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A Commercially viable synthesis of Tetrahydropyran-4-carboxylic acid as importantpharmaceutical intermediate.

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ABSTRACT:
The present invention is to provide safe. environmental friendly method for tetrahydropyran-4-carboxylic acid, Cyclisation of diethyl malonate & Bis-(2-chloroethyl) ether gives diethyl tetrahydropyran-4,4-dicarboxylate, further hydrolyzed to get tetrahydropyran-4,4'-dicarboxylic acid & controlled decarboxylation to get tetrahydropyran-4-carboxylic acid.. process optimizedon commercial scale

Key words: Synthesis, process, impurity and analysis

I. INTRODUCTION

Introduction

Invention relates with organic synthesis, in distinct to a preparation method of an important intermediate

Background

Pyran is an oxygen-containing six-membered heterocyclic system in which an oxygen atom replaces one carbon atom in a six-membered ring, and is a very important class of heterocyclic compounds. Pyranes have a wide range of biological activities, and the synthesis of these compounds is of great significance. It is an important structural core of many natural products such as carbohydrates, polyether antibiotics, and plays a very important role in their biological activities.

Tetrahydropyran is also an important synthetic intermediate for construction of other heterocyclic compounds. According to existing reports, such heterocyclic compounds have good application as Neurological Receptor Antagonists cognitive impairments and Alzheimer's disease azaspiro[4.5]decane derivatives having an affinity to Opioid receptor Structure-Based design of novel Class II C Met Inhibitor Structure-activity relationships of Cycloalkylamide Derivatives

Tetrahydropyran-4-carboxylic acid is widely used as catalyst in (Green chemistry photo redox) organo photo redox decarboxylation reaction Therefore, the synthesis methods of Tetrahydropyrans have received extensive attention from researchers and have become a research hotspot in organic synthesis.

II. RESULT & DISCUSSION

Synthesis of tetrahydropyran-4-carboxylic acid. reported [2,7,8,9,10 ,11]

In HELVETICA CHEMICA ACTA Vol -80 1528-1554 (1997) process explained is not having mild condition & time consuming mainly in Cyclisation / Hydrolysis & high temperature condition for decarboxylation. Following point is detailed discussed in above references [11]

Cyclisation: Cyclisation of Diethyl malonate & Bis-(2- chloroethyl) ether in presences of strong base like sodium hydride at 0°C takes longer time reaction 3 days i.e. reaction is bit harsh inall respect to get Diethyl tetrahydropyran-4,4-dicarboxylate

Hydrolysis: Diethyl tetrahydropyran-4,4-dicarboxylate in 30% NaOH at 0°C reaction is sluggish or take more time 3 days

Decarboxylation: In JP4561635B2,WO2008145963, WO 2008154642, Decarboxylation of Diethyl tetrahydropyran-4,4-dicarboxylate at 180°c. Which is industrially unsafe condition w.r.t evolution of carbon dioxide this operation looks complicated/ unsafe on industrial scale.

III. RESULT & DISCUSSION:

Step –I: Reaction / Mechanistic path for synthesis of Diethyl Tetrahydropyran-4,4-dicarboxylate.

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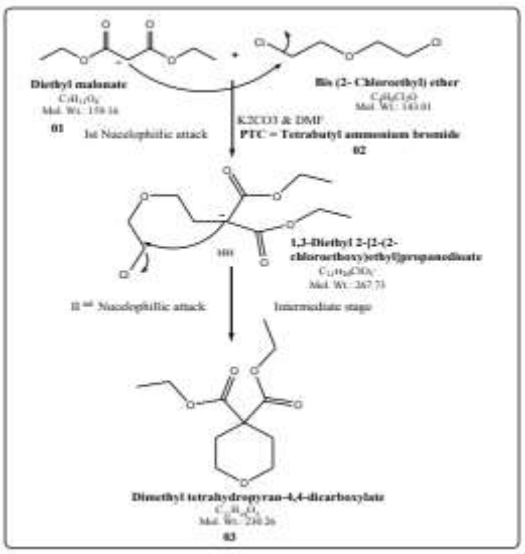
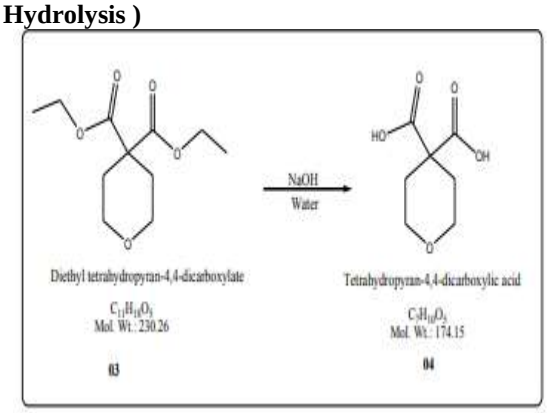


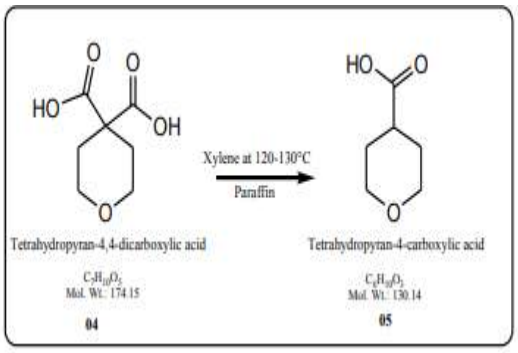
Chemistry :
Nucleophilic substitution of $-CH^-$ attack on electrophile of Bis (2- chloro ethyl ether to get intermediate stage **1,3-Diethyl 2-[2-(2-chloroethoxy)ethyl] propanedioate,** further(Nucleophilic substitution as shown in Scheme) cyclized to get Diethyl tetrahydropyran-4,4-dicarboxylate

Step –II: Reaction scheme for Synthesis of Tetrahydropyran-4,4- dicarboxylic acid (Hydrolysis)



Hydrolysis; Hydrolysis of Diethyl tetrahydropyran 4, 4, dicarboxylate to tetrahydropyran -4, 4 dicarboxylic acid in presences of base.

Step –III: Synthesis of Tetrahydropyran-4-carboxylic acid (Decarboxylation)



Decarboxylation: Controlled decarboxylation of above diacid in solvent media at 120-130°C gives tetrahydropyran- 4-carboxylic acid

IV. DISCUSSION

Cyclisation : Cyclisation of Diethyl malonate & Bis (2- chloro ethyl ether in presences of base like , alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; alkali metal carbonates such as sodium carbonate and potassium carbonate; alkalis such as sodium hydrogen carbonate and potassium hydrogen carbonate. Metal hydrogen carbonates; alkali metal alkoxides such as sodium methoxide etc.
These bases may be used alone or in combination of two or more.The amount of the base to be used is preferably 1 to 10 moles, most preferably 2 to 5 mole, per 1 mole of diethyl malonate.
Solvent : Reaction is carried out in solvent like Acetone , MIBK ,N,N Dimethyl formamide ,N,N dimethyl acetamide , N-Methylpyrolidone , DMSO or Acetonitrile, Ethers Dimethyl ethers Disopropyl ether , Tetrahydrofuran , Aromatic hydrocarbon Toluene ,Xylene
Amount of solvent used 1 to 40 volume w.r.t diethyl malonate. Cyclisation reaction temperature carried out 50-100 °C more.
Hydrolysis: Hydrolysis of Diethyl tetrahydropyran 4,4 dicarboxylate to tetrahydropyran 4,4 dicarboxylic acid in presences of base , alkali like NaOH , KOH ,or alkali metal likecarbonate Sodium carbonate , potassium carbonate , sodium hydrogen carbonate or potassium hydrogen carbonate etc.
The amount of base used is 1 to 6 mole w.r.t diethyl tetrahydropyran -4, 4 dicarboxylate at 40-50°c temperature after complete hydrolysis adjust pH =1.0 to 2.0
Decarboxylation: Decarboxylation of tetrahydropyran 4,4 dicarboxylic acid decarboxylated at 120-130°C in controlled maner by using solvent media like aromatic hydrocarbon

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Toluene, Xylene, Parraffin , paraffin & solvent is useful to avoid decomposition of 4-tetrahydropyranyl carboxylic acid at thermal condition or reaction condition. Also useful in control evolution of carbon dioxide

Temperature during decarboxylation is 120- to 130 °C after reaction completion extract product with solvent like ethyl acetate, aromatic hydrocarbon, and Chlorinated solvent likeMethylene dichloride.

Step-I-:Cyclisation

Diethyl malonate 1.0 mole and Bis(2-chloroethyl) ether 1.0mole

Solvent	Base	TBAB mole %	Yield
Toluene	1.5 mole	10.0	50.0 %
Toluene	2.0 mole	0.3	52.0 %
DMF	2.0 mole	0.4	65.0 %
DMSO	2.5 mole	1.2	55.0 %
THF	2.0 mole	1.8	30.0 %

Step-II-:Hydrolysis

Diethyl tetrahydropyran-4,4'-dicarboxylate 1.0 mole (stageI) and NaOH 5.0 mole

Base	Mole	Temperature	Hours	Yield
NaOH	5.0	50-60°C	2 to 3	70-72 %
NaOH	5.0	70-80°c	2 to 3	50-55 %
NaOH	3.0	90- 100°c	1 to 2	30-40 %

Experimental part:

Step-I: Synthesis of Diethyl tetrahydropyran-4,4'-dicarboxylate- Charge 250.0 lit DMF , 80.0 kg (0.5mole) Diethyl malonate (01) & Bis(2-chloroethyl) ether (02) 71.5 kg (1.0 mole) & Potassium carbonate 140 kg (2.0 mole) & tetra butyl ammonium bromide 5.0 kg (0.031 mole) reflux till completionof reaction by GC monitoring Filter potassium carbonate & distill DMF weight of oil = 70.0 to 75.0 kg purity 95 % by GC Molar yield = 65%.w.r.t Diethyl malonate

Step-II: Synthesis of Tetrahydropyran-4,4'-dicarboxylic acid: Charge water 300 ml ,75.0 kg step –I (03)& 112.5 kg of NaOH (5.0 mole) heat 50 to 60 °c at 7 to 8 hrs monitor reaction by GC after completion adjust pH 1 to 2 by Con HCl . Extract with methylene dichloride. Distill gas isolate product dry wt =40.5 kg Molar yield =72% purity 90-95% by titration

H^1-NMR ; 'H-NMR ;- DMSO): 12.79 (br. s, 2H COOH);

(3.43 (t. (CH2)2 -4H) 1.78 (t. (CH2)2 -4H)

Step-III: Synthesis of 4-Tetrahy dropyranylcarboxylic acid: Charge 150.0 lit xylene & 2.5 kg paraffin oil heat to 120 to 130°c. Carefully add lot wise add step –II 35.0 kg Tetrahydropyran-4,4'-dicarboxylic acid (during addition of step

–II (04) control evolution of carbon dioxide). Distill degas solvent & isolate 4-Tetrahydropyranylcarboxylic acid 20.9.0 kg GC purity = 98 -99 % Molar yield = 85%

H^1-NMR: (Solvent –DMSO) 9.35 (br.s, COOH); (3.9, (t,2 H,)

CH2) (3.46 (t ,2 H) CH2) (2.65 -2.55 – (m, 1H, CH) (1.9-1.75

(m- 4H (CH2)2 -4H)., Chemical ionization mass spectrometryCI-MS ;- 148 (M+ 1+ NH3).

Step-III- Decarboxylation

Tetrahydropyran-4,4'-dicarboxylic acid 1.0 mole andparaffin oil

Reagent	Temperature	Yield
Paraffin oil	**120-130°C**	**70 %**
Xylene + paraffin	**120-130°C**	**80-85 %**
Xylene	120 -130 °c	60%

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