Tetrahedron Letters, Vol.31, No.22, pp 3201-3204, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

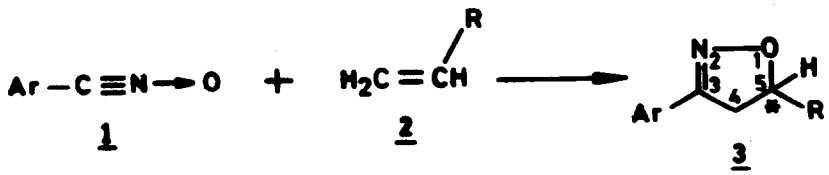
BAKER'S YEAST CATALYZED ASYMMETRIC CYCLOADDITION OF NITRILEOXIDES TO C=C BOND : IMPROVED CHIRAL RECOGNITION BY USING β-CYCLODEXTRIN+

K. Rama Rao*, N. Bhanumathi and P.B. Sattur
Organic Chemistry-I, Indian Institute of Chemical Technology
Hyderabad-500 007, India

Abstract : Baker's yeast catalyzes for the first time the asymmetric cycloaddition reaction of arylsubstituted nitrileoxides 1 to vinylpyridines 2 to yield optically active 2-isoxazolines 3. The stereoselectivity is enhanced by fixing the geometry of both dipole and dipolarophile by using β-cyclodextrin as an additional binding cavity along with Baker's yeast.

The use of enzymes as chiral catalysts in organic synthesis is becoming increasingly important due to their specificity, mild conditions, high yields and excellent stereoselectivities.[1] But their utility has not yet been explored for asymmetric induction in dipolar cycloaddition reactions. Hence, an attempt has been made for the first time to gain access into enzyme catalyzed asymmetric cycloaddition reactions by utilizing Baker's yeast (Saccharomyces cerevisiae) which is earlier known to induce chirality in various transformations for generating chiral synthons.[2,3]

Our continued interest on dipolar cycloaddition reactions of nitrileoxides[4] and on newer asymmetric synthesis through biomimetic modelling,[5] prompted us to investigate the asymmetric 1,3-dipolar cycloaddition reaction of nitrileoxides[6] 1 to the active C=C bond of 2- and 4-vinylpyridines 2 in presence of Baker's yeast, since this reaction gives heterocyclic substituted optically active 2-isoxazolines 3 which represent the masked form of an array of different functionalities.[7,8] The regioselective formation of only 5-pyridyl substituted 2-isoxazolines 3 also fits the LUMO (dipole)-HOMO (dipolarophile) interaction with the preferred attachment of the dipolarophilic carbon of greater spatial requirement of vinylpyridine i.e. α-carbon, with the oxygen of the nitrileoxide leading to the sterically most favoured transition state.[9,10]



1 2 3

Ar = 2,4,6-Trimethylphenyl, 2,4,6-Trimethoxyphenyl & 2,6-Dichlorophenyl
R = 2-Pyridyl & 4-Pyridyl

The stable nitrileoxides 1 (1.55 mmol) and vinylpyridines 2 (1.55 mmol) are taken in 30% ethanol (20 ml) and incubated at 37°C with Baker's yeast (0.5 g, Saccharomyces cerevisiae, Type-1, purchased from Sigma Chemical Co.,U.S.A) in pH 7.2 phosphate buffer (12.5 ml) for 20 h, extracted with chloroform and purified by flash chromatography. The optically active 2-isoxazolines 3 thus obtained are shown in the Table. It is seen from the results that the products from 4-vinyl series have shown better stereoselectivity. Amongst the compounds studied only 2-isoxazoline 3c formed from 2,6-dichlorophenyl nitrileoxide and 4-vinylpyridine has shown modest enantioselectivity with an ee upto 25%. This is probably due to poor chiral recognition during cycloaddition. Hence, a new concept has been envisaged in enzyme catalyzed reactions for improving the stereoselectivity by adopting two host cavities so that the geometry of both the dipole (nitrileoxide) and the dipolarophile (vinylpyridine) may be fixed during cycloaddition for attaining better enantioselectivity (Figure). This is further confirmed from the experimental results.

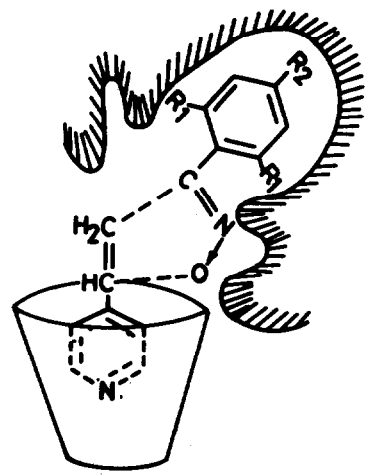


Figure Enzyme catalyzed asymmetric cycloaddition using β-cyclodextrin

The inclusion complex of 4-vinylpyridine (β-cyclodextrin did not form stable complexes with 2-vinylpyridine and nitrileoxides) with β-cyclodextrin has been prepared by adding 4-vinylpyridine (1.55 mmol) in acetone (2 ml) to an aqueous saturated solution of β-cyclodextrin (1.55 mmol) at 5°C. 4-Vinylpyridine formed inclusion compound on an equimolar basis with cyclodextrin as determined by ^{1}H NMR[11] and from the amount of 4-vinylpyridine extracted from known amount of the complex. The aqueous solution containing the inclusion complex of 4-vinylpyridine with cyclodextrin is then added to the buffer solution containing nitrileoxide (1.55 mmol) and Baker's yeast (0.5 g). It is then incubated at 37°C for 20 h and worked out.

Table Asymmetric cycloaddition of nitrileoxides to vinylpyridines

No.	Product 3[a] Ar	R	Yield % BY[b]	Yield % BY +β-CD[c]	$[\alpha]_D^{20}$ deg.[d] BY	$[\alpha]_D^{20}$ deg.[d] BY + β-CD	ee %[e] BY	ee %[e] BY + β-CD
A	2,4,6-Trimethylphenyl	4-Pyridyl	82	81	+ 5.1	+ 25.8	4.5	22.6
B	2,4,6-Trimethoxyphenyl	4-Pyridyl	88	89	-11.3	- 32.5	9.2	28.4
C	2,6-Dichlorophenyl	4-Pyridyl	83	85	+66.7	+160.0	25.6	64.0
D	2,4,6-Trimethylphenyl	2-Pyridyl	85	-	+ 2.8	-	2.5	-
E	2,4,6-Trimethoxyphenyl	2-Pyridyl	79	-	+ 5.6	-	3.6	-
F	2,6-Dichlorophenyl	2-Pyridyl	88	-	+11.5	-	8.8	-

a) All products were obtained in analytically pure form. ^{1}H NMR and mass spectra are in conformity with the structure. b) Baker's yeast. c) β-cyclodextrin. d) In acetone (C 0.1). e) Determined by ^{1}H NMR spectroscopy with $Eu(hfc)_3$ after reduction to the corresponding β-ketoalcohol with 10% Pd-C in $MeOH/H_2O$ using phosphate buffer (Ref. 12).

It is surprising to find for the first time that by fixing the geometry of dipolarophile in cyclodextrin and dipole in the natural binding cavity of the enzyme, it is possible to enhance the stereoselectivity of cycloaddition. It is again 2-isoxazoline 3C obtained from 2,6-dichlorophenyl nitrileoxide has shown higher enantioselectivity with an ee upto 64% (Table). The higher asymmetric bias observed for the cycloaddition with 2,6-dichlorophenyl nitrileoxide may be due to favourable control of geometry in the approach of the dipole and dipolarophile at the "active site". However, the cycloaddition of nitrileoxides with vinylpyridines in presence of only β-cyclodextrin without Baker's yeast has not yielded the expected cycloadduct but only nitriles of the corresponding nitrileoxides are isolated.

Thus, it has been demonstrated for the first time that enzymes can be used as chiral catalysts in asymmetric cycloaddition reactions and that the chiral recognition during cycloaddition can be improved by using cyclodextrin as an additional binding cavity.

References and Notes

1 a) Roberts, S.M., Chem.Ind.(London),1988,384. b) Riva, S.; Bovara, R.; Pasta, P. and Carrea, G., J.Org.Chem.,1986,51,2902.

2 Takeshita, M.; Terada, K. and Akutsu, N., Heterocycles,1987,26,3051.

3 Miura, S.; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Matsumoto, S. and Ishimoto, S., Tetrahedron,1976,32,1893.

4 a) Rama Rao, K.; Srinivasan, T.N. and Sattur, P.B., Heterocycles,1988,27,683.
b) Rama Rao, K.; Nageswar, Y.V.D.; Gangadhar, A. and Sattur, P.B.,Synthesis,1988,994.
c) Rama Rao, K.; Nageswar, Y.V.D. and Sattur, P.B., J.Heterocycl.Chem.,1989,26,255.

5 Rama Rao, K. and Sattur, P.B., J.Chem.Soc.,Chem.Commun.,1989,342.

6 Grundmann, C. and Dean, J.M., J.Org.Chem.,1965,30,2809.

7 Kozikowski, A.P. and Mugrage, B.B., J.Chem.Soc.,Chem.Commun.,1988,198.

8 Wade, P.A. and Bereznak, J.F., J.Org.Chem.,1987,52,2973.

9 Huisgen, R., Angew.Chem.Int.Ed.Engl.,1963,2,633.

10 Caramella, P. and Grunanger, P., 1,3-Dipolar Cycloaddition Chemistry Vol.1,Padwa,A., Wiley-Interscience, New York, 1984, pp324, 329.

11 Demarco, P.V. and Thakkar, A.L., Chem.Commun., 1970, 2.

12 Examples of reduction of 2-isoxazolines to β-ketoalcohols are known. Curran, D.P., J.Am.Chem.Soc.,1982,104,4024.

+ IICT Communication No.2430.

(Received in UK 11 April 1990)