Efficient resolution of 2-phenylbutyric acid

Marcel Cyrus Afraz[a], Gerry J.A. Ariaans[a,b] , Quirinus B. Broxterman[d] , and Alle Bruggink[a,c]

[a]*Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands*
[b] *Present address: Synthon,Microweg 22, 6545 CM Nijmegen*
[c] *DSM Corporate Technology, P.O. Box 6500, 6401 JH Heerlen, The Netherlands*
[d]*DSM Pharma Chemicals, P.O. Box 18 6160 MD Geleen, The Netherlands*
E-mail: alle.bruggink@dsm.com

Dedicated to Professor Binne Zwanenburg on his 70th birthday

(received 21 Oct 03; accepted 03 Dec 03; published on the web 13 Dec 03)

Abstract

A series of 12 chiral amino alcohols derived from the simple and readily available amino acids, alanine, phenylalanine and phenylglycine, was tested as resolving agent for 2-aryl-alkyl carboxylic acids. Resolution of 2-phenylpropionic acid (hydratropic acid) could be achieved with only one of these agents: (S)-(-)-2-amino-1,1-bis(4-tolyl)-2-phenyl-1-ethanol, derived from phenylglycine. Resolution of 2-phenylbutyric acid was possible with all four phenylglycine derivatives and three phenylalanine derivatives of which the 4-tolyl and 4-anisyl substituted representatives showed very high efficiencies with S-values around 0.9.

Keywords: 2-Phenylbutyric acid, resolution, diastereomeric salts

Introduction

Selective crystallization methods are still the most important techniques in preparing optically pure products.[1-3] In markets for chiral products, which show above average economic growth,[4] new concepts for chiral syntheses are being developed along-side with improvements of already established routes. However, certainly from an industrial point of view, selective crystallization of diastereomeric salts is the most widely applied method, through which 30-50 % of single enantiomers in fine chemicals are prepared.[1] Biocatalysis has taken a solid second place. [5] Design of new resolving agents, both through rational concepts [6] and practical experience, [7] is an ongoing subject of research and development. Increased fundamental understanding of resolutions and crystallization processes is becoming increasingly helpful in arriving at new

resolving agents and practical procedures.[8-10] The role of nucleation inhibition in understanding the phenomenon of Dutch Resolution [8] is a prime example of this approach. A continuous stream of new resolving agents is thus becoming available: cyclic phosphoric acids,[6] substituted glycolic acids,[11] new derivatives of phthalic acid,[7] several 1-aryl-1-butyl amines [12] and amino-alcohols derived from simple amino acids.[13] Recent compilations of resolving agents are available.[3,13]

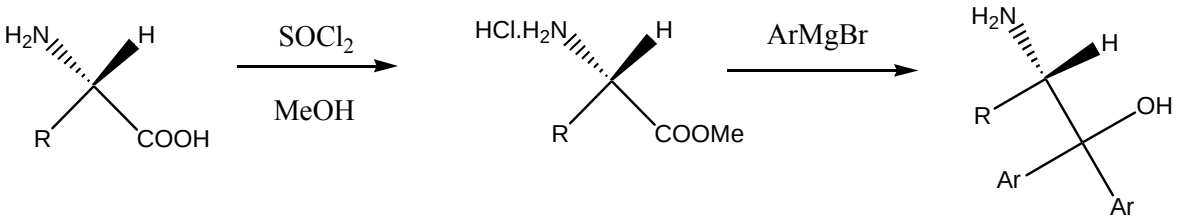
Through the years, resolution of amino acids and hydroxy acids have reached a sophisticated stage of technological development. Efficient procedures are available for resolution, [3,13] racemization of the undesired stereo-isomer[14] as well as processes for asymmetric transformation.[4,14, 15] The commercial importance of these acids has spurred development of several practical and well documented procedures. The presence of an additional polar substituent, i.e. hydroxy or amino groups, facilitates chiral discrimination in the formation of the crystal lattices of the diastereomeric salts. Both factors have played a role in the less developed methods available for the resolution of alkyl and/or aryl substituted carboxylic acids. The commercial success of several 2-aryl substituted propionic acids, i.e. Naproxen, Ibuprofen, Ketoprofen etc. has stimulated research in resolving these types of compounds. Because predictions of successful conditions and resolving agents are difficult and rather unreliable, trial and error and practical experience has served as the basis for a number of successful combinations of racemic arylpropionic acid and resolving agent[9]. Thus, Naproxen was well resolved by *N*-octyl-glucamine, *N*-methyl-D-(-)-glucamine, (-)-2-phenethylamine and other basic agents.[15,16] Ibuprofen was best resolved by 2-aryl-2-alkylamines such as 2-phenethyl amine, several 1,2-diarylethylamines and S-phenylglycinol as the most efficient resolving agent.[17] The phase diagram for the latter combination showed a very asymmetric shape, predicting a resolution efficiency of 0.80 (defined as 2 × e.e. × yield). In practice, efficiencies of around 0.5 were found. This may well be typical for this type of resolutions. In the series of amino acids and hydroxy acids numerous examples of resolutions with proven efficiencies of 0.80 or better are known: mandelic acid/2-phenethylamine: 0.86,[17] camphor-10-sulphonic acid/phenylglycine: 0.98.[18-20]

Results and Discussion

Resolution of 2-phenyl- 2-alkyl carboxylic acids

As part of a wider study on resolutions several 2-amino alcohols, derived from simple, cheaply available amino acids, were tested as resolving agent for 2-aryl-alkyl carboxylic acids. Preparation of these amino alcohols is straightforward using known general methods. A general procedure and a typical example are included in the Experimental Section. Twelve amino alcohols were prepared derived from L-alanine, L-phenylalanine and L-phenylglycine. Although most of these compounds are known in the literature,[22-24] they have not been used in systematic studies towards resolutions. As an extension of our studies [15, 17] on 2-arylpropionic acids we

tested resolution of hydratropic acid (2-phenylpropionic acid) and 2-phenylbutyric acid employing these aminoalcohols.



Scheme 1. Synthesis of a series of amino acid based potential resolving agents

R =	Ar = phenyl	Ar = p-tolyl	Ar = p-anisyl	Ar = p-Cl-phenyl
Methyl	**1** (58)*	**4** (45)	**7** (21)	**10** (30)
Benzyl	**2** (25)	**5** (25)	**8** (35)	**11** (55)
Phenyl	**3** (35)	**6** (42)	**9** (20)	**12** (31)

* Overall yields are given in brackets.

Within the series of Scheme 1 hydratropic acid could only be resolved with the p-tolyl derivative of phenylglycine, **6**. A low efficiency of 0.29, the result of 31 % e.e. and a yield of 48 % in the initial crystallization, was found. Methanol proved to be a suitable solvent. Compared to earlier work,[15, 21] applying 2-phenethylamine as resolving agent, less good results were found. The latter resolving agent showed a practical efficiency of 0.51,[21] whereas a theoretical maximum of ca. 0.6 could be derived from the phase diagrams.[25]

Unexpectedly, the more flexible 2-phenylbutyric acid was well resolvable with a large number of representatives of our amino-alcohol series. All phenylglycine derivatives achieved resolutions with S-values ranging from 0.25 – 0.76. Using the derivatives from alanine no resolving agent could be found. The high solubility of the salts of these amino-alcohols in common resolution solvents might be an explanation. Within the phenylalanine series all derivatives except for the p-chlorophenyl, showed good resolutions (Table 1). In particular the p-tolyl and p-anisyl derived agents **5** and **8** gave excellent results with S-values of 0.86 and 0.92 respectively in small scale experiments (0.9 mmol). In the L-phenylalanine series only the S-enantiomer was obtained, whereas in the phenylglycine series both (S)-and (R)-enantiomers can be obtained. These results confirm the awkward predictability of resolutions and show how small changes in molecular structure of the resolving agent can change the outcome. Using known methods, derived from the phase diagrams and DSC measurements [25, 26] we showed these results very well reflected the maximum results possible according to theory as given by the calculated maximum resolution efficiencies, S_{max}, and eutectic compositions, x_{eu}.

Table 1. Resolution efficiencies for 2-phenyl butyric acid

Resolving Agent	e.e(config.)	yield	$S_{exp.}$	$S_{max.}$(calc..)	x_{eu} (exp.)	x_{eu} (calc.)
2	37(S)	55	0.41	-	-	-
3	50(S)	25	0.25	-	-	-
5	80(S)	54	0.86	0.95	0.95	0.95
6	67(R)	57	0.76	0.97	0.93	0.93
7	76(S)	61	0.92; 0.83*	0.85	0.13	0.13
8	39(R)	43	0.33	-	-	-
12	62(R)	35	0.44	-	-	-

* Results at 15 mmol scale.

With respect to the literature available for resolution of 2-phenylbutyric acid we obtained substantially better results. Early work of Pettersson in 1956 mentions 2-phenethylamine as resolving agent in benzene/methanol mixtures.[27] Later studies also demonstrated the use of cinchonidine as resolving agent.[28] Of interest is the effect of the amount of 2-phenethylamine on this resolution result. With equimolar amounts S-values of 0.14 were found whereas 0.5 equivalents of resolving agent in a minimum of solvent (diethyl ether) gave salts in 95 % yield and 85 % e.e. representing an S-value of 0.81. Reproducing these results, however, gave a lower yield and an S-value of 0.6 only. Moreover, our excellent results were obtained in more suitable solvents such as methanol.

Experimental Section

General Procedures. ^{1}H-NMR spectra were recorded on a Bruker AC-100 or on a Bruker AC-300 (300 MHz, FT) spectrometer with tetramethylsilane as internal standard and the software WinNMR. IR spectra were run on a Perkin Elmer 298, Perkin Elmer FTIR 1720-X or ATI Mattson Genesis series FTIR spectrophotometer using Winfirst as software. Elemental analyses were performed with a Carlo Erba instruments CHNSO 1108 elemental analyser. For mass spectroscopy, a double focusing VG 7070E was used. For the chemical ionisation (CI) technique, methane was used as reacting gas. GC-separation was carried out on a fused silica-capillary column (DB-5, 30 m x 0.25 mm, film thickness 0.25 μm). Melting points were measured on a Reichert Thermopan microscope (uncorrected), a Büchi Melting Point B545 instrument or on a Perkin Elmer DSC7 instrument. Optical rotations were determined on a Perkin Elmer 241 polarimeter at 589 nm, equipped with a quartz cell of 1.00 dm path length. The polarimeter was connected with a thermostat for exact temperature control and a recorder for continuous optical rotation measurements. GC was performed on a Hewlett-Packard 5890 or 5890 Series II instrument, equipped with a capillary HP crosslinked methyl silicone (25 m x 0.31 mm) column, connected to a HP 5890 calculating integrator. Chiral GC was performed using a chiral B-DEX

120 capillary column (Supelco) or a WCOT Fused Silica 25mX0.25mm, CP Chirasil-Dex CB DF 25 m, Varian with H_2 as carriergas on a HP 6890 instrument. DSC thermograms were recorded using a Perkin Elmer DSC7 instrument. Calibration was performed with In and Zn, Sn or Pb depending on the temperature range. Samples were prepared by the method described by Jaques, Collet and Wilen.[29].Samples were measured in stainless steel large volume pans (75 µl) or aluminium pans (30µl) at a rate of 10°C/min. HPLC was performed on a Shimadzu 10A VP liquid chromatograph equipped with a reverse phase column by Alltech (Econosphere, C8, 5u, 0.46 cm Ø x 25 cm), a chiral Daicel Chiralcel OD-H column (25 x 0.46 cm, particle size: 5 µm) or a chiral Daicel Chiralcel OB column (25 x 0.46 cm, particle size: 5 µm) with filtered hexane/2-propanol mixtures as mobile phase. Detection was at 254 nm and 222 nm and the flow rate was 0.5 ml/min at ambient temperature. Class VP 5.0 was the software used. Capillary Electrophoresis was performed on a HP 3D CE with the software HP 3D CE-Chemstation. For column chromatography, the flash technique was used with silicagel 60H (Merck) as stationary phase and a pressure of about 1.5 bar. Thin layer chromatograms were run on glass supported silicagel 60 plates (0.25-layer, F_{254}, Merck). Compounds were detected using UV and oxidizing reagents, i.e. 5% H_2SO_4 in ethanol or a mixture of $(NH_4)_6Mo_7O_{24}{*}4H_2O$ (21 g), $(NH_4)_4Ce(SO_4)_4{*}2H_2O$ (1.8 g), water (469 ml) and 97% H_2SO_4 (31 ml). Dry solvents were obtained as follows: dichloromethane was distilled from phosphorous pentoxide. Diethyl ether was pre-dried on calcium chloride and distilled from calcium hydride. Hexane and benzene were distilled from calcium hydride. Triethylamine and phenylethylamine were distilled from potassium hydroxide. Tetrahydrofuran was distilled from lithium aluminium hydride and ethyl acetate from potassium hydrogen carbonate. All other solvents and reagents were either p.a. or technical quality and used as obtained from the supplier.

General procedure for esterification

A suspension of the amino acid (0.07mol) in methanol (150ml) was cooled to 0°C. While vigorously stirring, thionylchloride (39.4 g, 0.33 mol) was added dropwise over 30 minutes. The temperature was allowed to rise to room temperature. After stirring overnight, the excess of thionylchloride and methanol was evaporated. The resultant white solid was washed 3 x 200 ml of dry Et_2O and dried under reduced pressure.

General procedure for Grignard reactions

The Grignard reagents were prepared from magnesium turnings (21.6 g, 0.9 mol) in Et_2O (100 ml) and the respective bromoaryl compound (0.9 mol) in Et_2O (200 ml). The cooled Grignard solution was diluted with dry Et_2O (200 ml) and the ethyl L-lactate (35.4 g, 0.3 mol) added in etheral solution. The mixture was refluxed for 2 h and then stirred overnight at room temperature. Work-up of the reaction mixture, including hydrolysis (saturated NH_4Cl solution), extraction with Et_2O, washing, drying ($MgSO_4$), and evaporation of the solvent under reduced pressure yielded the crude product. Purification was effected by recrystallization from light petroleum (b.p. 60-90°C) or Et_2O.

General procedure for BuLi reaction

THF (100 ml) was added to a solution of 0.11 mol of butyllithium in 77 ml of hexane with cooling to below 0°C. The mixture was cooled (occasionally cooling in a bath with liquid nitrogen) to ca. –105°C. A mixture of 0.1 mol of the bromoaryl compound in 30 ml of Et_2O was added dropwise over 10 min, while keeping the temperature between –100 and –105°C. A white suspension was formed. After an additional 10 min, 0.03 mol (3.54 g) of ethyl lactate was added over 10 min with vigorous stirring while keeping the temperature below –80°C. During the addition, the suspension disappeared. The temperature was allowed to rise to 20°C. Ammonium chloride solution (100 ml) was added, after which the product was isolated in the usual way.

Synthesis of S-(-)-2-amino-1,1-di(4-methoxyphenyl)-3-phenyl-1-propanol (8). In the Grignard reaction *p*-bromoanisol and *L*-Ph-alanine methyl ester were used. Yield 35%. Mp: 109°C; ΔH=36.07 J/g; $[\alpha_D]^{20}$= -57 (c 1, $CHCl_3$); ^{1}H-NMR (100 MHz, $CDCl_3$): δ 7.35-6.66 (m, 13H, arom.), δ 4.28-4.16 (dd, 1H, NH_2-C<u>H</u>, J = 2.6 Hz), δ 3.55 (s, 6H, OC<u>H</u>$_3$), δ 2.60-2.45 (m, 2H, phenyl-C<u>H</u>$_2$), IR (film) ν 3403 (broad, s, OH), 3024-2950 (v, C-H, arom.) cm^{-1}; MS (CI) m/z calcd for $C_{23}H_{25}N_1O_3$ (M^+) 363, found 364(M^++H)

General execution of resolution experiments

The resolution experiments were all executed in methanol as solvent. In the commonly applied small scale experiments one equivalent of the racemic acid (0.88 mmol) and the corresponding amounts of resolving agents (amines **1-12**) were dissolved in hot methanol. In successful resolutions crystallization appeared after slow evaporation of the solvent at room temperature and normal pressure. The diastereomeric salt composition was determined with ^{1}H-NMR, HPLC and CE. The methods for the *e.e.* and *ratio* determination of the investigated acids and amines are given below.

Compound	Apparatus	Method
Hydratropic acid (racemic)	HPLC	Daicel OD-H, UV 254nm Isopropanol/hexane 5:95 (0.1% TFA), flow 0.5, t = 10.8 min
Phenylbutyric acid (racemic)	CE*	Hydroxypropylated γ-Cyclodextrine, c = 250 mg/ml, U = 30kV, T = 10°C, buffer pH = 9.3, t = 31 min
Amines 1-12	HPLC*	Daicel OD-H, UV 254nm Isopropanol/hexane 5:95, flow 0.4, t = 8min-15min
Phenylethylamine (racemic)	CE*	Hydroxypropylated β-Cyclodextrine sulfated, c = 100mg/ml, U = 30kV, T = 15°C, buffer pH = 9.3, t = 22min (L) and 23min (D)

*new methods developed by us.

Larger scale resolutions. Racemic 2-phenyl butyric acid (2.38g; 14.5mmol) and amine 8 (5.26g; 14.5mmol) were dissolved in hot methanol. The crystallisation yielded the results shown below:

Solid e.e. %	Solid Yield %	Filtrate e.e. %	Filtrate Yield %	Solvent (g)*	X_{eu} (S)	$S_{max.}$	$S_{exp.}$
86	48	74	52	12	0.13	0.85	0.82

* Total amount of solvent (MeOH) used.

Recrystallisation generated the amine **8** salt in 58% yield and an e.e.(*S*) of 100% (in 11.7g solvent). In this resolution experiment the theoretical and experimental *S* values are almost the same, indicating almost ideal conditions.

DSC. DSC thermograms were determined using a Perkin Elmer DSC 7 instrument, calibrated with In and Zn or Sn. Samples (2-10 mg) were weighted with an accuracy of 0.01 mg and encapsulated in stainless steel large volume pans (75 μl). Thermograms were recorded at a scanning rate of 10°C/min, a data rate of 0.4-0.8 sec/point and with an empty pan as reference under a nitrogen atmosphere. Melting points are given as the top of the peaks because of broad peaks.

Acknowledgements

The colleagues in the Dutch Resolution project are greatly acknowledged for their their fruitful collaborations: Dick Kellogg, Jan Dalmolen, Ton Vries, Jose Nieuwenhuijzen, Marcel van der Sluis, Kees Pouwer, Imre Markowitz, Simona Müller, Joanne Loh, Reinier Grimbergen, Willem van Enckevort, Elias Vlieg, Rene de Gelder, Henk Hiemstra, Bert Hulshof, Bernard Kaptein and Claire Gervais.

References

1. Kaptein, B.; Vries, T. R.; Nieuwenhuijzen. J. W.; Kellogg, R. M.; Grimbergen, R. F. P.; Broxterman, Q. B. *Pharma Chem.* **2003**, 17.
2. Villa, M. *Performance Chemicals* **1995**, 23.
3. Kozma, D. *Handbook of Optical Resolutions via Diastereomeric Salt Formation,* CRC Press: Boca Raton 2002.
4. Rouhi, A. M. *Chem. Eng. News* **2003**, 45.
5. Schoemaker, H. E.; Mink, D.; Wubbolts, M. G. *Science* **2003**, *299*, 1694.
6. Hoeve ten, W.; Wynberg, H. *J. Org. Chem*. **1985**, *50*, 4508.
7. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1117.
8. Nieuwenhuijzen, J. W.; Grimbergen, R.F.P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; Pouwer, K.; Echten van, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 4281.
9. Leusen, F. J. J. *Crystal Growth & Design* **2003**, *3*, 189.

10. Loh, J. S. C.;Enckevort, W. J. P.; Vlieg, E. *J. Crystal Growth* **2003**, to be published.
11. Kinbara, K.; Harada, Y.; Saigo, K. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2219.
12. Dalmolen, J.;Sluis van der, M.; Nieuwenhuijzen. J. W.; Meetsma, A.; Lange de, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Eur. J. Chem*. **2003**, to be published.
13. Kaptein, B.; Vries, T.R.; Nieuwenhuijzen, J.W.; Kellogg, R.M.; Grimbergen, R.P.F.; Broxterman, Q.B. In *Handbook of Chiral Fine Chemicals;* Vol.2; Ager, D. Ed.; Marcel Dekker: New York, in preparation.
14. Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417.
15. Ebbers, E. J.; Ariaans, G. J. A.; Bruggink, A.; Zwanenburg, B. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3701.
16. Yuan, X.; Li, J.; Tian, Y.; Lee, G-H.; Peng, X-M.;Zhu, R.; You, X. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3015.
17. Ebbers, E. J.; Plum, B. J. M.; Ariaans, G. J. A.; Kaptein, B.; Broxterman, Q. B.; Bruggink, A.; Zwanenburg, B. *Tetrahedron*: *Asymmetry* **1997**, *8,* 4047.
18. Bruggink, A. *Synthesis of β –lactam antibiotics;* Kluwer Academic Press, 2001.
19. Yoshioka, R.; Hiramatsu, H.; Okamura, K.; Tsujioka, I.; Yamada, S-i. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2121.
20. Bruggink, A. In *Chirality in Industry II;* Collins, A. N.; Sheldrake, G. N.; Crosby, J. Ed.; Wiley, 1997.
21. Leclerq, M.; Jacques, *J. Bull. Soc. Chim. Fr*. **1975**, 2052.
22. Weber, E.; Reutel, C.; Foces-Foces, C. ; Llamas-Saiz, A.L. *J. Phys. Org. Chem.* **1995**, *8,* 159.
23. Itsumo, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A. Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039.
24. Dammast, F.; Reissig, H.U. *Chem.Ber.* **1993**, *126*, 2449.
25. Ebbers, E. J.; Ariaans, G. J. A.; Zwanenburg, B.; Bruggink, A.;. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2745.
26. Kozma, D.; Pokol, G.; Acs, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 435.
27. Petterson, K. *Arkiv Kemi* **1956**, *10*, 283.
28. Vigneron, J. P.; Bloy, V. *J. Bull. Soc. Chim. Fr.* **1976**, 649.
29. Jaques, J., Collet, A., Wilen, S.H. *Enantiomers, Racemates and Resolutions;* John Wiley and Sons: New York, 1981; Ch. 2.1-2.3.