1,3-Dipolar Cycloaddition of Nitrones With α,β-Unsaturated Sulfones

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C,N-Diphenyl nitrones react with substituted α,β-unsaturated phenylsulfones yielding isoxazolidinic cycloadducts whose structure and stereochemistry were assigned on the basis of ^1H and ^{13}C nmr data. The cycloaddition regioselectivity is discussed in accordance with frontier orbital considerations.

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Introduction.

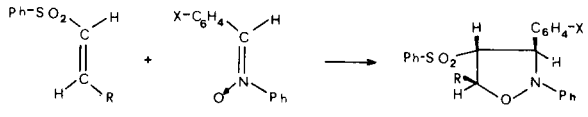
The use of α,β-unsaturated sulfones as dipolarophiles in 1,3-dipolar cycloaddition reactions is quite limited (2 – 6). In view of this we developed a systematic study on the reactivity of substituted vinylsulfones (R – CH = CH-$SO_2 - C_6H_5$) towards 1,3-dipoles. The aim of the work was to evaluate the effect of the group R (hydrogen, methyl, phenyl, benzoyl) on the regioselectivity of the cycloaddition reactions.

This paper deals with the reactivity of *C,N*-diphenylnitrones with some *trans*-α,β-unsaturated phenylsulfones.

Results.

Treatment of *trans*-vinylsulfones (**1**) with *C,N*-diphenylnitrones **2** in benzene or chloroform solution afforded the corresponding cycloadducts **3** in good yields.

CHART-I



1 2 3

The structural proofs of products **3** are based on elemental analyses and spectral data. The chemical shift values of isoxazolidine protons made it possible to assign the structure of 4-sulfonil-derivatives to compounds **3a – i**. The values of the methylene protons of derivatives **3a – c** (δ 4.30 – 4.55) were consistent with the presence of a vicinal oxygen atom and not with a vicinal carbon atom which would produce a resonance at higher fields. The

Table 1

Compound No.	X	R	Mp (°C)	Yield (%)	Reaction time, hours	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	H	H	121-123	80	24	$C_{21}H_{19}NO_3S$	69.03	5.24	3.83	69.11	5.19	3.81
3b	$NO_2(p)$	H	177-179	75	30	$C_{21}H_{18}N_2O_5S$	66.66	4.80	7.40	66.54	4.78	7.36
3c	$OCH_3(p)$	H	144-145	95	24	$C_{22}H_{21}NO_4S$	66.82	5.35	3.54	66.70	5.18	3.56
3d	H	C_6H_5	138-140	60	72	$C_{27}H_{23}NO_3S$	73.45	5.25	3.17	73.40	5.21	3.09
3e	H	CH_3	57-59	53	24	$C_{22}H_{21}NO_3S$	69.64	5.58	3.69	69.55	5.61	3.62
3f	$NO_2(p)$	CH_3	180-182	61	72	$C_{22}H_{20}N_2O_5S$	62.26	4.75	6.60	62.16	4.70	6.55
3g	H	C_6H_5-CO	141-143	78	4	$C_{28}H_{23}NO_4S$	71.63	4.94	2.98	71.44	4.86	2.95
3h	$NO_2(p)$	C_6H_5-CO	161-163	72	4	$C_{28}H_{22}N_2O_6S$	65.36	4.31	5.45	65.28	4.27	5.40
3i	$OCH_3(p)$	C_6H_5-CO	106-108	51	8	$C_{29}H_{25}NO_5S$	69.73	5.05	2.80	69.61	4.98	2.72

phenyl (**3d**) and the methyl derivatives (**3e, 3f**) were in line with above considerations. Also in the benzoyl derivatives (**3g—i**) the sulfonyl group was bounded at C_4 as evidenced by the spectrum recorded in the presence of triethylamine. Under these conditions the AMX system (J_{AX} = 6.5 Hz, J_{MX} = 3.0 Hz, J_{AM} = 0 Hz) associated to H_3, H_4 and H_5 evolved to a simpler AX system (J_{AX} = 6.5 Hz) because of the complete enolisation of the carbonyl group. This behaviour showed the position at C_5 of the benzoyl group and consequently the position of the sufonyl group at C_4.

CHART - II

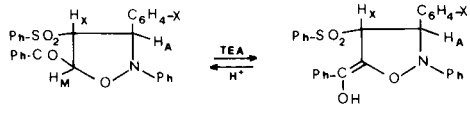


Table 2

^{1}H NMR Data for Compounds **3a-i**.

Compound	δ_3	δ_4	δ_5	$\delta_{5'}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
3a	4.95	4.16	4.50	4.35	4.7	5.4	6.7	9.3
3b	4.86	4.11	4.55	4.36	4.5	5.2	6.6	9.2
3c	5.20	4.13	4.47	4.30	4.5	6.2	8.0	9.2
3d	5.36	4.25	5.33	—	4.8	6.6	—	—
3e	4.76	5.25	5.80	—	6.5	3.0	—	—
3f	4.70	5.20	5.80	—	6.6	3.0	—	—
3g	4.95	5.15	5.78	—	6.5	3.0	—	—
3h	5.25	3.82	4.64	—	4.5	7.5	—	—
3i	5.35	3.70	4.60	—	4.5	7.5	—	—

The ^{13}C magnetic resonance spectra of the more representative **3d, 3f** and **3g** supported the considerations based on the nmr spectra. The direction of the cycloaddition was confirmed by the chemical shift values in product **3a**: the unsubstituted C_5, a triplet in off resonance decoupling mode, appeared at δ 66.6 and then had to be next to an oxygen and not to a carbon atom, a situation which would reasonably produce a resonance at about only δ 25 – 30.

In other cases, assignments of the individual resonance could not be safely based on the chemical shift rules, due to the highly crowed nature of the isoxazolidine ring and the anisotropic characteristics of the substituents. To circumvent this problem, an assignment based on differences in the long-range coupling pattern was used. With the compound **3g**, all ring carbon appeared in the δ 9 range and all were doublets in the total coupling mode, differing only in their fine structure and/or line width. The peak at δ 71.1 exhibited no fine structure but was broadened ($\triangle$ J ½ = 11.4 Hz) with respect to the others and was thus attributed to C_3 next to a nitrogen atom. The peak at δ 79.5 showed a long range coupling of about 3 Hz as a doublet and was attributed to C_5 which had only one vicinal hydrogen with which to couple, while the peak at δ 75.5 exhibited a triplet with J^2_{CH} = 4 Hz and belonged to C_4 which had two vicinal hydrogens. From this it followed that all peaks (See Table 3) at about δ 70 far away from the site of substitution could be safely attributed at C_3 and indeed in all total coupling experiments these peaks showed a broadened structure due to the effect of the quadrupole of nitrogen atom. In **3d**, the assignment of C_5 and C_4 to peaks at δ 83.7 and 80.7 was based on their respective band width in the TC experiment, since in this case both gave no resolved fine structure. The half band line widths were 8 and 13 Hz, respectively, thus pointing to the upfield peak as being C_4. In **3f** both peaks at δ 76.3 and 83.0 gave a highly complex coupling pattern in the TC experiment, C_5 being coupled also to the methyl hydrogens. Here assignments to C_5 and C_4 respectively were based on chemical shift consideration: substitution of a methyl group for a hydrogen atom would cause a downfield shift at C – α (δ 9.7) and C – β (δ 6.0) of comparable magnitude.

Table 3

^{13}C-NMR Chemical Shift

Compound	C_5	C_4	C_3	Others
3a	66.6	77.0	70.0	
3d	83.7	80.7	71.0	
3f	76.3	83.0	70.1	CH_3 17.9
3g	79.5	75.5	71.1	CO 196.5

The nature of the group X present on the nitrone and the solvent polarity did not influence the course of reaction. In fact preliminary kinetic data confirmed there was little solvent polarity effect on reaction rate. In all cases which were investigated the reaction gave only one of the two possible regioisomeric cycloadducts (nmr analysis on the crude reaction mixture did not reveal other isomers or diasteroisomers within experimental error).

As in other cases of cycloaddition reactions the more interesting consideration has to do with the observed regioselectivity. The perturbation theory has been used as a method for finding an explanation for regioselectivity in 1,3-dipolar cycloadditions and has allowed a qualitative treatment of the reactivity of 1,3-dipoles.

According to Salem (7) and Sustmann (8) three types of cycloadditions can be distinguished from the relative position of the frontier orbitals of the reagents. If ionisation potentials (IP) and electron affinities (EA) of the reagents

are available it is possible to deduce, by comparing these parameters, which type of cycloaddition has to be taken as a model. In our case a comparison (see Figure 1) of energy values of nitrones and vinylsulfones allows us to deduce that the cycloaddition is controlled by HOMO dipole/LUMO dipolarophile interactions.

Since the nitrone has the largest coefficient at the terminal oxygen in the HOMO and the unsaturated sulfones at the β carbon atom in the LUMO, the experimental formation of the 4-sulfonyl-substituted isoxazolidines agrees with the FMO theory.

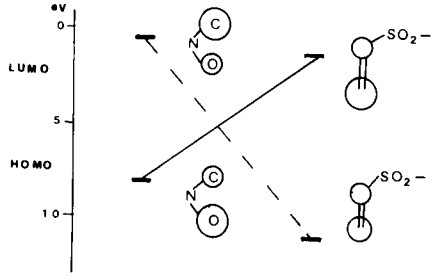


Figure 1. Estimated frontier orbital energies and coefficients of nitrones (9) and unsaturated sulfones (10).

An other consideration regards the stereochemistry of the reaction. The analysis of the coupling constants for vicinal hydrogen atoms can not be used as a basis to assign the steric configuration. The extremely fine correlation between the coupling constants and the configuration in isoxazolidinic system due to ring flexibility and the steric interactions between the substituents is a well known problem (11). Moreover it is not possible to predict the configuration of the phenyl group bound to the nitrogen atom owing to its rapid inversion and this fact influences the angles between the vicinal protons in the isoxazolidinic ring. The values of $J_{4,5}$ *cis* and $J_{4,5}$ *trans* in compounds **3a-i** are very close (see Table 2) and these slight differences can be cancelled or even inverted by eventual substituents at position 5.

In consideration of the stereospecificity of cycloaddition reaction a *trans* configuration for the hydrogen atoms at C_4 and C_5 was used. Even if the $J_{3,4}$ appears in a narrow value range (4.5 – 6.6 Hz) that does not allow for certain conclusions about the configuration of substituents bound to C_3 and C_4, nethertheless the *trans* configuration is the most probable. Because of the geometry of unsaturated sulfones (10) the approach of the dipole occurs at the opposite part with respect to the phenylsulfonyl group and then the rehybridisation leads to *trans* cycloadducts that, on the basis of the Dreiding models, are those that are the least crowded. Our findings are also confirmed by the work of Greé (12) on the cycloaddition of nitronic esters to activated olefines.

EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were recorded with Varian A – 90 spectrometer (TMS as the internal standard). The ^{13}C nmr spectra were obtained on a C T F – 20 Varian spectrometer in deuteriochloroform solution. Chemical shifts are expressed in ppm from TMS. Longe range coupling constant experimentals were run with retention of NOE (decoupling off only during acquisition) to improve sensitivity.

Unsaturated Sulfones (**1**) and Diphenylnitrones (**2**).

These are known compounds and were prepared following the standard procedure.

Preparation of Isoxazolidine Cycloadducts **3**. General Procedure.

A mixture of the nitrone (0.01 mole) and the unsaturated sulfone (0.01 mole) in benzene (50 ml) was boiled for the requisite time (see Table 1) until reagents disappeared in tlc. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with benzene/ethyl acetate (90:10) gave the products listed in Table 1.

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