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Economical, One-Pot Synthesis and Application of Schiff Base in Resolution-Racemization

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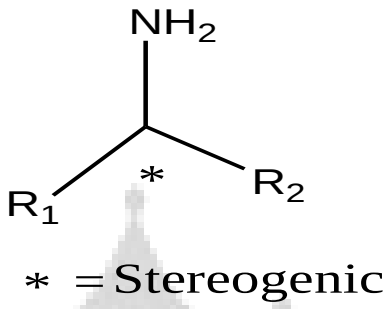
ABSTRACT

The pharmaceutical industry has a rising demand for chiral intermediates to improve drug efficacy. This in turn impacts on researchers involved in preclinical discovery work. An economical, one-pot process for resolution-racemization of primary amines with α-hydrogens via selective crystallization of diastereomeric chiral amine salts and the subsequent in situ racemization of the other enantiomer by the catalytic addition of aromatic aldehydes/ketones which permits the stereo-specific synthesis of the desired isomer.

INTRODUCTION

The importance of α-chiral amines as building blocks in pharmaceutical drugs, natural products, fine chemicals and agrochemicals have encouraged scientists to develop different methodologies for their preparation.

Chiral amines bearing a stereogenic carbon at the α-position to the amino functionality.



The development and use of newer synthetic methods for the stereoselective synthesis of chiral molecules have increased enormously in recent years especially in the chemical and pharmaceutical industry [1].

Optically active compounds are active ingredients of many pharmaceuticals, agrochemicals, flavours and fragrances. Indeed the essential components of life itself: proteins, carbohydrates, and other biomolecules are constructed from optically active building blocks. In recent times the increasing awareness of the importance of chirality in the context of biologically activity has stimulated an increasing demand for efficient methods for the industrial synthesis of homochiral compounds.

A number of elegant and impressive asymmetric procedures have been developed [2-4]. However, for industrial production of homochiral compounds methods based on optical resolution are still among the most important and more profitable means [5-7].

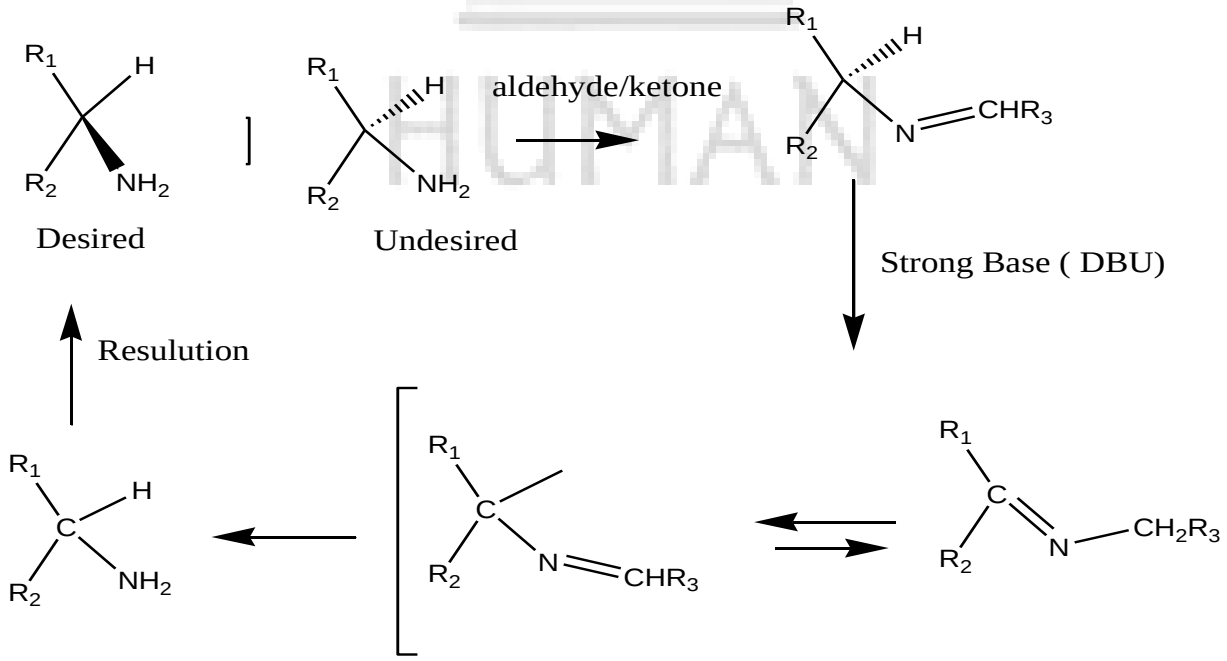
Overall yield of resolution methods can be improved by repeated racemization and resolutions or more elegantly by dynamic resolution or in situ inversion of configuration of the unwanted enantiomer.

Therefore, in order to get the maximum yield during the preparation of chiral amine derivatives and its pharmaceutically acceptable salts, there is a continuous need for the development of a cost-effective and efficient synthetic route by racemization of undesired amine intermediate and recycling it for the preparation of desired intermediates. The racemization of the unwanted -R- isomer is then achieved by addition of a catalytic amount of an aromatic aldehyde/ketone, and an equilibrium of imine is established. The acidity of the alpha proton is thus increased, allowing the chiral center to racemize at ambient temperature and basicity.

Mechanism

Azomethine plays important role by activating alpha proton (H) of asymmetric carbon. Both SN1 and SN2 reactions can invert the chirality of a carbon center. In the case of the SN1 mechanism, departure of a leaving group generates a prochiral intermediate which is then open to nucleophilic attack on either face. If both faces are equally acessible to the nucleophile this will result in racemisation of the molecule. In the case of the SN2 reaction the nucleophile will enter a trigonal bipyramidal intermediate with the molecule. Assuming the nucleophile has the same stereochemical precedence as the leaving group, the stereochemistry will be inverted.

Mechanism



MATERIALS AND METHODS

Racemization of (R)-3-(l-amino-ethyl)phenyl) para toluenesulphonate mandelate

Preparation of 3-(l –Aminoethyl phenyl)-mesylate

50 g of l-(3-hydroxyphenyl)ethyl amine and 200 ml of tert-butanol 24 g of potassium hydroxide was heated at 80°C. The reaction mass was then cooled to room temperature and 50 ml of toluene was added. The reaction mixture was further cooled to 0-5°C and methane sulphonyl chloride solution (52 g dissolved in 100 ml of toluene) was added under stirring at 0- 5°C. The temperature of the reaction mixture was allowed to rise to room tempertaure and stirred at same temperature for 2 hour. Subsequently the reaction mixture was filtered through hyflo bed. The layers were then separated and to the organic layer, 20% (w/v) sodium, hydroxide solution (20 g of sodium hydroxide in 100 ml of water) was added. After separating the aqueous layer, the organic layer was washed with water (4 x 200 ml) and concentrated under reduced pressure at 50-55°C to obtain the title compound as oily mass. Yield: 50 %

Preparation of (S)-3-(l-Ammoethyl)phenyl)-methane sulphonate mandelate

38 g of (+)-mandelic acid and 3-(l-aminoethyl)phenyl)- methane sulphonate was stirred in a mixture of acetone (200 ml) and water (40 ml) at 55-60°C for 30 minutes to obtain a clear solution. The solution was then cooled to room temperature and stirred for another 1 hour and filtered. The solid thus obtained was washed with acetone and dried at 45-50°C to obtain (S)-3-(l-aminoethyl)phenyl)-methanesulphonate mandelate.

The mother liquor obtained was concentrated to dryness under vacuum at 50°C, to obtain a residue that contained (R)-3-(l-amino-ethyl)phenyl) methanesulphonate mandelate.

Preparation of (R)-3-(l -Aminoethvnphenyl-methanesulphonate)

To a solution of (R)-3-(l-aminoethyl)phenyl- methanesulphonate mandelate, (V) (32.0 g) in toluene (160 ml), added water (64 ml). Adjusted the pH of reaction mass between 10-11 by addition of liquor ammonia (14 ml) at room temperature. Stirred the reaction mass for 15 minutes at room temperature and separated the organic layer. Combined the organic layers and

washed with water, distilled out the solvent completely under vacuum at 50-55°C to afford (R)-3-(l- aminoethyl)phenyl-methanesulphonate, as an oil. Yield: 99.4%

Preparation of methanesulfonic acid-3-(l-(benzylidene-aminoethyl phenyl ester)

To a solution of (R)- methanesulfonic acid-3-(l-amino-ethyl)-phenyl ester (20.0 g), in toluene (200 ml), added benzaldehyde (7.75 ml) and p- toluene sulphonic acid (1.3 g). The reaction mass was heated to 110-120°C using Dean- stark apparatus, and stirred at this temperature for 10 hour. The reaction mass after cooling was partitioned between toluene and water. The organic phase was separated, washed with water and evaporated to afford the title compound. Yield: 92.3%

Preparation of racemic methanesulfonie acid-3-[l-(benzylidene-aminoethyl -phenyl ester

methanesulfonic acid-3-[l-(benzylidene-amino)-ethyl]-phenyl ester, was dissolved in toluene (100 ml) at room temperature. To the solution, added l,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.07 ml) and heated the reaction mass to 70-80°C. Stirred the reaction mass at 70°C for 25 hour. Cooled the reaction mass to room temperature and partitioned between toluene and water. The organic layer was separated and concentrated under vacuum at 50-55°C to afford racemic methanesulfonic acid-3-[l-(benzylidene-amino)-ethyl]-phenyl ester as an oil. Yield: 98%

Preparation of racemic 3-(l-Aminoethyl)phenyl)-methanesulphonate

To a solution of methane sulfonic acid-3-[l-(benzylidene-amino)-ethyl]-phenyl ester in toluene, added concentrated hydrochloric acid (75 ml), tetra butyl ammonium bromide (0.22 g) and water (20 ml). The reaction mass was heated to 70-80°C and stirred for 50 hour. Cooled the reaction mass to room temperature and separated the aqueous layer. Washed the aqueous layer with toluene (3 x 40 ml). Adjusted the pH of aqueous layer to 9-10 with 40% sodium hydroxide with prior cooling to 10-15°C. The resulting reaction mass was then partitioned between toluene and water (200 ml). Aqueous layer was then washed with toluene (40 ml). The organic layer was distilled under vacuum at 50-55°C to afford racemic 3-(l- aminoethyl)phenyl)-methane sulphonate as an oil. Yield: 79%.

RESULTS AND DISCUSSION

We envisaged that the possibility of an efficient racemization of (R)-enatiomer would be by the enolisation of unwanted isomer under basic condition and formation of intermediate followed by deprotonation of the enol compound would produce (RS)- 3-(l-aminoethyl)phenyl derivative in good yield

Racemization using Schiff base providing an industrially applicable, cost effective and environment friendly process for the racemization of (R)-3-(l-aminoethyl)phenyl derivative and the use of racemized 3-(l-aminoethyl)phenyl derivative for desired S isomer

Treating the diastereomeric salt of undesired isomer with a base in a solvent to obtain a compound and reacting with an aldehyde (R'CHO) to obtain a compound of Schiff base and treating this compound with a base (DBU) to obtain a racemic compound and finally converting the compound with an acid in a solvent, to obtain racemic compound.

CONCLUSION

We believe that we have developed a novel method for recycling undesired (R)-3-(l-aminoethyl)phenyl derivative. This protocol has made the process of manufacturing (RS)- 3-(l-aminoethyl)phenyl derivative more efficient. Our newly developed method is highly reproducible and suitable for scale up.

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