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Racimisation of (R) –Alpha – Ethyl -2-Oxo-1-Pyrrolidine Acetic acid with Thionyl Chloride

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ABSTRACT

We report the new synthetic methodology and Racimisation of (R)-Alpha-ethyl-2-oxo-1-pyrrolidine acetic acid with thionyl chloride resulting compound is charactarised and confirmed by SOR, racimisation is occurs by using thionyl chloride, the resulting of the yield is 83%.

KEYWORDS

Thionyl chloride, Racimisation, SOR.

INTRODUCTION

Racimisation is the process in which one enantiomer of a compound converts to the other enantiomer. The compound then alternates between the each form while in the ratio between the R and S approaches 1:1, at which point it becomes optically in active. The absolute configuration of atoms in chiral molecules is commonly described using R and S.

In our laboratory we are able to measure the degree of racimisation using polarimetry, liquid chromatography, capillary electrophoresis and mass spectrometry, with these measurements scientists can estimate the rate at which one enantiomer is converted into other.

A. Horeau et al[1] reported that optically active alpha ethyl phenyl acetic acid chloride was easily racemised in pyridine (0.4M solution) at room temperature and that the rate of racimisation was such that the optical rotation decreased to one-seventh of its initial value in about 3 hours, in the same report Horeau described that optically active α-ethyl phenyl acetic anhydride was racemised in pyridine at room temperature. The rate of racemisation was such that the optical rotation decreased to one-half of the initial value in as long as 20 hrs when the concentration of the pyridine solution was 0.1M while the racemisation completely came to an end in about 8 hrs when the concentration was 0.6M. H. Collect et al[2] reported that optically active α-ethyl phenyl acetic acid is racemised by mixing with equimolar portions of trifluoro acetic acid and trifluoro acetic anhydride. Ph. Gold Aubert[3] reported that optically active N-alpha-(alpha-ethylphenylacetyl) urea was racemised to about 73% when heated under reflux for 90 minutes in 0.5N NaOH in 50% aqueous ethanol.

R.S.Stuart et al[4] examined the rate at which the hydrogen atom in the alpha position of phenyl acetic acids was exchanged with heavy hydrogen when the sodium salt of the phenyl acetic acids was placed in deuteriumoxide in the presence of an alkali based on these investigations they reported that the rate of heavy hydrogen exchange at 90°C [j.chem.soc,chem.commun,1068(1969)].

Japanese patent application 5134/78 discloses a process for racimising an optically active alkyli metal2-(4-chlorophenyl)-3-methyl butyrate by heating in the presence of alkyli etc, Japanese

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patent application (opi) NO 3035/79 discloses that optically active 2- (4-chlorophenyl)-3-methyl butyryl chloride can be very easily racimized by heating etc.

In a previous investigation Du Vigneaud and Sealock[5] have reported that the sodium salt of acetyl –i-tryptophane in aqueous solution at 35-40degree is completely racemized by acetic anhydride within a few hours. Shigeki yamada, chikara hongo, ryuzo yoshioka[6] reported a practical method for racemisation of optically active amino acids has been developed, amino acids could be racimised by heating in a medium of acetic acid at 80-100 ^{0}C for 1hr in the presence of 0.05 molar of an aliphatic or aromatic aldehyde. E.J.Hendy, P.Jtomiak, M.J Collins[7] assessing amino acid racemisation variability in coral intra –crystaline protein for geochronical applications.

Robert D Emmick, Niagarafalls, N.Y assignor[8] reported racemisation of lysine with phosphoric acid. Silvia M Glucck, Monika Pirker, Bettina M[9] reported biocatalytic racemisation of aliphatic,aryl aliphatic and aromatic alpha hydroxyl carboxylic acids. Barry LG, Pugnierem, Castrob, PrevieroA[10] reported racemisation of alpha-amino acid esters by aliphatic ketones in the presence of carboxylic acids.

The present investigation was therefore undertaken racimisatnion of carboxylic acids with thionyl chloride and followed by hydrolysis with 10% HCl solution.

The carboxylic acid selected for racimisation (R) –Alpha – ethyl -2-oxo-1-pyrrolidine acetic acid in various temperatures (5degree, 10degree, 15degree, 20 degree and RT). The ease of racimisation is differed with somewhat at various temperatures for obtaining out of these temperature we achieved better racimisation at 15-20 degree temp.

Chlorinated solvents are suitable (preferably Dichloro methane and Chloroform) for this racimisation.

EXPERIMENTAL PROCEDURE

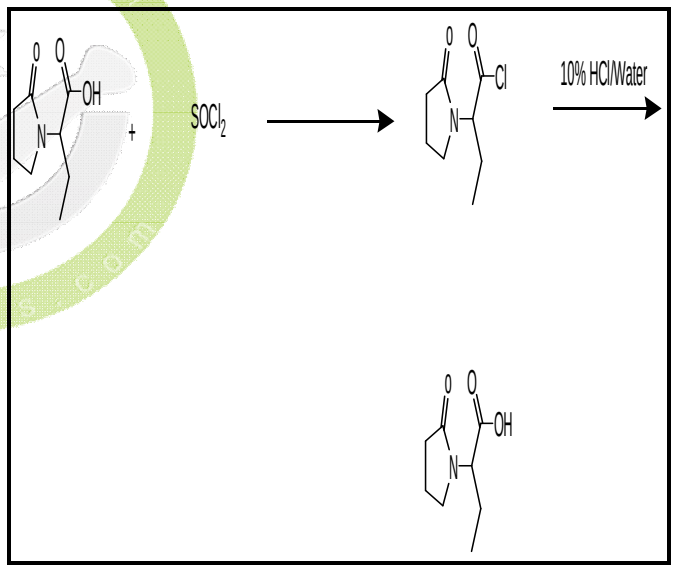
In 500ml 4 neck RB flask with condenser and $cacl_2$ guard tube, charged 50 gms of (R)- alpha –ethyl-2-oxo-1-pyrrolidine acetic acid, to this mass 250ml Di chloro methane added, cooled to 15-20degree.slowly added thionyl chloride (1.2mole) to the reaction mass at 15-20 degree ,maintained at 15-20 degree for 6 hrs, then temp raised to RT and acidified the mass with 10% HCl solution (150ml), settled and separated layers, aqueous layer extracted with Dichloromethane, until that no ppt in aqueous layer, combined the total Dichloro methane layer and distilled under reduced pressure to get pure racimised product, Yield (83%)

Analytical data:

SOR Before racimisation: +25degree

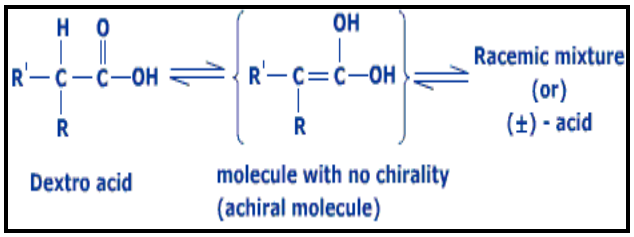
SOR After racimisation : +0.5 degree

Scheme:



MECHANISM OF RACEMISATION

A compound where the chiral carbon atom is attached to a hydrogen atom and an electron-attracting group can undergo racemisation readily. The mechanism is enolisation. For e.g., when the intermediate achiral enol form reverts to the stable form,



there are equal chances to produce the dextro and laevo forms. Therefore ready racemisation is possible.

RESULTS AND DISCUSSION

Racimisation is occurring through enol form when we are adding the thionyl chloride, there are equal chances to replace the OH Group by Cl and forming the acetyl chloride, to this we acidifing with 10% HCL and forming the racimic acid. Analytical results indicate racemisation is happening successfully.

Racemisation occurs with other methods also but advantage of this route is to operate easily within a short time with good yield (83%).

Physical properties:

Racemate may have different physical properties from either of the pure enantiomers because of the differential intermolecular interactions. The change from a pure enantiomer to a racemate can change its density, melting point, solubility, heat of fusion, refractive index, and in various spectra. Crystalisation of a racemate can result in separate (+) and (-) forms, or a single racemic compound.

Biological significance:

In general, only one form of a chiral molecule will participate in biochemical reactions while the other simply does not participate or can cause side-effects. Of note, the L form of amino acids and the D form of sugars (primarily glucose) are usually the biologically reactive form. Additionally, many psychotropic drugs show differing activity or efficacy between isomers, e.g. amphetamine is often dispensed as racemic salts while the more active dextroamphetamine is reserved for refractory cases or more severe indications; another example is methadone, of which one isomer has activity as an opioid agonist and the other as an NMDA antagonist

Racemization of pharmaceutical drugs, however, can occur *in vivo*. An example is thalidomide, its (*R*) enantiomer is effective against morning sickness, while the (*S*) enantiomer is teratogenic, causing birth defects. If only one enantiomer is administered to a human subject, both forms may be found later in the blood serum−The drug is therefore not considered safe for use by women of child-bearing age, and while it has other uses, its use is tightly controlled.

CONCLUSION

On a trivial level, racemization can be achieved by simply mixing equal quantities of two pure enantiomers. Racemization can also occur in a chemical interconversion. For example, when (*R*)-3-phenyl-2-butanone is dissolved in aqueous ethanol that contains NaOH or HCl, a racemate is formed. The racemization occurs by way of an intermediate enol form in which the former stereocenter becomes planar and hence achiral. An incoming group can approach from either side of the plane, so there is an equal probability that protonation back to the chiral ketone will produce either an *R* or an *S* form, resulting in a racemate.

Substitution reactions that proceed through a free carbocation intermediate (such as unimolecular substitution reactions) lead to non-stereospecific addition of substituents which results in racemization. While unimolecular elimination reactions also proceed through a carbocation, they do not result in a chiral center. Rather, they result in a set of geometric isomers in which *trans/cis* or *E/Z* forms will result. In an unimolecular aliphatic electrophilic substitution reaction, if the carbanion is planar or if it cannot maintain a pyramidal structure, then racemization should occur, though not always. In a free radical substitution reaction, if the formation of the free radical takes place at a chiral carbon, then racemization is almost always observed.

The rate of racemization (from L-forms to a mixture of L-forms and D-forms) has been used as a way of dating biological samples in tissues with slow rates of turnover, forensic samples, and fossils in geological deposits. This technique is known as amino acid dating.

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