Highly Selective Biocatalytic Cycloaddition of Azodicarboxylates to Vinylpyridines †,††

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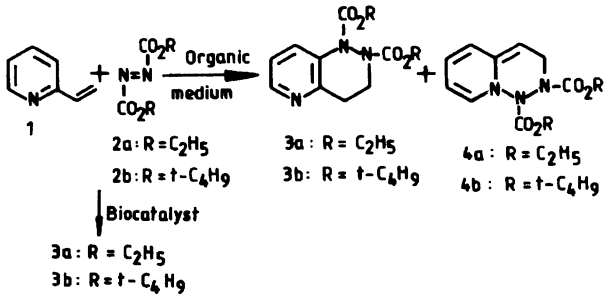
(Received February 4, 1993)

Synopsis. Biocatalytic [4+2] cycloaddition of vinylpyridines with azodicarboxylates in the presence of 'Saccharomyces cerevisiae' proceeds selectively in good yields.

So far, the studies on the [4+2] cycloaddition of vinylpyridines with azodicarboxylates have revealed that a mixture of cycloadducts was formed in poor yield.[1] Hence in continuation of our studies on the utility of enzymes as catalysts in organic synthesis,[2] an attempt has been made to investigate these reactions under biocatalytic conditions to see whether the selectivity and yields of these cycloadditions could be improved.

It is observed from the literature[1] that the reaction of 2-vinylpyridine **1** with diethyl and di-*t*-butyl azodicarboxylates **2** proceeds in organic medium to give a mixture of isomers **3** and **4** in < 20% yield (Scheme 1, Table 1).

In the present investigation, it is observed that in the presence of biocatalyst (Saccharomyces cerevisiae)[3] the



Scheme 1.

Table 1. Reaction of Vinylpyridines with Azodicarboxylates

Entry	Vinylpyridine	Azodicarboxylate	Medium	Products/%		
				3	**4**	**6**
1	**1**	**2a**	Organic	13	2	—
2	**1**	**2a**	Biocatalytic	80	—	—
3	**1**	**2b**	Organic	19	2	—
4	**1**	**2b**	Biocatalytic	84	—	—
5	**5**	**2a**	Organic	—	—	13
6	**5**	**2a**	Biocatalytic	—	—	61
7	**5**	**2b**	Organic	—	—	16
8	**5**	**2b**	Biocatalytic	—	—	63

†IICT communication No. 3063.
††Presented in part at the IUPAC-NOST international symposium on "Enzymes in Organic Synthesis," held at New Delhi, India, Jan 6—9, 1992.
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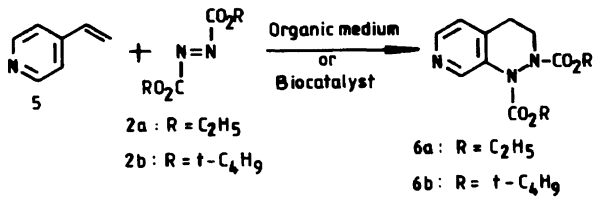

Scheme 2.

cycloaddition proceeds in a highly selective fashion giving only one isomer **3** in high yield. The yield of annulated pyridazine **6** obtained by the biocatalytic addition of 4-vinylpyridine **5** with azodicarboxylates **2** is also far greater (> 60%) than in organic medium (Scheme 2, Table 1). All compounds are obtained in analytically pure form and the spectral data are in conformity with the earlier observations.[1]

These cycloadditions do not take place in the absence of the biocatalyst. Boiled solutions of the biocatalyst have also not shown any catalytic effect. Thus it is observed from these results that the biocatalytic cycloadditions are more selective than classical synthesis in organic medium and can be performed under mild conditions in higher yields.

Experimental

General Procedure: 2-Vinylpyridine **1** or 4-vinylpyridine **5** (3 mmol) and diethyl or di-*t*-butyl azodicarboxylate **2** (3 mmol) were taken in 20% ethanol (19.2 ml) and then incubated at 37 °C with Baker's yeast (0.96 g, Saccharomyces cerevisae)[3] in pH 7.2 phosphate buffer (25 ml) for 24 h. The mixture was extracted with dichloromethane and the products were purified by flash chromatography.

References

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3) Baker's yeast (Saccharomyces cerevisiae, Type-1) was purchased from Sigma Chemical Company, U.S.A.