SYNTHESIS OF OPTICALLY ACTIVE HETERO ALKYLARYL ALCOHOLS BY BAKER'S YEAST

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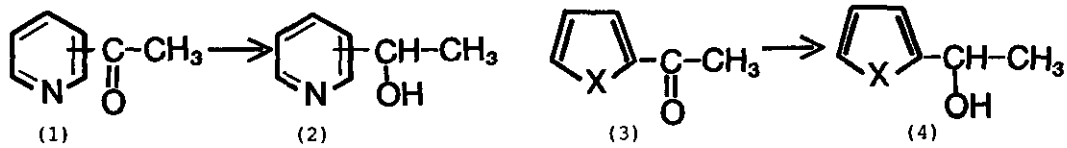
Abstract—— Synthesis of optically active hetero alkylaryl alcohols have been examined using baker's yeast.

The use of baker's yeast (Saccharomyces cerevisiae) in organic synthesis provides efficient access to the synthesis of chiral synthons. In the course of transformation with baker's yeast, various substrates were submitted to give versatile chiral compounds,but applications of this transformation to substrates, that have aromatic heterocycles, are not so many reported.[1,2]

Now, we investigated the synthesis of chiral synthons which have hetero aromatic ring using baker's yeast based on its reductive and hydrolytic abilities.

At first, α,β,γ-acetylpyridines(1a-c) were fermented with baker's yeast to give the chiral alcohols. The all pyridylethanols((-)-2a-c) obtained were found to have (S)-configuration[3]. The optical purities of both α-(2a) and γ-(2c) isomers were significantly high(96%ee), but of β-isomer(2b) were somewhat lower(67%ee).

In contrast, when α-acetyl five-membered heterocycles(3d-f) were treated under the same conditions, no satisfactory results were obtained. As shown(Table 1), α-acetylpyrrole(3f)was inert under these conditions, while both α-acetylfuran(3d) and α-acetylthiophene(3d) were reduced to give the corresponding alcohols,(4d) and (4e), however, diastereoselectivities were low(0 and15%ee).[4]



(1) (2) (3) (4)

a) α b) β c) γ d) X= O e) X= S f) X= N

Chart 1

Table 1 Asymmetric reduction of (1a-c) and (3d-f) with baker's yeast

Ketone	Time h	Alcohol	Yield[a]	$[\alpha]_D$ $CHCl_3$	$[\alpha]_D$ EtOH	Config.[b]	ee%[c]
1a	24	(-)-2a	36	-25.1° (c=1.5)	-55.5° (c=1.5)	S	96
1b	26	(-)-2b	40	-39.0° (c=0.8)	-25.4° (c=1.3)	S	67
1c	23	(-)-2c	18	-40.8° (c=2)	-43.8° (c=1)	S	96
3d	72	(-)-4d	25	-7.0° (neat)		S	15
3e	78	4e	28	———		——	——
3f	76	———	——	———		——	——

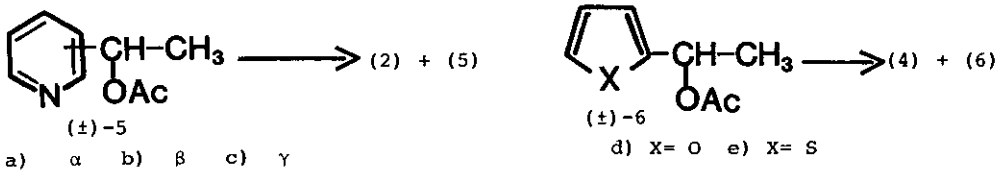
a) Isolated yield after column chromatography (SiO_2). b) Configurations were assigned based on the reported data (See reference 3 and 4). c) Calculated on the ^{1}H-n m r analysis of their (R)- or (S)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters.

Secondly, we tried the asymmetric hydrolysis of racemic pyridylacetates((±)-5a-c) using baker's yeast.[2]

When racemic acetates((±)-5a-c), prepared from corresponding racemic alcohols ((±)-2a-c), were fermented with baker's yeast at 31°C for 24-44 h, the substrates afforded the corresponding optically active alcohols(2a-c) in 24, 21, and 32% yield and the optically active acetates(5a-c) in 35, 25, and 30% yield, respectively. The optically active acetates(5a-c) thus obtained on hydrolysis gave the corresponding optically active alcohols(2a, 2b, and 2c) in 96, 67, and 96%ee, respectively. Very interestingly, it was found that diastereoselection was dependent on the position of the functional group. Namely, both of the α- and β-substrates((±)-5a and 5b) afforded (S)-alcohols(2a and 2b) in 47 and 28%ee and (R)-acetates(5a and 5b). On the contrary, the γ-substrate((±)-5c) afforded (R)-alcohol(2c) in 25%ee and (S)-acetate(5c). Unsatisfactory optical yield(∿ 47%ee) of the alcohols (2a-c), directory obtained by the microbial hydrolysis, may be owing to long reaction time which would allow competive non-diastereoselective hydrolysis by water.

We also tried to resolve the racemic α-furfurylethyl and α-thiophenylethyl acetates (6d-e) obtained from the corresponding alcohols(4d-e) with same condition. When acetates((±)-6d-e) were treated with baker's yeast at 22.5°C for 0.6-1 h, the corresponding acetates((+)-6d and 6e), which gave (R)-alcohols(4d and 4e) on hydrolysis in 35 and 40%ee, and (-)-alcohols(4d and 4e) with (S)-configuration in

30 and 54%ee were obtained, respectively (Chart 2) (Table 2).



a) α b) β c) γ d) X= O e) X= S

Chart 2

Table 2 Asymmetric hydrolysis of ((±)-5a-c) and ((±)-6d-e) with baker's yeast

Acetate	Time h	Major Product	Yield[a]	Alcohol	$[\alpha]_D(CHCl_3)$ of Alcohol	Config.[c]	ee%[d]
(±)-5a	18	(-)-2a	24	(-)-2a	-9.7°(c=1)	S	47
	24	(+)-5a	35	(+)-2a[b]	+20.7°(c=1.6)	R	96
(±)-5b	25	(-)-2b	21	(-)-2b	-19.7°(c=1.5)	S	28
	24	(+)-5b	25	(+)-2b[b]	+35.5°(c=1.2)	R	67
(±)-5c	18	(+)-2c	32	(+)-2c	+13.1°(c=2)	R	25
	44	(-)-5c	30	(-)-2c[b]	-39.5°(c=8.4)	S	96
(±)-6d	0.6	(-)-4d	33	(-)-4d	-10.5°(neat)	S	35
	1	(+)-6d	25	(+)-4d[b]	+10.7°(neat)	R	30
(±)-6e	0.5	(-)-4e	33	(-)-4e	-12.1°(neat)	S	40
	1.2	(+)-6e	14	(+)-4e[b]	+13.1°(neat)	R	54

a) Isolated yield after column chromatography (SiO_2). b) Obtained from acetate by Hydrolysis(10% aq.NaOH)in quantitative yield. c) Configurations were assigned based on the reported data(See reference 3 and 4). d) Calculated on the ^1H-n m r analysis of their (R)- or (S)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters.[5]

Typical experiments are as follows:

Asymmetric reduction of (1a) with baker's yeast.

A mixture of 5g of α-acetylpyridine(1a) and 1000g of baker's yeast (Purchased from Oriental Yeast Co.) in 500ml of water was incubated for 24h at 33°C. The mixture was extracted cotinuously with $CHCl_3$ using Soxlet aparatus, and the $CHCl_3$ extract was evaporated off. The crude oil obtained was purified by column chromatography (SiO_2 50g, CH_2Cl_2) to give 1.8g (36%) of (S)-pyridylethanol(2a).[3]

Asymmetric hydrolysis of ((±)-5a) with baker's yeast.

A mixture of 4.7g of acetate((±)-5a) and 1000g of baker's yeast in 500ml of water was incubated for 24h at 33°C. The mixture was extracted with ether, and after

solvent was evaporated, the residue was purified by column chromatography (SiO_2, 150g, CH_2Cl_2) to give 1.67g(35%) of acetate ((+)-5a), $[\alpha]_D^{24}$ +100.3(c=1.67, $CHCl_3$) and (R)-pyridylethanol((-)-1a),(1.15g)(24%), $[\alpha]_D^{22}$ -3.59°(c=1.3, $CHCl_3$).

Hydrolysis of ((+)-5a)

A mixture of 0.35g of acetate((+)-5a), 5ml of 20%NaoH, and 2ml of MeOH were stirred at room temperature for 12h. 35ml of 10%HCl was added, and whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed sat.NaCl and dried over Na_2SO_4. Removal of the solvent afforded a product, which was purified by column chromatography (SiO_2 5g, CH_2Cl_2) to give 0.18g(72%) of (S)-pyridylethanol((-)-1a), bp. 95-98/12mmHg.[3d]

ACKNOWLEDGMENT

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5 Our results (%ee) thus obtained are slightly better comparing with those of Ziffer (See reference 3d).

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