Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of (S)-(+)-2-(2-Methoxyphenyl) Propanoic Acid

S. Mutti [a], C. DaubiéA [a], F. Decalogne [a], R. Fournier [a], O. Montuori [a] & P. Rossi [a]
[a] RhóTne-Poulenc Rorer Central Research, Process Chemistry & Biochemistry, 13 quai Jules Guesde, BP 14, 94403, Vitry Sur Seine Cedex, France
Published online: 23 Aug 2006.

SYNTHETIC COMMUNICATIONS, 26(12), 2349-2354 (1996)

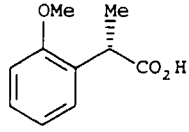
A CONVENIENT SYNTHESIS OF (S)-(+)-2-(2-METHOXYPHENYL) PROPANOIC ACID

S. Mutti*, C. Daubié, F. Decalogne, R. Fournier, O. Montuori, P. Rossi

Rhône-Poulenc Rorer Central Research, Process Chemistry & Biochemistry, 13 quai Jules Guesde, BP 14, 94403 Vitry Sur Seine Cedex France

Abstract : a short, convenient and large scale synthesis of (S)-(+)-2-(2-methoxyphenyl) propanoic acid, involving a resolution of the corresponding racemic acid with quinine, is reported.

As part of a new development program, we needed large amounts of (S)-(+)-2-(2-methoxyphenyl) propanoic acid (S)-1.



(S)-1

Prior art;

The synthesis of this compound has already been reported :

a) One of these preparations was based on an asymmetric alkylation of the corresponding Evans's Oxazolidinone enolate[1].The desired acid was obtained in good yield and with an excellent enantiomeric purity (e.e. $\geq$ 99%). The drawback of this method, from an industrial point of view, was the difficulty of scaling up this type of synthesis, due to low temperature and high cost of

* To whom correspondence should be addressed

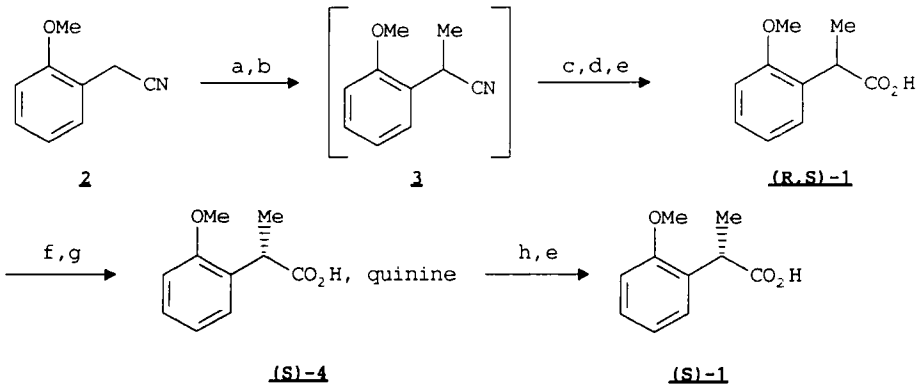
chiral auxiliary. Recycling of this auxiliary was troublesome.

b) The other one was based on the resolution of racemic 2-(2-methoxyphenyl) propanoic acid, using cinchonidine[2]. The drawback of this simple method was the poor enantiomeric purity (e.e.# 80%), which could not be improved by recrystallization.

We report herein a short and convenient synthesis of the racemic 2-(2-methoxyphenyl) propanoic acid **(R,S)-1** and its resolution using quinine, which overcomes these problems.

Results;

The present work is outlined in the following scheme.



a/ NaOtAm, MTBE, - 10°C b/ MeI or Me_2SO_4, -10°C c/ aq. NaOH, MeOH, reflux d/ MTBE e/ concentrated HCl f/ quinine, EtOAc g/ EtOAc recrystallization h/ CH_2Cl_2, aq. NaOH

The preparation of compound **3** was performed by methylation (MeI or Me_2SO_4, NaOtAm, MTBE, -10°C) of (2-methoxyphenyl) acetonitrile **2**. In these conditions, a mixture of mono- and dialkylated compounds was generated in a ratio of 92:8[3]. Compound **3** was used as a crude material, without any further purification, in the next step. Racemic acid **(R,S)-1** was readily prepared by basic

hydrolysis (aq. NaOH, MeOH, reflux) of compound 3. It can be noted that the hydrolysis of the dialkylated compound is much more difficult than the hydrolysis of the monoalkylated derivative 3. Therefore, it was very easy to purify the desired acid (R,S)-1 by a simple extraction into water, as its sodium salt. Then, (R,S)-1 was precipitated by addition of concentrated HCl. This procedure allowed us to scale-up the reaction to a 20 kg scale and to consistently isolate (R,S)-1 in 88.7% yield from 2 (2 steps). Resolution of racemic acid (R,S)-1 was readily achieved using quinine and EtOAc as the solvent. The quinine salt (S)-4 was obtained with a very good chemical yield (49.8%) and a good enantiomeric purity[4] (88% e.e.), which could be easily upgraded to $\geq$ 99.8% by recrystallization in EtOAc. (S)-1 was then extracted into water as its sodium salt and precipitated by addition of concentrated HCl. Thus, (S)-1 was isolated in good chemical yield from (R,S)-1 (44.8%) and with a very high enantiomeric purity[4] ($\geq$ 99.8% e.e.).

It is noteworthy that both quinine and the (R)-enantiomer of 1 could be readily recycled. Indeed the latter could be very easily racemized (for example : NaOtAm, MTBE reflux) in a very good yield (97.8%).

In conclusion, we have developed a short, high-yielding synthesis of (S)-(+)-2-(2-methoxyphenyl) propanoic acid (4 steps from 2 : 34.3% yield and $\geq$ 99.8% e.e.). Furthermore, we have demonstrated that the other enantiomer could be very efficiently recycled after racemization, and that this route was conveniently amenable to a pilot scale synthesis.

EXPERIMENTAL

General : Melting points (Kofler apparatus) are uncorrected. ^{1}H NMR spectra were recorded on Brucker AC 300 spectrometer. Chemical shifts are given in ppm relative to an internal tetramethylsilane standard. IR spectra were recorded on Nicolet 510 or 60 SXR spectro photometers. Mass spectra were obtained from a Finnigan 3300 (EI, 70 ev).

2-(2-methoxyphenyl) propionitrile, 3: In a 4-liter three necked flask equipped with a mechanical stirrer, a thermometer and a 0.5-liter dropping funnel, were introduced under nitrogen NaOtAm (95.3 g ; 0.95 mole) and MTBE (1.5 l). The resulting solution was chilled to 5°C, and then was added portionwise (2-methoxyphenyl) acetonitrile (100 g ; 0.679 mole) over 30 minutes. To the resulting pink suspension was added dropwise dimethylsulfate (119.8 g ; 0.950 mole) over 1 hour. Then the reaction mixture was allowed to warm up to reach 30 °C, and stirred for 1 hour. At that point, the reaction was complete according to HPLC analysis. The reaction was quenched with water (0.2 l). The organic layer was washed one more time with water (0.2 l). Then, MTBE was removed by distillation. The ratio of mono- and dialkylated compounds (92:8) was determined by HPLC. The crude product (106 g of a colourless oil) was used without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) : 1.47 (d, J = 7.5 Hz, 3H : CH_3) ; 3.73 (s, 3H : OCH_3) ; 4.13 (q, J = 7.5 Hz, 2H : ArCH) ; 6.78 and 6.87 (respectively d and t, J = 7.5 Hz, 2H : aromatic H in ortho of OCH_3 and aromatic H in ortho of OCH_3) ; 7.20 and 7.32 (respectively dt and dd, J = 7.5 and 1 Hz, 2H : aromatic H in meta of OCH_3); IR (CCl_4) : 3100-3000, 3000-2860, 2835, 2245, 1605, 1590, 1495, 1465, 1455, 1250, 1035 cm^{-1}; MS m/z : 161 ($M^{+\cdot}$), 146.

(R,S)-(2)-(2-methoxyphenyl) propanoic acid, (R,S)-1: In a 2-liter three necked flask equipped with an overhead stirrer, a thermometer and a condenser were introduced crude **3** (106 g), MeOH (0.6 l) and NaOH 30 % (0.3 l). The resulting solution was refluxed for 1 hour. Then water (0.3 l) was added, and the reaction mixture was refluxed for 12 hours. Then, MeOH was removed by distillation under atmospheric pressure. At this point, the reaction was complete according to HPLC analysis. The reaction mixture was chilled at 20 °C, and washed with MTBE (3 x 0.2 l). The aqueous layer was then chilled to 5°C and concentrated HCl (qsp pH # 2) was added dropwise. The white precipitate was filtered, washed thoroughly with water (3 x 0.1 l) and dried to afford 108.6 g of **(R,S)-1** (88.7% yield, 2 steps) as a white powder of excellent purity according to spectroscopic analysis.^{1}H NMR (300 MHz, $CDCl_3$) : 1.52 (d, J = 7.5 Hz, 3H : CH_3) ; 3.85 (s, 3H : OCH_3) ; 4.12 (q, J = 7.5 Hz, 2H : ArCH) ; 6.92 and 7.02 (respectively d and t, J = 7.5 Hz, 2H : aromatic H in

ortho of OCH_3 and aromatic H in ortho of OCH_3) ; from 7.20 to 7.40 (m, 2H : aromatic H in meta of OCH_3); IR (KBr) : 3150-2300, 2835, 1705, 1605, 1590, 1495, 1455, 1025, 760 cm^{-1}; MS m/z : 180 ($M^{+\cdot}$), 135; calculated for $C_{10}H_{12}O_3$: C66.65, H6.71, O26.63, found : C66.6, H6.7, O26.9.

Quinine (3)-(+)-2 (2-methoxyphenyl) propionate, (S)-4: In a 2-liter three necked flask equipped with an overhead stirrer, a thermometer and a condenser, were introduced quinine (180 g ; 0.555 mole), EtOAc (1 l). The resulting suspension was heated to reach reflux and to get a solution. Then, (R,S)-1 (100 g ; 0.555 mole) was added as a solid. Reflux was maintained for 15 minutes, and then the reaction mixture was allowed to cool down slowly to 20°C, and stirred for 6 more hours. The white precipitate was filtered, washed with EtOAc (2 x 0.3 l) and dried to afford 139.4 g of (S)-4 (49.8% yield, 88% e.e.) as a white powder. This was recrystallized from EtOAc (0.28 l) to give 125.5 g (44.8% yield, $\geq$ 99.8% e.e.). as a white solid of excellent chemical and optical purity according to spectroscopic analysis. mp = 96°C; $[\alpha]_D$ = +1.5 (c = 1, DMF); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) : 1.34 (d, J = 7.5 Hz, 3H : CH_3) ; from 1.40 to 1.85 (m , 4H : CH_2 in 3 and 5 of quinine) ; 1.83 (bs, 1H : CH in 2 of quinine) ; 2.32 (m, 1H : CH in 8 of quinine) ; 2.58 and 3.45 (2 m, 1H each : CH_2 in 6 of quinine) ; 2.68 and 3.04 (respectively m and dd, J = 14 and 10 Hz, 1H each : CH_2 in 7 of quinine) ; 3.18 (m, 1H : 1H each : CHO) ; 3.80 and 3.88 (2 s, 3H each : OCH_3) ; 3.93 (q, J = 7.5 Hz, 2H : ArCH) ; 4.93 and 5.00 (2 d, respectively J = 11.5 Hz and J = 17.5 Hz, 1H each : $=CH_2$) ; 548 (d, J = 4.5 Hz, 1H : OH) ; 5.83 (m, 1H : CH=) ; from 6.80 to 7.00 (m, 2H : aromatic H in ortho of OCH_3 and aromatic H in ortho of OCH_3) ; from 7.15 to 7.25 (m, 2H : aromatic H in meta of OCH_3) ; 7.36 (dd, J = 9 and.2 Hz, 1H : aromatic H in 7' of quinine) ; 7.50 (d, J = 2 Hz, 1H : aromatic Hin 5' of quinine) ; 7.56 (d, J = 5 Hz, 1H :aromatic H in 3' of quinine) ; 7.93 (dd, J = 9 Hz, 1H : aromatic H in 8' of quinine) ; 8.70 (d, J = 5 Hz, 1H : aromatic H in 2' of quinine); IR (KBr) : 3500-3350, 3070, 3000-2850, 2835, 2800-2350, 1620, 1510, 1495, 1465, 1455, 1590, 1245, 1035, 885, 750 cm^{-1}; MS m/z : 324 ($M_1^{+\cdot}$), 180 ($M_2^{+\cdot}$) 135; calculated for $C_{30}H_{36}N_2O_5$: C71.41, H7.19, N5.55, O15.85, found : C71.4, H7.5, N5.6, O16.0.

(S)-(+)-2-(2-methoxyphenyl) propanoic acid, (S)-1: In a 2-liter three necked flask equipped with an overhead stirrer, a thermometer, a 0.1-liter dropping funnel, were introduced **(S)-4** (100 g ; 0.198 mole), CH2Cl2 (0.55 l) and water (0.37 l). To the resulting suspension was added dropwise NaOH 30% (17.4 ml) to reach pH # 9-10. The organic layer was then discarded to the aqueous layer, precooled at 10°C, was added concentrated HCl (20 ml) to reach pH # 2. Then, this suspension was stirred for 1 hour, and filtered, washed with water (2 x 0.55 l) and dried to afford 30.8 g of **(S)-1** (86.3% yield, $\geq$ 99.8% e.e) as a white solid of an excellent purity according to spectroscopic analysis. mp = 102°C; $[\alpha]_D$ = +83.4 (c = 1, $CHCl_3$); MS m/z : 180 ($M^{+\cdot}$), 135; calculated for $C_{10}H_{12}O_3$: C66.65, H6.71, O26.63, found : C66.9, H7.0, O26.5.

Acknowledgement : We thank M. Vuilhorgne and its collaborators for spectroscopic analyses.

References and notes :

1. Fadel, A. *Synlett* **1992**, 48.

2. Matsumoto, T. ; Imai, S. ; Miuchi, S. ; Sugibayashi, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 340.

3. The ratio of mono- and dialkylated compounds was determined by HPLC.

4. Enantiomeric purity was determined by chiral HPLC.

(Received in the UK 19th October 1995)