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ASYMMETRIC SYNTHESIS BY CATALYTIC REDUCTIVE AMINOLYSIS OF p-FLUORO-α-ACETAMINOCINNAMIC ACID AZALACTONE. COMMUNICATION 18. PREPARATION OF S-(−)-p-FLUOROPHENYLALANINE

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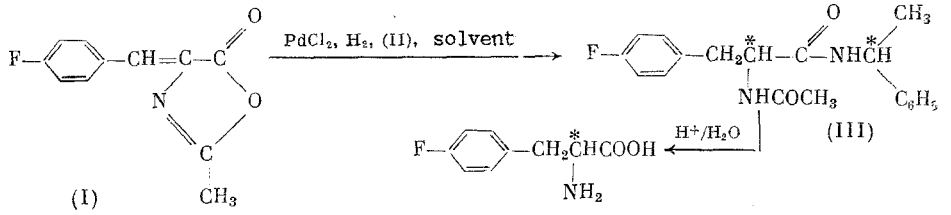
p-Fluorophenylalanine and its derivatives have antiviral [1] and antitumor activity [2]. Optically active p-fluorophenylalanine was obtained previously by cleavage of the racemate [3]. We carried out catalytic asymmetric synthesis of optically pure S-p-fluorophenylalanine by reductive aminolysis of p-fluoro-α-acetaminocinnamic acid azalactone (I).

DISCUSSION OF THE OBTAINED RESULTS

The reductive aminolysis (RA) of α-acetaminocinnamic acid azalactone in aprotic solvents in the presence of a chiral Pd catalyst gives N-acetyl-S-phenylalanine S-(−)-α-phenylethylamide, the hydrolysis of which affords S-phenylalanine [4]. When the reaction is carried out in alcohols, esters or amides are formed, in relation to the nature of the alcohol [5]. In the present paper, RA was used to synthesize optically active p-fluorophenylalanine. The RA of (I) was carried out in dimethoxyethane (DME) or isopropyl alcohol in the presence of $PdCl_2$ and H_2 with additions of S-(−)-α-phenylethylamine (II) and triethylamine (TEA).



The identification of the products and the determination of their ratio were carried out by IR and proton NMR spectroscopy. The proton signals were assigned by analogy with

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the data for unsubstituted derivatives of α-acetaminocinnamic acid and N-acetylphenylalanine [4]. In the RA of (I) in DME N-acetyl-p-fluorophenylalanine α-phenylethylamide (III), predominantly of SS configuration, was formed in quantitative yield. The SS-diastereomer excess (d. e.) was 28% (according to proton NMR). After its crystallization, pure SS-(III) was obtained. Hydrolysis of the latter with 6 N HCl gave optically pure S-(−)-p-fluorophenylalanine. When the reaction was carried out in isopropanol, not only the main product (III) was formed, but also an insignificant amount of the isopropyl ester of N-acetyl-p-fluorophenylalanine, which was separated easily by crystallization. In iso-PrOH the d. e. of SS-(III) was 46%. The RA of (I) in iso-PrOH and DME occurred at close rates. In consecutive aminolysis, i.e., hydrogenation of (I) in the presence of TEA and subsequent aminolysis of the saturated azalactone in the presence of (II) in both solvents the amide SS-(III) was also formed with d. e. 40-45%. The rates of RA and hydrogenation in the presence of TEA were identical. These data indicate the possibility of occurrence of RA via the saturated azalactone. In the hydrogenation of p-fluoro-α-acetaminocinnamic acid S-(+)-phenylethylamide (IV), which can be formed in the aminolysis of (I), the RS diastereomer would be obtained in excess (d. e. 7-10%). Therefore, the RA of (I) occurs, bypassing the step of formation of (IV).

Thus, it was shown that the stepwise mechanism and the stereochemical reaction path of the RA of the azalactones do not change when fluorine is introduced into the para position of the aromatic ring of α-acetaminocinnamic acid azalactone. Subsequently, we hope to elucidate the reason for the different effect of the solvent on the stereoselectivity of the reaction in the case of the RA of (I) and its unfluorinated analog, for which the values of the d. e. are 40% in both investigated solvents.

EXPERIMENTAL

The proton NMR spectra were recorded on a Bruker BW-250 radiospectrometer, and the IR spectra were recorded on a Specord spectrophotometer. Spectropolarimetric measurements were carried out on a Spectropol-1 spectropolarimeter. GLC analysis was carried out on a Biokhrom-1 chromatograph with a flame-ionization detector on a glass capillary column (15 m × 0.25 mm) with a tert-butylamidodocosanoyl-L-valine chiral phase [6], a nitrogen carrier-gas velocity of 1 ml/min, a column temperature of 145°C, a vaporizer temperature of 170°C, and a sample size of 1.5-2 μl. The $PdCl_2$ was pure. S-(−)-α-Phenylethylamine had $[\alpha]_D^{20}$ −39.5°C (without a solvent). p-Fluorobenzaldehyde was obtained according to [7], 68% yield, n_D^{20} 1.5170, bp 80-83°C (20 mm). p-Fluoroacetaminocinnamic acid azalactone (I) was obtained according to [8], 45% yield, yellow prisms with mp 154-155°C (from CCl_4). IR spectrum (KBr, ν, cm^{-1}): 1660 (C=N), 1780, 1820 (C=O). Proton NMR spectrum ($CDCl_3$, δ, ppm): 2.42 singlet (CH_3), 7.10 singlet (CH_β), 7.5 doublet (m-CH_{arom}, J = 8.7 Hz), 8.10 doublet, 8.13 doublet (o-CH_{arom}, J = 8.7 Hz). p-Fluoro-α-acetaminocinnamic acid S-(+)-α-phenylethylamide (IV) was obtained according to [4]. The proton NMR in CD_3OD (δ, ppm) was: 1.43 doublet (CH_3, J = 7 Hz), 2.01 singlet ($\underline{CH_3}CO$), 5.06 quartet (CH), 6.54-7.50 multiplet (H_{arom}).

The RA procedure was described in [3]. The RA with 0.5 mmole of (I), 0.75 mmole of (II), and 17 mg of $PdCl_2$ in 7 ml of the solvent was carried out at 20°C at a hydrogen pressure of 0.2 gauge atm. After termination of the reaction the catalyst was filtered, and the filtrate was evaporated in vacuo. The obtained oil was dissolved in $CHCl_3$, and (II) was extracted with 7% HCl. After washing with water, the chloroform solution was evaporated, and a yellowish precipitate was obtained. Pure SS-amide (III), mp 204-204.5°C, was recovered by crystallization from an ethanol–hexane mixture (9:1). Proton NMR spectrum (CD_3OD, δ, ppm): 1.34 doublet ($\underline{CH_3}CH$), 1.89 singlet ($\underline{CH_3}CO$), 2.85 quartet (CH_2), 4.54 triplet ($\underline{CH}CH_2$), 6.78-7.19 multiplet (C_6H_4). $[\alpha]_D^{20}$ −46.0, −59.5° (550 nm), −96.8° (450 nm), −238° (350 nm), −550° (290 nm) (C 1.54, ethanol). IR spectrum (KBr, ν, cm^{-1}): 3290, 3260 (NH), 1640 (amide I), 1550 (amide II). We hydrolyzed SS-(III) according to [4] and obtained optically pure p-fluorophenylalanine, 35% yield with respect to the azalactone, mp 250-255°C. Proton NMR spectrum (D_2O, δ, ppm): 3.33 quartet (CH_2), 4.32 quartet (CH, J = 7 Hz): 7.12-7.45 multiplet (H_{arom}). The optical purity of the product was confirmed by enantiomeric GLC analysis of isopropyl esters of N-(trifluoroacetyl) derivatives of p-fluorophenylalanine prepared according to [9].

Hydrogenation of (I) with TEA. Compound (I) (0.5 mmole) was hydrogenated in the presence of $PdCl_2$ (17 mg) and TEA (0.75 mmole) in 7 ml of the solvent. After completion of the reaction, (II) (0.75 mmole) was added to the reaction mixture, and the whole was left for 12 h. Further treatment was similar to that carried out in RA.

CONCLUSIONS

1. In reductive aminolysis of p-fluoroacetaminocinnamic acid azalactone by S-(−)-α-phenylethylamine in the presence of $PdCl_2$ and H_2 in dimethoxyethane or isopropyl alcohol, N-acetyl-p-fluorophenylalanine phenylethylamide was formed with 28 and 46% excesses of the SS diastereomer, respectively, the hydrolysis of which, after crystallization, afforded optically pure S-(−)-p-fluorophenylalanine.

2. Hydrogenation of p-fluoroacetaminocinnamic acid S-(+)-phenylethylamide in isopropyl alcohol and dimethoxyethane occurred stereoselectively and afforded N-acetyl-p-fluorophenylalanine phenylethylamide with 10% excess of the RS diastereomer.

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SYNTHESIS OF PERFLUOROVINYLBENZOCYCLOALKENES BY DECHLORINATION OF PRODUCTS OF REACTION OF POLYFLUOROBENZOCYCLOALKENES WITH 1,2-DICHLORODIFLUOROETHYLENE

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Perfluorobenzocycloalkenes react with tetrafluoroethylene, trifluorochloroethylene, and perfluoropropylene in the presence of SbF_5 to form polyfluoroalkylbenzocycloalkenes [1, 2]. A similar reaction with 1,2-dichlorodifluoroethylene was not studied. However this reaction is of interest for further study of the electrophilic reactions of polyfluorobenzocycloalkenes with fluoroolefins, as well as from the aspect of synthesis of functional derivatives (for example, vinyl) of polyfluorobenzocycloalkenes. Thus, in the reaction of polyfluorobenzocycloalkenes with CFCl=CFCl, formation can be expected of compounds containing a 1,2-dichlorotrifluoroethyl group, in the dechlorination of which perfluorovinylbenzocycloalkenes can be obtained (compare with dehalogenation of polyfluoroalkanes containing Cl atoms at adjacent C atoms [3]).

In this connection, we studied in the present work the reactions of perfluorinated benzocyclobutene (I), 1-methylbenzocyclobutene (II) indane (III), and tetraline (IV) with CFCl-CFCl, and also dechlorination of the products of these reactions by the action of Zn.

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