Bioresource Technology 219 (2016) 716–724

Contents lists available at ScienceDirect

Bioresource Technology

journal homepage: www.elsevier.com/locate/biortech

Review

Biotechnological production of alpha-keto acids: Current status and perspectives

Yang Song [a,b], Jianghua Li [a,b], Hyun-dong Shin [c], Long Liu [a,b], Guocheng Du [a,b,*], Jian Chen [a]

[a] Key Laboratory of Industrial Biotechnology, Ministry of Education, Jiangnan University, Wuxi 214122, China
[b] Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, Jiangnan University, Wuxi 214122, China
[c] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta 30332, USA

HIGHLIGHTS

- Present the different types of α-keto acids as well as their applications.
- Summarize the recent progresses in the production of some important α-keto acids.
- Discuss the future prospects for the production of keto acids.

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form 4 August 2016
Accepted 5 August 2016
Available online 8 August 2016

Keywords:
α-Keto acid
Pyruvate
α-Ketoglutarate
α-Ketoisovalerate
α-Ketoisocaproate
α-Keto-γ-methylthiobutyrate
2,5-Diketo-D-gluconate

ABSTRACT

Alpha-keto (α-keto) acids are used widely in feeds, food additives, pharmaceuticals, and in chemical synthesis processes. Although most α-keto acids are currently produced by chemical synthesis, their biotechnological production from renewable carbohydrates is a promising new approach. In this mini-review, we first present the different types of α-keto acids as well as their applications; next, we summarize the recent progresses in the biotechnological production of some important α-keto acids; namely, pyruvate, α-ketoglutarate, α-ketoisovalerate, α-ketoisocaproate, phenylpyruvate, α-keto-γ-met hylthiobutyrate, and 2,5-diketo-D-gluconate. Finally, we discuss the future prospects as well as favorable directions for the biotechnological production of keto acids that ultimately would be more environment-friendly and simpler compared with the production by chemical synthesis.

Contents

* Corresponding author at: Key Laboratory of Industrial Biotechnology, Ministry of Education, Jiangnan University, Wuxi 214122, China.
E-mail address: gcdu@jiangnan.edu.cn (G. Du).

http://dx.doi.org/10.1016/j.biortech.2016.08.015
0960-8524/

1. Introduction

Organic compounds that contain a carboxylic acid group and a ketone group are known as keto acids or oxoacids. Basically, the keto acids fall into three types: alpha (e.g., pyruvic acid), beta (e.g., acetoacetic acid), and gamma (e.g., levulinic acid). Among these, the alpha-keto (α-keto) acids, which have a carbonyl group at the alpha site related to the carboxylic group, are especially significant in biological systems as they are involved in the tricarboxylic acid cycle and glycolysis.

Generally, they share analogous applications in the food, feed, pharmaceutical, and chemical industries. As analogs of the protein amino acids, the α-keto acids are the penultimate products formed in amino acid biosynthesis and the first product formed during the degradative metabolism of amino acids (Cooper et al., 1983). They could be used as nitrogen-sparing substitutes for essential amino acids in patients with liver and kidney disease, which ultimately helps to significantly decrease the accumulation of nitrogen waste products in the body of these patients. The compound α-keto acid tablets (including α-KIC, α-KIV, α-keto-β-methylvalerate, PPA, α-KMTB, and five kinds of amino acids) have been seen on the international pharmaceutical market for several years (Hu and Ding, 2007). Another important application of α-keto acids is in organic chemical synthesis, owing to their stereogenic nature and functional carbonyl group. They are also precursors of the biofuel n-butanol (Atsumi et al., 2008; Sims et al., 2010), L- and D-amino acids (Pantaleone et al., 2001), the dietary sweetener aspartame, indole-3-acetic acid (Spaepen et al., 2007), as well as chiral α- and β-amino acids, which can be precursors of anti-HIV drugs and antibiotics (Porter et al., 2000; Prasad et al., 1998). In addition, they have been extensively used in foods and cosmetics. Therefore, the α-keto acids have immense market potential as a result of the growing demographic of the aging population and the popularity of fitness exercises among seniors as a means to improve their overall health status. The applications of biologically synthesized α-keto acids are shown in Table 1.

Most of the keto acids are currently being synthesized by chemical processes, which unfortunately are not only costly but can also cause environmental pollution. Therefore, the microbial production of α-keto acids is an excellent alternative, having several advantages such as high yield (Liu et al., 2007), productivity (Hossain et al., 2014a; Niu et al., 2014), and flexibility of substrate consumption (Kamzolova and Morgunov, 2013; Otto et al., 2011).

Generally, microbial production processes have focused on either the fermentation method or the bioconversion method (Shen et al., 2016). In the fermentation production process, all

Table 1
Summary of keto acids and their application.

Keto acids	Application	References
Pyruvate	Improve exercise endurance capacity	Koh-Banerjee et al. (2005)
	Weigh-control supplement	Onakpoya et al. (2014)
	Nutraceutical	McCarty (2000)
	Antioxidant	Wang et al. (2007)
	Precursor of pharmaceutical chemicals	Lütke-Eversloh et al. (2007)
α-Ketoglutaric acid	Ammonium ion receptor	Morgunov et al. (2013)
	Precursor of chemical compounds	Stottmeister et al. (2005)
	Improve athletic performance and wound healing	Otto et al. (2011)
	The poly α-KG used in tissue scaffolding and therapeutic delivery	Barrett and Yousaf (2008)
α-Ketoisovalerate	The precursor of 1-butanol	(Atsumi et al., 2008)
	Hepatitis B virus infection and chronic glomerulonephritis	Mou et al. (2013)
	Feed of lamb, pigs, chickens	Kuhlman et al. (1988)
α-Ketoisocaproate	The precursor of biofuel	Atsumi et al. (2008)
	Hepatitis B virus infection and chronic glomerulonephritis	Mou et al. (2013)
	Depression of silenced tumor with organoselenium compounds	Nian et al. (2009)
	Stimulate insulin secretion	Malaisse et al. (1983)
	Increase muscular power	Buford and Koch (2004)
	Promote the milk production and composition	Kuhlman et al. (1988)
Phenylpyruvate	Diet sweetener aspartame, indole-3-acetic acid	Spaepen et al. (2007)
α-Keto-γ-methylthiobutyric acid	Poultry industry, anti-cancer drug	Quash and Fournet (2009)
2,5-Diketo-D-gluconic acid	Precursors of 2-keto-L-gulonic acid	Hancock and Viola (2002)
2-Ketobutyric acid	Precursor for chemical synthesis of pesticide, spice and food additive	Zhang et al. (2016)
Oxaloacetic acid	A key metabolite in tricarboxylic acid cycle	Krebs and Lowenstein (1960)
2-Oxoadipic acid	A key metabolite of tryptophan and lysine	Shibata et al. (2011)
4-Hydroxyphenylpyruvate	A important metabolite in tyrosine degradation pathway	Serre et al. (1999)
N-acetyl-L-2-amino -6-oxopimelate	A metabolic intermediate in L-lysine synthesis	Eggeling and Bott (2015)
L-2-Amino-6-oxoheptanedioate	Lysine biosynthesis	Eggeling and Bott (2015)