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1,3-Dipolar Cycloadditions of N-Benzyl Furfuryl Nitrones to Vinyl Ethers and α,β -Unsaturated Esters.

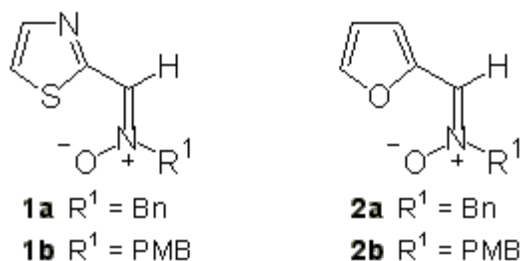
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Introduction

While abundant information on the reactivity of several classes of nitrones exists [1], hetaryl nitrones, *i.e.* nitrones bearing an heterocyclic ring at the carbon atom, have been the subject of very few investigations [2]. Recent publications from our laboratory have been concerned with the use of thiazolyl nitrones **1** as a suitable substrate for both nucleophilic additions [3] and 1,3-dipolar cycloadditions [4]. Our continued interest in the reactivity of hetaryl nitrones has led to investigate the reaction of the furfuryl nitrones **2** with several alkenes. In this communication we report our preliminary results on this topic.



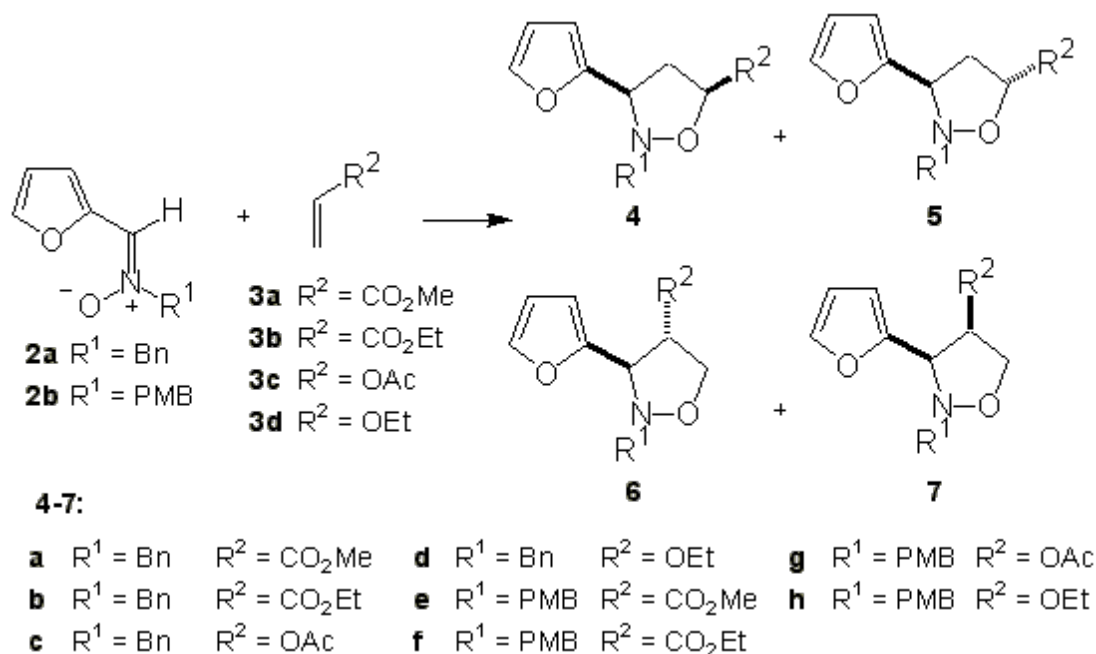
Scheme 1

Results

Furan-derived nitrones were prepared according to our method [5] from furfural and the corresponding benzyl hydroxylamine. In both cases only the Z-isomer was detected, the configuration being assigned on

the basis of NOE experiments (a 10-12% enhancement was observed in the difference spectra upon irradiation of the azomethine proton of the nitron and the benzylic protons. Further confirmation arose from the registration of the corresponding 1-H NMR spectra in deuteriochloroform and hexadeuterobenzene. The observed ASIS effect [6] confirmed the Z-configuration of nitron **2**. The configurational stability of nitrones **2** was also checked. After refluxing in toluene for a week no changes in their structure were observed and the E-isomer could not be detected in any instance.

Refluxing nitrones **2** either in a solvent or neat with an excess of alkene **3** until TLC indicated disappearance of the nitron afforded a mixture of isoxazolidines (Scheme 2). The obtained crude mixture was analyzed by NMR to determine the isomers ratio, and the corresponding adducts were separated by flash chromatography. The isoxazolidines obtained are indicated in Scheme 2 and the corresponding reaction conditions, selectivities and yields in Table 1.



Scheme 2

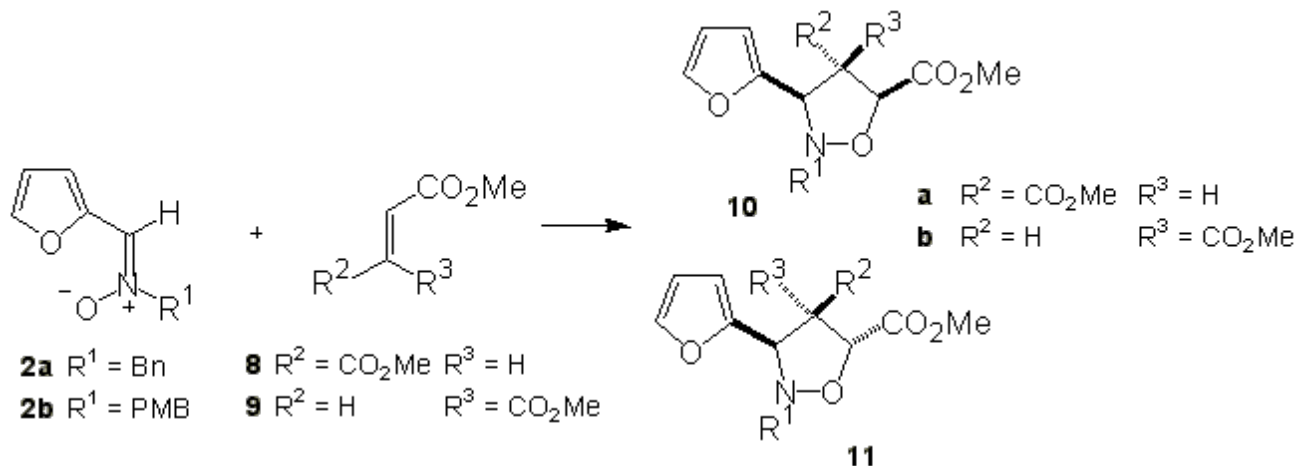
Table 1. Cycloaddition of nitrones **2** with alkenes **3**

entry	R1	R2	reaction conditions	4	5	6	7	yield(%)
1	Bn	CO ₂ Me	neat / reflux / 5h	17	70	13	0	80
2	Bn	CO ₂ Me	DCM / reflux / 48 h	40	54	6	0	60
3	Bn	CO ₂ Me	DCE / reflux / 16 h	28	58	14	0	96
4	Bn	CO ₂ Me	Toluene / reflux / 12 h	22	58	20	0	68
5	Bn	CO ₂ Me	CHCl ₃ / reflux / 24 h	36	50	14	0	93
6	Bn	CO ₂ Et	DCE / reflux / 16 h	16	67	13	0	75
7	Bn	CO ₂ Et	Toluene / reflux / 12 h	27	73	0	0	68
8	Bn	OEt	Toluene / reflux / 10 d	40	60	0	0	25
9	Bn	OAc	CHCl ₃ / reflux / 10 d	12	88	0	0	36
10	PMB	CO ₂ Me	Toluene / reflux / 12 h	22	61	17	0	96

11	PMB	CO ₂ Me	DCE / reflux / 16 h	19	64	17	0	91
12	PMB	CO ₂ Me	CH ₂ Cl ₂ / reflux / 9 d	20	60	20	0	85
13	PMB	CO ₂ Me	neat / reflux / 5h	10	82	8	0	91
14	PMB	CO ₂ Et	Toluene / reflux / 16 h	27	63	10	0	56
15	PMB	CO ₂ Et	DCM / reflux / 9 d	20	69	11	0	85
16	PMB	OEt	Toluene / reflux / 13 d	38	62	0	0	53
17	PMB	OAc	CHCl ₃ / reflux / 17 d	40	60	0	0	16
18	PMB	OAc	neat / reflux / 10 d	35	65	0	0	43

Bn: benzyl; PMB: p-methoxybenzyl; DCM: dichloromethane; DCE: 1,2-dichloroethane

The cycloaddition of nitrones **2** with disubstituted alkenes, e.g. dimethyl fumarate and dimethyl maleate was also studied. The results of this study are illustrated in Scheme 3 and summarized in Table 2.



Scheme 3

Table 2. Cycloaddition of nitrones **2** with alkenes **8-9**.

entry	R1	R2	R3	reaction conditions	10	11	yield(%)
1	Bn	CO ₂ Me	H	DCM/ reflux / 48 h	47	53	91
2	Bn	CO ₂ Me	H	Toluene / reflux / 12 h	61	39	54
3	Bn	H	CO ₂ Me	1,2-DCE / reflux / 16 h	81	19	79
4	Bn	H	CO ₂ Me	Toluene / reflux / 12 h	82	18	89
5	PMB	CO ₂ Me	H	Toluene / reflux / 12 h	93	7	86
6	PMB	H	CO ₂ Me	Toluene / reflux / 12 h	85	15	83

Bn: benzyl; PMB: p-methoxybenzyl; DCM: dichloromethane; DCE: 1,2-dichloroethane

The structure and stereochemistry of isoxazolidines **4-7** were ascertained by careful examination of the 1-H

NMR spectra (using, when necessary, homonuclear proton NMR decoupling) and nuclear Overhauser effect (NOE) experiments. Differentiation of 3,5- and 3,4- regioisomers was made on the basis of multiplicity for H-3 (isoxazolidine numbering). Compounds **4** and **5** showed the same 1-H NMR trend for H-3 and H-5 protons that allowed the assignment of the regiochemistry. Both compounds showed a doublet-of-doublets for H-3 whereas compound **6** (the only 3,4-regioisomer obtained) showed a doublet for the same proton (Figure 1). In addition compounds **6** displayed two vicinal hydrogen atoms (coupling constants $J > 12$ Hz) which were assigned to the H-5a and H-5b protons. The alternative 3,5-regioisomers **4-5** bearing the R² substituent at carbon C-5 showed two vicinal hydrogen atoms at higher fields than those corresponding to H-5a and H-5b in **6**, thus being assigned to H-4a and H-4b.

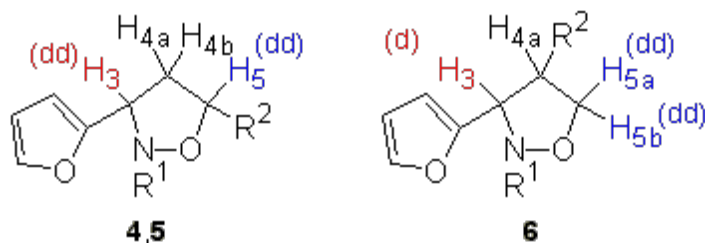


Figure 1. Determination of the regioselectivity

The analysis of vicinal coupling constants $J(3,4)$ and $J(4,5)$ did not result in an unambiguous configurational assignment of compounds **4-6**. We have used nuclear Overhauser effects obtained by difference spectroscopy experiments for establishing the relative stereochemistry of the ring substituents for isoxazolidines **4-6** (Figure 2). The irradiation of H-4b in **4** resulted in enhancement of the signals for H-3 and H-5. On the other hand, no effect was detected upon irradiation of H-4b. The same experiment performed on products **5** produced signal enhancements for H-3 when H-4b was irradiated and for H-5 upon irradiations of H-4a. The irradiation of H-3 of compound **6** showed an enhancement of the signals for H-4 thus suggesting that the two protons are spatially close. Similarly, H-4 was also affected upon irradiation of H-5b and viceversa.

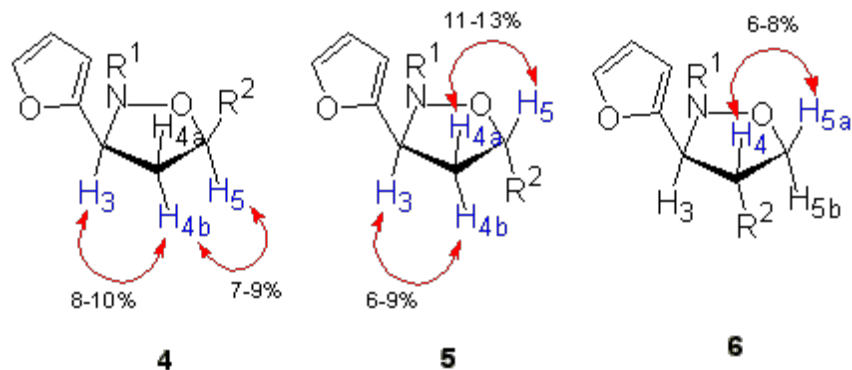


Figure 2. Determination of the stereoselectivity

All these effects are in agreement with a cis configuration for compounds **4** and a trans configuration for both **5** and **6**. The configuration of compounds **10** and **11** was also established by NOE experiments.

Discussion

The stereochemical outcome of the cycloadditions did not appear to be affected by the electron density of the dipolarophile. Both with electron-rich (Table 1, entries 1-7 and 10-15) and electron-deficient (Table 1, entries 8-9 and 16-18) alkenes similar results were obtained. In all cases the 3,5-regioisomers were obtained as major adducts. This observed regioselectivity is in agreement with previously reported data for other nitrones [7] and it can be deduced from a frontier molecular orbitals treatment in which the HOMO-nitrone LUMO-alkene interactions dominate. Only in the case of cycloaddition with ethyl vinyl ether the interactions LUMO-nitrone HOMO-alkene are more favourable [8]. In this case the smallest HOMO-LUMO

gap exists for the LUMO of the nitrone and the HOMO of the alkene. The energies and the coefficients of the HOMO and LUMO of nitrones **2** and alkenes **3** calculated at a semiempirical level (MOPAC97, PM3) [9] were shown in Figures 3 and 4, respectively. The observed regioselectivity can be explained by the magnitude of the atomic components in the FMO of interest. Thus, for cycloadditions with methyl acrylate **3a** and vinyl acetate **3b** the atom with the calculated larger HOMO coefficient on the nitrone reacts with the atom with the larger LUMO coefficient of the alkene. On the other hand, in the cycloaddition of nitrones **2** with ethyl vinyl ether **3c** the atom with the calculated larger LUMO coefficient on the nitrone reacts with the atom with the larger HOMO coefficient of the alkene. The PM3-calculated FMO energies and atomic contributions are also given in Table 3.

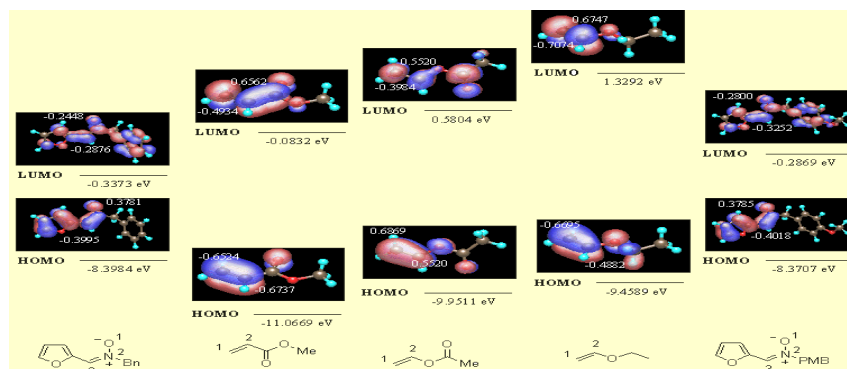


Figure 3. PM3-calculated FMO energies and atomic contributions for nitrones **2**

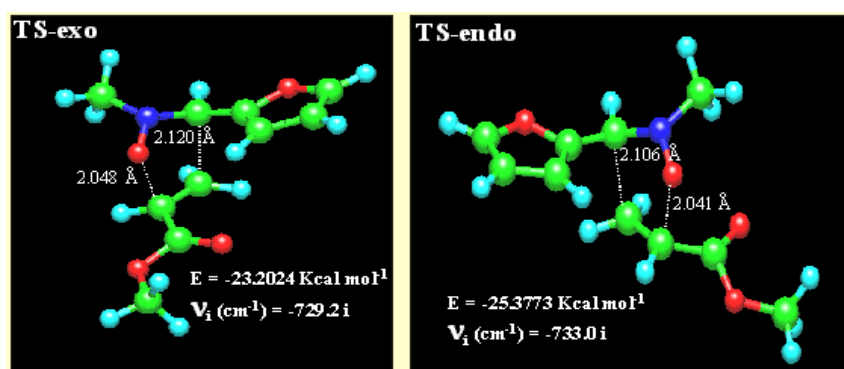


Figure 4. PM3-calculated FMO energies and atomic contributions for alkenes **3**

Table 3. PM3-calculated FMO energies and atomic contributions (favourable in blue)

		HOMO-nitron				LUMO-nitron			
LUMO-alkene		2a	2b	2c	2d	HOMO-alkene		2a	2b
3a	-0.0832	8.3152	8.2875	8.2875	8.2875	3a	-11.0669	10.7296	10.7800
3b	0.5804	8.9788	8.9511	8.9511	8.9511	3b	-9.9511	9.6138	9.6642
3c	1.3292	9.7276	9.7000	9.7000	9.7000	3c	-9.4589	9.1216	9.1720

To discuss the stereoselectivities observed in the 1,3-dipolar cycloadditions studies it is required a careful evaluation of the different effects which can operate in the transition states leading to two diastereomeric *cis* and *trans* cycloadducts. The possibility of interconversion of the E and Z forms of the nitrones, although suggested for several authors [10], can be discarded on the basis of the proved stability of compounds **2** (*vide supra*). The preferential formation of *trans* isoxazolidines **5** can be explained by assuming an *endo*-approach of the dipolarophile to the nitrone. In order to corroborate this hypothesis and once assumed the preferred formation of 3,5-regioisomers, we carried out a PM3 analysis of the cycloaddition reaction

between nitrone **2a** (in which the benzyl group was replaced by a methyl group) and methyl acrylate. PM3 methods have been successfully used by other authors to explain the stereochemical results of 1,3-dipolar cycloadditions^[11].

The theoretical study included the starting system, the transition state and the primary cycloadduct for both *endo* and *exo* approaches. The more stable conformation was chosen for nitrone and alkene. The PM3 calculated heats of formation of nitrone and alkene were 9.049 Kcal/mol and -67.4557 Kcal/mol, respectively. Sum of these values (-58.407 Kcal/mol) was considered to be the heat of formation of the reactants. The heat of formation of *cis*-isoxazolidine (coming from an *exo* approach) was -87.6031 Kcal/mol and that of the *trans* cycloadduct (coming from an *endo* approach) was -87.9558 Kcal/mol. The optimized transition structures are illustrated in Figure 5 and the PM3-calculated parameters are given in Table 3. By intrinsic reaction coordinate calculation the transition states, the reagents and the corresponding cycloadducts were confirmed to be in the same reaction coordinate. According to the data collected in Table 4 the TS-*exo* involves 35.20 Kcal/mol of activation enthalpy, significantly greater than that of TS-*endo* (33.03 Kcal/mol). These results are in good agreement with the experimental data.

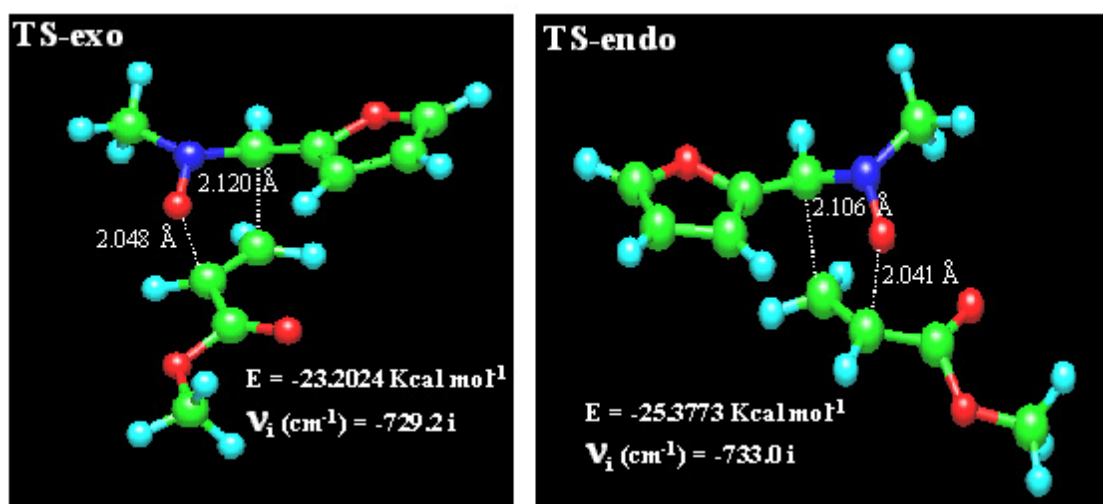


Figure 5. PM3-calculated transition states

Table 4. PM3-calculated selected data

compound	Heat of formation (Kcal/mol)
nitrone	9.0490
methyl acrylate	-67.4557
TS- <i>exo</i>	-23-2024
TS- <i>endo</i>	-25.3773
<i>cis</i> -isoxazolidine	-87.6031
<i>trans</i> -isoxazolidine	-87.9558

In conclusion, our studies have revealed that the 1,3-dipolar cycloaddition of C-furfuryl-N-benzyl nitrones with alkenes gives predominantly *trans*-3,5-disubstituted isoxazolidines. The regiochemistry of the cycloaddition seems to be controlled by FMO interactions, whereas the stereochemistry of the cycloaddition is mainly dominated by the preference for an *endo* approach. With these results in hand, we are now expanding this reaction to other hetaryl nitrones and applying it to the synthesis of several nitrogenated compounds.

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