FORMATION OF REGIOISOMERIC TETRAHYDROISOXAZOLO[2,3-d][1,4]BENZODIAZEPINES BY KINETIC AND THERMODYNAMIC CONTROLS

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Abstract - 1,3-Dipolar cycloaddition of 1,4-benzodiazepine N-oxide with acrylic esters produces annelated 4- and 5-substituted isoxazolidines. 4-Substituted regioisomers are unstable at higher reaction temperatures and rearrange presumably via a 1,3-dipolar cycloreversion to regenerate 5-substituted derivatives. Structure and stereochemistry of cycloadducts have been assigned by means of ^{1}H nmr spectroscopy assisted by NOE measurements. The experienced regiochemistry has been rationalized according to the electron-rich nature of benzodiazepine nitrones.

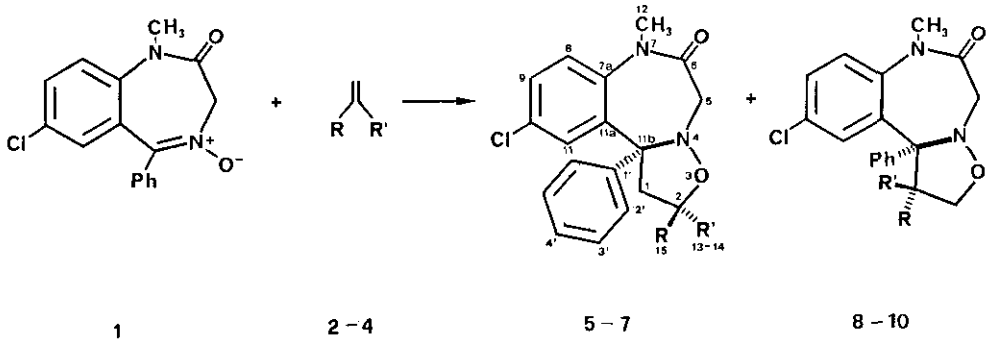
Reaction of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide 1 (diazepam N-oxide) with acrylic esters has been reported to produce annelated substituted isoxazolidines with high regiospecificity[1]. In the adopted experimental conditions, the cycloadducts obtained showed a normal orientation of addition with the alkoxycarbonyl group on C-2, adjacent to the oxygen atom (formation of 5-substituted isoxazolidine). The reaction was found stereoselective; the stereochemistry of the obtained tetrahydroisoxazolobenzodiazepin-2-ones was deduced largely by means of ^{1}H nmr spectroscopy assisted by computer simulation of the lanthanide induced shifts and broadening of the nmr spectral lines. The nature and substitution of the additional heterocyclic nucleus were related to the conformational properties of the new tricyclic system, where a small increase of the conformational rigidity of the seven-membered ring was observed with reference to the precursor diazepam.

Continuing our work on benzodiazepine derivatives[2-6] with regard to the synthesis and stereochemical characteristics of the new obtained derivatives with potential biological activity, we have reinvestigated the reaction pathway of the 1,3-dipolar cycloaddition of benzodiazepinic nitrones, varying the experimental conditions

and reaction period. The regioselectivity experienced in the cycloaddition of benzodiazepine nitrones to propiolates[7] allows, in fact, the electron rich nature of this 1,3-dipole, used in reaction under electronic control, to be defined. Therefore, on the basis of the FMO approach[3], a reversal of regioselectivity to give 4-substituted isoxazolidines must be expected. In this paper we show that the 1,3-dipolar cycloaddition is subject to both kinetic and thermodynamic controls; the regiochemistry of the obtained products can be controlled by the experimental conditions.

RESULTS AND DISCUSSIONS

The reaction of benzodiazepine N-oxide 1 with the electron-deficient alkenes 2-4 (Fig. 1) was performed in the absence of solvent at 70°C to give a mixture of two regioisomeric derivatives whose distribution varied with the reaction period (Table 1).



1 2 – 4 5 – 7 8 – 10

2,5,8 : R = H, R' = COOMe
3,6,9 : R = H, R' = CN
4,7,10: R = Me, R' = COOMe

Figure 1

Attempted cycloaddition reaction in THF or benzene resulted in recovery of the starting materials even at reflux and for prolonged reaction period.

The dramatic steric effects of the phenyl substituent at C-5 in 1 presumably control the rate of cyclization to isoxazolidines of type 5-10. Molecular models indicate, in fact, the existence of steric crowding between the phenyl substituent and the seven-membered ring in the transition state leading to cycloadducts in both the extended and folded conformations, which can be populated by the obtained compounds[1].

Table 1. Cycloadduct ratio at different reaction time.

Reaction Time (h)	8/5 Ratio	Yield (%)	9/6 Ratio	Yield (%)	10/7 Ratio	Yield (%)
3	30/70	54	42/58	60	70/30	50
15	40/60	65	50/50	70	77/23	70
24	50/50	70	60/40	90	97/3	90
48	65/35	80	73/37	90	100	95

The structures of the reported cycloadducts were determined on the basis of ^{1}H and ^{13}C nmr data; the various carbon resonances have been assigned according to the chemical shift theory[8]. DEPT and Jmod pulse sequences allowed for the differentiation of methyl, methylene, methine and quaternary carbon resonances. Tables 2 and 3 summarize the obtained results: ^{1}H nmr spectral parameters of adducts 5 and 7 have been previously reported[1].

The determination of the regiochemistry for the obtained cycloadducts rests primarily on the ^{13}C nmr spectroscopy: the two types of regioisomers 5-7 and 8-10 could easily be distinguished on the basis of the chemical shift values for the carbon of the pentatomic nucleus. These compounds only have two CH_2 groups, C-5 and C-1 in 5-7 or C-2 in 8-10. The ^{13}C nmr spectra of 5-10 all show a $^{13}CH_2$ signal at 57.0 ± 0.5 ppm, at the same place as found for the corresponding C-3 in 1 at 57.0 ppm. In compounds 5-7 the second $^{13}CH_2$ resonance appears at 50.6 ± 3.3 ppm, while in compounds 8-10, the second $^{13}CH_2$ signal is at 67.5 ± 0.5 ppm. These chemical shifts confirm that the second CH_2 group is attached to the more electronegative group in 8-10 compared with 5-7 and support the relative assignments of regioisomers. A similar reversed behaviour is also found for the sp^3 ^{13}CH signal. Thus, on going from 5 to 8, the CH signal moves from 74.5 to 57.0 ppm and on going from 6 to 9 from 63.5 to 44.3 ppm.

^{1}H Nmr spectrum of derivative 8 showed the expected AB pattern for the hydrogens at C-5, at 3.24 and 3.96 ppm (J=9.9 Hz), while the protons at C-2 gave rise to an ABC system which was analyzed by iterative computer fitting in benzene solution (Table 3). A 2D $^{13}C/^{1}H$ heteronuclear correlation experiment confirmed the observed connections, affording a further support to the attributed structure: C-2 is connected with protons at 4.42 and 3.62 ppm, while C-1 is linked to the proton at 3.74 ppm.

Table 2 - ^{13}C Nmr chemical shifts for compounds 5-10

	5	6	7	8	9	10
C-1	47.4	48.5	53.9	57.0	44.3	70.7
C-2	74.5	63.5	81.7	67.1	68.0	67.2
C-5	57.4	56.5	57.0	56.6	56.5	56.8
C-6	172.0	176.0	173.0	170.0	169.4	171.8
C-7a	143.4	142.7	144.7	141.4	141.1	143.9
C-8	126.0	125.9	125.8	126.5	124.9	125.6
C-9	129.5	130.0	129.6	130.0	129.9	130.0
C-10	141.6	141.3	141.6	140.6	140.1	141.0
C-11	127.4[b]	126.6[b]	127.5[b]	128.9[b]	127.8[b]	128.1[b]
C-11a	135.9	135.6	132.8	136.3	134.6	133.1
C-11b	73.8	73.6	74.7	74.3	73.2	74.7
C-12	34.2	34.1	34.0	34.0	33.9	33.9
C-13	165.0	164.4	165.2	164.0	164.4	164.8
C-14	52.6		52.8	51.8		52.4
C-15			26.6			26.8
C-1'	132.2	132.2	135.9	132.0	132.0	135.7
C-2'	125.5[a]	125.0[a]	125.5[a]	127.3[a]	126.1[a]	125.9[a]
C-3'	128.8[a]	128.9[a]	128.6[a]	127.9[a]	128.4[a]	128.4[a]
C-4'	128.0[b]	127.9[b]	128.1[b]	128.0[b]	127.1[b]	127.9[b]

[a] May be interchanged.

[b] May be interchanged.

The assignment of stereochemistry to compound 8 was based on ^{1}H nmr lanthanide probe analysis which also supported the results concerning the regiochemistry of the product. For methylene protons at C-2, the downfield resonating one is deshielded by the cis COOMe group, while the pseudoaxial proton at C-1 is cis to 11b-Ph. NOE experiments confirmed the results: a relevant enhancement of the signal at 4.42 ppm was observed by irradiation of COOMe protons, while no positive NOE for this resonance was detected when CH-1 was irradiated.

On the same basis, consideration of both computer simulation of ^{1}H nmr lanthanide-induced shifts and NOE experiments allows to define unambiguously the stereo-

chemistry of the other adducts obtained. In all cases, the ABC systems for the pentatomic ring protons have been simulated using an iterative computer fitting; 2D $^{13}C/^{1}H$ heteronuclear correlations confirmed the attributed structures.

Table 3. ^{1}H Nmr spectral data[a] of 10-chloro-7-methyl-11b-phenyl-1,2,7,11b-tetrahydroisoxazolo[2,3-d][1,4]benzodiazepin-6(5H)-ones 6, 8-10

Assignment	6 δ(ppm) [J(Hz)]	8 δ(ppm) [J(Hz)]	9 δ(ppm) [J(Hz)]	10[c] δ(ppm) [J(Hz)]
NMe	2.43s	2.24s	2.05s	2.38s
5-CH_2[b]	4.02d [-10.1] 3.22d	4.10d [-10.1] 3.15d	4.03d [-8.8] 2.99d	3.98d [-9.7] 3.28d
1-CH_2[d]	3.64dd [Jgem -14.0] 2.86dd [Jcis 8.9] [Jtrans 5.7]			
2-CH	4.89dd			
O-CH_3		2.86s		3.52s
C-CH_3				1.60s
2-CH_2[e]		4.42dd [Jgem -8.6] 3.62dd [Jcis 5.6] [Jtrans 7.9]	3.43dd [Jgem -9.0] 3.32dd [Jcis 6.0] [Jtrans 8.0]	4.38d[f] [-10.8] 4.20d
1-CH		3.74dd	3.75dd	

[a] s= singlet; d= doublet; dd= doublet of doublet; t= triplet; q= quartet; m= multiplet.

[b] The higher field resonance corresponds to the pseudoaxial proton, shielded by the fused benzene ring.

[c] In $CDCl_3$ solution.

[d] LIS data suggest that the higher field resonating proton is cis to 11b-Ph:presumably the C-1 trans-hydrogen atom is deshielded by the condensed benzene nucleus.

[e] LIS and NOE data indicate that the downfield resonating proton is cis to R' and trans to 11-Ph.

[f] The higher field resonance is cis to 11b-Ph and 1-CH_3.

For compound 6, the C-1 higher field resonance corresponds to the pseudoaxial proton, shielded by the fused benzene ring, which is also cis to CN group at C-2.

For regioisomer 9, proton at C-1 and 11b Ph occupy pseudoaxial positions, while the downfield resonating proton at C-2 and CN group are syn on the five-membered ring. The 4-substituted regioisomer 10, obtained as the minor product of the cycloaddition reaction together with the previously reported derivative 7, shows the methyl group at C-1, the 11b-phenyl and the C-2 higher field resonance in a cis relationship. Again, a combination of LIS data and NOE measurements supports the assigned configuration.

The regioisomeric distribution of the obtained cycloadducts changes with the reaction period (Table 1). For couples 5/8, 6/9, and 7/10, at longer reaction time and higher temperatures, 5-substituted isoxazolidines become predominant. Direct conversion of 4-substituted isoxazolidine derivatives into 5-substituted ones is effected and completed in 24 h at 85°C.

The isomerization proceeds presumably via a 1,3-dipolar cycloreversion[9] (Fig. 2).

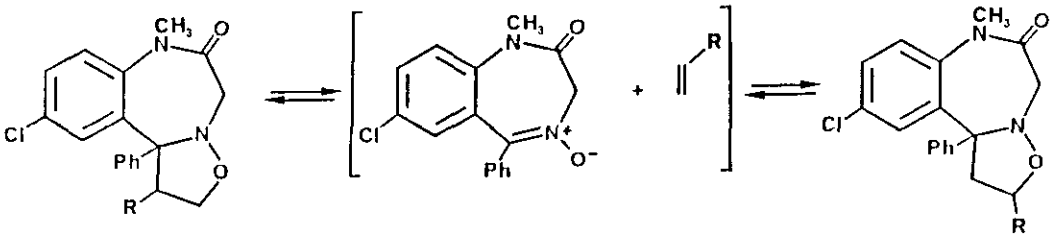


Figure 2

Retroaddition reactions previously have been observed for both intermolecular[10,11] and intramolecular[12] nitrone-olefin cycloadditions. Furthermore, LeBel and coworkers have provided an explanation of the variable distribution of isomeric isoxazolidines resulting from nitrone cycloadditions[13]. The rationale is based on a consideration of transition states resulting from both syn and anti configurations of the intermediate nitrone. The relevant stability of benzodiazepinic nitrone plays an important role in driving the thermal behaviour of isoxazolidines towards the 1,3-dipolar cycloaddition instead of the fragmentation of the weak N-O bond[14]. The cycloadducts ratio (4- vs 5-substituted isoxazolidines) reflects the relative thermodynamic stability of the regioisomers 5-10. 4-Substituted derivatives are formed under kinetic control, while the observed thermal isomerization is controlled by thermodynamic factors which favour the formation of 5-substituted regioisomers.

The regioselectivity in these reactions has been rationalized by use of the frontier-orbital theory[8]. It has been observed that the amount of 4-substituted isoxazolidines in general depends not only on the nature of the alkene but also on that of the nitrone. With electron-poor dipolarophiles, as the alkenes at hand, the proportion of the 4-substituted products increases as the nitrone becomes more electron-rich. As reported[7], the 1,4-benzodiazepinic nitrone studied has the chemical behaviour of an electron-rich 1,3-dipole; the electron-donating effect is due to the disubstitution on the C-terminus of the 1,3-dipole and also to the amide functional group enhancing the effect through the electron-releasing conjugation experienced on the nitrone function of the molecule via the aromatic ring. On this basis, in the examined cycloadditions, the HOMO dipole interaction competes effectively with the alternative one; a stronger interaction with the polarized LUMO of alkenes 2-4, having FMO shapes whose difference on the carbon atoms of the reacting system favours the formation of the more stabilized transition state for the 4-substituted regioisomer, leads preferentially to 8 and 9 derivatives. In the reported reactions, performed under kinetic control, the electronic factors override any steric effect which might favour 5-substituted regioisomers.

The thermal isomerization of 4-substituted adducts into the 5-substituted ones reveals, on the contrary, the important effect of steric factors. At higher reaction temperature, under thermodynamic control conditions, derivatives 5-7 become dominant in the reaction mixture: the 5-substituted isoxazolines are, in fact, favoured on the basis of steric factors as the nitrone reagent is fully substituted at the C-terminus. The regioselectivity is now influenced by the steric restrictions which overcome the electronic factors: the steric compression of isoxazolidine nucleus in 8-10 accounts well for the observed isomerization of 4- into 5-substituted derivatives.

The relevant importance of steric factors in these 1,3-dipolar cycloadditions is further supported by the regioisomeric distribution experienced for the couple 7/10. The less sterically hindered derivative 7 is always the predominant one also when the reaction is performed under kinetic control conditions.

In conclusion, the reaction of benzodiazepine nitrone 1 with electron-deficient alkenes 2-4 proceeds with complete stereoselectivity. On the contrary, the regioselectivity is dependent on the experimental conditions: longer reaction times and higher temperatures afforded exclusively thermodynamic 5-substituted regioisomers.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage and are uncorrected. Elemental analyses were performed on a Perkin Elmer 240 elemental analyzer. IR spectra were recorded on a Perkin Elmer 225 and nmr spectra on a Bruker WP 80 SY spectrometer for $CDCl_3$ or C_6D_6 solutions with TMS as internal standard. The Bruker iterative spin simulation program PANIC 82 was used on an Aspect 2000 computer to fit the observed NMR spectra, as stated in the text. For LIS measurements, series of spectra were obtained at constant substrate concentration (0.4 M) by the incremental dilution method[15]; $Eu(fod)_3$ was used as lanthanide shift reagent. The proton NOE measurements were made by the FT difference method[16]. Compounds 5 and 7 have been already reported[7]. Mass spectra were measured on a Hewlett Packard mod. 5995 GC/MS.

Cycloaddition reactions of diazepam N-oxide (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one N-oxide) with acrylic derivatives. - The general procedure is as follows. Diazepam-N-oxide 1 and an excess (30:1) of acrylates were heated under nitrogen; the reaction was monitored by tlc with ether as an eluent. When no further increase in the amount of reaction products could be observed by GC/MS, the excess of dipolarophile was distilled off under reduced pressure and the residue worked up with ether to allow the crystallization of unchanged compound 1. The residual ethereal solution was then concentrated and the cycloadducts separated by column chromatography with ethyl acetate-light petroleum 1:1 as an eluent.

10-Chloro-2-cyano-7-methyl-11b-phenyl-1,2,7,11b-tetrahydroisoxazolo[2,3-d][1,4]-benzodiazepin-6(5H)-one 6

White crystals, mp 181-182° C; ir: 2250, 1680, 1600 cm^{-1}. Found: C,64.6; H, 4.4; N, 12.0. $C_{19}H_{16}ClN_3O_2$ requires: C, 64.5; H, 4.6; N, 11.9.

10-Chloro-1-methoxycarbonyl-1,2,7,11b-tetrahydro-7-methyl-11b-phenylisoxazolo-[2,3-d][1,4]benzodiazepin-6(5H)-one 8

White crystals, mp 150-152° C; ir: 1725, 1680, 1670 cm^{-1}. Found: C, 62.4; H, 5.1; N, 7.1. $C_{20}H_{19}ClN_2O_4$ requires C, 62.1; H, 5.0; N, 7.2.

10-Chloro-1-cyano-7-methyl-11b-phenyl-1,2,7,11b-tetrahydroisoxazolo[2,3-d][1,4]-benzodiazepin-6(5H)-one 9

White crystals, mp 75-77° C; ir: 2250, 1680, 1600, 1570 cm^{-1}. Found: C, 64.2; H, 4.7; N, 11.7. $C_{19}H_{16}ClN_3O_2$ requires C, 64.5; H, 4.6; N, 11.9.

10-Chloro-1-methoxycarbonyl-1,7-dimethyl-11b-phenyl-1,2,7,11b-tetrahydroisoxazolo-[2,3-d][1,4]benzodiazepin-6(5H)-one 10

White crystals, mp 169-171° C; ir: 1740, 1680, 1590 cm^{-1}. Found: C, 62.7; H, 5.7; N, 7.2. $C_{21}H_{21}ClN_2O_4$ requires C, 62.9; H, 5.3; N, 7.0.

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