STERIC CONFIGURATION AND REACTIVITY OF 2-BENZYLIDENE-4-METHYL-2*H*-1,4-BENZOXAZIN-3(4*H*)-ONE[#]

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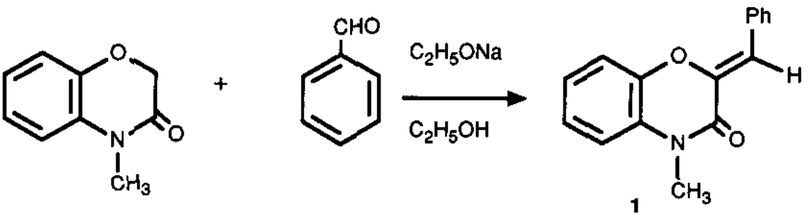
Abstract - The reactivity of 2-benzylidene-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**1**) towards N- and C-nucleophiles, nucleophilic and electrophilic alkenes, dienes and 1,3-dipoles was investigated. Nitrones (**2**) reacted with **1** giving through a regioselective process a mixture of the two diastereoisomeric spiro compounds (**3**) and (**4**) whose structure and relative steric configuration have been assigned on the basis of ^{1}H and ^{13}C nmr data.

Our previous works dealt with the preparation of arylidene or ethylidene derivatives of 1,4-dihydro-2-methylimidazol-5-ones,[1] 2,3-dihydro-2-methyl-1,2-benzothiazin-4-one 1,1-dioxides[2] and with their use in the synthesis of polycyclic or spiro heterocyclic compounds.[3-6] As part of our interest in this field we report here the reactivity of the 2-benzylidene-4-methyl-1,4-benzoxazin-3-one (**1**), a little studied substrate.[7,8]

Compound (**1**) has been previously prepared in 28 % yield, condensing benzaldehyde with 2,3-dihydro-4-methyl-3-oxo-1,4-benzoxazine in xylene / sodium hydride[8] or benzene / sodium amide.[7] Taking into account our recent results on the preparation of 3-arylmethylene-2-methyl-1,2-benzothiazin-4-ones 1,1-dioxides[5] we obtained **1** in 70 % yield, using sodium ethoxide in ethanol (Scheme 1). These simpler conditions represent a good improvement in respect to the reported methods.

[#] Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.



Scheme 1

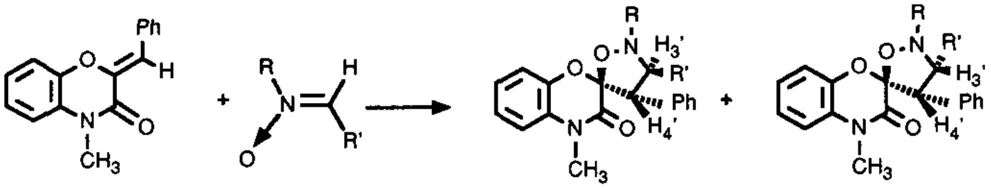
The steric configuration of the exocyclic double bond in **1** was unknown to date. According to Scheme 1 the synthesis gives only one of the two possible stereoisomers, that with Z configuration whose assignment was based on the chemical shift value of the olefinic proton. However, correct assignment requires the availability of spectroscopic data for both stereoisomers. In the case of **1** the Z-E isomerisation was affected photochemically in acetone solution by irradiation at 3650 °A for 8 h at room temperature. The photostationary Z:E ratio in the reaction mixture was calculated to be 52/48 from nmr spectrum based on the intensity of the olefinic proton signals at δ_H = 6.95 ppm (Z isomer) and δ_H = 6.75 ppm (E isomer). This last value agrees with an E configuration of the double bond in which the olefinic proton is not deshielded by the carbonyl group and so it is shifted upfield.

The formation of the only Z isomer was explained with a steric hindrance between the carbonyl and phenyl groups as pointed out by molecular models. In order to estimate the stability of the Z, E isomers , we employed a Molecular Mechanics method[9] to calculate their steric energy values, minimised with the MM2 force field as implemented in the program Macromodel.[10] The found values (E=16.0 Kcal/mol and E=19.6 Kcal/mol for the Z and E isomers respectively) confirmed the complete preference, experimentally observed, for the Z isomer.

Compound (**1**) may be assumed as related to an α,β-unsaturated carbonyl compound or to a vinyl ether depending on whether the electron-withdrawing effect of the carbonyl group or the electron-donating effect of the oxygen is predominant on the β-carbon. The ^{13}C nmr spectrum of **1** shows for this β-carbon a chemical shift of 112.6 ppm, a middle value between that typical of an α,β-unsaturated carbonyl compound (140 ppm) and that of a vinyl ether (90 ppm).

With a semiempirical method (AM1) we calculated the charge density of the two carbon atoms of the exocyclic double bond and founded d_β= - 0.082 D and d_α= - 0.028 D respectively. On the basis of these results it is possible to predict that **1** should behave as a vinyl ether rather than an α,β-unsaturated carbonyl compound. To prove the proposal we studied the behaviour of compound (**1**) with: a) nucleophiles (hydrazine, sulphur and phosphorous ylides); b) electron rich (ethyl vinyl ether) and electron poor (*N*-phenylmaleimide) dienophiles; c) dienes (cyclopentadiene, 2,4-hexadiendioic acid diethyl ester); d) 1,3-dipoles.

Product (**1**) resulted unaffected by nucleophiles, dienophiles (confirming the absence of α,β-unsaturated carbonyl character), and dienes. Among the 1,3-dipoles only nitrones gave successful results.[11a] The reaction of **1** with **2** performed in toluene solution, at 110° C for 96 h, gave a mixture of two diastereoisomeric cycloadducts (**3**) and (**4**) (ratio 75/25)[11b] deriving from a [3+2]π cycloaddition reaction on the exocyclic double bond (Scheme 2). The products were separated by column chromatography and further purified by crystallization. Analytical, physical and spectroscopic data (summarized in Table 1) agree with the general structure of 4-methyl-3-oxospiro[2*H*-3,4-dihydro-1,4-benzoxazine-2,5'-isoxazolidine] (**3**) and (**4**).



1 **2** **3** **4**

(2,3,4a) : R=R'=C_6H_5

(2,3,4b) : R=C_6H_5 R'=4-NO_2-C_6H_4

(2,3,4c) : R=C_6H_5 R'=4-CH_3O-C_6H_4

(2,3,4d) . R=C_6H_5 R'=2-Py

(2,3e) : R=CH_3 R'=C_6H_5

Scheme 2

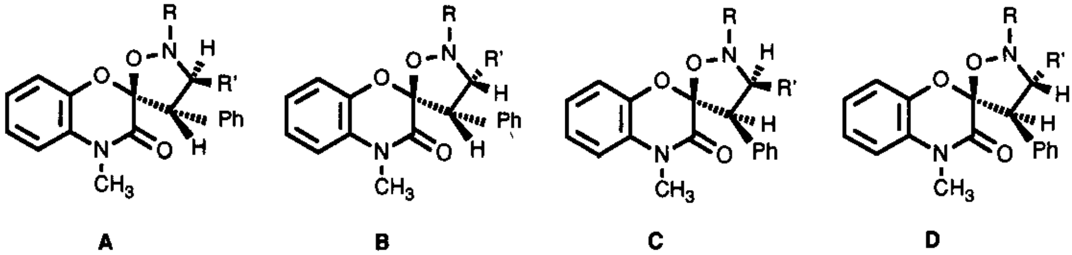
The reaction is completely regioselective as confirmed by the ^{1}H nmr data. In the spectra of adducts (**3**) and (**4**) an AB system for $H_{3'}$ and $H_{4'}$ is present. Consequently both the adducts derive from the same regiochemical attack which binds the carbon of the nitrone to the C_β of **1**.[12] The observed regioselectivity can be explained qualitatively by the FMO method. Comparing energy values of nitrones with those of a vinyl ether, the reaction results LUMO dipole controlled.[13] The predominant interaction is that deriving from the preferential combination between the atoms with larger orbital coefficients.

Table 1. Physical, analytical and spectroscopic data of compounds (**3** - **4**).

Compound	Yield (%)	mp (° C) (solvent)	^{1}H - Nmr δ (ppm), J (Hz)	Elemental Analysis (%) Found (Calculated) C	H	N
3a	50	203-205 (A)	3.4(s,3H,N-CH_3);4.9(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =11.46);5.2(d,1H,$H_{3'}$);6.6-7.55(m,19H, aromatics)	77.51 (77.68)	5.50 (5.35)	6.17 (6.24)
4a	17	173-175 (B)	3.4(s,3H,N-CH_3);5.1(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =9.19);5.4(d,1H,$H_{3'}$);6.85-7.35(m,19H, aromatics)	77.58 (77.68)	5.51 (5.35)	6.20 (6.24)
3b	60	206-208 (B)	3.3(s,3H,N-CH_3);4.8(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =11.59);5.6(d,1H,$H_{3'}$);6.6-8.2(m,18H, aromatics)	70.71 (70.59)	4.70 (4.66)	8.63 (8.52)
4b	23	204-206 (B)	3.3(s,3H,N-CH_3);5.1(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =9.40);5.7(d,1H,$H_{3'}$);6.8-8.3(m,18H, aromatics)	70.68 (70.59)	4.87 (4.66)	8.65 (8.52)
3c	33	211-213 (B)	3.4(s,3H,N-CH_3);3.75(s,3H,O-CH_3); 4.85(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$=11.53);5.2 (d,1H,$H_{3'}$);6.6-7.4(m,18H,aromatics)	75.60 (75.31)	5.36 (5.44)	5.74 (5.86)
4c	9	193-195 (B)	3.4(s,3H,N-CH_3);3.75(s,3H,O-CH_3); 5.0(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$=9.09);5.35(d,1H, $H_{3'}$);6.8-7.3(aromatics)	75.64 (75.31)	5.68 (5.44)	5.50 (5.86)
3d	39	199-201 (A)	3.4(s,3H,N-CH_3);5.1(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =11.31);5.4(d,1H,$H_{3'}$);6.5-8.5(m,18H, aromatics)	74.71 (74.80)	5.37 (5.12)	9.40 (9.35)
4d	12	145-146 (C)	3.4(s,3H,N-CH_3);5.2(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$ =9.57);5.35(d,1H,$H_{3'}$);6.95-7.3(m,18H, aromatics)	74.60 (74.80)	5.35 (5.12)	9.28 (9.35)
3e	16	234-236 (A)	2.8(s,3H,$N_{2'}$-CH_3);3.4(s,3H,N_4-CH_3); 4.6(d,1H,$H_{4'}$,$JH_{4'}$-$H_{3'}$=11.38);4.9(d,1H, $H_{3'}$);7.0-7.4(m,14H,aromatics)	74.80 (74.60)	5.78 (5.70)	7.10 (7.25)

(A): isopropanol; (B): ethanol / toluene; (C): n-hexane

The structures (3)/(4) contain three stereocentres, therefore four diastereoisomers (**A**),(**B**),(**C**),(**D**) with the relative enantiomers, can be theoretically drawn (Scheme 3).



Scheme 3

Diastereoisomers (**C**) and (**D**) can be ruled out on the basis of the steric configuration of benzoxazine (**1**), (Z), and of the concerted nature of 1,3-dipolar cycloadditions.[14,15]

To assign to the isolated compounds (**3**) and (**4**) the structures (**A**) and (**B**) respectively, as shown later, we considered their ^1H and coupled ^{13}C nmr spectra.

In ^1H-nmr spectra, protons $H_{3'}$ and $H_{4'}$ present a middle value of $^3JH_{3'}$-$H_{4'}$=11.5 Hz in the major diastereoisomers and of $^3JH_{3'}$-$H_{4'}$=9.3 Hz in the minor ones.

The coupled ^{13}C nmr spectrum of the major adduct obtained in the reaction of **1** with **2a** shows for the spiro carbon C_2 a signal at δ= 102.98 ppm with a $^3JC_2$-$H_{3'}$=4.45 Hz, whereas the minor one shows a signal at δ=103.06 ppm with none coupling constant $^3JC_2$-$H_{3'}$.

It is known[16] that the long range coupling constants ^{3}JC-H depend on the dihedral angle C-C-C-H and follow a Karplus- type curve.

Considering molecular models of **A** and **B** and the differences in spatial relationships of the carbon and hydrogen atoms among them, it is apparent that the spirocentre C_2 must have a long range coupling $^3JC_2$-$H_{3'}$ in **A** (dihedral angle *ca.* 160°) but none in **B** (dihedral angle *ca.* 90°). Moreover the trans relationship between $H_{3'}$ and $H_{4'}$ in **A** agrees with a higher value of $^3JH_{3'}$-$H_{4'}$.

So to the major cycloadduct (**3a**) and to the minor one (**4a**) the structures (**A**) and (**B**) were assigned respectively.

These considerations for products (**3a**) and (**4a**) can be extended to the products derived from the others (**2**) as the mechanism of the cycloaddition reaction is independent of the nitrone substitution.

Starting from Z-nitrones (**2**)[17] and Z-benzoxazine (**1**), taking in the account the fact that **3** and **4** didn't interconvert when refluxed in toluene solution for 48 h, the formation of diastereoisomers (**3**) and (**4**) can be explained as an ENDO and EXO attack of Z-nitrones (**2**) on the Z-benzoxazine (**1**).

Nitrones have been demonstrated to exist as an equilibrium mixture Z / E at high temperatures.[17] Consequently, we cannot exclude a partial Z / E isomerization of nitrones (**2**) under experimental conditions, since the same diastereoisomers (**3**) and (**4**) could derive from an EXO and ENDO approach between E-nitrones (**2**) and Z-benzoxazine (**1**).

The appropriate molecular models show that the transition state leading to the diastereoisomer (**B**) suffers from a remarkable stereochemical hindrance due to the $C_β$ and $C_{nitrone}$ phenyl rings.

The preferential formation of the spiro-adducts (**3**) with a trans relationship between these phenyl groups can be hence explained.

EXPERIMENTAL

Melting points were measured with a Buchi apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts are expressed as δ values (ppm) from tetramethylsilane. J values are expressed in Hz. $CDCl_3$ was used as solvent for **3a**, **3c**, **3d**, **4d**, **3e**; DMSO-d_6 for **4a**, **3b**, **4b**, **4c**.

Nitrones (**2a**)[18],(**2b**)[19],(**2c**)[20],(**2d**)[21] and (**2e**)[22] were prepared following the reported methods.

(Z)-2-Benzylidene-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**1**)

To a suspension of 2,3-dihydro-4-methyl-3-oxo-1,4-benzoxazine[7] (5.35 g, 33 mmol) in dry ethanol (80 ml), benzaldehyde (4.31 ml, 43 mmol) and a sodium ethoxide 5M solution in ethanol (8.6 ml, 43 mmol) were added dropwise. The mixture was stirred at 80° C for 24 h. The solvent was evaporated off and the residue was treated with water and acetic acid (pH 5), then extracted with chloroform. After evaporation of the solvent the residue was purified by column chromatography(silica gel, toluene/ethyl acetate = 9/1) and crystallized from isopropyl alcohol. Yield : 5.8 g (70%); mp 156-158° C [Lit.,[7] 155-156° C]. ^1HNmr ($CDCl_3$) : 3.5 (s,3H,N-CH_3); 6.95 (s,1H, H_β); 6.98-7.22 (m,4H,benzoxazine ring aromatics); 7.31 (t,1H,$H_p$phenyl ring); 7.42 (t,2H,$H_m$phenyl ring); 7.85 (d,2H,$H_o$phenyl ring). ^{13}C Nmr ($CDCl_3$) : 28.5 (N-CH_3); 112.6 (C_β); 140.9 (C_α); 157.0 (C=O).

Cycloaddition reactions of **1** with **2**. General procedure.

A mixture of **1** (10 mmol) and **2** (11 mmol) in toluene (50 ml) was heated at 110° C for 4 days. The solvent was evaporated off and the residue was chromatographed on silica gel. Elution with toluene/ethyl acetate = 9/1 gave the products (**3**) and (**4**) (Table 1).

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11. a) The reaction with some others 1,3-dipoles (nitrilimines, munchnones) was not successful probably because these dipoles are not stable in the experimental conditions necessary to have good yields. b) Nitrone (**5e**), very unreactive, furnished only the adduct (**6e**).
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