Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Resolving Agents. I. (R)-(-)-2-Amino-1-benzyloxybutane, a New Base for the Resolution of Racemic Acids

Joel Touet , Thierry Ruault & Eric Brown

SYNTHETIC COMMUNICATIONS, 24(3), 293-300 (1994)

RESOLVING AGENTS. PART 1. (R)-(-)-2-AMINO-1-BENZYLOXYBUTANE, A NEW BASE FOR THE RESOLUTION OF RACEMIC ACIDS

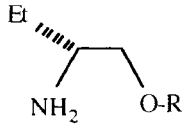
Joël Touet, Thierry Ruault and Eric Brown*
Laboratoire de Synthèse Organique (URA-CNRS 482), Faculté des Sciences, avenue Olivier Messiaen, BP 535, F-72017 Le Mans, France.

Abstract : Treatment of the readily available (R)-(-) enantiomer of 2-aminobutan-1-ol **1** with sodium hydride followed by benzyl chloride afforded the O-benzyl base (R)-(-)-**2**. The latter was successfully used for the resolution of racemic α-methylsuccinic and α-bromosuccinic acids, as well as of the racemic α-benzylhemisuccinic esters **8** and **9** respectively.

The resolution of racemic acids, by means of solid salt formation with an optically active amine, remains a useful process despite the progress of asymmetric synthesis. However, apart from a few cases such as α-methylbenzylamine, glutamic acid and dehydroabietylamine, most available resolving bases are very expensive and/or highly toxic, as exemplified with strychnine, brucine and yohimbine. Consequently, there is a need for new resolving bases that would meet the following requirements : low cost, low toxicity and availability in both enantiomeric forms. For this reason, we considered preparing simple new derivatives of (R)-(-)-

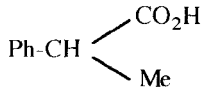
*To whom correspondence should be addressed.

and (S)-(+)-2-aminobutan-1-ol **1** in order to study their scope as resolving agents for racemic acids. Indeed, (±)-2-aminobutan-1-ol (±)-**1** is a cheap chemical which can be easily resolved into both its enantiomers on the industrial scale.[1] Although racemic mandelic acid,[2] glutamic acid[3] and N,O-diacetyl (4-hydroxyphenyl) glycine[4] were successfully resolved by means of optically active 2-aminobutan-1-ol **1**, we found that this base very seldom gives crystalline salts with racemic acids, the reason presumably being that it has a primary hydroxy group and too small a molecular weight. The aminoalcohol (R)-(-)-**1** was treated with sodium hydride in refluxing THF for 15 hours and the resulting sodium alkoxide was reacted with benzyl chloride, thus affording the O-benzyl base (R)-(-)-**2** in 72% yield. The resolving properties of the base (R)-(-)-**2** were next tested towards a series of racemic acids.

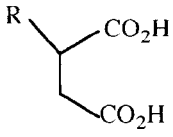


(R)-(-)-**1**, R = H

(R)-(-)-**2**, R = $PhCH_2$



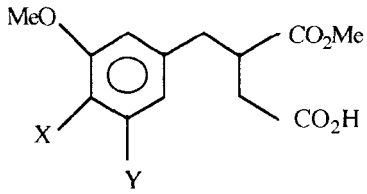
3



4, R = Ph

5, R = Me

6, R = Br



7, X = OH; Y = H

8, X = OMe; Y = H

9, X = Y = OMe

In the first place, (±)-α-phenylpropionic acid (±)-**3**, (±)-α-phenylsuccinic acid (±)-**4** and the hemisuccinic ester (±)-**7** were but partially resolved using the base (R)-(-)-**2** in an appropriate solvent, and afforded the optically active acids (S)-(+)-**3** (70% yield, enantiomeric excess, ee = 61.7%), (S)-(+)-**4** (55% yield, ee 32.6%), (R)-(+)-**7** (80% yield, ee = 76.8%) and (S)-(-)-**7** (32% yield, ee = 69%), respectively. Resolution of (±)-α-methylsuccinic acid (±)-**5** with (R)-(-)-**2** in ethyl acetate afforded both optically pure enantiomers (S)-(-)-**5** (60% yield) and (R)-(+)-**5** (77% yield). Similary, resolution of (±)-α-bromosuccinic acid (±)-**6** afforded the optically pure levorotary enantiomer (-)-**6** in 90% yield and after only one crystallization experiment. The optically pure enantiomers (S)-(-)-**8** and (S)-(-)-**9** were similarly obtained from the corresponding racemic acids.

Conclusion

Selection of new adequate resolving agents is not an easy task. For instance, we have synthesized about ten new N-alkyl and N,N-dialkyl derivatives of (R)-(-)-**1** which all proved unsatisfactory as resolving agents for racemic acids, in our hands at least. [5] On the contrary, the new base (R)-(-)-**2** was successfully used for the resolution of four substituted succinic acid derivatives. Since the base **2** can be easily obtained on a kilogram scale [1] and in both enantiomeric forms, its use can be recommended for any resolution studies of racemic acids.

Experimental section

IR spectra were recorded with a Nicolet 5DX spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM 390 spectrometer, using Me_4Si as an internal

standard. The optical rotations were measured at 22°C with Jobin-Yvon and Perkin-Elmer 241 micropolarimeters.

(R)-(-)-2-aminobutan-1-ol, $[\alpha]_D$ -10 (neat), was kindly provided by SmithKline Beecham Laboratories (Mayenne, France).

(R)-(-)-2-Amino-1-benzyloxy butane (R)-(-)-**2**

In a 500 mL three-necked flask equipped with a nitrogen inlet, a tap funnel and a reflux condenser, oil-free sodium hydride (134 mmol, 5.36g) was placed under nitrogen, followed by anhydrous THF (50 mL). To the refluxing suspension a solution of (R)-(-)-2-aminobutan-1-ol (R)-(-)-**1** (112 mmol, 10g) in anhydrous THF (75 mL) was added dropwise. After heating at reflux for 17 h, a solution of benzyl chloride (112 mmol, 14.7 mL) in anhydrous THF (75 mL) was added in 2 h. After refluxing for a further 20 h, the solution was cooled and poured into brine (400 mL). After filtration, the two layers were separated and the aqueous phase was extracted with ether (3x150 mL). The organic extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Vacuum distillation of the viscous brown residue gave the base (R)-(-)-**2** as a viscous colourless oil (14.8g, 74% yield), bp 95°C (0.1mm Hg) and $[\alpha]_D$ -15.7 (c 1.5, EtOH). Molecular distillation of a sample led to an $[\alpha]_D$ -18.9 (c 1.5, EtOH). The same experiment was repeated on a larger scale and afforded the purified base (R)-(-)-**2** (115g) $[\alpha]_D$ -16 (c 1.5, EtOH), in 72% yield after distillation. IR (film) : 3400 (NH), 1102 (C-O-C), 856 (NH), 740, 699 (aryl) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.33 (s, 5H), 4.5 (s, 2H), 3.3 (m, 2H), 2.85 (m,1H), 1.3 (m, 4H), 0.9 (t, 3H).

Hydrochloride of (R)-(-)-2-amino-1-benzyloxybutane(R)-(-)-**2**

A sample of the base (R)-(-)-**2** was dissolved in a mixture of ether and ethanol (1/1 w/w) and was treated with dry hydrochloric acid. The precipitated solid was isolated and recrystallized from a mixture of AcOEt/EtOH (10/1 w/w), thus affording the pure hydrochloride as white crystals (65% yield), mp 138-139°C and $[\alpha]_D$ -20.6 (c 0.5, EtOH). Another preparation of this hydrochloride, starting from a solution of crude base (R)-(-)-**2**, gave after recrystallization white crystals, $[\alpha]_D$ -18 (c 1.1, EtOH), in 45% yield. Anal. Calcd for $C_{11}H_{18}ClNO$: C, 61.24; H, 8.40; N, 6.49; O, 7.41. Found : C, 61.02; H, 8.57; N, 6.65; O, 7.66.

Resolution of racemic α-methylsuccinic acid (±)-**5**

Racemic α-methylsuccinic acid (±)-**5** (3.78 mmol, 0.5g) was dissolved in warm AcOEt (10 mL) in a 25 mL conical flask and (R)-(-)-2-amino-1-benzyloxybutane (R)-(-)-**2** (3.77 mmol, 0.675g) was then added. After having settled at room temperature, the solid salt thus formed (577 mg), $[\alpha]_D$ -14.6 (c 1, EtOH) was recrystallized from AcOEt, thus affording a purified salt (426 mg), $[\alpha]_D$ -15.8 (EtOH). The latter (350 mg) was treated with 10% aqueous hydrochloric acid (4 mL) followed by extraction with ether (3x20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure at 20°C, thus affording white crystals of the acid (S)-(-)-**5** (60% yield), $[\alpha]_D$ -13.5 (c 1.15, EtOH) and mp 113-114.5°C. Lit. [6] $[\alpha]_D$ -15 (c 1.9, EtOH) and mp 111-113°C.

Evaporation of the mother-liquor followed by treatment of the viscous brown resi-

due, in the same way as for the crystalline salt above, gave white crystals of the acid (R)-(+)-**5** (77% yield), $[\alpha]_D$ +13.3 (c 1, EtOH).

Resolution of racemic α-bromosuccinic acid (±)-**6**

In a 100 mL conical flask, racemic α-bromosuccinic acid (±)-**6** (25 mmol, 5g) was dissolved in AcOEt (50 mL), (R)-(-)-2-amino-1-benzyloxybutane (R)-(-)-**2** (25 mmol, 45 g) was then added and the resulting pale yellow solution was kept at -8°C for 15 h. The solid salt thus formed (4.56 g), $[\alpha]_D$ -26 (EtOH), was isolated by filtration. An aqueous suspension of this salt was treated with 10% aqueous hydrochloric acid (15 mL) followed by extraction with ether (3x50 mL). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure at room temperature, thus giving white crystals of (-)-α-bromosuccinic acid (-)-**6** (2.21g, 90% yield), $[\alpha]_D$ -55.7 (c 1, EtOH). A recrystallization from ether afforded the purified acid (-)-**6**, $[\alpha]_D$ -61 (c 0.7, EtOH) and mp 170.5-173°C. Lit. [7] $[\alpha]_D$ -65 (c 6, EtOH) and mp 177-178°C. Evaporation of the mother-liquor, followed by treatment of the crystalline residue with 10% aqueous hydrochloric acid as above, gave the partially resolved acid (+)- **6** whose $[\alpha]_D$ (EtOH) was comprised between +10 and +19.

Resolution of racemic methyl α-(3,4-dimethoxybenzyl) hemisuccinate (±)-**8**

The racemic hemiester (±)-**8** [8] (3.55 mmol, 1.0 g) was dissolved in warm AcOEt (5 mL) in a 25 mL conical flask and (R)-(-)-2-amino-1-benzyloxybutane (R)-(-)-**2** (3.55 mmol, 0.626 g) was then added. After leaving at -8°C for 15 h, crystals (1.24 g) were formed and whose specific rotation, $[\alpha]_D$ -8 (MeOH), was very clo-

se to that of an equimolecular mixture of both diastereomeric salts. Evaporation of the mother-liquor gave an oil which was treated with 10% aqueous hydrochloric acid (3 mL), followed by extraction with ether (3x20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure at room temperature, thus affording the levorotary hemiester (S)-(-)-**8** (0.11g, 22% yield), $[\alpha]_D$ -27.7 (c 1, EtOH). Lit.[8] $[\alpha]_D$ -27.6 (c 1, EtOH).

Resolution of racemic methyl α-(3,4,5-trimethoxybenzyl) hemisuccinate (±)-**9**

The racemic hemiester (±)-**9**[9] (3.12 mmol, 1.0 g) was dissolved in warm AcOEt (5 mL) in a 25 mL conical flask, and (R)-(-)-2-amino-1-benzyloxubutane (R)-(-)-**2** (0.526 g) was then added. After leaving at room temperature for two days, the crystalline salt thus formed (0.77 g) was recrystallized from AcOEt, giving a purified salt (0.4 g). The latter was dissolved in water containing 10% aqueous hydrochloric acid (3 mL), followed by extraction with ether (3x20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure at 20°C. Crystallization of the oily residue from ether furnished the crystalline hemiester (S)-(-)-**9** (0.222 g, 44% yield), $[\alpha]_D$ -20 (c 2, MeOH). Lit.[9] $[\alpha]_D$ -21 (MeOH).

Aknowledgements

We thank ANVAR (Nantes) and SmithKline Beecham Laboratories (Mayenne, France) for their financial support.

References

1. Le Goff, J. P. (SmithKline Beecham Laboratories (Mayenne, France), personal communication.

2. Nohira, H., Fujii, H., Yajima, M. and Fujimara, R., European patent n° 36, 265 (1981) ; Chem. Abstr., 1982, 96, 122427x.

3. Radke, F.H., Fearing, R.B. and Fox, S.W., J. Amer. Chem. Soc., 1954, 76, 2801.

4. Chae, Y.B. and Kim, D.W. (Hoechst), German patent n°2, 735, 834 (1979); Chem Abstr., 1979, 91, 21116m.

5. Brown, E., Touet, J., Ruault, T. and Faveriel, L., unpublished work.

6. Eisenbraun, E.J. and Mc Elvain, S.M., J. Amer. Chem. Soc., 1955, 77, 3383.

7. Clough, G.W., J. Chem. Soc., 1926, 129, 1674.

8. Brown, E. and Daugan, A., Tetrahedron, 1989, 45, 141.

9. Lalami, K., Dhal, R. and Brown, E., J. Nat. Prod., 1991, 54, 119.

(Received in the UK 07 July 1993)