Supplementary Material (ESI) for CrystEngComm

Efficient Havinga-Kondepudi Resolution of Conglomerate Amino Acid Derivatives by Slow Cooling and Abrasive Grinding

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Materials

Reagents were obtained from commercial sources and were used without further purification.

Chiral HPLC analysis of compound 2 and 3

The separation of the enantiomers was carried out on a Chiralcel OJ-H column with a gradient of heptane:EtOH as eluent at 20°C and 0.7 mL·min^{-1}: 95:5 (20 min) in 20 min to 90:10 (10 min) in 20 min to 75:25 (40 min). UV-VIS detection at 254 nm. The solids were dissolved in MeOH and injected as such. Retention times: *(S)*-**3** R_f: 25.23 min, *(R)*-**3** R_f: 38.81 min, *(S)*-**2** R_f: 48.79 min, *(R)*-**2** R_f: 64.39 min.

Alternatively, the enantiomeric excess of **2** could be determined on a Lichrosphere diol 150 x 4.6 mm ID with n-Hexane / 2-propanol, 90 / 10 as eluent at room temperature and 1.0 mL·min-1 UV-VIS detection at 254 nm.

NMR spectra

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Mercury 300MHz machine. Chemical shifts are denoted in δ (ppm) and are referenced to the residual protic solvent. The coupling constant *J* is given in Hz. Splitting patterns are as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), m (multiplet) and bs (broad singlet).

Mass spectra

Mass spectra were recorded by API-ES (electron spray ionization) by dissolving the samples in MeOH and injecting the solution as such. Mobile phase: acetonitrile : 0.1% formic acid in water 50 : 50 (1 min.), flow: 0.2 ml/min, injection volume: 5 µl.

Procedure for the deracemization of compound 2 by the Havinga/Kondepudi-type resolution.

Two new 100 mL round-bottom flask were each charged with (±)-**2** (6.02 g, 23.9 mmol, 1.0 eq), DBU (1.07 mL, 7.16 mmol, 0.3 eq), MeCN (35.0 g) and an egg-shaped PTFE coated stirring bar (1.0 x 2.0 cm). One flask was charged with 15.0 g solid glass beads (Ø 2 mm) also. The loosely stoppered flasks were placed in a stirred water bath (1250 rpm), which was kept at 70°C by a thermostat (Huber, ministat cc) until complete dissolution was observed. The flasks were then cooled to 20°C at 0.05, 0.5, 1.0 or 2.0°C·min^{-1}. After the mixture had reached 20°C, stirring was continued for another 10 minutes. A sample was taken and the solids were collected by filtration (P4), washed with TMBE and dried on air. The *ee* of the solids were determined by chiral HPLC (see above). The suspension was then reheated to dissolution and cooled to 20°C at a different rate. Samples of the mixture at 70°C confirmed the complete racemization of the material upon reheating. After a couple of heating/cooling runs 3.18 g (53%) **2** was isolated. The results of these experiments can be found in Table 1 in the main article.

Preferential crystallisation of 2 from solution with seeding.

The preferential crystallisation experiments of (*RS*)-**2** have been performed by cooling crystallization starting with a 4 wt% solution in toluene and using 1 mol% of DBU as a racemization catalyst. Turbidity measurements

showed that under these conditions this results in a dissolution temperature of 71°C and a nucleation temperature of 50°C.

Therefore 3.29 g of (*RS*)-**2** was suspended in 78 g of toluene and 60 mg of DBU was added. The magnetically stirred suspension was heated to 80°C for dissolution and kept at this temperature for 30 minutes to dissolve all seeds. After cooling in 1.5 hours to the saturation temperature of 65°C the clear solution was seeded with 76 mg of (*R*)-**2** and stirred for 30 minutes at this temperature. Next the mixture was cooled from 65°C to 20°C using a controlled temperature programme of 5°C/h. Total cooling time of 9 hours. The crystal suspension was then filtered, washed with a 5 ml of toluene and dried. This resulted in 2.78 g of (*R*)-**2** (86% yield, 98% *ee*). The remaining **2** in the saturated toluene mother liquor was racemic according to chiral HPLC.

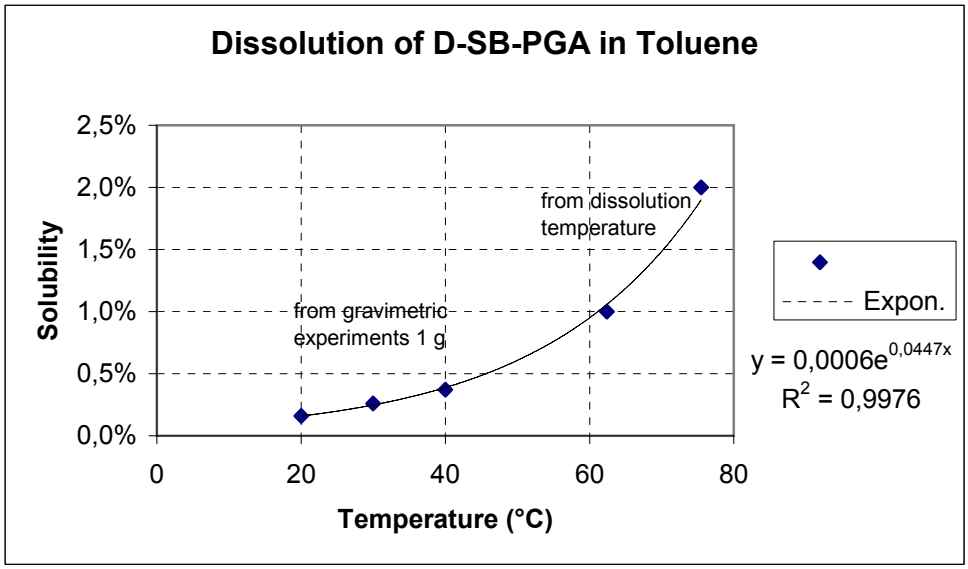
Under identical conditions a saturated solution of (*RS*)-**2** was seeded with 74 mg of (*S*)-**2**, resulting in an isolated yield of 2.73 g of (*S*)-**2** (84% yield, 98% *ee*).

Solubility determination of (R)-2 in toluene

The solubility was measured by dissolving an excess of (*R*)-**2** in toluene. Samples of the clear solution were taken at different temperatures after stirring for 1 hour and of each sample the weight was determined of the solution and after evaporating to dryness. For each temperature the solubility was determined in duplicate.

Thus a mixture of 0.99 wt% of concentration was prepared by adding 66.59 g of toluene to 0.6673 g of (*R*)-**2**. The samples were taken at 20°C, 30° C and 40° C. In addition the dissolution temperature of this 1 wt% solution was determined, as well as of a 2 wt% solution (see table). From these results it was possible to plot the calculated curve for the dissolution of (*R*)-**2**(see figure below).

wt% of (R)-2	**T_{diss} (°C)**
1.0%	62.4
2.0%	75.5
0.16%	20
0.26%	30
0.37%	40



Racemization of (R)-2 under various conditions

The racemization experiments were performed using polarimetry by the determination of the optical rotation on a c = 0.5 g / 100 ml solution in methanol or toluene.

Specific rotation of (*R*)-**2**:
$[\alpha]^{25}_{D}$ -29.9 (c 0.50, toluene)
$[\alpha]^{30}_{D}$ -20.6 (c 0.35, toluene)

Because racemization with KO^{t}Bu and NaOMe was too fast to determine the racemization experiments were done with weaker organic bases like DBU, DABCO and triethylamine. Therefore the calculated amount of racemization base was added to the 5 ml polarimeter cell and the optical rotation was measured over time. The results of the various racemization experiments are shown in the figure below (results in methanol unless stated otherwise).

From these results the $t_{1/2}$ of racemization of (*R*)-**2** has been calculated (see table).

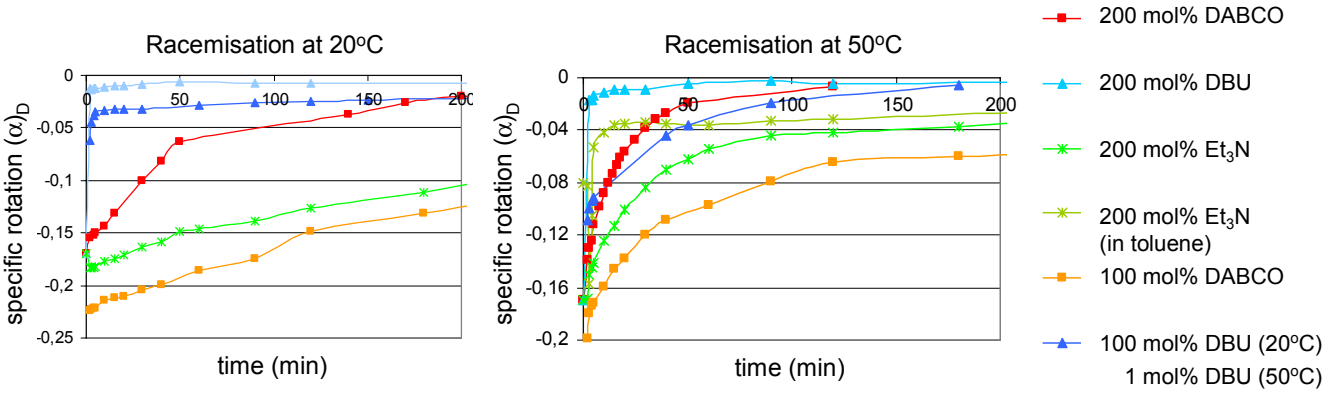
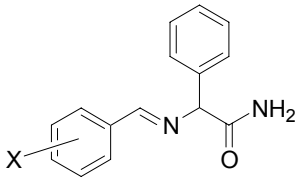


Table: Halflife times $t_{1/2}$ of racemization of (*R*)-2

Base	Solvent	$t_{1/2}$ (min)	
		20ºC	50ºC
200 mol% Et_3N	methanol	176	35
200 mol% Et_3N	toluene	--	17
200 mol% DBU	methanol	<0.5	<0.5
100 mol% DBU	methanol	0.6	--
1 mol% DBU	methanol	--	17
200 mol% DABCO	methanol	38	19
100 mol% DABCO	methanol	143	40

pK_a (Et_3N) = 10.7 ; pK_a (DBU)=11.3 ; pK_a (DABCO) = 8.8

DSC results of substituted N-benzylidene-DL- and D-phenylglycinamides



X = H
2-F, 3-F, 4-F
2-Cl, 3-Cl, 4-Cl
2-Br, 3-Br, 4-Br
2-OCH_3, 3-OCH_3, 4-OCH_3
2-CH_3, 3-CH_3, 4-CH_3

Table: DSC results of substituted D- and DL-benzylidene-phenylglycinamides

Subst. X	$Mp._D$ (°C)	ΔH^f_D (J/g)	$Mp._{DL}$ (°C)	ΔH^f_{DL} (J/g)	$Mp._{DL}$ Calcd[4]	ΔT^f (ΔT calcd)[4]	Conglomerate Racemic compound
H	146.2	130	126.2	134	116	20 (30)	Racemic compound?
2-Cl	177.9	138	153.6	143	149	24 (28)	Conglomerate?
3-Cl	124.0 [3]	121 [3]	116.7	135	--	7 (--) [3]	Racemic compound
4-Cl	153.6	129	139.5	129	--	14 (--)	Racemic compound
2-Br	162.7	113	139.7 [1]	-- [1]	134	23 (29)	Conglomerate at rt? [1]
3-Br	133.4	110	123.2	111	--	10 (--)	Racemic compound
4-Br	173.2	122	157.3	128	145	16 (28)	Racemic compound
2-F	157.0	137	129.9 [1]	-- [1]	129	27 (28)	Conglomerate at rt? [1]
3-F	112.8	119	119.8	119	--	-7 (--)	Racemic compound
4-F	121.1	120	153.9	154	--	-33 (--)	Racemic compound
2-OH	140.3	128	156.0	130	--	-16 (--)	Racemic compound
3-OH	141.4	112	n.a.[2]	n.a.[2]	--	-- (--)	--
4-OH	137.3 [3]	72 [3]	151.5	80	--	-14 (--)	Racemic compound
2-OCH_3	188.4	157	188.0	114	--	0 (--)	Racemic compound
3-OCH_3	129.1 [3]	189 [3]	141.8	148	--	-13 (--) [3]	Racemic compound
4-OCH_3	91.3	87	130.6	107	--	-39 (--)	Racemic compound
2-CH_3 (2)	**180.3**	**159**	**156.5**	**136**	**153**	**24 (27)**	**Conglomerate?**
3-CH_3	120.2	118	54 (glas)	1.0	--	-- (--)	--
4-CH_3	154.5 [3]	157 [3]	129.5	132	129 [3]	25 (26) [3]	Conglomerate?

[1] For the 2-Br and 2-F derivative an exothermic phase transition occurs upon melting.

2-Br: 2nd melt 157.4°C, 2-F: 2nd melt 138.5°C (racemic compound?)

[2] Not available

[3] No sharp melting point (impure or partial racemization?) / $Mp._{DL}$ difficult to calculate

[4] The theoretical melting point ($Mp._{DL}$) and ΔT for conglomerate behaviour were calculated from the $Mp._D$ and ΔH^f_D of the pure enatniomer by the Schöder-Van Laar equation.

The compounds with a $\Delta T > 20^{o}C$ (in red) have been further analysed by Raman spectroscopy (only for X = H), PXRD and SHG for potential conglomerate behaviour.

SHG analysis of substituted N-benzylidene-DL-phenylglycinamides

Reference: 6 samples (*N*-benzylidene-DL-phenylglycine amide)
X = -H, 2-Cl, 2-Br, 2-F, 2-CH_3, 4-CH_3

Description: white powders

Second Harmonic Generation (SHG) set-up:
Laser Nd: YAG Brillant (Coherent) - 1064 nm-
Pulse: 5 ns
Frequency: 10 Hz
Energy: 360 mJ/pulse
Spectrophotometer: USB 4000(Ocean Optics)
SHG effect measured at 532 nm
Reference samples: KDP and QUARTZ

Sample reference	**SHG effect**	**I/I_0**	
		KDP 75-175 µm	**Quartz 44 µm**
H	yes	0.01	0.03
2-Cl	yes	0.98	2.15
2-Br	yes	0.11	0.25
2-F	yes	0.01	0.03
2-CH_3 (2)	yes	0.02	0.04
4-CH_3	no	----------	----------

Conclusion:

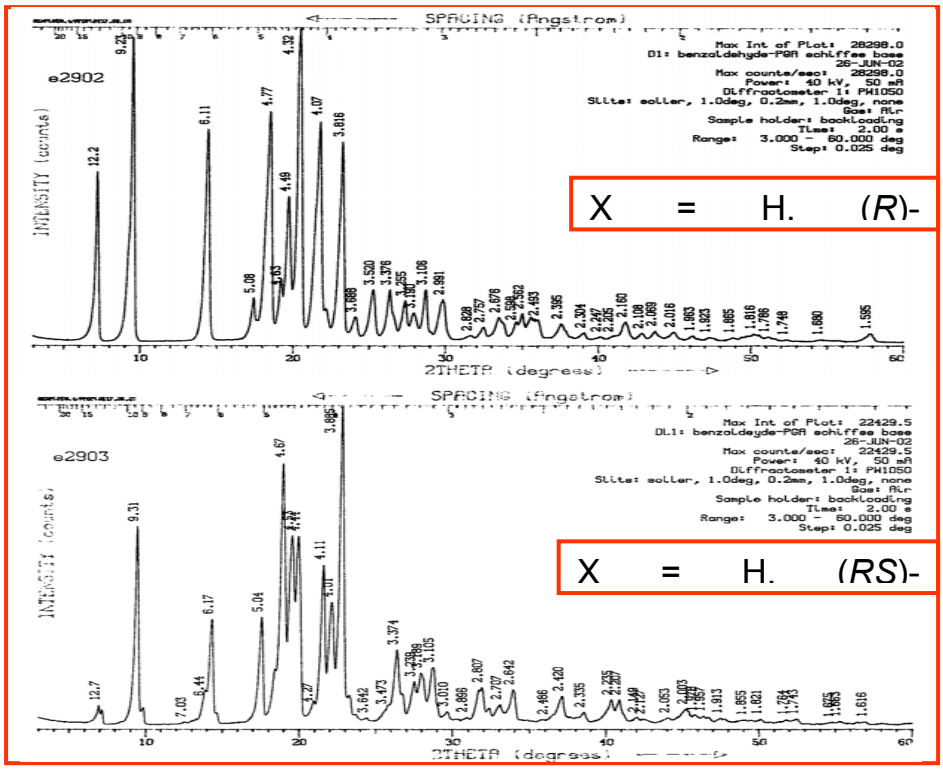
All the samples have generated a SHG signal except sample 4-CH_3.
Sample 2-Cl presents a SHG effect equivalent to KDP (good SHG effect)

XRPD analysis of substituted N-benzylidene-phenylglycinamides

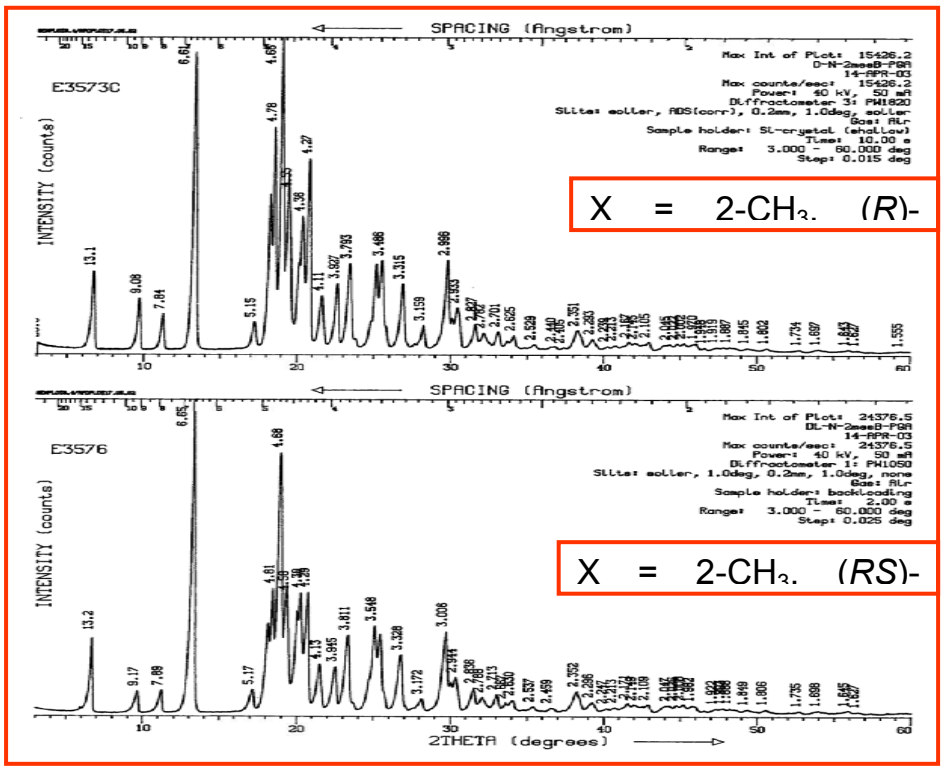
Reference: 6 samples (N-benzylidene-DL-phenylglycine amide)
X = -H, 2-CH_3, 4-CH_3, 2-F, 2-Cl, 2-Br,
Description: white powders

XPRD set-up:
Diffractometer: PW1050
Power: 40kW, 50 mA
Slitts: soller, 1.0 deg, 0.2mm, 1.0 deg, none
Gas: air
Sample holder: back loading
Time: 2 sec
Range: 3 – 60 deg

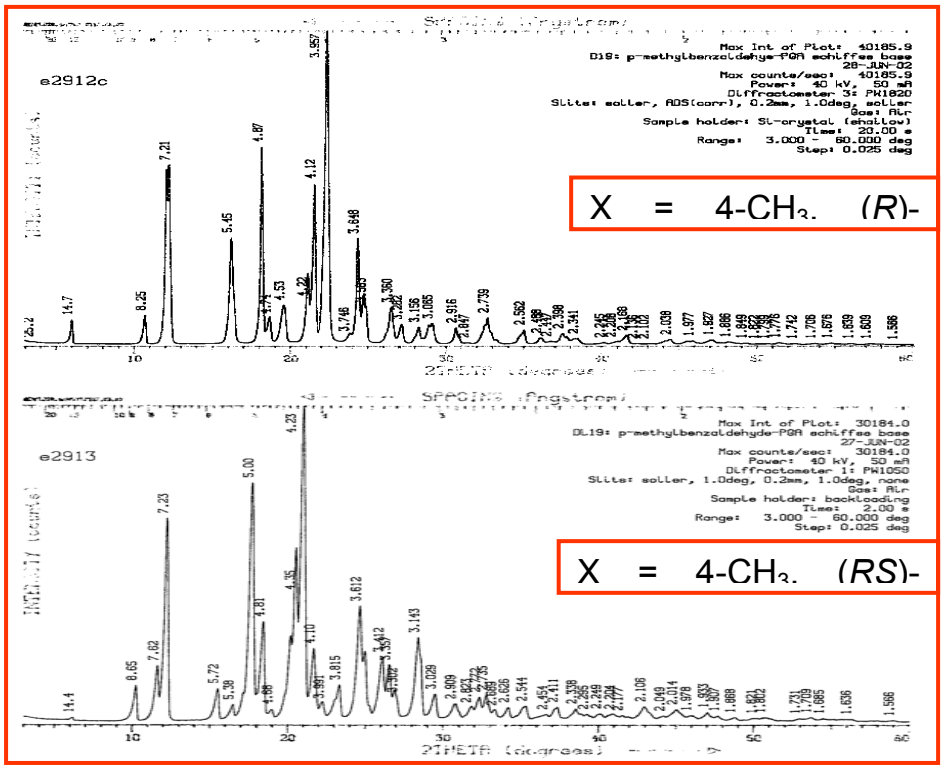
N-benzylidene-phenylglycine amide: racemic compound



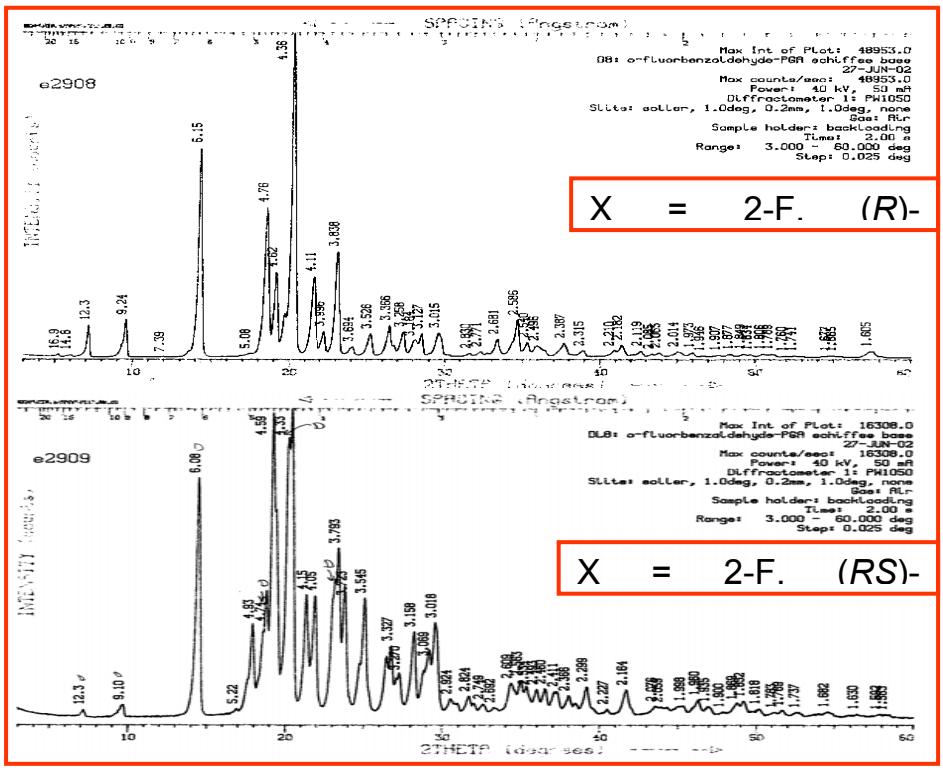
N-2-methylbenzylidene-phenylglycine amide (**2**): **conglomerate**



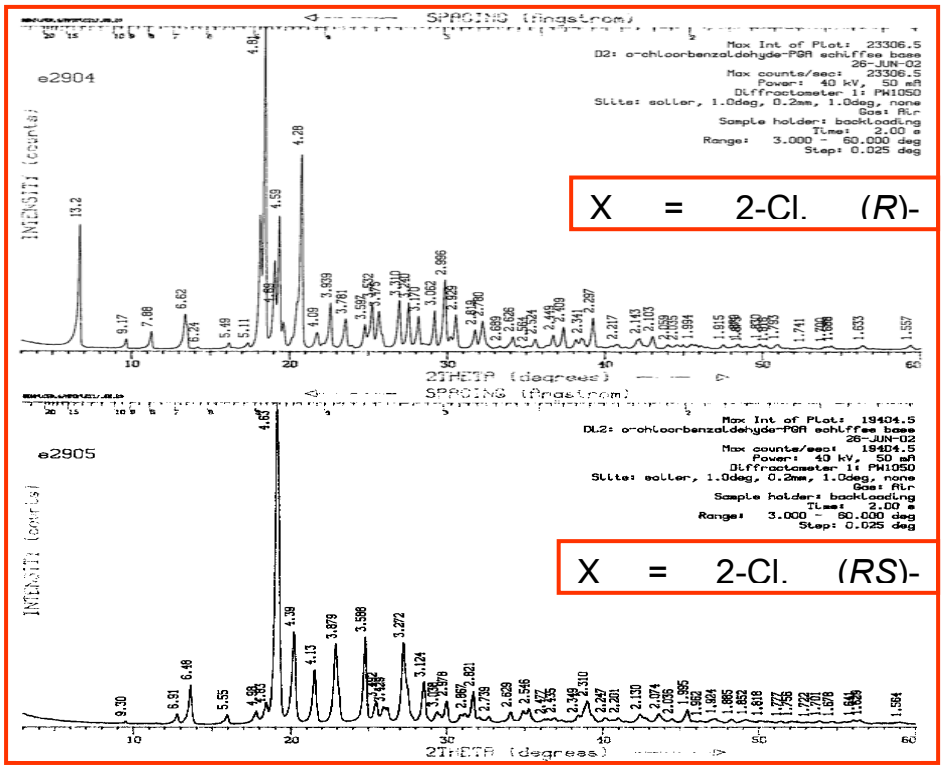
N-4-methylbenzylidene-phenylglycine amide: racemic compound



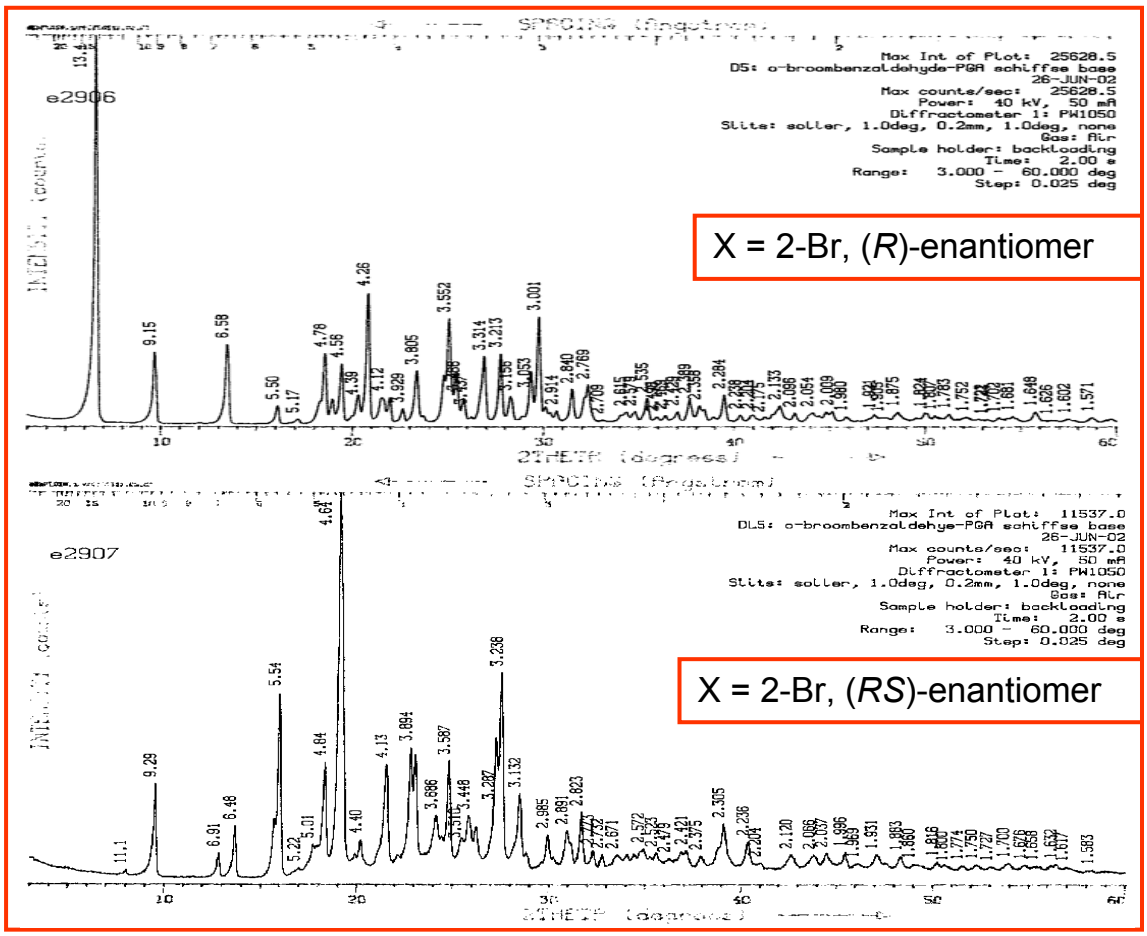
N-2-fluorobenzylidene-phenylglycine amide: conglomerate?



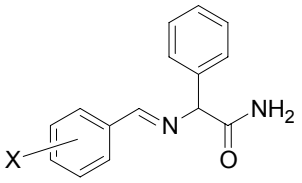
N-2-chlorobenzylidene-phenylglycine amide: racemic compound



N-2-bromobenzylidene-phenylglycine amide: racemic compound

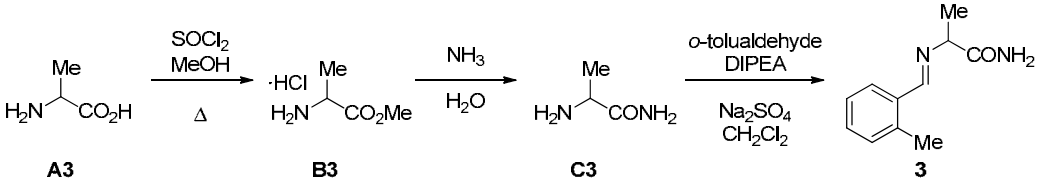


Synthesis

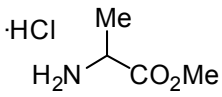


X = H
2-F, 3-F, 4-F
2-Cl, 3-Cl, 4-Cl
2-Br, 3-Br, 4-Br
2-OCH_3, 3-OCH_3, 4-OCH_3
2-CH_3, 3-CH_3, 4-CH_3

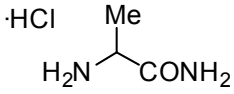
The (*R*) and (*RS*)-enantiomers of all substituted *N*-benzylidene-phenylglycinamides described above were synthesized according to the procedure described by Dalmolen et al.[1] Large scale preparation of compound **2** (X = 2-CH_3) has been described by Noorduin et al.[2] The Schiff base **3** was synthesized according to Scheme 1.



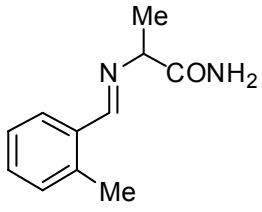
Scheme 1: Synthesis of compound 3.



(±)-methyl 2-aminopropanoate hydrochloride (B3). Thionyl chloride (17.4 mL, 0.24 mol, 1.2 eq) was added dropwise to a suspension of (±)-alanine (**A3**) (17.8 g, 0.2 mol, 1.0 eq) in MeOH (100 mL) upon which the reaction mixture started to boil. The reaction mixture was concentrated at 50°C when ^{1}H-NMR showed full conversion after 1.5 hours. The residue was stirred in TBME (200 mL) and 27.4 g (98%) of the title compound was isolated as a white solid. ^{1}H-NMR (300MHz, *d6*-DMSO): δ= 1.40 (d, *J*=7.2 Hz, 3H), 3.69 (s, 3H), 3.99 (q, *J*=6.9 Hz, 1H), 8.76 (bs, 3H) ppm. ^{13}C-NMR(75MHz, *d6*-DMSO): δ= 15.7, 47.8, 52.8, 170.4 ppm. MS (EI): *m/z*= 104 [M+H^{+}].



(±)-2-aminopropanamide hydrochloride (C3). To a concentrated solution of ammonia in water (150 mL) was added **B3** (27.4 g, 0.2 mol, 1.0 eq) and the resulting solution was stirred over the weekend. ^{1}H-NMR showed full conversion and the solution was concentrated to dryness and stripped with toluene to remove remaining water. This yielded the title compound (23.0 g, 92%) as a white solid. ^{1}H-NMR (300MHz, *d6*-DMSO): δ= 1.34 (d, *J*=6.9 Hz, 3H), 3.71 (q, *J*=7.2 Hz, 1H), 7.41 (bs, 1H), 7.98 (bs, 1H), 8.18 (bs, 3H) ppm. ^{13}C-NMR(75MHz, *d6*-DMSO): δ= 17.3, 48.3, 171.5 ppm. MS (EI): *m/z*= 89 [M+H^{+}].



(±)-2-(((2-methylphenyl)methylidene)amino)propanamide (3). To a suspension of **C3** (17.7 g, 142 mmol, 1.0 eq) in CH_2Cl_2 (250 mL) was added Na_2SO_4 (25 g), *o*-tolualdehyde (16.4 mL, 142 mmol, 1.0 eq) and DIPEA (23.5 mL, 142 mmol, 1.0 eq). The mixture was stirred overnight at room temperature. Subsequently, the mixture was filtered and the residue washed with CH_2Cl_2. The filtrate was concentrated to a white solid which was washed with TBME (250 mL), H_2O (50 mL) and again TBME (100 mL). The filter cake was dried *in vacuo*. The solid was recrystallized from MeCN to yield 16 g (59%) **3** as a white solid. ^{1}H-NMR (300MHz, *d6*-DMSO): δ= 1.30 (d, *J*=6.6 Hz, 3H), 3.90 (q, *J*=6.9 Hz 1H), 7.07 (bs, 1H), 7.13 (bs, 1H), 7.23 (t, *J*=7.7 Hz, 2H), 7.33 (t, *J*=8.1 Hz, 1H), 7.91(d, *J*=8.1 Hz, 1H), 8.61 (s, 1H) ppm. ^{13}C-NMR(75MHz, *d6*-DMSO): δ= 19.0, 20.6, 68.3, 125.9, 127.5, 130.5, 130.8, 133.7, 137.8, 160.3, 174.7 ppm. MS (EI): *m/z*= 191 [M+H^{+}]. Optically pure Ala-Schiff was prepared via the same method.

References

[1] Dalmolen, J., van der Sluis, M., Nieuwenhuijzen, J.W., Meetsma, A., de Lange, B., Kaptein, B., Kellogg, R.M., Broxterman, Q.B., *Eur. J. Org. Chem.*, **2004**, *7*, 1544-1557.

[2] Noorduin, W.L., Millemaggi, A., Izumi, T., Leeman, M., Meekes, H., Van Enkevort, W.J.P., Kellogg, R.M., Kaptein, B., Vlieg, E., Blackmond, D.G., *J. Am. Chem. Soc.* **2008**, *130*, 1158-1159.