5,6-Dihydro-4*H*-1,3-oxazines from Olefins

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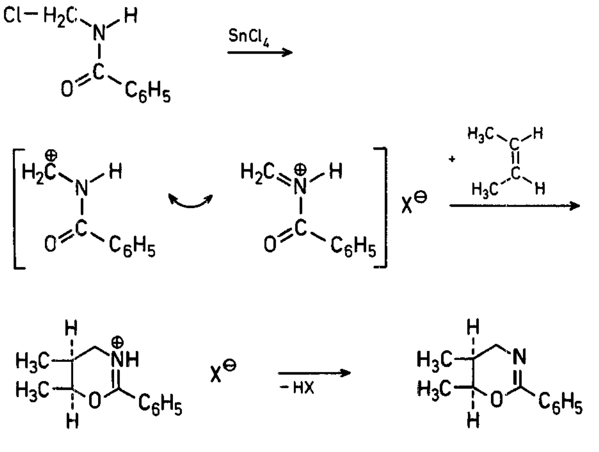
It is well known that 5,6-dihydro-4*H*-1,3-oxazines can be obtained by reaction of olefins with N-(hydroxymethyl)-amides[1,2] or N-(chloromethyl)-amides[3] in the presence of acid catalysts.

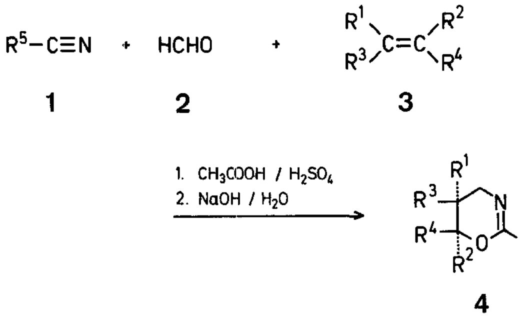
It appears to be proved that the reaction proceeds via a 1,4-polar cycloaddition of the amidomethyl ion to the olefin[3,4,5]:



Scheme A

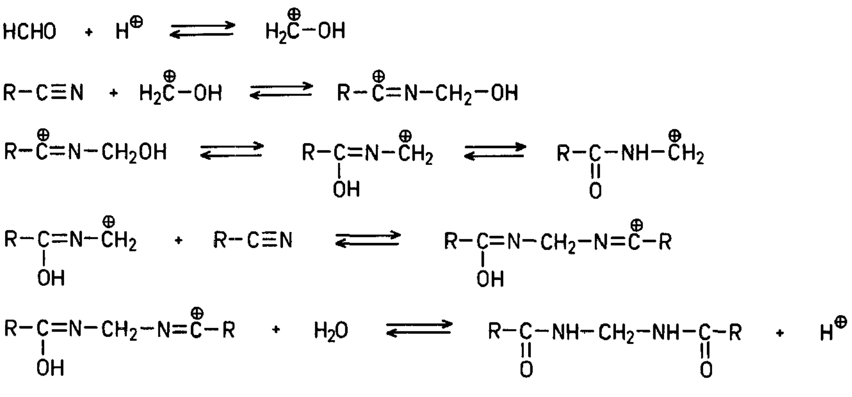
We now wish to report that the same results can be achieved by reacting olefins with reagents for which evidence indicates they may be in equilibrium, under certain conditions, with the amidomethyl ion.

Our method[6,7] of synthesizing 5,6-dihydro-4*H*-1,3-oxazines consists of the addition of an olefin to a solution of formaldehyde, a nitrile, and an acid catalyst (sulfuric acid, hydrogen chloride, or *p*-toluenesulfonic acid) in acetic acid at 70–100°.



Scheme **B**

The reaction of formaldehyde with nitriles in the presence of acids forms the amidomethyl ion according to Scheme **C**:



$$HCHO + H^{\oplus} \rightleftharpoons H_2\overset{\oplus}{C}-OH$$

$$R-C\equiv N + H_2\overset{\oplus}{C}-OH \rightleftharpoons R-\overset{\oplus}{C}=N-CH_2-OH$$

$$R-\overset{\oplus}{C}=N-CH_2OH \rightleftharpoons R-\underset{OH}{\underset{|}{C}}=N-\overset{\oplus}{C}H_2 \rightleftharpoons R-\underset{O}{\underset{\|}{C}}-NH-\overset{\oplus}{C}H_2$$

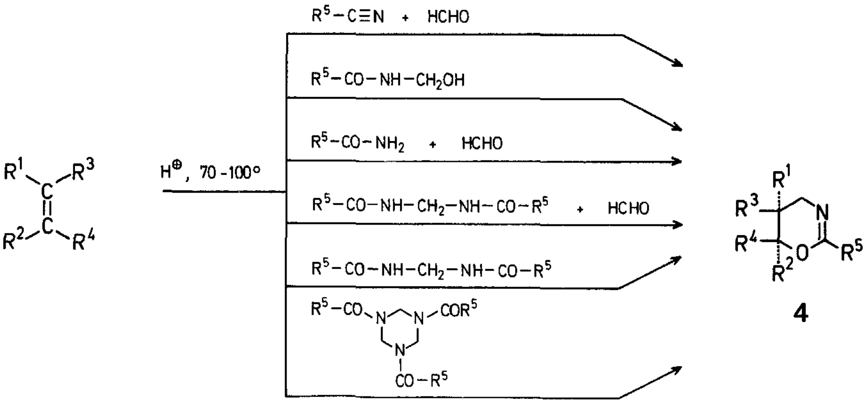
$$R-\underset{OH}{\underset{|}{C}}=N-\overset{\oplus}{C}H_2 + R-C\equiv N \rightleftharpoons R-\underset{OH}{\underset{|}{C}}=N-CH_2-N=\overset{\oplus}{C}-R$$

$$R-\underset{OH}{\underset{|}{C}}=N-CH_2-N=\overset{\oplus}{C}-R + H_2O \rightleftharpoons R-\underset{O}{\underset{\|}{C}}-NH-CH_2-NH-\underset{O}{\underset{\|}{C}}-R + H^{\oplus}$$

Scheme **C**

Alternatively, other reagents[9,10] such as carboxamides and formaldehyde[5], N,N′-methylene-bis-amides and formaldehyde, N,N′-methylene-bis-amides, or 1,3,5-triacylhexahydro-1,3,5-triazines[11] can be used as the amidomethylating agent, at a temperature of 70–100° (Scheme **D**).

To our knowledge, 1,3,5-triacylhexahydro-1,3,5-triazines have not been used by other authors in amidoalkylation reactions[9,10,12].



Scheme **D**

Further work was carried out in order to investigate the equivalence, under our experimental conditions, of these amidomethylating agents and the N-(hydroxymethyl)-amides in the reaction with olefins, both from synthetic and steric viewpoints.

In acid medium, all these amidomethylating agents behave analogously towards the olefins at 70–100° (Table 2); at lower temperatures (15–20°), such equivalence is no longer found, since there is a marked difference in the rates at which they equilibrate with the amidomethyl ion.

The similarity of the steric course of the reaction of olefins with the reagents investigated by us (at 70–100°) with the course of the analogous reaction with N-(hydroxymethyl)-carboxamides[1,2] or N-(cloromethyl)-carboxamides[3] (carried out, however, at lower temperatures) clearly indicates that also in our case there is a polar 1,4-cycloaddition of the amidomethyl ion to the olefin.

From the preparative viewpoint, the use of nitrile-formaldehyde and amide-formaldehyde systems has the advantage over those utilising the N-(hydroxymethyl)-amides or N-(chloromethyl)-amides of requiring no preliminary preparation and isolation of the reagents that will supply the amidomethyl ion, and of starting from readily available products.

Several experiments are at present being carried out to extend the possibility of synthesis of 5,6-dihydro-4*H*-1,3-oxazines, starting from olefins and amidoalkylating agents able to supply ions of the type:

$$R^1-\underset{O}{\underset{\|}{C}}-NH-\overset{\oplus}{C}H-R^2 \leftrightarrow R^1-\underset{O}{\underset{\|}{C}}-\overset{\oplus}{N}H=CH-R^2$$

Table 1. α-Amidomethylation of Olefins with Nitriles and Formaldehyde (Scheme **B**)

R^1	R^2	R^3	R^4	R^5	Yirld %[a]	n_D^{20}	b.p./torr
H	H	H	CH_3	CH_3	44	1.4452	144–145°/760
H	H	H	$-(CH_2)_9-CH_3$	CH_3	46[b]	1.4600	130–132°/2
H	H	H	$-(CH_2)_3-CH_3$	CH_3	38[h]	1.4519	70– 71°/1.5
H	H	$-(CH_2)_4-$		CH_3	44[c]	1.4840	78°/2
H	CH_3	CH_3	H	CH_3	45[d]	1.4450	59°/18
H	H	CH_3	CH_3	CH_3	47	1.4485	56– 57°/18
CH_3	CH_3	CH_3	CH_3	CH_3	58	1.4515	63– 65°/18
H	H	H	C_6H_5	CH_3	54 60.5[1]	1.5412 1.5383[1]	99–100°/1 93– 94°/0.4
H	H	H	$-CH=CH_2$	CH_3	31[e] 30[1]	1.4655 1.4646[1]	71°/27 99°/85
H	CH_3	H	$-CH=CH_2$	CH_3	18	1.4612	58– 60°/15
$-(CH_2)_4-$		$-(CH_2)_4-$		CH_3	38	1.5101	78°/0.15
H	C_6H_5	C_6H_5	H	CH_3	54		(m.p. 70–78°)
H	CH_3	CH_3	H	C_6H_5	80[f]		70°/0.005[3] (m.p. 44°)
H	H	CH_3	CH_3	C_6H_5	76		105°/0.5 77°/0.005[3]
H	H	H	C_6H_5	C_6H_5	78 79.2[1]	1.6010 1.6008[1]	177–179°/1 155–156°/0.005[1]
H	H	$-(CH_2)_4-$		C_6H_5	65 69[1]	1.5629 1.5630[1]	118–120°/0.3 119–120°/0.3
H	H	H	$-CH_2Cl$	C_6H_5	59		(m.p. 53–58°)
H	H	H	$-CH_2Br$	C_6H_5	60		135°/0.1
H	H	H	$-CH_2-CH_2Cl$	C_6H_5	62	1.5600	123–124°/0.1
H	H	H	CH_3	$-CH=CH_2$	40[g]	1.4777	64°/10

[a] The yields reported in the table may have slight variations, due particularly to the ease of hydrolysis of the 5,6-dihydro-4*H*-1,3-oxazines (formation of γ-hydroxy-N-acylamines).

[b] A yield of 27 % is obtained with sulfuric acid without solvent.

[c] A yield of 32 % is obtained with sulfuric acid without solvent.

[d] A yield of 35 % is obtained with hydrogen chloride in acetic acid.

[e] A yield of 32 % is obtained with 1,3,5-triacetylhexahydro-1,3,5-triazine.

[f] A yield of 76 % is obtained with 1,3,5-tribenzoylhexahydro-1,3,5-triazine.

[g] A yield of 42 % is obtained with 1,3,5-triacryloylhexahydro-1,3,5-triazine.

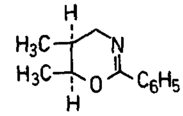
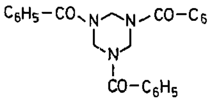
[h] The same result is obtained using N-(hydroxymethyl)-acetamide in trifluoroacetic acid under the conditions suggested by W. D. SCHAEFFER[13]. We have not been able to isolate unsaturated amides as the main product, as stated in Lit.[13].

The experimental procedure followed in carrying out the reaction of olefins with nitriles and formaldehyde (Scheme **B**, Table 1) is that described in the preparation of 2,6-dimethyl-5,6-dihydro-4*H*-1,3-oxazine (**4**, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = CH_3$) and 2-methyl-6-decyl-5,6-dihydro-4*H*-1,3-oxazine (**4**, $R^1 = R^2 = R^3 = H$, $R^4 = n\text{—}C_{10}H_{21}$, $R^5 = CH_3$).

Where other amidomethylating agents are used, before the addition of the olefin the mixture of amidomethylating agent, acetic acid, and acid catalyst is stirred at 60–70° until a clear solution is obtained (~15 min.).

Work-up is performed in all cases by diluting with ice and basifying the reaction mixture at low temperature (0–5°) in order to prevent hydrolysis of the 5,6-dihydro-4*H*-1,3-oxazines.

Table 2. Amidomethylation of *cis*-2-Butene at 70° (Scheme **D**)[a]

Amidomethylating agent (mol)	*cis*-2-Butene (mol)	Sulfuric acid (mol)	Acetic acid (g)	Yield % 
$C_6H_5-CO-NH-CH_2-NH-CO-C_6H_5$ (0.2)	0.2	0.2	250	72
$C_6H_5-CO-NH-CH_2-NH-CO-C_6H_5$ (0.1) + HCHO (0.1)	0.2	0.2	80	77
 (0.2)	0.6	0.6	240	73
$C_6H_5-C{\equiv}N$ (0.2) + HCHO (0.2)	0.2	0.2	80	76
$C_6H_5-CO-NH_2$ (0.2) + HCHO (0.2)	0.2	0.2	80	75
$C_6H_5-CO-NH-CH_2OH$ (0.2)	0.2	0.2	80	75

[a] This set of experiments was performed with *cis*-2-butene, because the yield of 5,6-dimethyl-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine obtained by using this olefin is unaffected by the formation of hydrolysis by products.

The structures of the 5,6-dihydro-4*H*-1,3-oxazines were determined by I.R. and N.M.R. spectra.

2,6-Dimethyl-5,6-dihydro-4*H*-1,3-oxazine: A mixture of 1,3,5-trioxane (12 g = 0.4 mol of formaldehyde), glacial acetic acid (160 g), and 100% sulfuric acid (39.2 g, 0.4 mol) is stirred at room temperature until the solid has dissolved. To the clear solution heated at 50° is added, dropwise, acetonitrile (16.4 g, 0.4 mol) and stirring is continued until the spontaneous reaction is completed. The solution is kept at 50° for 30 min., flushed with propene and brought to a constant pressure of 1 atm. at 70°. After 16.8 g (0.4 mol) of propene has been absorbed, the reaction mixture is cooled, poured on crushed ice, made alkaline with 40% aqueous sodium hydroxide, and extracted with ether. The ether extracts are evaporated and the residual oil is distilled at atmospheric pressure to give a colorless oil; yield: 20 g (44 %); b.p. 144–145°; n_D^{20}: 1.4452.

$C_6H_{11}NO$	calc.	C 63.68	H 9.80	N 12.38	O 14.14
	found	63.70	9.73	12.41	14.16

6-Decyl-2-methyl-5,6-dihydro-4*H*-1,3-oxazine: A mixture of 95% paraformaldehyde (6.3 g = 0.2 mol of formaldehyde), glacial acetic acid (80 g), and 100 % sulfuric acid (19.6 g, 0.2 mol) is heated at 70° with stirring until the solid material has completely dissolved. The mixture is then cooled to 50° and acetonitrile (8.2 g, 0.2 mol) added dropwise, while the temperature, which rises rapidly during the addition, is maintained at ~ 50° by cooling. The solution is stirred at 50° for 30 min., then heated to 70°, and 1-dodecene (33.6 g, 0.2 mol) added dropwise. After the addition is completed, the reaction mixture is heated at 100° for 2 hr, then cooled, poured on crushed ice, made alkaline with 40 % aqueous sodium hydroxide, and extracted with ether. The combined ether extracts are evaporated and the residual oil is distilled under reduced pressure to give a colorless oil; yield: 22 g (46 %); b.p. 130–132°/2 torr; n_D^{20}: 1.4600.

$C_{15}H_{29}NO$	calc.	C 75.23	H 12.20	N 5.85
	found	75.41	12.11	5.79

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