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Synthesis and some Transformations of Substituted 5,6-Dihydro-4*H*-1,3-oxazines

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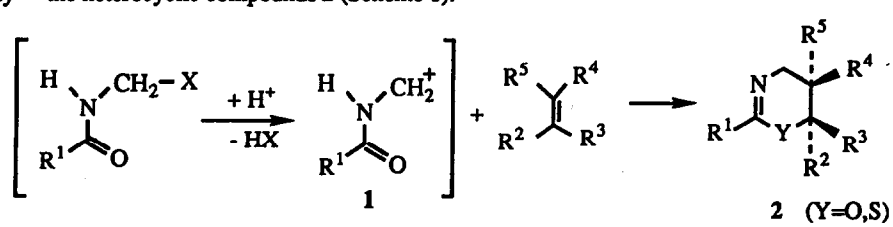
Abstract: *Substituted 5,6-dihydro-4H-1,3-oxazines are prepared by the acid-catalyzed amidoalkylation of the terminal olefins. 5,6-Dihydro-4H-oxazines undergo further transformations involving the hetero-ring and/or the substituent leading to alkyl amino-substituted 5,6-dihydro-4H-1,3-dihydrooxazines and/or to ring-opened products, 3-hydroxypropylamides.*

INTRODUCTION

Amidoalkylations of various olefins in the presence of acid catalysts are good preparative methods for the synthesis of 1,3-oxazines and -thiazines[1,2]. The primary products from amidoalkylations of olefins are normally[3-5] the heterocyclic compounds **2** (Scheme 1).



Scheme 1

These reactions proceed via 1,4-polar cycloadditions of the amido- or thioamido-methyl ion **1** to the olefin[6-8]. Formation of both 1,3-oxazines (Y=O)[8,9] and 1,3-thiazines (Y=S)[10] **2** are step-wise additions which

occur regiospecifically in accord with Markovnikov's rule and stereospecifically *cis*. Detailed mechanistic studies[7,8] strongly suggest that the cycloaddition process is nearly synchronous. Various reagent combinations, such as nitriles and formaldehyde[11], carboxamides and formaldehyde[8] or individual reagents such as N,N'-methylene-bis-amides or 1,3,5-triacylhexahydro-1,3,5-triazines[12] can be used for the amidoalkylation.

In addition to the amidoalkylation of olefins, several synthetic routes to partly or fully substituted 5,6-dihydro-4*H*-1,3-oxazines have been described: (i) from olefins by acylamidation with acyltetrafluoroborate and nitrile to 6-fluorosubstituted derivatives[13], (ii) from olefins by [4+2] cycloaddition[14], (iii) by intramolecular cyclization of 3-acylamino-1-propanols[15], (iv) from oxetanes and nitriles by cycloaddition followed by ring expansion[16]. The compounds thus obtained have been shown to be hydrocarbon antioxidants[17] and choline acetyltransferase inhibitors[18], and useful in the syntheses of polymers[19], liquid crystals[20], surfactants[19], and chemically- and heat-resistant resins[21]. 2-Alkyl- and 2-vinyl-5,6-dihydro-4*H*-1,3-oxazines are valuable synthons for the synthesis of aldehydes and other compounds as shown by Meyers[22].

The present paper describes our efforts to generalize procedures for the preparation of substituted 5,6-dihydro-4*H*-1,3-oxazines by the amidoalkylation of unactivated olefines with carboxamides/formaldehyde or N-(hydroxymethyl)carboxamides in the presence of acids. Ring-opening of these heterocycles has been assumed for the transformation of alkenes into hydroxy and/or amido or amino alkyl derivatives, and we describe further transformations of 5,6-dihydro-4*H*-1,3-oxazines involving the hetero-ring and/or the substituent.

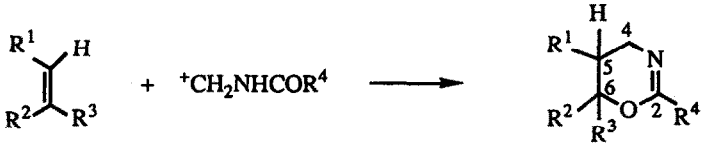
RESULTS AND DISCUSSION

In previous syntheses of 5,6-dihydro-4*H*-1,3-oxazines by the amidoalkylation of olefins[7,8,11,23-27], the use of nitrile/formaldehyde or amide/formaldehyde systems[8,11] had the advantage over N-(hydroxymethyl)-amides or N-(chloromethyl)-amides[2] of requiring no preliminary preparation and isolation of the reagents and of starting from readily available materials. However, we have found no published general procedures for the olefin amidoalkylation giving good yields of 5,6-dihydro-4*H*-1,3-oxazines. The best results (50-80% yields) are reported for styrene derivatives, but the use of alkyl-substituted alkenes resulted in yields of 15 to 60% of compounds **2** (Scheme 1), see ref.[2] and papers quoted theirin. The use of trifluoroacetic acid as a catalyst for amidoalkylation was reported to give N-alkenylamides[25].

In the present work, we used benzamide/paraformaldehyde, acrylamide/paraformaldehyde or N-(hydroxymethyl)acrylamide, and N-(hydroxymethyl)formamide as the source of amidoalkylating ions **4 a-c**, together with alkenes **3 a-g**, in the presence of acetic and sulfuric acids, or trifluoroacetic acid (Scheme 2). Substituted 5,6-dihydro-4*H*-1,3-oxazines **5 a-p** (Scheme 2 and Tables 1 and 2) were obtained in 50-85% yields, and the optimum conditions depended upon the structure of the olefin, amidoalkylating agent and catalyst used. The structural proofs for compounds **5 a-p** were based on the NMR spectral data (Table 2). The proton and carbon signal assignments and the conformations of dihydro-4*H*-1,3-oxazine rings are discussed together with the COSY and HETCOR experiments used in a separate paper[28].

Oct-1-ene (**3a**), cyclohexene (**3b**), 2,4,4-trimethylpent-1-ene (TMP-1), (**3c**) octadec-1-ene (**3f**) and icos-1-ene (**3g**) each smoothly yielded the corresponding dihydrooxazine **5** (Scheme 2, Tables 1 and 2). On

amidoalkylation with benzamide/paraformaldehyde or N-(hydroxymethyl)acrylamide, *cis*-hept-2-ene (**3e**) gave mixtures of two isomeric oxazines **5 k,l** and **5 m,n** respectively, in ratios of 1.7:1 in each case (comparison of the integrals in the ^{1}H NMR spectrum). A similar experience with *cis*-pent-2-ene had been reported[8]. We failed to separate the mixture by distillation, and the distillate had the same isomer ratio. The ^{13}C NMR spectra also clearly showed signals for two isomers in each case, and the difference in the CHO signals was ~4.0 ppm (Table 2).



3 a-g **4 a-c** **5 a-p**

3 a R^1=R^2=H, R^3=Me$(CH_2)_5$; **b** R^1+R^2=$(CH_2)_4$, R^3=H; **c** R^1=H, R^2=Me, R^3=CH_2CMe_3; **d** R^1=CMe_3, R^2=R^3=Me; **e** R^1=Me, R^2=$(CH_2)_3$Me, R^3=H; **f** R^1=R^2=H, R^3=$(CH_2)_{15}$Me; **g** R^1=R^2=H, R^3= $(CH_2)_{17}$Me; **4 a** R^4=Ph; **b** R^4= CH=CH_2; **c** R^4= H

Scheme 2

Table 1. *5,6-Dihydro-4H-1,3-oxazines* **5** *a-p.*

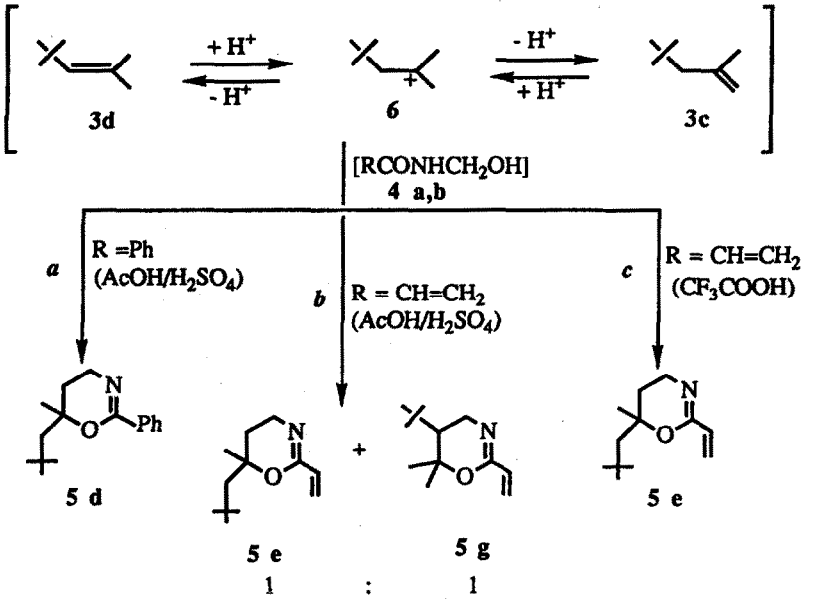
Compd 5	R^1	R^2	R^3	R^4
a	H	H	$(CH_2)_5$Me	Ph
b	H	H	$(CH_2)_5$Me	CH=CH_2
c	H	H	$(CH_2)_5$Me	H
d	H	Me	CH_2CMe_3	Ph
e	H	Me	CH_2CMe_3	CH=CH_2
f	H	Me	CH_2CMe_3	H
g[a]	CMe_3	Me	Me	CH=CH_2
h	-$(CH_2)_4$-		H	Ph
i	-$(CH_2)_4$-		H	CH=CH_2
j	-$(CH_2)_4$-		H	H
k[b]	$(CH_2)_3$Me	Me	H	Ph
l[b]	Me	$(CH_2)_3$Me	H	Ph
m[c]	$(CH_2)_3$Me	Me	H	CH=CH_2
n[c]	Me	$(CH_2)_3$Me	H	CH=CH_2
o	H	H	$(CH_2)_{15}$Me	Ph
p	H	H	$(CH_2)_{17}$Me	Ph

[a] Obtained from **3d** and isolated as a mixture of **5g** and **5e** in 1.3:1 ratio.

[b] Obtained from **3e** and isolated as a mixture of isomers **5k** and **5l** in 1:1.7 ratio.

[c] Obtained from **3e** and isolated as a mixture of isomers **5m** and **5n** in 1:1.7 ratio.

The products of amidoalkylation of 2,4,4-trimethylpent-2-ene (TMP-2) (**3d**) depend upon the amidoalkylating agent and acid used (Scheme 3) in a manner which is explained by an acid-catalyzed equilibrium between **3d** and **3c**. Both **3d** and **3c** are converted mainly into cation **6** in CF_3COOH at room temperature [($CDCl_3$-CF_3COOH, 1:1), ^1H NMR, δ:1.05 (s, 9H, 3Me), 1.67 (s, 6H, 2Me), and 1.90 (s, 2H, CH_2); ^{13}C NMR: 23.32 (Me), 30.88 ($\underline{C}Me_3$), 31.78 ($\underline{C}Me_3$), 52.69 (CH_2), 93.36 (-C^+<)]. Hence, the results of the amidoalkylations of **3d** and **3c** are determined by their comparative rates of amidoalkylation and protonation: under conditions *a* and *c* the protonation rate is higher whereas the amidoalkylation rate is higher for conditions *b* (Scheme 3). Similar isomerization of a double bond was observed for some vinylcyclopropane derivatives[29] and for TMP-2[30] under the conditions of the Vilsmeier reactions and was explained by the reduction in steric strain. We have not found any literature report of a double bond isomerization in the amidoalkylation of olefins.

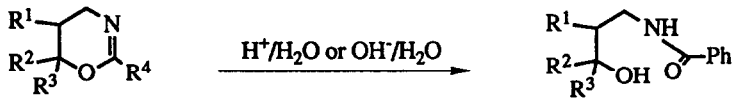


Scheme 3

Trifluoroacetic acid is the best catalyst for the amidoalkylation of alkenes **3 a-e** to dihydro-4*H*-1,3-oxazines **5 a-n** (Method E, Table 2 and Experimental part) in contrast to the earlier reports of the formation of N-alkenylamides in this reaction[25].

The products of the 5,6-dihydro-4H-1,3-oxazine ring scission, 3-hydroxypropylamides, were isolated in some cases as side-products of the olefin amidoalkylation[2,6,7,31]. Δ^2-Oxazolines, cyclic imidic esters, are known to be readily hydrolyzed[32], and it was assumed that 5,6-dihydro-4*H*-1,3-oxazines would react similarly. However, the ring-opening reactions of **5 a-p** were not so easy. Thus, acid-catalyzed hydrolysis of the isomeric mixture **5 k,l** at 100°C for 24 h, gave only 12% of amido alcohols **7 c,d** (Scheme 4), and the starting oxazines **5 k,l** were recovered in 85% yield. Refluxing oxazines **5 a,h,(k,l)** in 25% aqueous NaOH solution for 24 h

left the starting materials unchanged, but the use of ethanol as a co-solvent gave the desired amido alcohols **7 a,b,(c,d)** in 70-80% yield. 2-Vinyl-substituted oxazines **5 b,i** (Table 1) gave complex mixtures of 10-15 components (GC), in which neither the starting materials nor the desired ring-opened products could be found. The 6,6-disubstituted derivatives **5 d,e** (Table 1) were surprisingly unreactive under these conditions, the starting materials were recovered in 92-95% yield.

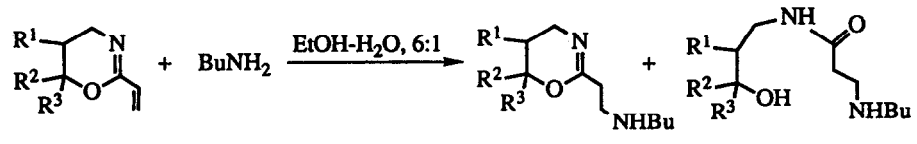


5 a,h,(m,n) **7 a,b,(c,d)**

7 a R^1=R^2=H, R^3=$(CH_2)_5$Me; **b** R^1+R^2=-$(CH_2)_4$, R^3=H; **c** R^1= Me, R^2=$(CH_2)_3$Me, R^3=H; **d** R^1=$(CH_2)_3$Me, R^2=Me, R^3=H

Scheme 4

The 2-vinyl substituent can activate the dihydrooxazine ring to ring opening. On the interaction of 2-vinyl-substituted oxazines **5 b,e,i,(m,n)** with butylamine in ethanol, adducts **8** and/or ring-opened products **9** were obtained (Scheme 5). Thus the primary activation by the heterocycle is of the vinyl fragment to nucleophilic



5 b,e,k,(o,p) **8 a-c,(d,e)** **9 a,c,(d,e)**

Δ

8 a-c,(d,e)

8, 9 a R^1=R^2=H, R^3=$(CH_2)_5$Me; **b** R^1=H, R^2=Me, R^3=CH_2CMe_3; **c** R^1+R^2=-$(CH_2)_4$-, R^3=H; **d** R^1=Me, R^2=$(CH_2)_3$Me, R^3=H; **e** R^1=Me, R^2=$(CH_2)_3$Me, R^3=H

Scheme 5

addition. The result of the reaction depends upon the ratio of the reagents, the nature of the starting oxazines and the amount of water added. Thus, on refluxing equimolecular amounts of **5e** and butylamine in ethanol for 24 h, amino adduct **8b** was obtained in 85% yield. Increasing the amounts of amine or water did not change the result of this reaction. However, oxazines **5 b,i,(m,n)** gave mixtures of **8a** and **9a** (4:5), **8 c** and **9 c** (3:5), and **8(d,e)** and **9(d,e)** (3:5) (GC). Increasing the amounts of amine or water slightly changed the ratio of **8** to **9** in the mixtures. The ring-opened compounds **9 a,d** could easily be separated from amines **8 a,d** by washing with ether: the crystalline amides were insoluble in this solvent but the liquid amines disolved. Analytically pure amide **9c** was isolated as a non-volatile residue after vacuum distillation of the crude mixture **8,9 c**. We failed to obtain amines **8 a-c** analytically pure - on distillation these compounds partially eliminate butylamine giving

Table 2. Synthesis of 5,6-Dihydro-4*H*-1,3-oxazines 5 a-p.

Compd	Bp (°C/mm) [lit. bp]	Method	^{1}H NMR, δ, ppm ($^3J_{4(a)5(a),4(a)5(e),4(e)5(a),4(e)5(e)}$, Hz)	^{13}C NMR, δ, ppm	Molecular formula	*m/z* (calcd)	Yield, %
5a	123-125/0.01	A E	0.89 (m, 3H, CH_3), 1.23-1.75 (m, 7H), 1.87 (m,1H), 3.51, 3.62 (2 dd, 2H, 4-CH_2) (10.3, 5.1, 5.4, 2.9), 4.22 (m, 1H), 7.35 (m, 3H), 7.95 (m, 2H)	13.8,.22.4,.24.7, 27.1, 29.0, 31.5,35.4, 42.8, 74.6, 126.7, 127.7, 130.0, 134.0, 155.6	$C_{16}H_{23}NO$	245.1780 (245.1779)	50 65
5b	67-69/0.01	C D E	0.90 (m, 3H,CH_3), 1.25-1.70 (m, 7H), 1.89 (m, 1H), 3.48, 3.65 (2 dd, 2H, 4-CH_2) (10.3, 5.1, 5.3, 2.9), 4.08 (m, 1H), 5.90 (dd,1H) and 6.06 (dd, 2H)[a]	13.9, 22.4, 24.6, 27.1, 29.0, 31.6, 42.8, 74.3 121.2, 132.5, 155.8	$C_{12}H_{22}NO$	196.1698 (196.1701)	52 62 74
5c	83-85/0.01	F	0.85 (m, 3H, CH_3), 1.22-1.72 (m, 7H), 1.85 (m, 1H), 3.25-3.40 (m, 2H, 4-CH_2), 4.05 (m, 1H), 6.98 (s, 1H)	13.9, 22.4, 24.5, 27.5, 29.0, 31.6, 35.3, 41.6, 74.0, 150.2	$C_{10}H_{20}NO$	170.1163 (170.1160)	50
5d	120-123/2.5	B	1.09 (s, 9H, $CH_2C\underline{Me}_3$), 1.40 (s, 3H, Me), 1.65 (d, 1H) and 1.51 (d, 1H) (^2J=14.9) ($\underline{CH_2}CMe_3$), 1.65 and 1.84 (m, 2H,5-CH_2), 3.57-3.62 (m, 2H, 4-CH_2), 7.35 (m, 2H), 7.95 (m, 3H)	26.1, 31.0, 31.5, 33.1, 40.6, 53.0, 77.3, 126.8, 127.7, 134.4, 155.1	$C_{16}H_{23}NO$	245.1774 (245.1779)	75
5e	65/0.01	C D E	1.09 (s, 9H, $CH_2C\underline{Me}_3$), 1.37 (s,3H, Me), 1.64 (d, 1H) and 1.51 (d, 1H) (^2J=14.9) ($\underline{CH_2}CMe_3$), 1.60 and 1.78 (m, 2H,5-CH_2), 3.51-3.46 (m, 2H, 4-CH_2), 5.90 (dd, 1H) and 6.07 (dd, 2H)[a]	26.1, 31.0, 31.4, 33.1, 40.5, 52.7, 76.8, 121.1, 133.0, 155.2	$C_{12}H_{21}NO$	195.1621 (195.1623)	68 65 75
5f	62-65/0.01	F	1.02 (s, 9H, $CH_2C\underline{Me}_3$), 1.38 (s, 3H, Me), 1.62 (d, 1H) and 1.51 (d, 1H) (^2J=14.9) ($\underline{CH_2}CMe_3$), 1.60 and 1.78 (m, 2H, 5-CH_2), 3.38-3.32 (m, 2H, 4-CH_2), 6.99 (s, 1H)	26.5, 29.9, 31.3, 33.6, 39.4, 52.7, 76.5, 149.9	$C_{10}H_{19}NO$	161.1464 (161.1466)	53
5g[b]	58/0.1	C	1.03 (s, 9H, 5-CMe_3), 1.30 (s, 3H, Me), 1.49 (s, 3H, Me), 1.58-1.68 (m, 1H), 3.34, 3.58 (2 dd, 2H, 4-CH_2) (11.7, <1, 4.8, <1), 5.90 (dd, 1H) and 6.09 (dd, 2H)[a]	23.3, 30.1, 30.9, 32.2, 44.4, 50.4, 79.5, 121.1, 132.5, 155.5	$C_{12}H_{21}NO$	195.1620 (195.1623)	67
5h	119/0.3 [119/0.3[33]]	A	1.22-1.68 (m, 7H), 1.70 (m,1H), 2.09 (m, 1H), 3.34, 3.60 (2 dd, 2H, 4CH_2) (<1, 5.3, <1, 2.4), 4.35 (m, 1H), 7.35 (m, 3H),7.95 (m, 2H)	20.1, 24.3, 25.2, 30.3, 31.9, 48.7, 72.5, 126.7, 127.8, 130.0, 134.0, 154.9	$C_{14}H_{17}NO$	- (215.1778)	85
5i	67-69/0.01 [67-68/0.01[33]]	C D E	1.22-1.72 (m, 5H), 1.73 (m,1H), 2.00 (m, 1H), 3.32, 3.58 (2 dd, 2H, 4CH_2) (<1, 5.3, <1, 2.4), 4.28 (m, 1H),5.90 (dd,1H) and 6.04 (dd, 2H)[a]	20.0, 24.1, 25.1, 30.1, 31.8, 48.6, 72.0, 121.0, 132.1, 154.9	$C_{10}H_{15}NO$	- (165.1159)	55 62 72
5j	72-75/0.01	F	1.28-1.93 (m, 8H), 3.28, 3.46 (2 dd, 4-CH_2) (<1, 5.3, <1, 2.4), 4.26 (m,1H), 7.02 (s, 1H)	19.9, 23.9, 25.0, 29.9, 32.1, 47.2, 71.8, 149.3	$C_8H_{13}NO$	139.1213 (139.1215)	50

Table 2 (continuation).

5k[c]	118-124/0.1	A	0.93 [m, 6H, Me(CH_2)$_3$ and MeCH], 1.20-1.70 [m, 6H, Me(CH_2)$_3$], 1.95-2.02 (m, 1H), 3.28, 3.55 (2 dd, 2H, 4-CH_2) (<1, 5.3, <1, 4.3), 4.45 (m, 1H), 7.32 (m, 3H), 7.90 (m, 2H)	13.8, 15.4, 22.4, 27.6, 28.8, 34.5, 50.1, 73.1, 126.8, 127.7,130.0, 133.8, 154.9	$C_{15}H_{21}NO$	231.1624 (231.1623)	78
5l[c]	118-124/0.1	A	0.93 [m, 3H, Me(CH_2)$_3$], 1.20-1.70 [m, 6H, Me(CH_2)$_3$], 1.28 (d, 3H, MeCH), 1.90-1.95 (m, 1H), 3.25, 3.48 (2 dd, 2H, 4-CH_2) (<1, 5.3, <1, 4.3), 4.19 (m, 1H), 7.32 (m, 3H), 7.90 (m, 2H)	12.0, 13.9, 22.7, 27.7, 29.0, 30.8, 45.8, 77.3, 126.8, 127.7, 130.0, 133.8, 154.9	$C_{15}H_{21}NO$	231.1620 (231.1623)	78
5m[d]	58-63/0.1	C E	0.92 [m, 6H, Me(CH_2)$_3$ and MeCH], 1.23-1.65 [m, 6H, Me(CH_2)$_3$], 1.93-2.30 (m, 1H), 3.25, 3.56 (2 dd, 2H, 4-CH_2) (<1, 5.3, <1, 4.3), 4.40 (m, 1H), 5.90 (dd, 1H) and 6.09 (dd, 2H)[a]	13.8, 15.2, 22.3, 27.6, 28.9, 34.3, 50.0, 72.6, 121.0, 132.4, 154.9	$C_{11}H_{19}NO$	181.1467 (181.1466)	58 63
5n[d]	58-63/0.1	C E	0.92 [m, 3H, Me(CH_2)$_3$], 1.23-1.65 [m, 6H, Me(CH_2)$_3$], 1.21 (d, 3H, MeCH), 1.90-1.95 (m, 1H), 3.25, 3.48 2 dd, 2H, 4-CH_2) (<1, 5.3, <1, 4.3), 4.10 (m,1H), 5.95 (dd, 1H) and 6.07 (dd, 2H)[a]	11.8, 13.7, 15.2, 22.5, 27.3, 28.6, 45.7, 76.8, 121.0, 132.1, 154.9	$C_{11}H_{19}NO$	181.1467 (181.1466)	58 63
5o	[e]	A	0.86 (m, 3H, Me), 1.16-2.12 (m, 32H), 3.51-3.69 (m, 2H, 4-CH_2), 4.18 (m, 1H), 7.33 (m, 3H), 7.90 (m, 2H)	14.1, 22.7, 25.0, 27.3, 29.3, 29.4, 29.52, 29.55, 29.59, 29.7, 31.9, 35.6, 43.0, 74.9, 126.9, 127.9, 130.2, 134.2, 155.9	$C_{26}H_{43}NO$	[f]	85
5p	[e]	A	0.87 (m, 3H, Me), 1.25-1.78 (m, 35H), 1.92-2.08 (m, 1H), 3.51-3.68 (m, 2H, 4-CH_2), 4.20 (m, 1H), 7.32 (m, 3H), 7.85 (m, 2H)	14.1, 22.7, 25.0, 27.3, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 35.6, 43.0, 74.9, 127.0, 127.9, 130.2, 134.2, 155.9	$C_{28}H_{47}NO$	[f]	50

[a] Vinylic fragment (*ABX*) system): $^2J_{AB}$=1.5 Hz, $^3J_{AB}$=17.5 Hz, $^3J_{BX}$=10.5 Hz. [b] A mixture with **5e** (see Table 1). [c] A mixture **5k** and **5l** (Table 1). [d] A mixture **5m** and **5n** (Table 1).
[e] M.p.: **5o** 57°C, **5p** 62°C. [f] **5o**, Found: C, 81.12; H, 11.48; N, 3.50. Requires: C, 81.04; H, 11.26; N, 3.64%. **5p**, Found: C, 81.11; H, 11.59; N, 3.33. Requires: C, 81.35; H, 11.38; N 3.39%.

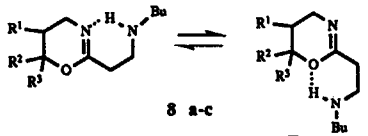
Table 3. Synthesis of 2-Alkylamino-5,6-dihydro-4*H*-1,3-oxazines 8 a-c and 3-Hydroxypropylamides 7 a,b,(c,d) and 9 a,c,d.

Compd	Mp (°C) [Bp (°C/mm)]	^{1}H NMR, δ, ppm	^{13}C NMR, δ, ppm	Molecular formula	Found (requires), % C	H	N	Yield, %
7 a	111-112 (benzene)	0.86 (t, 3H, *J*=7 Hz, Me), 1.24-1.75 (m, 12H, 6CH_2), 3.33-3.39 (m, 1H), 3.63 (m, 1H + 1H[a]), 3.79 (m, 1H), 7.33-7.47 (m, 3H + 1H[a]), 7.77 (d, 2H, J=7 Hz)	14.0, 22.5, 25.7, 29.3, 31.7, 36.4, 37.4, 69.8, 126.9, 128.4, 131.3, 134.1, 168.2	$C_{16}H_{25}NO_2$	73.12 (73.00)	9.64 (9.50)	5.11 (5.32)	80
7 b	116-118 (benzene)	1.19-1.78 (m, 9H), 3.12-3.20 (m, 1H, CH_2N), 3.31-3.39 (m, 1H, CH_2N), 3.79 (broad s, 1H, C<u>H</u>-OH), 4.38 (broad s, 1H[a]), 7.38-7.48 (m, 3H, Ph), 7.85 (d, 2H, *J*=7 Hz, Ph), 8.35 (m, 1H[a])	19.9, 24.2, 24.9, 32.4, 41.1, 41.8, 65.0, 126.9, 127.8, 130.7, 134.3, 166.8	$C_{14}H_{19}NO_2$	72.42 (72.10)	8.32 (8.20)	6.14 (6.00)	80
7c[b]	oil	0.83-0.95 [m, 6H, <u>Me</u>(CH_2)$_3$ and <u>Me</u>CH], 1.20-1.60 [m, 6H, Me(<u>CH_2</u>)$_3$], 1.68-1.73 (m, 1H), 3.28, 3.55 (m, 2H, 4-CH_2), 3.63 (m, 1H), 3.95 (m, 2H[a]), 7.48 (m, 3H, Ph), 7.85 (d, 2H, *J*=7 Hz, Ph)	10.8, 13.9, 18.4, 22.8, 27.1, 29.8, 37.8, 41.3, 43.3, 69.1, 126.9, 128.4, 131.3, 134.1, 168.0	$C_{15}H_{24}NO_2$	250.1802 (250.1807)[c]			30
7d[b]	oil	0.83-0.95 [m, 6H, <u>Me</u>(CH_2)$_3$ and <u>Me</u>CH], 1.20-1.60 [m, 6H, Me(<u>CH_2</u>)$_3$], 1.73-1.85 (m, 1H), 3.28, 3.55 (m, 2H, 4-CH_2), 3.69 (m, 1H), 4.01 (m, 2H[a]), 7.48 (m, 3H, Ph), 7.85 (d, 2H, *J*=7 Hz, Ph)	10.8, 14.0, 18.5, 22.7, 28.6, 33.4, 37.8, 43.3, 43.7, 71.6, 126.9, 128.4, 131.4 134.3, 168.5	$C_{15}H_{24}NO_2$	250.1802 (250.1807)[c]			50
8a[d]	[125-128/0.1]	0.82, 0.91 (2 t, 6H, *J*=7 Hz, 2Me), 1.24-1.56 (m, 15H), 1.72-1.88 (m, 1H), 2.33 (t, 2H, *J*=6.3 Hz, CH_2), 2.59 (t, 2H, *J*=6.7 Hz, CH_2), 2.81 (t, 2H, *J*=6.1 Hz, CH_2), 3.33-3.46 (m, 2H, CH_2), 3.95-4.05 (m, 1H)[e]	13.9, 20.3, 22.4, 24.5, 26.9, 29.0, 31.5, 32.1, 35.3, 42.2, 46.2, 49.3, 50.2, 53.3, 74.1, 159.2[e]	$C_{16}H_{32}N_2O$	197 [M-NHBu]$^+$ (268)[f]			40
8b[d]	[95-98/0.35]	0.90 (t, 3H, *J*=7 Hz, Me), 1.02 (s, 9H, Me_3C), 1.31 (s, 3H, Me), 1.30-1.63 (m, 7H), 1.67-1.79 (m, 1H), 2.31 (t, 2H, *J*=7 Hz, CH_2), 2.59 (t, 2H, *J*=7 Hz, CH_2), 2.81 (t, 2H, *J*=7 Hz, CH_2), 3.33-3.35 (m, 2H)[e]	13.8, 20.3, 26.2, 30.9, 31.3, 32.0, 32.8, 35.5, 39.9, 46.1, 49.2, 50.3, 52.9, 76.5, 158.7[e]	$C_{16}H_{30}N_2O$	195 [M-NHBu]$^+$ (266)[f]			40
8c[d]	[101-106/0.1]	0.92 (t, 3H, *J*=7 Hz, Me), 1.25-1.95 (m, 13H), 2.35 (t, 2H, *J*=7 Hz, CH_2), 2.60 (t, 2H, *J*=7 Hz, CH_2), 2.85 (t, 2H, *J*=7 Hz, CH_2), 3.09-3.19 (m, 1H, CH_2N=), 3.35-3.49 (m, 1H, CH_2N), 4.25 (broad s, 1H, C<u>H</u>-OH)[e]	13.5, 19.7, 19.9, 23.9, 24.2, 24.7, 29.8, 31.3, 31.7, 34.6, 45.8, 48.9, 71.8, 158.1[e]	$C_{14}H_{24}N_2O$	165 [M-NHBu]$^+$ (236)[f]			40

Table 3 (continuation).

9a	48-49 (hexane)	0.87, 0.92 (2 t, 6H, *J*=7.0 Hz, 2Me), 1.27-1.61 (m, 16H, 8CH_2), 2.36 (t, 2H, *J*=6.3 Hz, CH_2), 2.61 (t, 2H, *J*=6.8 Hz, CH_2), 2.86 (t, 2H, *J*=6.1 Hz, CH_2), 3.07-3.17 (m,1H), 3.52-3.67 (m, 2H), 8.05 (m, 1H[a])	13.9, 14.0, 20.4, 22.5, 25.8, 29.3, 31.8, 31.9, 35.4, 35.9, 37.3, 37.4, 45.6, 49.1, 68.4, 173.7	$C_{16}H_{34}NO_2$	70.32 (70.58)	12.21 (12.50)	5.12 (5.14)	50
9c	oil	0.91 (t, 3H, *J*=7 Hz, Me), 1.20-1.86 (m, 13H), 2.36 (t, 2H, *J*=6.3 Hz, CH_2), 2.63 (t, 2H, *J*=6.7 Hz, CH_2), 2.85 (t, 2H, *J*=6.1 Hz, CH_2), 3.37 (m, 2H), 3.79 (broad s, 1H), 8.28 (m, 1H[a])	13.5, 19.9, 20.0, 24.3, 25.0, 31.2, 32.0, 35.0, 41.1, 41.7, 45.3, 48.7, 65.0, 173.7	$C_{14}H_{28}NO_2$	69.31 (69.42)	11.32 (11.57)	5.58 (5.78)	50
9d	82-84 (benzene)	0.83-0.94 (m, 9H, 3Me), 1.23-1.59 (m, 11H, 5CH_2 and >CHMe), 2.37 (t, 2H, *J*=6.8 Hz, $NHCH_2\underline{CH_2}CO$), 2.61 (t, 2H, *J*=6.8 Hz, $NH\underline{CH_2}C_3H_7$), 2.85-2.95 (m, 3H, $NH\underline{CH_2}CH_2CO$ and 1H from $>\underline{CH_2}NHCO$), 3.45-3.57 (m, 2H, >CHOH and 1H from $>\underline{CH_2}NHCO$), 8.13 (m, 1H[a], NHCO)	10.7 (MeCH), 13.9, 14.1 (2Me), 20.4, 22.8, 28.8, 32.0, 33.6, 35.3, 45.6, 49.1 (CH_2), 38.5 (MeCH), 42.4 (CH_2NH), 70.2 (CHOH), 174.1 (C=O)	$C_{15}H_{32}NO_2$	66.32 (66.18)	12.11 (11.84)	10.13 (10.29)	30

[a] Exchangeable with D_2O. [b] A mixture 7c and 7d in 1:1.7 ratio. [c] GC/HR MS: *m/z* (calcd). [d] The ^1H and ^{13}C NMR spectra of the crude amines 8 a-c in $CDCl_3$ solutions show the presence of two isomers in 4:1 ratio in each case. The use of DMSO as a solvent slightly changes the ratio of isomers to 3:1. We assume the existance of amines 8 a-c in solutions as mixtures of two isomers with a different type of the hydrogen bond:



8 a-c

Currently, the behaviour of amines 8 a-c in solutions is under investigation. [e] The spectrum of the major isomer in $CDCl_3$. [f] GC/LR MS: *m/z* (calcd).

mixtures containing the corresponding vinyl-substituted oxazines (GC and GC/MS) (Scheme 5). After interaction of the isomeric mixture **5 (m,n)** with butylamine, we could isolate the single pure amide **9d** along with mixtures of amines **8(d,e)** and of ring-opened isomers **9(d,e)** (GC/MS) (Scheme 5). The structure of 5,9-diaza-12-hydroxy-11-methylhexadecan-8-one (**9d**) was established with the use of DEPT, ^{1}H, ^{1}H COSY and ^{1}H, ^{13}C HETCOR experiments; the assignments of the proton and carbon signals are given in Table 3.

CONCLUSION

The functionalization of unactivated alkenes can be successfully accomplished by the amidoalkylation reaction. Depending upon the structure of the 5,6-dihydro-4*H*-1,3-oxazines obtained, further transformations of the hetero-ring and/or a substituent can lead to alkylamino substituted 5,6-dihydro-4*H*-1,3-oxazines and/or amino hydroxamides which are difficult to access in other ways. The reactions described are simple to carry out and mainly give good yields.

EXPERIMENTAL PART

Melting points were determined on a Thomas-Hoover capillary m.p. apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer (300 and 75 MHz, respectively), using $CDCl_3$ as solvent and tetramethylsilane as internal reference. On GC experiments, a Hewlett-Packard HP 5890 gas chromatograph, equipped with FID and split injection port, was used. A capillary column, "Supelco" SPB-1, 15 m long was used with a split ratio of 30:1. GC/MS spectra were recorded on a Varian Finnigan MAT-700 instrument. Mass spectra were recorded on a Krafts AEI MS 30 spectrometer. Elemental analyses were performed on a Carbo Erba 1106 elemental analyser.

General Procedures for the Synthesis of 5,6-Dihydro-4H-1,3-oxazines 5 a-p.

Method A. A mixture of benzamide (0.01 mol), paraformaldehyde (0.01 mol) and the olefin (0.01 mol) was stirred in 10 ml of glacial acetic acid over 10 min at room temperatute, and a mixture of 12.5 ml of glacial acetic acid and 1.5 ml of 98% sulfuric acid was added dropwise at 10-15°C for 10 min. The mixture was stirred at 65-70°C for 1h and poured into ice-water (50 ml). It was washed with ether (30 ml x 2), basified with 25% aqueous sodium carbonate solution to pH 7-7.5 while stirring vigorously and exctracted with ether (30 ml x 2). The ether layer was dried ($MgSO_4$), and the solvent removed under vacuum.

Method B. A mixture of benzamide (0.01 mol) and paraformaldehyde (0.01 mol) in 12.5 ml glacial acetic acid and 1.5 ml 98% sulfuric acid was heated at 70°C for 30 min under vigorous stirring. The olefin (0.01 mol) was added dropwise and the dark-red solution was stirred at 60-70°C for 15 min. The work-up was as was described in Method A.

Method C. A mixture of acrylamide (0.01 mol) and paraformaldehyde (0.01 mol) in 12.5 ml glacial acetic acid and 1.5 ml 98% sulfuric acid was heated at 70°C for 10 min under vigorous stirring and the olefin (0.01 mol) was added dropwise over 10 min. The mixture was stirred at 80-85°C for 30 min and worked-up as described in Method A.

Method D. A mixture of olefin (0.01 mol), N-(hydroxymethyl)acrylamide (0.01 mol) and glacial acetic acid (10 ml) was stirred at 50°C for 10 min, and a mixture of 12 ml glacial acetic acid and 2.5 ml 98% sulfuric acid was added dropwise over 10 min. The mixture was stirred at 70°C for 1 h and worked-up as described in Method A.

Method E. A mixture of olefin (0.01 mol), the corresponding amidoalkylating agent (0.01 mol) and trifluoroacetic acid (10 ml) was heated at 70°C for 1h under vigorous stirring. Trifluoroacetic acid was distilled off under vacuum, and the residue poured onto ice-cold 15% aqueous NaOH solution (20 ml) and extracted with ether (30 ml x 2). The ether layer was dried over $MgSO_4$, and the solvent removed under vacuum.

Method F. To a stirred mixture of the olefin (0.01 mol) and trifluoroacetic acid (10 ml), N-(hydroxymethyl)formamide (0.01 mol)[34] was added dropwise at room temperature. The mixture was vigorously stirred at 85°C for 1h and worked-up as described in Method E.

Compounds **5 a-n** were purified by distillation, and **5 o,p** were recrystallized from ethanol (Table 2).

General Procedure for the Synthesis of 7 a,b,(c,d).

A mixture of the appropriate oxazine **5** (0.01 mol), ethanol (5 ml) and 25% aqueous NaOH solution (8 ml) was heated at 100°C for 24 h, diluted with water (30 ml) and extracted with chloroform (20 ml x 3). The chloroform layer was dried over $MgSO_4$, and the solvent removed under vacuum. The mixture of **7(c,d)** was isolated analyticaly pure. Compounds **7 a,b** were recrystallized (Table 3).

Reactions of 2-Vinyl-substituted Derivatives 5 b,e,i,(m,n) with Butylamine.

A mixture of the appropriate oxazine **5** (0.01 mol), butylamine (0.012 mol), ethanol (6 ml) and water (1 ml) was refluxed for 24 h. Ethanol and excess butylamine were removed under vacuum, and the residue was diluted with ether (10 ml). Crystalline **9a** and **9d** were separated from the corresponding mixtures (Table 3). The ether solutions of amines **8 a-c** were dried, the solvent removed and the residues distilled. GC/MS revealed the increased amounts of the starting oxazines **5 b,e,k** in the distillates in comparison with crude mixtures. Compound **9c** was obtained analyticaly pure after vacuum distillation of the crude mixture.

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