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Biocatalytic Asymmetric Diels-Alder Reaction. Cycloaddition of Pyridazin-3-ones with Diethyl Azodicarboxylate[1)]

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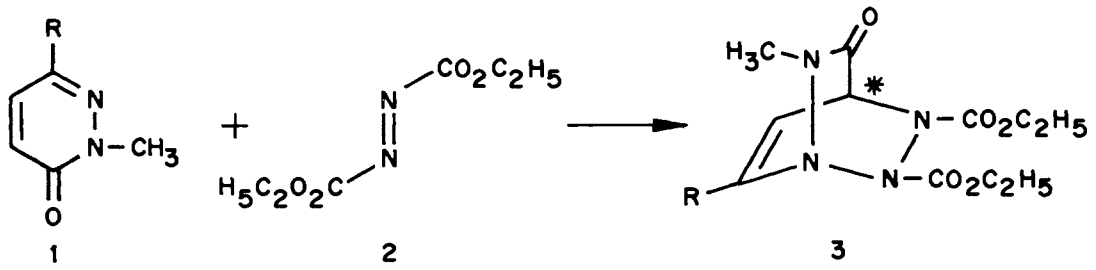
Baker's yeast catalyses for the first time the asymmetric Diels-Alder reaction of pyridazinones with diethyl azodicarboxylate to yield optically active cycloadducts with an enantiomeric excess (ee) of upto 63%.

Of recent, the use of enzymes and microorganisms as chiral catalysts in organic synthesis is becoming increasingly important due to the mild conditions employed and excellent stereoselectivities obtained.[2)] However, their utility for studying the versatile asymmetric Diels-Alder reactions has not yet been explored. Hence, an attempt has been made in this communication to gain access into biocatalytic asymmetric Diels-Alder reactions by utilizing Baker's yeast (Saccharomyces cerevisiae) which is earlier known to induce chirality in various transformations.[3,4b,d)]

In continuation of our ongoing research program on various biocatalytic regio- and asymmetric cycloaddition reactions,[4)] we report herein the first biocatalytic asymmetric Diels-Alder reaction of biologically active pyridazinone 1 with diethyl azodicarboxylate 2 leading to optically active condensed pyridazinones 3. This is a highly favoured reaction leading to stable cycloadducts. These enantioselective cycloadditions proceed without any chiral auxiliary either in the diene or in the dienophile.



1 2 3

a : R= C_6H_5
b : R=4-$H_3CC_6H_4$
c : R=4-$H_3COC_6H_4$
d : R= 4-ClC_6H_4
e : R= 3,4-di$H_3CC_6H_3$

2-Methyl-3-oxo-6-arylpyridazine[5] 1 (1.5 mmol) and diethyl azodicarboxylate 2 (1.5 mmol) are taken in 20% ethanol (20 ml) and incubated at 37°C with Baker's yeast (0.5 g, Saccharomyces cerevisiae, Type-I, purchased from Sigma Chemical Co., U.S.A.) in pH 7.2 phosphate buffer (12.5 ml) for 24 h, extracted with dichloromethane and purified by flash chromatography. The results for the optically active cycloadducts 3, obtained are shown in Table 1. Apart from the regular analysis carried for characterisation, further confirmation of the products is obtained by retro Diels-Alder fragmentation in the mass spectrum and the appearance of asymmetric carbon at 62.1 ppm in ^{13}C NMR. These cycloadditions do not take place in the absence of Baker's yeast. Boiled solutions of Baker's yeast have not shown any catalytic effect. The controlled experiments with the racemic cycloadduct 3 using Baker's yeast under essentially the same conditions of enzymatic cycloaddition have also not yielded any optically active product 3. These experiments clearly demonstrate the catalytic effect of Baker's yeast.

Amongst the compounds studied (Table 1) the cycloadduct 3b obtained from 2-methyl-3-oxo-6 (4-methylphenyl) pyridazine 1b has shown the highest enantioselectivity with an ee upto 62.7%. The higher asymmetric bias observed for the cycloaddition with 1b may be due to favourable control of geometry in the approach of the diene and dienophile at the active site.

Thus, it is demonstrated for the first time that the enzymes can be used as chiral catalysts in asymmetric Diels-Alder reactions to give chiral fused heterocycles. Further work on various applications of this biocatalytic cycloaddition is currently under study.

Table 1. Biocatalytic asymmetric Diels-Alder reaction

Product[a]	R	Yield/%	$[\alpha]_D^{20}$ /deg[b]	ee%[c],[d]
3a	Phenyl	76	+ 7.9	33.3
3b	4-Methylphenyl	72	- 8.7	62.7
3c	4-Methoxyphenyl	73	- 1.7	9.1
3d	4-Chlorophenyl	82	+ 4.2	28.5
3e	3,4-Dimethylphenyl	79	+ 5.8	35.3

a) All products are obtained in analytically pure form. b) In acetone (c 0.1) c) Determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ as chiral shift reagent. d) Absolute configuration not known.

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