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O-Benzyl Derivatives of (S)-(+) and (R)-(-)-2-Aminobutan-1-ol as New Resolving Agents for Racemic Acids. Practical Resolutions of N-Acyl Derivatives of Phenylglycine and 4-Hydroxyphenylglycine

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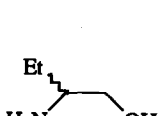
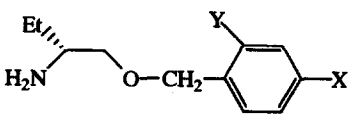
Abstract : Treatment of the readily available (S)-(+) and (R)-(-)-2-aminobutan-1-ol **1** with sodium hydride followed by benzyl chloride, or a substituted benzyl halide, afforded the corresponding O-benzyl bases **2-5** in high yields. These new bases are recommended for the large scale resolution of racemic acids. For instance, they proved efficient for the practical resolutions of N-acetylphenylglycine (±)-**7**, N-acetyl-(4-hydroxyphenyl) glycine (±)-**9** and N-chloroacetyl-(4-hydroxyphenyl) glycine (±)-**10**.

Despite the progress of asymmetric synthesis, resolution of racemates by means of diastereomeric salts formation still remains an industrially attractive process.[1] However industrial resolution of racemic acids is limited because of the dearth of adequate optically active bases. Indeed, apart from a few isolated cases such as α-methylbenzylamine or dehydroabietylamine, most available resolving bases are very expensive and/or highly toxic, as exemplified with brucine, quinine or strychnine. In order to be practical for large scale resolution of racemic acids, an optically active base must meet the following requirements : low cost, low toxicity, low molecular weight and availability in both enantiomeric forms. This led us to contemplate using simple derivatives of (R)-(-) and (S)-(+)-2-aminobutan-1-ol **1** for the resolution of racemic acids. Indeed, racemic 2-aminobutan-1-ol (±)-**1** is a cheap chemical which can be resolved easily into both its enantiomers on an industrial scale.[1] Although racemic mandelic acid,[2] glutamic acid[3] and N-acetyl-(4-acetoxyphenyl) glycine[4] were successfully resolved by means of optically active 2-aminobutan-1-ol **1**, our preliminary studies have shown that this base seldom gives crystalline salts with racemic acids, the reason presumably being that it has a primary alcohol group and too small a molecular weight. We subsequently synthesized a variety of N-alkyl and N, N-dialkyl derivatives of (R)-(-)-**1** which, however, proved unsatisfactory as resolving agents for racemic acids, in our hands at least.[5] Therefore, we next considered synthesizing simple O-alkyl derivatives of (S)-(+) or (R)-(-)-**1**, and this led us to develop some new and useful optically active bases, as described below.

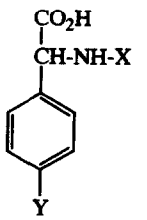
(R)-(-)-2-aminobutan-1-ol (R)-(-)-**1**[6], $[\alpha]_D$-10 (neat), was treated with sodium hydride in refluxing tetrahydrofuran for 17 hours. To the suspension of the sodium alkoxide thus formed, one equivalent of benzyl chloride in tetrahydrofuran was added. After heating under reflux for a further 20 hours, the reaction mixture was worked up and the final residue was distilled under vacuum, thus giving the O-benzyl base (R)-(-)-**2**[7,8] (Scheme).



(R)-(-)-**1**, α-Et
(S)-(+)-**1**, β-Et



(R)-(-)-**2**, X=Y=H
(R)-(-)-**3**, X=Cl ; Y=H
(R)-(-)-**4**, X=Br ; Y=H
(R)-(-)-**5**, X=Y=Cl



6, X=Y=H
7, X=Ac ; Y=H
8, X=H ; Y=OH
9, X=Ac ; Y=OH
10, X=$ClCH_2CO$; Y=OH

SCHEME

The O-(4-chlorobenzyl), O-(4-bromobenzyl) and O-(2,4-dichlorobenzyl) bases (R)-(-)-**3**, **4** and **5**[8], respectively, were next prepared in the same way as (R)-(-)-**2** using the corresponding substituted benzyl chloride or bromide, and using toluene as a solvent instead of tetrahydrofuran.

Having these bases in hand, we decided to use them for the resolution of simple acidic derivatives of (±)-phenylglycine (±)-**6** and (±)-(4-hydroxyphenyl) glycine (±)-**8**. Indeed, the levorotary enantiomers of both **6** and **8** are key-intermediates in the syntheses of two major antibiotics of the penicillin group, nameley ampicillin and amoxycillin, respectively, the latter being the most important one clinically.[1]

Treatment of (±)-phenylglycine (±)-**6** with excess acetic anhydride in cold aqueous sodium hydroxide, followed by acidification, afforded the crystalline N-acetyl derivative (±)-**7**.[8] This compound was treated with one equivalent of the 4-chlorobenzyl base (R)-(-)-**3** in 95% EtOH, and the mixture was seeded with the pure salt of (R)-(-)-**3** and (R)-(-)-**7**. The salt which crystallized out (in 75% yield) was treated with a biphasic mixture of toluene and aqueous sodium hydroxide solution. After complete dissolution of the salt, the aqueous phase was acidified and the precipitated product was recystallized from 30% aqueous EtOH, thus affording optically pure (R)-(-)-**7**[8] in 61% yield, and with physical properties in agreement with the literature.[9] The partially resolved acid (S)-(+)-**7**, contained in the filtrate of the first crystallization procedure, was isolated and further resolved with the enantiomeric base (S)-(+)-**3** in the same way as above, and this gave optically pure (S)-(+)-**7**[8] in 39% yield.

(±)-(4-Hydroxyphenyl)glycine (±)-**8** in oxygen free, aqueous sodium hydroxide solution (pH 10) was treated with 2 molar equivalents of acetic anhydride under nitrogen at 5°C, the pH being kept

constant by addition of 3N NaOH solution. After stirring for 30 min, the pH was brought to 12.5 by further addition of 3N NaOH solution. After 2 hours, the mixture was acidified and the precipitated N-acetyl derivative (±)-**9**[8,10] was filtered and recrystallized from water. So far as we know, this appears to be the best method for preparing (±)-**9** in a one pot reaction and in good yield. An equimolecular solution of the acid (±)-**9** and the O-(2,4-dichlorobenzyl) base (R)-(-)-**5** in 95% EtOH was seeded with the pure salt of the base (R)-(-)-**5** and the acid (R)-(-)-**9**. After standing at room temperature for 36 hours,the crystalline salt was treated with a biphasic mixture of toluene and aqueous NaOH solution. On acidification of the aqueous phase, the crystalline, optically pure acid (R)-(-)-**9**[8] was isolated in 85% yield, and with physical properties in agreement with the literature.[10]

The aminoacid (±)-**8** in oxygen free, aqueous NaOH solution (pH 9), was treated at 0-5°C with chloroacetyl chloride (2 equivalents), the pH remaining constant by addition of 3N NaOH. After stirring for 1 hour, the mixture was acidified and the precipitated N-chloroacetyl derivative (±)-**10**[8] was recrystallized from 30% EtOH after treatment with charcoal in the same solvent. An equimolecular solution of the acid (±)-**10** and the base (R)-(-)-**2** in EtOH was seeded with the pure salt of the acid (R)-(-)-**10** and the base (R)-(-)-**2**. After standing at room temperature for 24 hours, the precipitated salt was recrystallized from EtOH. The pure salt thus obtained was treated with toluene and aqueous NaOH solution as above, and this gave the acid (R)-(-)-**10**. Recrystallization form ethyl acetate afforded optically pure (R)-(-)-**10**[8] in 69% yield.

Similarly, resolution of the acid (±)-**10** with the O-(4-bromobenzyl) base (R)-(-)-**4** gave the optically pure acid (R)-(-)-**10** in 61% yield. Finally, resolution of the same racemic acid with the O-(2,4-dichlorobenzyl) base (R)-(-)-**5** gave optically pure (R)-(-)-**10** in 59% yield.

Conclusion

The new bases (R)-(-)-**2** to -**5** were obtained in high yields by O-benzylation of the readily available (R)-(-)-2-aminobutan-1-ol (R)-(-)-**1**. As exemplified with (S)-(+)-**3**,[8] the (S)-(+) enantiomers of the bases **2**-**5** can be similarly prepared from (S)-(+)-2-aminobutan-1-ol (S)-(+)-**1**.[6] Besides their being available in both enantiomeric forms, these bases present the additional advantage of having a low cost and a low molecular weight. Therefore, they can be recommended for the large scale resolution of racemic acids. Indeed these bases were successfully used for the resolution of N-acyl phenylglycine derivatives, which are key-intermediates for two major penicillin antibiotics. Thus (R)-(-)-N-acetyl phenylglycine (R)-(-)-**7** was obtained in 61% yield by resolution of (±)-**7** with the base (R)-(-)-**3**. Similarly, (R)-(-)-N-chloroacetyl-(4-hydroxyphenyl) glycine (R)-(-)-**10** was obtained in 69% yield using the base (R)-(-)-**2**, and (R)-(-)-N-acetyl-(4-hydroxyphenyl) glycine (R)-(-)-**9** was obtained in 85% yield using the base (R)-(-)-**5**. The above results compare favourably with other resolution procedures described for the same compounds.[10-13] Since the undesired (S)-(+) enantiomers of these N-acyl aminoacids can be racemized and recycled in view of further resolution,[1,10] and since the resolving bases can be equally recycled, we believe that the present methodology could be applied industrially. Indeed, part of this work formed the subject of a patent.[14]

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

6. Both enantiomers of the base **1** were obtained in kilogram quantities from SmithKline Beecham Laboratories, Mayenne (France).

7. Compound (R)-(-)-**2** was prepared for the first time by Ruault, T. in our laboratory.

8. Physical properties and yields of purified compounds. (R)-(-)-**2**, oil, b.p. 95°C (0.1 mm), $[\alpha]_D$ -19 (1.5, EtOH), 72% ; (R)-(-)-**2** hydrochloride, m.p. 138-139°C, $[\alpha]_D$ -21 (0.5, EtOH) ; (R)-(-)-**3**, oil, b.p. 104°C (0.07 mm), $[\alpha]_D$ -15 (1.21, EtOH), 79% ; (R)-(-)-**3** hydrochloride, m.p. 127-128°C ; (S)-(+)-**3**, oil, b.p. 109°C (0.1 mm), $[\alpha]_D$ +16 (1.31, EtOH), 70% ; (S)-(+)-**3** hydrochloride, m.p. 126-127.5°C, $[\alpha]_D$ +16 (1.0, EtOH) ; (R)-(-)-**4**, oil, b.p. 108°C (0,07 mm), $[\alpha]_D$ -13 (2.13, EtOH), 78% ; (R)-(-)-**4** hydrochloride, m.p. 137.5-139°C, $[\alpha]_D$ -15 (1.03, EtOH) ; (R)-(-)-**5**, oil, b.p. 112°C (0.1 mm), $[\alpha]_D$ -15 (1.74, EtOH), 76% ; (R)-(-)-**5** hydrochloride, m.p. 163.5-164°C, $[\alpha]_D$ -17 (0.78, EtOH) ; (±)-**7**, m.p. 198-199°C (30% EtOH), 92% ; (R)-(-)-**7**, m.p. 190-191°C, $[\alpha]_D$ -215 (1.3, 95% EtOH) ; (S)-(+)-**7**, m.p. 190-191°C, $[\alpha]_D$ +210 (1.0, 95% EtOH) ; (±)-**9**, m.p. 199.5-201°C (H_2O), 77% ; (R)-(-)-**9**, m.p. 199-200.5°C, $[\alpha]_D$ -218 (1.04, 95% EtOH) and $[\alpha]_{546}$ -267 (1.04, 95% EtOH) ; (±)-**10**, m.p. 190-191°C (30% EtOH), 82% ; (R)-(-)-**10**, m.p. 187-189°C, $[\alpha]_D$ -202 (1.05, MeOH) ; (S)-(+)-**10**, m.p. 187-188°C, $[\alpha]_D$ +200 (1.1, MeOH).

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