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EFFICIENT SCALABLE APPROACH FOR CLOPIDOGREL BISULFATE THROUGH PREFERENTIAL CRYSTALLIZATION OF(±)-2-(2-CHLOROPHENYL)-(6,7-DIHYDRO-4H-THIENO[3,2,C]PYRIDINE-5-YL-ACETAMIDE.

[1]M. M. V. Ramana* and [1]Rajesh K. Rao.

Department of Chemistry, University of Mumbai, Vidyanagari,Santacruz (East), Mumbai, 400098, India.

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***Correspondence for Author**
M. M. V. Ramana
Department of Chemistry, University of Mumbai, Vidyanagari,Santacruz (East), Mumbai, 400098, India.

ABSTRACT

The present work deals with the efficient synthesis of Clopidogrel Bisulfate (Generic name : Plavix by Sanofi) through resolution of an important precursor (±) -2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide by preferential crystallization. This compound was synthesized in its racemic form as per the known process and was resolved by preferential crystallization. These efforts led to a successful isolation of enantiomerically pure isomers of (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide.

KEYWORDS: Clopidogrel Bisulfate, Preferential Crystallization, Racemic compound, Conglomerate, Racemization.

INTRODUCTION

Thrombosis is a process involving aggregation of platelets, resulting in blood coagulation, which may form blood clot in the vasculature. Generic drug Clopidogrel Bisulfate's (IV) (Figure 1) is an antithrombotic drug patented by Sanofi (France) and marketed as Plavix [1, 2]. This drug inhibits aggregation of platelets acts as a blood thinner. Intake of Clopidogrel Bisulfate controls adenosine diphosphate a platelet activator[3]. This generic drug is marketed worldwide in more than 110 countries with a sale of $6.6 billion in 2009 and may continue to grow by at least 20%. US FDA has extended the patent protection for six month exclusivity, which expired on May 2012[4]. Generic version of the drug has already hit the market. Racemic (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide (I)

(Figure 1)[1, 2] is an important intermediate used in the synthesis of Clopidogrel Bisulfate. Presently this intermediate is resolved by using conventional method[1,2], Direct Crystallization[5], Chromatographic resolution[6,7], Kinetic resolution[7] and Resolution by diastereomer formation, are well established over a period of time[7-8]. We have recently reported that (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide (I) is a conglomerate and was successfully resolved by Direct Crystallization[5], which is a batch process. In spite of the usefulness, these methods are less efficient and may have a disadvantage in bulk scale operations. Separation of enantiomers by Preferential Crystallization of conglomerates is well reported in literature[9 – 12]. The method of resolution by crystallization has been successful for most of the amino acid derivatives such as ethyl amine salt of Naproxen[13], hydroxyl acid intermediate of Diltiazem after N-acetylation[14], threo-chloramphenicol base[15], S-methyl DOPA[6] and glutamic acid[16]`. These are few examples in the history of drug synthesis at commercial scale application. This approach if implemented will have a great impact on the cost of chiral life saving drugs.

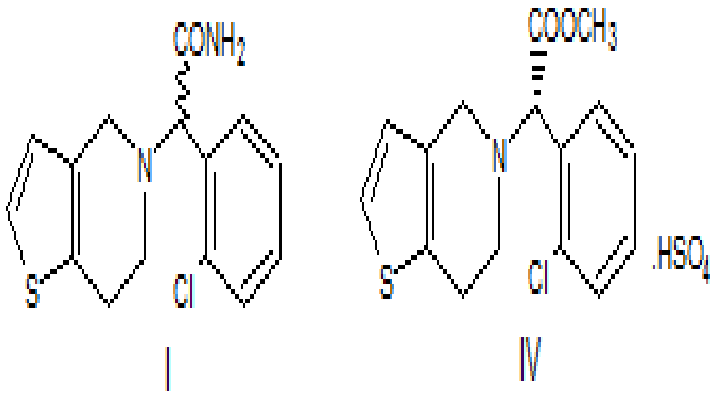


Fig 1. Clopidogrel Bisulfate's precursor–I, Clopidogrel Bisulfate-IV.

MATERIALS AND METHODS

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Melting points were measured on Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured using a sodium D line on Jasco DIP 370. IR spectra were recorded on Shimadzu FTIR-IR-4200 spectrophotometer in KBr discs. Chiral HPLC analysis was carried out on a Perkin Elmer 2000 series Chiral AGP : 100mm X 4mm. packing 5micron scanned at 215nm.

Resolution of (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno [3, 2-c] pyrid-5-yl)-acetamide (I) by Preferential Crystallization

Compound I (20 gm, 0.648 mole) was taken in 2-propyl alcohol (100ml) and heated to 60 - 70ºC under stirring for 1 hr. The solution was filtered hot through filter bed. The reaction mass was gradually cooled to 35 - 40ºC under stirring at low speed. Compound III (0.2 gm) was added[17, 18, 19] as a seed under stirring. Stirring was continued for 90 minutes at ambient temperature. The solid on filtration afforded compound III, (3.90gm, yield : 19.5%), m.p.144 - 146ºC, ($^{25}[\alpha]_D$ +26º, c=1, methanol).

The mother liquor or the filtrate is preserved for the isolation of compound II. After separation of compound III, compound I (3.90gm) was added along with 2-propyl alcohol (20ml) to the above preserved mother liquor, in order to prepare solution of the same volume as in the previous stage. It was heated at 60 - 70ºC under stirring for 1 hr. The solution was filtered hot through filter bed. The reaction mass was gradually cooled to 35 - 40ºC under stirring at low speed. Seed of compound II (0.2gm) was added[17, 18, 19] and stirred for 90 minutes at the same temperature. The solid on filtration afforded crude compound II, (3.70gm, yield : 18.5%), m.p.138 - 144ºC, $^{25}[\alpha]_D$ -22º, c=1, methanol.

The mother liquor or the filtrate is preserved for the isolation of compound III.The above steps were repeated alternatively to get crude compounds II and III respectively, thus making it a continuous process. The crude compounds II and III obtained in the above separation were combined separately and crystallized separately in 2-propyl alcohol to afford compound II (yield : 85%), m.p.151 - 153ºC, (lit[1, 2]. m.p.152 - 155ºC), $^{25}[\alpha]_D$ +39º, c=1, methanol, (lit[1, 2]. $^{25}[\alpha]_D$ +40º, c=1, methanol), Chiral HPLC purity, 99.44%, and compound III (yield : 87%), m.p.151 - 153ºC, (lit[, 2]. m.p.152 - 155ºC), $^{25}[\alpha]_D$ -38º, c=1, methanol, (lit[1, 2]. $^{25}[\alpha]_D$ -40º, c=1, methanol).

RESULTS AND DISCUSSION

Recently we reported Direct Crystallization of (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide (I)[5], which involved batch cycle and has scalable issues with high volume product. In order to overcome this limitation, Preferential Crystallization of (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2,c]pyridine-5-yl-acetamide (I) was carried out in 2-propanol and was succesful. The process sequence is depicted in Figure 2, which afforded compounds II and III from compound I. Clopidogrel

Bisulfate is high volume product. This being a continuous process will have a commercial implication in the synthesis of Clopidogrel Bisulfate production.

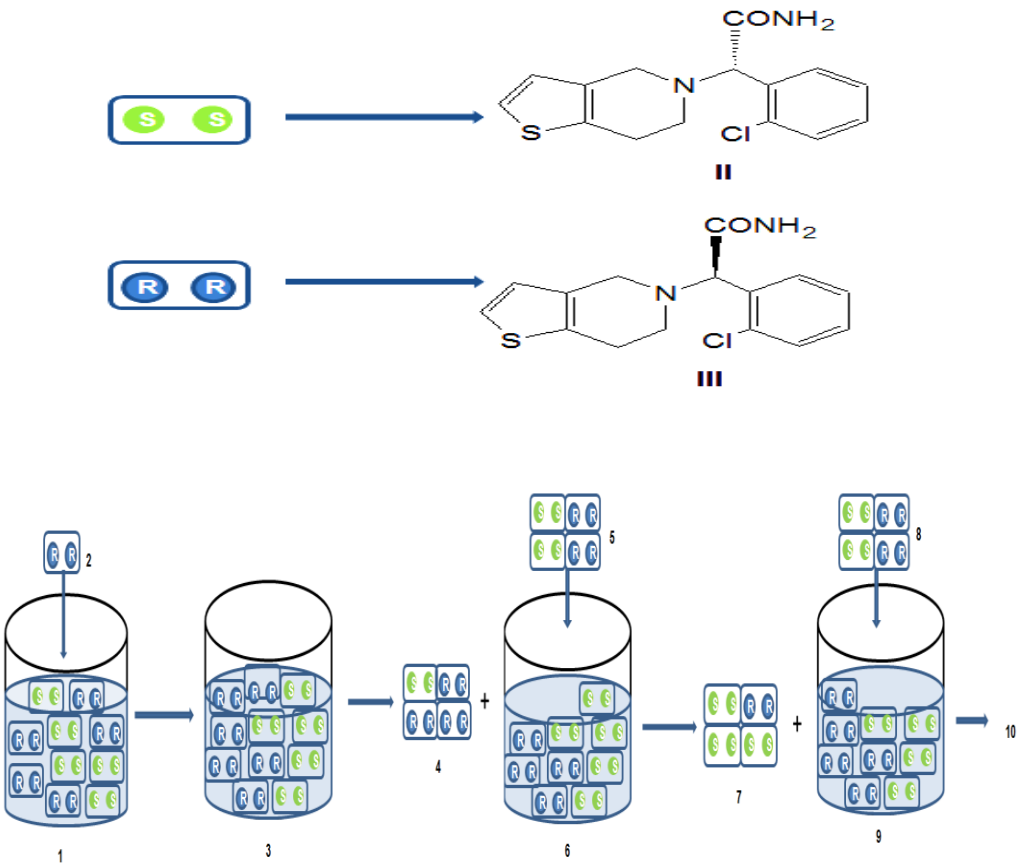
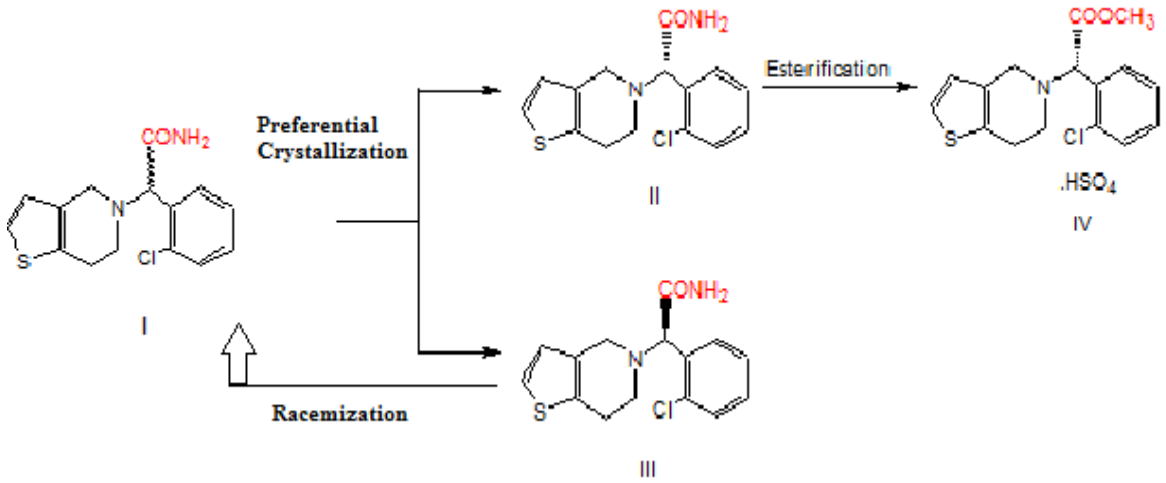


Fig 2. 1- Conglomerate compound I dissolved in solvent at elevated temperature. 2- Seed of pure compound III added to the saturated solution for crystal growth at ambient temperature. 3- Saturated solution with seed of pure compound III at ambient temperature. 4- First crop of crude compound III collected by filtration. 5- compound I added to the first filtrate, approximately equal in amount to the solid filtered out in step 4. 6- The filtrate was heated to get clear solution. 7- crude compound II collected by filtration on cooling. 8. compound I added to the second filtrate, approximately equal in amount to the solid isolated in step 7. 9- Second filtrate heated to get clear solution. 10. The steps 3 to 8 are repeated to get compounds II and III in crude form.

Preferential crystallization for compound I will work best, as the chiral entity is of low value and high volume and the manufacturing process becomes continuous. The process requires seeding only once, that is during the start of reaction. However we have continued with the addition of seed as explained in experimental section. The results generated are slightly better

than without the addition of given seed [20]. It is also significant to note that compound III could be racemised to compound I by treatment with sodium hydroxide (Scheme 1)[17, 18, 19], hence the unwanted enantiomer that is compound III after conversion to compound I can be further subjected to preferential crystallization to afford compound II at a higher yield than the conventional methods. The compound II has been converted to Clopidogrel Bisulfate in a single step[18, 19]. This in-turn is a formal synthesis of Clopidogrel Bisulfate.



Scheme 1. Formal Synthesis Of Clopidogrel Bisulfate involving Preferential Crystallization and Racemization.

CONCLUSION

It was for the first time an important drug intermediate (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno [3, 2-c] pyrid-5-yl-acetamide (I) of Clopidogrel bisulfate has been resolved successfully by preferential crystallization to afford (+)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno [3, 2-c] pyrid-5-yl-acetamide (II) and (-)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno [3, 2-c] pyrid-5-yl-acetamide (III) in reasonable chemical yield with excellent optical purity.

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REFERENCES

1. Auber D, Ferrand C, Jean-Pierre M : (Sanofi Syntholab), US Patent 4529596, 1985.
2. Jean-Marc H, Daniel F, Andre B, Alain B, Pierre S, Denis D, Gilles K, Ghislain D, Jean-Pierre M: (Sanofi Elf.), US Patent 5576328, 1996.
3. Li JJ, Sliskovis DR, Roth BD : Contemporary Drug Synthesis, Wiley Int. Sci. 2004; 1–10.
4. Walsh S : FDA Approves Generic Version of Thinner Plavix, 17 May 2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm304489.htm.
5. Ramana MMV and Rajesh RK : Int. J. Pharm. Sci. Rev. Res., 2014; 24(2) : 271 – 275.
6. Eliel EL, Samuel HW : Stereochemistry Of Organic Compounds, Wiley Int. Sci. 1994; 297.
7. Sheldon RA : Specialty Chemicals Innovation in Industrial Synthesis and Applications, Elsevier Science Pub. 1991; 473.
8. Maureen AR : Chem. & Eng. News, 2003; 57.
9. Elemer F, Mihaly N, David K, Gabriella E, Emese P, Violetta K : Org. Biomol. Chem. 2006; 4 : 3011 – 3030.
10. Jaques J, Collet A, Wilen : Enantiomers, Racemates and Resolution, Wiley Int. Sci. New York, 1981; 43.
11. Mc Bride JM, Carter RL : Angew. Chem. Int. Ed. Engl. 1991; 30 : 293-295.
12. Tamura R, Susuki S, Azuma N, Matsumoto A, Toda F, Kamimura A, Hori K : Angew. Chem. Int. Ed. Engl. 1994; 33 : 878 – 879.
13. Piselli FL : (Industria Chemica Profarmaco S.P.A.), European Patent 298395, 1989.
14. Piselli FL : (Industria Chemica Profarmaco S.P.A.), European Patent 325965, 1989.
15. Amiard G : Experientia, 1959; 15 : 1.
16. Wakamatsu H : Food Eng. 1968, Nov. 32.
17. Maria B, Tiborne B, Zsolt D, Katalin S, Attila G : (Sanofi Synthelabo), WO 00/27840, 2000.
18. Ramakrishna A, Ajaysingh R, Mahesh G, Abhinay P, Rajesh R, Venkat JR : (Merck Generics, UK Ltd.), WO 03/035652, 2003.
19. Bipin P, Vidya BL, Bhushan BL : (Cadilla Health Care Ltd.), WO 02/059128, 2002.
20. Courvoisier L, Gervais C, Mignot L, Petit MN, Coquerel G : J.Phys. IV, France, 2001; 11 : PR10-PR77.