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A REGIOSELECTIVE ENZYME CATALYZED CYCLOADDITION[+]

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Abstract: Baker's Yeast catalyzed the regioselective cycloaddition of nitrileoxides 1 to cinnamic esters 2. Reversal of regioselectivity is observed in these cycloadditions by using β-cyclodextrin as an artificial enzyme along with baker's Yeast.

Of recent, the catalytic activity of enzymes has been the focus of interest in organic synthesis due to their specificity, mild conditions and excellent stereoselectivities.[1] But their utility has not yet been explored for studying the versatile dipolar cycloaddition reactions with different regioselectivities. Nonetheless, the existing non-enzymatic methodologies are still not ideal to steer the regioselectivity of cycloadditions in the desired direction.

In the present study, we have found for the first time that Baker's Yeast (Saccharomyces Cerevisiae) catalyzes regioselective 1,3-dipolar cycloaddition reactions such as nitrileoxides 1 to cinnamic esters 2. Higher regioselectivities can be achieved by varying the substitution in the dipolarophile. A novel modification of the enzyme catalyzed cycloaddition has been introduced by using β-cyclodextrin as an artificial enzyme to totally reverse the regioselectivity of cycloaddition. Thus, this reaction becomes the first valuable tool for the enzyme catalyzed synthesis of desired regioisomers of 2-isoxazolines 3 and 4, which are important for various stereocontrolled synthesis of highly functionalized molecules.[2,3]

Stable nitrileoxides 1 (1.5 mmol) and cinnamic ester 2 (1.5 mmol) are taken in 30% ethanol (20 ml) and Baker's Yeast[4] (0.5 g) in pH 7.2 buffer (12.5 ml) is added and incubated at 37°C for 30 h. The mixture is then extracted with chloroform (2x20 mL), dried, evaporated and purified by flash chromatography on silicagel using chloroform as eluant. Highly regioselective cycloaddition leading exclusively to one regioisomer 3 is observed with all the nitrileoxides 1a-c when the dipolarophile contains tert-butyl group as in 2c. However, a lower level of selectivity is seen in cycloaddition of nitrileoxide 1b with ethylcinnamates 2a,b giving a mixture of regioisomers[5] 3 and 4 (in the ratio of 65:35 respectively) with preponderance of the former. But, when the nitrileoxide containing electron releasing groups as in 1a,c underwent cycloaddition with 2a,b, only one regioisomer 3 is obtained. The isomer 4 could not be obtained exclusively in any case.

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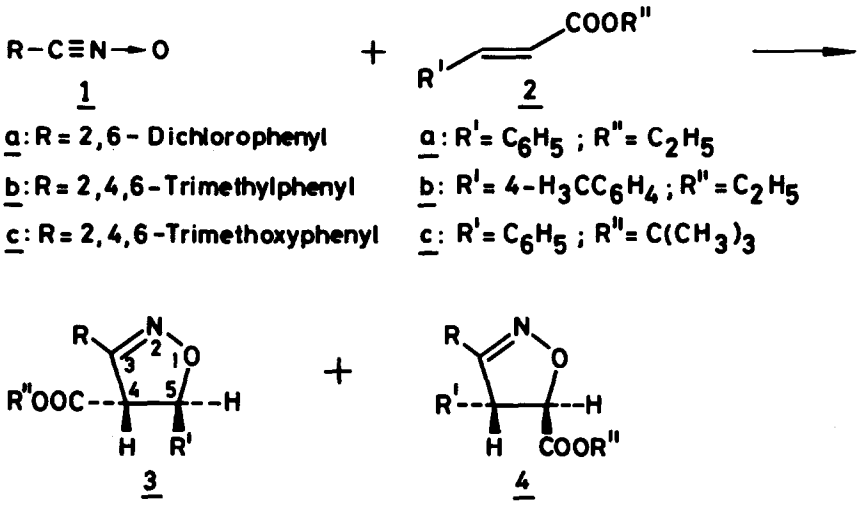
Scheme I



At this stage, a novel approach has been envisaged to improve the regioselectivity of ethylcinnamates 2a,b with the nitrileoxide 1b by adopting two host cavities so that the geometry of both the dipole and the dipolarophile would be rigidly fixed during the cycloaddition. Cyclodextrins, which have excited much interest in various biomimetic syntheses due to their ability to bind substrates selectively and catalyse reactions,[6] have been used presently as artificial enzymes for the dipolarophile (1.5 mmol) by making 1:1 complex with β-cyclodextrin.[7] The addition of the aqueous solution containing the inclusion complex of the dipolarophile with cyclodextrin to the buffer solution of nitrileoxide (1.5 mmol) and Baker's Yeast (0.5 g) yielded surprisingly the regioisomer 4, so far not possible to generate exclusively by the cycloaddition of 1b to 2a,b. It is thus shown for the first time that the regioselectivity in cycloadditions can be totally changed in the reverse direction without altering the substituents by fixing the diplarophile in cyclodextrin which acts as an artificial enzyme and the dipole in the binding cavity of the natural enzyme. However, this reversal of regioselectivity could not be observed in the cycloaddition of nitrileoxides having electron releasing groups as 1a,c with 2a,b and also in the cycloaddition of nitrileoxides 1a-c with tert-butyl substituted cinnamic ester 2c. Only the regioisomer 3 is isolated in these cases as observed in enzymatic catalysis alone. These results may be interpreted as follows.

In terms of FMO theory, cinnamic esters contain larger HO coefficient on the carbon attached to the ester, whereas LU coefficients are nearly the same.[8] Nitrileoxides as 1,3-dipoles have increased electrophilicity and nitrilium carbon is the terminus that possesses higher coefficient in the LUMO. Then the origin of regioselectivity can be accounted by the principle of maximal overlap, according to which the preferred isomers from each interaction can be predicted by the union of two sites of reactants having largest coefficients.[9] In the present case, with nitrileoxides 1a-c and tert-butylcinnamate 2c the results indicate that the regioselective effect of cycloaddition is clearly by LUMO (dipole)-HOMO (dipolarophile) interaction to form exclusively the isomer 3. It could be further seen from the experimental results that the selectivity decreases in the cycloaddition of nitrileoxide 1b with ethyl substituted esters 2a-b. However, when the nitrileoxide contains electron releasing groups in the phenyl ring as in 1a,c, 3 is preferentially formed with 2a,b. The surprising steering of regioselectivity of cycloaddition with nitrileoxide 1b and ethyl cinnamates 2a,b to give exclusively 4 by forming inclusion complex of the dipolarophile with β-cyclodextrin may be due to the dependence of the coefficients in the frontier MOs on effective hydrogen bonding of β-cyclodextrin hydroxyls with the ester group.

The ability to control the regioselectivity of enzyme catalyzed cycloaddition reactions by using β-cyclodextrin as an artificial enzyme, apart from its synthetic value for nitrileoxide cycloaddition to alkenes, if understood mechanistically (currently under study) may find far reaching application in various stereocontrolled syntheses.

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4. Baker's Yeast (Saccharomyces cerevisiae, Type 1) was purchased from Sigma Chemical Co., U.S.A.

5. Regioisomers 3 and 4 were identified by ^{1}H-NMR spectroscopy from the chemical shift differences and coupling constants of H4 and H5 protons as given in Christl M.; Huisgen, R. and Sustmann R., Chem.Ber., 1973, 106, 3275. These aqueous cycloaddition reactions do not take place in the absence of Baker's Yeast.

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7. The inclusion complex of ethylcinnamate with β-cyclodextrin was prepared by adding the ester in alcohol to an aqueous saturated solution of β-cyclodextrin. The ester formed inclusion compound on an equimolar basis with β-cyclodextrin as determined by ^{1}H NMR and from the amount of ester extracted from known amount of the complex.

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