SHORT PAPER

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Influence of the solvent on the stereoselectivity of 1,3-dipolar cycloaddition of nitrile oxides on several 4-substituted 2-cyclopentenones†

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The diastereofacial selectivity in 1,3-dipolar cycloadditions of 2,6-dichlorobenzonitrile oxide on 2-cyclopentenones **1–5** is strongly dependent on the solvent when an hydroxyl group is present at C(4) (**1–2**) while if this group is protected (**3–4**) or absent (**5**) the reaction is solvent independent.

Keywords: 1,3-dipolar cycloadditions, 2-cyclopentenones, diastereoselectivity, solvent effect

The 1,3-dipolar cycloadditions of nitrile oxides to alkenes are very important reactions for obtaining isoxazolines. Isoxazolines can also be valuable as intermediates leading to β-hydroxy ketones or γ-amino alcohols.[1] Stereochemistry and regiochemistry are key features of these reactions. In several studies it has been found that the nature of the solvent can influence the stereoisomer or regioisomer ratios.[2–8] In particular the presence of an allylic hydroxy group should direct the attack through hydrogen bonding with the oxygen of the nitrile oxide.[9] Indeed in a study on the 1,3-dipolar cycloaddition of 2,4,6-trimethybenzonitrile oxide to *cis* cyclobut-3-ene-1,2-diol it has been found that *syn* addition is strongly favoured in benzene while in methanol *syn* and *anti* stereoisomers are formed in almost equal amounts.[6] This difference in stereoselectivity is a consequence of hydrogen-bonding between hydroxy groups and methanol.[10]

In a recent study we found that 1,3-dipolar cycloadditions of various nitrile oxides on several 4-substituted 2-cyclopentenones (**1**–**5**) are completely regioselective regardless of the nature of the nitrile oxides or the nature of the substituent(s)[11] (see Scheme 1). On the other hand the diastereofacial selectivity is strongly influenced by the substituents.[11]

The nature and the interplay of the substituents present on the allylic centre of cyclopentenones **1**–**5** make these compounds suited for a study on the influence of solvent on 1,3-dipolar cycloadditions.

In our case, certain solvents can compete with the nitrile oxide in the formation of hydrogen bond with the hydroxyl group and this fact could bring about a change in the diastereo facial selectivity of the reaction.

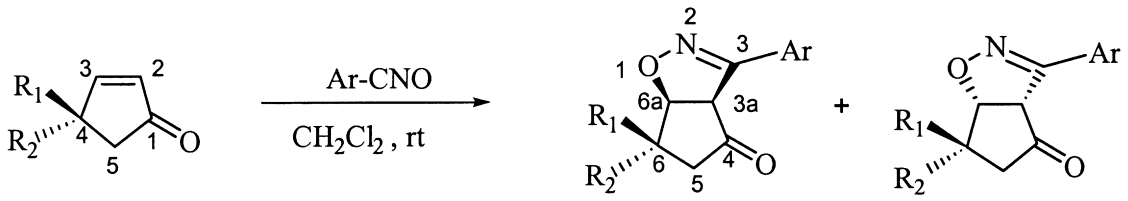
The reactions were carried out in the same conditions using as solvents dichloromethane, toluene, methanol, tetrahydrofuran, dioxane and dioxane–water (65:35). The results are shown in Table 1.

For compound **1** there is a clear change in facial diastereoselectivity in going from CH_2Cl_2 to toluene. However attack from the hydroxyl face is still favoured; in methanol the two diastereoisomers are formed in almost the same amounts while passing to THF, dioxane, and dioxane-water (65:35) the diastereoselectivity is reversed with preferential approach of the nitrile oxide from the methyl face.

This trend is even more evident in compound **2** where the attack from the H(4) face is already preferred in toluene with respect to CH_2Cl_2. In the other solvents this trend is enhanced.

The greater solvent effect found for compound **2** with respect to **1** must be due to the greater steric effect exerted by the methyl group (Me(4)) in **1** with respect to that determined by the hydrogen atom (H(4)) in **2**.

The same experiments with compounds **3**, **4** and **5** clearly show that the ratios of the two corresponding diastereoisomers are independent on the solvent. Thus if the OH(4) is missing or protected there is no solvent effect.



(±) - **1-5** (±) - **1a-5a** (±) - **1b-5b**

1 R_1 = OH R_2 = Me
2 R_1 = OH R_2 = H
3 R_1 = OAc R_2 = Me
4 R_1 = OAc R_2 = H
5 R_1 = Me R_2 = H

Ar-CNO = 2,6-dichlorobenzonitrile oxide
4-chlorobenzonitrile oxide
4-methylbenzonitrile oxide
benzonitrile oxide
CH_3-CNO

(Scheme 1)

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Solvent influence on diastereofacial selectivity in the reactions of 2-cyclopentenones **1**, **2**, **3**, **4** and **5** with 2,6-dichlorobenzonitrile oxide[a]

Compound	Solvent	**a**/%	**b**/%	Yield (**a** + **b**)/%
1	CH_2Cl_2	85	15	87
	Toluene	71	29	85
	MeOH	50	50	85
	THF	38	62	80
	Dioxane	44	56	80
	Dioxane/water (65:35)	44	56	85
2	CH_2Cl_2	55	45	81
	Toluene	42	58	80
	MeOH	27	73	80
	THF	22	78	83
	Dioxane	27	73	80
	Dioxane/water (65:35)	25	75	78
3	CH_2Cl_2	57	43	74
	Toluene	55	45	70
	MeOH	58	42	75
	THF	55	45	75
	Dioxane	55	45	72
	Dioxane/water (65:35)	57	43	70
4	CH_2Cl_2	0	100	71
	Toluene	0	100	70
	MeOH	0	100	65
	THF	0	100	68
	Dioxane	0	100	65
	Dioxane/water (65:35)	0	100	67
5	CH_2Cl_2	32	68	75
	Toluene	30	70	78
	MeOH	35	65	74
	THF	35	65	72
	Dioxane	32	68	70
	Dioxane/water (65:35)	33	67	72

[a]Diastereoisomers ratios were determined by integration of suitable ^{1}H NMR resonances
(Me(6) signals for compounds **1a**,**b**, **3a**,**b** and **5a**,**b** and H(6) for compounds **2a**,**b**).

This evidence is a proof that there is an interaction between the OH group and the nitrile oxide. This interaction is hampered in polar solvents leading to a change in the diastereoselectivity. The change observed in toluene should be due to strong association between this solvent and the nitrile oxide.

Thus it is possible to preferentially direct the attack of the nitrile oxide to one of the two faces of **1** and **2** by changing the solvent. This is very important for the stereochemistry of the isoxazolines but also in view of a stereocontrolled functionalisation of the cyclopentenones. The results are dominated by the complete regioselectivity of these reactions that is not affected by the solvent.

Experimental

All compounds were synthesised according to the literature methods.[11]

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