**INTRODUCTION**

Histamine is a major mediator in allergic diseases and has multiple effects that are mediated by specific surface receptors on target cells. Histamine is one of the chemical mediators of inflammation, deriving from the decarboxylation of histidine by histidine decarboxylase. Antihistamine agents inhibit the activity of H₁ histamine receptors, mainly present in the skin and in the bronchi, by blocking histamine release. Several different mediators are involved in the pathophysiology of allergic diseases; histamine remains the principal one and plays a fundamental role. Thus, antihistamines represent the primary class of medications used for the treatment of allergic rhinitis over the past 60 years. Fexofenadine is an active metabolite of the second generation histamine H₁ receptor antagonist (antihistamine).

Fexofenadine hydrochloride, the active ingredient of ALLEGRA tablets, is a histamine H₁-receptor antagonist with the chemical name (±)-4-[4-(4-hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzene acetic acid hydrochloride (Fig. 1). Fexofenadine is used to relieve the allergy symptoms of seasonal allergic rhinitis ("hay fever"), including runny nose; sneezing; red, itchy, or watery eyes; or itching of the nose, throat, or roof of the mouth in adults and children 2 years of age and older. It is also used to relieve symptoms of urticaria (hives; red, itchy raised areas of the skin), including itching and rash in adults and children 6 months of age and older. Allergic diseases are very common human disease, such as allergic rhinitis, chronic sudden rubella and hay fever. Formally, fexofenadine was known as terfenadine carboxylate. Fexofenadine, a well known, most widely used, potent, non-sedating, oral second generation antihistamine drug, which is used for the treatment of seasonal allergic rhinitis and chronic urticaria, symptomatic relief of seasonal allergy.

Terfenadine is a non-sedating antihistamine. It is known to be specific H₁-receptor antagonist that is also devoid of any anticholinergic, antiserotonergic and antiadrenergic affects both in vivo and in vitro. In animal and human metabolite studies, Terfenadine was shown to undergo high first pass side effects. It results in readily measurable plasma concentrations of the major metabolite 4-[4-(4-hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethyl phenyl acetic acid, also known as terfenadine carboxylic acid metabolite or fexofenadine. Fexofenadine possess antihistamine and anti-allergic activity in animal and is believed to lack the cardiac side effects seen with terfenadine. Moreover, it has been postulated that terfenadine is in fact a prodrug and fexofenadine is the active agent. There are several methods known in the literature for preparation of fexofenadine.
In many reported methods however there seems to be only few methods like one disclosed in European patent application number 2289867, preparing fexofenadine without involving any fancy synthetic route. However none of the method known in the literature has disclosed the synthesis of fexofenadine in high yields with the contribution of less affluent purification techniques. It is been observed from the known literature that the methods involving use of inexpensive starting materials like benzene, cumene or related compounds need to undergo Friedel craft acylation to bring substitution at para-position but a major side product i.e. meta-isomer, cannot be neglected which is formed in an amount of 20-25%. The present work is focused towards the reduction of meta-isomer to a level that it does not require any tedious workups and purification for removal of this side impurity. The present study relates to the synthetic routes to synthesize highly regio-selective intermediates which are useful in the preparation of antihistaminic drug fexofenadine and related compounds. This work also proposes a new simple, efficient and ecofriendly route for fexofenadine intermediates synthesis from and easily available and inexpensive raw materials as shown in General Scheme-I.

Table-1, shows the effect of different types of substitutions on the amount of preparation of undesired side impurity i.e meta-isomer. It is observed that the size of alkyl group represented by abbreviation R1, plays a major role in reducing the amount of formation of meta-isomer to a great extent.

**EXPERIMENTAL**

The reagent grade chemicals were purchased from the commercial sources. Progress of reaction was monitored by HPLC. 1H NMR spectra were measured on a Bruker 500 spectro-meter in CDCl3 at 500 MHz using TMS as an internal standard. All chemical shifts were reported on δ scales. The analytical data of all the compounds were highly satisfactory.

**Synthesis of 1-chloro-2-methyl-2-phenylpropane (2):**
To 200 g of 3-chloro-2-methylpropene in 1200 mL of benzene was added 34 g of sulfuric acid and stirred the reaction for 12 h at ambient temperature. Quenched the reaction mass with aq. sodium chloride solution and separated the layers. Dried the organic layer over sodium sulfate and concentrated under reduced pressure to get compound 2.

Mol. formula (mol. wt.): C10H13Cl (168.66); Yield: 85.7 %; purity (HPLC): 99.2 %; 1H NMR (500 MHz in CDCl3): δ 7.37-7.16 (m, 5H, Ar-H), 4.10 (s, 2H, CH2Cl), 1.42 (s, 6H, 2 × CH3).

**General method for the synthesis of 1-oxoalkoxy-2-methyl-2-phenylpropane (3):**
A solution of 318 g of 1-chloro-2-methyl-2-phenylpropane in 1200 mL of N-methyl-pyrroldione was added 2.82 mol of potassium salt of aliphatic carboxylic acid and heated the reaction mass at 200 °C till completion. Reaction mixture was cooled to room temperature, filtered through hyflow bed and washed with 190 mL of N-methyl pyrrolidone. Filtrate was subjected to distillation at 120-135 °C under the vacuum to obtain compound 3.

R1 is CH2CH3 (3a): Mol. formula (mol. wt.): C13H18O2 (206.28); Yield of the product: 89 %; purity (GC): 97.20 %; 1H NMR (500MHz in CDCl3): δ 7.41-7.24 (m, 5H, Ar-H), 4.16 (s, 2H, CH2O), 2.30 (q, 2H, J = 7.0 Hz, -COCH2), 1.38 (s, 6H, 2 × CH3). 1.10 (t, 3H, J = 7.0 Hz, CH2CH3).

R1 is CH2CH2CH3 (3b): Mol. formula (mol. wt.): C14H20O2 (220.3); Yield of the product: 87 %; purity (GC): 94.10 %;
and concentrated to yield the oily product having compound hydrochloride followed by aqueous solution of sodium chloride rated the organic layer. Washed the organic layer with dilute reaction, quenched the reaction mixture with water and separated the organic mass at ambient temperature for 15 h. After completion of oxoalkoxy-2-methyl-2-phenylpropane and stirred the reaction aluminum chloride followed by slow addition of 292 g of 1-chloride in 2100 mL of dichloromethane was added 3.52 mol (desired meta-isomer) in a ratio of 1: 0.09- 0.15 as confirmed by HPLC.

General method for the synthesis of 1-oxoalkoxy-2-methyl-2-[4-(4-chloro-1-oxobutyl)phenyl]propane (4) and 1-oxoalkoxy-2-methyl-2-[3-(4-chloro-1-oxobutyl)phenyl]propane (5): To the solution of 2.14 mol of 4-chlorobutyryl chloride in 2100 mL of dichloromethane was added 3.52 mol aluminum chloride followed by slow addition of 292 g of 1-oxoalkoxy-2-methyl-2-phenylpropane and stirred the reaction mass at ambient temperature for 15 h. After completion of reaction, quenched the reaction mixture with water and separated the organic layer. Washed the organic layer with dilute hydrochloride followed by aqueous solution of sodium chloride and concentrated to yield the oily product having compound (desired para-isomer) and compound (undesired meta-isomers) in a ratio of 1: 0.09- 0.15 as confirmed by HPLC.

R₁ is CH₂CH₃ (4a and 5a): Mol. formula (mol. wt.): C₁₈H₂₅O₃Cl (324.84); Yield of the product: 91 %; purity (HPLC): 91.6 %; 1H NMR (500 MHz in CDCl₃): \( \delta \) 7.95-7.43 (m, 4H), 4.25 (s, 2H), 3.72 (t, 2H), 3.21 (t, 2H), 2.59-2.64 (m, 1H), 2.31-2.23 (m, 2H), 1.40 (s, 6H), 1.24 (d, 6H).

R₁ is CH₂CH₂CH₃ (4b and 5b): Mol. formula (mol. wt.): C₁₉H₂₆O₃Cl (324.84); Yield of the product: 91 %; purity (HPLC): 91.6 %; 1H NMR (500 MHz in CDCl₃): \( \delta \) 7.97-7.46 (m, 4H), 4.25 (s, 2H), 3.72 (t, 2H), 3.21 (t, 2H), 2.59-2.64 (m, 1H), 2.31-2.23 (m, 2H), 1.40 (s, 6H), 1.24 (d, 6H).

R₁ is CH(CH₃)₂ (4c and 5c): Mol. formula (mol. wt.): C₁₇H₂₃O₃Cl (310.81); Yield of the product: 88.75 %; purity (HPLC): 91.6 %; 1H NMR (500 MHz in CDCl₃): \( \delta \) 7.92-7.43 (m, 4H), 4.25 (s, 2H), 3.72 (t, 2H), 3.21 (t, 2H), 2.59-2.64 (m, 1H), 2.31-2.23 (m, 2H), 1.40 (s, 6H), 1.24 (d, 6H).

RESULTS AND DISCUSSION

Table-1 shows the result of substitution and it is observed that the substitution using acetic acid (as per EP2289867) results into formation of countable amount of meta-isomer. The amount of meta-isomer formed during Friedel craft acylation is significantly reduced by use of higher group of carboxylic acid. It is clear from Table-1 that substitution with the carboxylic acids like isobutyl and propyl ester results into drastic decrease in the formation of undesired meta-isomer. The present invention fulfills the objective of preparation of fexofenadine which is economical because of use of cheap raw materials like benzene; environmental friendly as less number of purifications are employed to remove meta-isomer hence incurring use of less volume of solvents.

The present work describes highly efficient route for the regio-selective synthesis of compound which is key intermediate for fexofenadine preparation. All the synthesized compounds are purified by chromatographic methods (HPLC or GC) and analyzed by chemical and spectral techniques.

Conclusion

In conclusion, we have found a method, based on one major qualitative i.e., bulkier carboxylic acids as one of major reagents for the synthesis of desired key intermediate, 1-oxoalkoxy-2-methyl-2-[4-(4-chloro-1-oxobutyl)phenyl]propane employed for the preparation of fexofenadine. The process has the advantage of technically simple and economical to be used at large scale production.

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