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Synthesis of Biological Active Esters of the Isovaleric Acid by Isobutylene Hydroalkoxycarbonylation

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Abstract

Hydroalkoxycarbonylation of 2-methylpropene with carbon monoxide and alcohols under condition of homogeneous catalysis with transition metal complexes allows facile one-step synthesis of practically useful isovaleric acid esters. Many of them exhibit biological activity and are constituents of drugs (Validolum, Corvalolum, etc.) or valuable intermediate products in drug synthesis. Biological active isovaleric acid esters (1-menthylisovalerate, ethylisovalerate, cyclohexylisovalerate, benzylisovalerate, α-monoglyceryde of isovaleric acid) were prepared by isobutylene hydroalkoxycarbonylation. New efficient technologies for preparation of drugs (Validolum, Ethyl ester of α-bromisovaleric acid and Corvalolum) are based on the isovaleric acid esters were worked out.

Keywords: Ethylisovalerate; Hydroalkoxycarbonylation; Isovaleric

Introduction

Isobutylene as an accessible and inexpensive feedstock is of interest for synthesis of many practically useful compounds. Isobutylene carbonylation with carbon monoxide and alcohols under conditions of homogeneous catalysis with transition metal complexes allows facile one-step synthesis of practically useful isovaleric acid esters [1-5]. Many of them have biological activity and are components of pharmaceuticals (Validolum, Corvalolum, etc) or valuable intermediates for their synthesis. Some isovalerate esters possess a characteristic odor and are used as fragrance compounds in the manufacture of perfumes, cosmetics and food essences [6].

We applied hydroalkoxycarbonylation of isobutylene with carbon monoxide and mono(poly)hydric alcohols in the presence of catalytic systems based on the phosphinpalladium complexes ($Pd(PPh_3)_4$-PPh_3-TsOH and Pd(Acac)2-PPh3-TsOH) to prepare of biological active isovaleric acid esters: l-menthylisovalerate (possesses spasmolytic properties; it used as main active component of the spasmolytic medicine Validolum), ethylisovalerate (possesses aromatic (fruit) odor; intermediate product for obtaining sedative and spasmolytic medicines Ethyl ester of α-bromisovaleric acid and Corvalolum), cyclohexylisovalerate (bactericide activity (against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*); antifungal activity (against *Candida albicans*)), benzylisovalerate (bactericide activity (against *Escherichia coli, Staphylococcus aureus*)) and α-monoglyceryde of isovaleric acid (bactericide activity (against *Escherichia coli, Pseudomonas aeruginosa*); antifungal activity (against *Candida albicans*)).

New efficient technologies for preparation of drugs are based on isovaleric acid esters – Validolum, Ethyl Ester of α-bromisovaleric acid (EEBIA) and Corvalolum – were worked out. Validolum – is a spasmolytic (sedative) medicine. It has a sedative effect on the nervous system and a moderate reflex vaso-dilating effect. EEBIA possesses sedative and spasmolytic properties. It is included in Corvalolum composition and may be used for producing other medicines. Corvalolum is a combined medicine and consists of EEBIA, phenobarbital, sodium hydroxide, peppermint oil, ethyl alcohol and water. Corvalolum possesses anetic and spasmolytic properties.

Due to the more advanced technology of production the Medicines will have better qualitative characteristics. The cost of production of the Medicines with the use of new technologies is 2-3 times lower as compared to the medicines produced by existing at the present traditional technologies.

Experimental

The complexes Pd $(PPh_3)_4$ and Pd $(Acac)_2$ was obtained according to the known procedures [7]. p-Toluenesulfonic acid was recrystallized from 96% ethanol and dried until the composition $TsOH*H_2O$. Triphenylphosphine was recrystallized from an ether-ethanol mixture to a constant melting point. Absolute ethanol, isobutylene of 99,5% purity, carbon monoxide of 99,8% purity, l-menthol of 99,7% purity, cyclohexanol of 99,5% purity, benzyl alcohol of 99,2% purity and glycerin of 99,5% purity were used. The experiments were carried out in the solvent-free mode in a laboratory stainless steel autoclave unit. The determination of the purity and the analysis of the products were carried out by means of a GLC technique, thin-layer chromatography, IR-spectroscopy and ^1H NMR techniques. Gas chromatography was performed on a Hewlett-Packard 3890-II-Plus chromatograph with a flameionization detector; HP-Innowax cross-linked PEG capillary column (30000*0,25mm), film thickness 0,25 μm. Injector temperature 200°C, detector temperature 200°C, carrier gas nitrogen (25 ml/min). The oven temperature was programmed from 75 to 175°C at a rate of 10°C/min. The ^1H NMR spectra were measured on a Varian Mercury-300 instrument (300 MHz) against internal TMS.

L-Menthyl Isovalerate

The 100 ml autoclave equipped with a stirrer and a carbon monoxide and isobutylene feeding device was charged with 0,133 g

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