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LIPASE-CATALYZED KINETIC RESOLUTION OF THE RACEMIC MIXTURES OF 1-ARYLOXY-3-NITRATO- AND 1-ARYLOXY-3-AZIDO-2-PROPANOLS

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Abstract. The racemic mixtures of 1-aryloxy-3-nitrato-2-propanols and 1-aryloxy-3-azido-2-propanols were resolved with moderate selectivity by the lipase-mediated acylation with vinyl acetate. The effects of the nature, position, and spatial requirements of the phenyl-ring substituents on the resolution degree were investigated.

The enantiomers of 1,3-disubstituted secondary propanols are known as useful chiral building blocks in the synthesis of biologically active compounds[1] such as β-blockers (propranolol, timolol, and other), antidepressant drugs (tomoxetine, norfluoxetine) or muscle relaxants (mephenesin, chlorphenesin, guaifenesin). Most of them are still manufactured and marketed as racemates[2]. However, in the case of the 1-aryloxy-3-alkylamino-2-propanol β-blockers, their adrenolytic activity was found to be strongly dependent on the configuration of the chiral carbon atom[1], the (S) enantiomers being more active than their (R) counterparts. Preparation of the optically active 1,2-diols by chemical methods include ring opening of epoxides[3], asymmetric hydroxylation[4], or reduction of the

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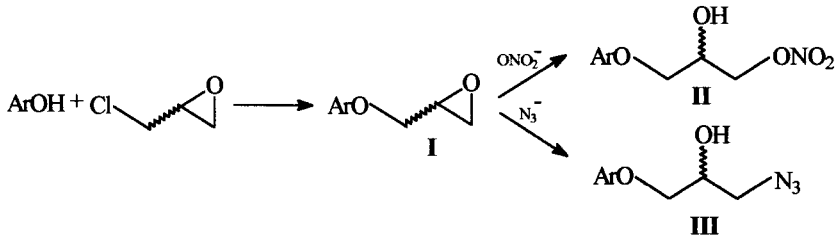
optically active 2-hydroxycarboxylic acid derivatives[5]. Several attempts have been also made at kinetic separation of enantiomers, such as lipase-catalyzed transesterification or hydrolysis of monoacylated diols[6], lipase-catalyzed alcoholysis of diacylated diols[7], or lipase-catalyzed kinetic resolution of racemic 2-hydroxycarboxylic esters followed by subsequent reduction[8]. A sequential transesterification process catalyzed by the Amano PS lipase has been also developed for 1-aryloxy-2,3- propanediols[9]. A number of racemic mixtures of 1-aryl- and 1-aryloxy-2-propanols carrying various 3-substituents have been resolved[10] into single enantiomers by the enzyme-catalyzed kinetic method. The compounds substituted in the phenyl ring and with a 3-halogen, -amino, -hydroxy or -carboxy group in the propanol chain are investigated most frequently. New methods of their synthesis were reported in numerous publications[11] which appeared in the last few years and this is the best evidence for the importance of this class of compounds.

Our attention was focused on the search for a simple method of the preparation of some synthetically useful 1-aryloxy-3-nitrato- and 1-aryloxy-3-azido-2-propanols. To the best of our knowledge no data are available on the lipase-catalyzed reactions of the nitrato-substituted alcohols. These compounds, however, seem to be of interest since hydrolysis of the nitrato group can easily convert them into the corresponding 1-aryloxy-2,3-propanediols or aryloxymethyl-oxiranes. The reaction proceeds with the inversion of configuration which is of particular value in the case of optically pure compounds. As far as 1-aryloxy-3-azido-2-propanols are concerned, the multidirectional reactivity of the azido and hydroxy groups can be used to

advantage in the resolution attempts. Thus far, only enantiomers of the phenyl-unsubsituted derivative have been separated[10b] with approximately 80% enantiomeric excess.

In the present paper we report the preparation of several racemic 1-aryloxy-3-nitratopropanols-2 and 1-aryloxy-3-azidopropanols-2 as well as the results of their kinetic lipase-catalyzed resolution into enantiomers.

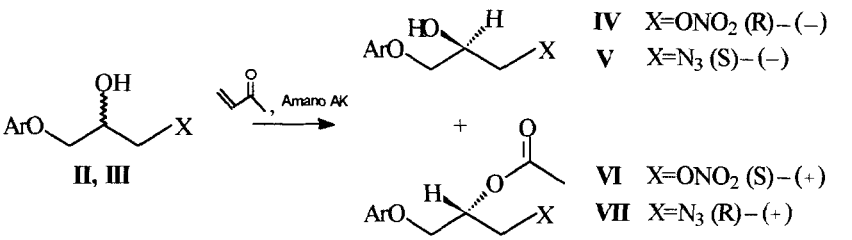
The arylglycidyl ethers (I) were obtained in the Williamson reaction from the appropriate phenols and epichlorhydrin according to the known procedures[12] and were chromatographically separated from the corresponding 1-aryloxy-3-chloropropanols-2 which were formed as by-products. The racemic mixtures of the nitratoalcohols (II) were prepared[13] from the appropriate arylglycidyl ethers by the reaction with an excess (3 mole) of ammonium nitrate in an acetonitrile-water (6:1v/v) solution in the presence of 0.3 mole of cerium ammonium nitrate. Similarly, the racemic azidoalcohols (III) were prepared in the reaction of aryglycidyl ethers with sodium azide (5 mole) and ammonium chloride (2 mole) in a methanol-water (8:1v/v) solution according to the reaction scheme:



The prepared 1-aryloxy-3-nitrato-2-propanols and 1-aryloxy-3-azido-2-propanols were purified by column chromatography on silica gel. All the compounds were

obtained as viscous colorless or yellowish oils. The presence of the nitrato or azido group in all of the investigated compounds was confirmed by the characteristic bands in their IR spectra taken as films. The yields, results of C,H,N elemental analyses, IR characteristic bands frequencies and ^{1}HNMR data of the synthesized compounds of the general formula **II** and **III** are collected in the Table 1 and Table 2.

The kinetic resolution of the synthesized racemic mixtures of the alcohols (**II**, **III**) were performed by the *Pseudomonas fluorescens* (Amano AK) lipase-catalyzed transesterification with vinyl acetate. The reactions with the nitrato derivatives were carried out in *tert*-butyl methyl ether while those with the azido derivatives, in hexane, always at room temperature. The reaction time was adjusted so as to obtain an approximately 50% substrate conversion which was monitored by comparing the intensity of the TLC spots of the unreacted alcohols (**IV**, **V**) and the acetates formed (**VI**, **VII**).



The yields and properties of the obtained acetates and the residual alcohols are summarized in Table 3.

The results presented in the Table 3 show that the stereoisomers of variously ring-substituted 1-aryloxy-3-nitrato- and 1-aryloxy-3-azido-2-propanols can be separated by the Amano AK lipase-catalyzed transesterification with vinyl

Table1. Yields, elemental analyses and IR characteristic bands of 1-aryloxy-3-nitrato-(**II**), and 1-aryloxy-3-azido-2-propanols(**III**):

No	Ar	X	Yield	Analyses						ν_{NO_2} or ν_{N_3} respectively
				Calculated			Found			
			(%)	%C	%H	%N	%C	%H	%N	(cm^{-1})
1	C_6H_5-	ONO_2	79	50.71	5.20	6.57	50.93	5.31	6.36	1630,1275
2	2-$CH_3C_6H_4$-	ONO_2	70	52.84	5.77	6.17	52.48	5.85	5.93	1640,1230
3	3-$CH_3C_6H_4$-	ONO_2	67	52.84	5.77	6.17	52.94	5.83	6.09	1635,1230
4	4-$CH_3C_6H_4$-	ONO_2	69	52.84	5.77	6.17	52.74	6.09	6.11	1640,1230
5	4-ClC_6H_4-	ONO_2	70	43.65	4.07	5.66	43.96	4.14	5.28	1630,1230
6	2,6-$Cl_2C_6H_3$-	ONO_2	68	38.32	3.22	4.49	38.58	3.54	4.28	1630,1230
7	C_6H_5-	N_3	76	55.97	5.70	21.76	55.81	5.52	21.53	2100
8	2-$CH_3C_6H_4$-	N_3	66	57.96	6.32	20.28	57.67	6.43	19.95	2100
9	3-$CH_3C_6H_4$-	N_3	84	57.96	6.32	20.28	57.82	6.30	20.31	2090
10	4-$CH_3C_6H_4$-	N_3	94	57.96	6.32	20.28	58.14	6.21	20.01	2090
11	4-ClC_6H_4-	N_3	79	47.48	4.43	18.46	47.63	4.52	18.21	2100
12	3-CH_3-4-Cl-C_6H_3-	N_3	73	49.70	5.01	17.39	49.82	5.12	17.19	2100
13	1-Naphthyl-	N_3	86	64.19	5.38	17.27	64.43	5.48	17.01	2090

Table 2. ^{1}H NMR data of 1-aryloxy-3-nitrato- (**II**), and 1-aryloxy-3-azido-2-propanols (**III**):

No	Ar	X	δ ppm in $CDCl_3$
1	C_6H_5-	ONO_2	2.62(1H,s,OH);4.05-4.08(2H,m,CH_2ONO_2);4.29-4.34(1H,m,CH);4.64-4.68,(2H,m,CH_2O);6.89-7.36(5H,m,Ar)
2	2-$CH_3C_6H_4$-	ONO_2	2.26(3H,s,CH_3);2.71(1H,s,OH);4.04-4.08(2H,m,CH_2ONO_2);4.30-4.41(1H,m,CH);4.58-4.75 (2H,m,CH_2O); 6.80-7.26(4H,m,Ar)
3	3-$CH_3C_6H_4$-	ONO_2	2.34(3H,s,CH_3);2.36(1H,s,OH);3.99-4.12(2H,m,CH_2ONO_2);4.26-4.36(1H,m,CH);4.64-4.68(2H,m,CH_2O);6.70-7.26(4H,m,Ar)
4	4-$CH_3C_6H_4$-	ONO_2	2.31(3H,s,CH_3);2.80(1H,s,OH);4.01-4.09(2H,m,CH_2ONO_2);4.25-4.34(1H,m,CH);4.63-4.73(2H,m,CH_2O); 6.79-7.26(4H,m,Ar)
5	4-ClC_6H_4-	ONO_2	2.36(1H,s,OH);4.01-4.03(2H,m,CH_2ONO_2);4.26-4.36(1H,m,CH);4.63-4.69(2H,m,CH_2O);6.80-7.27(4H,m,Ar)
6	2,6-$Cl_2C_6H_3$-	ONO_2	3.12(1H,s,OH);4.11-4.15(2H,m,CH_2ONO_2);4.31-4.35(1H,m,CH);4.67-4.79(2H,m,CH_2O);6.97-7.30(3H,m,Ar)
7	C_6H_5-	N_3	2.55(1H,s,OH);3.40-3.62(2H,m,CH_2N_3);4.01(2H,d,J=5.1Hz,CH_2O);4.08-4.22 (1H,m,CH); 6.72-7.0(3H,m,Ar); 7.11-7.39(2H,m,Ar)
8	2-$CH_3C_6H_4$-	N_3	2.23(3H,s,CH_3);2.49(1H,s,OH);3.50-3.62(2H,m,CH_2N_3);4.05(2H,d,J=5.2Hz,CH_2O);4.15-4.30(1H,m,CH);6.81-6.95(2H,m,Ar);7.12-7.23(2H,m,Ar)
9	3-$CH_3C_6H_4$-	N_3	2.33(3H,s,CH_3);2.65(1H,s,OH);3.42-3.58(2H,m,CH_2N_3);4.0(2H,d,J=5.6Hz,CH_2O); 4.1-4.22(1H,m,CH);6.68-6.83(3H,m,Ar);7.15 (1H,m,Ar)
10	4-$CH_3C_6H_4$-	N_3	2.25(3H,s,CH_3);2.5(1H,s,OH);3.45-3.65(2H,m,CH_2N_3);4.04(2H,d,J=5.3Hz, CH_2O); 4.15-4.25(1H,m,CH);6.73-6.95(2H,m,Ar);7.12-7.22 2H,m,Ar)
11	4-ClC_6H_4-	N_3	2.55(1H,s,OH);3.42-3.62(2H,m,CH_2N_3);3.94(2H,d,J=5.2Hz,CH_2O);4.21-4.31 (1H,m, CH);6.82-6.91(2H,m,Ar); 7.20-7.34(2H,m,Ar)
12	3-CH_3-4-Cl-C_6H_3-	N_3	2.35(3H,s,CH_3);2.72(1H,s,OH);3.39-3.61(2H,m,CH_2N_3);3.95(2H,d,J=5.2Hz, CH_2O);4.05-4.21(1H,m,CH);6.59-6.82(2H,m,Ar);7.19-7.30(1H,m,Ar)
13	1-Naphthyl	N_3	2.7(1H,s,OH);3.49-3.71(2H,m,CH_2N_3);4.15(2H,d,J=5.3Hz,CH_2O);4.19-4.40 (1H,m,CH);6.75(1H,d,J=7.2Hz, Ar);7.28-7.63(4H,m,Ar);7.75-7.85(1H,m,Ar); 8.16-8.25 (1H,m,Ar)

Table 3. Optical rotations and enantiomeric excess data for 1-aryloxy-3-nitrato- (**IV**) and 1aryloxy-3-azido-2-propanols (**V**) and their acetates (**VI** and **VII**, respectively):

No	Ar-	X	reaction time (hrs)	conversion (%)	acetates $[\alpha]_D^{20}$	acetates ee (%)	acetates E	alcohols $[\alpha]_D^{20}$	alcohols ee (%)	alcohols E
1	C_6H_5-	-ONO_2	26	49	+25.0	77	16.9	-16.0	73	16.8
2	2-$CH_3C_6H_4$-	-ONO_2	55	46	+29.7	67	8.8	-12.2	56	8.8
3	3-$CH_3C_6H_4$-	-ONO_2	35	48	+31.0	92	60.4	-14.8	85	6.0
4	4-$CH_3C_6H_4$-	-ONO_2	29	45	+24.0	65	7.9	-4.6	53	7.8
5	4-ClC_6H_4-	-ONO_2	28	62	+15.5	55	10.1	-5.5	89	9.5
6	2,6-$Cl_2C_6H_3$-	-ONO_2	70	57	+29.7	62	10.7	-4.4	83	0.6
7	C_6H_5-	-N_3	24	46	+33.8	67	9.0	-32.3	57	8.9
8	2-$CH_3C_6H_4$-	-N_3	55	50	+31.0	70	12.0	-24.5	70	1.7
9	3-$CH_3C_6H_4$-	-N_3	27	37	+35.1	76	11.3	-29.2	44	0.7
10	4-$CH_3C_6H_4$-	-N_3	24	35	+44.8	78	12.2	-17.2	42	2.2
11	4-ClC_6H_4-	-N_3	25	63	+20.8	43	5.2	-20.7	72	5.0
12	3-CH_34Cl-C_6H_3-	-N_3	21	37	+38.1	79	13.4	-23.7	47	14.3
13	naphthyl-1	-N_3	24	50	+61.5	89	51.3	-32.4	87	41.0

ee(%) of alcohols was determined by HPLC on a Chiracel ODH chiral column.

ee(%) of acetates was determined from ^{1}HNMR spectra of the $Eu(tfc)_3$ complex.

Optical rotation was determined in methanol solution.

Enantioselectivities of the reactions (E) were determined from the equations[14]:

$$E = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]} \text{ or } E = \frac{\ln[(1-c)(1+ee_p)]}{\ln[(1-c)(1-ee_p)]}$$

where: ee_s = enantiomeric excess of the unreacted alcohol

ee_p = enantiomeric excess of the prepared acetate

conversion of the substrate $c = \frac{ee_s}{ee_s + ee_p}$ (%)

acetate though with moderate optical purity. The position of the substituent in the phenyl ring does influence the time of the reaction (e.g., entries 2 and 4), but we did not observe any straightforward dependence between the character of the substituent and the enantiomeric excess of the reaction products.

The R-(+) configuration of the acetates obtained in the *Pseudomonas sp.* lipase catalyzed acyl transfer reaction of 1-aryloxy-3-azido-2-propanols was assigned by referring to the compound prepared by Schneider[10b]. According to the

literature[10a,b,c] data in similar reactions of 1-aryloxy-3-chloro-, and 1-aryloxy-3-bromo-2-propanols S-(+) acetates (inverse order of substituents priority) were always formed. This suggests the S-(+) configuration of the acetates of 1-aryloxy-3-nitrato-2-propanols prepared by us and the unidirectional stereopreference of the *Pseudomonas sp.* lipase in the acetylation of 1-aryloxy-3-substituted-2-propanols.

To substantiate this suggestion, the levorotatory R-(-)-1-phenoxy-3-nitrato-2-propanol was treated with a potassium carbonate solution. The resulting dextrorotatory product was identified as S-phenoxymethyl-oxirane[15]. This assignment agrees well with the „Kazlauskas - rule"[16].

General remarks and procedures.

^{1}HNMR spectra were recorded on a Bruker AC-250 spectrometer in $CDCl_3$ with TMS as the internal standard. IR spectra were taken on a Carl Zeiss Specord M80 instrument. Optical rotation measurements were recorded on a P20 Bellingham and Stanley polarimeter. HPLC analyses were performed on a Thermo-Separation Products P-100 instrument. The determination of the products purity, and reaction monitoring were accomplished by TLC on Silica gel 60 F_{254} plates and the column chromatography on Silica Gel 60 (less than 230 mesh). Lipase Amano AK was generously provided by Amano Co.

1-Aryloxy-3-nitrato-2-propanols (II).

The arylglycidyl ether (0.05m) and ammonium nitrate 12g (0.15mol) were dissolved in 200 ml. of an acetonitrile/water 6:1 mixture. Cerium ammonium nitrate (8.22g, 0.015mol) was then added in small portions. The mixture was gently refluxed and the reaction course was monitored by TLC chromatography with ethyl acetate/hexane 1:6 v/v as the developing solution. Upon completing the reaction, the mixture was cooled and the solvents were evaporated under reduced pressure. Water (200 ml) was added to the residue and the product was extracted with ethyl ether (4 x 50 ml). The extract was dried over anhydrous magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate 15:1 (v/v) mixture.

1-Aryloxy-3-azido-2-propanols (III).

The arylgycidyl ether (0.05mol), sodium azide 16.25g (0.25mol), and ammonium chloride 6.4g (0.12mol) were added to 150ml of a methanol/water 8:1 mixture and gently refluxed for 8-10 hours. The reaction course was monitored on TLC plates with ethyl acetate/hexane 1:10. Upon completing the reaction, the

methanol was evaporated under reduced pressure, 50ml of water was added to the residue, and the product was extracted with ethyl ether (4x50ml). The extract was dried and evaporated and the product was purified on a silica gel column with a hexane/ethyl acetate 1:10 (v/v) eluent.

Kinetic resolution of the racemates of 1-aryloxy-3-nitrato-2-propanols (II):

To the nitratoalcohol (0.015mol) dissolved in 100ml of *tert*-butyl methyl ether 5.5 ml of vinyl acetate, 1g of Amano AK lipase and 2.5g of dried, crushed molecular sieves (4A) were added. The reaction flask was flushed with nitrogen and tightly closed and its content was stirred at room temperature for the time length indicated in Table 2. The solid material was filtered off and the filtrate was evaporated. The residue was separated on a silica gel column with hexane/ethyl acetate, first 25:1 (elution of the acetate) and next 10:1 (elution of the alcohol).

The separations of enantiomers of *1-aryloxy-3-azido-2-propanols (III)* were carried out in a similar manner except that hexane was used as the solvent.

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