ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA CATALYTIC REDUCTION OF AZALACTONE-SUBSTITUTED ACYLAMINOACRYLIC ACIDS.

21. CATALYTIC ASYMMETRIC SYNTHESIS OF THE PHENYLETHYLAMIDE OF N-ACYL-p-DIFLUOROMETHOXYPHENYLALANINE

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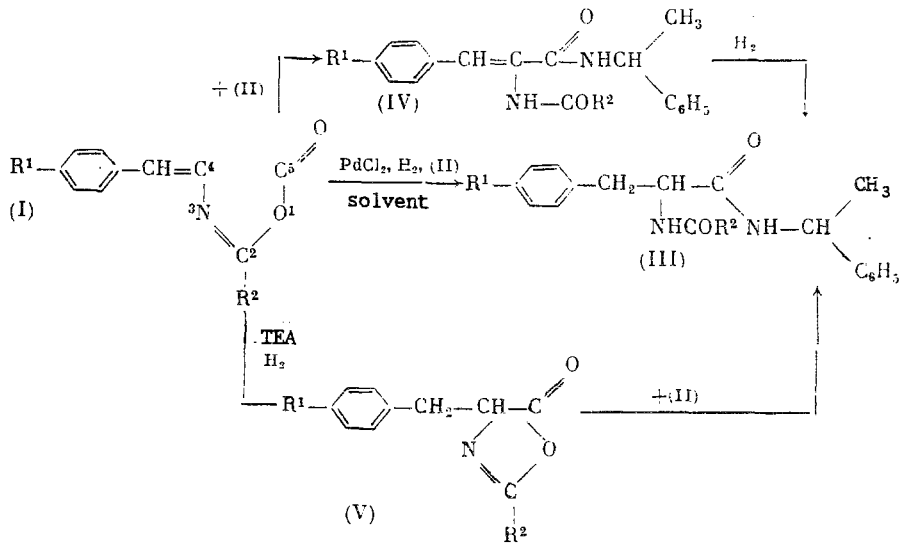
Fluorine-containing amino acids and their derivatives possess biological activity [1, 2]. A method we developed for the catalytic reductive aminolysis (RA) of an azalactone during the preparation of aliphatic and aromatic amino acids [3] was successfully used in the preparation of optically active p-fluorophenylalanine [4]. In this paper we consider the possibility of asymmetric synthesis of the phenylethylamide of N-acyl-p-difluoromethoxyphenylalanine – a potential starting material for the preparation of optically active amino acids.

DISCUSSION OF RESULTS

High-grade azalactones of N-benzoyl- and N-acetyl-p-difluoromethoxy-α-aminocinnamic acids (Ia) and (Ib) respectively, were used as starting materials. Reductive aminolysis of the azalactones by S-(−)-α-phenylethylamine (II) in the presence of $PdCl_2$ and H_2 was studied in dimethoxyethane (DME), isopropanol, and tert-butanol at ~20°C. Possible reaction pathways are deduced in the scheme:



(Ia): $R^1 = F_2CHO$, $R^2 = C_6H_5$; (Ib): $R^1 = F_2CHO$, $R^2 = CH_3$; (Ic): $R^1 = F$, $R^2 = CH_3$

The reaction products were identified by IR and NMR spectroscopic methods. Assignment of the proton signals in the NMR spectra was in accordance with NMR data for derivatives of N-acetyl-p-methoxy-α-aminocinnamic acid [5]. Further data for comparison was derived from RA of the azalactone of N-acetyl-p-fluoro-α-aminocinnamic acid (Ic) [4]. During RA of (Ia) and (Ib) the principal products were the α-phenylethylamides of N-acyl-p-difluoromethoxyphenylalanines (IIIa) and (IIIb) (Table 1). By-products obtained were the α-phenylethylamides

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TABLE 1. Reductive Aminolysis and Two-Stage Process with the Azalactones of N-Benzoyl- and N-Acetyl-p-difluoromethoxy-α-aminocinnamic Acids (Ia) and (Ib) (0.09 mmole $PdCl_2$, 0.5 mmole (I), 0.75 mmole (II) or TEA, 8 ml solvent)

Substrate	Solvent	$k \cdot 10^2$, min^{-1}	Yield of (III) + (IV), %	Reaction product, %		ED of (III), %
				(III)	(IV)	
Reductive aminolysis						
(Ia)	DME	5.0	85	88	12	3
(Ia)	*i*-PrOH	1.0	85	80	20	17
(Ia)	*t*-BuOH	–	67	91	9	25
(Ib)	DME	4.5	80	93	7	30
(Ib)	*i*-PrOH	2.9	68	95	5	39
(Ib)	*t*-BuOH	2.6	72	90	10	47
(Ic)	DME	–	80	95	5	28
(Ic)	*i*-PrOH	–	78	91	9	46
Two-stage process						
(Ia)	*i*-PrOH *		85	90	10	30
(Ia)	DME	1.0	87	100	–	10
(Ia)	*t*-BuOH *		70	88	12	42
(Ib)	DME	2.0	82	100	–	40
(Ib)	*i*-PrOH *		87	100	–	44
(Ib)	*t*-BuOH		77	90	10	55
(Ic)	DME		85	100	–	40
(Ic)	*i*-PrOH †		80	90	10	45

*Hydrogenation with TEA in DME, aminolysis in alcohol.
†Hydrogenation and aminolysis in i-PrOH. Amounts of (III) and (IV) determined without taking ester into account.
Experiments in tert-butanol were carried out at 23°C.

of N-acyl-p-difluoromethoxy-α-aminocinnamic acids (IVa) and (IVb), produced during the aminolysis of (I). The content of (IV) changed as a function of initial substrate and solvent. Production of (IV) was observed to a larger extent during RA in i-PrOH, but increasing the amount of catalyst led to a reduction in the content of this by-product. As a result of lowering the temperature of RA to 15°C, 60% of initial (I) remained in the reaction mixture. Tests of RA of (Ia) in tert-butanol were poorly reproducible; from some of them conversion (X) reached 20-80%. The reaction rate for RA of both azalactones is described by a first-order equation in substrate. For (Ia) in DME and for (Ib) in all of the solvents used a linear relationship ln C (C = concentration of (I), mole/liter) versus time was maintained up to X = 85-90%, for (Ia) in alcohol up to X = 60%. The maximum reaction rate for RA ($k = (4.5\text{-}5.0) \cdot 10^{-2}$, min^{-1}) was observed in DME, and a reduction in the reaction rate was noticed in alcohol. Reductive aminolysis of (Ia) and (Ib) proceeded stereoselectively with the formation of (IIIa) and (IIIb) preferentially in the S,S-configuration. The excess of S,S-diastereoisomer (ED) of (III), determined by an NMR method, was dependent on the nature of the solvent. The minimum ED of S,S-(III) was produced during reaction in DME, the maximum in tert-butanol. Replacing Ph by Me in the 2-position of the azalactone ring of (I) gave an increase in the stereoselectivity of the process. During RA of (Ib) in DME, in comparison with (Ia), ED of (III) was increased from 3 to 30%, in isopropanol from 17 to 39%, and in tert-butanol from 25 to 47%. An analogous effect has been observed when replacing Ph by Me in the 2-position in (I) for other azalactones [3]. For the two-stage process, in which hydrogenation of (I) is carried out first in the presence of $PdCl_2$ and triethylamine (TEA), and then the saturated azalactone (V) produced undergoes aminolysis in the presence of (II), from the reaction of both azalactones in DME only the amides (III) are formed, and the stereoselectivity of the process is enhanced. During this, the ED of S,S-(III) increased from 3 to 10% for (IIIa), and from 30 to 40% for (IIIb). The two-stage process in isopropanol or tert-butanol is accompanied by the formation of 5 to 25% of ester. If the first step is carried out in DME, but the second in alcohol, this leads to an increase in the yield of (III). Just as in DME, the two-stage process in alcohol proceeds with higher stereoselectivity than RA: ED of (IIIa) increases in isopropanol from 17 to 30%, of (IIIb) from 39 to 44%, and in tert-butanol of (IIIa) from 25 to 42%, and of (IIIb) from 47 to 55%. As can be seen, an increase in the stereoselectivity of the reaction was observed for both azalactones during the two-stage process, as with RA, for the series of solvents DME < isopropanol < tert-butanol. For another series of azalactones the fact that stereoselectivity increased during the transition from DME to tert-butanol was also noticed [3]. For the aza-

TABLE 2. Hydrogenation of the α-Phenylethylamides of N-benzoyl- and N-acetyl-p-difluoromethoxy-α-aminocinnamic Acids (IVa) and (IVb) to (III) (0.04 mmole $PdCl_2$, 0.2 mmole (IV), 6 ml solvent)

Substrate	Solvent	Degree of conversion, %	ED of R, S-(III), %	Substrate	Solvent	Degree of conversion, %	ED of R, S-(III), %
(IVa)	*i*-PrOH	90	16	(IVb)	*t*-BuOH	88	15
(IVb)	DME	70	18	(IVc)	DME	80	10
(IVb)	*i*-PrOH *	100	9	(IVc)	*i*-PrOH	75	7

*Hydrogenation time 15 h, in the remaining cases 10-12 h.

lactone (Ic), increased stereoselectivity was observed during the two-stage process, compared with RA, and in the transition from DME to isopropanol.

Hydrogenation, especially in the synthesis of (IVa) and (IVb), proceeds at a negligible rate. The reaction reaches completion only after 15 h. Amides were formed with 9-18% ED of R,S-(III) (Table 2). Analogous data was obtained during hydrogenation of other unsaturated amides [3]. Formation of the amides of (III) with the R,S-configuration indicates that the RA reaction does not proceed via formation of an intermediate unsaturated amide (IV). Comparison of data for RA of (Ia-c) and the corresponding unsubstituted (I) [3, 5] in DME, isopropanol, and tert-butanol indicates that in all cases formation of (III) with similar ED of S,S-(III) is observed. This fact indicates that introduction of a fluorine-containing substituent into the aromatic ring of the azalactone has little influence on the stereoselectivity of RA and does not influence the configuration of the amide produced or, apparently, the mechanism of the process. One crystallization of the amides of S,S-(III) with 40-50% ED led to optically pure amide, which should, through hydrolysis, give S-difluoromethoxyphenylalanine. We have established that hydrolysis of S,S-(III) in 6 N HCl, as with the acid methanolysis described in [6], is accompanied by abstraction of the difluoromethyl group and yields S-tyrosine.

EXPERIMENTAL

NMR spectra were obtained on a "Bruker WM-250" radiospectrometer, and IR spectra on a UR-20 spectrometer. Polarimetric measurements were made using a Jasco polarimeter. $PdCl_2$ (AR grade) was used, S-(−)-α-phenylethylamine [α] −39.4° (solvent free). p-Difluoromethoxybenzaldehyde was prepared as in [7], n_D^{20} = 1.5015, bp 94-96°C (5 mm).

The azalactone of N-acetyl-p-difluoromethoxy-α-aminocinnamic acid (Ib) was prepared as in [8], yield 45%, yellow prisms, mp 120-121°C (from heptane). UV spectrum (dioxane, λ_{max}, nm (ε)): 234 (8100), 333 (32,000). IR spectrum ($CHCl_3$, ν, cm^{-1}): 1805, 1780 (C=O), 1660 (C=N), 1130, 1060 (C-F). NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 2.41 s (CH_3), 6.6 t (CHF_2, J = 72), 7.1 s (CH=), 7.16 d (m-CH^1, C_6H_4, J = 9), 8.11 d (o-CH^2, C_6H_4, J = 9).

The azalactone of N-benzoyl-p-difluoromethoxy-α-aminocinnamic acid (Ia) was prepared as in [8], yield 70%, bright-orange powder, mp 156.5-157.5°C (from heptane). UV spectrum (dioxane, λ_{max}, nm (ε)): 253 (7300), 368 (17,300). IR-spectrum ($CHCl_3$, ν, cm^{-1}): 1790, 1770 pl (C=O), 1660 (C=N), 1130, 1060 (C-F). NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 6.6 t (CHF_2, J = 74), 7.2 s (CH=), 7.21 d (m-CH^1, C_6H_4, J = 8), 8.23 d (o-CH^2, C_6H_4, J = 8), 7.59 m (3H, C_6H_5), 8.18 d (2H, C_6H_5, J = 7). The S-(+)-α-phenylethylamide of N-acetyl-p-difluoromethoxy-α-aminocinnamic acid (IVb) was prepared as in [5], yield 80%, white crystals, mp 188-189°C (from absolute ethanol). IR spectrum, ($CHCl_3$, ν, cm^{-1}): 3235 (NH), 1650, 1630 (amide (I)), 1510 (amide (II)), 1130, 1050 (CF). NMR spectrum (CD_3OD, δ, ppm J, Hz): 1.48 d (CH_3-CH, J = 7), 2.05 s (CH_3CO), 5.08 q (CH), 6.8 t (CHF_2, J = 74), 7.0 s (CH=), 7.08-7.55 m (C_6H_5, C_6H_4), $[\alpha]_D^{20}$ 34° (C 1.56, absolute ethanol).

The S-(+)-α-phenylethylamide of N-benzoyl-p-difluoromethoxy-α-aminocinnamic acid (IVb) was prepared in DME by the method of [5], yield 78%, white crystals, mp 186-187°C (from absolute ethanol). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3230 (NH), 1645 (amide (I)), 1520 (amide (II)), 1130, 1050 (CF). NMR spectrum (CD_2OD, δ, ppm, J, Hz): 1.48 d (CH_3-CH, J = 7), 5.1 q (CH), 6.78 t (CHF_2, J = 74), 6.80 s (CH=), 6.98-7.97 m (C_6H_5, C_6H_4), $[\alpha]_D^{20}$ 46° (C 1.01, absolute ethanol.

Reductive aminolysis was carried out by the method described in [5]. After completion of the reaction the catalyst was filtered off, and for separation of the amine from the catalysis it was passed through a column of Dowex (H^+-form) 50 × 4 cm, eluted with a suitable solvent, and evaporated to dryness under vacuum. The ratio of diasteromers of the amides was determined by NMR. The mixture of amides, with a 40-50% excess of the S,S-diastereomer, was crystallized from a mixture of ethyl acetate and hexane (2:1). The solubility of S,S-(IIIb) was greater in that mixture than R,S-(IIIb); S,S-(IIIa) was obtained from the mother liquor after separation of the racemate. Optically pure amides were obtained.

S,S-(−)-α-Phenylethylamide of N-acetyl-p-difluoromethoxyphenylalanine (IIIb), mp 215-216°C. IR spectrum (KBr, ν, cm^{-1}): 3300, 3280 (NH), 1630 (amide (I)), 1540 (amide (II)), 1130, 1030 (CF). NMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.35 d ($\underline{CH_3}$=CH, J = 7), 1.88 s (CH_3CO), 2.85 m (CH_2), 4.52 t ($\underline{CH}$-NH), 4.85 q ($\underline{CH}$-C_6H_5), 6.68 t (CHF_2, J = 74), 6.82-7.22 m (C_6H_5, C_6H_4). $[\alpha]_D^{25}$ −34° (C 1.05, absolute ethanol).

S,S-(−)-α-Phenylethylamide of N-benzoyl-p-difluoromethoxyphenylalanine (IIIa), mp 211-212°C. IR spectrum (KBr, ν, cm^{-1}): 3280 (NH), 1630 (amide (I)), 1540 (amide (II)), 1130, 1060 (CF). NMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.38 d (CH_3, J = 7), 3.0 m (CH_2), 4.75 t (CH-NH), 4.9 q (CH-C_6H_5), 6.66 t (CHF_2, J = 74), 6.8-7.7 m (C_6H_5, C_6H_4), $[\alpha]_D^{20}$ −44° (C 0.45, absolute ethanol).

Hydrogenation with TEA. Compound (I) (0.5 mmole) was hydrogenated in the presence of $PdCl_2$ (17 mg) and TEA (0.75 mmole) in DME (8 ml). The saturated azalactone produced (V) was opened with phenylethylamine by one of two processes: 1) if aminolysis was carried out in DME, then (II) (0.75 mmole) was added to the reaction mixture containing (V) and it was left for 12 h: 2) to carry out aminolysis in alcohol solution, (V) formed in DME was separated from the catalyst by filtration, and concentrated under vacuum. The oily product obtained was dissolved in the appropriate alcohol, (II) was added, and it was left for 12 h.

The azalactone of N-acetyl-p-difluoromethoxyphenylalanine (Vb), oil; IR spectrum ($CHCl_3$, ν, cm^{-1}), 1830 (C=O), 1690 (C=N), 1130, 1060 (CF). NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.99 s (CH_3), 3.15 m (CH_2), 4.82 q (CH), 6.5 t (CHF_2, J = 72), 7.01 d (m-CH^1, C_6H_4, J = 7), 7.16 d (o-CH^2, C_6H_4, J = 7).

The azalactone of N-benzoyl-p-difluoromethoxyphenylalanine (Va), oil; IR spectrum ($CHCl_3$, ν, cm^{-1}): 1820 (C=O), 1660 (C=N), 1130, 1050 (CF).

CONCLUSIONS

1. Catalytic reductive aminolysis of the azalactones of N-acyl-p-difluoromethoxy-α-aminocinnamic acid in dimethoxyethane, isopropanol, and tert-butanol proceeds stereoselectively, leading to the α-phenylethylamides of N-acyl-p-difluoromethoxyphenylalanine with a 3-55% excess of the S,S-diastereomer.

2. Replacement of dimethoxyethane by isopropanol or tert-butanol leads to an increase in the stereoselectivity of the process.

3. Hydrogenation of the S-(+)-α-phenylethylamide of N-acyl-p-difluoromethoxy-α-aminocinnamic acid proceeds stereoselectively, and leads to production of the α-phenylethylamide of N-acyl-p-difluoromethoxyphenylalanine with a 9-18% excess of the R,S-diastereomer.

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