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Catalytic reduction: Efficient synthesis of chiral key intermediate of besifloxacin hydrochloride

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ABSTRACT

*Current study describes a methodfor the preparation of chiral (3R)-azepan-3-amine**(Compound 2)**with high purity and yield, which may useas an intermediate or starting material to synthesize one of the most popular antibioticbesifloxacin hydrochloride. Chiral moiety of (3R)-azepan-3-amine **(Compound 2)**is prepared from (3R)-3-aminoazepan-2-one**(Compound 1)**by reducing it with novel reducing agent viz. $NaBH_4$/ $AlCl_3$, $NaBH_4$/ $CaCl_2$, $NaBH_4$/ DMS, $NaBH_4$/ BF_3 or$LiAlH_4$ using appropriate solvents viz. tetrahydrofuran (THF), isopropylether (IPE), toluene or acetonitrile (ACN).Purity and yield of furnished chiral amine is very highcompared to reported methods. The method is cost effective and commercial applicable.*

Keywords: Catalytic Reduction, Besifloxacin Hydrochloride Intermediate, Azepan-3-amine, $LiAlH_4$, $NaBH_4$

INTRODUCTION

Conjunctivitis, commonly known as red eye or pink eye, is frequently the result of a bacterial infection but can also be caused by viruses or fungi or result from non-infectious origins, such as allergens, toxins or the extended use of contact lenses[1]. Bacterial conjunctivitis results from infections caused by a variety of aerobic and anaerobic bacteria. Aerobic bacteria tend to predominate and most commonly include *Haemophilusinfluenzae*, *Streptococcuspneumoniae*, *Streptococcispecies*, *Staphylococcusaureus*, *Staphylococcusepidermidis*, and *Moraxellaspecies*[2-4]. Acute bacterial conjunctivitis is demographically unbiased in its prevalence. It affects individuals of both genders, all ages and all races. Acute or mucopurulent bacterial conjunctivitis is characterized by mucopurulent or purulent discharge, irritation and diffuse conjunctival hyperemia. Besifloxacinis one of the most useful antibiotic for conjunctivitis and other eye infections[5]. Fluoroquinolones, a class of broad spectrum synthetic anti-infective agents, were introduced in the late 1980s and are the most commonly used anti-infective for the treatment of acute bacterial conjunctivitis. Besifloxacin chemically known as 7-[(3*R*)-3-aminoazepan-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Fig. 1)is used to treat bacterialeyeinfections. Besifloxacin is the newest fluoroquinolone approved for topical ophthalmic treatment however, it has unique chemical, structural and biological features that differentiate it from others in its class. Drug frequently possess one or more chiral centres. In medicinal chemistry, it is recognised that different enantiomers of a compound will possess different biological activities, safety profiles, pharmacokinetic properties and pharmacodynamics properties. It is therefore desirable tobe able to administer only the enantiomer of a given compound that has the most advantageous drug properties. It is thus desirable to have synthetic routes that allow a given drug to be prepared with high enantiomeric purity. Additionally, the synthetic route need to be scalable, reproducible and cost effective.

In the progress of cost effective and highly pure besifloxacin hydrochloride preparation, efficient preparation of its intermediates plays important role. (3*R*)-azepan-3-amine**(Compound 2)**is one of the key intermediate for the

preparation of besifloxacin hydrochloride which is produced by the reduction of (3*R*)-3-aminoazepan-2-one**(Compound 1)**[6-11]. Several synthetic approaches have been reported for the preparation of (3*R*)-azepan-3-amine and these methods comprises of certain disadvantages which include long reaction time, poor yield, use of large volume of solvents and inferior quality of finished product. Herein, describe a convenient synthesis of (3*R*)-azepan-3-amine**(Compound 2)**from (3*R*)-3-aminoazepan-2-one**(Compound 1)** by using reducing agents like $NaBH_4$/ $AlCl_3$, $NaBH_4$/ $CaCl_2$, $NaBH_4$/ DMS, $LiAlH_4$ or$NaBH_4$/ BF_3in the presence of appropriate solvents[12-15] such as tetrahydrofuran (THF), isopropylether (IPE), toluene or acetonitrile (ACN).

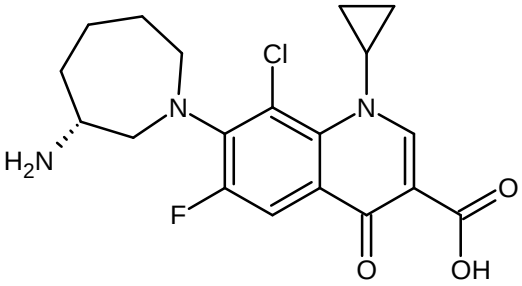
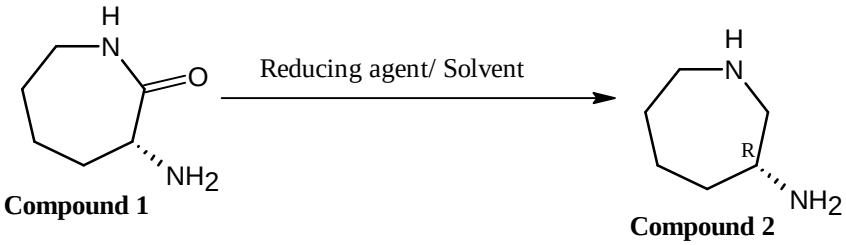


Fig. 1 : Structure of Besifloxacin

The transformation of one functional group to another one using non-hazardous chemicals in economically feasible and environmentally benign conditions is a formidable task for synthetic organic chemists. Selectivity and atom economy have been the crucial points because they define the overall length of a series of reactions that constitutes a synthetic strategy. Reduction provides an important method for functional group transformation in organic synthesis. A variety of reagents have been employed to achieve this transformations.Despite the fact that a plethora of reducing agents is available for this operation, new reagents especially the catalytic versions are still highly desirable.

Our research is mainly devoted to finding a noble procedure for reduction and reducing agent for organic functionalities particularly for **Compound 1**.We report herein a simple and convenient procedure for the reduction of**Compound 1**using inexpensive and easily available catalyst and solvents (listed in Table 1) to the corresponding amine. Present study provides the industrial applicable & economical method of preparation for the one of the most important intermediate of besifloxacin hydrochloride(Scheme 1).



Compound 1 **Compound 2**

Scheme 1: Synthesis of (3*R*)-azepan-3-amine **Compound 2**.

MATERIALS AND METHODS

The reagent grade chemicals were purchased from the commercial sources viz. Sigma-Aldrich.^{1}HNMR spectra were measured on a Bruker-500 spectrometer in DMSO at 500MHz using TMS as an internal standard. All chemical shifts were reported on δ scales. IR spectra were recorded in NaClplate (film) on a Perkin Elmer Spectrum ES Version and the LC-MS spectra were recorded on a Xevo TQD Waters LC-MS spectrometer.Purity of product analysed by Gas Chromatography using Shimadzu 2010 plus model. The analytical data was highly satisfactory.

General Procedure for the preparation of (3R)-azepan-3-amine, Compound 2:

To a solution of **Compound 1**and $NaBH_4$ (3.0 equivalent) in THFadded BF_3.THF (3.0 equivalent)drop wise at room temperature under an inert atmosphereand stirred for 15-20 hr.After the completion of the reaction, quenched the reaction mass in conc. HCl followed by reflux. The **Compound 2**thus formed is extracted with THF under basic condition using NaOH solutionand product distilledunder reduced pressure to get light yellow colour liquid.

Mol. Formula (Mol. Wt.): $C_6H_{14}N_2$ (114.19); Yield of the product: 88.8%; purity (GC): 98.20%; FT-IR (NaCl) : cm^{-1}3353.2, 3281.07, 2855.06;^{1}HNMR (500MHz in DMSO): *δ*2.81-2.65 (m, 4H), 2.36-2.32 (m, 1H), 1.84 (m, 3H), 1.70-1.69 (m, 1H), 1.55-1.38 (m, 4H), 1.32-1.26 (m, 1H); LC-MS (m/z): 115.27 (M+1).

RESULTS AND DISCUSSION

In the present study, different reducing agent were used in combination with different appropriatesolventslike tetrahydrofuran (THF), isopropylether (IPE), toluene or acetonitrile (ACN) for the reduction of carbonyl group of compound 1. Results of preparation of (3*R*)-azepan-3-amine**(Compound 2)**as shown in Table-1 (Example 1) which indicates that reaction catalysed by $NaBH_4/BF_3$ in the presence of THF is the best reducing agent for the preparation of compound 2 asit gives better reaction yield (88.8%) in 24 hr.It is also noticeable that further increment of reaction time, $NaBH_4/BF_3$ does not affect the conversion of the product and$NaBH_4/BF_3$ in the presence of ACN gives moderate yield (example 3, Table-1). $NaBH_4/BF_3$ in the presence of other solvents like IPE and toluene as per examples6&7respectively in Table-1 gives low yield and high reaction time as compared to example1(Table-1).$NaBH_4$ also gives moderate yield68.25&57.60% in the presence of $AlCl_3$ and DMS respectively (example4&5, Table-1). It is also observedthat reaction does not carried out in the presence of $CaCl_2$ (example2, Table-1). $LiAlH_4$is also one of the efficient reducing catalyst for current transformationgives 69.7% yield (example8, Table-1) butnot better in compare to $NaBH_4/BF_3$.

Table 1: Comparative study of reaction time, conversion, yield and purity of compound 2

Example	Catalyst	Time (hr)	% Conversion	% Yield	% Purity	Solvent
1.	**$NaBH_4$/ BF_3**	**24**	**95.50**	**88.80**	**98.20**	**THF**
2.	$NaBH_4$/ $CaCl_2$	48	-	Not Isolated	NA	THF
3.	$NaBH_4$/ BF_3	46	82.64	59.90	68.53	ACN
4.	$NaBH_4$/ $AlCl_3$	24	73.33	68.25	69.18	THF
5.	$NaBH_4$/ DMS	40	78.67	57.60	58.35	THF
6.	$NaBH_4$/ BF_3	60	43.48	Not Isolated	NA	IPE
7.	$NaBH_4$/ BF_3	46	47.73	Not Isolated	NA	Toluene
8.	$LiAlH_4$	16	95.60	69.70	95.80	THF

CONCLUSION

Different reducing agent were used for the current research. In thisstudy,$BF_3$with sodium borohydride in the presence of appropriate solvents viz. THF, ACN, toluene or IPE and $LiAlH_4$ in the presence of THF are used. The yield of the (3*R*)-azepan-3-amine**(Compound 2)** is higher with $NaBH_4/BF_3$ than $LiAlH_4$. Purity and yield of furnished chiral amine is very high compared to reported methods. The method used to obtain chiral amine is cost effective and commercial applicable.

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REFERENCES

[1] G. Hovding,*ActaOpthalmol,***2008**, *86*, 5-17.
[2] A. Sheikh;B. Hurwitz,*Cochrane Database Syst Rev.*,**2006,***2*, CD001211.
[3] P. W. Rose;A. Harden;A. B. Brueggemann;R. Perera;A. Sheikh;D. Crook;D. Mant,*Lancet.***2005,***366*, 37-43.
[4] Dermatologic and Ophthalmic Drugs advisory committee meeting briefing document,Besifloxacin 0.6% w/v ophthalmic suspension for the treatment of Bacterial Conjunctivitis.
www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4397b1-02-BauschLomb.pdf.Accessed**Aug 2009**.
[5] J. Z. Zhang;K. W. Ward,*J. Antimicrob.Chemother.***2008,***61*, 111-116.
[6] M. Ishikawa; Y. Hiraiwa; D. Kubota; M. Tsushima; T. Watanabe; S. Murakami; S. Ouchi; K. Ajito,*Bioorg. Med. Chem.*,**2006,***14(7)*, 2131-2150.
[7] S. Bahmanyar;R. J. Bates;K. Blease;A. A. Calabrese;T. O. Daniel;M. E. J. Delgado;P. Erdman;B. Fahr;G. Ferguson;B. Lee;L. Nadolny;G. Packard;P. Papa;V. Plantevin-Krenitsky;J. Riggs;P. Rohane;S. Sankar;J. Sapienza;Y. Satoh;V. Sloan;R. Stevens;L. Tehrani;J. Tikhe;E. Torres;A. Wallace;B. W. Whitefield;J. Zhao,PCT International publication number 2010027500, date of publication March11, **2010.**
[8] G. Lelais;R. Epple; T. H.Marsilje III; P.-Y. Michellys;M. H. McNeill;Y. Long;W. Lu;B. Chen;B. Bursulaya;S. Jiang,PCT International publication number 2013184757, date of publication December12, **2013.**
[9] K. G. Rasmussen;A. F. Jensen;L. Nygaard,PCT International publication number 2004033455, date of publication April22, **2004**

[10] A. B. Kanstrup;C. K. Sams;J. M. Lundbeck;L. B. Christiansen;M. Kristiansen, PCT International publication number 2003004496, date of publication January16, **2003.**
[11] C. Botteghi;A. Schionato;G. Chelucci;H. Brunner;A. Kuerzinger;U. Obermann,*Journal of Organometallic Chemistry*,**1989,** *370(1-3),* 17-31.
[12] M. B. Wallace;J. Cody;R.Fornicola;S. Garcia-Rubio;P. B.Kisanga;M. M. Reeve;C. Wilson, PCT International publication number2007112368, date of publication October04, **2007.**
[13] S.-D. Cho; Y.-D. Park; J.-J. Kim; J. R. Falck; Y.-J. Yoon,*Bull. Kor. Chem. Soc.*,**2004**, *25(3),* 407-409.
[14] A. E. Harms;R. Arul; A. K. Soni,US patent publication number20100029936, date of publication February 04, **2010.**
[15] M. N. Rajadhyaksha;R. Nair;N. B. Shrigadi;A. Panandikar, Indian patent application, IN 23/MUM/2013, date of publication September 26, **2014.**