DOI: 10.6060/ivkkt.20226508.6637

УДК: 547.43

ЭНАНТИОСЕЛЕКТИВНЫЙ СИНТЕЗ (S)-(-)-1-(4-ФТОРФЕНИЛ)ЭТАНОЛА

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(S)-(–)-1-(4-фторфенил)этанол является промежуточным звеном в синтезе антагониста хемокинового рецептора CCR5, применяемого для терапии ВИЧ-инфекции. Наряду с о-фторзамещенными аналогами (S)-(–)-1-(4-фторфенил)этанол может быть использован для изучения роли заместителей в хиральном распознавании молекулярных комплексов, а (R)-(+)-1-(4-фторфенил)этанол является компонентом противомалярийного препарата и модулятором гамма-секретазы, необходимой для лечения болезни Альцгеймера. Предложен подход к синтезу (S)-(-)-1-(4-фторфенил)этанола, основанный на энантиоселективном восстановлении прохирального 1-(4-фторфенил)этанона, в присутствии клеток Daucus carota. Найдены условия, позволяющие получать (S)-(–)-1-(4-фторфенил)этанол путем биовосстановления 1-(4-фторфенил)этанона в присутствии биокатализатора D. carota в течение 48 ч с выходом 55% (98% ее). Исследована возможность оптимизации трансформации 1-(4-фторфенил)этанона в реакционной среде, содержащей различные экзогенные восстановители (этанол, изопропанол или глюкозу), которые, как известно, существенно влияют на выход продукта и энантиоселективность процесса. При биотрансформации 1-(4-фторфенил)этанона в присутствии этанола (1-5%) в качестве экзогенного восстановителя образуется (S)-(-)-1-(4-фторфенил)этанол с различными выходами 7-85% и оптической чистотой 10-98% ее. Энантиоселективное восстановление исходного кетона в присутствии изопропанола (1-5%) не приводит к существенному увеличению выхода и оптической чистоты S-спирта (7-57% (18-98% ее). Биотрансформация 1-(4-фторфенил)этанона в присутствии эквимолярного количества глюкозы в течение 48 ч дает (S)-(-)-1-(4-фторфенил)этанол с выходом 66% (98% ее). Дальнейшая трансформация исходного кетона (144 ч) как в отсутствии экзогенного восстановителя, так и в присутствии эквимолярного количества глюкозы, приводит к повышению выхода спирта до 73% и 76%, соответственно, однако при этом оптическая чистота спирта снижается до 62% ее и 80% ее, что указывает на протекание стереоинверсии.

Ключевые слова: асимметрический синтез, 4-фторацетофенон, (S)-(–)-1-(4-фторфенил)этанол, энантиоселективный биокатализ

ENANTIOSELECTIVE SYNTHESIS OF (S)-(-)-1-(4-FLUOROPHENYL)ETHANOL

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(S)-(–)-1-(4-Fluorophenyl)ethanol is an intermediate in the synthesis of an antagonist of the CCR5 chemokine receptor that can be protective against HIV infection. Along with o-fluoro-

substituted analogs, (S)-(–)-1-(4-fluorophenyl)ethanol can be used to study the role of substituents in the chiral recognition of molecular complexes, and (R)-(+)-1-(4-fluorophenyl)ethanol is a component of an antimalarial drug and a γ-secretase modulator necessary for the treatment of Alzheimer's disease. We proposed an approach to the synthesis of (S)-(-)-1-(4-fluorophenyl)ethanol based on the enantioselective reduction of prochiral 1-(4-fluorophenyl)ethanone catalyzed by Daucus carota cells. We found the conditions that make it possible to obtain (S)-(–)-1-(4-fluorophenyl)ethanol by bioreduction of 1-(4-fluorophenyl)ethanone in the presence of a D. carota biocatalyst for 48 h with 55% yield (98% ee). We also studied the possibility of optimizing the transformation of 1-(4-fluorophenyl)ethanone in a reaction medium containing various exogenous reducing agents (ethanol, isopropanol, or glucose), which are known to significantly affect the product yield and the enantioselectivity of the process. Biotransformation of 1-(4-fluorophenyl)ethanone in the presence of ethanol (1-5%) gives (S)-(-)-1-(4-fluorophenyl)ethanol with 7-85% yields and optical purity 10-98% ee. Enantioselective reduction of the initial ketone in the presence of isopropanol (1-5%) does not lead to a significant increase in the yield and optical purity of S-alcohol (7-57% (18-98% ee). In the case of biotransformation of 1-(4-fluorophenyl)ethanone in the presence of an equimolar amount of glucose for 48 h the yield of (S)-(-)-1-(4-fluorophenyl)ethanol is 66% (98% ee). Further transformation of the initial ketone (144 h) both in the absence of an exogenous reducing agent and in the presence of an equimolar amount of glucose leads to an increase in the yield of alcohol to 73% and 76%, respectively, however, the optical purity of the alcohol decreases to 62% ee and 80% ee, which suggests the stereoinversion.

Key words: asymmetric synthesis, 4-fluoroacetophenone, (S)-(–)-1-(4-fluorophenyl)ethanol, enantioselective biocatalysis

Для цитирования:
Чанышева А.Р., Суфиярова А.Л., Привалов Н.В., Зорин В.В. Энантиоселективный синтез (S)-(-)-1-(4-фторфенил)этанола. *Изв. вузов. Химия и хим. технология*. 2022. Т. 65. Вып. 8. С. 111–116. DOI: 10.6060/ivkkt.20226508.6637.

For citation:
Chanysheva A.R., Sufiyarova A.L., Privalov N.V., Zorin V.V. Enantioselective synthesis of (S)-(-)-1-(4-fluorophenyl)ethanol. *ChemChemTech* [*Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol*.]. 2022. V. 65. N 8. P. 111–116. DOI: 10.6060/ivkkt.20226508.6637.

INTRODUCTION

Stereoisomerically pure compounds are often key components in the synthesis of highly effective biologically active substances, since their stereochemistry determines the level and direction of their biological activity. Approaches based on stereocontrolled metal complex catalysis [1-2] and biocatalysis are widely used in modern organic synthesis.

(S)-(–)-1-(4-Fluorophenyl)ethanol is an intermediate in the synthesis of an antagonist of the CCR5 chemokine receptor that can be protective against HIV infection [3]. Along with o-fluoro-substituted analogs, (S)-(–)-1-(4-fluorophenyl)ethanol can be used to study the role of substituents in the chiral recognition of molecular complexes [4]. (R)-(+)-1-(4-Fluorophenyl)ethanol is a component of an antimalarial drug [5] and γ-secretase modulator necessary for the treatment of Alzheimer's disease [6].

EXPERIMENTAL

1-(4-Fluorophenyl)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. Enantioselective column Astec CHIRALDEXB-PM (30m×0.25mm×0.12μm); column temperature 110 °C; oven temperature 200 °C, detector temperature 230 °C; helium as a carrier gas.

^1H and ^{13}C NMR spectra were measured on Bruker AM-300 and AMX-300 spectrometeres. As internal standards TMS δ (0.00) for ^1H NMR and $CDCl_3$ δ (77.0) for ^{13}C NMR spectroscopy served.

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 Limited» model AA-55.

Reduction of 1-(4-Fluorophenyl)ethanone by *D. carota*

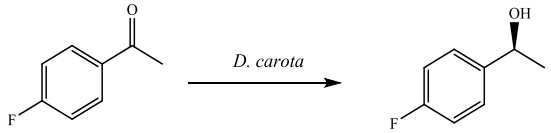
1-(4-Fluorophenyl)ethanone (0.1 g) was added to a suspension of *D. carota* cells (15 g) in distilled water (70 ml) under constant stirring in a conical Erlenmayer flask. The reaction mixture was then placed in an orbital shaker (150 rpm) at room temperature. After achieving the necessary conversions, the suspension was filtered, and *D. carota* 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-Fluorophenyl)ethanol

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.47 d (3H, CH_3), 2.05 s (1H, CH-OH), 4.87 q (1H, CH-OH), 6.99-7.05 м (2H, CH_{Ar}), 7.28-7.35 м (2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ=25.26 (CH_3), 69.73 (CH-OH), 115.31 ($2CH_{Ar}$), 127.07 ($2CH_{Ar}$), 141.5 (C_{Ar}), 161.13 (C_{Ar}-F), 163.08 (C_{Ar}-F). GC/MS (m/z (%)): 140 ([M^+], 21.5), 125 (100), 123 (10.8), 97 (79.2), 96 (19.9), 95 (21.1), 77 (29.9), 75 (15.3), 51 (10.7), 43 (38.9).

RESULTS AND DISCUSSION

We proposed an approach to the synthesis of (S)-(-)-1-(4-fluorophenyl)ethanol based on the enantioselective reduction of prochiral 1-(4-fluorophenyl)ethanone catalyzed by Daucus carota cells.



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

1-(4-Fluorophenyl)ethanone was reduced enantioselectively by *D. carota* cells in water at 23-27 °C for 48 h to produce (S)-(-)-1-(4-fluorophenyl)ethanol with 55% yield (98% ee). Further transformation (144 h) led to an increase in the yield of alcohol up to 73%, however, the optical purity decreased to 62% ee, which is possibly due to the stereoinversion of the S-alcohol.

In order to develop more efficient method for the production of (S)-(-)-1-(4-fluorophenyl)ethanol based on the *D. carota* biocatalyst, which exhibit rather high reductase activity [7], we studied the possibility of transforming 1-(4-fluorophenyl)ethanone in a reaction medium containing various exogenous reducing agents (ethanol, isopropanol, or glucose), which are known to significantly affect the yield of the product and the enantioselectivity of the process [8-22].

Biotransformation of 1-(4-fluorophenyl)ethanone in the presence of ethanol (1-5%) as an exogenous reducing agent leads to formation of (S)-(-)-1-(4-fluorophenyl)ethanol with 7-85% yields and optical purity 10-98% ee.

When transformation is carried out in presence of ethanol (5%) for 144 h, (S)-(–)-1-(4-fluorophenyl)ethanol is formed with a maximum yield of 85%, but a low optical purity of 40% ee (Table 1).

Table 1

Dependence of the yield and enantiomeric excess (ee) of (S)-(-)-1-(4-fluorophenyl)ethanol on the time of bioreduction of 1-(4-fluorophenyl)ethanone catalyzed by *D. carota* cells and ethanol concentration

***Таблица 1.* Зависимость выхода и оптической чистоты (S)-(-)-1-(4-фторфенил)этанола от продолжительности биовосстановления 1-(4-фторфенил)этанона клетками *D. carota* и концентрации этанола**

Ethanol concentration, %	Time, h			
	24	48	72	144
	Yield, % / *ee*,%	Yield, % / *ee*,%	Yield, % / *ee*,%	Yield, % / *ee*,%
0%	40/98 (S)	55/98 (S)	65/94(S)	73/62(S)
1%	20/98(S)	32/(84 (S)	40/94(S)	50/94(S)
2%	10/97(S)	14/76(S)	28/52(S)	54/30(S)
3%	7/92(S)	8/90(S)	21/10(S)	24/16(S)
4%	9/97 (S)	13/94 (S)	21/80(S)	29/76(S)
5%	7/97 (S)	10/80 (S)	52/48(S)	85/40 (S)

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

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

Enantioselective reduction of the initial ketone in the presence of isopropanol (1-5%) for 144 h does not lead to a significant increase in both the yield (7-57%) and the optical purity of S-alcohol (18-98% ee), which vary in a wide range (table 2).

Biotransformation of 1-(4-fluorophenyl)ethanone in the presence of an equimolar amount of glucose for 48 h gives (S)-(-)-1-(4-fluorophenyl)ethanol in 66% yield (98% ee), and further reduction both in presence and absence of an exogenous reducing agent leads to an increase in the yield of the product, but a decrease in its optical purity to 76% and 80% ee, respectively (Table 3).

The conversion and enantiomeric excess (ee) of product were determined by enantioselective GC and polarimetry analysis.

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

Table 2

Dependence of the yield and enantiomeric excess (ee) of (S)-(-)-1-(4-fluorophenyl)ethanol on the time of bioreduction of 1-(4-fluorophenyl)ethanone catalyzed by *D. carota* cells and isopropanol concentration

***Таблица 2.* Зависимость выхода и оптической чистоты (S)-(-)-1-(4-фторфенил)этанола от продолжительности биовосстановления 1-(4-фторфенил)этанона клетками *D. carota* и концентрации изопропанола**

Isopropanol concentration, %	Time, h			
	24	48	72	144
	Yield, % / *ee*,%	Yield, % / *ee*,%	Yield, % / *ee*,%	Yield, % / *ee*,%
0%	40/98 (S)	55/98 (S)	65/94(S)	73/62(S)
1%	30/98(S)	38/97(S)	41/97(S)	45/94(S)
2%	23/97(S)	25/97(S)	27/98(S)	30/96(S)
3%	22/97(S)	27/97(S)	30/97(S)	39/62(S)
4%	18/97 (S)	21/94 (S)	24/94(S)	25/94(S)
5%	7/97 (S)	13/90 (S)	15/17(S)	57/18(S)

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

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

CONCLUSIONS

In this work we proposed an approach to the synthesis of (S)-(-)-1-(4-fluorophenyl)ethanol based on the enantioselective reduction of prochiral 1-(4-fluorophenyl)ethanone catalyzed by *D. carota* cells.

We found the conditions that allow us to obtain (S)-(–)-1-(4-fluorophenyl)ethanol by bioreduction of 1-(4-fluorophenyl)ethanone in the presence of *D. carota* biocatalyst for 48 h with 55% yield (98% ee). Biotransformation of 1-(4-fluorophenyl)ethanone in the presence of an equimolar amount of glucose for 48 h gives (S)-(-)-1-(4-fluorophenyl)ethanol in 66% yield (98% ee).

Further transformation of the initial ketone (144 h) both in the absence of an exogenous reducing agent and in the presence of an equimolar amount of glucose leads to an increase in the yield of alcohol to 73% and 76%, respectively, however, the optical purity of the alcohol decreases to 62% ee and 80% ee, which suggests stereoinversion.

Table 3

Dependence of the yield and enantiomeric excess (ee) of (S)-(-)-1-(4-fluorophenyl)ethanol on the time of bioreduction of 1-(4-fluorophenyl)ethanone catalyzed by *D. carota* cells in the presence of glucose

***Таблица 3.* Зависимость выхода и оптической чистоты (S)-(-)-1-(4-фторфенил)этанола от продолжительности биовосстановления 1-(4-фторфенил)этанона клетками *D. carota* в присутствии глюкозы**

	Time, h			
	24	48	72	144
	Yield, % / ee,%	Yield, % / ee,%	Yield, % / ee,%	Yield, % / ee,%
With glucose	40 /98 (S)	55/98(S)	65/94 (S)	73/62 (S)
In the presence glucose*	50 /98(S)	66/98 (S)	67/98 (S)	76/80(S)

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

* equimolar ratio of ketone and glucose

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

* эквимолярное количество кетона и глюкозы

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.

ACKNOWLEDGEMENT

This study was funded by the Ministry of Education and Science of Russian Federation.

Работа выполнена в соответствии с Государственным заданием Минобрнауки РФ.

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Поступила в редакцию 11.04.2022
Принята к опубликованию 25.05.2022

Received 11.04.2022
Accepted 25.05.2022