1,3-DIPOLAR CYCLOADDITIONS OF FIVE AND SIX MEMBERED CYCLIC NITRONES TO α,β-UNSATURATED ACID DERIVATIVES

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Abstract - The cycloadditions of 3,4-dihydro-2*H*-pyrrole 1-oxide, 3,4,5,6-tetrahydropyridine 1-oxide, and (*S*)-3,4-dihydro-2-hydroxymethyl-2*H*-pyrrole 1-oxide to α,β-unsaturated acid derivatives have been reviewed. As *Z*-olefins, several five, six, and seven membered lactones with different functionalization at the γ-position were employed. As *E*-olefins, γ-hydroxy-, γ-alkoxy-, and γ-oxo-α,β-unsaturated esters have been incorporated to this study. Steric factors play a very important role in the regio- and stereochemical outcome of these 1,3-dipolar cycloadditions. *cis*-Olefins yield products derived mainly from an *exo* transition state, while the cycloadducts of *trans*-olefins result mainly from *endo* approaches.

INTRODUCTION

One of the most important reactions leading to heterocycles is the 1,3-dipolar cycloaddition, a concept introduced by Huisgen[1] in the mid of this century and used since then by thousands of chemists. The great variety of heteroatoms and combinations of them that can be present in the 1,3-dipole as well as in the dipolarophile opens the way to a wide number of heterocycles. Although the reaction parallels the Diels-Alder cycloaddition, it is much more scope wide. In this sense it has been thoroughly studied both theoretically and mechanistically: regiochemistry and stereochemistry being the highlights of these studies.[2] In addition, during the last years the asymmetric 1,3-dipolar cycloadditions have received much attention.[3]

The cycloaddition of nitrones to olefins is a widely used method for the preparation of isoxazolidines.[2,4] Great advantages of employing this reaction are the high regio- and stereoselectivity often achieved in the process and the synthetic versatility of the adducts which can be readily converted into cyclic or acyclic polyfunctionalized compounds.

After exploring exhaustively the use of 2(5*H*)-furanones (α,β-butenolides) as dienophiles in Diels-Alder reactions,[5] we initiated in 1989 a study of the reaction of these olefins as dipolarophiles in front of cyclic nitrones, as part of a program on alkaloid synthesis, mainly of the *Securinega* type. Later on, this work was expanded to other α,β-unsaturated lactones and *trans*-α,β-unsaturated esters. At that time, very few cases of 1,3-dipolar cycloadditions using α,β-butenolides, including only one example with nitrones, had been described.[6] Moreover, the precise regiochemistry of the cycloaddition of nitrones to different

electron demanding olefins, as well as their complete stereochemical details, were almost unknown. Difficulties for this comprehension were the establishment of the *endo/exo* and diastereofacial selectivity of the reaction, too much dependent on the cyclic or acyclic nature of both the dipole and the dipolarophile, and the correct assignment of the relative stereochemistry present in the formed adducts.
In this review we give a summary of all the work done in our laboratories in this field during the last decade, dealing mainly with the reaction of simple cyclic nitrones as 3,4-dihydro-2*H*-pyrrole 1-oxide (**1**) and 3,4,5,6-tetrahydropyridine 1-oxide (**2**) with α,β-unsaturated acid derivatives, either in permanent cyclic *Z*-configuration (α,β-unsaturated lactones) or in open chain *E*-configuration, with an allylic substituent (Figure 1). We have also performed several cycloadditions with **3**, a substituted enantiopure five membered cyclic nitrone. The results are summarized in Tables 1-7, where the dipolarophiles are numbered. There are three main aspects of the cycloaddition reactions which influence the structural features of the cycloadducts: the regio-, the *endo/exo*- and the diastereofacial selectivity. In the following discussion these three issues are addressed consecutively. The stereoselectivity of the reaction may only be established provided that the stereochemistry of the cycloadducts is unambiguously assigned. Quite often this assignment requires a detailed conformational study. Therefore, in this review we have also included some comments on the conformational trends of the isoxazolidinic adducts.

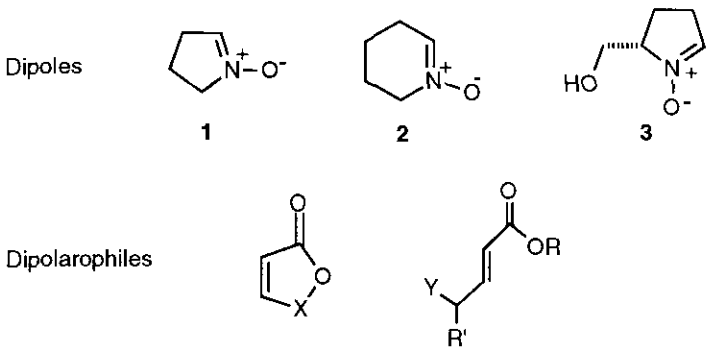


Figure 1

REGIOSELECTIVITY

The dominant FMO interaction for the addition of a nitrone to an electron-poor olefin is HOMO(dipole)-LUMO(dipolarophile).[2,4] Nevertheless, since the HOMO terminal coefficients of the nitrone are very similar, it has been suggested that its LUMO, with a much larger coefficient on the carbon atom, controls the regioselectivity in some cases.[19] Cycloadditions of monosubstituted electron-deficient olefins with nitrones give rise to mixtures of 4- and 5-substituted isoxazolidines, the process lacking of regioselectivity. Much luckily, when 1,2-disubstituted olefins, in which one of the substituents is an electron-withdrawing group, are used as the dipolarophile component, a high regioselectivity is usually observed that favors the isoxazolidine adducts with the electron-withdrawing substituent attached to the 4-position. This regioselectivity has been observed in almost all our cases with nitrones (**1**-**3**), independently that the dipolarophile be an α,β-unsaturated ester or a lactone. Even if another electron-withdrawing group, mainly a ketone, is present at the β-position of the acrylic moiety, the ester group

Table 1. Cycloadditions of nitrone (**1**) to unsaturated lactones.

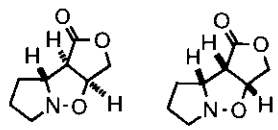
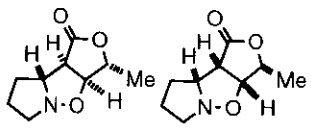
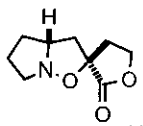
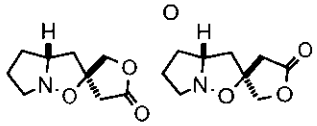
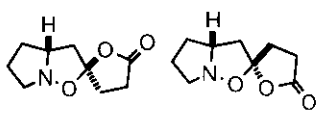
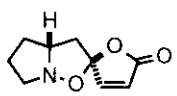
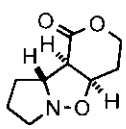
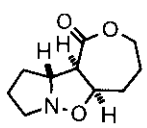
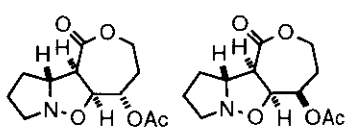
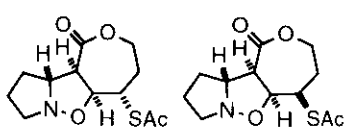
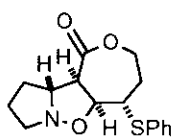
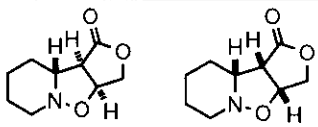
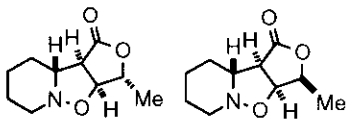
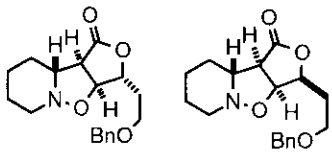
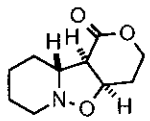
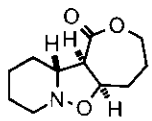
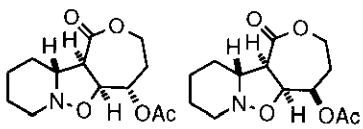
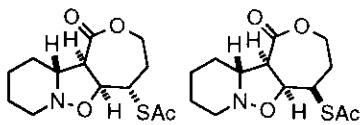
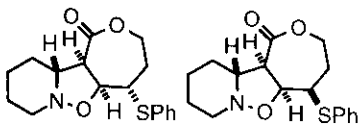
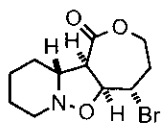
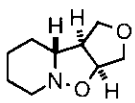
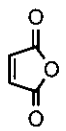
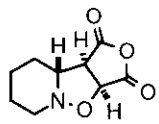
Entry	Dipolaroph.	Conditions	Global yields (%)	*exo/endo*	*exo anti/syn*	Main adducts	Ref.
1	**4**	20 °C, 40 d 110 °C, 2 h	74 84	7 3	- -		6,7
2	**5** (Me)	20 °C, 40 d 110 °C, 3 h	70 85	6 3	11 4		7
3	**6**	60 °C, 1 h	96	<0.02	-		8
4	**7**	60 °C, 16 h	35	-	-		8
5	**8**	60 °C, 14 d	55	-	-		8
6	**9**	60 °C, 4 h	52	0.04	-		8
7	**10**	20 °C, 82 d 110 °C, 22 h	73 88	>50 43	- -		7
8	**11**	20 °C, 180 d 110 °C, 4 h	22 69	>50 23	- -		7
9	**12** (AcO)	110 °C, 4 d	91	>50	6		9
10	**13** (AcS)	110 °C, 4 h	53	>50	2.5		9
11	**14** (PhS)	110 °C, 19 h	77	76	10		9

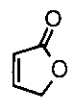
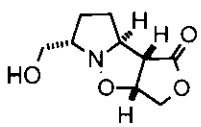
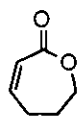
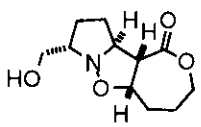
Table 2. Cycloadditions of nitrone (**2**) to unsaturated lactones.

Entry	Dipolarop.	Conditions	Global yields (%)	*exo/endo*	*exo anti/syn*	Main adducts	Ref.
1	**4**	4 °C, 30 d 110 °C, 15 h	90 79	31 6	- -		10
2	**5** (Me)	40 °C, 17 h 110 °C, 15 h	73 84	21 7	8 2		11
3	**15** (BnO)	25 °C, 18 d 110 °C, 9 h	70 79	>50 14	10 6		10
4	**10**	20 °C, 13 d 110 °C, 15 h	86 85	>50 >50	- -		10
5	**11**	20 °C, 24 d 110 °C, 9 h	31 59	>50 >50	- -		10, 12
6	**12** (AcO)	100 °C, 2 h	98	>50	3		13
7	**13** (AcS)	100 °C, 1.5 h	96	>50	4		13
8	**14** (PhS)	110 °C, 9 h	80	>50	9		9
9	**16** (Br)	100 °C, 5 h	70	>50	>50		13
10		20 °C, 7 d	44	-	-		10
11							10, 14

leads the regiocontrol, being always attached at the 4-position of the adduct.

Examples of this high regioselectivity can be seen in Tables 1-7 (where reaction products in the cycloadditions of nitrones (**1-3**) to different sized α,β-unsaturated lactones and esters are given). However three exceptions to this general trend have been found: i) the reaction has poor chemoselectivity with methyl sorbate, although the regioselectivity is still as expected; a complex mixture of cycloadducts formed on the α,β and γ,δ double bonds as well as 2:1 adducts are obtained with nitrone (**2**);[11] ii) the trisubstituted olefin methyl 2-methyl-4-oxo-2-pentenoate (**26**) gives rise, in excellent yields, to "abnormal" cycloadducts with nitrones (**1**) and (**2**) (Table 6, Entry 4 and Table 7, Entry 5); iii) the exocyclic double bond of α-methylene-γ-butyrolactone (**6**) also reacts with nitrone (**1**) (Table 1, Entry 3) with an "abnormal" regiochemistry giving, in 96% yield, (3*RS*,3a'*SR*)-hexahydrospiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazol]-2-one. Similar results are obtained with the non-conjugated exocyclic double bonds present in β-methylene-γ–butyrolactone (**7**) and γ-methylene-γ-butyrolactone (**8**) (Table 1, Entries 4 and 5), and with the conjugated exocyclic double bond present in protoanemonin (**9**) (Table 1, Entry 6). Moreover, in this last example we can observe that the exocyclic double bond of **9** reacts with nitrones faster than the endocyclic, an observation that parallels previous findings with nitrile oxide[20] and Diels-Alder reactions.[5]

Table 3. Cycloadditions of nitrone (**3**) to unsaturated lactones.

Dipolarop.	Conditions	Global yields (%)	*exo/endo*	*exo anti/syn*	Main adducts	Ref.
4 	110 °C, 18 h	45	>50	>50		15
11 	110 °C, 26 h	45	>50	>50		15

The results so far obtained seem to indicate that in these reactions electronic effects are overwhelmed by steric interactions. The less sterically demanding oxygen end of the nitrone always links to the more crowded carbon atom of the olefin. This would explain the inversion of regioselectivity observed with compounds (**6**), (**9**), and (**26**).

All the cycloadducts derived from nitrones (**1**) and (**3**) contain in their structure the perhydropyrrolo[1,2-*b*]isoxazole system, which presents exclusively the *cis* fusion. A careful examination of the coupling constants of this set of adducts allows to determine the preferred envelope conformation of the isoxazolidine ring, which depends on the number and nature of the substituents allocated in the *c*-position of the heterocycle (Figure 2). The work performed with dipole (**1**) has conducted to describe the first examples of the following heterocyclic skeletons: spiro[furo-3(2*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole] (Table 1, Entries 3 and 4), spiro[furo-2(3*H*),2'(3'*H*)-pyrrolo[1,2-*b*]isoxazole] (Table 1, Entries 5 and 6), pyrano[3,4-*d*]pyrrolo[1,2-*b*]isoxazole (Table 1, Entry 7), and oxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazole

(Table 1, Entries 8-11).

In the reactions performed with nitrone (**2**) the cycloadducts formed contain a perhydroisoxazolo[2,3-*a*]pyridine, system which may exist in solution as a mixture of a rigid *trans* and two flexible *cis* conformers, due to both nitrogen and six membered ring inversion processes (Figure 2). An accurate conformational analysis based on NMR data demonstrates that the value of the vicinal coupling constant J_{ab} is definitive for the stereochemical assignment only in a few cases. When using α,β-unsaturated lactones as dipolarophiles, important differences in the conformational behaviour of these adducts in solution have been found, depending on the lactone ring size. Looking for an explanation to this observation, we also studied the cycloadducts derived from 2,5-dihydrofuran and maleic anhydride (Table 2, Entries 10 and 11). The results obtained point out to the existence of an attractive interaction between the nitrogen lone pair and the carbonyl group of the lactone moiety, which induces the preference for *cis* conformer **B** in the adducts derived from α,β-butenolides (Table 2, Entries 1-3), while *trans* invertomer **A** predominates in all the other cases, where the distance between the nitrogen lone electron pair and the carbonyl group is too large. Moreover, these tricyclic systems adopt in the solid state the preponderant conformation observed in solution.[21] The cycloadditions of **2** to α,β-unsaturated lactones has conducted to prepare the first compounds containing the following heterocyclic skeletons: pyrano[3',4':4,5]isoxazolo[2,3-*a*]pyridine (Table 2, Entry 4) and oxepino[3',4':4,5]isoxazolo[2,3-*a*]pyridine (Table 2, Entries 5-9).

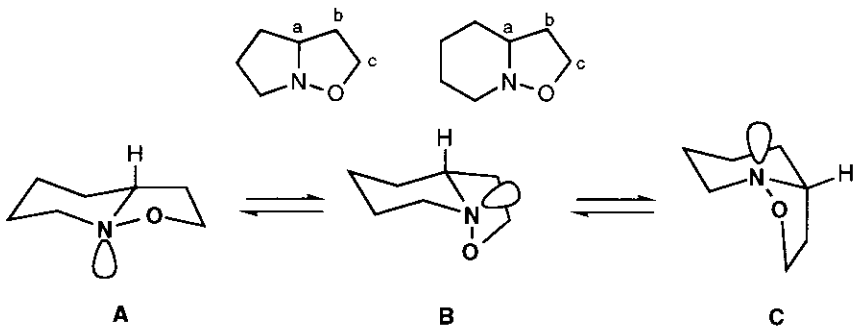


Figure 2

ENDO/EXO SELECTIVITY

The dipole can approach the dipolarophile in the transition state in an *endo* or *exo* mode affording diastereoisomeric products that can be followed through the relative stereochemistry of protons *a* and *b* of the isoxazolidine ring, *i.e. trans* for the *exo* adducts and *cis* for the *endo* (See Tables for the relative geometry of these protons). *Endo* and *exo* approaches are referred to the ester group of the dipolarophile. Cyclic nitrones, incapable of *E/Z* isomerization, are "frozen" 1,3-dipoles and this fact ensures the correlation of the final diastereoisomeric products with their corresponding transition states. The stereochemical assignment has been performed mainly using two dimensional NMR techniques and has been published elsewhere;[7,8,10,12,16,17] we will not present in this review prove of the assignments and they will be given as granted.

The α,β-unsaturated lactones, *cis*-olefins, give preferentially *exo* adducts. The cycloadditions run under

Table 4. Cycloadditions of nitrone (**1**) to γ-oxy-α,β-unsaturated esters.

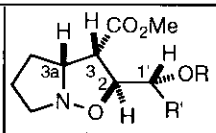
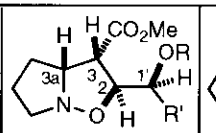
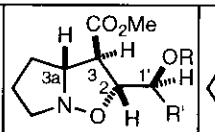
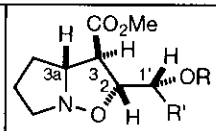
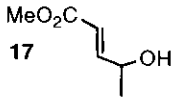
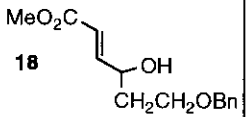
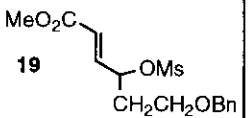
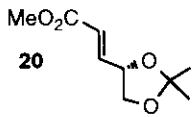
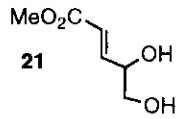
Entry	Dipolarophile	Conditions	Global Yields (%)	 *endo-erythro*	 *endo-threo*	 *exo-erythro*	 *exo-threo*	*endo/exo*	Ref.
1	 **17**	60 °C, 40 h	89	28	57	≈3	≈1	>20	16
2	 **18**	60 °C, 2 d	84	60	22	≈1	≈1	>40	16, 17
3	 **19**	60 °C, 2 d	81	59	18	≈2	≈2	≈20	16
4	 **20**	60 °C, 2 d	86	70	14	≈1	≈1	>40	16, 17
5	 **21**	60 °C, 1 d	85	34	49	≈1	≈1	>40	16

Table 5. Cycloadditions of nitrone (**2**) to γ-oxy-α,β-unsaturated esters.

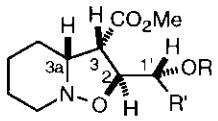
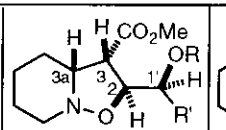
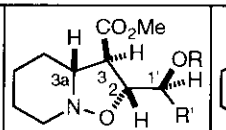
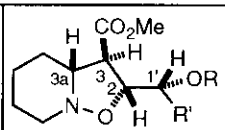
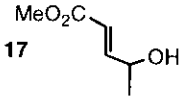
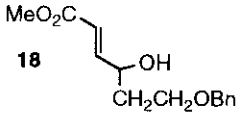
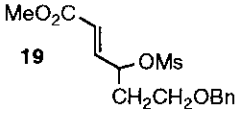
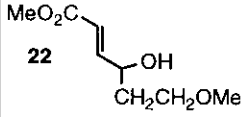
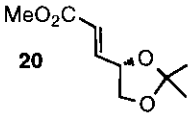
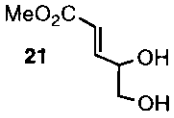
Entry	Dipolarophile	Conditions	Global Yields (%)	 *endo-erythro*	 *endo-threo*	 *exo-erythro*	 *exo-threo*	*endo/exo*	Ref.
1	 **17**	20 °C, 20 h	94	33	37	5	19	3	16
2	 **18**	20 °C, 2 d	92	52	22	4	14	4	16, 17
3	 **19**	20 °C, 4 d	88	48	20	8	12	3.5	16
4	 **22**	20 °C, 2 d	78	44	23	≈1	10	6	16
5	 **20**	20 °C, 20 h	93	50	26	≈5	12	4.5	16
6	 **21**	20 °C, 3 d	94	35	42	4	13	4.5	16

Table 6. Cycloadditions of nitrone (**1**) to γ-oxo-α,β-unsaturated esters.

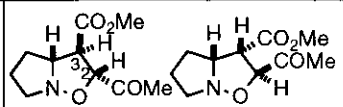
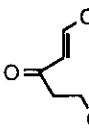
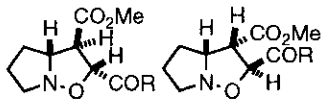
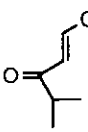
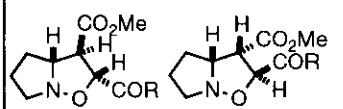
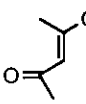
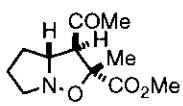
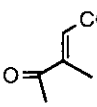
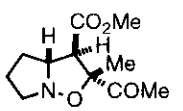
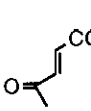
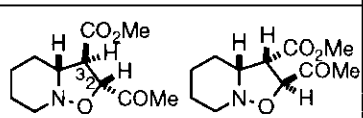
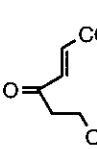
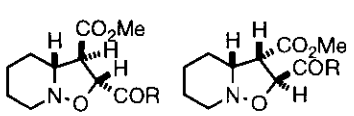
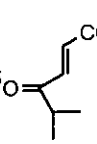
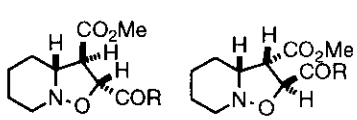
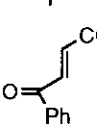
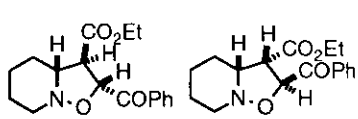
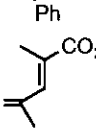
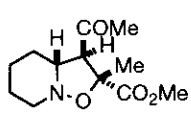
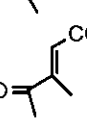
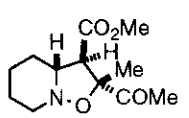
Entry	Dipolarophile	conditions	Global yields (%)	*exo*-ester/ *endo*-ester	ester/acyl at C-3	Main adducts	Ref.
1	**23** 	rt, 3 d 110 °C, 10 h	87 80	2 1.1	21 17		18
2	**24** 	rt, 2 d	87	3	> 30		18
3	**25** 	rt, 3 d	81	3	> 30		18
4	**26** 	rt, 14 d	87	-	< 0.02		18
5	**27** 	rt, 14 d	86	> 50	> 50		18

Table 7. Cycloadditions of nitrone (**2**) to γ-oxo-α,β-unsaturated esters.

Entry	Dipolarophile	conditions	Global yields (%)	exo-ester/ *endo*-ester	ester/acyl at C-3	Main adducts	Ref.
1	**23** 	rt,18 h 110°C, 6 h	90 88	1.1 13	5.4 21		18
2	**24** 	rt, 18 h 110 °C, 15 h	87 83	1.1 12	4.8 11		18
3	**25** 	rt, 18 h	85	1.2	9.5		18
4	**28** 	rt, 16 h	81	1.3	6.4		18
5	**26** 	rt, 18 h	91	-	< 0.02		18
6	**27** 	rt, 18 h	90	> 50	> 50		18

kinetic control, giving rise mainly to the adduct that was also expected to be more stable. No thermodynamic control operates in any reaction (except when it is indicated) as it has been proved by boiling at reflux in toluene for 24 hours all the *endo* stereoisomers obtained: always unchanged products were found. At room temperature or lower, nitrones (**1**) and (**2**) react slowly with these dipolarophiles, but leaving time to the reaction, sometimes months, good yields of the *exo* adducts are isolated. At higher temperatures (up to 110 °C) the reactions become faster, but still *exo* adducts are predominant. This means that there is no crossing of the reaction coordinates.

However some comments have to be done. From the results of Tables 1 and 2 it can be deduced that the reactivity of the lactones diminishes with the increasing of its ring size, and therefore the cycloadditions with the seven membered lactones were performed at higher temperatures. The low dipolarophilic activity of these medium sized lactones may be related to the less efective conjugation of the unsaturated system due to a lack of planariry and evidenced by the small chemical shift differences between their olefinic protons.[9,10,12,13] Nitrone (**1**) is clearly less reactive than nitrone (**2**), both with *cis*- and *trans*-olefins. With the *cis*-dipolarophiles, **1** is also less selective with respect to the *endo/exo* approaches. In the *endo* transition state both substituents of the *cis*-olefin present steric repulsion with the dipole, that overwhelms the possible stabilization by secondary orbital interactions or electrostatic effects,[22] resulting in a predominance of the *exo* adducts (Figure 3). For the six membered nitrone (**2**) the *exo* selectivity is still higher, since the competitive *endo* transition state will be more crowded than in the case of **1**, due to the pseudoaxial hydrogen atoms of the former pointing to the olefin moiety.

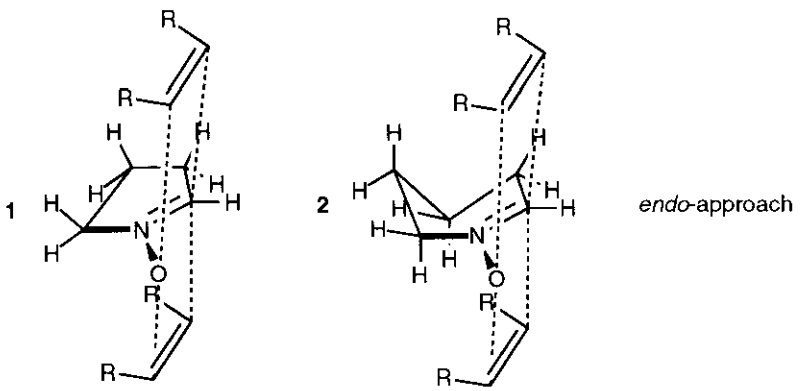
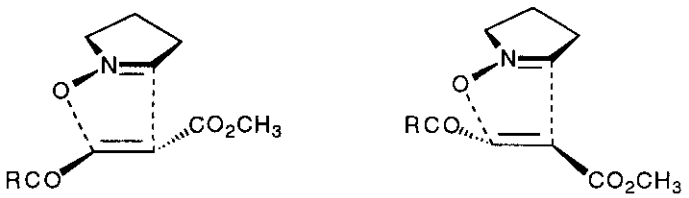


Figure 3

With *trans*-1,2-disubstituted olefins (or better β-substituted acrylic esters) the *exo/endo* selectivity depends strongly on the chemical nature of the β-substituent (Tables 4-7). Nitrone (**1**) gives almost exclusively *endo* diastereoisomers when this group in the acrylic ester is an alkyl chain (Table 4). Nitrone (**2**) is not so selective, but still *endo* stereoisomers predominate in a ratio of 3:1 or higher (Table 5). We have used mainly 1-oxygenated alkyl substituents for ulterior synthetic strategy reasons, but the argument that follows will not be affected for it. *Endo* transition states in these reactions have the quite small methoxycarbonyl moiety lying directly above/below the nitrone ring (*i.e.* they may benefit of favorable electrostatic effects or secondary orbital interactions[22]) and the β-grouping lies far away of

steric hindrances. *Exo* transition states must overcome the steric hindrance among the nitrone ring and the β-alkyl chain, without any electronic stabilization. Therefore, with these *E*-dipolarophiles *endo* transition states are preferred yielding the probably more stable diastereoisomers.

However when the β-substituent in the acrylic ester is an acyl group (Tables 6 and 7), there is very low *endo/exo* stereoselectivity, at least under kinetic control (room temperature). Both approaches can present favorable electronic interactions either with the ester or the keto group in *endo* position. In all these cases a slight preference for the formation of the *exo*-ester *versus* the *endo*-ester isomer is observed. When the ester is *endo* oriented it lies directly above/below the methylene group adjacent to the carbon atom of the dipole (Figure 4). If the ester group is *exo* oriented the acyl substituent lies away from the nitrone ring. Since both competitive transition states benefit from a favorable electronic interaction, the observed preference must be explained considering mainly steric factors.



endo-ester *exo*-ester

Figure 4

We have proved that at higher temperatures the cycloadditions with the γ-oxo esters follow a thermodynamic control: pure samples of a single cycloadduct heated at 110 °C afford mixtures of all the cycloadducts obtained at this temperature, in which the more thermodynamically stable stereoisomer predominates. The adducts derived from nitrone (**1**) present a flexible isoxazolidine ring and the substituents at C-2 and C-3 can always be accomodated in pseudoequatorial positions. Therefore both adducts with the ester group at C-3 must have similar stabilities and the corresponding reactions under thermodynamic control give similar regio- and stereoselectivities than those run under kinetic control (Table 6, Entry 1). For nitrone (**2**) the *exo*-ester selectivity, as well as the regioselectivity, are dramatically improved under thermodymanic conditions (Table 7, Entries 1 and 2). The greater stability of the main adduct may be due to the fact that in its preferred rigid *trans*-fused invertomer both substituents at C-2 and C-3 are allocated in pseudoequatorial positions.

DIASTEREOFACIAL SELECTIVITY

When a substituent is present at the γ-position of the dipolarophile or at an sp^3 carbon atom of the nitrone ring an additional set of diastereoisomers can be produced in the cycloaddition process due to this new stereogenic centre.

With cyclic α,β-unsaturated lactones one can talk of an *anti/syn* selectivity depending on the relative stereochemistry between this γ-substituent and the hydrogen atom at *c*-position of the adduct (See Tables for the relative geometry of these substituents). *Anti* stereoisomers are highly predominant, evidently due

to steric reasons, although the reaction is not so stereoselective as the Diels-Alder cycloadditions performed by ourselves with these kind of lactones.[5] For instance, at room temperature nitrones (**1**) and (**2**) react with β-angelica lactone (**5**) (Tables 1 and 2, Entry 2) giving up to *anti* diastereoisomers in approximately 10:1 ratio respect to the *syn* products. But, at 110 °C this stereoselectivity decreases considerably. Diels-Alder cycloadditions with the same lactone give almost exclusively *anti* adducts even at 210 °C. However, when the γ-substituent is large enough (e.g. bromine atom, as in Table 2, Entry 9) also only the *anti* adduct is formed in the herein studied 1,3-dipolar cycloadditions.

With *trans* open chain olefins, *i.e.* (*E*)-γ-oxy-α,β-unsaturated esters, the γ-stereogenic centre also induces stereoselection, but now the stereoisomers are defined by the relative stereochemistry between the hydrogen linked to the carbon atom *c* of the isoxazolidine ring and the hydrogen of this γ-stereogenic centre, giving rise to *erythro* or *threo* adducts. To rationalise the stereochemical outcome of 1,3-dipolar cycloadditions of nitrile oxides to allylic ethers and alcohols, Houk[23] developed a transition-state model, that was later extended to nitrone cycloadditions. According to this work the *inside alkoxy* and the *outside alcohol effects* are responsible for the predominance of *erythro* or *threo* stereochemistries of the cycloadducts, starting with allylic ethers and alcohols, respectively: alcohols benefit from hydrogen bonding with the oxygen atom of the dipole in the transition state. This model can explain the results shown in the Tables 4 and 5 where the cycloadducts formed in the reactions of nitrones (**1**) and (**2**) with different (*E*)-γ-functionalised α,β-unsaturated esters are indicated: *threo* configurations predominate when free allylic alcohols are used as substrates and *erythro* configurations when the allylic oxygen is protected. However, when the allylic alcohol can form an intramolecular hydrogen bond with another oxygen present in the molecule, as is the case for dipolarophiles (**18**) and (**22**) (Table 4 Entry 2 and Table 5, Entries 2 and 4), *erythro* configurated cycloadducts are mainly obtained in ratios ≈2.5:1. The typical alcohol selectivity shown by diol (**21**) (Table 4, Entry 5 and Table 5, Entry 6) can be attributed to the fact that this olefin is able to form simultaneously intra- and intermolecular hydrogen bonds in the transition state. These results have shown that the Houk transition state model can be extended to *endo* adducts of 1,2-disubstituted electron-poor olefins, but the possibility of intramolecular hydrogen bonding must be taken into account. For the minor *exo* adducts the *threo* isomers predominate over the *erythro* in all the cases studied and we have proposed for the first time an explanation for the observed selectivity: the smallest group (proton) occupies the most steric demanding *inside* position in the transition state.[16]

With nitrone (**3**) with a stereogenic centre at 2-position, the facial selectivity is referred to the approaching orientation of the dipolarophile in relation to the nitrone substituent. In this case *anti* adducts are obtained exclusively (Table 3).

CONCLUSIONS

The 1,3-dipolar cycloadditions of nitrones (**1**) and (**2**) with a variety of acid derivatives give adducts in high yields, even at room temperature although with larger reaction times. Theoretically, some of these cycloadditions could generate up to 8 isomeric pairs of enantiomers considering the two possible regioisomeric orientations and taken into account that the cycloadditions are concerted processes (with retention of the original olefin configuration). The regio- and stereochemical outcome of these reactions

selects in most cases a single diastereoisomer (as a pair of enantiomers) that can be easily purified by column chromatography. If the reaction is performed either with enantiopure dipolarophiles, like **18**, **19**, and **20**, or enantiopure dipoles, as in the case of **3**, high yields of enantiopure isoxazolidines are obtained. The large number of examples dealing with the *endo/exo* selectivity may help to clarify and/or predict in the immediate future the features governing this stereoselectivity. The results herein described indicate that steric factors play an important role in controlling the regio- and stereochemical course of the reactions with cyclic nitrones. Several of the synthesised compounds are potential starting materials for the stereoselective preparation of a plethora of natural substances.

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