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Preparation of racemic 2,3-diaminobutane and the resolution of its (2*S*,3*S*) enantiomer

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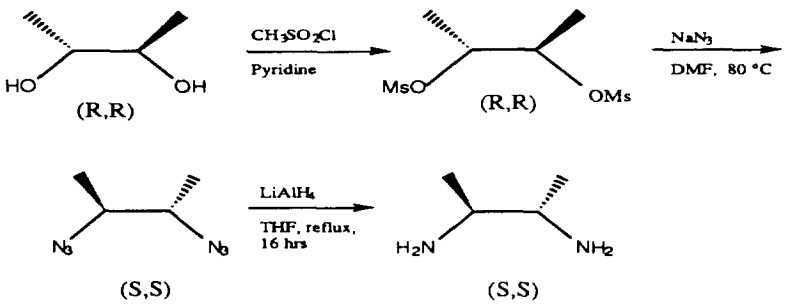
Abstract: A three-step procedure for large scale preparation of pure racemic 2,3-diaminobutane from relatively inexpensive meso 2,3-butanediol is described. Also, an efficient method for the resolution of (*S,S*) 2,3-diaminobutane from the racemic mixture in <95% ee has been developed. © 1997 Elsevier Science Ltd

Introduction

The present trend in the pharmaceutical industry is moving towards single-isomer drugs in response to policy statement by Food and Drug Administration to do so where applicable.[1] Towards that end, a need arose for a process to prepare multi-kilo quantities of a chiral starting material, (*S,S*) 2,3-diaminobutane. A literature search revealed several syntheses.[2–8] Our aim was to find the simplest and the most cost-effective method that did not involve a hazardous step or chemical. With this in mind, our first approach was the reductive amination of 2,3-butanedione with NH_4OH and various amines. This approach was dropped because of lack of reactivity or mixture of products. Our attempts at hydrogenation of dimethylglyoxime that had been reported earlier,[2,4] with some modifications, was also unsuccessful.

Results and discussion

Because of these problems, our attention became focused on a recent paper[8] which described a 3-step synthesis of (*S,S*) 2,3-diaminobutane from (*R,R*) 2,3-butanediol in 78% yield (Scheme 1).



Scheme 1

However, there were two major problems with this sequence. One was the high cost and availability of (*R,R*) 2,3-butanediol in large quantities. The second problem was the potentially explosive nature of the diazido intermediate which would certainly preclude its preparation on a large scale in our facility. We, therefore, modified the last two steps of this procedure in which NaN_3 was replaced by benzylamine followed by catalytic debenzylation with Pd/C. Because of various reasons other amines (including ammonia) were not tried.

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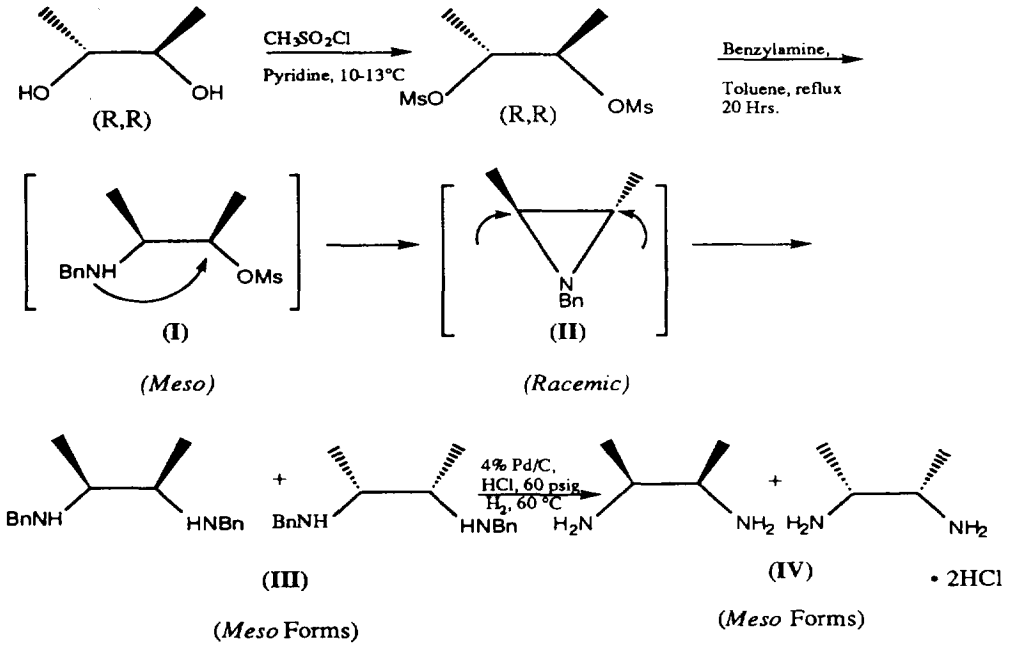
However, when this sequence was carried out the product consisted of only 4% (*S,S*). The major isomer was 92% *meso* together with 4% (*R,R*). This clearly indicated that there were *three* inversions occuring not *two*. The proposed mechanism, based on the results obtained, is shown in Scheme 2.



Scheme 2.

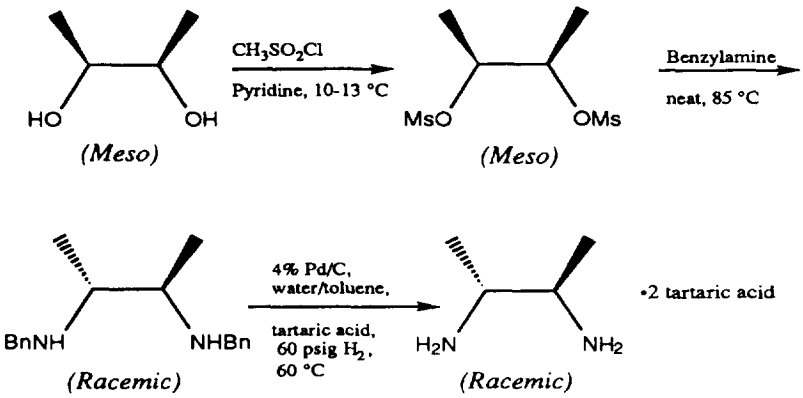
The first inversion occurs when benzylamine displaces one of the mesylate groups to give compound (I). Then an intramolecular displacement occurs (with inversion) to give aziridine (II) (racemic). This is followed by a third inversion of opening the aziridine ring (from either side) by benzylamine to give the *meso* forms (III). Subsequent debenzylation produces *meso* 2,3-diaminobutane (IV). The same results would be expected if we started with (*S,S*) 2,3-butanediol. We, therefore, reasoned that if we started with *meso* 2,3-butanediol we should obtain pure racemic 2,3-diaminobutane.

Thus, when *meso* 2,3-butanediol dimesylate was reacted with benzylamine in boiling xylene (137°C) a 3:1 ratio of racemic to *meso* of the dibenzyl compound was obtained. The unexpected presence of *meso* could be explained that under these reaction conditions some of the dibenzyl compound was not produced through the aziridine intermediate but by the competing double intermolecular displacement. Because when the reaction was carried out neat (without solvent) at 110°C, the product consisted of 95% racemic and 5% *meso*. Further improvement was accomplished when the reaction was run (neat) at 85°C where the product consisted of 99% racemic and only 1% *meso*.

The resolution of the racemic 2,3-diaminobutane was done on the tartrate salt in water/methanol, necessitating the conversion of the hydrochloride salt into tartrate salt. Consequently, a change was made in the hydrogenation step by substituting hydrochloric acid with tartaric acid and performing the reaction in a two-phase system of water/toluene (1:1) *instead* of ethanol. The following improved sequence was adopted (Scheme 3). Low molecular weight aziridines are toxic, however, since they were produced only as transient intermediates *in situ*, no special precautions were taken.

Resolution of racemic 2,3-diaminobutane

The reaction mixture from hydrogenation step was filtered to remove the catalyst and the aqueous layer containing racemic 2,3-diaminobutane ditartrate was separated from toluene layer. The aqueous layer was then directly used in the resolution crystallization. Using one stirred and four static



Scheme 3.

Table 1. Resolution of *racemic* 2,3-diaminobutane tartrate *(water/methanol process)*

Crystallization Method	Water/MeOH (Ratio)	Chiral GC Analysis (area %) S,S	R, R	Meso	ee (%)
Stirred Crystallization	1:2.7	57.7	41.3	1.1	16
1st Static Crystallization	1:1	77.0	22.1	0.9	55
2nd Static Crystallization	1:1	90.0	8.8	1.2	81
3rd Static Crystallization	1:1	96.1	3.4	0.5	93
4th Static Crystallization	1:1	98.5	1.2	0.4	97

Table 2. Resolution of *racemic* 2,3-diaminobutane tartrate *(water/acetone process)*

Crystallization Method	Water/Acetone (Ratio)	Chiral GC Analysis (area %) S,S	R, R	Meso	ee (%)
1st Static Crystallization	1:1.2	77.7	21.5	0.7	56
2nd Static Crystallization	1:1.2	92.3	7.1	0.6	85
3rd Static Crystallization	1:1	97.6	2.25	0.1	95.3

crystallizations employing water/methanol, we were able to obtain 2,3-diaminobutane ditartrate comprising of 98.5% (*S,S*), 1.2% (*R,R*) and 0.4% *meso*. The details are described in Table 1.

Using a second crystallization protocol of water/acetone, we were able to obtain 2,3-diaminobutane ditartrate comprising of 97.6% (*S,S*), 2.25% (*R,R*) and 0.1% *(meso)* in only three static crystallizations. The results are shown in Table 2.

There was a concern with the use of acetone in the second crystallization protocol since it might form a schiff base with the diamine. Consequently, an experiment was performed where a lot of pure racemic mixture of 2,3-diaminobutane ditartrate was divided into two equal portions. One portion was crystallized from water/methanol and the other from water/acetone. Both the crystals and the mother liquors (after stripping off solvent) from each crystallization were analyzed by chiral G.C. The results show no evidence of schiff base formation as the two crystallizations are comparable except that water/acetone crystallization produced better resolution than water/methanol. Also, proton NMRs that were run on all four samples were identical and corresponded exactly to pure racemic 2,3-diaminobutane ditartrate.

Experimental section

meso *2,3-Butanediol dimesylate*

The method of synthesis of *meso* 2,3-butanediol dimesylate was similar to that reported in the literature[9] with minor modification. A 3L-3-necked R. B. Flask fitted with mechanical stirrer, thermometer and addition funnel was charged with 100 g (1.111 moles) of *meso* 2,3-butanediol (Aldrich, 97% pure) and 1 L pyridine and cooled to 5°C. Then, with vigorous stirring, 300 g (2.608 moles) of methanesulfonyl chloride was added dropwise during 30 minutes while keeping the temperature at 10–13 °C with cooling (ice bath). The reaction was stirred for an additional hour at this temperature range when it became thick and was left to stand overnight at room temperature. The thick reaction mixture was poured portionwise into a 4 L beaker containing 2.5 L of ice–water with vigorous stirring as the product precipitated out. After stirring for an additional one-half hour, it was filtered cold and the crystals were washed with 1 L of cold water and sucked dry. After drying further in a vacuum oven at 40°C overnight, the crystals weighted 249.1 g (91.0% yield) m.p. 66–8°C. A sample crystallized from acetone–ether melted at 70–71°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.43 (d, 6H), 3.08 (S, 6H), 4.90 (M, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 16.41 (C–*C*H$_3$), 39.14 (–O–SO$_2$*C*H$_3$), 79.55 (–*C*–H–) Anal. Calcd. for $C_6H_{14}O_6S_2$ [246.30]: C, 29.26; H, 5.73; S, 26.04. Found: C, 29.25; H, 6.07; S, 25.89.

Racemic bis-2,3-N,N′-dibenzyl diaminobutane

To a 1 L-3-necked R. B. flask was charged 120 g (0.4878) of *meso* 2,3-butanediol dimesylate and 220 g (2.056 moles) of benzylamine. The reaction mixture was stirred and heated at 85 ± 2°C for 24 hrs. The gold-colored reaction was cooled to 60°C and 500 mL toluene and 400 mL water was added. The layers were separated and the toluene layer was washed with 5×300 mL water, dried over Na_2SO_4, filtered and the toluene removed in a rotovap under vacuum at 60°C. The residual oil (crude) weighing 120.5 g was pure enough (by NMR) for the next step. It contained small amounts of benzylamine, starting material and toluene. Some was fractionally distilled at 170–172 /1mm (Lit.[10] 130°C/0.1 mm). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.06 (d, 6H, –CH$_3$), 1.70 (S, 2H, –NH), 2.45 (m 2H, –CH), 3.75 (A,B system, 4H, –N–CH$_2$–Φ), 7.15–7.30 (m, 10 arom.). ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm): 17.16 (–C–*C*H$_3$), 51.94 (–N–*C*H$_2$–Φ), 57.93 (–*C*H–), 127.31, 128.65, 128.88, 141.55 (arom.). Anal: Calc. for $C_{18}H_{24}N_2$ [268.39]: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.47; H, 8.96; N, 10.09. Chiral HPLC 2*R*,3*R*, 2*S*,3*S* 49.62%, 50.32%, *meso* 0.06%.

Racemic 2,3-diaminobutane ditartrate

One hundred grams (0.3726 moles) of bis-2,3-N,N′-dibenzyldiaminobutane (racemic) was charged to a 2 L Parr shaker bottle. Then a solution of 112 g (0.7467 moles) of L-tartaric acid in 600 mL of de-ionized water was added to the bottle, followed by 400 mL of toluene. To this reaction was then added 40 g of 4% Pd/C (50% wet). The Parr bottle was purged with N_2 (5×) and hydrogen (5×) and the reaction mixture was shaken with hydrogen and hydrogenated at 60 psig and 60°C until the reaction was complete (10 hrs). The Parr bottle was cooled to room temperature, vented and purged with N_2 (5×) and the catalyst was removed by filtration through a layer of powdered cellulose. The two layers were separated and the aqueous layer had a volume of 700 mL. Some of this was stripped at 65–70°C under vacuum to give white solid which was analyzed by chiral G.C. to consist of 49.27% 2*S*,3*S*; 49.39% 2*R*,3*R* and 1.34% *meso* 2,3-diaminobutane ditartrate.

Resolution of 2S,3S-diaminobutane ditartrate (water/methanol method)

Stirred crystallization

Five hundred and fifty milliliters of the above aqueous layer containing about 102 g of racemic 2,3-diaminobutane ditartrate was placed in a 3 L R. B. Flask and heated to 50°C. Then 1200 mL of hot methanol was added slowly with stirring. The clear solution was stirred and cooled in ice bath (5°C) where the product precipitated out. After 2 hrs at 5°C, the crystals were filtered and washed with

some cold methanol and dried in vacuum oven at 60°C for 18 hrs. The dried crystals weighed 63.1 g. ^{1}H-NMR (300 MHz, D_2O) δ (ppm): 1.38 (d 6H,–CH_3), 3.73 (m 2H,–CH), 4.48 (S, tartaric acid). ^{13}C-NMR (300 MHz, D_2O) δ (ppm): 12.90 (–C–*CH_3*), 49.11 (–*CH*–), 73.34 (–*C*(OH)–, tartaric acid), 176.83 (–COOH, tartaric acid). Anal. Calcd. For $C_{12}H_{24}N_2O_{12}.H_2O$ [406.35]: C, 35.47; H, 6.45; N, 6.90. Found: C, 35.52; H, 6.44; N, 6.87. Chiral G.C. 2*S*,3*S* 57.7%; 2*R*,3*R* 41.3%; *meso* 1.1%.

1st static crystallization

Fifty grams of the above crystals was dissolved by heating in 150 mL de-ionized water and 150 mL of hot methanol was added. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried as before: weight 30.7 g (see Table 1 for chiral analysis).

2nd static crystallization

Thirty grams from the 1st static crystallization was dissolved by heating in 90 mL de-ionized water and 90 mL of hot methanol was added. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried: weight 22.9 g (see Table 1 for chiral analysis).

3rd static crystallization

About 23 g from the 2nd static crystallization was dissolved by heating in 70 mL de-ionized water, then 70 mL of hot methanol was added. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried: weight 18.9 g (see Table 1 for chiral analysis).

4th static crystallization

About 19 g from the 3rd static crystallization was dissolved by heating in 75 mL de-ionized water, then 75 mL of hot methanol was added. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried: weight 15 g (see Table 1 for chiral analysis). Overall yield for 5 crystallizations=18.6%.

Resolution of 2S,*3S-diaminobutane ditartrate* (water/acetone method)

1st static crystallization

Thirty two grams of racemic 2,3-diaminobutane ditartrate was dissolved in 100 mL hot de-ionized water, then added 125 mL hot acetone. The solution was allowed to stand at room temperature overnight. The crystals formed were filtered and dried: weight 15.0 g (see Table 2 for chiral analysis).

2nd static crystallization

About 15 g from the 1st crystallization was dissolved in 50 mL of hot de-ionized water, then added 60 mL hot acetone. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried: weight 9.0 g (see Table 2 for chiral analysis).

3rd static crystallization

About 9 g from the 2nd crystallization was dissolved in 60 mL of hot de-ionized water, then added 60 mL hot acetone. The solution was allowed to stand at room temperature overnight. The crystals were filtered and dried: weight 5.5 g (see Table 2 for chiral analysis). Overall yield for the 3 crystallizations=17.2%.

Analytical section

A chiral GC separation of the racemic 2,3-diaminobutane ditartrate utilized a Chiraldex G-TA column and flame ionization detector (FID). The tartrate salt was converted to the free amine by the addition of 30% NaOH and the free amine was extracted with methylene chloride. Trifluoroacetic anhydride was added to the methylene chloride vortex and evaporated to dryness. The residue was reconstituted with 200 proof ethanol and injected.

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