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Short communication

Optical resolution of racemic carboxylic acids by gas chromatography

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Abstract

The synthesis of racemic acid amides was performed by using benzotriazol-l-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate as a condensing reagent, under mild conditions. The obtained enantiomers are easily separated by gas chromatography which yields good resolution for the majority of the products. © 1998 Elsevier Science B.V.

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1. Introduction

The analysis of enantiomers following conversion to diastereomers is a convenient approach for chiral compounds with easily derivatized functional groups [1]. Using this indirect approach, the enantiomers react with a chiral reagent and the obtained diastereomers are subsequently separated by chromatographic methods in an achiral environment. With a second strategy, called direct approach, the enantiomers are separated in a chiral environment, usually represented by a chromatographic column coated with a chiral phase. In both cases, the enantiomers are converted to diastereomers, covalent in the first case and noncovalent in the second. Using the indirect approach, care must be exerted in the optimization of the reaction to avoid differential derivatization due to different reaction rates of the enantiomers and a careful choice of an optically pure chiral reagent should be made.

Gas chromatography (GC) [2], together with high-performance liquid chromatography (HPLC) and, more recently, high-performance capillary electrophoresis (HPCE) are used for enantiomer separation. Chiral carboxylic acids not containing additional functional groups easily derivatizable, i.e. amino acids and hydroxy acids, have been chromatographically resolved as amide derivatives [3–5].

We report here the use of benzotriazol-l-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) for preparing amides from racemic carboxylic acids and chiral amines. The use of this coupling agent is recommended because it rapidly yields reasonably thermostable derivatives by a highly reproducible method, good enantioselectivity and minimal risk of racemization. The synthesis occurs under mild conditions and diastereomeric

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amides from a number of alkyl-α-halo- and α-hydroxy acids can easily be separated by GC.

2. Experimental

GC was performed by using a Shimatzu G-C 14A equipped with a chromatopac C-R 6A integrator. Fused-silica capillary column OV-1701, 30 m×0.25 mm I.D., film thickness 0.25 μm was from Quadrex (New Haven, CT, USA).

2.1. Chemicals

Racemic α-substituted carboxylic acids (see Table 1) were pure commercial products. (*S*)-(+)-α-chloropropionic acid, (*R*)-(+)-α-bromopropionic acid, (*S*)-(−)-α-bromopropionic acid, (*S*)-(+)-mandelic acid were commercially available from Aldrich (St. Quentin, France). Other enantiomers were prepared by optical resolution, i.e.: (−)-α-chlorobutanoic acid [6]), (−)-α-bromoisovaleric acid [7], (−)-α-bromo-*n*-caproic acid [7], (+)-α-phenoxypropionic acid [8], (−)-α-(2-chlorophenoxy)propionic acid [9], (−)-α-(3-chlorophenoxy)propionic acid [9], (−)-α-(4-chlorophenoxy)propionic acid [10], (−)-α-(2,4-dichlorophenoxy)propionic acid [11]. BOP was obtained from France Biochemicals (Meudon, France) and other chemicals were pure commercial products.

2.2. Sample preparation

2.2.1. Coupling with optically active amino acid esters

α-Substituted carboxylic acids (~$3\cdot10^{-5}$ mol) of each enantiomer, BOP (10 mg, i.e. $2.2\cdot10^{-5}$ mol) and the chosen amino acid ester hydrochloride (10^{-4} mol) were dissolved in 100 μl of dimethylformamide. Triethylamine (30 μl) was added and the reaction mixture allowed to rest 30 min at 50°C under shaking. After diluting it with ethyl acetate (2 ml) the organic phase was washed with 0.1 *M* HC1, 5% $NaHCO_3$ in 0.7 ml water and dried over anhydrous Na_2SO_4. The residual organic phase (1 ml) was diluted to 5 ml and 20–80 μl of the solution were injected into the chromatograph.

2.2.2. Coupling with optically active amines

α-Substituted carboxylic acids were treated as above, using *S*-(−)-1-phenylethylamine (15 μl) instead of the amino acid ester hydrochlorides without addition of triethylamine.

3. Results and discussion

Table 1 summarizes the values of the retention times and those of the enantiomeric resolution factors (R_S) which are a function of the shape of the peak and its position in the elution pattern. The majority of the R_S values indicate good resolution. The chromatographic peaks are sharp and a quantitative determination of the two enantiomers was easily performed. The high sensitivity of GC also allows determination of optical impurities up to about 1%, as observed in separated experiments. Only three enantiomers show poor resolution.

The best resolution obtained in the present work were those with leucine methyl ester and phenylethylamine (Fig. 1) but several amines not shown in Table 1 gave satisfactory results.

The present procedure can be used for microscale preparations and generally in that case the acids are first converted into acyl chlorides by thionyl chloride or other acylating reagents and then reacted with the corresponding amine. The activation of carboxylic acids as acyl chlorides may however induce some racemization and cannot be performed in the presence of reactive functional groups other that the carboxylic one. The present method can obviate those inconveniences.

The chiral reagent can be considered as pure because a single peak was obtained when pure enantiomers were used. Under our conditions there is no differential rate of the two enantiomers since an identical quantitative evaluation of the two peaks was obtained.

The preparation of the amides was accomplished under mild conditions and the separation method is quick and efficient so that its use in enantiomeric analysis can be recommended. The maximum retention times of about 20 min imply a rapid elution from the column while the thermic stability of the products allow for the use of relatively high working temperatures.

Table 1
Retention times (t_R) and resolution of racemic acid amides by gas chromatography

Racemic acid[a]	L-Ala OEt		L-Val OMe		L-Leu OMe		L-Phe OMe		*S*-(−)-1-Phenylethyl amine	
	t_R (min)	R_S^b (column temp.,°C)	t_R (min)	R_S (column temp.,°C)	t_R (min)	R_S (column temp.,°C)	t_R (min)	R_S (column temp.,°C)	t_R (min)	R_S (column temp.,°C)
$CH_3CH(Cl)CO_2H$	(*R*)(+)8.85	1.7	10.36	3.6	8.04	2.3	14.01	2.2	9.15	2
	(*S*)(−)9.15	(140)	11.12	(140)	8.39	(160)	14.58	(190)	(9.49)	(170)
$CH_3CH(Br)CO_2H$	(*R*)(+)7.52	1.6	8.58	3.7	11.84	2.8	10.72	2.1	10.10	1.7
	(*S*)(−)7.75	(160)	9.20	(160)	12.49	(160)	11.11	(210)	10.42	(180)
$CH_3CH_2CH(C1)CO_2H$	(+)7.18	2.5	8.15	4.7	11.17	3.3	10.18	2.3	12.35	3.7
	(−)7.54	(160)	8.90	(160)	11.91	(160)	10.64	(210)	13.24	(170)
$(CH_3)_2CHCH(Br)CO_2H$	(+)6.88	3.6	7.68	5.6	10.00	4.3	15.85	3.7	8.66	4.1
	(−))7.32	(180)	8.52	(180)	10.84	(180)	16.99	(210)	9.32	(200)
$CH_3(CH_2)CH(Br)CO_2H$	(+)7.69	3.4	8.57	4.6	11.03	3.1	16.08	2	7.2	3.9
	(−)8.17	(190)	9.32	(190)	11.69	(190)	16.68	(220)	7.69	(220)
$CH_3(CH_2)_5CH(Br)CO_2H$	6.76	3.3	7.38	4	8.92	2.7	15.56	1.7	9.68	4.9
	7.14	(220)	7.92	(220)	9.36	(220)	16.02	(240)	10.5	(230)
$CH_3(CH_2)_{13}CH(Br)CO_2H$	10.65	3.1	11.45	3.7	13.21	2.3	26.18	1.2	18.78	4.5
	11.22	(270)	12.20	(270)	13.76	(270)	26.71	(280)	20.43	(270)
$C_6H_5OCH(CH_3)CO_2H$	(−)12.53	1.5	(+)19.82	1	(+)12.78	3.2	(+)10.11	1.8	(−)11.85	4.3
	(+)12.88	(190)	(−)20.23	(180)	(−)13.59	(200)	(−)10.43	(250)	(+)12.80	(215)
$C_6H_5CH(OH)CO_2H$	(*R*)(−)22.43	1.1	(−)7.57	2.4	(−)8.94	2.9	(−)11.65	2.2	(+)13.46	1.5
	(*S*)(+)22.9	(190)	(+)7.9	(230)	(+)9.42	(230)	(+)12.12	(260)	(−)13.80	(230)
$C_6(1\text{-}Cl)H_4OCH(CH_3)CO_2H$	(−)12.12	1.6	(+)26.15	1.4	(+)11.84	3.2	(+)15.23	2.9	(−)7.60	3.1
	(+)12.51	(210)	(−)26.87	(190)	(−)12.54	(220)	(−)15.99	(250)	(+)8.03	(250)
$C_6(2\text{-}Cl)H_4OCH(CH_3)CO_2H$	(−)11.82	1.8	(+)23.72	1.3	(+)7.03	2.7	(+)11.39	2.3	(−)9.64	4.2
	(+)12.28	(210)	(−)24.17	(192)	(−)7.35	(240)	(−)11.84	(260)	(+)10.45	(240)
$C_6(3\text{-}Cl)H_4OCH(CH_3)CO_2H$	(−)9.37	2.5	N.R.		(+)12.36	2.7	(+)15.77	2.7	(−)7.91	4.8
	(+)9.85	(220)	25.5	(190)	(−)12.97	(220)	(−)16.53	(250)	(+)8.65	(250)
$C_6(1\text{-}Cl_i3\text{-}Cl)H_3OCH(CH_3)CO_2H$	(+)10.42	3.2	N.R.		(−)13.34	2.5	(−)16.17	2.9	(+)8.295.3	
	(−)10.98	(230)	46.2	(190)	(+)14.07	(230)	(+)17.15	(260)	(−)9.06	(260)

[a] The absolute configuration is unknown for a number of enantiomers.
[b] $R_s=(t_D-t_L)/(W_{D/2}+W_{L/2})$ where t_D and t_L are the retention times and $W_{D/2}$ and $W_{L/2}$ are the widths at half-height.

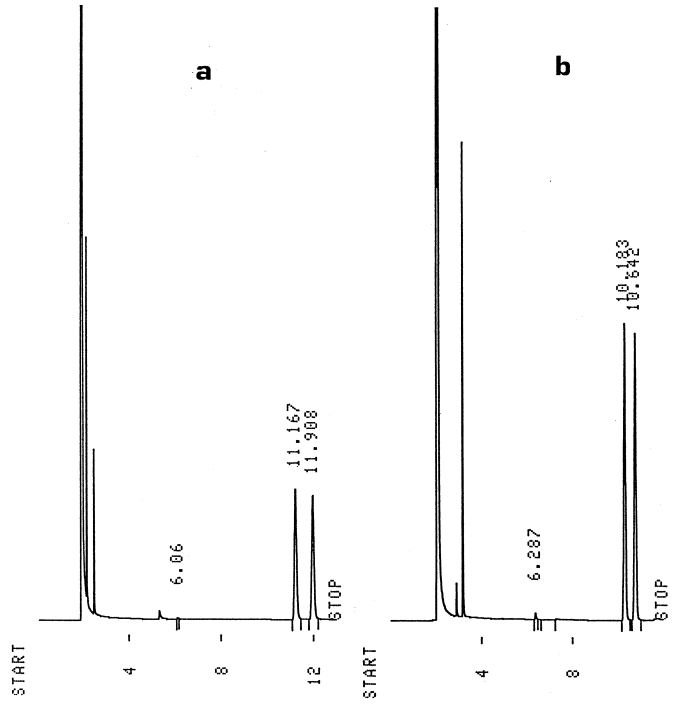

Fig. 1. Example of separation of (a) 2-chlorobutyricleucine amide and (b) 2-chlorobutyricphenylethyl amide at 160°C and 210°C, respectively.

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