTS AND DISCUSSION

Lewis acid mediated reaction of allyltrimethylsilane with the α-chloroglycinate **1**,[5] gave the expected racemic C-allylglycine **2** (Scheme 1). A few similar amidoal-



1 2

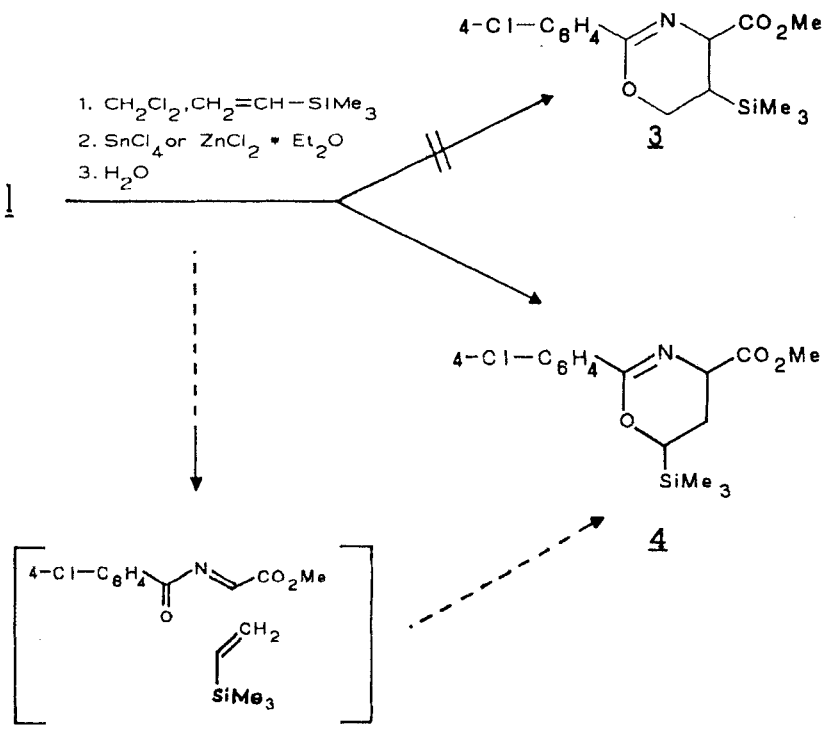
SCHEME 1

kylations with corresponding glycidyl cation equivalents have been reported very recently.[6] The spectroscopic properties of **2** were similar to those observed for the corresponding ethyl ester, prepared[7] by the hydroximinomalonate route.[8]

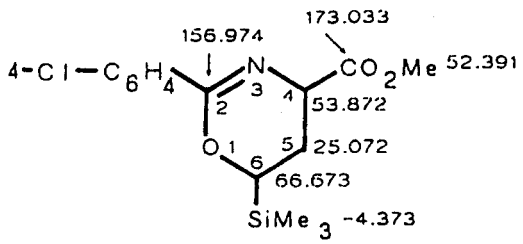
In contrast, treatment of vinyltrimethylsilane under the same conditions gave one major product, a low melting solid, whose proton n.m.r. spectrum unexpectedly exhibited the presence of a trimethylsilyl group. The infrared spectrum of the compound showed an ester absorption at 1745 cm^{-1} and an absorption at 1645 cm^{-1}, attributable to either an amide carbonyl or imine group, but no N-H signal. Furthermore, the absence of characteristic vinyl resonances[9] in the ^1H-n.m.r. spectrum indicated that a vinylglycine derivative had not been formed. Based on this and other evidence (see below), it was concluded that an inverse electron demand, (4+2)-cycloaddition, between the silane and an N-acylimin intermediate as hetero-1,3-diene, leading to one of the regioisomeric heterocycles **3** or **4** had occurred[10] (Scheme 2).

(4+2)-Cycloaddition reactions of vinyltrimethylsilane itself are not well known but related 1,3-dipolar ion cycloadditions of this silane with oxygen containing 4π components such as nitrile oxides and nitrones have been reported by Cunico[11] and DeShong[12] respectively.

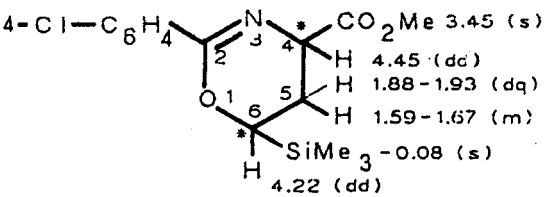
The proton decoupled ^{13}C-n.m.r. chemical shifts of the product (Figure 1A) and carbon resonance multiplicities (DEPT-135 experiments) were consistent with an oxazine structure. In particular, the carbon resonance at 156.97 ppm is characteristic of the aryl imino ether group[13] and has been found in the 155–158 ppm range for



SCHEME 2

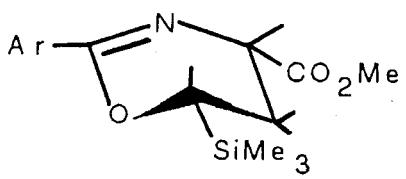


(A)

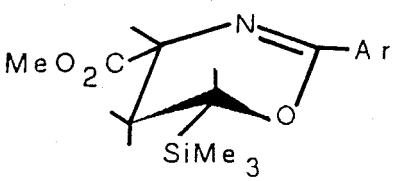


(B)

FIGURE 1 (A) ^{13}C n.m.r. chemical shifts and (B) ^{1}H n.m.r. chemical shifts (δ(ppm), C_6D_6, TMS) of **4**.

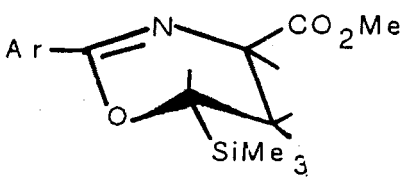


4a

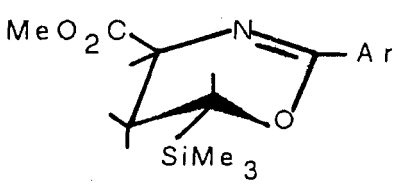


4b

cis - enantiomers



4c



4d

trans - enantiomers

FIGURE 2 Stereoisomeric structures of **4**.

related dihydro-oxazines.[14] The carbon resonance at 25.07 ppm, assigned to a methylene group bonded to two tertiary carbons, clearly favours structure **4**. Carbons of methylene groups directly linked to an oxygen atom have resonances in the region of 64–70 ppm.[15] Further support for the oxazine structure was derived from its ^{1}H-n.m.r. chemical shifts (Figure 1B).

Owing to the presence of two chiral centres at C—4 and C—6, four stereoisomers are possible for structure **4**. But, in accordance with the chromatographic and spectroscopic uniformity of the compound and the absence of optical activity, one of the two enantiomeric pairs **4a**, **b** or **4c**, **d** was deemed to be present (Figure 2).

More detailed information on the preferred stereochemistry of the compound was deduced from examination of the ^{1}H-n.m.r. coupling constants (Table I) which clearly favour the *trans*-enantiomers **4c**, **d**.

TABLE I

Correlations of ^{1}H-n.m.r. coupling constants of **4**

chemical shifts [δ(ppm)] structure group	J (Hz)	coupling relations
1.59 - 1.67 (m)	14.2	5a - 5e
H_aC-5	12.8	5a - 6a
	5.8	5a - 4e
1.88 - 1.93 (dq)	14.2	5e - 5a
H_eC-5	3.2	5e - 6a
	1.8	5e - 4e
4.22 (dd)	12.8	6a - 5a
O-HC-6	3.2	6a -5e
4.45 (dd)	5.8	4e - 5a
N-HC-4	1.8	4e - 5e

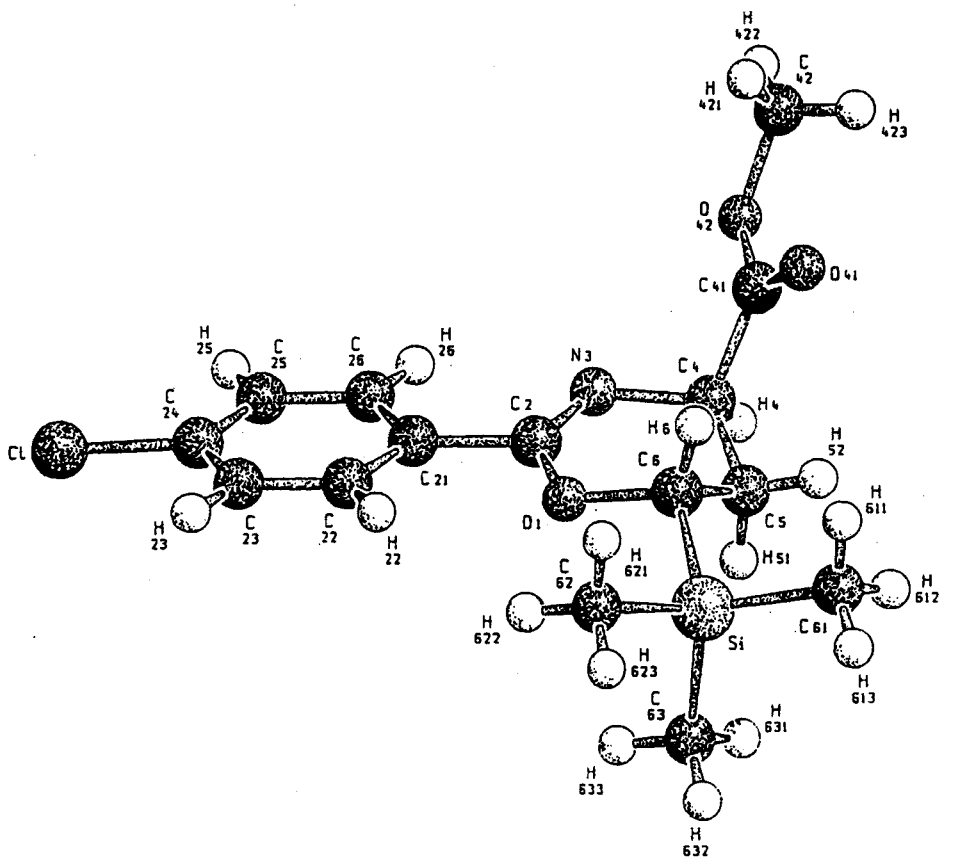


FIGURE 3 SCHAKAL plot, showing the crystal structure of **4c**.

Stereochemical determinations based on the magnitudes of observed coupling constants alone must be treated with some caution, particularly in the case of heterocyclic compounds which cannot adopt a true chair conformation.

For final structure resolution, a single crystal X-ray analysis of **4** was carried out.[16] The "SCHAKAL"[17] plot (Figure 3), showing structure **4c**, confirms the concluded *trans*-enantiomers.

The successful structure determination of **4**, prompted us to attempt the synthesis of analogous compounds by changing the carboxamide and ester carbonyl moieties of **1**. However, the use of α-chloroglycine derivatives, prepared from either aliphatic carboxamides or aromatic glyoxals was equally unsuccessful in yielding oxazines similar to **4**.

Transformations of **4c**, **d** into novel amino acid derivatives are now in progress.

EXPERIMENTAL

M.ps. are uncorrected. IR spectra were obtained from KBr tablets and are reported in cm^{-1}. N.m.r. spectra were recorded at 270; 400 MHz (^1H) and at 62; 67 MHz (^{13}C). Chemical shifts are given in σ(ppm) downfield from TMS. All reactions were carried out in dry solvents.

TABLE II

Bond lengths (Å) with standard deviations

CL(1)—C(24)	1.7490(70)	SI(1)—C(6)	1.8720(70)	SI(1)—C(61)	1.8380(100)	SI(1)—C(62)	1.8690(80)
SI(1)—C(63)	1.8820(80)	O(1)—C(2)	1.3400(70)	O(1)—C(6)	1.4580(80)	O(41)—C(41)	1.1720(90)
O(42)—C(41)	1.2880(90)	O(42)—C(42)	1.4200(100)	N(3)—C(2)	1.2500(80)	N(3)—C(4)	1.4640(80)
C(2)—C(21)	1.5120(90)	C(4)—C(5)	1.5110(100)	C(4)—C(41)	1.5330(90)	C(5)—C(6)	1.5290(90)
C(21)—C(22)	1.3830(90)	C(21)—C(26)	1.3670(90)	C(22)—C(23)	1.3890(90)	C(23)—C(24)	1.3650(110)
C(24)—C(25)	1.3490(110)	C(25)—C(26)	1.3840(100)	C(4)—H(4)	0.9590(100)	C(5)—H(51)	0.9590(90)
C(5)—H(52)	0.9610(90)	C(6)—H(6)	0.9600(90)	C(22)—H(22)	0.9600(100)	C(23)—H(23)	0.9600(100)
C(25)—H(25)	0.9600(100)	C(26)—H(26)	0.9610(90)	C(42)—H(421)	0.9600(90)	C(42)—H(422)	0.9600(80)
C(42)—H(423)	0.9600(100)	C(61)—H(611)	0.9600(130)	C(61)—H(612)	0.9600(130)	C(61)—H(613)	0.9600(130)
C(62)—H(621)	0.9590(110)	C(62)—H(622)	0.9590(110)	C(62)—H(623)	0.9590(110)	C(63)—H(631)	0.9600(130)
C(63)—H(632)	0.9590(120)	C(63)—H(633)	0.9600(130)				

X-ray analysis of **4**.
Structural parameters are given for **4c**.

TABLE III

Angles (degree) with standard deviations

C(6)—SI(1)—C(61)	106.90(40)	C(6)—SI(1)—C(62)	108.40(30)	C(6)—SI(1)—C(63)	107.50(40)
C(61)—SI(1)—C(62)	112.60(40)	C(61)—SI(1)—C(63)	111.60(40)	C(62)—SI(1)—C(63)	109.70(40)
C(2)—O(1)—C(6)	116.60(50)	C(41)—O(42)—C(42)	118.10(60)	C(2)—N(3)—C(4)	118.40(50)
O(1)—C(2)—N(3)	129.90(60)	O(1)—C(2)—C(21)	111.00(50)	N(3)—C(2)—C(21)	119.10(50)
N(3)—C(4)—C(5)	113.80(50)	N(3)—C(4)—C(41)	108.70(50)	C(5)—C(4)—C(41)	113.10(60)
C(4)—C(5)—C(6)	110.70(50)	SI(1)—C(6)—O(1)	107.20(40)	SI(1)—C(6)—C(5)	115.50(40)
O(1)—C(6)—C(5)	108.40(50)	C(2)—C(21)—C(22)	120.80(60)	C(2)—C(21)—C(26)	119.30(60)
C(22)—C(21)—C(26)	119.90(60)	C(21)—C(22)—C(23)	120.00(60)	C(22)—C(23)—C(24)	118.30(60)
CL(1)—C(24)—C(23)	117.90(50)	CL(1)—C(24)—C(25)	119.50(60)	C(23)—C(24)—C(25)	122.50(60)
C(24)—C(25)—C(26)	119.10(70)	C(21)—C(26)—C(25)	120.20(60)	O(41)—C(41)—O(42)	124.30(60)
O(41)—C(41)—C(4)	124.70(70)	O(42)—C(41)—C(4)	111.00(60)	N(3)—C(4)—H(4)	109.10(70)
C(5)—C(4)—H(4)	102.90(70)	C(41)—C(4)—H(4)	109.00(70)	C(4)—C(5)—H(51)	109.10(80)
C(4)—C(5)—H(52)	109.40(70)	C(6)—C(5)—H(51)	109.00(70)	C(6)—C(5)—H(52)	109.20(80)
H(51)—C(5)—H(52)	109.40(80)	SI(1)—C(6)—H(6)	107.00(60)	O(1)—C(6)—H(6)	113.90(70)
C(5)—C(6)—H(6)	105.00(70)	C(21)—C(22)—H(22)	120.00(70)	C(23)—C(22)—H(22)	120.10(80)
C(22)—C(23)—H(23)	120.70(80)	C(24)—C(23)—H(23)	120.90(80)	C(24)—C(25)—H(25)	120.50(90)
C(26)—C(25)—H(25)	120.40(90)	C(21)—C(26)—H(26)	119.80(70)	C(25)—C(26)—H(26)	120.00(70)
O(42)—C(42)—H(421)	110.30(70)	O(42)—C(42)—H(422)	109.40(70)	O(42)—C(42)—H(423)	108.70(80)
H(421)—C(42)—H(422)	109.50(90)	H(421)—C(42)—H(423)	109.50(80)	H(422)—C(42)—H(423)	109.40(80)
SI(1)—C(61)—H(611)	109.40(90)	SI(1)—C(61)—H(612)	109.70(90)	SI(1)—C(61)—H(613)	109.10(90)
H(611)—C(61)—H(612)	109.50(120)	H(611)—C(61)—H(613)	109.50(130)	H(612)—C(61)—H(613)	109.50(110)
SI(1)—C(62)—H(621)	109.50(80)	SI(1)—C(62)—H(622)	109.70(80)	SI(1)—C(62)—H(623)	109.10(70)
H(621)—C(62)—H(622)	109.50(100)	H(621)—C(62)—H(623)	109.50(110)	H(622)—C(62)—H(623)	109.50(100)
SI(1)—C(63)—H(631)	110.30(80)	SI(1)—C(63)—H(632)	109.30(90)	SI(1)—C(63)—H(633)	108.80(70)
H(631)—C(63)—H(632)	109.50(100)	H(631)—C(63)—H(633)	109.40(120)	H(632)—C(63)—H(633)	109.50(110)

Methyl-2-(p-chlorobenzoylamino)-2-hydroxy-ethanoate.[5] The mixture of 4.8 g (55 mmol) methyl glyoxylate and 7.7 g (50 mmol) of p-chlorobenzamide in 15 mL of ethyl acetate was refluxed for 45 min. After addition of 10 mL of light petroleum (40–60°C) at r.t. the resulting precipitate was purified by washing and suction with 15 mL of ether.

Yield: 9.0 g (73%); m.p. 113–114°C. IR: 3420 (OH), 3320, 3000 (NH), 1750 (CO—O), 1650 (CO—N). ^{1}H-n.m.r. ($CDCl_3$): 3.80 (s; 3H, CH_3) 5.80 (d; 1H, CH), 7.38–7.84 (dd; 4H, aromat.), 8.56 (d; 1H, NH).

Anal. calc. for $C_{10}H_{10}ClNO_4$: C 49.30, H 4.14, Cl 14.55, N 5.75.

Found: C 49.23, H 4.19, Cl 14.50, N 5.76.

Methyl-2-chloro-2-(p-chlorobenzoylamino)-ethanoate (**1**).[5] The suspension of 4.8 g (20 mmol) of the foregoing adduct in 30 mL of CH_2Cl_2 + 10 mL of THF was treated with 5.5 g (46 mmol) of $SOCl_2$ under reflux for 25 min. The homogeneous solution then was concentrated i.vac. and the remaining crystals were purified by washing and suction with a mixture of 40 mL of light petroleum (40–60°C) + 10 mL of ether under nitrogene. The moisture sensitive product must not be recrystallized.

Yield: 4.9 g (94%); m.p. 155–156°C. IR: 3305 (NH), 1740 (CO—O), 1660 (CO—N). ^{1}H-n.m.r. ($CDCl_3$): 3.93 (s; 3H, CH_3), 6.48 (d; 1H, CH), 7.38 (d; 1H, NH), 7.46–7.80 (dd; 4H, aromat). ^{13}C-n.m.r. ($CDCl_3$): 53.907 (CH_3), 60.160 (CH), 128.701, 128.857, 129.054, 129.180, 130.689, 139.279 (aromat), 164.957 and 167.077 (2 CO).

Anal. calc. for $C_{10}H_9Cl_2NO_3$: C 45.83, H 3.46, Cl 27.05, N 5.34:

Found: C 45.93, H 3.52, Cl 27.08, N 5.45.

Methyl-2-(p-chlorobenzoylamino)-4-pentenoate (**2**). To a stirred suspension of 3.4 g (13 mmol) of **1** in a solution of 3.0 g (26 mmol) of allyltrimethylsilane in 40 mL of CH_2Cl_2 a solution of 3.4 g (13 mmol) of $SnCl_4$ (or 1.1 equiv. = 6 mL of 2.2M $ZnCl_2 \cdot Et_2O$ in CH_2Cl_2) in 5 mL of CH_2Cl_2 was added dropwise (reflux condenser, ice cooling). After standing at r.t. for 24 h the homogeneous mixture was poured onto 50 g of ice. The separated organic layer was washed with H_2O (3 × 10 mL) and sat. $NaHCO_3$-solution adjusting pH 7, dried over Na_2SO_4 and evaporated i.vac. to give a viscous oil which solidified under 15 mL of light petroleum (40–60°C).

Recrystallization from cyclohexane yielded 2.5 g (72%); m.p. 80–81°C. IR: 3315 (NH), 1742 (CO—O), 1635 (CO—N). ^{1}H-n.m.r. ($CDCl_3$): 2.61–2.71 (m; 2H, =CH—C$\underline{H}_2$—), 3.78 (s; 3H, CH_3), 4.85 (q; 1H, C$\underline{H}$—N), 5.13–5.19 (m; 2H, $\underline{H}_2$C=CH—), 5.67–5.80 (m; 1H, CH_2=C$\underline{H}$—) 6.85 (d; 1H, NH). ^{13}C-n.m.r. ($CDCl_3$): 36:485 (=CH—$\underline{C}H_2$—), 52.098 ($\underline{C}$H—N), 52.529 (CH_3), 119.416 ($H_2\underline{C}$=CH—), 132.215 (H_2C=$\underline{C}$H—), 165.941 and 172.252 (2 CO).

Anal. calc. for $C_{13}H_{14}ClNO_3$: C 58.33, H 5.27, Cl 13.24, N 5.23.

Found: C 58.19, H 5.28, Cl 13.04, N 5.34.

(±)-*Trans-2-(p-chlorophenyl)-5,6-dihydro-4-methoxycarbonyl-6-trimethylsilyl-4H-1,3-oxazine* (**4c, d**). According to the preceding procedure, starting from 2.6 g (10 mmol) of **1**, 2.0 g (20 mmol) of vinyltrimethylsilane, 1.1 equiv. (5 mL of 2.2M sol. in CH_2Cl_2) of $ZnCl_2 \cdot Et_2O$ (or 2.9 g/1.1 equiv. of $SnCl_4$ in 5 mL of CH_2Cl_2), 30 mL of CH_2Cl_2, there was obtained a homogeneous mixture after standing at r.t. for 2 d. The work up by pouring onto 40 g of ice, washing of the organic layer with 3 × 10 mL of sat.$NaHCO_3$-sol. and 2 × 10 mL of H_2O, drying over Na_2SO_4 afforded a yellow oil. Extraction with 2 × 20 mL of boiling n-hexane and concentration of the combined extracts i.vac. gave 3.2 g of a whitish oily residue which yielded after centrifugal chromatography with ether (silica gel 60 F_{254}) 2.7 g (83%) of the crystallizing product **4c, d**; m.p. 71–73°C.

IR: 1745 (CO—O), 1645 (C=N). ^{1}H-n.m.r. and ^{13}C-n.m.r. chemical shifts, Figure 1. ^{1}H-n.m.r. coupling constants, Table I.

Anal. calc. for $C_{15}H_{20}ClNO_3Si$: C 55.29, H 6.19, Cl 10.88, N 4.30.

Found: C 55.26, H 6.26, Cl 10.88, N 4.38.

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