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http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 5: (2), 2015, 241-244

A SIMPLE AND CONVENIENT ROUTE FOR THE SYNTHESIS OF (R)-3-AMINOBUTANOL, AN INTERMEDIATE FOR THE SYNTHESIS OF DOLUTEGRAVIR

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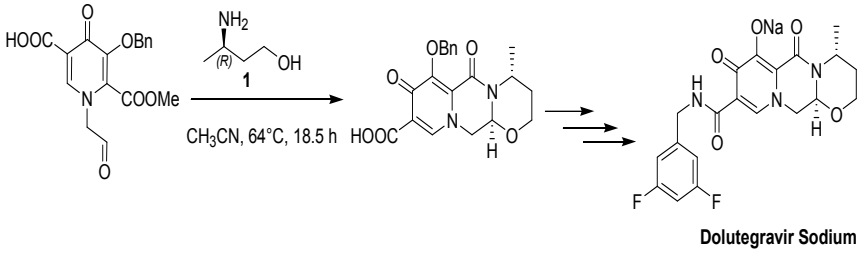
Abstract: An effective synthetic process for the preparation of (R)-3-aminobutanol, an intermediate of anti-viral drug Dolutegravir sodium, is achieved in simple synthetic transformations by using D-(-)-tartaric acid as a resolving agent. The process developed is highly efficient and can be applied for large scale synthesis also.

Keywords: (R)-3-Amino butanol, Dolutegravir sodium, Ethylacetoacetate.

Introduction:

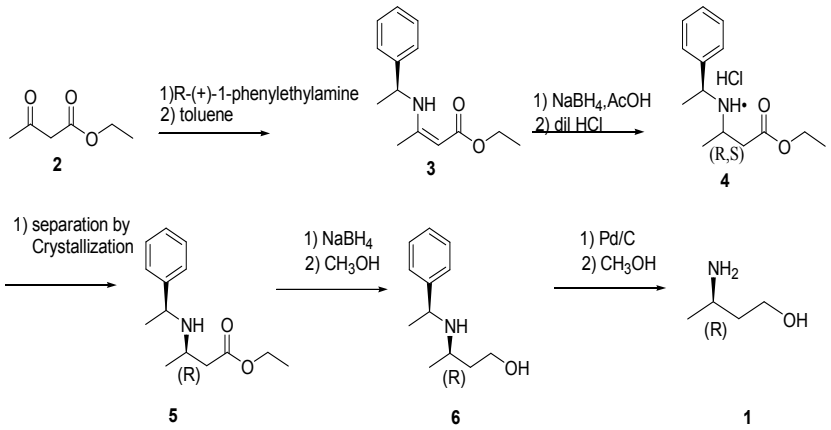
Dolutegravir sodium, a US-FDA approved antiviral drug for the treatment of HIV infection [i-iii]. The drug is a second generation HIV integrase inhibitor designed to deliver potent antiviral activity[iv-v]. Dolutegravir sodium was developed by research collaboration between Shionogi and GlaxoSmithKline (GSK) [vi].

Synthesis: The synthetic procedure reported for the synthesis of Dolutegravir sodium involves the reaction of (R)-3-aminobutanol with methyl1-(2,2-dihydroxyethyl)-4-oxo-3--[(phenylmethyl)oxy]- 1,4-dihydro-2-pyridine carboxylate (**Scheme 1**).



Scheme 1. Synthesis of Dolutegravir sodium.

(R)-3-aminobutanol is a key unit for the synthesis of Dolutegravir sodium. Even though (R)-3-aminobutanol is a potential unit, there are only a few reports that describe its synthesis in the literature (**Scheme 2**) [vii-xi]. The procedure reported by Jing[vii] for the synthesis of (R)-3-aminobutanol starts from the condensation of ethyl acetoacetate (**2**) with R-(+)-1-phenylethylamine to get the corresponding aminoester intermediate **3**, which further undergoes reduction using $NaBH_4$ to get **4** followed by separation of diastereomers and crystallization to get **5**. Intermediate **5** again undergoes reduction using $NaBH_4$ to yield **6** on which the benzyl deprotection was carried out to obtain (R)-3-aminobutanol (**1**). Very low yields and usage of expensive 'Pd' catalyst are the main limitations associated with this procedure. The other reaction methodologies reported [viii-xi] for the synthesis of this intermediate employs tedious chiral synthetic precursors, expensive ruthenium catalysts, harsh reaction conditions, hazardous reagents, elevated temperatures and long reaction times which is inappropriate for large scale operations. So, in the present investigation an attempt was made to develop an efficient, inexpensive and convenient route for the synthesis of (R)-3-aminobutanol.

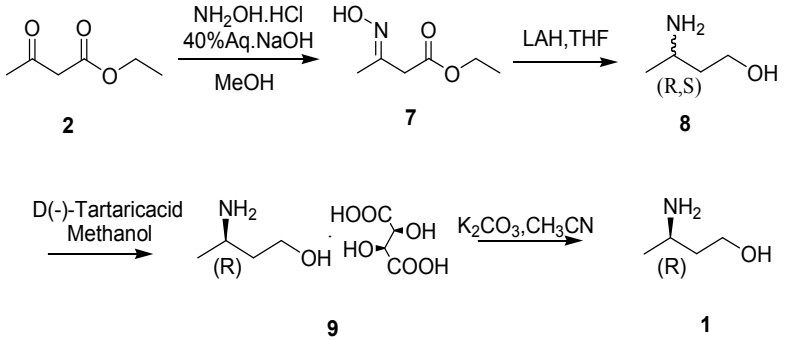


Scheme 2. Synthesis of (R)-3-aminobutanol

Results and Discussion:

In an attempt to devise alternate route for the synthesis of (R)-3-aminobutanol using inexpensive and readily accessible starting materials and reagents, resolution of chemical substrates using chiral resolving agent pathway was chosen. D-(-)-mandelic acid and D-(-)-tartaric acid are cheap and widely used as resolving agents. Numerous reports are available based on D-(-)-mandelic acid and D-(-)-tartaric acid catalyzed resolutions [xii-xv]. In the present communication we report a simple, unique and practical synthetic procedure for (R)-3-aminobutanol using D-tartaric acid as a resolving agent. Economically cheap materials, simple reaction procedures are the main advantages of present method.

The (R)-3-aminobutanol (**1**) was synthesized in a four-step synthetic protocol using ethyl acetoacetate (**2**) as starting material (**Scheme 3**).



Scheme 3. Synthesis of (R)-3-aminobutanol.

In the first step, ethylacetoacetate was converted to the corresponding oxime, **7,** by reacting with hydroxylamine hydrochloride in presence of NaOH. Reduction of the oxime **7** with Lithium Aluminum Hydride (LAH) resulted in the formation of corresponding amino alcohol, **8**, which further resolved using D-(-)-tartaric acid to obtain (R)-3-aminobutanol tartarate salt (**9**). Neutralization of the (R)-3-aminobutanol tartarate salt using K_2CO_3 in acetonitrile medium generated the title compound (R)-3-Aminobutanol (**1**) in pure form. The detailed synthetic procedures are provided in the experimental section. All the intermediates and final compound are well characterized and the data matches with that of reported literature. The present method is highly economical and eliminates the use of expensive catalysts. The reaction conditions adopted for this method are mild and suitable for scale up. We have synthesized (R)-3-aminobutanol up to 100 gm scale using this method and the yields are quite good. Hence we hope the present process is extremely useful for the synthesis of (R)-3-aminobutanol at commercial scale.

Conclusions:

A simple and efficient method was developed for the synthesis of (R)-3-aminobutanol from ethylacetoacetate in this investigation. The inexpensive D-(-)-tartaric acid was employed as a resolving agent. The present method requires very cheap resolving agent, experimental procedures are highly convenient and the yields are impressive. We have found that the method is best suitable for the preparation of (R)-3-aminobutanol in large scale.

Experimental Section:

The starting materials were purchased from Sigma-Aldrich chemical Company. All the solvents were distilled prior to use. The NMR spectra recorded on a Bruker 300 instrument, ESI-MS spectra were recorded on a Bruker Micro TOF II instrument and IR spectra were recorded on Perkin- Elmer BXF1 FT-IR spectrometer. The melting points were determined in open capillary tubes on Toshniwal apparatus and were uncorrected.

General procedure for the synthesis of (R)-3-aminobutanol. In the first step the ethylacetoacetate (0.7684 mol) (**2**) starting material was added to hydroxyl amine hydrochloride (0.922 mol) in methanol (500 ml) at ice cold condition and later it was heated to 40-45 ˚C with stirring for 2h yielded corresponding oxime (**7**) In order to maintain the pH at 4.2 40% (w/v) aq.NaOH was used. Then the compound (**7**) (0.6896 mol) was reduced to

3-amino butanol (R&S) (**8**) (0.4494 mol) in presence of LAH (2.7586 mol) and THF (1500 ml) compound further the mixture was D-(-)-Tartaric acid(0.3146 mol) yielded (R)-3-aminobutanoltartrate salt. Finally, (R)-3-aminobutanol (**1**) product was obtained by neutralization of tartrate salt (**9**) (0.1255 mol) with K_2CO_3 (0.7531 mol) in acetonitrile(300 ml).

Acknowledgements:
The authors are highly thankful to Acharya Nagarjuna University for constant encouragement.

Supporting Information:
Supporting Information is also available electronically on the LOC-Journal Web site.

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Received on December 30, 2014.