RESOLUTION OF THE (DL)-CIS-TRANS-2,2-DIMETHYL-3-(2,2- DISUBSTITUTEDVINYL)-CYCLOPROPANE-1- CARBOXYLIC ACID FROM ITS OPTICAL ISOMERS USING CHIRAL AMINES

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Abstract:

The present work relates to a new process for separating the two optical isomers of optically active 2,2-dimethyl-3(2,2-disubstituted vinyl)-cyclopropane carboxylic acid using N-benzyl-d-2-aminobutanol. Thus, the resolving agent for the present work can be prepared from readily available starting materials and also can easily be recovered from the reaction mixture after the resolution reaction in a high yield and further shows excellent resolving effect, and hence, it is a promising resolving agent. Further the resolution process is optimised by using suitable polar solvent to enhance enantiomeric excess. A method of present work, wherein (±)-cis or (±)-trans-cypermethric acid is reacted with a resolving agent; the resultant diastereomer salt is separated from the reaction mixture; the separated diastereomer is treated first with an acid and then with a base to obtain resolving agent. It is accordingly an object of this work to provide a process for optically resolving (±)-trans- cypermethric acid to obtain intended products of high purity in high yield at low costs.

Keywords: Chirality, resolution of drug intermediates, preferential crystallisation, diastereomeric salt formation, enantiomeric excess.

I. INTRODUCTION:

In this present work, the attempts were made to develop an industrially feasible and economical method to separate 1R-trans-cypermethric acid[1]and 1R-cis-cypermethric acid[2], from racemic cis-and trans-cypermethric acid. The above stereo conformer (1R-trans-cypermethric acid) is widely used as pyrethroids insecticide to control indoor environment against flies, mosquitoes and cockroaches whereas 1R-cis-cypermethric acid is used for variety of household pests.

The resolving amine was chosen from commercially available D-2-aminobutanol and it's another isomer L-2-aminobutanol. D-2-aminobutanol was used for the synthesis of ***Ethambutol,*** an anti-tuberculosis drug. Efficient use of these resolving agents (its stoichiometry), recovery and recyclability were attempted. Apart from developing a commercially viable process for optically active acids, we also developed a suitable analytical technique to estimate the Enantiomeric excess of these acids preferably by use of GC instead of use of chiral HPLC.

Several processes of obtaining an optically active product of dl-cis or trans Cypermethric acid are known by using different resolving agents such as D-menthol[3], R-phenylglycine ethyl ester[4], D-N-benzyl-2 aminobutanol[5], D-or L-N-methyl ephedrine[6], 1-(p-tolyl) ethylamine[7].

A major setback of the reported methods is that pure cis and trans isomers can only be obtained by several recrystallisation with high losses of material. Another disadvantage of these processes is the use of expensive resolving agents and costly accomplishments suitable only for the separation of either one of the racemates of enantiomers. Optical purity of the enantiomer, was increased by repeated recrystallisation which is expensive process causing high material loss, the recovery of the resolving agent is not so far reported. Also, the yield is not very high and the process is expensive. Whereas major disadvantage of previous resolution done using ephedrine[8] is narcotic which is not readily available in India. Hence, ephedrine is not recommended as resolving agent.

This work is based on the recognition that the enantiomeric N-benzyl-2 amino butanol is useful for the separation of the enantiomers from an isomeric mixture containing the cyclopropane carboxylic acids of thedl–cis-trans-2,2-dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid. The main part of the process is that resolving agent used is remarkably useful for the separation of the optical isomers of dl trans cypermethric acid.

The major advantage of this method is the resolution of each racemate is accomplished in aqueous solutions under nearly identical conditions. Thus, this method is more simple, versatile and efficient than the processes known so far.

II. MATERIALS AND METHODS:

***Chemicals*:**

All chemicals used were of AR grade. All reagents and solvents were commercially available and used as supplied. High trans and high cis–cypermethric acid were bought from Himani Industries Ltd. These were used to prepare Transfluthrin and Deltamethrin respectively. L-menthol was bought from Lobo Chem. Industries Pvt. Ltd.

Method:

The resolving agents N-benzyl-D-2-aminobutanol and N-benzyl-l -2-aminobutanol were prepared and then used to separate cis-cypermethric acid and trans-cypermethric acid to get optically pure isomer as required for Deltamethrin[9]and Transfluthrin[9] respectively. Both the resolved optically active acids were analysed by derivatizing with suitable chiral auxiliary, so that we could analyse it using GC instead of chiral HPLC.

III. EXPERIMENTAL:

A. Preparation of d-N-benzyl -2-aminobutanol:

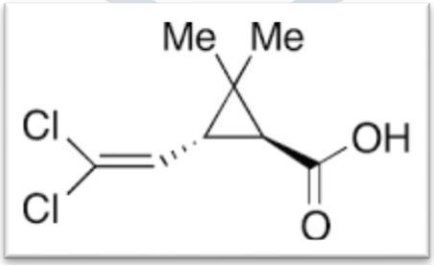
Methanolic solution of D-2-aminobutanol (44.5 gm) was taken in round bottom flask and benzaldehyde (54.5 gm) was added slowly with constant stirring for one hour. The reaction mixture was stirred continuously for at least two hours by keeping temperature below 30^0C. Then the reaction mixture is cooled in ice bath and brought to 0^0C. Then sodium borohydrate (23.75gm) was added slowly with constant stirring for next five hours which is further equilibrated for half an hour. Then methanol was distilled out under reduced pressure at 40^0C till the reaction mass remains in stirrable slurry form which was then cooled to 30^0C, then added 800 ml water and it was further stirred for next two hours and filtered and then washed twice with water. Dried in oven at 45^0C

B. Preparation of L-N-benzyl -2-aminobutanol:

Methanolic solution of L-2-aminobutanol (44.5 gm) was taken in round bottom flask and benzaldehyde (54.5 gm) was added slowly with constant stirring for one hour. The reaction mixture was stirred continuously for at least two hours by keeping temperature below 30^0C. Then the reaction mixture is cooled in ice bath and brought to 0^0C. Then sodium borohydrate (23.75gm) was added slowly with constant stirring for next five hours which is further equilibrated for half an hour. Then methanol was distilled out under reduced pressure at 40^0C till the reaction mass remains in stirrable slurry form which was then cooled to 30^0C, then added 800 ml water and it was further stirred for next two hours and filtered and then washed twice with water. Dried in oven at 45^0C.

Procedure for the resolution of the dl–cis-trans-2,2-dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid from its optical Isomers:

The present work discussed here exemplifies the use of salts [10,11]of chiral amines as resolving agent for resolving the optical isomers of dl–cis-trans-2,2-dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid as follows:



The procedure is divided in four parts as follows:

A. Preparation of sodium salt of the dl–cis-trans-2, 2-dimethyl-3-(2, 2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid:

1M of aqueous high trans-cypermethric acid (TCMA) from racemic mixture of cis & trans-CMA was taken in a round bottom flask and then caustic lye (8.87ml) was added at 35^0C with continuous stirring till clear solution of trans-cypermethric acid is obtained. The reaction mixture was stirred for 10 more minutes. Temperature rises as reaction was exothermic (Temp=40^0C). Reaction mass of trans-cypermethric acid becomes clear solution because ***Na-salt*** was prepared.

B. Addition of RA-HCl solution to form diastereomeric salt:

An aqueous solution of d-N-benzyl-2-aminobutanol (0.5M) was taken in a beaker to which conc. HCl was added till it becomes acidic. Then this RA-HCl solution was added to the above reaction mixture with continuous stirring and heating over a period of one hour. The reaction mixture was allowed to cool for next two hours with continuous stirring at room temperature. It was then filtered and washed with water.

C. Resolution of acid using resolving amine:

Filtrate of above reaction mixture was acidified with conc. HCl (10N) to p^H=1 at 50^0C to 60^0C and the product obtained was filtered and dried in oven which was derivatized [12]and the purity of isomer was checked by GC.

The purity of the **1-S-TRANS CMA = 81.82 %**

Above diastereomeric salt (B) is acidified with 10N HCl, slurry of the cake obtained was filtered. Resulting cake was washed with 5 ml water twice. Caustic lye was added in the filtrate to isolate resolving agent. The resultant cake is derivatized to isolate geometrical isomers.

The purity of isomers obtained as follows: **0.29% CIS CMA & 99.70 % TRANS CMA.**

The resolved trans CMA was derivatized to isolate optical isomers as follows:

1-R-TRANS- CMA = 83.98 % & 1-S- TRANS CMA= 16.01 %

M.P. of 1-R-TRANS- CMA = 73^0 -75^0C.

D. Resolution of TRANS-CMA by using l-N-Benzyl-2-amino butanol:

The procedure described here for the resolution of trans-CMA by using d-N-Benzyl-2-amino butanol was followed except that resolving agent used was l-N-Benzyl-2-amino butanol. The resultant cake was derivatized to isolate geometrical isomers as follows:

0.15% CIS CMA & 99.84 % TRANS CMA.

The resultant cake was derivatized to isolate optical isomers as follows:

1-R-TRANS- CMA = 47.53 % & 1-S- TRANS CMA= 51.80 %

M.P. of 1-S -TRANS- CMA = 73^0 -75^0 C

- The above procedure was repeated for the stoichiometric proportion of

1M TRANS CMA: 1M d-N-Benzyl-2-amino butanol and 1M TRANS CMA: 1M l-N-Benzyl-2-amino butanol

- The above procedure was repeated for the stoichiometric proportion of CIS-CMA

1M CIS CMA: 1M d-N-Benzyl-2-amino butanol and 1M CIS CMA: 1M l-N-Benzyl-2-amino butanol

Optimizing the method of resolution to enhance enantiomeric excess:

An aqueous solution of the resolving agent of d-N-benzyl-2-aminobutanol (0.5M) was added to an aqueous solution of Na-salt of ***trans-CMA***(1M) over a period of 3 to 4 hours at 50^0-to 60^0c at neutral pH then the reaction mass was filtered and small portion of it was acidified with conc. HCl (10N). Heating and stirring continued for next 3 hours. Slurry cooled at room temp & filtered. This crude cake was dried in oven and derivatized to check purity of optical isomers.

Optical purity of resolved isomer of trans-CMA: ***1-R-trans-CMA = 89.75 %***

Balance crude cake was refluxed in acetone about 2 hours at 45^0C, the slurry obtained was cooled to room temp and then filtered. The small portion of cake so obtained was again acidified with conc. HCl. Temp was maintained between 50^0C to 60^0C and pH$\leq$2, then the slurry obtained was cooled to room temp and filtered. This first purified cake was dried in oven and derivatized to check optical purity of resolved isomer of the trans-CMA.

Optical purity of resolved isomer i.e. ***1-R-trans-CMA after first purification was 96.06%***

Balance first purified cake was again refluxed in **acetone** about 2 hours at 40^0-50^0C, the slurry obtained was cooled to room temp and filtered. This second purified cake was dried in oven and derivatized to check optical purity of resolved isomer of the trans-CMA.

Optical purity of resolved isomer i.e.***1-R-trans-CMA after second purification was 98.06%***

IV. RESULTS AND DISCUSSION:

Aim of Expt	No. of moles Of acid	Resolving agent	No. of moles of Resolving agent	Analysis	
				1-S-TCMA %	1-R-TCMA %
Resolution of TCMA	1M	d-N-benzyl-2-aminobutanol	0.5 M	16.01	83.98
Resolution of TCMA	1M	l-N-benzyl-2-aminobutanol	0.5M	51.80	47.53
Resolution of TCMA	1M	d-N-benzyl-2-aminobutanol	1M	50.53	48.75
Resolution of TCMA	1M	l-N-benzyl-2-aminobutanol	1M	59.82	40.17
Resolution of CIS-CMA	1M	d-N-benzyl-2-aminobutanol	0.5 M	46.23	51.24
Resolution of CIS-CMA	1M	l-N-benzyl-2-aminobutanol	0.5 M	55.43	44.30
Resolution of CIS-CMA	1M	d-N-benzyl-2-aminobutanol	1M	50.98	48.47
Resolution of CIS-CMA	1M	l-N-benzyl-2-aminobutanol	1M	52.62	46.50

d-N-benzyl-2- amino butanol works to resolve trans-CMA (83.98 % 1-R-TCMA and 16.01 % 1-S-TCMA). Therefore, process needs to be further optimized to enhance the optical purity of enantiomers. It is obtained by acetone purification method. The results of which are tabulated as follows:

	1-R-TCMA (%)	1-S -TCMA (%)
Crude product	89.75	10.24
First purification	96.06	3.92
Second purification	98.06	1.93

After repeating the procedure several times, samples of both enantiomers in high enantiomeric excess could be obtained. A second recrystallisation produced R-rich enantiomer. (enantiomeric excess =98 %)

V. CONCLUSION:

- When d-N-benzyl-2-aminobutanol is used as resolving agent, the diastereomeric salt of the following acid crystallises out from the solution:

R trans isomer by resolving racemic mixture of trans cypermethric acid.

- When l-N-benzyl-2-aminobutanol is used as resolving agent, the appropriate opposite antipode crystallises out in all cases.

- CIS-CMA can't be resolved by using either d-N-benzyl-2-aminobutanol or l-N-benzyl-2-aminobutanol since enantiomeric excess (measure of optical purity) of their acid preferably by the use of GC is 50 – 50 %

VI. ACKNOWLEDGEMENT:

We would like to thank Dr. Dhanjay Rane (Director, Alchem Synthon) for providing me all the necessary instrumentation facilities & their technical support without whom we wouldn't be able to complete our project. It also gives me immense pleasure to thank group of Alchem Synthon for guidance. We also thank to the Principal & Head, Department of chemistry, Ramnarain Ruia Autonomous college for their co-operation & support.

VII. REFERENCES:

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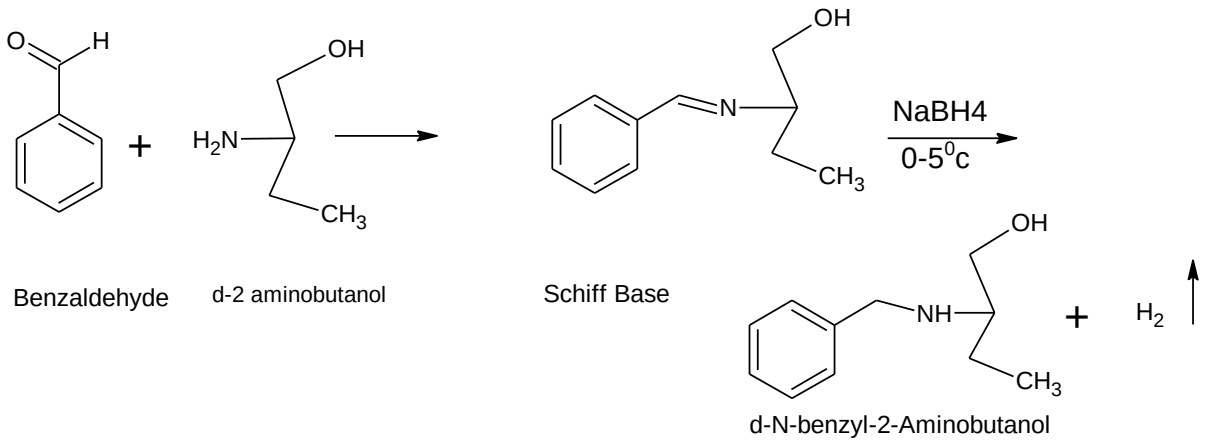
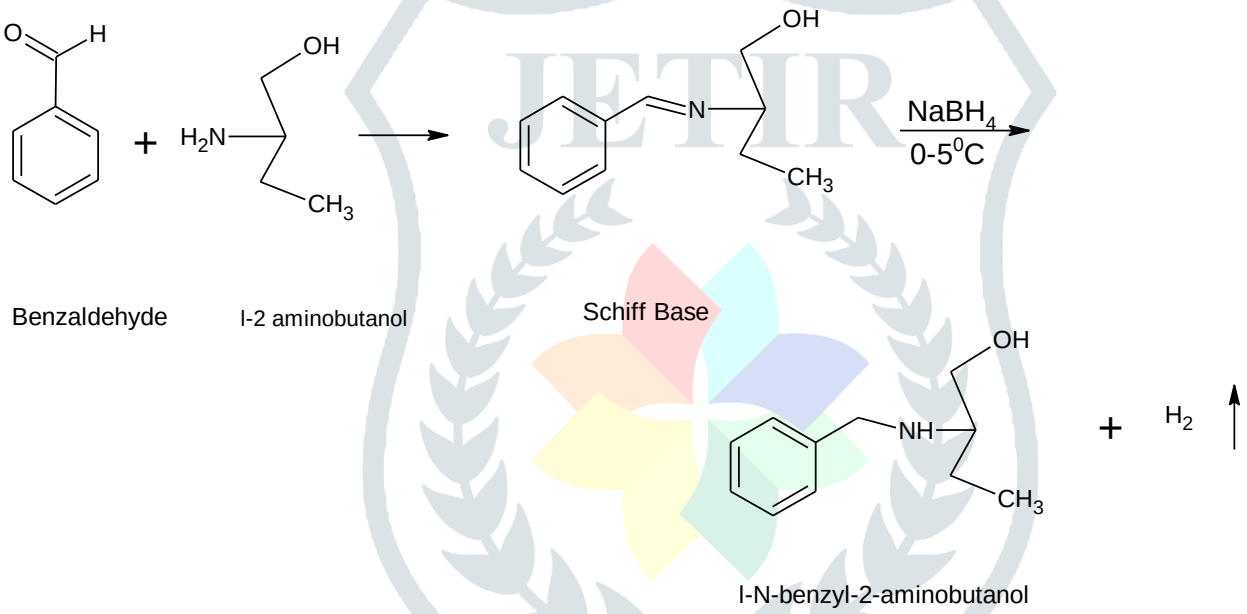
VIII. GRAPHICAL ABSTRACT:

Synthesis of d-N-benzyl-2-aminobutanol and l-N-benzyl-2-aminobutanol:



Benzaldehyde d-2 aminobutanol Schiff Base

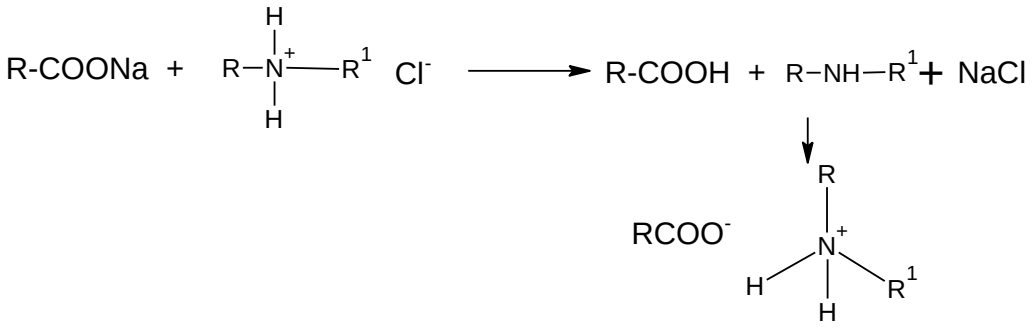
d-N-benzyl-2-Aminobutanol

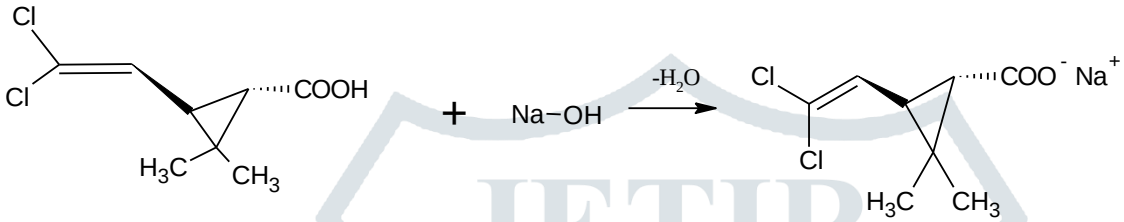


Benzaldehyde l-2 aminobutanol Schiff Base

l-N-benzyl-2-aminobutanol

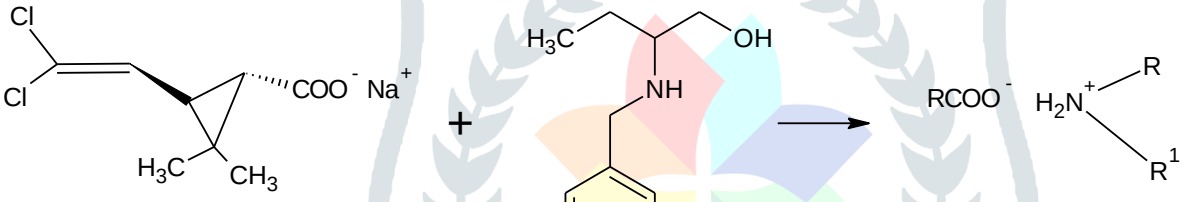
Resolution of cypermethric acid:





Trans-Cypermethric acid

Sodium salt of CMA



sodium salt of CMA

N-benzyl -d-2-aminobutanol

Amino carboxylate ion pair