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The Regiochemistry of the Radical Addition of N-Chloroamides to Enol Ethers

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This paper is dedicated to Professor D.H.R. Barton on the occasion of his 75th birthday.

Abstract. The orientation of the radical addition of N-chloroamides (ZCONHCl) to enol ethers was studied as a function of Z and the enol ether structure and compared with the orientation of radical addition of thioacetic acid and the orientation of typical electrophilic additions.

INTRODUCTION

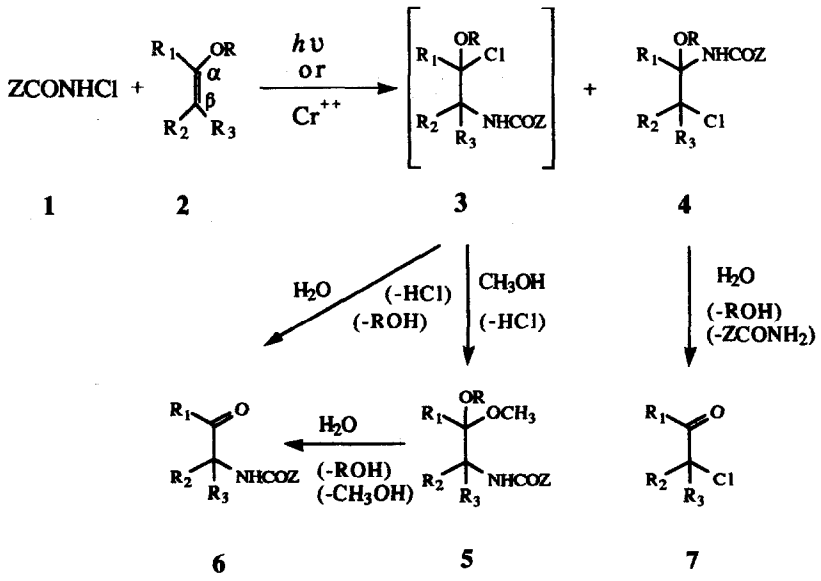
We have shown that the photochemical[1-4] and chromous chloride[2,5-7] promoted additions of N-haloamides to olefins proceed by a radical chain mechanism. The amidyl radical, like most radicals, preferentially attacks the less substituted carbon atom of the olefin. According to several authors,[8-12] steric effects are primarily responsible for the attack of radicals at the less substituted carbon atom of olefins.

This paper describes a study of the orientation of the radical addition of N-chloroamides, ZCONHCl (**1**), to enol ethers **2** (Scheme 1). The carbon atom of the enol ether **2** bearing the OR group is denoted as the α-carbon, substituent R_1 as the α-substituent, the neighboring carbon as the β-carbon, and substituents R_2 and R_3 as the β-substituents. The ratio adduct **5** (and/or **6**) to adduct **4** (and/or **7**) is denoted as the β/α ratio. The orientation of the radical addition of ZCONHCl (**1**) to methoxymethylenecyclohexane (**2g**) is compared with that of the radical addition of thioacetic acid and with the orientation of electrophilic additions (ionic chlorination, hydroboration, addition of nitrosyl chloride).

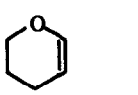
RESULTS

Radical addition of ZCONHCl (**1**) *to enol ethers* **2**

The yields of addition together with the β/α ratios are recorded in Tables 1 and 2. The photochemically initiated additions were carried out in dry methylene chloride at -70°C[3] and the chromous chloride initiated additions in a mixture of chloroform-methanol at ca. -78°C[7]. For the photochemical additions, the presence of methanol up to 50% (v/v) did not have a significant influence on the β/α ratio (compare entries 11 and 12 of Table 2). The adducts **4** with R_1 = H were quite resistant to hydrolysis even when treated with 70% perchloric acid in ether for a few minutes (see Table 1, entry 11). Adducts **4g** (Z = C_2H_5O) and **4i** (Z = C_2H_5O) were hydrolyzed to the

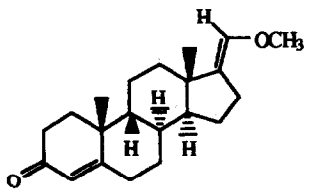


a: R=C_2H_5, R_1=R_2=R_3=H
b: R=CH_3, R_1 R_2=$(CH_2)_4$, R_3=H
c: R R_3=$(CH_2)_3$, R_1=R_2=H
d: R=R_1=CH_3, R_2 R_3=$(CH_2)_5$
e: R=R_2=R_3=CH_3, R_1=H
f: R=CH_3, R_1=H, R_2=R_3=n-C_3H_7
g: R=CH_3, R_1=H, R_2 R_3=$(CH_2)_5$
h: R=CH_3, R_1=H, R_2 R_3=$(CH_2)_4$
i: R=CH_3, R_1=H, R_2 R_3=steroid
j: R=t-C_4H_9, R_1=H, R_2 R_3=$(CH_2)_5$
k: R=CH_3, R_1=R_3=H, R_2=CH_3CO
l: R=R_3=CH_3, R_1=H, R_2=CH_3OCO
m: R=R_1=CH_3, R_2=CH_3OCO, R_3=H
n: R=R_1=CH_3, R_2=CH_3CO, R_3=H
o: R=R_2=R_3=CH_3, R_1=CH_3OCO



(RR$_3$=(CH$_2$)$_3$, R$_1$=R$_2$=H)

2 c

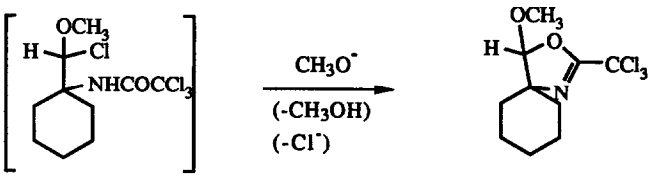


(R=CH$_3$, R$_1$=H, R$_2$R$_3$=steroid)

2 i

SCHEME 1

corresponding α-chloro aldehydes **7g** (88% yield) and **7i** (82% yield) (Scheme 1) upon treatment with 70% aqueous acetic acid at 70°C for 2h (see ref. 7 for the hydrolysis of **4i**). However, when R = CH_3 as in the addition of N-chlorourethane (**1**, Z = C_2H_5O) to (1-methoxyethylidene)cyclohexane (**2d**), hydrolysis of **4d** to 1-acetyl-1-chlorocyclohexanone (**7d**) occurred during the work-up and chromatographic separation; an aqueous acid-work-up was used to ensure complete hydrolysis before chromatographic analysis and separation (Table 1, entry 4). The usual work-up procedure involved the addition of absolute methanol and silver carbonate in the photochemically initiated reactions, and for the chromous chloride promoted reactions, the addition of sodium methoxide. The small amounts (2 to 7%) of carbonyl compound **6** detected and/or isolated in a few cases come from the reaction of the chloro ether **3** with the water present in the reactions medium.[3-7] An aqueous work-up following the photochemical reaction led to **6** (Table 2, entry 11). An aqueous acid-work-up following the chromous chloride promoted addition did not cause the hydrolysis of acetal **5** (R_1 = H) to aldehyde **6** (R_1 = H) (Table 1, entry 11), but did cause the hydrolysis of ketal **5** (R_1 = CH_3) to ketone **6** (R_1 = CH_3) (Table 1, entries 4, 13, and 14). In one instance (Table 2, entry 7), the work-up following the light initiated reactions involved the addition of sodium methoxide and the intermediate chloro ether **3g** (Z = CCl_3) was converted to the oxazoline **8** (Scheme 2).



3 g **8**

SCHEME 2

In the chromous chloride promoted additions, products arising from the reduction of the radical adduct by the chromous ion followed by hydrolysis of the organochromium derivative (1, H-adducts)[5,6] were obtained in the additions to dihydropyran (**2c**) (Table 1, entry 3) (see **9**),[7] to methoxymethylenecyclohexane (**2g**) (Table 2, entry 2) (see **11**), and to enol ethers **2k**, **2l**, **2m**, **2n** and **2o** (Table 1, entries 11 to 15) (see **12**, **13**, and **14**). Products **11** and **13** come from the 1, H-adducts **10** (not isolated) and **12** respectively by loss of methanol. The elimination of methanol was complete after a few minutes when an etheral solution of the crude reaction product was treated with 70% aqueous perchloric acid (Table 1, entries 11 to 14). It is noteworthy that, from the additions to enol ethers **2k**, **2l**, **2m**, and **2n**, no 1,2-adduct **4** was detected and, from the addition to enol ether **2o**, no adduct **5** was detected. This means that the chromous ion reduction of the radical adduct, in which a carbonyl group is attached to the radical center, is faster than chlorine-atom abstraction from ZCONHCl (and/or from Cr(III) Cl)[6] as was found in the chromous chloride promoted addition of N-chlorourethane (**1**, Z = OC_2H_5) to methylvinyl ketone and to methylacrylate.[5,6]

Table 1. Orientation of the chromous chloride promoted addition of N-chlorourethane (**1**, Z = C_2H_5O) to enol ethers **2**[a] (Scheme 1)

	Enol ether							
Entry	R	R_1	R_2	R_3	(N°)	Yield of addition[b] (%)	β/α[c]	Material balance[d] (%)
1[e]	C_2H_5	H	H	H	(**2a**)	81	> 25[f]	95-97
2[e]	CH_3	—— $(CH_2)_4$ ——		H	(**2b**)	85(90)[g]	> 25[f]	95-98
3[e]	—— Dihydropyran ——				(**2c**)	98[h]	7.2	98
4[e]	CH_3	CH_3	—— $(CH_2)_5$ ——		(**2d**)	72[i]	≥ 6	95
5	CH_3	H	CH_3	CH_3	(**2e**)	89	0.41	97
6	CH_3	H	n-C_3H_7	n-C_3H_7	(**2f**)	88	0.20	98
7	CH_3	H	——$(CH_2)_5$——		(**2g**)	96	0.31	96
8	CH_3	H	——$(CH_2)_4$——		(**2h**)	75	0.23	95
9[e]	CH_3	H	—— steroid ——		(**2i**)	75	< 0.05[j]	--[k]
10	t-C_4H_9	H	——$(CH_2)_5$——		(**2j**)	89	0.85	97
11[l]	CH_3	H	CH_3CO	H	(**2k**)	69[m]	0.41	92
12[l]	CH_3	H	CH_3OCO	CH_3	(**2l**)	76-79[m,n]	≤ 0.05[j]	90-94
13[l]	CH_3	CH_3	CH_3OCO	H	(**2m**)	85-90[m,o]	1.5	92-96
14[l]	CH_3	CH_3	CH_3CO	H	(**2n**)	84[m,o]	1.8	95
15	CH_3	CH_3OCO	CH_3	CH_3	(**2o**)	31[m](28[p])	≥ 25[q]	90

[a] The reactions were carried out under the usual conditions (see ref. 5-7) at a cooling bath temperature of -78°C, in a mixture of chloroform-methanol (4:1 to 5:1, v/v) as solvent, using a 2:1 molar ratio of enol ether to N-chloroamide. The sodium methoxide work-up (see ref. 7) was used unless otherwise stated.

[b] The yields refer to the sum of adducts **4** and **5** (plus small amounts of **6** (2 to 7%) in some cases) separated by preparative layer chromatography (PLC) and homogeneous by thin layer chromatography (TLC) unless specified otherwise. The yields are based on the N-chloroamide.

[c] Ratio of adduct **5** and/or **6** (addition to carbon β) to adduct **4** and/or **7** (addition to carbon α).

[d] Addition products plus parent amide.

[e] Taken from ref. 7.

[f] The adduct **4** (or the α-chloro carbonyl derivative **7** resulting from its hydrolysis) was not detected.

[g] Acid work-up (see ref. 7). Yield in brackets was obtained by vapor phase chromatography (VPC).

[h] Adducts **5c** (4% *cis*, 77% *trans*) and **6c** as cyclic hemiacetal (5%), and a mixture of adducts **4c** (*cis* + *trans*, ~ 5%) and **9** (~ 7%) (see ref. 7).

[i] The acid work-up afforded 1-acetyl-1-ethoxycarbonylaminocyclohexane (**6d**) (62% by VPC) and 1-acetyl-1-chlorocyclohexane (**7d**) (10% by VPC).

[j] The adduct **5** (or **6**) was not detected.

[k] Not determined.

[l] In these experiments, the ethereal extract was treated with 70% perchloric acid for a few minutes. The addition at the α-carbon gave the 1,H-adduct **12** which lost methanol in the work-up to afford the enamide **13** (see text).

[m] By VPC.

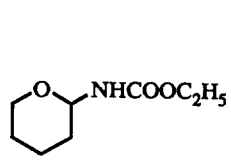
Table 1. (cont'd).

n In one experiment, the ethereal extract was not treated with perchloric acid and the adduct **12** (R_1 = H, R_3 = CH_3, R_4 = OCH_3) was isolated (53% yield) together with some enamide **13** (R_1 = H, R_3 = CH_3, R_4 = OCH_3).

o The adduct **5** was completely hydrolyzed to **6** by the perchloric acid treatment.

p Yield of isolated (PLC) **14**.

q No adduct **4o** (Z = OC_2H_5), nor α-chloroketone **7o** (R_1 = $COOCH_3$) was detected.



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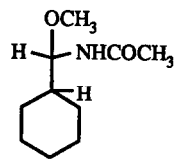

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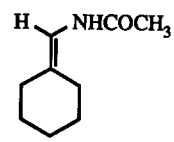

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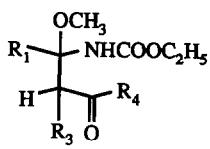

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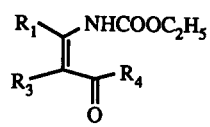

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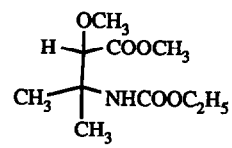

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As can be seen from Table 2, the best yields of addition were obtained with N-chlorourethane (**1**, Z = OC_2H_5), both in the light initiated and in the chromous chloride promoted reactions as was observed previously with other enol ethers,[3,7] as well as with olefins in general:[2,3,5,6] N-chlorocarbamates usually give better yields of addition than N-chlorocarboxamides. In most cases, the material balance (addition products plus parent amide) is very good (≥ 95%) thus showing that processes such as telomerization, disproportionation and dimerization of intermediate radicals are not important. Therefore, the β/α ratio should reflect the regioselectivity of the addition of the amidyl radical to the enol ether. When the yields of addition are low (≤ 50%) and the material balance lower than 85%, the β/α ratio might differ from the true regioselectivity.

The most likely candidate for an electrophilic addition of ZCONHCl (**1**) to an electron-rich olefin such as an enol ether is N-chlorotrifluoroacetamide (**1**, Z = CF_3). Such an electrophilic addition to ethoxyethylene (**2a**) would give the adduct **4a** (Z = CF_3) (Scheme 1). The light-initiated addition of $CF_3CONHCl$ to **2a** followed by addition of methanol gave exclusively the acetal **5a** (Z = CF_3) in high yield (92%).[3] Thus the intervention of the electrophilic addition of ZCONHCl (**1**) in the light initiated reaction with the other enol ethers, including methoxymethylenecyclohexane (**2g**), is very unlikely.

Table 2. Orientation of the radical addition of ZCONHCl (1) to methoxymethylene cyclohexane (2g)[a]

Entry	Z	Initiation	Yield of addition[b] (%)	β/α[c]	Material balance[d] (%)
1	CH_3	hv	35-46[e]	≤ 0.05[e]	85-90
2		Cr^{++}	75[f]	0.12 (0.18)	98
3	CH_2Cl	hv	71	0.36 (0.38)	93
4		Cr^{++}	76	0.31 (0.33)	96
5	$CHCl_2$	hv	67	0.13 (0.33)	86
6		Cr^{++}	34-38	≤ 0.05[e]	80-83
7	CCl_3	hv	77-81[g]	0.32 (0.30)	95-98
8		Cr^{++}	42-46	≤ 0.05[e]	84
9	CF_3	hv	60	0.26 (0.21)	90
10		Cr^{++}	43-45	~ 0.05	83-87
11	C_2H_5O	hv	87[h]-93	0.40 (0.33)	94-97
12[i]		hv	88	0.42 (0.40)	--[j]
13		Cr^{++}	96	0.29 (0.31)	96
14	$(CH_3)_2N$	hv	27	--[k]	--[j]

[a] The irradiations (254 nm) were carried out at -70°C in methylenechloride solutions 0.05 to 0.06 M in N-chloroamide, using a 2:1 molar ratio of enol ether to N-chloramide (see ref. 3) and were followed by the addition of methanol at -70°C then of silver carbonate and drierite (see Experimental). For the chromous chloride promoted reactions, see footnote a of Table 1.

[b] Yields of **4g** plus **5g** isolated by PLC and homogeneous by TLC unless specified otherwise. When two or more additions were carried out, the range of yields obtained is given.

[c] The ratio between brackets was determined by ^1H NMR on the crude product.

[d] Addition product plus parent amide.

[e] The adduct **5g** (or **6g**) was not detected.

[f] Adducts **4g** (30%), **5g** (4%), **6g** (4%) (Z = CH_3), and **11** (37%).

[g] In one experiment, sodium methoxide was added for the work-up (see ref. 3) and the oxazoline **8** was isolated in a 16% yield (65% yield of **5g**).

[h] Water was added for the work-up and the β-carbon adduct was isolated as the aldehyde **6g** (Z = C_2H_5O).

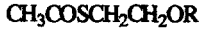
[i] The photolysis was carried out in a 1:1 mixture of methylenechloride and methanol.

[j] Not determined.

[k] The ratio could not be determined due to the decomposition of the products upon chromatographic analysis (VPC) and separation (PLC).

Radical addition of thioacetic acid to enol ethers **2**

The photochemical addition of $CH_3\dot{C}OSH$ to ethoxyethylene (**2a**) and methoxymethylenecyclohexane (**2g**) was carried out in dry methylenechloride at -70°C and 254 nm. With **2a**, the adduct **15** (R = C_2H_5) was the sole product formed in 80% yield according to VPC analysis. Prilezhaeva and Shostakovskii[13] obtained a 92% yield of **15** (R = *n*-C_4H_9) for the AIBN initiated addition of CH_3COSH to *n*-butyl vinyl ether. The photochemical addition of CH_3COSH to **2g** was quantitative giving the adducts **16** and **17** in 22% and 77% yield (of isolated product by PLC) respectively for a β/α ratio of 0.29.



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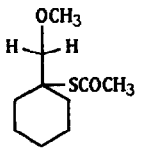

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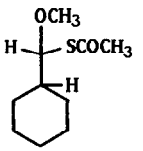

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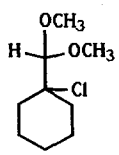
Electrophilic additions to methoxymethylenecyclohexane (**2g**)

We studied the following electrophilic additions to methoxymethylenecyclohexane (**2g**): electrophilic chlorination with N-chlorourethane (**1**, Z = OC_2H_5) in methanol at room temperature which gave a near quantitative yield (by VPC) of α-chloroacetal **17** (95%) and urethane (98%); hydroboration with diborane in THF at 0°C which, after peroxide oxidation of the intermediate borane, afforded the hydroxy-ether **18** (52% yield) as the sole product (no cyclohexanecarbonaldehyde was detected); addition of nitrosyl chloride in ether at -70°C followed by methanolysis (silver perchlorate in methanol) which gave the nitroso dimer **19** (83%) which was catalytically hydrogenated to the hydroxylamine **20** (100% yield). All these electrophilic additions were regiospecific, the electrophile adding on the more substituted β-carbon exclusively.



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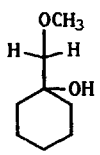

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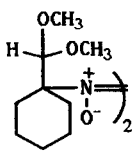

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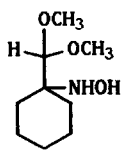

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Structure of the products

The products of addition to enol ethers **2a**, **2b**, **2c**, **2d**, **2i** and **2g** have been described.[3,7] All the addition products not previously described had IR, ^{1}H NMR and mass spectra, and an elemental analysis consistent with their structure. The spectral data are given in the Experimental; their interpretation and analysis are quite straightforward and will not be discussed here.

DISCUSSION

According to Tedder and Walton[10,11] and Giese[12] who have studied the rate and regioselectivity of the addition of carbon centered radicals to olefins, the regioselectivity is controlled principally by steric effects. For an exact prediction of the regioselectivity, polar effects have to be taken into account. If the steric effects are similar at both ends of the double bond, polar affects can be the deciding factor. The addition of a carbon centered radical to an alkene is strongly exothermic (early transition state)[14] and stabilization by delocalization of the unpaired electron in the radical adduct is of small importance. Fossey,[15] Fleming,[16] and Giese[12] have pointed out that polar effects in exothermic radical additions can be described in terms of frontier molecular orbital theory: a SOMO-LUMO interaction would correspond to a nucleophilic behavior, a SOMO-HOMO interaction, to an electrophilic behavior.

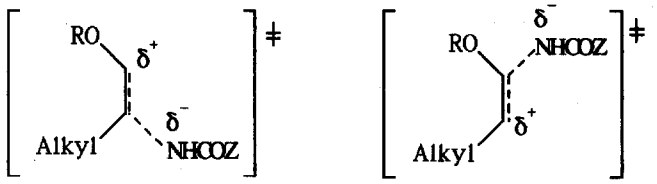
A C-N σ-bond is weaker than a C-C σ-bond (by about 10 kcal/mol from the average bond energies[17]). The addition of nitrogen centered radicals to alkenes should then be less exothermic than the addition of carbon centered radicals and the transition state could be less early on the reaction coordinate. If it is the case, the formation of the new bond would be more advanced on the case of nitrogen centered radicals and the steric compression associated with this bond formation more important. As shown in Tables 1 and 2, the addition of $\dot{\text{N}}$HCOZ to enol ethers **2** having an unsymmetrically substituted double bond always occurs preferentially on the less substituted, less hindered, carbon atom. For instance, in the case of the β,β-disubstituted enol ethers **2e** to **2f** (R_1 = H, R_2 and R_3 being alkyl groups), the product resulting from the addition of $\dot{\text{N}}$HCOZ on the less substituted α-carbon atom predominates: β/α = 0.2 to 0.4 for OR = OCH_3 (Tables 1 and 2). An increase of the bulk of the OR group, from OCH_3 (see **2g**, Table 1, entry 7) to O-*t*-C_4H_9 (**2j**, Table 1, entry 10), leads to a decrease of the proportion of attack on the α-carbon, from 76% to 54%. An increase of the size of the substituents at the β-carbon causes a decrease of the β/α ratio as expected: compare entries 5 (**2c**, $R_2 = R_3 = CH_3$; β/α = 0.41) and 6 (**2f**, $R_2 = R_3 = n$-C_3H_7; β/α = 0.20) of Table 1. When the β-carbon is very hindered as in the addition to the steroidal enol ether **2i**, the addition occurs exclusively at the α-carbon (Table 1, entry 9; β/α ≤ 0.05).

In contrast to the addition of $\dot{\text{N}}$HCOZ, the addition of electrophiles such as "positive" chlorine (from NCU), diborane, and "positive" nitroso group (from nitrosyl chloride) to methoxymethylenecyclohexane (**2g**) occurs exclusively on the more substituted β-carbon. This can be readily

accounted for by the classical explanation of the Markownikoff addition: the stabilization of the intermediate carbenium ion at the α-carbon by the p electrons of the methoxy group overrides both the steric effect of the two ring methylene groups attach to the β-carbon and their stabilizing effect (hyperconjugation) on the intermediate carbenium ion on C-β.

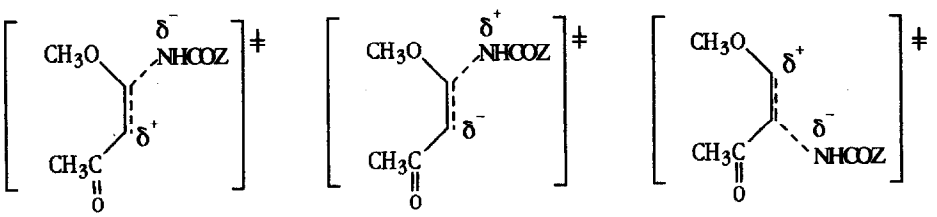
The addition of NCU (**1**, Z = OC_2H_5) to dihydropyran (**2c**), to (1-methoxyethylidene)cyclohexane (**2d**), and to 4-methoxy-3-buten-2-one (**2k**) shows clearly that effects other than steric effects also have an influence on the regioselectivity of the addition of $ZCO\dot{N}H$ to enol ethers. These three enol ethers have the same number of substituents at both ends of the double bond and the steric effects at C-α and C-β, although not identical (C-O bonds shorter than C-C bonds in **2c**, methoxy group *vs* a methyl group in **2d**, methoxy group *vs* an acetyl group in **2k**) should not be appreciably different. In the additions to **2c** and **2d**, more than 85% of the attack of the amidyl radical occurs at the β-carbon (β/α ≥ 6; Table 1, entries 3 and 4[18]), whereas, in the addition to **2k** about 70% of the attack occurs at the α-carbon (β/α ≃ 0.41; Table 1, entry 11). An alkoxy group is comparable to an acyl group and only slightly better than a methyl group in reducing the spin density on the C-atom to which it is attached[19] and thus, the radical-stabilizing effect of an alkoxy group should be nearly the same as that of an acyl group and slightly better than that of a methyl group.[9] As a consequence, stabilization of the unpaired electron by delocalization in the radical adduct should have a small effect on the regioselectivity of radical additions to enol ethers **2c** and **2d**, and still a smaller effect for the additions to **2k** even if the transition state does not occur very early on the reaction coordinate. The addition of $ZCO\dot{N}H$ to an alkene, although less exothermic than that of an alkyl radical, should still be exothermic as already pointed out. Therefore, when the steric effects are similar at both ends of the double bond, polar effects become the deciding factor in determining the regioselectivity of the addition of amidyl radicals to an olefin, as for the addition of carbon-centered radicals.[10-12]

Consideration of the charge separation in the transition state as first discussed by Walling[20] could explain the preferred orientation of the addition of $ZCO\dot{N}H$ to enol ethers **2c** and **2d** since an alkoxy group should be better to stabilize an adjacent cationic center than an alkyl group (transition state **21** preferred over transition state **22**). This implies that $ZCO\dot{N}H$ should have an electrophilic behavior towards an enol ether. In terms of frontier orbital theory (exothermic reaction, see above), it corresponds to a SOMO-HOMO interaction.[12,15,16] And indeed, the SOMO-HOMO energy difference should be small since the energy of the SOMO of $ZCO\dot{N}H$ should be low (nitrogen-centered radical bearing an electron-withdrawing group[21]) and the energy of the HOMO of an enol ether should be relatively high (electron donating substituent with a lone pair of electrons delocalized into the double bond[22]). The HOMO of an $\ddot{X}$-substituted ethylene has the larger coefficient on the less substituted carbon[23]. Therefore, the HOMO of enol ethers **2c** and **2d** should also have the larger coefficient on the β-carbon and the attack of $ZCO\dot{N}H$ on that carbon should be faster[12,16] as observed (β/α > 6, Table 1, entries 3 and 4).



21 22

The presence of the electron-withdrawing acetyl group in enol ether **2k** should lower the energy of the HOMO[22] with respect to that of enol ethers **2c** and **2d**. Nevertheless, the behavior of $\dot{ZCONH}$ with respect to enol ether **2k** could still be electrophilic (dominant SOMO-HOMO interaction[12,15,16]), in which case the HOMO of **2k** would have the larger coefficient on the α-carbon since the addition of $\dot{ZCONH}$ occurs predominantly at the α-carbon(β/α = 0.41, Table 1, entry 11). The behavior could also be ambiphilic (SOMO-LUMO and SOMO-HOMO interactions of similar importance[12]), in which case the regioselectivity would be determined by electrostatic effects (e.g. dipole-dipole interactions as suggested by Tedder[11]) that would weaken the N-C_β bond with respect to the N-C_α bond or conversely strengthen the N-C_α bond with respect to the N-C_β bond. The charge separation picture of the transition state[20] cannot satisfactorily explain the fact that, when opposed to an alkoxy substituent as in **2k**, an acyl substituent has a stronger influence than the former in directing the attack of $\dot{ZCONH}$ on the carbon remote from it. Indeed, an acyl group should destabilize a cationic center next to it (transition state **23**) or the nitrogen of an acylamino group would not likely give away some of its electrons (transition state **24**). So transition state **25** should be favored over transition states **23** or **24** contrarily to the experimental finding (β/α = 0.41). Whatever the cause (polar and/or electrostatic effects), it is clear that an acyl or acyloxy substituent has a stronger influence than an alkoxy substituent in directing the attack of $\dot{ZCONH}$ on the carbon of the double bond away from the substituent.



23 24 25

The addition of NCU (**1**, Z = OC_2H_5) to the α,β-disubstituted enol ethers **2m** and **2n** (Table 1, entries 13 and 14) show that a carbomethoxy group (**2m**) and an acetyl group (**2n**) have a similar effect on the regioselectivity of the addition of $\dot{ZCONH}$: about 60-65% of the addition occurs on

the less substituted β-carbon atom. When compared to the regioselectivity of the addition of ZCONH to an other α,β-disubstituted enol ether, 1-methoxycyclohexene (**2b**), the β/α ratio is much lower for **2m** and **2n** (1.5-1.8) than for **2b** (> 25). This illustrates once more the large influence of a carbonyl group in directing the attack of $ZCO\dot{N}H$ on the carbon of the double bond not bearing the substituent. The importance of such a substituent effect on the orientation would then decrease in the order: acyl ≥ acyloxy > alkoxy > alkyl.

When both a carbonyl group and an alkoxy group are on the same carbon and opposed to two alkyl groups as in enol ether **2o**, the addition of the amidyl radical occurs exclusively on the carbon bearing the two alkyl groups, the β carbon (β/α > 25, see Table 1, entry 15), in agreement with the order of the orienting effect of alkyl, alkoxy and carboalkoxy substituents given above. The high regioselectivity of addition to **2o** is probably not due to capto-dative stabilization of the intermediate radical adduct.[24,25] If such a stabilization had a determining influence on the orientation of the addition of an amidyl radical, it should also have an influence on the reactivity of the double bond towards the amidyl radical. The enol ether **20** would then be expected to be more reactive than enol ether **2d**, an other α,β,β-trisubstituted enol ether. However, the yield of addition of NCU (**1**, Z = OC_2H_5) to enol ether **2o** is much lower (28-31%, Table 1, entry 15) than the yield of addition to enol ether **2d** (72%, Table 1, entry 4) and this reflects the lower reactivity of enol ether **20** towards the amidyl radical. Indeed, the yield of addition does reflect the reactivity of the olefin towards the amidyl radical in these chromous ion promoted additions because the addition of the amidyl radical to the olefin and its reduction to the parent amide by the chromous ion are the two main processes occurring (as shown by the high material balances based on the amide) and they compete with each other.[6]

We have studied the effect of the electron-withdrawing power of Z on the orientation of the radical addition of ZCONHCl (**1**) to methoxymethylenecyclohexane (**2g**). The results recorded in Table 2 show that increasing the electron-attracting power of Z in the order $CH_3 < CH_2Cl < CHCl_2 < CCl_3 < CF_3$ (entries 2 to 5, 7, and 9) has little effect on the β/α ratio which remains in the range of 0.2 to 0.4 and is about the same as that observed with NCU (**1**, Z = OC_2H_5) (β/α = 0.3 to 0.4, entries 11 to 13). Thus, the electrophilicity of the amidyl radical has no influence on the regioselectivity of its addition to a β,β-dialkyl vinyl ether.

The regioselectivity of the radical addition of thioacetic acid to methoxymethylenecyclohexane (**2g**), β/α = 0.3, is the same as that of the radical addition of ZCONHCl (**1**), β/α = 0.2 - 0.4. This shows again that the electrophilicity of a radical has little influence on the regioselectivity of the addition to a β,β-dialkyl vinyl ether since the acetylthiyl radical should be less electrophilic (SOMO of higher energy) than an amidyl radical (the sulfur atom being less electronegative than the nitrogen atom). The addition of $CH_3C\dot{O}S$ to an olefin should be less exothermic than that of $ZCO\dot{N}H$, a C-S bond being weaker than a C-N bond (by about 8 kcal/mol from the average bond energies[17]), if exothermic at all (ΔH ≃ -2 kcal/mol from the average bond energies of C-S and C=C[17]) so the position of the transition state on the reaction coordinate should differ for the

addition of these two radicals to a double bond. The transition state for the addition of $CH_3\dot{C}O\dot{S}$ should be less early. The fact that the orientation of the addition is the same for both radicals suggests that the stability of the radical adduct has probably little influence on the regioselectivity of addition of these two radicals to an enol ether as in the case of the addition of carbon-centered radicals to olefins.[9-12]

CONCLUSION

The addition of amidyl ($ZCO\dot{N}H$) and acetylthiyl ($CH_3CO\dot{S}$) radicals to β,β-substituted (dialkyl) enol ethers occurs predominantly on the less substituted α-carbon. An increase of the steric bulk of the OR group causes a decrease in the proportion of α-addition whereas an increase of the steric bulk of the β substituents causes an increase of the proportion of α-addition. Thus, steric effects must be primarily responsible for the regioselectivity observed as is generally the case for the addition of radicals to unsymmetrical olefins.[8-12] The electrophilicity of the radical (varying the electron-withdrawing power of Z in $ZCO\dot{N}H$, acetylthiyl *vs* amidyl) has no influence on the regioselectivity of addition to methoxymethylenecyclohexane (**2g**) which suggests that the electron-donating power of an alkoxy group would be equivalent to that of two alkyl groups: coefficients of the HOMO having the same size at carbon α and carbon β[23]; similar polarization of the transition state[20] for the addition at carbon α and at carbon β. The addition of an amidyl radical to dihydropyran (**2c**) and to (1-methoxyethylidene)cyclohexane (**2d**) is regiospecific. Since steric effects are similar at both ends of the double bond, the polar effect (an alkoxy group being a better electron donor than an alkyl group) must be responsible for such a high regioselectivity. For the addition of an amidyl radical to an enol ether bearing also an electron-withdrawing group such as an acyl group on the other end of the double bond (see **2k**), the addition occurs preferentially on the carbon bearing the alkoxy group which suggests that an acyl group has a stronger influence in directing the attack of the radical on the carbon atom remote from the substituent. From the regioselectivity of the additions reported in Table 1, the effect of a substituent in directing the attack of an amidyl radical to an unsymmetrical double bond would decrease in the order acyl ≥ acyloxy > alkoxy > alkyl.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 257 spectrometer. ^1H NMR spectra were recorded on a Brucker HX-90 or a Varian A-60 spectrometer using tetramethylsilane as internal reference. Mass spectra were taken on a Hitachi RMU-6E spectrometer. Column chromatography was done using Davison's silica gel No 923 or 950, or Fluorisil 100-200 mesh. Merck silica gel CF_{254} was used for thin and preparative layer chromatography. Vapor phase chromatography analyses and preparative separations were performed on a Hewlett-Packard chromatograph model 5750 equipped with both a flame ionization and a thermal conductivity detector using an OS-138 column (15% polyphenylether on dimethylsilylated chromosorb W). Microanalyses were performed by Schwarzkopf Laboratory, New York, and by Mr. J.

Tamas, Département de chimie, Université de Sherbrooke. Organic phases from extraction were dried over anhydrous sodium sulfate.

N-Chloroamides **1**

N-Chlorourethane (**1**, Z = OC_2H_5) and the N-chlorocarboxamides (**1**, Z = CH_3, CH_2Cl, $CHCl_2$, CCl_3, CF_3) were prepared by the sodium hypohalite method as previously described.[26] N-Chloro-N',N'-dimethylurea (**1**, Z = $N(CH_3)_2$) was prepared as reported in the literature by Bredereck *et al*:[27] mp 54-58°C (90% active chlorine by iodometric titration).

Enol Ethers **2**

Ethoxyethylene (**2a**), dihydropyran (**2c**) and 4-methoxy-3-buten-2-one (**2k**) were obtained commercially. The following enol ethers were prepared as described in the literature; 1-methoxycyclohexene (**2b**),[28] (1-methoxyethylidene)cyclohexane (**2d**),[29] 1-methoxy-2-methylpropene (**2e**),[30] (1-methoxymethylene)cyclohexane (**2g**),[31] (1-methoxymethylene)cyclopentane (**2h**),[32] 20-methoxy-4,17-androstadien-3-one (**2i**),[7] methyl 2-methyl-3-methoxy-2-propenoate (**2l**),[33] methyl 3-methoxy-2-butenoate (**2m**),[34] 4-methoxy-3-penten-2-one (**2m**),[34] methyl 2-methoxy-3-methyl-2-butenoate (**2o**).[35]

The following enol ethers were prepared by known procedures.

1-Methoxy-2-n-propyl-1-pentene (**2f**). It was prepared by a Wittig reaction[34] from methoxymethylenetriphenylphosphonium chloride (52.3 g, 150 mmol) and 4-heptanone (9.0 g, 75 mmol) in ether (200 mL) at -30°C using phenyllithium (100 mmol) as base. The crude product obtained after the usual work up was distilled under reduced measure: 5.2 g (50%); bp 50-52°C (20-25 mmHg). IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR (CCl_4) δ 5.80 (m, 1H), 3.50 (s, 3H), 2.5-1.8 (m, 4H), 1.9 (m, 10H); LRMS *m/z* 142 (M^+).

(Tertiobutoxymethylene)cyclohexane (**2j**). It was prepared according to Corey's modification[35] of the Wittig reaction from methoxymethylenetriphenylphosphonium chloride (19.23 g, 50 mmol), sodium hydride (2.1 g of a 57% suspension, 50 mmol) and cyclohexanone (4.90 g, 50 mmol) in DMSO (50 mL). The crude product isolated after the usual work up was distilled under reduced pressure (15-18 mmHg). The fraction distilling between 70-85°C was collected and dissolved in pentane. The solution was washed with a saturated solution of sodium carbonate, dried, and the solvent removed by distillation. The residue was distilled under reduced pressure (15-18 mmHg). The fraction distilling between 65-68°C consisted of a mixture of enol ether **2j** (82%) and cyclohexanone (18%) according to vapor phase chromatography (VPC) analysis. The pure enol ether **2j** was obtained by preparative VPC: bp 78-80°C (15 mmHg); IR (CCl_4) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00 (m, 1H), 2.2 and 1.9 (two m, 4H), 1.5 (m, 6H), 1.20 (s, 9H). **Anal.** Calcd for $C_{22}H_{34}O_2$: C, 78.51; H, 11.80. Found: C, 78.54; H, 11.99.

Chromous Chloride Promoted Additions

The additions were carried out at -78°C, in chloroform-methanol using a 2:1 molar ratio of enol ether **2** to N-chloroamide **1** as already described.[7] A sodium methoxide work-up was used in most cases but an acid work-up was carried out in some cases. They both were carried out as described.[7] The products were separated by column and/or preparative layer chromatography, or preparative vapor phase chromatography. They were purified by bulb-to-bulb distillation or

crystallization.

Photochemically Initiated Additions

The irradiations were carried out at -70°C, in methylenechloride on a 0.05 M to 0.06 M solution of N-chloroamide **1**, using a 2:1 molar ratio of enol ether **2** to N-chloroamide **1**. A methanol/silver carbonate/drierite work-up was used in most cases, a sodium methoxide work-up was used after the reaction of **2g** with **1** (Z = CCl_3), and an aqueous work-up for the reaction of **2g** with **1** (Z = OC_2H_5). The irradiation and the work-up procedures were carried out exactly as previously described.[3] The separation and purification procedures were the same as those used for the chromous chloride promoted additions.

Product Characterization

The characterization of the following products resulting form the addition of N-chlorourethane (**1**, Z = OC_2H_5) has been reported in ref. 7: 2-ethoxycarbonylaminopropanal ethylmethyl acetal (**5a**), 2-ethoxycarbonylaminocyclohexanone (**6b**), *cis* and *trans* 2-methoxy-3-ethoxycarbonylaminotetrahydropyran (**5c**), *cis* and *trans* 2-ethoxycarbonylamino-3-chlorotetrahydropyran (**4c**), 2-hydroxy-3-ethoxycarbonylaminotetrahydropyran (hemiacetal of **6c**), 2-ethoxycarbonylaminotetrahydropyran (**9**), 1-acetyl-1-ethoxycarbonylaminocyclohexane (**6d**), 1-acetyl-1-chlorocyclohexan (**7d**), the adduct **4i** obtained from the addition to the steroidal enol ether **2i**. The characterization of the following adducts (Z = OC_2H_5) has been reported in ref. 3: 1-ethoxycarbonylaminocyclohexanecarboxaldehyde dimethyl acetal (**5g**) and (1'-chlorocyclohexyl)-ethoxycarbonylaminomethoxymethane (**4g**).

For the compounds listed below, only the most characteristic spectral data are reported.

2-Ethoxycarbonylamino-2-methylpropanal dimethylacetal (**5e**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 40-42°C (0.1 mmHg); IR (CCl_4) 3440, 3350, 1725, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.90 (broad s, 1H), 4.43 (s, 1H), 4.10 (q, J = 7 Hz, 2H), 3.53 (s, 6H), 1.22 (t, J = 7 Hz, 3 H); LRMS *m/z* 174 (M^+ - 31). **Anal.** Calcd for $C_9H_{19}NO_4$: C, 52.66; H, 9.33; N, 6.82. Found: C, 54.42; H, 9.32; N, 6.60.

1-Ethoxycarbonylamino-1-methoxy-2-chloro-2-methylpropane (**4e**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 45-46°C (0.1 mmHg); IR (CCl_4) 3420, 1730, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (broad d, J = 10 Hz, 1H), 4.77 (d, J = 10 Hz, 1H), 4.22 (q, J = 7 Hz, 2H), 3.42 (s, 3H), 1.28 (t, J = 7 Hz, 3H); LRMS *m/z* 178, 180 (3:1, M^+ - 31). **Anal.** Calcd for $C_8H_{16}ClNO_3$: Cl, 16.91. Found: Cl, 17.21.

2-Ethoxycarbonylamino-2-n-propylpentanal dimethylacetal (**5f**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 42-45°C (0.1 mmHg); IR (CCl_4) 3420, 1725, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (broad s, 1H), 4.45 (s, 1H), 4.05 (q, J = 7 Hz, 2H), 3.50 (s, 6H), 1.22 (t, J = 7 Hz, 3H); LRMS *m/z* 230 (M^+ - 31). **Anal.** Calcd for $C_{13}H_{27}NO_4$: C, 59.74; H, 10.41; N, 3.56. Found: C, 59.94; H, 10.29; N, 5.12.

1-Ethoxycarbonylamino-1-methoxy-2-n-propylpentane (**4f**, Z = OC_2H_5). - It was purified by bulb-to bulb distillation at 52-55°C (0.1 mmHg); IR (CCl_4) 3430, 1730, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (broad d, J = 10 Hz, 1H), 4.85 (d, J = 10 Hz, 1H), 4.05 (q, J = 7 Hz, 2H), 3.38 (s, 3H), 1.28 (t, J = 7 Hz, 3H); LRMS *m/z* 234, 236 (3:1, M^+ - 31). **Anal.** Calcd for $C_{12}H_{24}ClNO_3$: Cl, 13.37. Found: Cl, 13.01.

1-Ethoxycarbonylaminocyclopentanecarboxaldehyde dimethylacetal (**5h**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 64-65°C (0.1 mmHg); IR (CCl_4) 3450, 3360, 1730, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (broad s, 1H), 4.65 (s, 1H), 4.15 (q, J = 7 Hz, 2H), 3.50 (s, 6H), 1.20 (t, J = 7 Hz, 3H); LRMS *m/z* 200 (M^+ - 31). **Anal.** Calcd for $C_{11}H_{21}NO_4$; C, 57.12; H, 9.15; N, 6.06. Found: C, 57.03; H, 8.95; N, 6.10.

(1'-Chlorocyclopentyl)-ethoxycarbonylaminomethoxymethane (**4h**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 65-68°C (0.1 mmHg); IR (CCl_4) 3420, 3320, 1725, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (broad d, J = 10 Hz, 1H), 4.80 (d, J = 10 Hz, 1H), 4.15 (q, J = 7 Hz, 2H), 3.40 (s, 3H), 1.25 (t, J = 7 Hz, 3H); LRMS *m/z* 204, 206 (3:1, M^+ - 31). **Anal.** Calcd for $C_{10}H_{18}ClNO_3$: Cl, 15.00. Found: Cl, 14.62.

1-Ethoxycarbonylaminocyclohexanecarboxaldehyde methoxytertiobutoxyacetal (**5j**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 75-80°C (0.1 mmHg); IR (CCl_4) 3420, 1725, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.80 (broad s, 1H), 4.54 (s, 1H), 4.10 (q, J = 7 Hz, 2H), 3.47 (s, 3H), 1.22 (s, 9H), 1.21 (t, J = 7 Hz, 3H); LRMS *m/z* 182 (M^+ - 100). **Anal.** Calcd for $C_{15}H_{24}NO_4$: C, 62.19; H, 10.17; N, 4.87. Found: C, 62.78; H, 9.90; N, 5.07.

(1'-Chlorocyclohexyl)-ethoxycarbonylamino-tertiobutoxymethane (**4j**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 75-77°C (0.1 mmHg); IR (CCl_4) 3430, 1725, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (broad d, J = 10 Hz, 1H), 5.05 (d, J = 10 Hz, 1H), 4.20 (q, J = 7 Hz, 2H), 1.25 (t, J = 7 Hz, 3H), 1.24 (s, 9H); LRMS *m/z* 218, 220 (3:1, M^+ - $OC(CH_3)_3$). **Anal.** Calcd for $C_{14}H_{26}ClNO_3$: Cl, 12.15. Found: Cl, 12.25.

1-Acetylaminocyclohexanecarboxyaldehyde dimethylacetal (**5g**, Z = CH_3). - It was purified by recrystallization from ether, mp 131-132°C; IR ($CHCl_3$) 3470, 3300, 1660, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (broad s, 1H), 4.83 (s, 1H), 3.57 (s, 6H), 2.02 (s, 3H); LRMS *m/z* 184 (M^+ - OCH_3). Upon standing, the product slowly lost methanol to give *N-(methylenecyclohexane)acetamide* (**11**) which was purified by recrystallization from ether-petroleum ether, mp 110-111°C; IR ($CHCl_3$) 3460, 3330, 1690 (sh), 1670, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (m, 1H), 6.58 (d, J = 10 Hz, 1H), 2.05 (s, 3H); LRMS *m/z* 153 (M^+).

(1'-Chlorocyclohexyl)acetylaminomethoxymethane (**4g**, Z = CH_3). - It was recrystallized from ether-petroleum ether, mp 112-113°C; IR (CCl_4) 3440, 3360, 1695, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.41 (broad d, J = 10 Hz, 1H), 5.16 (d, J = 10 Hz, 1H), 3.45 (s, 3H), 2.12 (s, 3H); LRMS *m/z* 180, 190 (3:1, M^+ - OCH_3). **Anal.** Calcd for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; Cl, 16.14. Found: C, 54.61; H, 8.06; Cl, 16.15.

1-Chloroacetylaminocyclohexanecarboxaldehyde dimethylacetal (**5g**, Z = CH_2Cl). - It was recrystallized from pentane-ether, mp 85-86°C; IR ($CHCl_3$) 3400, 1690, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.35 (broad s, 1H), 4.73 (s, 1H), 3.52 (s, 6H), 4.02 (s, 2H). **Anal.** Calcd for $C_{11}H_{20}ClNO_3$: C, 52.90; H, 8.07; N, 14.19. Found: C, 52.71; H, 8.02; N, 14.25.

(1'-Chlorocyclohexyl)-chloroacetylaminomethoxymethane (**4g**, Z = CH_2Cl). - It was recrystallized from pentane-ether, mp 67°C; IR ($CHCl_3$) 3400, 1690, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (broad d, J = 10 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 4.18 (s, 2H), 3.42 (s, 3H). **Anal.** Calcd for $C_{10}H_{17}Cl_2NO_2$: C, 47.26; H, 6.74; N, 5.51. Found: C, 47.52; H, 7.01; N, 3.56.

1-Dichloroacetylaminocyclohexanecarboxaldehyde dimethylacetal (**5g**, Z = $CHCl_2$). - It was recrystallized from hexane, mp 124-125°C; IR ($CHCl_3$) 3400, 1695, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.38 (broad s, 1H), 6.00 (s, 1H), 4.72 (s, 1H), 3.60 (s, 6H); LRMS *m/z* 252 (M^+ - OCH_3). **Anal.** Calcd for $C_{11}H_{19}Cl_2NO_3$: C, 46.49; H, 6.74; Cl, 24.94. Found: C, 46.74; H, 6.58; Cl, 24.99.

(1'-Chlorocyclohexyl)dichloroacetylaminomethoxymethane (**4g**, Z = $CHCl_2$). - It was recrystallized from pentane-ether, mp 128-129°C; IR ($CHCl_3$) 3420, 3300, 1695, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (broad d, J = 10 Hz, 1H), 6.15 (s, 1H), 5.14 (d, J = 10 Hz, 1H), 3.48 (s, 3H). **Anal.** Calcd for $C_{10}H_{16}Cl_3NO_2$: C, 41.62; H, 5.59. Found: C, 41.60; H, 5.63.

1-Trichloroacetylaminocyclohexanecarboxaldehyde dimethylacetal (**5g**, Z = CCl_3). - It was recrystallized from pentane, mp 104.5-105.5°C; IR ($CHCl_3$) 3400, 1695, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.54 (broad s, 1H), 4.73 (s, 1H), 3.60 (s, 6H); LRMS *m/z* 287 (M^+ - OCH_3). **Anal.** Calcd for $C_{11}H_{18}Cl_3NO_3$: C, 41.47; H, 5.69; Cl, 33.38. Found: C, 41.42; H, 5.51; Cl, 33.39.

(1'-Chloroacyclohexyl)trichloroacetylaminomethoxymethane (**4g**, Z = CCl_3). - It was purified by bulb-to-bulb distillation at 82°C (0.2 mmHg). IR ($CHCl_3$) 3400, 3300, 1775, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (broad d, J = 10 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 3.52 (s, 3H); LRMS *m/z* 292, 294 (3:1, M^+ - OCH_3). **Anal.** Calcd for $C_{10}H_{15}Cl_4NO_2$: Cl, 43.93. Found: Cl, 44.17.

1-Trifluoroacetylaminocyclohexanecarboxaldehyde dimethylacetal (**5g**, Z = CF_3). - The product isolated by PLC had mp 65-67°C; IR ($CHCl_3$) 3430, 3250, 1730, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 (broad s, 1H), 4.79 (s, 1H), 3.56 (s, 6H); LMRS *m/z* 238 (M^+ - OCH_3). It was not possible to obtain an adequate analytical sample neither by recrystallization nor by sublimation at 42°C (1 mm Hg).

(1'-Chlorocyclohexyl)trifluoroacetylaminomethoxymethane (**4g**, Z = CF_3). - It was purified by sublimation at 25°C (1 mmHg), mp 71-73°C; IR ($CHCl_3$) 3400, 1730, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (broad d, J = 10 Hz, 1H), 5.16 (d, J = 10 Hz, 1H), 3.48 (s, 3H). **Anal.** Calcd for $C_{10}H_{15}F_3NO_2$: Cl, 5.52. Found: Cl, 5.69.

(1'-Chlorocyclohexyl)-N,N-dimethylcarbonylaminomethoxymethane (**4g**, Z = $N(CH_3)_2$). - It was isolated as an oil by PLC (ether); IR ($CHCl_3$) 3460, 3300, 1655, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (broad d, J = 10 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 3.49 (s, 3H), 3.02 (s, 6H); LRMS *m/z* 219, 219 (3:1, M^+ - OCH_3). Decomposition occurred upon bulb-to-bulb distillation at 90°C (0.1 mm Hg).

1-Acetylaminocyclohexanecarboxaldehyde (**6g**, Z = CH_3). - It was isolated from the chromous chloride promoted addition of N-chloroacetamide to **2g** by PLC (ether-pentane 1:1), mp 75-77°C; ^1H NMR ($CDCl_3$) δ 10.1 (s, 1H), 6.45 (broad s, 1H), 2.05 (s, 3H).

2-Ethoxycarbonylamino-3-ketobutyraldehyde dimethylacetal (**5k**, Z = OC_2H_5). - It was isolated by preparative VPC and purified by bulb-to-bulb distillation at 68-70°C (0.5 mmHg); IR (CCl_4) 3430, 1715, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.87 (broad d, J = 6 Hz, 1H), 4.54 (m, 2H), 4.21 (q, J = 7 Hz, 2H), 3.53 (s, 3H), 3.48 (s, 3H), 2.28 (s, 3H), 1.27 (t, J = 7 Hz, 3H); LRMS *m/z* 219 (M^+).

4-Ethoxycarbonylamino-3-buten-2-one (**13**, R_1 = R_3 = H, R_4 = CH_3). - It was isolated by VPC and recrystallized in ether, mp 91-92°C; IR (CCl_4) 3420, 1750, 1670, 1600, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00 (m, 1H), 7.28 (dd, J = 8.5 and 1.0 Hz, 1H), 5.52 (d, J = 8.5 Hz, 1H), 4.31 (q, J = 7 Hz, 2H), 2.27 (s, 3H), 1.34 (t, J - 7 Hz, 3H); LRMS *m/z* 157 (M^+). **Anal.** Calcd for $C_7H_{11}NO_3$: C, 53.99; H, 7.05. Found: C, 53.92; H, 6.92.

Methyl 2-methyl-3-ethoxycarboxylamino-3-methoxypropanoate (**12**, R_1 = H, R_3 = CH_3, R_4 = OCH_3). - It was isolated by PLC as an oil; ^{1}H NMR ($CDCl_3$) δ 6.18 (d, J = 10 Hz, 1H), 4.97 (dd, J = 4.5 and 1.0 Hz, 1H), 4.22 (q, J = 7 Hz, 2H), 3.77 (s, 3H), 3.35 (s, 3H), 2.88 (m, 1H), 1.25 (t, J = 7 Hz, 3H), 1.22 (d, J = 4.5 Hz, 3H). This compound lost methanol upon standing to give, after 24 hours, *2-methyl 3-ethoxycarboxylamino-2-methyl-2-propenoate* (**13**, R_1 = H, R_3 = CH_3, R_4 = OCH_3) which was purified by bulb-to-bulb distillation at 45°C (0.5 mmHg); IR (CCl_4) 3420, 3330, 1740, 1690, 1640, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (dq, J = 11 and 1.5 Hz, 1H), 4.31 (q, J = 7 Hz, 2H), 3.82 (s, 3H), 1.89 (d, J = 1.5 Hz, 3H), 1.37 (t, J = 7 Hz, 3H), the NH signal was not detected; LRMS *m/z* 187 (M^+. **Anal.** Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00. Found: 51.35; H, 7.18.

Methyl 2-ethoxycarbonylamino-3-ketobutanoate (**6m**, Z = OC_2H_5). - It was isolated by preparative VPC and distilled (bulb-to-bulb) at 80-85°C (0.5 mmHg); IR (CCl_4 3430, 1730, 1710, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (broad d, J = 8 Hz, 1H), 5.10 (d, J = 8 Hz, 1H), 4.17 (q, J = 7 Hz, 2H), 3.85 (s, 3H), 2.35 (s, 3H), 1.25 (t, J = 7 Hz, 3H); LRMS *m/z* 203 (M^+).

Methyl 3-ethoxycarbonylamino-2-butenoate (**13**, R_1 = CH_3, R_3 = H, R_4 = OCH_3). - It was isolated by preparative VPC and purified by sublimation at 25°C (1 mmHg), mp 47-48°C; IR ($CHCl_3$) 3500, 1735, 1700, 1650, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.70 (m, 1H), 4.94 (q, J = 1.5 Hz, 1H), 4.25 (q, J = 7 Hz, 2H), 3.71 (s, 3H), 2.36 (d, J = 1.5 Hz, 3H), 1.33 (t, J = 7 Hz, 3H); LRMS *m/z* 187 (M^+). **Anal.** Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00. Found: C, 51.22; H, 7.24.

3-Ethoxycarbonylamino-2,4-pentanedione (**6n**, Z = OC_2H_5). - It was isolated by preparative VPC and purified by sublimation at 80°C (1 mmHg), mp 76-77°C; IR ($CHCl_3$) 3420, 1720, 1600, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.00 (s, 1H, enol form), 6.35 (m, 1H), 5.04 (d, J = 8 Hz, 1H), 4.24 (q, J = 7 Hz, 2H), 2.27 (s, 3H), 2.12 (s, 3H, enol form), 1.20 (t, J = 7 Hz, 3H). **Anal.** Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00. Found: C, 51.46; H, 7.10.

4-Ethoxycarbonylamino-3-penten-2-one (**13**, R_1 = CH_3, R_3 = H, R_4 - CH_3). - It was isolated by preparative VPC and purified by sublimation at 25°C (0.5 mmHg), mp 46°C; IR ($CHCl_3$) 3430, 1745, 1645, 1595, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.90 (m, 1H), 5.45 (q, J = 1.4 Hz, 3H), 4.27 (q, J = 7 Hz, 2H), 2.35 (s, 3H), 2.13 (s, 3H), 1.30 (t, J = 7 Hz, 3H); LRMS *m/z* 171 (M^+).

Methyl 2-methoxy-3-methyl-3-ethoxycarbonylaminobutanoate (**5o**, Z = OC_2H_5). - It was purified by bulb-to-bulb distillation at 60°C (0.5 mmHg); IR (CCl_4) 3440, 1745, 1725, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.12 (broad s, 1H), 4.10 (q, J = 7 Hz, 2H), 4.04 (s, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 1.32 (s, 6H), 1.22 (t, J = 7 Hz, 3H); LRMS *m/z* 233 (M^+ - 15). **Anal.** Calcd for $C_{10}H_{19}NO_5$: C, 51.19, H, 8.21; N, 6.00. Found: C, 51.27; H, 8.33; N, 5.86.

Oxazoline **8**. - It was obtained as an oil from the photochemical addition of N-chlorotrichloroacetamide (**1**, Z = CCl_3) to methoxymethylenecyclohexane (**2g**) followed by the sodium methoxide work-up[3] and PLC; IR ($CHCl_3$) 1660, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.41 (s, 3H).

Photochemical addition of thioacetic acid to ethoxyethylene (**2a**)

To a solution of **2a** (20 mmol) in methylenechloride (30 mL) cooled to -70°C, was added a solution of thioacetic acid (0.76 g, 10 mmol) in methylenechloride (10 mL). The solution was irradiated for 1 h at 254 nm in a Rayonnet RPR-100 reactor. The solution was then allowed to warm-up to room temperature and the solvent removed in a rotatory evaporator. PLC of the crude product (pentane-ether 10:1) afforded *1-ethoxy-2-thioacetylethane* (1.14 g, 80%) as an oil which was

purified by bulb-to-bulb distillation at 60-62°C (25 mmHg); IR 9CCl_4) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (q, J = 7 Hz, 2H), 3.41 and 3.14 (A_2B_2 system, 4H), 2.37 (s, 3H), 1.20 (t, J = 7 Hz, 3H); LRMS *m/z* 73 (M^+ - $COCH_3$). **Anal.** Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63. Found: C, 48.88; H, 8.21; S, 21.09.

Photochemical addition of thioacetic acid to methoxymethylenecyclohexane (**2g**)

The reaction was carried out exactly as described above. PLC of the crude product (pentane-ether 1:1) afforded two fractions. The less polar consisted of *thioacetylcyclohexylmethoxymethane* (**17**) (1.55 g, 77%) which was purified by bulb-to-bulb distillation at 50-32°C (0.1 mmHg); IR (CCl_4) 1685, 1130, 1100, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (d, J = 4 Hz, 1H), 3.35 (s, 3H), 2.38 (s, 3H), 2.0-0.9 (11H); LRMS *m/z* 127 (M^+ - $SCOCH_3$). **Anal.** Calcd for $C_{10}H_{18}O_2S$: C, 59.36; H, 8.97; S, 15.85. Found: C, 59.30; H, 8.93; S, 15.43.

The more polar fraction consisted of *1-methoxymethyl-1-thioacetylcyclohexane* (**16**) as an oil (450 mg, 22%); IR (CCl_4) 1680, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 2H), 3.43 (s, 3H), 2.28 (s, 3H), 2.3-1.0 (10H); LRMS *m/z* 157, 159 (M^+ - CH_2OCH_3). The product underwent decomposition upon bulb-to-bulb distillation at 58-60°C (0.1 mmHg).

Electrophilic chlorination of methoxymethylenecyclohexane (**2g**) *with N-chlorourethane* (**1**, Z=OC_2H_5).

The enol ether **2g** (1.23 g, 10 mmol) in anhydrous methanol (6 mL) was added to a solution of N-chlorourethane (0.64 g, 5 mmol) in chloroform (6 mL) at room temperature. The mixture was stirred in the dark until the KI-starch paper test was negative (5 h). Water (10 mL) was added, the mixture was extracted with ether and the ether partly removed by distillation. The yield of *1-chlorocyclohexanecarboxaldehyde dimethylacetal* (**17**) was determined by VPC (95%) using a pure sample obtained by preparative VPC; IR (CCl_4) 1130, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.18 (s, 1H), 3.60 (s, 6H), 2.0-1.4 (10H). The 2,4-dinitrophenylhydrazone derivative was prepared directly from the acetal **17** and recrystallized from methanol, mp 214-215°C (lit.[36] 220-221°C).

Hydroboration of methoxymethylenecyclohexane (**2g**)

Diborane in THF (5 mmol) was added to a solution of **2g** (0.63 g, 5 mmol) in dry THF (20 mL) cooled to 0°C. The solution was stirred for 30 min at 0°C. Addition of an aqueous solution of sodium acetate (4 mL of a 5 M solution) was followed by the addition of hydrogen peroxide (3 mL of a 30% solution). The mixture was extracted with ether and the organic phases washed with water and dried. The solvent was removed at the rotatory evaporator. The yield of *1-hydroxy-1-methoxymethylcyclohexane* (**18**) was determined by VPC (66%) using a pure sample obtained by preparative VPC; IR (CCl_4) 3560, 3490 cm^{-1}; ^1H NMR 3.58 (s, 3H), 3.23 (s, 2H), 2.17 (s, 1H, exchanged with D_2O), 1.7-1.1 (m, 10H); LRMS *m/z* 99 (M^+ - CH_2OCH_3). The product underwent decomposition upon bulb-to-bulb distillation at 70-75°C (5 mmHg).

Addition of nitrosylchloride to methoxymethylenecyclohexane (**2g**)

A solution of **2g** (505 mg, 4 mmol) in ether (12 mL) cooled to -70°C is treated with nitrosylchloride until the color of the solution changed from blue to yellow. The excess of nitrosylchloride was removed with a stream of nitrogen. Sodium perchlorate (1.25 g, 6 mmol) in anhydrous

methanol (20 mL) and pyridine (5 mmol) were added to the reaction mixture which was stirred for 20 min at -70°C. It was allowed to warm up at room temperature. The organic phase was washed with water, dried and the solvent removed at the rotatory evaporator to give the *dimer* of *1-nitrosocyclohexanecarboxaldehyde dimethylacetal* (**19**), mp 81-82°C (620 mg, 83%). One recrystallization from ether gave the analytical sample, mp 82-83°C; IR ($CHCl_3$) 1560 (dimer), 1450 (monomer), 1290, 1270, 1130, 1090 (sh), 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.48 (s, 1H, monomer), 4.82 (s, 1H, dimer), 3.53 (s, 6H, dimer), 3.42 (s, 6H, monomer), 2.5-1.1 (10H). **Anal.** Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.16; N, 7.48. Found: C, 57.94; H, 9.46; N, 7.39.

Catalytic hydrogenation of the nitroso dimer **19**

The nitroso dimer **19** (204 mg, 1.1 mmol) was added to methanol (20 mL) containing prehydrogenated platinum oxide (20 mg). After stirring for 4 h at room temperature under hydrogen at atmospheric pressure, the hydrogenation stopped. The catalyst was removed by filtration and the solvent was removed at the rotatory evaporator to give *1-hydroxylaminocyclohexanecarboxaldehyde dimethylacetal* (**20**), mp 64-66°C (210 mg, 100%). One recrystallization from pentane gave the analytical sample, mp 67-67.5°C; IR ($CHCl_3$) 3600, 3250, 1100, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) 6.00 (broad s, 2H), 4.32 (s, 1H), 3.58 (s, 6H), 1.9-1.2 (10H). **Anal.** Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.42. Found: C, 57.27; H, 10.41; N, 7.73.

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