DOI: 10.6060/ivkkt.20246701.6885

УДК: 547.43

БИОКАТАЛИТИЧЕСКОЕ ВОССТАНОВЛЕНИЕ 1-(4-МЕТИЛФЕНИЛ)ЭТАНОНА

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R- и S-1-(4-Метилфенил)этанолы являются компонентами эфирных масел некоторых растений семейства имбирных, используются для производства духов, отдушек для мыла и синтетических моющих средств. Эти соединения обладают антибактериальной активностью в отношении Pseudomonas aeruginosa. Нами изучено биовосстановление 1-(4-метилфенил)этанона, катализируемое клетками P. crispum, обладающими карбонилредуктазной активностью. Энантиоселективное восстановление 1-(4-метилфенил)этанона, протекающее в присутствии клеток P. crispum в водной среде при температуре 23-27 °C в течение 48 ч, приводит к образованию (S)-(–)-1-(4-метилфенил)этанола с выходом 49% (96% ее). Дальнейшая трансформация исходного кетона в течение 144 ч, как и в случае использования катализатора D. carota, приводит к незначительному повышению выхода спирта до 51%, однако при этом оптическая чистота продукта снижается до 80% ее. Исследовано также биовосстановление 1-(4-метилфенил)этанона, катализируемое клетками P.crispum, в присутствии экзогенных восстановителей (этанола, изопропанола или глюкозы), которые существенно влияют на выход продукта и энантиоселективность процесса. Установлено, что трансформация 1-(4-метилфенил)этанона в присутствии этанола (1-5%) или изопропанола (1-5%) в течение 144 ч приводит к образованию (S)-(–)-1-(4-метилфенил)этанола с удовлетворительными выходами и оптической чистотой. Восстановление 1-(4-метилфенил)этанона в присутствии изопропанола (1-3%) на 72 ч реакции приводит к снижению выхода (S)-(–)-1-(4-метилфенил)этанола, при этом возрастает концентрация исходного кетона. Биотрансформация 1-(4-метилфенил)этанона в течение 144 ч в присутствии эквимолярного количества глюкозы приводит к увеличению выхода (S)-(–)-1-(4-метилфенил)этанола до 52% (96% ее).

Ключевые слова: биотрансформация, энантиоселективное восстановление, 1-(4-метилфенил)этанон, (S)-(–)-1-(4-метилфенил)этанол

BIOCATALYTIC REDUCTION OF 1-(4-METHYLPHENYL)ETHANONE

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R- and S-1-(4-Methylphenyl)ethanols serve as a component of the essential oil from some plants in the ginger family and are used as flavoring agents in the production of perfumes, soap fragrances, and synthetic detergents. These compounds exhibit antibacterial activity against Pseudomonas aeruginosa. In this article we studied biotransformation of 1-(4-methylphenyl)ethanone catalyzed by P. crispum cells. It was found that enantioselective reduction of 1-(4-methylphenyl)ethanone catalyzed by P. crispum cells in an aqueous medium at 23-27 °C for 48 h

results in formation of (S)-(–)-1-(4-methyl)ethanol with 49% yield (96% ee). Further transformation of initial ketone for 144 h as in the case of similar reduction catalyzed by D. carota cells leads to a slight increase in the yield of alcohol to 51%. However, the optical purity decreases to 80% ee. The bioreduction of 1-(4-methylphenyl)ethanone catalyzed by P.crispum cells was also studied in the presence of exogenous reducing agents (ethanol, isopropanol, or glucose), which are known to significantly affect the yield of the product and the enantioselectivity of the process. Transformation of 1-(4-methylphenyl)ethanone in the presence of ethanol (1-5%) or isopropanol (1-5%) for 144 h leads to (S)-(–)-1-(4-methylphenyl)ethanol with poor yields and optical purity. The reduction of 1-(4-methylphenyl)ethanone in the presence of isopropanol (1-3%) for 72 h leads to a decrease in the yield of (S)-(–)-1-(4-methylphenyl)ethanol, while the concentration of the initial ketone increases. Biotransformation of 1-(4-methylphenyl)ethanone for 144 h in the presence of an equimolar amount of glucose leads to an increase in the yield of (S)-(–)-1-(4-methylphenyl)ethanol to 52% (96% ee).

Key words: biotransformation, enantioselective reduction, 1-(4-methylphenyl)ethanone, (S)-(–)-1-(4-methylphenyl)ethanol

Для цитирования:
Чанышева А.Р., Дибаева С.Т., Зорин В.В. Биокаталитическое восстановление 1-(4-метилфенил)этанона. *Изв. вузов. Химия и хим. технология*. 2024. Т. 67. Вып. 1. С. 104–109. DOI: 10.6060/ivkkt.20246701.6885.

For citation:
Chanysheva A.R., Dibaeva S.T., Zorin V.V. Biocatalytic reduction of 1-(4-methylphenyl)ethanone. *ChemChemTech* [*Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol*.]. 2024. V. 67. N 1. P. 104–109. DOI: 10.6060/ivkkt.20246701.6885.

INTRODUCTION

Enantioselective reduction of prochiral ketones, catalyzed by environmentally friendly cellular biocatalysts, is an efficient, convenient method for the preparation of optically active alcohols [1-10].

R- and S-1-(4-Methylphenyl)ethanols serve as a component of the essential oil from some plants in the ginger family and are used as flavoring agents in the production of perfumes, soap fragrances, and synthetic detergents. These compounds exhibit antibacterial activity against Pseudomonas aeruginosa.

EXPERIMENTAL

1-(4- Methylphenyl)ethanone was purchased from commercial sources.

Racemic alcohols were prepared from the corresponding ketone by reduction with $NaBH_4$.

Gas chromatographic analyses were performed on Khromatek-crystall-5000.2 with flame-ionization detector using the enantioselective column Astec CHIRALDEXB-PM (30m×0.25mm×0.12μm). Column temperature was 110 °C; oven temperature was 200 °C, detector temperature was 230 °C; helium was a carrier gas.

^{1}H and ^{13}C NMR spectra were measured on Bruker AM-300 and AMX-300 spectrometeres. As internal δ (0.00) for standards served TMS ^{1}H NMR and CDCl3 δ (77.0) for ^{13}C NMR spectroscopy.

GC-MS analyses were performed using GCMS-QP2010S Shimadzu. A mass spectrometer with an ion trap detector in full scan mode under electron impact ionization (70 eV) in the 35-500 amu range was used. The chromatographic column used for the analysis was an HP-1MS capillary column (30 m×0.25 mm×0.25 μm). The vaporizer temperature was 280 °C, the ionization chamber temperature was 200 °C. Helium was used as carrier gas at a flow rate of 1.1 mL/min. The injections were performed in mode at 100 -230 °C at a heating rate of 20 °C/min.

The absolute configurations of the compounds were determined with Optical Activity Polarimeter model AA-55.

Reduction of 1-(4- methylphenyl)ethanone

1-(4-Methylphenyl)ethanone (0.1 g) was added to a suspension of *P. crispum* cells (15 g) in distilled water (70 ml) under constant stirring in a conical Erlenmayer flask. The reaction mixture was then placed in an orbital shaker (150 rpm) at room temperature. After achieving the necessary conversions, the suspension was filtered, and *P. crispum* cells were washed three times with water. The filtrates were extracted with diethyl ether (3 × 125 mL). The organic phase was dried over $MgSO_4$, evaporated and monitored by GLC.

(S)-(–)-1-(4-Methylphenyl)ethanol

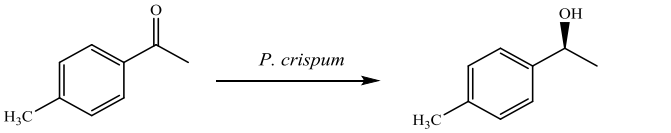
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.47 d (3H, CH_3), 2.34 s (3H, CH_3-C_{Ar}), 4.85 q (1H, C<u>H</u>-OH), 7.13–7.35 m (4H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 21.05 (<u>C</u>H_3-C_{Ar}), 25.03 (CH_3), 70.15 (CH-OH), 125.33 ($2CH_{Ar}$), 129.1 ($2CH_{Ar}$), 137.04 (C_{Ar}), 142.89 (C_{Ar}). GC/MS (m/z (%)): 136 ([M^+], 42.6), 121 (100), 93 (86), 92 (20.9), 91(69.4), 77 (41.9), 65 (22.9), 51 (11.6), 43 (57.7), 39 (17.1).

RESULTS AND DISCUSSION

We previously reported the enantioselective biotransformation of 1-(4-methylphenyl)ethanone catalyzed by *D. carota* cells leading to (S)-(–)-1-(4-methylphenyl)ethanol with 98% yield (76% *ee*) and bioreduction of 1-(4-methylphenyl)ethanone in the presence of this biocatalyst and glucose as an exogenous reducing agent resulting in formation of (S)-(–)-1-(4-methylphenyl)ethanol with 76% yield (96% *ee*) [13].

In this study, we examined the bioreduction of 1-(4-methylphenyl)ethanone catalyzed by *P. crispum* cells, which is known to exhibit a rather high reductase activity.

1-(4-Methylphenyl)ethanone was enantioselectively reduced by *P. crispum* cells in water at 23-27 °C for 48 h to produce (S)-(–)-1-(4-methylphenyl)ethanol with 49% yield (96% *ee*). Further transformation of initial ketone for 144 h as in the case of similar reduction catalyzed by D. carota cells leads to a slight increase in the yield of alcohol to 51%, however, the optical purity decreases to 80% ee, which can be explained by the S-alcohol stereoinversion.



1-(4-methylphenyl)ethanone (S)-(-)-1-(4-methylphenyl)ethanol

We have also studied the bioreduction of 1-(4-methylphenyl)ethanone catalyzed by *P.crispum* cells in the presence of exogenous reducing agents (ethanol, isopropanol, or glucose), which are known to significantly affect the yield of the product and the enantioselectivity of the process [14-23].

The transformation of 1-(4-methylphenyl)ethanone in the presence of ethanol (1-5%) or isopropanol (1-5%) for 144 h gives (S)-(–)-1-(4-methylphenyl)ethanol with poor yields and optical purity (Table 1, 2).

The bioreduction of 1-(4-methylphenyl)ethanone in the presence of isopropanol (1-3%) for 72 h leads to a decrease in the yield of (S)-(–)-1-(4-methylphenyl)ethanol, while the concentration of the initial ketone increases (Table 2). It apparently can be explained by the fact that ketone reduction and alcohol oxidation can be catalyzed by the same enzyme, mainly by NAD(P)H-dependent alcohol dehydrogenase.

The increase in ethanol and isopropanol concentration (5-30%) in the reaction mixture results in formation of the target (S)-(–)-1-(4-methylphenyl)ethanol with low yield and optical purity, that can be probably caused by inhibition of *P.crispum* cell dehydrogenase.

Biotransformation of 1-(4-methylphenyl)ethanone for 144 h in the presence of an equimolar amount of glucose leads to an increase in the yield and optical purity of (S)-(–)-1-(4-methylphenyl)ethanol to 52% (96% ee).

Table 1

Dependence of the yield and optical purity (ee) of (S)-(–)-1-(4-methylphenyl)ethanol on the duration of bioreduction of 1-(4-methylphenyl)ethanone catalyzed by *P.crispum* cells and ethanol concentration

***Таблица 1.* Зависимость выхода и оптической чистоты (S)-(–)-1-(4-метилфенил)этанола от продолжительности биовосстановления 1-(4-метилфенил)этанона клетками *P.crispum* в присутствии этанола**

Ethanol concentration, %	Time, h			
	24	48	72	144
	Yield, % / ee,%			
0	45/96(S)	49/96(S)	50/94(S)	51/80(S)
1	27/97(S)	29/97(S)	36/96(S)	36/78(S)
2	17/97(S)	20/96(S)	22/94(S)	32/56(S)
3	11/97(S)	13/95(S)	14/89(S)	23/44(S)
4	12/97(S)	14/96(S)	15/94(S)	25/56(S)
5	7/96(S)	8/90(S)	9/86(S)	14/61(S)

Note: T = 23-27 °C, solvent - water, substrate concentration 1.4 g/l, biocatalyst *P. crispum*

Примечание: T=23-27 °C, растворитель – вода, концентрация субстрата 1,4 г/л, катализатор *P. Crispum*

Table 2

Dependence of the yield and optical purity (ee) of (S)-(–)-1-(4-methylphenyl)ethanol on the duration of bioreduction of 1-(4-methylphenyl)ethanone catalyzed by *P.crispum* cells and isopropanol concentration

***Таблица 2*. Зависимость выхода и оптической чистоты (S)-(–)-1-(4-метилфенил)этанола от продолжительности биовосстановления 1-(4-метилфенил)этанона клетками *P.crispum* в присутствии изопропанола**

Isopropanol concentration, %	Time, h			
	24	48	72	144
	Yield, % / ee,%			
0	45/96(S)	49/96(S)	50/94(S)	51/80(S)
1	32/96(S)	46/98(S)	36/94(S)	30/61(S)
2	23/97(S)	44/97(S)	39/94(S)	47/54(S)
3	17/97(S)	19/97(S)	17/94(S)	22/54(S)
4	10/98(S)	12/97(S)	13/96(S)	18/52(S)
5	10/96(S)	11/97(S)	13/97(S)	16/76(S)

Note: T = 23-27 °C, solvent - water, substrate concentration 1.4 g/l, biocatalyst *P. crispum*

Примечание: T=23-27 °C, растворитель – вода, концентрация субстрата 1,4 г/л, катализатор *P. Crispum*

Table 3

Dependence of the yield and optical purity (ee) of (S)-(–)-1-(4-methylphenyl)ethanol on the duration of bioreduction of 1-(4-methylphenyl)ethanone catalyzed by *P.crispum* cells in the presence of glucose

***Таблица 3*. Зависимость выхода и оптической чистоты (S)-(–)-1-(4-метилфенил)этанола от продолжительности биовосстановления 1-(4-метилфенил)этанона клетками *P.crispum* в присутствии глюкозы**

Time, h	24	48	72	144
	Yield, % / ee,%			
Without glucose	45/96(S)	49/96(S)	50/94(S)	51/80(S)
In the presence glucose *	32/97(S)	50/97(S)	51/96(S)	52/96(S)

Note: T = 23-27 °C, solvent - water, substrate concentration 1.4 g/l, biocatalyst *P. crispum*

* equimolar ratio of ketone and glucose

Примечание: T=23-27 °C, растворитель – вода, концентрация субстрата 1,4 г/л, катализатор *P. Crispum*

* эквимолярное количество кетона и глюкозы

The conversion and optical purity (*ee*) of product were determined by enantioselective GC and polarimetry analysis.

The structure of (S)-(–)-1-(4-methylphenyl)ethanol was confirmed by ^{1}H and C^{13} NMR spectroscopy, chromato-mass spectrometry.

CONCLUSIONS

In this study, we examined the bioreduction of 1-(4-methylphenyl)ethanone into (S)-(–)-1-(4-methylphenyl)ethanol catalyzed by *P. crispum* cells.

We have found that 1-(4-methylphenyl)ethanone was enantioselectively reduced by *P. crispum* cells in water at 23-27 °C for 48 h to produce (S)-(–)-1-(4-methylphenyl)ethanol with 49% yield (96% *ee*). Further transformation of initial ketone for 144 h as in the case of similar reduction catalyzed by D. carota cells leads to a slight increase in the yield of alcohol to 51%, however, the optical purity decreases to 80% ee, which can be explained by the S-alcohol stereoinversion.

The transformation of 1-(4-methylphenyl)ethanone in the presence of ethanol (1-5%) or isopropanol (1-5%) for 144 h gives (S)-(–)-1-(4-methylphenyl)ethanol with satisfactory yields and optical purity. The bioreduction of 1-(4-methylphenyl)ethanone in the presence of isopropanol (1-3%) for 72 h leads to a decrease in the yield of (S)-(–)-1-(4-methylphenyl)ethanol, while the concentration of the initial ketone increases.

Biotransformation of 1-(4-methylphenyl)ethanone for 144 h in the presence of an equimolar amount of glucose leads to an increase in the yield and optical purity of (S)-(–)-1-(4-methylphenyl)ethanol to 52% (96% ee).

Comparison of results obtained for enantioselective reduction of 1-(4-methylphenyl)ethanone in the presence of *P. crispum* cells and glucose (52%, 96% *ee*) with the results of transformation catalyzed by *D. carota* cells in the presence of glucose (76%, 96% *ee*), shows that *D. carota* enzymes make it possible to obtain (S)-(–)-1-(4-methyl)ethanol with a higher yield.

CONFLICT OF INTERESTS

The authors declare the absence a conflict of interest warranting disclosure in this article.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

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Поступила в редакцию 02.05.2023
Принята к опубликованию 05.07.2023

Received 02.05.2023
Accepted 05.07.2023