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Original Article

Synthesis of Stable Imidapril Hydrochloride

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A B S T R A C T

The main objective of this invention is to establish a new de-esterification procedure for an active pharmaceutical ingredient Imidapril hydrochloride, its synthesis involved a selective de-alkylation process in its penultimate stage, with respect to the available literature is concern most of the hydrolysis techniques reported in dry hydrogen chloride gas in 1, 4-dioxane. Here the author innovate a new method for its hydrolysis with sulphuric acid in 1, 4-dioxane and resulting product was more stable than regular.

Keywords: Synthesis, Economical process, De-alkylation, Conc. H_2SO_4 in 1, 4-dioxane, Stability.

INTRODUCTION

Imidapril acts as an **ACE** inhibitor to suppress the conversion of angiotensin I to angiotensin II and thereby reduce total peripheral resistance and systemic blood pressure (BP).

Its clinical trials evident that oral Imidapril was an effective antihypertensive agent in the treatment of mild to moderate essential *hypertension*[1]. Some evidence suggests that Imidapril also improves exercise capacity in patients with chronic heart failure (CHF) and reduces urinary albumin excretion rate in patients with type 1 diabetes mellitus.

Kimiaki hayashi et al[2]prepared some cyclic imino acid moiety incorporating a ureido group in the ring would be effective as the C-terminal of ACE inhibitors, and therefore, we aimed at introduction of a 2-oxoimidazolidine-4-carboxylic acid moiety and de alkylation has done with 15% HCl in 1,4 –dioxane.

Shiba etal[3] reported the synthesis of its intermediates (4S)-3-(benzyloxy carbonyl)-oxoimidazolidine-4- carboxylic acid and was prepared by Hoffman rearrangement of N-(benzyloxycarbonyl)-L-asparagine is a new angiotensin I converting enzyme (ACE) inhibitor, from the pre-

hypertensive stage on morphological change and mechanical property related to sodium ion permeability in aorta of spontaneously hypertensive rats (SHRs) was studied by *Kubo M et al*[4].

Saito S et al[5] was investigated the optimal structure for long-acting ACE inhibitors**,** and as per as our invention is concern hydrolysis of tertiary butyl ester most available literature and patents[6-8] with dry hydrochloric acid in 1,4-dioxane, But none of them reported in Conc. sulfuric acid in 1,4-dioxane. Here in present invention the author tried to improve the stability[9-19] of the Imidapril hydrochloride, during the course of experimentation he got this idea and implemented. Generally Imidapril hydro-chloride (**II**) made from 1,4-dioxane is found to be less stability, after couple of months it's getting converted free base of earlier stage. So that the author developed a new process that hydrolysis of tertiary butyl ester with concentrated sulphuric acid in 1, 4-dioxane at room temperature and finely made hydrochloride salt with isopropyl alcohol and which is stable for six months.

MATERIALS & METHODS

The chemicals, reagents and solvents used for its synthesis are purchased from Aldrich chemicals and Merck. . The structure of the compound confirmed by elemental analysis, 1HNMR

(Bruker instrument with 400MHz), Mass (Bruker) and FT-IR (Perkin Elmer) data. The stability of the product is confirmed by HPLC degradative studies.

EXPERIMENTAL

This process involves two stages, in the first stage de esterification of tertiary butyl ester is incorporated and the second step involves more stable hydrochloride salt preparation as shown as In figure- II.

Synthesis of (S)-3-(N-(S)-1-ethoxycarbonyl-3-phenyl)-L-alanyl)-1-methyl-2-oxo-imidazoline-4-carboxylic acid (I)

In a 1litre round bottom flask, slowly added 29.5 grams (0.301moles) of concentrated sulfuric acid to 150 ml of 1,4-dioxane solvent at temperature not exceed 25-30^{0}C and maintain the reaction mass for 30-45 minutes, then added

50 grams of (S)-3-N-((S)-1-ethoxycarbonyl-3-phenyl-L-alanyl)- tertiary butyl (1-methyl-2-oxo-imidazoline)-4-carboxylic acid ester**(VI-A)** (0.100 moles) on lot wise (took 15 minutes) at 25 to 30^0 C. maintain the reaction mass for 6 hours at the same temperature and check the TLC , if it complies then, adjust the pH with Sodium bicarbonate up to neutral pH~7 and the resulting solution was given organic washings with methylene chloride (3x100ml) to remove the organic impurities. Again adjust the pH for aqueous layer with dilute hydrochloric acid (60ml) up to pH~3.98, then acidified mother liquor extracted with methylene chloride (3x150ml), the combined organic layers washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get desired product (S)-3-(N-(S)-1-ethoxycarbonyl-3-phenyl)-L-alanyl)-1-methyl-2-oxoimidazoline-4-carboxylic acid (**I**) as a yellow color oily mass afford 36.5 gram (yield: 93%)Analysis: Purity by HPLC: 98.9%

Synthesis of (S)-3-(N-(S)-1-ethoxycarbonyl-3-phenyl)-L-alanyl)-1-methyl-2-oxo-imidazoline-4-carboxylic acid Hydrochloride salt (II)

In a 250 ml RB flask, the above obtained yellow color oily mass (I) 36.5 grams taken in 80ml of isopropyl alcohol and adjusted pH with 15% dry hydrochloric acid in isopropyl alcohol (18 ml) up to pH~3 at 25 to 30 ^{0} C and then the reaction mass

was stirred for 2-3 hours at the same temperature, and cool it to 0-5 0 C, the precipitated white solid was filtered and washed with chilled isopropyl alcohol (1O ml) afford 31.2 grams (yield : 80%)

Elemental Analysis

1H NMR (DMSO-D6); δ10.0 (s 1H), δ 7.29 (t 2H), δ 7.20 (d 3H), δ 5.01(s 1H), δ 4.68(s 1H), δ 4.10, (t 2H), δ 3.76 (t 2H), δ 3.43 (d 2H) δ 2.7 (s 4H),δ 2.6 (m 1H), δ 1.46 (s 3H), δ 1.2 (s 3H)**Mass (M^+:** 405.44 **)** (Negative (-ve) Scan mode **):** 404.1 (M^{+1})

FT-IR (K Br pellet): 1734 Cm^{-1} (-C=O), 3448 Cm^{-1} (-N-H), 2940 Cm^{-1}(-C-H), 1396 Cm^{-1}(-C-O-C=O). **Purity by HPLC**: 99.98%

The above said mechanism (figure-II) may generate some sulfur trioxide gas which is more environmental hazardous, so that for prevention purposes we have done the work up in sodium bicarbonate to avoid the poisonous gases to acid rain in environment.

RESULTS AND DISCUSSION

In earlier literatures the tertiary butyl ester was hydrolyzed by 15% to 20 % of dry hydrochloride in 1, 4-dioxane more selectively, but its hydrochloride salt is not much stable than for 2-3 months. Then we attempt with sulfuric acid hydrolysis followed by hydrochloride salt formation by isopropyl alcohol.

The stability of drug was examined by HPLC degradative studies for every six months and the results shown that the drug substance is stable for approximately more than 2 year. Here we conducted acid, base and thermal degradative studies for its method of synthesized imidapril hydrochloride.

CONCLUSION

As per above result is concern, the invented method is more selective for de-esterification of tertiary butyl eater of imidapril, followed by hydrochloride salt preparation is suitable method , stable and economically viable at commercial scale of synthesis of Imidapril hydrochloride stable form.Hence the selected process is authentic and superficial.

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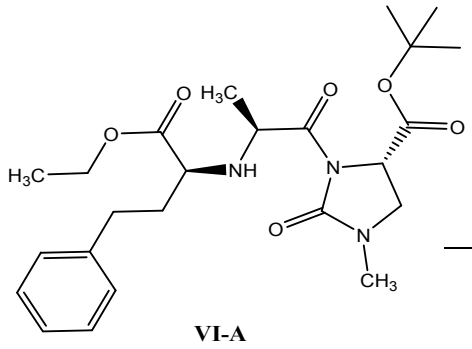
Scheme-I

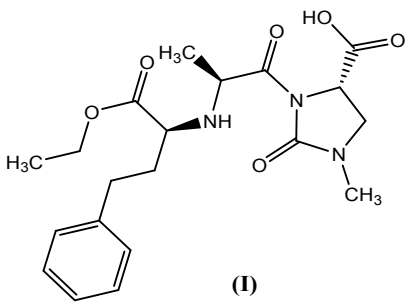


VI-A

(S)-3-(N-((S)-1-Ethoxycarbonyl-3-phenylpropyl)- L-alanyl)-Tertiary butyl(1-methyl-2-oxoimidazoline)-4-carboxylic acid ester

Conc. H_2SO_4
1, 4-dioxane

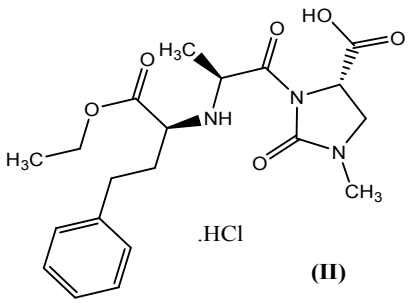
R.T



(I)

(S)-3-(N-((S)-1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl)-1-methyl-2-oxoimidazoline-4-carboxylic ac

IPA Hcl



.HCl

(II)

(S)-3-(N-((S)-1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl)-1-methyl-2-oxoimidazoline-4-carboxylic ac hydroxy chloride .

Figure 1: Route of synthesis for stable Imidapril hydrochloride

Plausible Reaction Mechanism

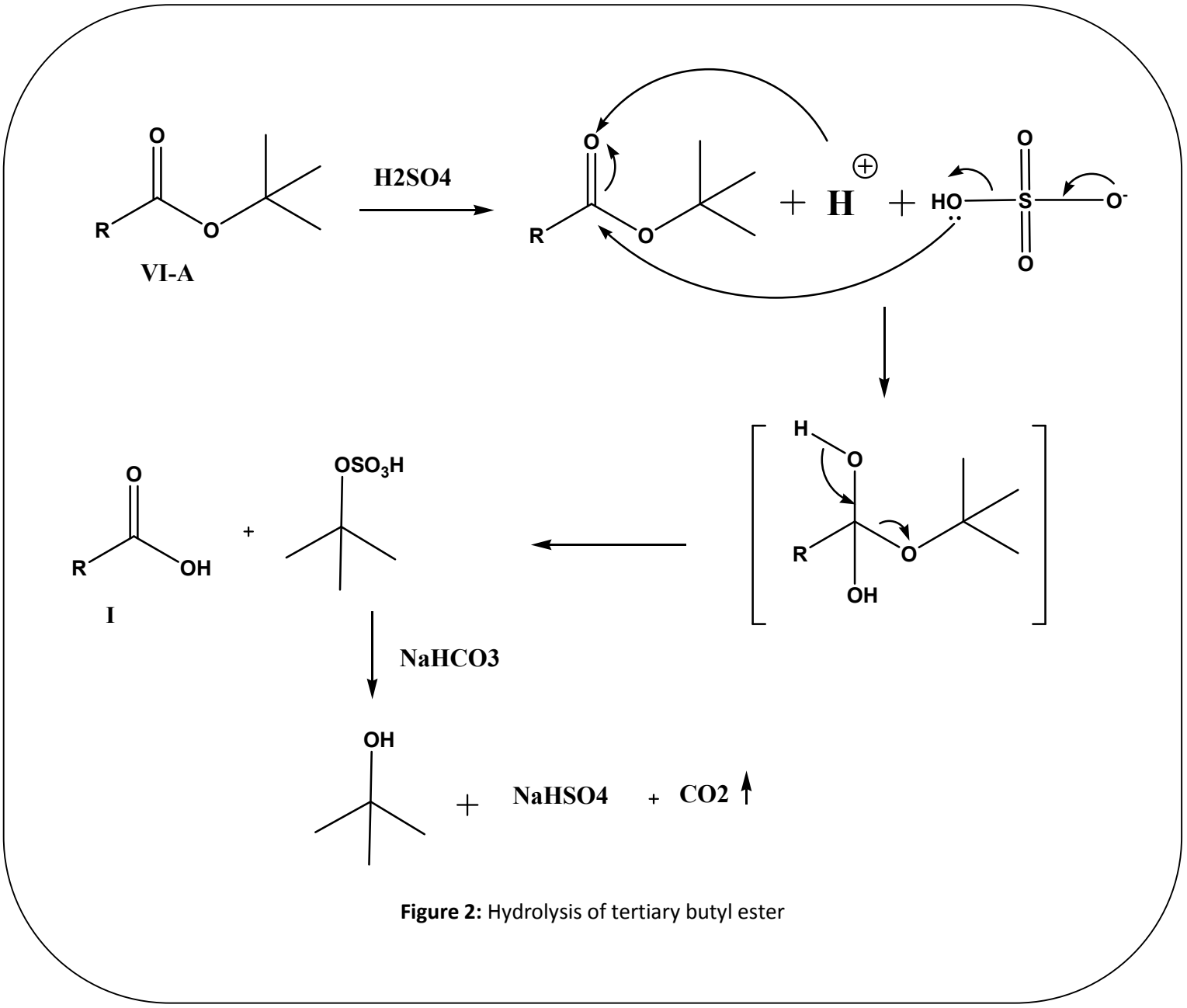


Figure 2: Hydrolysis of tertiary butyl ester