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ASYMMETRIC REDUCTIVE ALKYLATION OF ALANYLPROLINE BY THE ETHYL ESTERS OF 4-SUBSTITUTED 2-OXOBUTENOIC ACIDS

V. Slavinska, Dz. Sile, G. I. Chipens, Yu. Balodis, G. Rozenthal, K. Venteris, and E. Lukevics

A method was developed for the synthesis of N-[1-(S)-(ethoxycarbonyl)-3-phenylpropyl]alanylproline (enalapril) by reductive alkylation of alanylproline with ethyl 2-oxo-4-phenylbutenoate under the conditions of hydrogenation in the presence of palladium black and 1.6% Pd/C. The yield of enalapril amounted to 65%. With the ethyl ester of the α-oxo acid the diastereoselectivity of formation of the S,S,S-diastereomer was higher than with the saturated synthon. It is assumed that with ethyl 2-oxo-4-phenylbutenoate as synthon a conformationally restricted surface complex is formed between the unsaturated synthon and the active centers of the catalyst. During reductive alkylation of alanylproline by ethyl 2-oxo-4-(2-thienyl)butenoate poisoning of the catalyst occurs.

Keywords: alanylproline, angiotensin-converting enzyme inhibitors, palladium black, 4-substituted ethyl 2-oxobutenoates, asymmetric reductive alkylation.

Inhibitors of angiotensin-converting enzyme – enalapril and its analogs – are highly effective antihypertensive preparations and agents for the treatment of heart failure, glaucoma, and other diseases [1, 2].

Numerous methods have been proposed for the synthesis of these compounds. One method for the synthesis of enalapril is the condensation of alanylproline with 4-substituted ethyl 2-oxobutyrates with $NaB(CN)H_3$ and molecular hydrogen in the presence of hydrogenation catalysts (Ni, Pd black, Pd/C, Ir, etc.) as reducing agents.

Only the (*S*,*S*,*S*)-diastereomer of N-[1-(*S*)-(ethoxycarbonyl)-3-phenylpropyl]alanylproline, which is more active than the (*R*,*S*,*S*)-diastereomer, is used in medicine. If the reductive alkylation of alanylproline by ethyl 2-oxo-4-phenylbutyrate is conducted in the presence of $NaB(CN)H_3$ as condensing agent or in the presence of Pd black, both stereomers are formed in equal amounts, (*S*,*S*,*S*):(*R*,*S*,*S*) ~ 1:1 [3]. During the reductive alkylation of alanylproline by ethyl 2-oxo-4-phenylbutyrate under the conditions of hydrogenation at Pd/C (5 and 10% Pd/C) or IrO_2 the ratio of the diastereomers is better, (*S*,*S*,*S*):(*R*,*S*,*S*) = 1.5:1 [3, 4]. In industry Raney nickel is used as catalyst. High diastereoselectivity in the formation of the (*S*,*S*,*S*)-diastereomer was achieved when potassium fluoride, acetic acid, and other additions were used [3, 5].

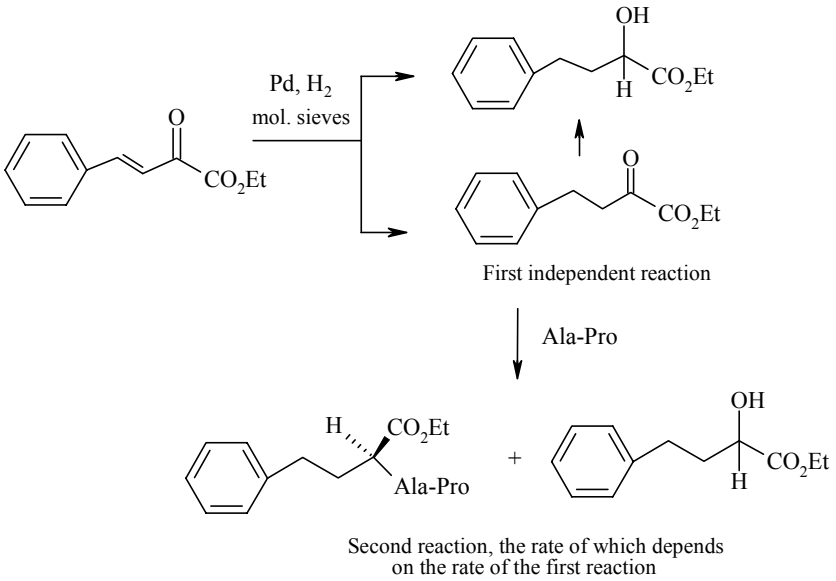
* Dedicated to highly respected Academician Janis Stradins with feelings of gratitude for his consent and support for research on peptide chemistry and catalysis.

Latvian Institute of Organic Synthesis, Riga, LV-1006; e-mail: dzsile@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1794-1799, December, 2003. Original article submitted October 25, 2003.

We showed for the first time that industrial 1.6% Pd/C catalyst (with a low Pd content) can be used successively in the synthesis of enalapril after previous activation. The ratio of diastereomers is (*S*,*S*,*S*):(*R*,*S*,*S*) ~ 1.5:1 [5], and the product yields are comparable with the results obtained with 10% Pd/C [1].

We assumed that the stereoselectivity of the process could be increased substantially if the structure of the agent for alkylation of the alanylproline was varied. Using appropriate methods for the production of the 4-substituted 2-oxobutenoic acid derivatives [6-9], we realized the reductive alkylation of alanylproline with the unsaturated synthon ethyl 2-oxo-4-phenylbutenoate in the presence of palladium black. Alkylation was realized in reactions of the conjugated type (Scheme 1).

Scheme 1



Hydrogenation of the salts and ethyl esters of 4-substituted 2-oxobutenoic acids (the first reaction) (R = phenyl, 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl) at palladium and nickel catalysts was described in [10-13].

The derivatives of 4-substituted 2-oxobutenoic acids are hydrogenated by a parallel-consecutive reaction scheme with the formation of the named oxo and hydroxy compounds. The selectivity in the formation of the oxo compounds is increased if palladium catalysts and the salts of the respective 4-substituted 2-oxobutenoic acids are used. The selectivity in formation of the respective oxo compounds decreases in the following order, depending on the structure of the initial compound: 4-(2-thienyl)- > 4-(2-furyl)- > 4-phenyl- > 4-(3-pyridyl)- > 4-(4-pyridyl)-2-oxobutyric acid (Na salt).

During the synthesis of enalapril and its analogs by conjugated hydrogenation of the unsaturated ethyl esters of 4-substituted 2-oxobutenoic acids and condensation of the saturated oxo compound with alanylproline it is possible to expect more complete utilization of the saturated keto compound. The rate of transformation of the keto compound into the respective hydroxy compound in the consecutive reaction and the rate of the transformations of the keto compound into the bimolecular condensation products, established during the hydrogenation of the esters of the unsaturated α-keto acids, decrease [14]. In addition, there is no need to isolate the saturated ester of the α-keto acid from the hydrogenation product (in the case where the synthon is obtained by hydrogenation of the respective unsaturated compound).

The two reactions have the same main side product – the ethyl ester of the respective saturated hydroxy compound, and the retardation of the second reaction by the side products of the first reaction is therefore unlikely to be increased.

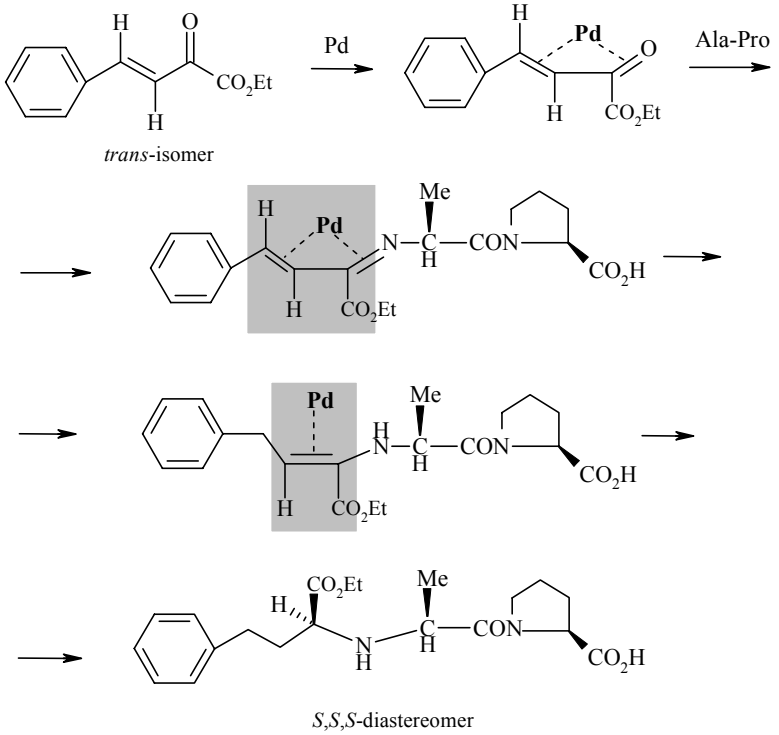
During the synthesis of enalapril by reductive alkylation of alanylproline by ethyl 2-oxo-4-phenylbutenoate under optimum conditions (room temperature, ratio of alanylproline to ethyl 2-oxo-4-phenylbutenoate 1:(1.5-2.5), ratio of Pd black to alanylproline ~ 1:1, in absolute ethanol in the presence of molecular sieves) the average yield of enalapril is 50-65%. During the synthesis a significant increase in the diastereoselectivity of formation of the (*S*,*S*,*S*)-diastereomer was observed. In the investigated region of reaction conditions (*S*,*S*,*S*):(*R*,*S*,*S*) = (2.3-3.1):1.

During the synthesis of enalapril according to the conjugated scheme it can be supposed that the reaction takes place at other active centers of the catalyst with other degrees of surface coverage with the reagents. It is possible that the orientation of the individual structural elements on the surface of the catalyst and the structure of the complexes change under these conditions, leading to some change in the diastereoselectivity of the reaction.

It is not, however, possible to exclude the probability that the unsaturated oxo ester will condense with the alanylproline to form a conformationally restricted complex according to Scheme 2.

This would give rise to attack by the adsorbed hydrogen at the C atom of the enamine group and the formation of the (*S*,*S*,*S*)-diastereomer. There are, however, no published data on the relative reactivity of saturated and unsaturated keto esters with alanylproline in the presence of palladium catalysts.

Scheme 2



We realized the reductive alkylation of alanylproline with sodium 2-oxo-4-phenylbutenoate and the corresponding saturated compound using $NaBH_4$ and $NaB(CN)H_3$ [15]. Under the conditions of condensation the saturated oxo compound is characterized by higher reactivity than its unsaturated analog. When the latter was used, the unsaturated analog of enalapril was obtained.

It is possible that the saturated and the unsaturated oxo esters both participate in the reductive alkylation of alanylproline by the unsaturated oxo ester at the palladium catalyst.

We also studied the synthesis of the enalapril analog containing a 2-thienyl radical by the reductive alkylation of alanylproline with ethyl 2-oxo-4-(2-thienyl)butenoate in the presence of palladium black. This reaction also takes place asymmetrically. Here, however, strong poisoning of the catalyst by the sulfur-containing compounds is observed, and it is not therefore advisable to obtain the above-mentioned analog by this method.

Thus, the ethyl esters of the respective unsaturated 4-substituted 2-oxobutenoic acids can be used as synthons for the synthesis of enalapril and, probably, its analogs if the palladium catalyst is not poisoned by the unsaturated oxo compound or its transformation products.

EXPERIMENTAL

Ethyl 2-oxo-4-phenyl- and 2-oxo-4-(2-thienyl)butenoates were synthesized by the method in [7, 16].

Ethyl 2-oxo-4-phenylbutenoate was determined by chromatography on a Varian 3700 chromatograph with a flame-ionization detector, a 2000 × 2 mm column, 5% of OV-17 sorbent on Chromosorb WHP (8077/100 mesh), helium, programmed temperature 80 → 240°C.

Ala-Pro and N-[1-(*S*)-(ethoxycarbonyl)-3-phenylpropyl]alanylproline were determined by HPLC on a Du Pont 850 chromatograph on a column measuring 4.6 × 150 mm, filled with Zorbax C_8. The mobile phase was acetonitrile; 0.1 M $KH_2PO_4 \cdot H_3PO_4$, pH 2.5, λ 215-230 nm. The condensation reaction was monitored by TLC (*n*-BuOH–Py–AcOH–H_2O = 15:10:3:6).

Reductive Alkylation of Alanylproline by Ethyl 2-Oxo-4-phenylbutenoate. Anhydrous ethanol (13 ml) and palladium black (~0.2 g, from a suspension in anhydrous ethanol) were added to a flask provided with a magnetic stirrer and a tube for the delivery of hydrogen, where Ala-Pro·HCl (2.00 g, 0.898 mmol), triethylamine (0.13 ml), calcined 4A molecular sieves (1.44 g), and ethyl 2-oxo-4-phenylbutenoate (0.91 g, 4.34 mmol, purity 97%) were placed. The mixture was hydrogenated with molecular hydrogen at room temperature for 44 h. In the course of the reaction (~20 h) a fresh portion of the catalyst (0.1 g) and ethyl 2-oxo-4-phenylbutenoate (0.25 g) were added to the reaction mixture.

At the end of the reaction the catalyst and the molecular sieves were filtered off and washed with anhydrous ethanol (20 × 4 ml). The ethanol solution was combined with the filtrate and evaporated. 10% sodium chloride solution (40 ml) was added to the residue, and the pH was brought to 8-9 with a saturated solution of potassium carbonate. The alkaline solution was extracted with ethyl acetate (20 × 3 ml). The aqueous solution was then acidified with 1 M phosphoric acid (pH 4-5) and extracted with ethyl acetate (20 × 5 ml). The ethyl acetate solution, obtained by extraction from the acidic solution, was dried by stirring for 45 min with sodium sulfate. The sodium sulfate was filtered off and washed with ethyl acetate. The ethyl acetate solution was evaporated. We obtained 3.25 g of the unpurified product, which contained 2.20 g of the (*S*,*S*,*S*)-diastereomer of enalapril. The yield at the condensation stage was 65%. The obtained precipitate was dissolved in 10 ml of hot acetonitrile, 6.7 g of maleic acid dissolved in 3 ml of hot acetonitrile was added, and the mixture was left overnight at +10°C. The precipitate was washed with 8 ml of acetonitrile. We obtained 2.3 g of enalapril maleate; mp 142-143°C (mp 143-144°C [1]). The NMR spectra of the enalapril maleate agreed with published data [1].

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