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The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes

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ABSTRACT

A quantitative evaluation of the H-bond directing effect on the stereoselectivity in the cycloaddition of nitrile oxides to 2-cyclopenten-1-ol and allylic cyclopentenyl amides is reported. In apolar solvents the H-bond directing effect promotes a high *syn* stereoselectivity while H-bond acceptor solvents divert the reactions to the *anti* face of the dipolarophile. Taft's β parameter gives a good description of the solvent effect on the H-bond directing effect. The persistence of some *syn* stereoselectivity even in good H-bond acceptor solvents points out the existence of some residual hydrogen bond direction. The *syn* stereoselectivity in the presence of M(II) salts was also investigated and the results discussed in the light of the potential application of these scaffolds in nucleoside synthesis.

1. Introduction

Among the directing effects which assume relevance in the control of stereoselectivity in many organic reactions, the intermolecular Hydrogen Bond (HB) between reactants is perhaps the most known, powerful and extensively explored for synthetic purposes.[1] One of the earliest examples of HB directed reactions is the Henbest peracid epoxidation[2] of cyclic allylic alcohols (2-cyclohexenol, 2-cyclopentenol) which causes a remarkably *syn* stereoselection when the reaction is performed in apolar solvents, while the substrates are stereorandomly oxidized when alcohols are used as solvents. A quantitative assessment of the solvent effect on the stereoselectivity of the peracid epoxidation is however difficult since the solvent can interact either with the alcoholic function or with the peracid hydroxyl group. In the latter case a rate retardation is observed, as shown by kinetic measurements in the epoxidation of cyclohexene.[3] Other reagents have been developed and of special interest are catalytic procedures which utilize transition-metal catalysts, mainly TBHP/Ti(O*i*Pr)$_4$,[4] VO(acac)$_2$,[5] methyl-trioxorhenium (MTO)[6] and Mn(Salen)[7] complexes, achieving best results in term of stereoselection. Besides peracids, dimethyl dioxirane (DMD)[8] is another purely organic non-metal oxidant which is less prone to HB effects[9] and hexafluoroacetone perhydrate (HFAH)[10] which is a non-metal catalyst for higher *syn*-selective oxidations *via* a hydrogen bonded transition structure similar to that of a peracid with a catalytic oxygen transfer process.

HB directing effects have been observed in nitrile oxide cycloadditions and affect stereoselection remarkably.[11–13] We have exploited the HB directing effects for the stereoselective synthesis of bicyclic isoxazolines, which serve as building blocks for the synthesis of modified nucleosides.[15] With the exception of one case where an intramolecular HB prevents the establishment of the intermolecular HB needed for the heteroatom directing effect, stereoselectivity was satisfactorily tuned with the appropriate solvents.

On pursuing our interests in cyclopentene-based nucleoside analogues synthesis,[16] we report here a quantitative evaluation of the solvent effect on the HB directing effects in the cycloaddition of nitrile oxide to 2-cyclopenten-1-ol and allylic *N*-cyclopentenyl amides, which serve as reference data for more complex systems. The persistence of some *syn* stereoselectivity even in good H-bond acceptor solvents and comparisons with the stereoselectivities of the *O*- and *N*-methyl derivatives point out the existence of some residual hydrogen bond direction. The *syn*-stereoselectivity in the presence of M(II) salts was also investigated and a brief discussion is given, in light of potential applications in nucleoside analogue synthesis using 2-cyclopenten-1-ol or allylic *N*-cyclopentenyl amides as scaffolds for these targets.

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2. Results

2.1. Solvent effect in nitrile oxide cycloaddition reactions

2.1.1. Cycloadditions to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene

Cycloadditions of benzonitrile oxide (BNO) to 2-cyclopenten-1-ol (**1A**) and 3-methoxy-cyclopentene (**1B**) afforded the known four regio and stereoisomeric cycloadducts **2Aa-d** and **2Ba-d**, respectively (Scheme 1).[12] The solvent effect was investigated by performing the reactions in 13 solvents of different polarities and Hydrogen Bond Acceptor (HBA) abilities and the product distribution was determined with quantitative HPLC analyses. Table 1 gives the reaction yields and the regio and stereoisomeric ratios of **2a-d** along with the Taft's β parameter,[14] a descriptor of the HBA ability of the solvents.

As a whole, cycloadditions to cyclopentenol give good yields (60–95%) of the adducts, while the product distribution shows a remarkable solvent dependence.

In non-HBA solvents (β = 0.00–0.10; entries 1–6), the *6syn* cycloadduct **2Aa**, which derives from the HB directed cycloaddition shown in **3**, is the major regioisomer and amounts to 55–68% of the cycloaddition products. In HBA acceptor solvents (entries 7–13) the HB directing effect decreases because of the competing effect of the solvent for the HB and the amount of cycloadduct **2Aa** steadily drops with the increasing β values of the solvent. Meanwhile, the *anti* adducts **2Ad** and **2Ab** steadily increase maintaining between them a rather constant ratio **2d**/**2b**, ranging from 2.5 to 3.0. The major *anti* cycloadduct is the *4anti* stereoisomer **2Ad**, in accordance with Frontier Orbital (FO) and electrostatic expectations.[12a] The *4syn* cycloadduct **2Ac** is nearly negligible in all the cases owing to the steric hindrance between the hydroxyl substituent and the nitrile oxide phenyl substituent.[11,12,17]

A graphical illustration of the effect is given in Fig. 1, where the log of the percentage of the adduct *6syn* **2Aa** in the mixture is plotted against solvent β values. In non-HBA solvents (β equal or proximal to 0.00), the HB directing effect is fairly active and constant and all the points cluster together. HBA solvents cause the drop of the points along a line with slope −1.02. The linear regression is fair (r^2 = 0.95) and shows that the β parameter satisfactorily accounts for the solvent effect on the stereoselectivity. Conversely, the related cycloaddition to 3-methoxy-cyclopentene does not show any noticeable solvent dependence (Table 1, entries 14–17). At the bottom of Fig. 1 the red squares show the constance of the *6syn* adduct **2Ba** in the mixtures. The major adducts are the *anti* regioisomer **2Bd** and **2Bb** in a ratio *ca.* 2:1 similar to that reported in the case of the alcohols.

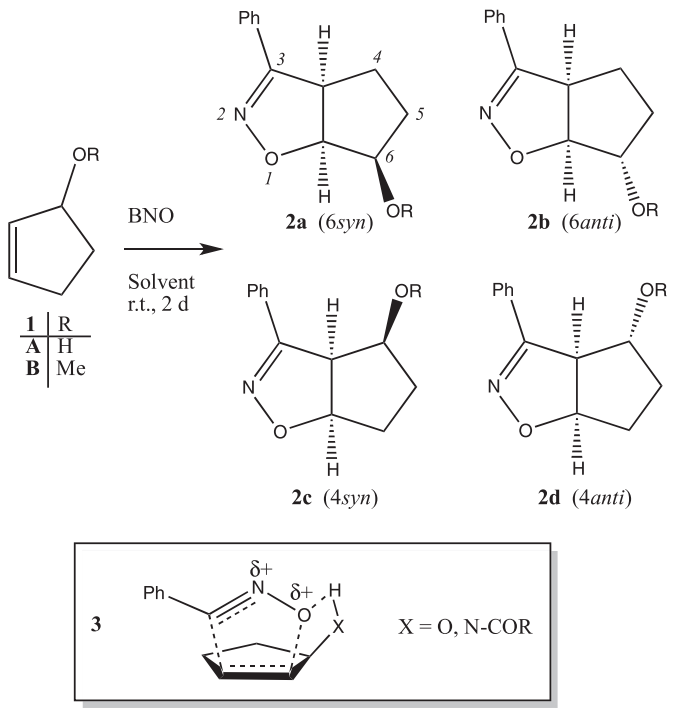
Table 1
Reaction yields and regioisomeric ratios of cycloadducts **2a-d** in the cycloadditions to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene.

Entry	Solvents (β)[a]	Yield %	2a	2b	2c	2d	2d/2b
*2-cyclopenten-1-ol (**1A**)*							
1	Cy (0.00)	82	68	8	–	24	3.0
2	*n*Hex (0.00)	87	60	10	1	29	2.9
3	CCl_4 (0.00)	65	64	9	–	27	3.0
4	CH_2Cl_2 (0.00)	82	58	11	1	30	2.7
5	$CHCl_3$ (0.00)	81	55	12	2	31	2.8
6	Bz (0.10)	88	58	11	3	28	2.5
7	DIOX (0.37)	95	20	22	5	53	2.4
8	AcOEt (0.45)	79	23	21	2	54	2.6
9	Acetone (0.48)	86	21	21	1	57	2.7
10	THF (0.55)	90	20	22	5	53	2.4
11	MeOH (0.62)	66	12	23	1	64	2.8
12	DMF (0.69)	63	10	24	5	61	2.5
13	EtOH (0.77)	60	13	22	1	64	2.9
*3-methoxy-cyclopentene (**1B**)*							
14	CH_2Cl_2 (0.00)	72	6	30	5	58	1.9
15	Bz (0.10)	84	7	30	7	56	1.9
16	AcOEt (0.45)	82	6	31	5	58	1.9
17	MeOH (0.62)	72	7	30	5	58	1.9

[a] β values, see ref. 14.

2.2. Cycloadditions to cyclopentenyl amides

We have investigated the solvent effect in the cycloadditions of BNO to the *N*-cyclopentenyl amides **4A-D** which afford the regioisomeric adducts **5a-d** (Scheme 2). Preparative cycloaddition of BNO



Scheme 1. BNO cycloaddition reaction to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene.

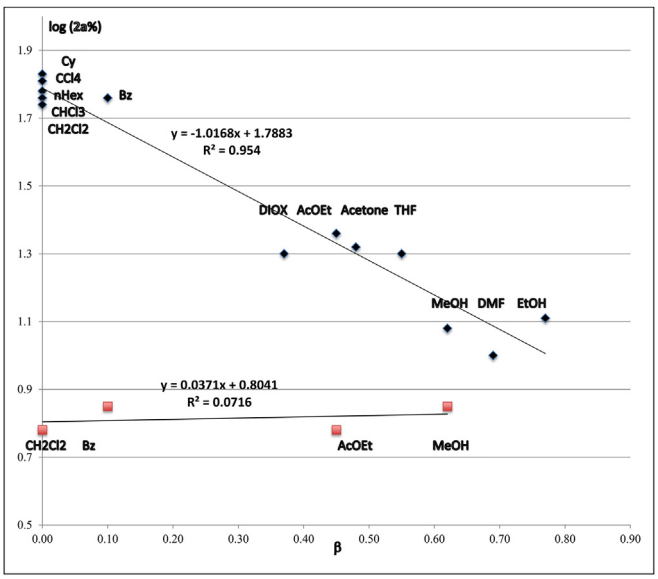


Fig. 1. Plot and linear regression of the log(**2a**%) *vs* solvents β values.

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