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Hydrophobic Effect on 1,3-Dipolar Cycloaddition Reactions

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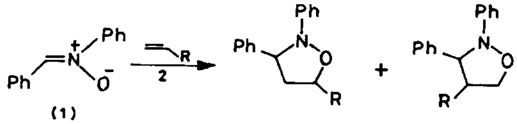
Abstract: Rate and selectivity of 1,3-dipolar cyloaddition reactions of C,N-diphenylnitrone are influenced by hydrophobic effect. © 1997 Elsevier Science Ltd.

The remarkable rate acceleration and the reversal of stereoselectivity of Diels-Alder reactions in water have generated considerable interest in aqueous organic chemistry[1]. The reversal of stereochemistry, in particular, has found its useful application in the synthesis of natural products[2]. 1,3-Dipolar cycloaddition reactions have also attracted considerable attention in recent years with regard to their application in organic synthesis[3]. One of the challenges in this field is to control the regio- and diastereoselectivities. Although optically active starting materials and chiral metal catalysts have been used to induce the diastereo and enantioselectivities in 1,3-dipolar cycloaddition reactions[4], the influence of hydrophobic effect on these reactions has not yet been explored. In this context, we considered that the study of the influence of hydrophobic effect on the rate and selectivity of 1,3-dipolar cycloadditions would be of particular interest.

As a model we have chosen to study the aqueous 1,3-dipolar cycloaddition of C,N-diphenylnitrone with monosubstituted olefins because it is one of the most extensively studied systems in respect of its regio- and stereochemical course of reaction and could provide necessary information for the comparative studies. Thus, the 1,3-dipolar cycloadditions of C,N-diphenylnitrone 1 with excess of methyl acrylate, acrylonitrile and vinyl acetate were studied in aqueous medium. In general, reactions were conducted at ambient temperature with vigorous stirring, employing 0.25 mM nitrone and an excess of dipolarophile (5 mM) in 5 ml water. The extraction with dichloromethane followed by evaporation of the solvent and excess dipolarophile under reduced pressure at room temperature gave the corresponding isoxazolidines. The reaction products were analysed by ^{1}H-NMR.

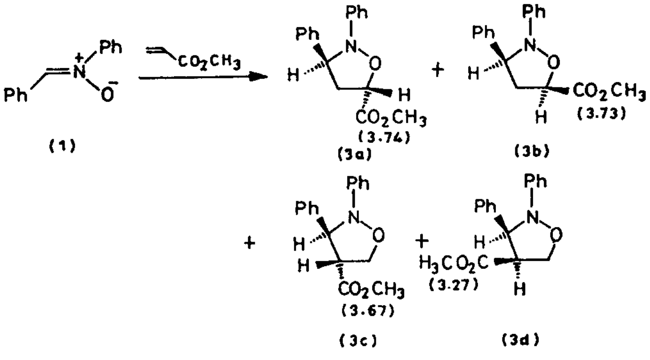


R = CO_2CH_3,CN,$OCOCH_3$

Reactions of C,N-Diphenylnitrone 1 with Dipolarophiles 2

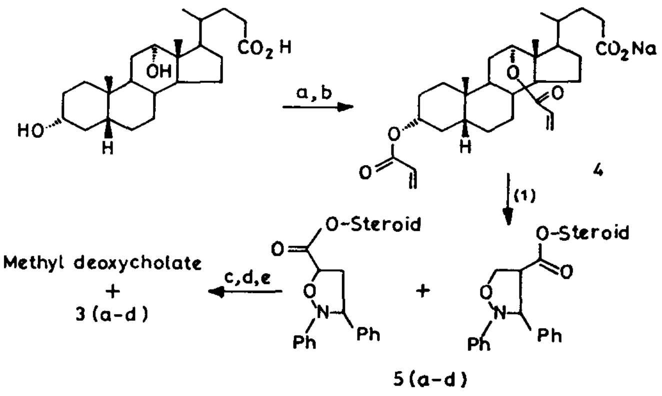
S.No.	Dipolarophiles	Media	Temp (°C)	Time(h)	Yield(%)
1.	Methyl acrylate	Benzene	25	3.0	30
		Water	25	3.0	95
2.	Acrylonitrile	Benzene	25	2.5	15
		Water	25	2.5	95
3.	Vinyl acetate	Benzene	25	18.0	05
		Water	25	18.0	45

The above table reveals that 1,3-dipolar cycloaddition reactions of C,N-diphenylnitrone with dipolarophiles 2 show considerable rate enhancement on changing the solvent from benzene to water. As 1,3-dipolar cycloaddition reactions, in general, do not depend on the polarity of the solvent[5], only the hydrophobic effect seems capable of explaining these results. We have also examined the aspect of selectivity in aqueous 1,3-dipolar cycloaddition reaction. The 1,3-dipolar cycloaddition reaction of C,N-diphenylnitrone with methyl acrylate gives a mixture of four isomeric isoxazolidines 3(a-d) which can be identified by their carbomethoxy peaks in ^{1}H-NMR (δ3.74, 3.73, 3.67, 3.27)[6]. It was found that there was no significant change in the ratio of the diastereoisomers (28:44:16:12) on changing the medium from benzene to water.



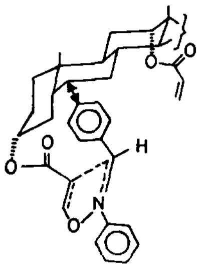
Further, we have examined the effect on selectivities of a chiral and hydrophobic environment in aqueous 1,3-dipolar cycloaddition. We considered sodium deoxycholate as an ideal system for the creation of such environment in water which might facilitate the hydrophobic binding of the dipole and the dipolarophile. Thus, treatment of 3,12-diacryloyl sodium deoxychlolate (4, 0.5 mM) with C,N-diphenylnitrone (1, 0.5 mM) in water (10 ml) at room temperature for 10 h resulted in the formation of the steroidal isoxazolidines 5(a-d) in 70% yield. There was no indication of the formation of the cycloadduct with the dipolarophile at 12-position.

Hydrolysis of the steroidal isoxazolidines followed by esterification as indicated in the following scheme afforded a mixture of the isomeric carbomethoxy isoxazolidines 3(a-d). The analysis of the mixture of isoxazolidines by ^{1}H-NMR indicated the presence of the diastereomers 3(a-d) in the ratio (28:45:3:24) respectively.

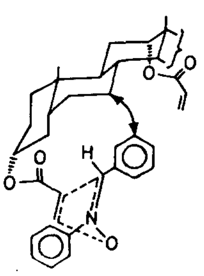


a:$CH_2=CHCOCl/CHCl_3$; b:$NaHCO_3$; c:K_2CO_3/acetone-water; d:H^+; e:$HC(OCH_3)_3/CHCl_3$, H^+

This result clearly indicates that the *exo*-orientation of the dipole and the dienophile is favoured over the *endo*-orientation giving preferentially *cis*-products. Remarkably, in the case of 4-substituted isoxazolidines, very high stereoselectivity is observed with the preferential formation of *cis*-isomer. This is in contrast with the results in organic solvents where *trans*-4-substituted isomer is always favoured. We consider that the hydrophobic interaction between the steroid and the C-phenyl substituent in the transition state may be one of the principal contributors of this selectivity. As shown below, the hydrophobic interaction in the *exo*-orientation would be expected to be much larger than that in the *endo*-orientation.



Exo-orientation



Endo-orientation

In summary, the 1,3-dipolar cycloaddition reactions of C,N-diphenylnitrone with methyl acrylate, acrylonitrile and vinyl acetate are considerably faster in water than in benzene. Surprisingly, there is no marked increase in the regio- and/or stereoselectivity. However, dipolarophile attached to sodium deoxycholate appears to give high diastereoselectivity at least in the case of 4-substituted regioisomer.

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