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BAKER'S YEAST REDUCTION OF 5-ACETYL-2-ISOXAZOLINES
SYNTHESIS OF ENANTIOMERICALLY PURE 2,3-DIHYDROXY KETONES AND 1,2,4-TRIOLS

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Abstract: Saccharomyces cerevisiae reduces enantioselectively racemic 5-acetyl-2-isoxazolines to 5-ethanol-2-isoxazolines in high yields and high enantiomeric excess. Subsequent ring hydrogenolysis of the alcohols thus produced leads to enantiomerically pure 2,3-dihydroxy ketones and 1,2,4-triols.

2-Isoxazolines are known as versatiles intermediates for the syntesis of various classes of compounds such as β-hydroxy ketones, β-hydroxy nitriles, γ-amino alcohols, sugars, and amino sugars.[1]

The utility of the isoxazoline route to the molecules of nature[1d] would be greatly enhanced if 2-isoxazolines could be easily prepared in optically active form.

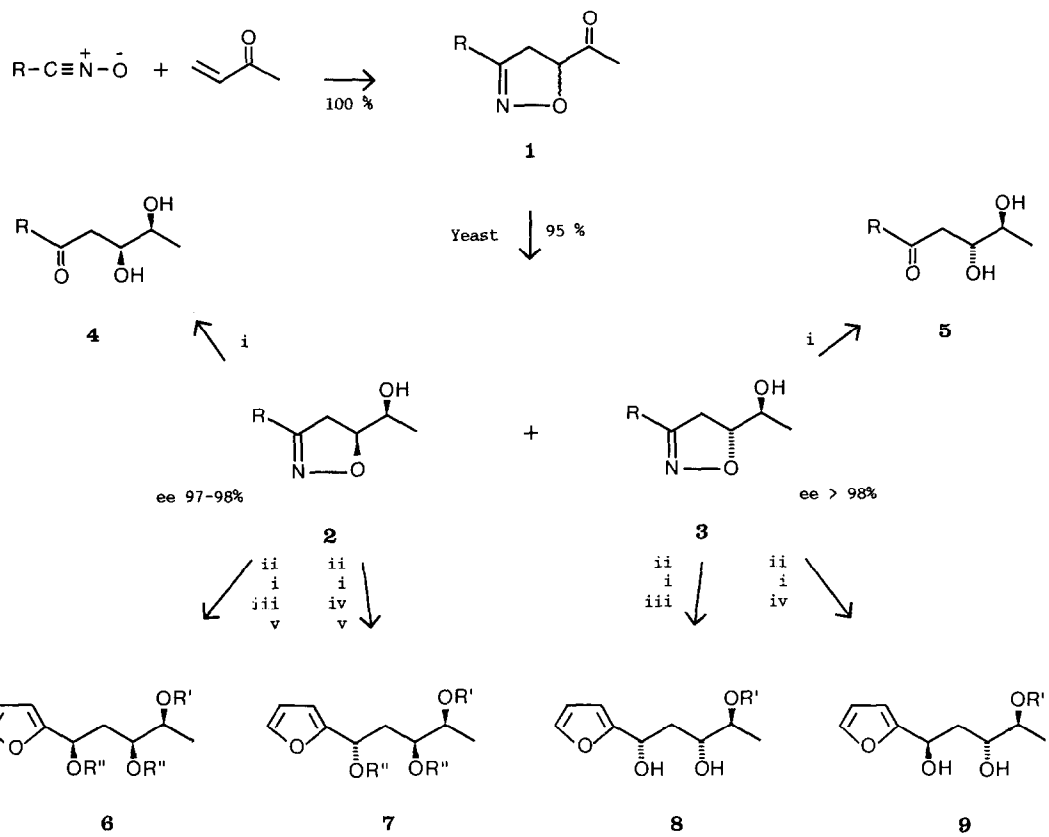
A remarkable amount of research is currently devoted to the synthesis of optically pure isoxazolines;[2] in particular, intermolecular[2b-e] and intramolecular[2a,2g-j] cycloaddition of nitrile oxides with olefins possessing an allylic chiral centre has been the object of extensive studies: the reaction has shown, in same case, good diastereofacial selectivity[2d] but severe structural requirements prevent a general application of the method.[2e]

In the present communication we report our initial results on the enantioselective baker's yeast reduction of 5-acetyl-2-isoxazolines. Aim of the research is the synthesis of fragments with a dense array of centres of chirality for use in natural products synthesis as advanced precursors.

5-Acetyl-2-isoxazolines 1 can be obtained in quantitative yield by 1,3-dipolar cycloaddition of a nitrile oxide on methyl vinyl ketone. 2-Isoxazolines 1a and 1b have been used as model compounds for the study of the reduction.

When made to react with baker's yeast racemic isoxazolines 1a and 1b give alcohols 2 and 3 in nearly quantitative yields. Alcohols 2a and 2b are produced with an enantiomeric excess of 97-98%, 3a and 3b with an ee of over 98%. We have performed the reaction at 35°C at pH ranging from 3.3 to 8.0: in all cases the reaction starts as soon as the substrate is added to fermenting yeast and

Scheme (absolute configuration shown)



a R = 2-Furyl
b R = Ph
c R = Me
d R = COOEt
R' = CH_2OCH_3
R" = CH_2Ph

i) H_2, Ni-Raney, H_3BO_3, H_2O-MeOH; 95-100%. ii) $ClCH_2OCH_3$; 85-95%. iii) $Zn(BH_4)_2$; 89-93% (6: 80% syn; 8: 82% syn). iv) $Me_4NHB(OAc)_3$; 92-95% (7: 63% anti; 9: 85% anti). v) $PhCH_2Br$.

	$[\alpha]_D$	c ($CHCl_3$)	mp (°C)
2a	165	2.0	58
2b	144	1.5	76
3a	-150	1.9	87
3b	-140	1.5	97
4a	-49.4	1.1	55
4b	-67.2	1.6	108
5a	58.1	1.5	66
5b	65.5	1.6	64
6	41.6	1.4	-
7	-84.2	1.4	-
8	5.6	1.5	-
9	51.6	1.4	-

is complete in 2 h with identical results.[3] The reduction occours as well under non-fermenting conditions and with cell-free extracts the only difference being a longer reaction time.

Alcohols 2 and 3 are formed at different rates allowing a partial kinetic resolution: for instance, when 1b is reduced with resting yeast cells in 10:1 water:ethanol 2b:3b ratio is 3.9 at 50% conversion:[4] as compounds 2a and 2b are obtained in crystalline form, their isolation and purification was fast; moreover both compounds are obtained in 100% ee after crystallization from cyclohexane-benzene. If the reaction is allowed to reach 100% conversion the diastereoisomeric products of the reaction, 2a and 3a, 2b and 3b, can be readily separated by normal flash chromatography (200 g of silica gel for 1g of mixture; hexane/ethyl acetate 6/4 as the eluent).

We have ascertained, only by HPLC analysis on small scale experiments, that the reduction of 5-acetyl-isoxazolines with different substituents in 3-position, such as 1c and 1d, proceeds in an identical way.

The relative configuration of the products has been established from the values of the ^{1}HNMR coupling constants between the cyclic and exocyclic protons of the compounds as such (2a and 2b: 5.4 Hz; 3a and 3b: 3.3 Hz) and of their derivatives.[2d]

The absolute configuration and the enantiomeric excess have been assigned on the basis of the following results: (1) racemic 5-acetyl-2-isoxazoline 1a was reduced by $NaBH_4$ and the two diastereoisomers obtained were separately reacted with (+)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (MTPA-Cl); the two couples of diastereoisomers thus produced were easily distinguished by HPLC as four quite separated peaks;[5] (2) 2-furyl nitrile oxide was made to react with the MTPA derivative of (S)-allyl methyl alcohol: the two products so obtained were identical to the MTPA derivatives of the alcohols 2a and 3a obtained from the yeast reduction. The stereochemistry of the reduction is thus in agreement with Prelog's rule on the biological reduction of ketones.

The known isoxazoline ring scission process[1d] proved to be very efficient: when compounds 2 or 3 were subjected to hydrogenation[6] in the presence of Raney nickel, boric acid, and water[1c] 2,3-dihydroxyketones 4 and 5 were obtained in nearly quantitative yield. Finally, the ketones obtained in the same way on the methoxymethyl derivatives of 2a and 3a were reduced with $Me_4NHB(OAc)_3$ and with $Zn(BH_4)_2$: triols 6 - 9 were produced in high yields[7] and, except 7, with good diastereoselecivity.

In conclusion, the present procedure, which starts from readily available compounds, is simple and fast and is characterized by high yields. The method can require a diastereoisomer separation but provides a source of functionalized enantiomerically pure intermediates otherwise difficult to access.

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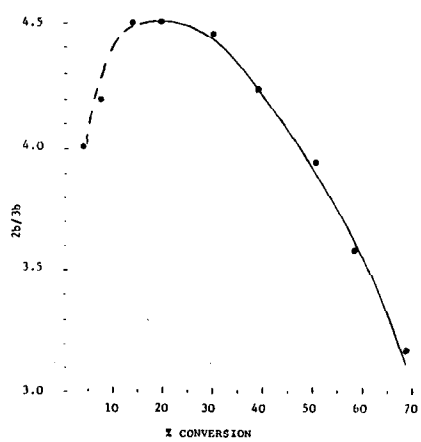
3. The reaction occours with resting yeast cells in pure water or in various different conditions of fermentation and at different temperatures. When the reaction is performed with fermenting yeast at pH 5.5-6.0 and 35 °C (tap water, KH_2PO_4, $(NH_4)_2HPO_4$, $MgSO_4$, yeast extract, glucose) is fast and the work-up is easy.

4. The course of the reaction has been followed by HPLC (silica gel column, hexane:ethyl acetate 7:3 as eluent, UV detection: λ 270nm). Reaction conditions: pure water (1 L), ethanol (100mL), dry yeast (20g, S.I.Lesaffre France), 1b (2 g), 33 °C. A graph is reported.



5. Silica gel column (0.3 x 10 cm; CP Sphere Si) hexane/ethyl acetate 9/1; flow rate 0.7ml/min. Retention times of the MTPA derivatives: racemic syn isomer 14 and 17 min; racemic anti isomer 15 and 16 min; 2a 17 min, 3a 16 min.

6. Crystallized, optically pure compounds have been used for hydrogenolysis reactions.

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