Pergamon

Tetrahedron Letters 40 (1999) 2307–2310

TETRAHEDRON
LETTERS

Resolution of (±)-mandelic- and (±)-2-(chlorophenoxy)propionic-acid derivatives by crystallization of their diastereomeric amides with (*R*)- or (*S*)-α-arylethylamines

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Received 8 December 1998; accepted 18 January 1999

Abstract : An alternative and cost effective route for the resolution in high ees (95-99%) of (±)-mandelic- and (±)-2-(chlorophenoxy)propionic- acid derivatives is reported. The key step involves the covalent derivatization and separation of their diastereomeric amides with (*R*)- or (*S*)-α-arylethylamines.

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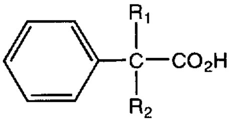
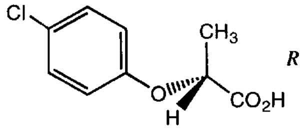
The optically active acids such as mandelic acid **1**, atrolactic acid **2**, 2-methoxy-2-phenylacetic acid **3** and 2-(4-chlorophenoxy)propionic acid **4** are used for the synthesis of chiral phosphine ligands,[1] as intermediates for the synthesis of anticholesteremics or herbicides.[2, 3] They are also used for the NMR analysis of absolute configuration.[4] Resolution of these acids has therefore presented a significant challenge in recent years.[5, 6] Atrolactic acid (±)-**2** can be resolved with phenylglycinol,[7, 8] or with 1-phenyl-2-(*p*-tolyl)ethyl amine (98% ee) by crystallization of the diastereomeric salts.[9, 10]



$R_1 = OH ; R_2 = H$ **1**
$R_1 = OH ; R_2 = CH_3$ **2**
$R_1 = OCH_3 ; R_2 = H$ **3**



R-(+)-**4**

Only a few procedures are available however for the preparation of the enantiomerically pure forms of the 2-methoxy-2-phenylacetic acids **3** and 2-(4-chlorophenoxy)propionic acids **4**. *R*-(-)-2-methoxy-2-phenylacetic acid **3** can be prepared by acid-catalyzed reaction of (2*S*-*trans*)-3-phenyloxiranemethanol with methanol and oxidation of the resulting (2*S*, 3*R*)-3-methoxy-3-phenyl-1,2-propanediol.[11] 2-Methoxy-2-phenylacetic acid (±)-**3** can be resolved by chiral alcohols (60% ee).[12] *R*-(+)-2-(4-chlorophenoxy)propionic acid **4** can be prepared by reaction of 4-chlorophenol on the O-*p*-toluenesulfonylester of the *S*-(-)-ethyl lactate, followed by crystallization of its salt with cyclohexylamine.[13] (±)-**4** can be resolved by the lipase OF 360, modified by a bioimprinting procedure.[14] The most practical procedure so far described for the preparation in large scale of enantiopure (-)-**4** and (+)-**4** seems to be the resolution of (±)-**4** by brucine via diastereomeric salt formation.[15] In light of the large number of reactions, we were prompted to consider a more widely applicable methodology.

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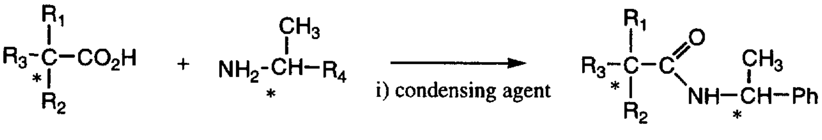
PII: S0040-4039(99)00169-0

Furthermore, the preparation and separation of diastereomeric amides, applied for the resolution of mandelic- and 2-(chlorophenoxy)propionic- acid derivatives has not yet been developed. Enantiopure derivatives of α-methylbenzylamine (α-MBA) have proved to be valuable resolving agents and various carboxylic acids were resolved via their diastereomeric salts,[16] or through the chromatographic separation of diastereomeric amides.[17] In this paper, we report the resolution of these racemic acids via the covalent derivatization and separation of diastereomeric amides with optically active α-arylethylamines.

The optically active mandelic **1**, atrolactic **2** and 2-methoxy-2-phenylacetic acids **3** were condensed respectively with the optically active α-methylbenzylamines **8** (R_4 = Phenyl) or α-(1-naphthyl)ethylamines **9** (R_4 = 1-naphthyl) using dicyclohexylcarbodiimide (DCC), *p*-toluenesulfonic acid (pTsOH) or $ClCO_2Et$ as an activating agent (Scheme1).[18] The amine **9** did not allow us to prepare the corresponding amides in satisfactory yields (20-25%). We also prepared for this study the diastereomeric mixtures **13-16** between (±)-2-(4-chlorophenoxy)propionic **4** ; (±)-2-(3-chlorophenoxy)propionic **5** ; (±)-2-(2-chlorophenoxy)propionic **6** ; (±)-2-(phenoxy)propionic acids **7** and *R*-(+)-and *S*-(-)-α-MBA **8**.



1 - 7 **8** R_4 = Ph **10 - 16**

Scheme 1

Amide formation between the enantiopure acids and amines took place without epimerisation of the acid moiety. The pure amides **10-12** were obtained by recrystallization from an acetone/heptane or a methanol/water mixture with yields ranging between 56 and 83% (Table 1).

Table 1. Preparation of amides **10-16** between acids **1-7** and α-methylbenzylamines **8**.[a-d]

Entry	Acid	R_1	R_2	R_3	Amine	i)	Amide	Yield (%)	$[\alpha]_D^{25}$	M.p. (°C)
1	(-)-**1**	OH	H	Ph	(+)-**8**	*p*-TsOH	(+)-**10a**	21	+52.4	110
2	(+)-**1**	"	"	"	(-)-**8**	"	(-)-**10b**	20	-52.4	112
3	(-)-**2**	"	CH_3	"	(+)-**8**	DCC	(+)-**11a**	57	+87.9	116
4	(+)-**2**	"	"	"	(-)-**8**	"	(-)-**11b**	56	-87.9	118
5	(-)-**3**	OCH_3	H	"	(+)-**8**	$ClCO_2Et$	(+)-**12a**	83	+30.3	122
6	(+)-**3**	"	"	"	(-)-**8**	"	(-)-**12b**	82	-30.3	123
7	(-)-**3**	"	"	"	"	"	(-)-**12c**	83	-145	105
8	(+)-**3**	"	"	"	(+)-**8**	"	(+)-**12d**	82	+145	105
9	(±)-**4**	CH_3	"	4-ClPhO	"	"	(+)-**13a** ; (+)-**13d**	85	ref. 20	ref.20
10	"	"	"	"	(-)-**8**	"	(-)-**13b** ; (-)-**13c**	85	ref.20	ref.20
11	(±)-**5**	"	"	3-ClPhO	"	"	(-)-**14b** ; (-)-**14c**	87	e	e
12	(±)-**6**	"	"	2-ClPhO	"	"	(-)-**15b** ; (-)-**15c**	83	e	e
13	(±)-**7**	"	"	PhO	"	"	(-)-**16b** ; (-)-**16c**	84	e	e

a) The de (%) were determined by HPLC using a Chiralcel OD column. Eluent system : 2-propanol/heptane (1:9) and ranged from 97 to 99% ; b) The notation a, b, c and d denotes the 2*R*, 1'*R*, 2*S*, 1'*S*, 2*R*, 1'*S* and 2*S*, 1'*R* amides respectively ; c) See ref.19 ; d) Crude yields for entries 9-13 ; e) SeeTable 2 for the separation of the diastereomeric mixture.

Next, we examined the ability of the diastereomeric mixtures of amides to be separated by crystallization and to determine how efficient this methodology could be for the optical resolution of these carboxylic acids.

Thus (±)-**2-7** were condensed with optically active α-MBA **8**. The resulting diastereomeric mixture of amides **11** obtained from the racemic atrolactic acid **2** and *R*-(+)-α-MBA **8** was remarkably separated by one single recrystallization from a mixture of methanol/water : the pure amide (+)- **11a** (99% de) was obtained in 25% yield. The amide (-)-**11b** was similarly obtained from (±)-**2** and *S*-(-)-**8**. Successive crystallizations from a mixture of methanol/water of the diastereomeric mixture of amides **12** afforded (+)- **12a** in 38% yield. The pure (-)- **12c** amide was also obtained in the same conditions from (±)-**3** and *S*-(-)-**8**.

A total separation of the diastereomeric mixture **13** between (±)-2-(4-chlorophenoxy)propionic acid **4** and *S*-(-)- **8** was efficiently achieved. Thus, (-)-**13c** amide was obtained by crystallization of the mixture **13** from a mixture of methanol/water in 38%yield. The recovery of (-)-**13b** from the mother liquor of the crystallization of (-)-**13c** was carried out by evaporating the solution to dryness, thus producing a residue which was recrystallized from a toluene/heptane mixture. Similar results were obtained when *R*-(+)-**8** is used for resolution. A total separation of the mixture **16** between (±)-**7** and *S*-(-)-**8** was also carried out. Both the (-)-**16b** and (-)-**16c** amides were obtained : crystallization from ethanol/water provided (-)-**16c** in 37% yield, and the suspension in the mother liquor was found to be the pure (-)-**16b** amide. Recrystallization of the mixture **14** from ethanol/methanol afforded (-)-**14c** in 39% yield. Repeated recrystallization of the diastereomeric mixture of amides **15** prepared from (±)-**6** and *S*-(-)-**8** did not lead to any significant separation of either (-)-**15b** or (-)-**15c**.

A notable advantage is that a variation of the molar ratio solvent/amides did not greatly affect the resolution efficiency unlike what was often observed for diastereomeric salts.[21] The hydrolysis (75%) of the amides **12-16** with hydrochloric acid led to the desired (+)- and (-)-acids in high ees (95-99% ; Table 2). It should be emphasized that for the resolutions of both acids **4** and **7**, one resolving agent *S*-(-)-**8** afforded both enantiomers in optically pure forms from the same resolving solution without seeding. The resolution of the acids **3-5** and **7** was carried out in 1 mmol as well as in 0.1 mol scale, using this procedure.[22]

Table 2. Resolution of mandelic- and 2-(chlorophenoxy)propionic- acid derivatives

Acid	Resolving agent	Condensing agent	Solvent of crystallization	Separated amide (yield %)$^{a, b}$	Hydrolysis conditions	Resolved acid	ee (%)^{c}	Overall yield	M.p. (°C)	$[\alpha]_D^{25}$
(±)-**2**	(+)-**8**	DCC or *p*-TsOH	$MeOH/H_2O$ (2 : 1)	(+)-**11a** (25)	d	-	-	-	-	-
(±)-**2**	(-)-**8**	DCC	"	(-)-**11b** (26)	d	-	-	-	-	-
(±)-**3**	(+)-**8**	$ClCO_2Et$	"	(+)-**12a** (38)	HCl 6N, 20h	(-)-**3**	95	29	67	-145
(±)-**3**	(-)-**8**	"	"	(-)-**12b** (38)	"	(+)-**3**	96	29	68	+146
(±)-**4**	(+)-**8**	$ClCO_2Et$ or *p*-TsOH	$MeOH/H_2O$ (1 : 1)	(+)-**13d** (38)	HCl 6N, 17h	(-)-**4**	98	28	103	-36
			Toluene/heptane (3: 1)^{e}	(+)-**13a** (30)	"	(+)-**4**	97	24	102	+35
(±)-**4**	(-)-**8**	$ClCO_2Et$ or *p*-TsOH	$MeOH/H_2O$ (1 : 1)	(-)-**13c** (38)	"	"	97	29	103	+36
			Toluene/heptane (3: 1)^{e}	(-)-**13b** (32)	"	(-)-**4**	97	24	103	-36
(±)-**5**	(-)-**8**	$ClCO_2Et$ or *p*-TsOH	EtOH/MeO (1: 1)	(-)-**14c** (39)	"	(+)-**5**	99	33	91	+31
(±)-**7**	(-)-**8**	$ClCO_2Et$	$EtOH/H_2O$ (10 : 1)	(-)-**16c** (37)	"	(+)-**7**	98	30	88	+39
			suspension^{e}	(-)-**16b** (25)	"	(-)-**7**	98	21	87	-38

a) The notation a, b, c and d denotes the 2*R*, 1'*R*, 2*S*, 1'*S*, 2*R*, 1'*S* and 2*S*, 1'*R* amides respectively ; b) yield from the racemic acid ; c) The ee (%) was determined by HPLC analysis using a Chiralpak-WH column with 2mM $CuSO_4$ aq. solution ; d) the hydrolysis conditions were not determined ; e) See text.

In summary, we have developed an alternative method for the resolution of 2-methoxy-2-phenylacetic acid, 2-(4-chlorophenoxy)-, 2-(3-chlorophenoxy)- and 2-(phenoxy)- propionic acids in high ees (95-99%) and relatively good overall yield (25-30%), through the preparation and facile separation of the corresponding diastereomeric mixtures of amides with (*R*)- or (*S*)-α-methylbenzylamine. These results confirm the advantages of the α-methylbenzylamine as a simple, yet powerful resolving agent. This procedure is inexpensive since the α-MBA is recovered, and seems to be a complementary route to resolve these acids.

Acknowledgement

One of the authors (F. J) is grateful to the Science and Technology Agency for a Research Fellowship (ID-196079). Thanks are also due to Dr. Murai and Mr. Hiroi for analytical support.

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20. A Typical procedure for the preparation of these new amides is the following : to a solution of (±)-**4** acid (40 g, 0.2 mol) in THF (300 mL) was added dropwise triethylamine (21.3 g, 0.21 mol) and $ClCO_2Et$ (22.8 g, 0.21 mol) at 0 °C over a period of 20m. Then *S*-(-)- **8** (25.4 g, 0.21 mol) was added and the reaction was stirred for 3h at 0 °C. After filtration, concentration and recrystallization from $MeOH/H_2O$ (1 : 1), 23.3 g (38%) of $\mathbf{13_c}$ were obtained. $[\alpha]_D^{25}$= -22.1 (c 0.48, MeOH) ; mp = 127 °C ; ^1H NMR ($CDCl_3$) δ : 1.40 (CH_3CH, d, J = 6.83) ; 1.54 ($OCHC\underline{H}_3$, d, *J* = 6.83) ; 4.64 ($OC\underline{H}CH_3$, qd, *J* = 6.83) ; 5.13 ($NC\underline{H}CH_3$, qt, *J* = 7.32) ; 6.57 (NH, d, *J* = 6.83) ; 6.86 - 7.36 (Ph, 9H, m). ^{13}C NMR ($CDCl_3$) δ : 18.6 ($OCH\underline{C}H_3$) ; 21.6 ($NCH\underline{C}H_3$) ; 48.2 ($N\underline{C}HCH_3$) ; 75.5 ($O\underline{C}HCH_3$) ; 116.8 - 155.4 (12C, Ph) ; 170.9 (C=O). IR (KBr) ν : 3332 (NH) ; 1655 (C=O). MS : 304 (MH^+). Anal. Calc. for $C_{17}H_{18}NO_2Cl$: C 67.21 ; H 5.97 ; N 4.61 ; % found : C 67.15 ; H 6.18 ; N 4.46. $\mathbf{13_b}$ was obtained from the filtrate of the crystallization of (-)- $\mathbf{13_c}$: thus the filtrate was evaporated to dryness and the residue recrystallized from toluene/heptane (3 : 1) to afford 20.5 g (32.5%) of $\mathbf{13_b}$ $[\alpha]_D^{25}$= -60.2 (c 0.5, MeOH) ; mp = 130 °C. (98.1% de) ; ^1H NMR ($CDCl_3$) δ : 1.49 ($C\underline{H}_3CH$, d, *J* = 6.83) ; 1.57 ($OCHC\underline{H}_3$, d, *J* = 6.83) ; 4.61 ($OC\underline{H}CH_3$, qd, *J* = 6.34) ; 5.11 ($NC\underline{H}CH_3$, qt, *J* = 7.32) ; 6.53 (NH, d, *J* = 6.35) ; 6.78 - 7.22 (Ph, 9H,m). ^{13}C NMR ($CDCl_3$) δ : 18.6 ($OCH\underline{C}H_3$) ; 21.8 ($NCH\underline{C}H_3$) ; 48.3 ($N\underline{C}HCH_3$) ; 75.5 ($O\underline{C}HCH_3$) ; 116.9 - 155.4 (12C, Ph) ; 170.9 (C=O). IR (KBr) ν : 3267 (NH) ; 1659 (C=O). MS : 304 (MH^+). Anal. Calc. for $C_{17}H_{18}NO_2Cl$: C 67.21 ; H 5.97 ; N 4.61 ; % found : C 67.27 ; H 5.89 ; N 4.51. Anal. Calc. for $C_{17}H_{18}NO_2Cl$: C 67.21 ; H 5.97 ; N 4.61 ; % found : C 67.11 ; H 5.86 ; N 4.57. : C 75.62 ; H 7.37 ; N 4.93.
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22. Typical procedure for the resolution of (±)-**4-5** and **7** acids : the resolution of (±)-**4** with *S*-(-)- α-methylbenzylamine **8** afforded *R*-(+)-2-(4-chlorophenoxy)propionic acid **4** : the hydrolysis of (-)- $\mathbf{13_c}$ (21 g, 0.07 mol) with 450 mL of HCl (6 mol dm^{-3}) under reflux for 17h led to 10.3 g (74%) of pure *R*-(+)-**4** (97% ee). mp = 103 °C, $[\alpha]_D^{25}$= +36 (c 0.5, MeOH) after recrystallization from petroleum ether.