



Process for The Separation of the (DI) Cis-Trans-2, 2-Dimethyl-3-(2, 2-Disubstitutedvinyl)-Cyclopropane-1-Carboxylic Acid from Its Optical Isomers

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Received: 12 Oct 2018 / Accepted: 6 Nov 2018 / Published online: 1 Jan 2019

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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 R-N-(1-naphthylmethyl)- α -methyl benzyl amine and its enantiomer S-N-(1-naphthylmethyl)- α -methyl benzyl amine. Thus, the resolving agent of the present work can be prepared and also can 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 non-polar solvent to enhance enantiomeric excess. A method of present invention, wherein (\pm)-cis or (\pm)-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 a base and then with an acid to obtain resolving agent. It is accordingly an object of the proposed work to provide a process for optically resolving (\pm)-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.

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 later 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 would be chosen from synthesized R-N-(1-naphthylmethyl)- α -methyl benzyl amine and its other isomer S-N-(1-naphthylmethyl)- α -methyl benzyl amine, key raw material for manufacturing Captopril [3]. Captopril is used to

treat hypertension, heart failure and to improve survival after a heart attack. (the optically active amine is useful in the optical resolution of DL-3-acylthio-2-methylpropanoic acid wherein acyl is acetyl or benzoyl. The optically active D-(+)-3-acylthio-2-methylpropanoic acids are used as intermediates for preparing antihypertensive agents, such as Captopril).

Efficient use of these resolving agents (its stoichiometry), recovery and re-cyclability would be attempted. Apart from developing a commercially viable process for optically active acids, we would also develop a suitable analytical technique to estimate the Enantiomeric excess of these acids preferably by use of GLC 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 [4], R-phenylglycine ethyl ester [5], D-N-benzyl-2-aminobutanol[6], D-or L-N-methyl ephedrine⁷, 1-(p-tolyl) ethylamine[8].

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 expensive process is 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. The major disadvantage of previous resolution done using ephedrine is narcotic which is not readily available in India commercially. Hence, ephedrine is not recommended as resolving agent.

A drawback of the methods mentioned above is that pure cis and trans isomers can only be obtained by several recrystallisation and thus with high losses of material. Another disadvantage of these processes is in the use of expensive resolving agents and costly accomplishments suitable only for the separation of either one of the racemates or of the cis or trans pair of enantiomers. For increasing the optical purity of the enantiomer, recrystallisation is used which is expensive process causing high material loss, the recovery of the resolving agent is not published. Also, the yield of optically active cis or trans cypermethric acid obtained by resolution is not very high, thus leading to the problem that the optically active trans or cis cypermethric acid is expensive.

This work is based on the recognition that R-N- (1-naphthylmethyl)- \ propto -methyl benzyl amine and

it's other isomer S-N- (1-naphthylmethyl)- \ propto -methyl benzyl amine were useful for the separation of the enantiomers from an isomeric mixture containing the cyclopropane carboxylic acids of the dl-cis-trans-2, 2-dimethyl-3-(2, 2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid in any ratio. A main part of our process also consists in the observation that resolving agent used by us is remarkably useful for the separation of the optical isomers of the pure dl trans cypermethric acid.

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

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 was bought from Himani Industries Ltd. These were used to prepare Transfluthrin and Deltamethrin respectively. 1-Chloro Methyl Naphthalene was bought from Benzo chem Industries Pvt. Ltd. R (+) Alpha Methyl Benzyl Amine and S (-) Alpha Methyl Benzyl Amine were bought from R.L. chemical Industries Pvt. Ltd. L-menthol was bought from Lobo chem. Industries Pvt. Ltd.

Method:

We prepared first both resolving compound i.e. R-N- (1-naphthylmethyl)- α -methyl benzyl amine (key raw material for manufacturing Captopril, an anti-hypertensive drug) and it's another isomer S-N-(1-naphthylmethyl)- α -methyl benzyl amine. Later, we used these resolving amines to separate Cis-cypermethric acid and trans- cypermethric acid to get optically pure isomer as required for Deltamethrin⁹ and Transfluthrin⁹ respectively. We analysed these prepared optically active acids by derivarizing it with suitable chiral auxiliary, so that we could analyze it is using GLC instead of chiral HPLC.

Experimental:

A. Preparation of R-N-(1-naphthylmethyl)- α -methyl benzyl amine

- Dimethyl formamide (500 ml) was charged in a one litre, four necked round bottom flasks to which K₂CO₃ (214.21 gm) was added with stirring at room temperature(24°C) and then added R-(+) Alpha Methyl Benzyl Amine (122 gm). Since the reaction was exothermic, temperature rises to 30°C. Then added 1-Chloromethyl

Naphthalene (176.64 gm) within 1 to 1.5 hours. This reaction mass was heated to 43⁰ to 45⁰C and maintained the temperature for 12 to 16 hours. Reaction was completed when Naphthalene chloride was less than 0.5%. Then the sample was drawn, filtered and filtrate was analysed on GLC.

• **Filtration of inorganic content:**

After completion of reaction, above reaction mass was cooled to 28 to 30⁰C. Reaction mass was filtered using Buchner funnel under mild vacuum and cake was washed with DMF and sucked till dryness. This filtrate was taken for DMF recovery and product isolation. Then concentrated the filtrate + washings under vacuum below 90⁰C. To bottom layer added methylene dichloride and washed the organic layer with water to remove DMF and soluble inorganics. At the end concentrated MDC layer under vacuum till liquid temperature becomes 80-85⁰ C and 10 mm.

• **Preparation of S-N-(1-naphthylmethyl)- α -methyl benzyl amine**

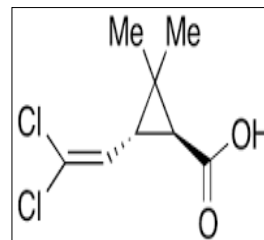
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Procedure for the resolution of the dl -cis-trans-2,2-dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid from its optical isomers:

The invention described here exemplifies the use of salts [11,12] of chiral amines as resolving agents for resolving the optical isomers of dl -cis-trans-2,2-dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropane-1-carboxylic acid.



The procedure is divided in five parts as follows to enhance the enantiomeric excess.

A. Preparation of distereomeric salt of the said acid:

20.9 gm of high trans cypermethic acid (CMA) from racemic mixture of cis & trans CMA was taken in a round bottom flask to which 40ml hexane + R-N-(1-naphthylmethyl)- α -methyl benzyl amine 13.05 gm was added at room temp. The reaction mass was stirred for four hours at room temp. Slurry filtered and cake was washed with hexane (2 \times 20 ml). This crude cake was oven dry.

B. Reflux process:

The crude cake was refluxed in hexane at a temp 60⁰ to 70⁰C, cooled to room temp and filtered. Thus, the crude was partly purified which was further subjected to purification processes.

C. Basification process of crude cake:

The crude cake on a small scale was basified by 1N NaOH and also added 15 ml hexane at a temp between 30⁰ to 40⁰ C. The two layers were separated. The organic layer contains amine. So, it was kept aside. An aqueous layer was acidified with 10N HCl till pH becomes full acidic. Solids were filtered and derivatized to check purity of optical isomers of Trans CMA with the help of GLC. Optical purity of resolved isomer of the said acid from crude cake:

1-R-TRANS CMA=70.15%

D. First purification process:

The partly purified cake was basified by 1N NaOH (70 ml) and also added 15 ml hexane at a temp between 30⁰ to 40⁰ C. The two layers were separated. The organic layer

contains amine. So, it was kept aside. An aqueous layer was acidified with 10N HCl till P^H becomes full acidic. Solids were filtered and derivatized to check purity of optical isomers of Trans CMA with the help of GLC. Optical purity of resolved isomer of the said acid from first purified cake =

1-R-TRANS CMA=79.44 %

Second purification process:

The first purified cake was basified by 1N NaOH (20 ml) and also added 15 ml hexane at a temp between 30° to 40° C. The two layers were separated. The organic layer contains amine. So, it was kept aside. An aqueous layer was acidified with 10N HCl till P^H becomes full acidic. Solids were filtered and derivatized to check purity of optical isomers of Trans CMA with the help of GLC.

Optical purity of resolved isomer of the said acid from second purified cake =

1-R-TRANS CMA=94.45 %

Resolution of TRANS-CMA by using S-N-(1-naphthylmethyl)- α -methyl benzyl amine:

The procedure described here for the resolution of TRANS-CMA by using R-N-(1-naphthylmethyl)- α -

methyl benzyl amine was repeated except that resolving agent used was S-N-(1-naphthylmethyl)- α -methyl benzyl amine.

- Optical purity of resolved isomer of the said acid from crude cake:

1-S-TRANS CMA=71.07%

- Optical purity of resolved isomer of the said acid from first purified cake =

1-S-TRANS CMA=87.74 %

- Optical purity of resolved isomer of the said acid from second purified cake =

1-S-TRANS CMA=93.60 %

RESULTS AND DISCUSSION

R-N-(1-naphthylmethyl)- α -methyl benzyl amine and S-N-(1-naphthylmethyl)- α -methyl benzyl amine works to resolve trans-CMA. Therefore, process needs to be further optimized to enhance the optical purity of enantiomers. It is obtained by non-polar solvent like hexane. The results of which are tabulated as follows:

Resolution of Trans CMA by R-N-(1-naphthylmethyl)- α -methyl benzyl amine:

	1-R-TCMA (%)	1-S-TCMA (%)
Crude cake:	70.15	29.84
First purified cake	79.44	20.55
Second purified cake	94.45	5.54

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 =94%)

Resolution of Trans CMA by S-N-(1-naphthylmethyl)- α -methyl benzyl amine:

	1-R-TCMA (%)	1-S-TCMA (%)
Crude cake:	28.93	71.07
First purified cake	12.25	87.74
Second purified cake	6.49	93.60

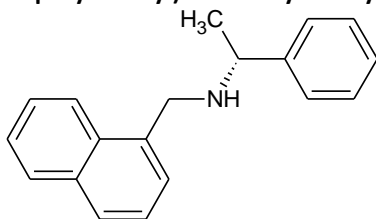
After repeating the procedure several times, samples of both enantiomers in high enantiomeric excess could be obtained. A second recrystallisation produced S-rich enantiomer. (enantiomeric excess =93%)

CONCLUSION:

- When R-N-(1-naphthylmethyl)- α -methyl benzyl amine is used as resolving agent, the distereomeric salt of the following acid crystallises out from the solution: R Trans isomer by resolving racemic mixture of Trans cypermethic acid.

- When S-N-(1-naphthylmethyl)- α -methyl benzyl amine is used as resolving agent, the appropriate opposite antipode crystallises out in all cases.
- CIS-CMA can't be resolved by using either R-N-(1-naphthylmethyl)- α -methyl benzyl amine or S-N-(1-naphthylmethyl)- α -methyl benzyl amine since solids of distereomeric salts are not obtained at -10 °C.
- The characterization of R-N-(1-naphthylmethyl)- α -methyl benzyl amine and S-N-(1-naphthylmethyl)- α -methyl benzyl was confirmed by spectroscopic studies like IR, 1H NMR and ^{13}C NMR. On the basis of this data following structure has been established.

R-N-(1-naphthylmethyl)- α -methyl benzyl amine



(1R)-N-(1-Naphthylmethyl)-1-phenylethanamine

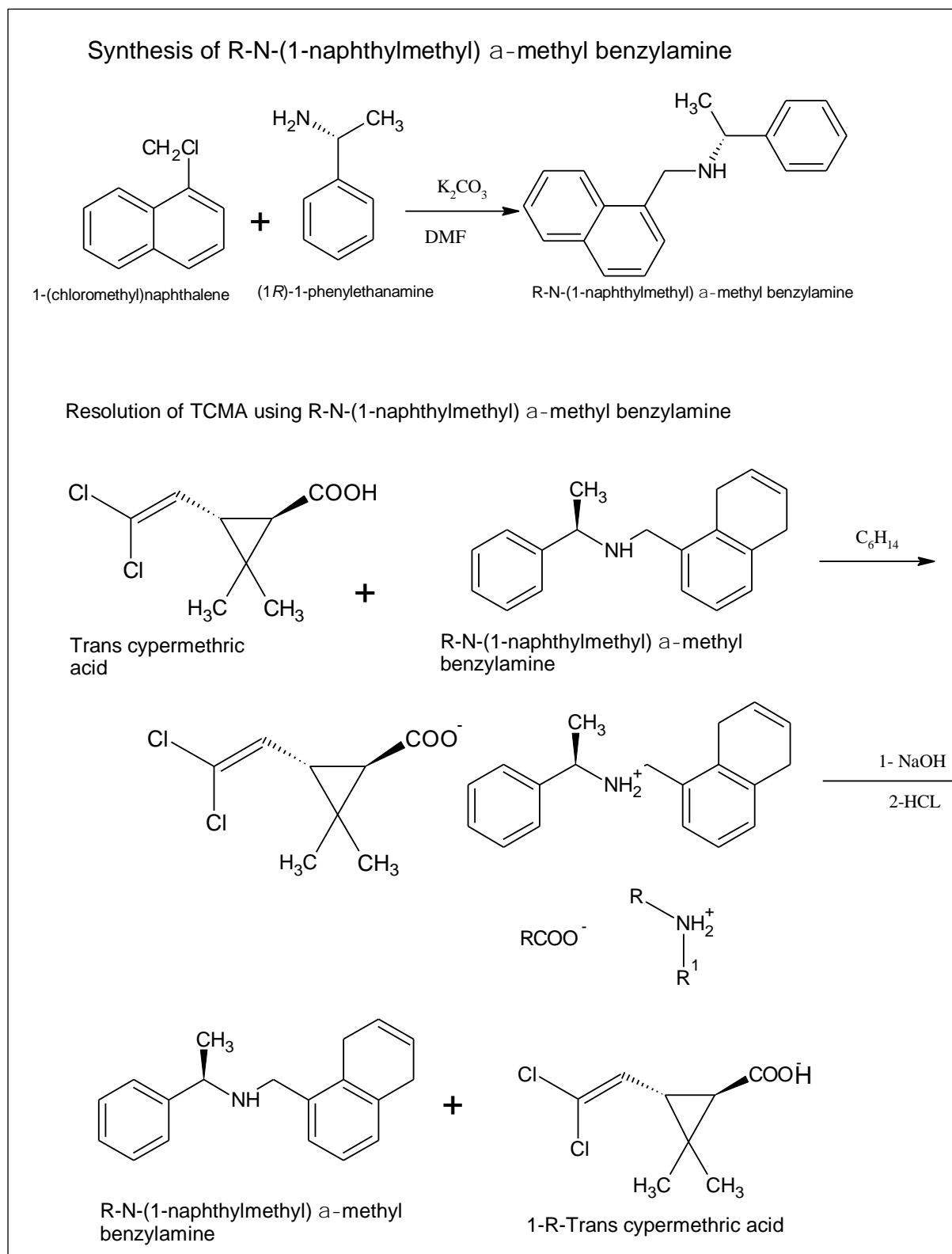
ACKNOWLEDGEMENT

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

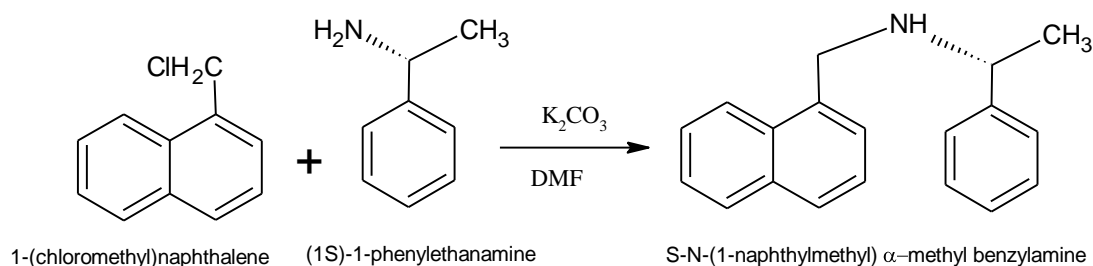
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Graphical abstract



Synthesis of S-N-(1-naphthylmethyl) α -methyl benzylamine



Resolution of TCMA using S-N-(1-naphthylmethyl) α -methyl benzylamine

