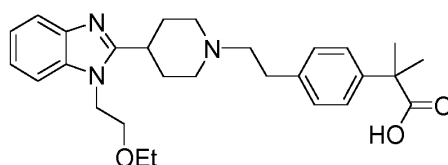


PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BILASTINE**Field of the Invention**

The invention relates to a process for the preparation of key intermediates in the synthesis of Bilastine and to new intermediates in said process.

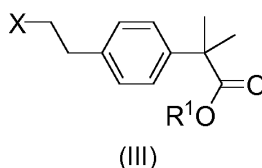
5 Background of the Invention

Bilastine is a second-generation antihistamine medication which is used in the treatment of allergic rhinoconjunctivitis and urticaria.



Bilastine

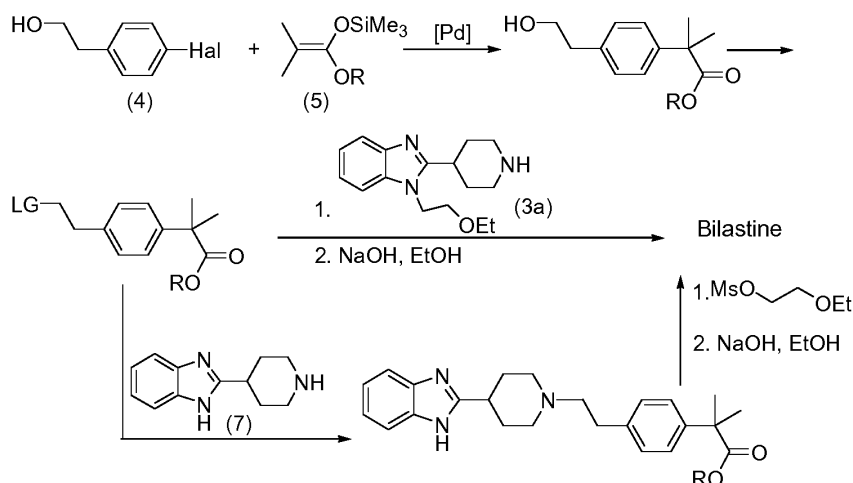
- 10 Several synthesis of Bilastine has been disclosed in the last years using a compound of formula (III) as key intermediate as it provides a straightforward synthetic route for Bilastine, minimizing protecting group chemistry.



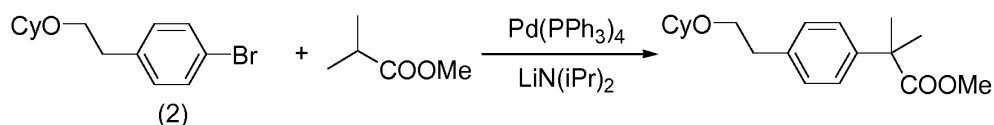
(III)

- 15 For instance, WO 2009/102155 discloses the preparation of this key intermediate by reacting compound 4 and methyltrimethylsilyl dimethylketene acetal (5) in the presence of a Palladium catalyst, t-Bu₃P and ZnF₂. This key intermediate is then converted into Bilastine by either reaction with 1-(2-ethoxyethyl)-2-piperidin-4-yl-1H-benzimidazole (3a) followed by hydrolysis of the ester group or by reaction with 2-(4-
- 20 piperidinyl)-1H-benzimidazole (7), followed by alkylation of the benzimidazole nitrogen and hydrolysis of the ester group. However, this cross coupling approach lacks industrial interest due to the instability, availability and cost of the ketene acetal and the phosphine used in the key step of the synthesis.

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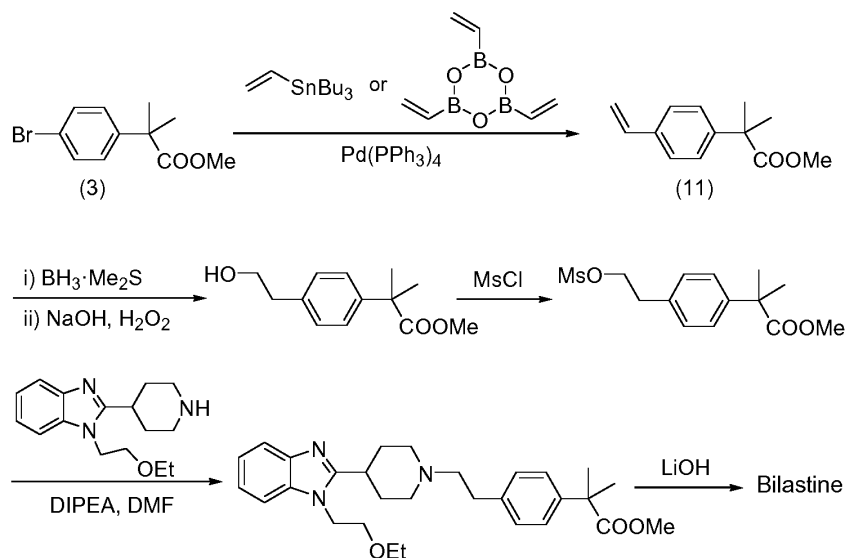


CN 104151160 A refers to the synthesis of compounds similar to key intermediate (III), but which lack a leaving group. The compound is synthesized through the alkylation of the halobenzene compound (2) in the presence of a palladium catalyst and a lithium amide. Then again, this approach uses organometallic reagents and an amide base, which is highly unstable and expensive.

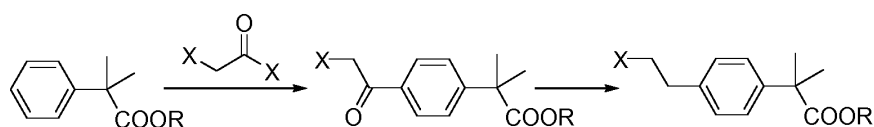


The process for preparing Bilastine disclosed in Synthetic Communications 2011, 41(9), 1394-1402 includes palladium catalyzed vinylation of aryl bromide (3) with vinyl tributylstannane or with vinylboronic anhydride followed by hydroboration of the resulting styrene (11). This alternative cross coupling approach uses in the first step high cost and low available vinyl synthons (and highly toxic in the case of the tin compound). Besides, the anti-Markovnikov hydroxylation step is performed using the well-known and undesirable borane (highly toxic and flammable gas), which also undermines its industrial applicability.

3



CN 104326909 A and CN 102675101 A refer to a process for the synthesis of key intermediate (III) which comprises acylation of 2-methyl-2-phenyl-propanoic acid or an ester thereof in the presence of a Lewis acid and subsequent reduction of the oxo group. This approach, even if industrially applicable, uses stoichiometric reagents both in the acylation and the reduction step and involves the generation of high amounts of residues.



In general, the methods disclosed in the prior art for the preparation of compounds of formula (III) according to the present invention, require the use of organometallic reagents, toxic reagents, harsh reaction conditions or have a low productivity and, therefore, are not suitable for industrial production.

It is therefore necessary to develop a new process for obtaining compounds of formula (III), which are key intermediates in the synthesis of Bilastine, which overcome all or part of the problems associated with the known processes belonging to the state of the art.

Summary of the Invention

The invention faces the problem of providing a new process for the preparation of formula (III) and to intermediates thereof.

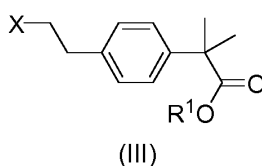
In contrast to processes of the prior art, the process of the invention meets the

needs of industrial production. It allows preparing compounds of formula (III) in the absence of organometallic and toxic reagents, in short reaction times, is a simple and low cost process and gives rise to the desired product with a very high productivity.

The inventors have found that compounds of formula (III) can be obtained in a very straightforward manner by acylation and subsequent oxidative rearrangement of readily available and economical starting materials. As shown in the experimental section, this process not only avoids the use of highly toxic, unstable and/or expensive reagents, but also leads to the compounds of formula (III) in shorter reaction times and with higher productivity than prior art processes. All these features make the process of the invention very cost-efficient and therefore highly suitable for industrial scale production.

The compounds of formula (III) obtained by the process of the invention already include the leaving group required for subsequent reaction with the piperidinyll compound and so does not require additional reaction steps for its use in the preparation of Bilastine.

Thus, in a first aspect the invention is directed to a process for preparing a compound of formula (III)

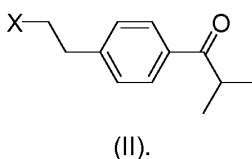


or a solvate thereof wherein

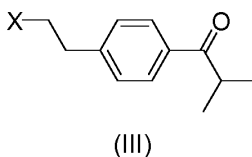
X is a leaving group; and

R¹ is C₁-C₆ alkyl;

which comprises oxidative rearrangement of a compound of formula (II) or a solvate thereof

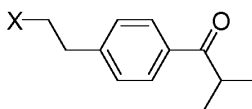


In a second aspect the invention is directed to the use of a compound of formula (II)



or a solvate thereof wherein X is a leaving group as an intermediate in the preparation of Bilastine.

In a third aspect, the invention is directed to a compound of formula (II')



5

(II')

or a solvate thereof wherein X is selected from Cl, I, OMs, OTs and OTf.

Detailed Description of the Invention

The term "alkyl" refers to a linear or branched alkane derivative containing from 1 to 6 ("C₁-C₆ alkyl"), preferably from 1 to 3 ("C₁-C₃ alkyl"), carbon atoms and which is bound to the rest of the molecule through a single bond. Illustrative examples of alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl, hexyl. Preferably, it is methyl.

The term "aryl" refers to an aromatic group having between 6 and 10 ("C₆-C₁₀ aryl"), preferably 6 or 10 carbon atoms, comprising 1 or 2 aromatic nuclei fused to one another. Illustrative examples of aryl groups include phenyl, naphthyl, indenyl, phenanthryl, etc. Preferably, it is phenyl.

The term "(C₆-C₁₀)aryl(C₁-C₆)alkyl" refers to an alkyl group as defined above substituted with an aryl group as defined above. Examples of such groups include benzyl, phenylethyl, phenylpropyl, naphthylmethyl, etc. Preferably, it is benzyl.

The term "haloalkyl" refers to an alkyl group as defined above containing from 1 to 6 ("C₁-C₆ haloalkyl"), preferably from 1 to 3 ("C₁-C₃ haloalkyl"), carbon atoms wherein at least one hydrogen atom has been replaced by halogen. Examples of haloalkyl groups include but are not limited to CF₃, CCl₃, CHF₂, CF₂CF₃. Preferably, it is -CF₃.

The term "halogen" refers to bromine, chlorine, iodine or fluorine.

The term "leaving group" refers to a functional group or an atom that can be displaced by another functional group in a substitution reaction, such as a nucleophilic substitution reaction. Suitable leaving groups are well known in the art. In a particular embodiment, the leaving group is selected from halogen, C₁-C₆ alkylsulfonates, C₁-C₆ haloalkylsulfonates and (C₁-C₆)alkyl(C₆-C₁₀)arylsulfonates, such as chloro, bromo, iodo, mesylate (OMs), triflate (OTf), tosylate (OTs) and the like.

The invention also refers to "salts" of the compounds described in the present description. By way of illustration, said salts can be acid addition salts, base addition

salts or metal salts, and can be synthesized from the parent compounds containing a basic or acid moiety by means of conventional chemical processes known in the art. Such salts are generally prepared, for example, by reacting the free acid or base forms of said compounds with a stoichiometric amount of the suitable base or acid in water or

5 in an organic solvent or in a mixture of the two. Non-aqueous media such as ether, ethyl acetate, ethanol, acetone, isopropanol or acetonitrile are generally preferred. Illustrative examples of said acid addition salts include inorganic acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc., organic acid addition salts such as, for example, acetate, maleate,

10 fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate, *p*-toluenesulfonate, trifluoroacetate, camphorsulfonate, etc. Illustrative examples of base addition salts include inorganic base salts such as, for example, ammonium salts and organic base salts such as, for example, ethylenediamine, ethanolamine, *N,N*-dialkylmethanolamine, triethanolamine, glutamine, amino acid basic salts, etc.

15 Illustrative examples of metal salts include, for example, sodium, potassium, calcium, magnesium, aluminum and lithium salts. In a particular embodiment, the salt is an acid addition salt, such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate, *p*-toluenesulfonate, trifluoroacetate or

20 camphorsulfonate. Preferably, it is selected from HCl, HBr, H₃PO₄, H₂SO₄, MsOH, pTsOH, TFA, citrate and fumarate salt.

Likewise, the compounds described in the present description can be obtained or used both as free compounds or as solvates (e.g., hydrates, alcoholates, etc.), both forms being included within the scope of the present invention. The solvation methods

25 are generally known in the state of the art. Preferably, the solvate is a hydrate.

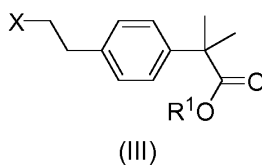
The term "organic solvent" includes for example cyclic and acyclic ethers (e.g. Et₂O, iPr₂O, tBu₂O, MeOtBu, 1,4-dioxane, tetrahydrofuran, methyltetrahydrofuran), hydrocarbon solvents (e.g. pentane, hexane, heptane), halogenated solvents (e.g. dichloromethane, chloroform, chlorobenzene), aromatic solvents (e.g. toluene, xylene),

30 ketones (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), esters (e.g. EtOAc, iPrOAc), nitriles (e.g. acetonitrile, benzonitrile), amides (e.g. DMF, DMA, HMPA, NMP), alcohols (e.g. methanol, ethanol, propanol, isopropanol, sec-butanol, t-butanol), sulfoxides (DMSO) and mixtures thereof.

In a first aspect, the invention is directed to a process for preparing a compound

35 of formula (III)

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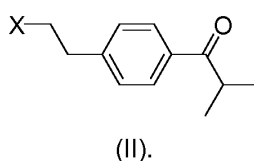


or a solvate thereof wherein

X is a leaving group; and

5 R¹ is C₁-C₆ alkyl;

which comprises oxidative rearrangement of a compound of formula (II) or a solvate thereof

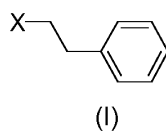


10 In an embodiment, X is selected from Cl, Br, I, OMs, OTs and OTf. Preferably, X is selected from Cl, Br and I; more preferably from Cl and Br; even more preferably X is Cl.

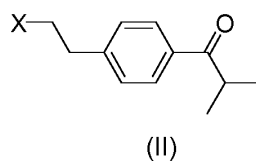
In another preferred embodiment, R¹ is C₁-C₃ alkyl; preferably Me or Et; even more preferably R¹ is Me.

15 In a particular embodiment, the process of the invention comprises:

(a) acylation of a compound of formula (I)

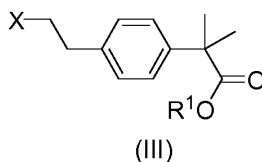


or a solvate thereof wherein X is a leaving group, to provide a compound of
20 formula (II)



or a solvate thereof, and

(b) oxidative rearrangement of a compound of formula (II), or a solvate thereof, to
25 provide a compound of formula (III)



or a solvate thereof wherein R¹ is C₁-C₆ alkyl.

In an embodiment, X is selected from Cl, Br and I and R¹ is C₁-C₃ alkyl.

Though compounds of formula (II) contain a leaving group in beta-position to the aromatic ring, the inventors have found that oxidative rearrangement of these
5 compounds proceeds very efficiently (e.g. Olah et al., J. Am. Chem. Soc. 1982, 104, 5168-5172, reports the instability of this type of compounds under acidic conditions). Consequently, this process allows preparing compounds of formula (III) in a very straightforward manner.

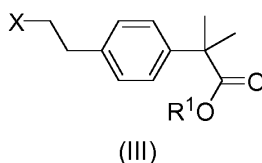
Additionally, the inventors have found that the process of the invention leads to
10 compounds of formula (III) in high yield and short reaction times. It does not require the use of organometallic or toxic reagents, is simple and low cost and gives rise to the desired product with a very high productivity. Consequently, this process is very suitable for industrial scale production.

In a particular embodiment, the process of the invention further comprises
15 converting the compound of formula (III), or a solvate thereof, into Bilastine, or a salt or solvate thereof.

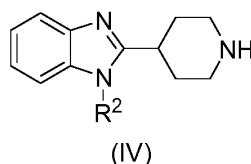
Compounds of formula (III) can be converted into Bilastine through processes known from the prior art (e.g. WO 2009/102155, CN 104326909 A, CN 102675101 A, Synthetic Communications 2011, 41(9), 1394-1402).

20 In a particular embodiment, converting the compound of formula (III), or a solvate thereof, into Bilastine, or a salt or solvate thereof, comprises:

(c) reacting a compound of formula (III)

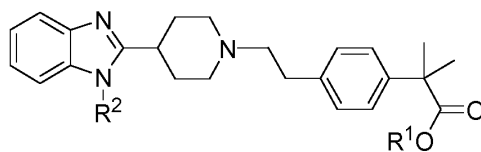


25 or a solvate thereof wherein X and R¹ are as defined above,
with a compound of formula (IV)



or a salt or solvate thereof wherein R² is selected from H and -CH₂CH₂OEt;
30 to provide a compound of formula (V)

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(V)

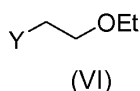
or a salt or solvate thereof; and

- (d) converting the compound of formula (V), or a salt or solvate thereof, into
 5 Bilastine, or a salt or solvate thereof.

When R^2 in the compound of formula (IV), or a salt or solvate thereof, is $\text{CH}_2\text{CH}_2\text{OEt}$, a compound of formula (V) wherein R^2 is $\text{CH}_2\text{CH}_2\text{OEt}$ is obtained after step (c). In this case, step (d) comprises hydrolysis of the ester group in the compound
 10 of formula (V) wherein R^2 is $\text{CH}_2\text{CH}_2\text{OEt}$, or a salt or solvate thereof, to provide Bilastine, or a salt or solvate thereof.

When R^2 in the compound of formula (IV), or a salt or solvate thereof, is H, a compound of formula (V) wherein R^2 is H is obtained after step (c). In this case, step (d) comprises:

- 15 (d1) reacting a compound of formula (V), or a salt or solvate thereof, wherein R^2 is H, with a compound of formula (VI)



(VI)

wherein Y is a leaving group,

- 20 to provide a compound of formula (V), or a salt or solvate thereof, wherein R^2 is $-\text{CH}_2\text{CH}_2\text{OEt}$; and

(d2) hydrolysis of the ester group in the compound of formula (V), or a salt or solvate thereof, wherein R^2 is $-\text{CH}_2\text{CH}_2\text{OEt}$ to provide Bilastine or a salt or solvate thereof.

- 25 In an embodiment, Y is selected from Cl, Br, I, OMs, OTs and OTf.

The inventors have surprisingly found that reaction of the compound of formula (V), or a salt or solvate thereof, wherein R^2 is H, with a compound of formula (VI) as defined above, can be carried out under reaction conditions that also hydrolyze the ester group, thus directly giving rise to Bilastine, or a salt or solvate thereof, from the
 30 compound of formula (V), or a salt or solvate thereof, wherein R^2 is H.

In this way, when the hydrolysis of the ester group in the compound of formula (V), or a salt or solvate thereof, takes place under the reaction conditions used for step (d1), Bilastine is obtained in a very straightforward manner: just 4 synthetic steps from

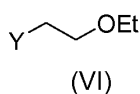
the starting compound of formula (I).

Surprisingly, said process proceeds in a very efficient way, leading directly to Bilastine in a high yield and purity and avoiding the need of an additional hydrolysis step, in contrast to other processes in the prior art.

5 In a particular embodiment, steps (d1) and (d2) are carried out in a one pot process. That is, both steps are carried out in the same reaction vessel or the same reactor without the isolation of the intermediate of formula (V) wherein R^2 is -CH₂CH₂OEt. This avoids the need of lengthy separation process and purification of the intermediate. Consequently, said one-pot process shortens the number of reaction
10 steps required overall to obtain Bilastine, and saves time and resources.

In a further embodiment, hydrolysis of the ester group in the compound of formula (V), or a salt or solvate thereof, takes place under the reaction conditions used for step (d1). In this case, Bilastine, or a salt or solvate thereof, is directly obtained from a compound of formula (V), or a salt or solvate thereof, wherein R^2 is H.

15 Therefore, in a further embodiment of the invention, step (d) comprises reacting a compound of formula (V), or a salt or solvate thereof, wherein R^2 is H with a compound of formula (VI)



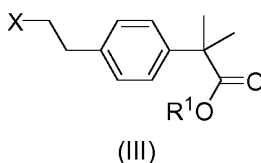
20 wherein Y is a leaving group,
and hydrolysis of the ester group in a compound of formula (V), or a salt or solvate thereof, to provide Bilastine or a salt or solvate thereof.

In this case, both reaction with the compound of formula (VI) and hydrolysis of the ester group take place in a single reaction step.

25 In another embodiment, the compound obtained after step (d1) is isolated, and optionally purified, before performing step (d2).

According to another embodiment of the invention, converting the compound of formula (III), or a solvate thereof, into Bilastine, or a salt or solvate thereof, comprises:

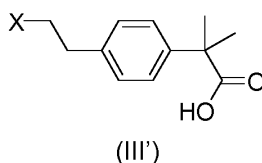
(c') hydrolysis of a compound of formula (III)



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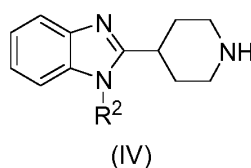
or a solvate thereof wherein X and R^1 are as defined above,
to provide a compound of formula (III')

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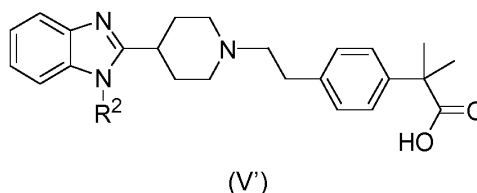


or a salt or solvate thereof;

(d') reacting a compound of formula (III'), or a salt or solvate thereof, with a compound of formula (IV)



or a salt or solvate thereof wherein R² is selected from H and -CH₂CH₂OEt;
to provide a compound of formula (V')



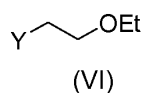
or a salt or solvate thereof; and

(e') if needed, converting the compound of formula (V'), or a salt or solvate thereof, into Bilastine, or a salt or solvate thereof.

Step (e') is needed if R² in the compound of formula (IV) is H.

Otherwise, when R² in the compound of formula (IV) is -CH₂CH₂OEt, Bilastine is obtained after step (d'). In this case, the above mentioned process to convert the compound of formula (III) into Bilastine only comprises steps (c') and (d').

When R² in the compound of formula (IV), or a salt or solvate thereof, is H, a compound of formula (V') wherein R² is H is obtained after step (d'). In this case, step (e') comprises reacting a compound of formula (V'), or a salt or solvate thereof, wherein R² is H, with a compound of formula (VI)



wherein Y is a leaving group, to provide Bilastine or a salt or solvate thereof.

In an embodiment, Y is selected from Cl, Br, I, OMs, OTs and OTf.

Preferably, the processes for preparing Bilastine according to the invention, comprise the above disclosed steps (steps (a) to (d) or steps (a) to (e')) in a sequential order without further reaction steps (e.g. protection or deprotection of functional

groups). That is, in a preferred embodiment, the processes for preparing Bilastine according to the invention, consist of the above disclosed reaction steps (steps (a) to (d) or steps (a) to (e')). Unless otherwise specified, the process can include isolation and purification steps after some or all of these reaction steps.

5 Oxidative Rearrangement of a compound of formula (II)

In an embodiment, oxidative rearrangement of a compound of formula (II), or a solvate thereof, to provide a compound of formula (III), or a solvate thereof, is carried out in the presence of an oxidizing agent and a tri(C₁-C₆)alkyl orthoester, or a (C₁-C₆)alkanol or a mixture thereof.

10 In an embodiment, the tri(C₁-C₆)alkyl orthoester is selected from trimethyl and triethyl orthoester.

In a particular embodiment, the triethyl-trimethylorthoester is selected from triethyl-trimethylorthoformate.

In an embodiment, the (C₁-C₆)alkanol is selected from MeOH and EtOH.

15 Preferably, the tri(C₁-C₆)alkyl orthoester, (C₁-C₆)alkanol or the mixture thereof is used as solvent of the reaction.

Suitable oxidizing agents include iodine oxidizing agents, such as I₂, ICl, ICl₃, HIO₃, PhI(OAc)₂, PhI(OCOCF₃)₂, PhI(OTf)₂, PhI(OH)OTs, PhIO, NIS, IBX, DMP. In an embodiment, the oxidizing agent is selected from I₂, ICl, HIO₃ and PhI(OAc)₂.

20 In a particular embodiment, the oxidizing agent is present in an amount of from 1.0 to 10.0 molar equivalents with respect to the compound of formula (II); preferably from 1.0 to 5.0, more preferably from 1.0 to 3.0 molar equivalents.

In a preferred embodiment, the reaction is carried out in the presence of an acid. Suitable acids that can be used as catalyst include inorganic acids and organic acids
25 such as, for example, sulfuric acid, hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, acetic acid, trifluoroacetic acid, camphorsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, maleic acid, fumaric acid, citric acid, oxalic acid, succinic acid, tartaric acid and malic acid. In a particular embodiment, the acid is selected from HCl, HBr, H₃PO₄, H₂SO₄, MsOH, pTsOH and TFA. Preferably, it is H₂SO₄
30 or HCl.

Preferably, the acid catalyst is generated *in situ* from an acid precursor. Therefore, in a preferred embodiment, the reaction is carried out in the presence of an acid precursor. Suitable acid precursors are known by the skilled person and include alkylacid chloride or alkyl chloroformate, such as, for example, 2,2-dimethyl propionyl
35 chloride, acetyl chloride, propionyl chloride, ethyl chloroformate, methyl chloroformate,

propyl chloroformate, benzyl chloroformate, trichloromethyl chloroformate. In an embodiment, the reaction is carried out in the presence of a hydrochloric acid precursor, such as 2,2-dimethyl propionyl chloride or ethyl chloroformate.

In a particular embodiment, the acid is present in an amount of from 0.01 to 0.9
5 molar equivalents with respect to the compound of formula (II); preferably from 0.05 to 0.6, more preferably from 0.1 to 0.5 molar equivalents.

In an embodiment, the reaction is performed at a temperature between -20°C and 150°C, preferably at a temperature between 20°C and 130°C, preferably between 20°C and 100°C.

10 In an embodiment of the invention, the oxidative rearrangement is carried out in the presence of a tri(C₁-C₆)alkyl orthoester, a (C₁-C₆)alkanol or a mixture thereof, an oxidizing agent and an acid catalyst.

In a particular embodiment, the oxidative rearrangement is carried out in the presence of a tri(C₁-C₆)alkyl orthoester, an iodine oxidizing agent and an acid catalyst.

15 In a particular embodiment, the reaction is carried out in the absence of a solvent (other than the reagents used for the reaction). Preferably, the tri(C₁-C₆)alkyl orthoester is used as solvent of the reaction.

In another embodiment, the oxidative rearrangement is carried out in the presence of an organic solvent. In an embodiment, the organic solvent is selected from
20 cyclic and acyclic ethers (e.g. Et₂O, iPr₂O, tBu₂O, MeOtBu, 1,4-dioxane, THF, 2-methyl-THF), hydrocarbon solvents (e.g. pentane, hexane, heptane), halogenated solvents (e.g. dichloromethane, chloroform, chlorobenzene), aromatic solvents (e.g. toluene, xylene), alcohols (e.g. methanol, ethanol, propanol, isopropanol, sec-butanol, t-butanol) and mixtures thereof. Preferably, the organic solvent is an alcohol; more
25 preferably a C₁₋₆ alkanol, such as methanol, ethanol, propanol, isopropanol, sec-butanol, t-butanol; even more preferably it is methanol.

In an embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent and an acid catalyst.

30 In another embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent, an acid catalyst and an organic solvent.

In another embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent selected from I₂, ICl, HIO₃ and PhI(OAc)₂, and an acid selected from HCl, HBr, H₃PO₄, H₂SO₄, MsOH,
35 pTsOH and TFA.

In a further embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent selected from I_2 , ICl, HIO_3 and $PhI(OAc)_2$, an acid selected from HCl, HBr, H_3PO_4 , H_2SO_4 , MsOH, pTsOH and TFA, and an organic solvent.

- 5 In a further embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent selected from I_2 , ICl, HIO_3 and $PhI(OAc)_2$, an acid selected from H_2SO_4 and HCl.

In another embodiment, the oxidative rearrangement is carried out in the presence of trimethyl orthoformate (TMOF), an iodine oxidizing agent selected from I_2 ,
10 ICl, HIO_3 and $PhI(OAc)_2$, an acid selected from H_2SO_4 and HCl, and an organic solvent.

Acylation of a compound of formula (I)

Acylation of a compound of formula (I), or a solvate thereof, is carried out in the presence of a suitable acylating agent. In an embodiment, the acylating agent is selected from $(iPrCO)_2O$ and a compound of formula $iPrCO-Z$, wherein Z is selected
15 from OH, Cl, Br and I. Preferably, the acylating agent is $iPrCO-Cl$.

In a particular embodiment, the acylating agent is present in an amount of from 1.0 to 10.0 molar equivalents with respect to the compound of formula (I); preferably from 1.0 to 5.0, more preferably from 1.0 to 3.0 molar equivalents.

In an embodiment, the reaction is carried out in the presence of a protic acid
20 and/or a Lewis acid. Suitable protic and Lewis acid for the Friedel Crafts acylation are known in the prior art. In an embodiment, the acid is selected from $AlCl_3$, $AlBr_3$, $FeCl_3$, $FeBr_3$, BF_3 , BBr_3 , BCl_3 , ZnO, $ZnCl_2$, $ZnBr_2$, $TiCl_4$, $SnCl_4$, $SiCl_4$, $POCl_3$, $FeSO_4$ and hydrates or solvate thereof, HCl, H_2SO_4 , H_3PO_4 , $HClO_4$, HBF_4 , $ClSO_3H$, MsOH and TfOH. Preferably, the acid is $AlCl_3$.

25 In a particular embodiment, the acid is present in an amount of from 0.1 to 10.0 molar equivalents with respect to the compound of formula (I); preferably from 0.1 to 5.0, more preferably from 0.5 to 3.0 molar equivalents.

In a particular embodiment, the acylation reaction is carried out in the presence of an organic solvent. Suitable solvents include, for example, ethers, hydrocarbon
30 solvents, halogenated solvents, aromatic solvents, ketones, esters, and mixtures thereof. In an embodiment, the solvent is a hydrocarbon solvent, such as pentane, hexane or heptane. In an embodiment, the reaction is carried out in the presence of a non-polar organic solvent, such as an ether (e.g. Et_2O , iPr_2O , tBu_2O , MeOtBu, 1,4-dioxane), a hydrocarbon solvent (e.g. pentane, hexane, heptane) a halogenated
35 solvent (e.g. dichloromethane, chloroform) or an aromatic solvent (e.g. toluene,

xylene).

In another preferred embodiment, the reaction is carried out neat, that is, in the absence of a solvent.

Preferably, the reaction is carried out neat or in the presence of a non-polar
5 organic solvent.

In an embodiment, the reaction is performed at a temperature between -78°C and 100°C, preferably at a temperature between -20°C and 60°C, preferably between 0°C and 40°C.

In a particular embodiment, the acylation reaction is carried out in the presence
10 of a suitable acylating agent and an acid.

In another embodiment, the acylation reaction is carried out in the presence of an acylating agent is selected from (iPrCO)₂O and a compound of formula iPrCO-Z, wherein Z is selected from OH, Cl, Br and I, and a protic acid and/or a Lewis acid.

In a preferred embodiment, the acylation reaction is carried out in the presence of
15 iPrCO-Cl and AlCl₃.

Reaction of a compound of formula (III) or (III') with a compound of formula (IV)

Reaction of a compound of formula (III) or (III') with a compound of formula (IV) to provide a compound of formula (V) or (V'), respectively, can be carried out as disclosed previously in the prior art.

20 In a particular embodiment of the invention, the reaction is carried out in the presence of a base and an organic solvent.

Suitable bases include inorganic and organic bases, such as an alkali metal carbonate or bicarbonate (e.g. Na₂CO₃, K₂CO₃, Cs₂CO₃, Li₂CO₃, NaHCO₃, KHCO₃, CsHCO₃, LiHCO₃), an alkali metal phosphate (e.g. Na₃PO₄, K₃PO₄, Na₂HPO₄, K₂HPO₄,
25 NaH₂PO₄, KH₂PO₄), an alkali metal alkoxide (e.g. NaOMe, KOMe, NaOEt, KOEt, NaOtBu, KOtBu), an alkali metal hydroxide (e.g. NaOH, KOH, LiOH, CsOH), an aliphatic or aromatic amine (e.g. Me₂NH, Et₂NH, iPr₂NH, Bu₂NH, Me₃N, Et₃N, Bu₃N, iPr₂EtN, N-methylmorpholine, pyridine, DMAP, aniline, N,N-dimethylaniline). Preferably, the base is an inorganic base, more preferably it is an alkali metal carbonate,
30 bicarbonate or phosphate.

In an embodiment, the organic solvent is a polar organic solvent, such as THF, a ketone (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), an ester (e.g. EtOAc, iPrOAc), a nitrile (e.g. acetonitrile, benzonitrile), an amide (e.g. DMF, DMA, HMPA, NMP), a sulfoxide (DMSO), alcohol (e.g. methanol,
35 ethanol, propanol, isopropanol, sec-butanol, t-butanol), or mixtures thereof. In a further

embodiment, the organic solvent is a polar aprotic organic solvent, such as THF, a ketone (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), an ester (e.g. EtOAc, iPrOAc), a nitrile (e.g. acetonitrile, benzonitrile), an amide (e.g. DMF, DMA, HMPA, NMP), a sulfoxide (DMSO), or mixtures thereof.

- 5 In a preferred embodiment, the reaction is carried out in the presence of an inorganic base and a polar aprotic organic solvent.

In an embodiment, the reaction is performed at a temperature between 20°C and 180°C, preferably at a temperature between 20°C and 160°C, preferably between 50°C and 150°C.

- 10 Reaction of a compound of formula (V) or (V') wherein R^2 is H with a compound of formula (VI)

Reaction of a compound of formula (V) or (V') wherein R^2 is H with a compound of formula (VI) to provide a compound of formula (V) wherein R^2 is $-\text{CH}_2\text{CH}_2\text{OEt}$ or Bilastine, respectively, can be carried out as disclosed previously in the prior art.

- 15 In a particular embodiment of the invention, the reaction is carried out in the presence of a base and an organic solvent.

- Suitable bases include inorganic and organic bases, such as an alkali metal carbonate or bicarbonate (e.g. Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , Li_2CO_3 , NaHCO_3 , KHCO_3 , CsHCO_3 , LiHCO_3), an alkali metal phosphate (e.g. Na_3PO_4 , K_3PO_4 , Na_2HPO_4 , K_2HPO_4 , NaH_2PO_4 , KH_2PO_4), an alkali metal alkoxide (e.g. NaOMe, KOMe, NaOEt, KOEt, NaOtBu, KOtBu), an alkali metal hydroxide (e.g. NaOH, KOH, LiOH, CsOH), an aliphatic or aromatic amine (e.g. Me_2NH , Et_2NH , iPr_2NH , Bu_2NH , Me_3N , Et_3N , Bu_3N , iPr_2EtN , N-methylmorpholine, pyridine, DMAP, aniline, N,N-dimethylaniline). Preferably, the base is an inorganic base; more preferably an alkali metal hydroxide or alkoxide; even more preferably an alkali metal hydroxide such as NaOH, KOH, LiOH or CsOH.

- In an embodiment, the organic solvent is a polar organic solvent, such as THF, a ketone (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), an ester (e.g. EtOAc, iPrOAc), a nitrile (e.g. acetonitrile, benzonitrile), an amide (e.g. DMF, DMA, HMPA, NMP), a sulfoxide (DMSO), alcohol (e.g. methanol, ethanol, propanol, isopropanol, sec-butanol, t-butanol), or mixtures thereof. In a further embodiment, the organic solvent is a polar aprotic organic solvent, such as THF, a ketone (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), an ester (e.g. EtOAc, iPrOAc), a nitrile (e.g. acetonitrile, benzonitrile), an amide (e.g. DMF, DMA, HMPA, NMP), a sulfoxide (DMSO), or mixtures thereof.

- 35 In a preferred embodiment, the reaction is carried out in the presence of an

inorganic base, preferably an alkali metal hydroxide, and a polar organic solvent.

In an embodiment, the reaction is performed at a temperature between 0°C and 180°C, preferably at a temperature between 20°C and 160°C, preferably between 30°C and 100°C.

- 5 In a preferred embodiment of the invention, hydrolysis of the ester group to the carboxylic acid takes place under the reaction conditions for reacting the compound of formula (V) wherein R² is H with a compound of formula (VI). In this case, Bilastine or a salt or solvate thereof is directly obtained without the need of an additional reaction step. In a particular embodiment, this is carried out in the presence of an inorganic
10 base, preferably an alkali metal hydroxide (e.g. KOH or NaOH), and a polar organic solvent (e.g. DMSO).

Hydrolysis of the ester group

- Hydrolysis of the ester group in a compound of formula (V) wherein R² is -CH₂CH₂OEt or in a compound of formula (III) to provide Bilastine or a compound of
15 formula (III'), respectively, can be carried out as disclosed previously in the prior art.

- In an embodiment, the reaction is carried out by acid or basic hydrolysis. In a particular embodiment, hydrolysis is carried out by treatment with an acid or a base under heat. Suitable acids include acetic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, HCl, HBr, HF, HClO₄, H₂SO₄, HNO₃, H₃PO₄, formic
20 acid, propionic acid, butyric acid, malic acid, citric acid, benzoic acid, p-toluenesulfonic acid, oxalic acid and succinic acid, preferably HCl, HBr and H₂SO₄. Suitable bases include alkali metal carbonates or bicarbonates (e.g. Na₂CO₃, K₂CO₃, Cs₂CO₃, Li₂CO₃, NaHCO₃, KHCO₃, CsHCO₃, LiHCO₃), alkali metal phosphates (e.g. Na₃PO₄, K₃PO₄, Na₂HPO₄, K₂HPO₄, NaH₂PO₄, KH₂PO₄), alkali metal alkoxides (e.g. NaOMe, KOMe,
25 NaOEt, KOEt, NaOtBu, KOtBu), and alkali metal hydroxides (e.g. NaOH, KOH, LiOH, CsOH). Preferably, the base is an alkali metal hydroxide or alkoxide; more preferably an alkali metal hydroxide such as NaOH, KOH, LiOH or CsOH.

In an embodiment, the reaction is carried out in the presence of water, an organic solvent, or mixtures thereof.

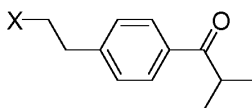
- 30 In a particular embodiment, the reaction is carried out in the presence of an organic solvent, preferably a polar organic solvent such as THF, a ketone (e.g. acetone, butanone, pentanone, methyl ethyl ketone, ethyl isopropyl ketone), an ester (e.g. EtOAc, iPrOAc), a nitrile (e.g. acetonitrile, benzonitrile), an amide (e.g. DMF, DMA, HMPA, NMP), a sulfoxide (DMSO), alcohol (e.g. methanol, ethanol, propanol,
35 isopropanol, sec-butanol, t-butanol), or mixtures thereof.

In a preferred embodiment, the reaction is carried out in the presence of an inorganic base, preferably an alkali metal hydroxide, and a polar organic solvent.

In an embodiment, the reaction is performed at a temperature between 0°C and 180°C, preferably at a temperature between 20°C and 160°C, preferably between 30°C and 100°C.

In a preferred embodiment, hydrolysis of the ester group takes place under the basic conditions used of the reaction of the compound of formula (V) wherein R² is H with a compound of formula (VI), so that Bilastine, or a salt or solvate thereof, is directly obtained in a single reaction step from the compound of formula (V) wherein R² is H, or a salt or solvate thereof.

In another aspect, the invention is directed to the use of a compound of formula (II)



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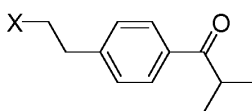
(III)

or a solvate thereof wherein X is a leaving group as an intermediate in the preparation of Bilastine.

In an embodiment, X is selected from Cl, Br, I, OMs, OTs and OTf; preferably X is Cl or Br; more preferably X is Cl.

20

In a further aspect, the invention is directed to a compound of formula (II')



(II')

or a solvate thereof wherein X is selected from Cl, I, OMs, OTs and OTf.

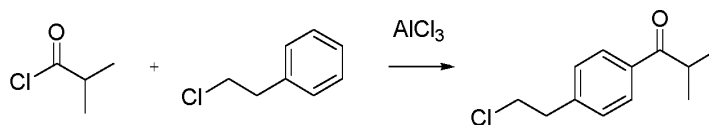
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In a preferred embodiment, X is Cl.

It should be understood that the scope of the present disclosure includes all the possible combinations of embodiments disclosed herein.

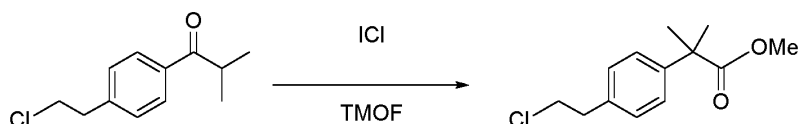
EXAMPLES

30 **Example 1: Preparation of 1-(4-(2-chloroethyl)phenyl)-2-methylpropan-1-one**



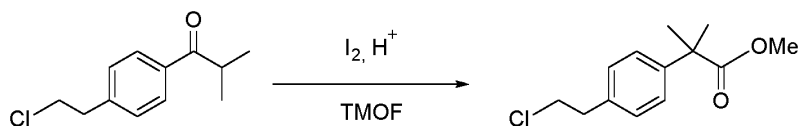
In a reaction vessel iPrCOCl (8.2 g) was cooled to 9°C and mixed with AlCl_3 (5.2 g). 2-Chloroethylbenzene (4.3 g) was added dropwise and the mixture was stirred for 60 minutes, poured over HCl 1M (50 mL) at 0°C . TBME (10 mL) was added and the mixture was stirred. The organic layer was washed with NaOH 1M (25 mL), separated, dehydrated with anhydrous sodium sulfate and then condensed and the solvent was removed under vacuum. 7.4 g of 1-[4-(2-chloro-ethyl)phenyl]-2-methylpropan-1-one were obtained in a 100% yield and a 90% purity.

Example 2: Preparation of 2-[4-(2-Chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester



In a round-bottom flask with a reflux condenser, ICl (9.6 mL) was added to a solution of 1-[4-(2-chloro-ethyl)-phenyl]-2-methyl-propan-1-one (13.42 g) in TMOF (55 mL). The mixture reacted fairly vigorously in an exothermic reaction. After few minutes, when the bubbling and the reflux had stopped, the mixture was cooled down and the workup was performed as follows: it was quenched with a saturated solution of sodium bicarbonate (120 mL) and extracted with dichloromethane (80 mL x 3). The organic layer was washed with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 150 mL), dried with anhydrous sodium sulfate and concentrated. 15.03 g of 2-[4-(2-chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester were obtained in a 98% yield and 85% purity.

Example 3: Preparation of 2-[4-(2-Chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester



I_2 (794 mg) was added to a round-bottom flask with 1-[4-(2-chloro-ethyl)-phenyl]-2-methyl-propan-1-one (200 mg) in TMOF (913 μL). The mixture was stirred for five minutes before sulphuric acid (22 μL) was added. At this point, the vessel was heated at 80°C . After 1 hour, workup was accomplished by the addition of a solution of NaHCO_3 (5 mL) and then extraction with dichloromethane (5 mL x 3). The organic layer was washed with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL), dried with anhydrous sodium sulfate

and concentrated under vacuum. 0.226 g of 2-[4-(2-Chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester were obtained in a 99% yield and 86% purity.

Example 4: Preparation of 2-[4-(2-Chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester

5 I₂ (290 mg) was dissolved in 1.65 mL of a 0.23M solution of HCl in MeOH. It was mixed with 1-[4-(2-chloro-ethyl)-phenyl]-2-methyl-propan-1-one (200 mg) and with TMOF (400 mg). The mixture was heated at 100°C for 10 minutes, cooled to room temperature and poured over 5 mL of a Na₂S₂O₃ solution. The mixture was extracted with DCM (2 x 5 mL). The organic layer was washed with a solution of Na₂S₂O₃ (5 mL), dried with
10 anhydrous sodium sulfate and concentrated under vacuum. 0.220 g of 2-[4-(2-chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester were obtained in a 96% yield and 70% purity.

Alternatively, [4-(2-Chloro-ethyl)-phenyl]-2-methyl-propionic acid methyl ester was also obtained as in Example 4 but using ethyl chloroformate as the acid source instead of
15 the solution of HCl in MeOH.

Productivity comparison

In the following table, the productivity and process cycle times of the process of the invention is compared to those of the best or closest examples from the prior art. The
20 productivity refers to the amount of product of formula (III) obtained based on the total amount of starting materials, reagents and solvents used in the process. This is a measure of the cost-efficiency of a process and so is of great importance for industrial scale production.

Reference ^[a]	Examples	Productivity kg _{output} /kg _{input} ^[b]	Process cycle time ^[c]	Comment
WO2009/102155	Ex. 1 and Ex. 5	0.062	20 h	Best results -OMs product
WO2009/102155	Ex. 1 and Ex. 7	0.017	20 h	-Cl product
CN104151160A	Ex. 1	0.094 ^[d]	1 h	Best results -OEt product (Not a leaving group)
Synth. Comm.	Via Stille	0.010	21 h	-OMs product

2011, 41, 1394.	Coupling			
CN104326909A	Ex. 1 and Ex. 4	0.063	24 h	Best results -Br product
Invention	Ex. 1 and Ex. 2	0.106	2 h	-Cl product

^[a] Patent CN 102675101 A does not contain a detailed experimental procedure.

^[b] Measuring of the sum of the amounts of starting materials, reagents and solvents used in the reaction steps. Solvents and solutions used during the work up are not taken into account.

5 ^[c] Considering reaction times, without workup.

^[d] Considering 1M concentration in toluene (typical commercial presentation) as there is no data of solvent volume.

As shown above, the process of the invention allows the preparation of compounds of formula (III) in a very high productivity and short reaction times. Consequently, this process is very cost-efficient and so very suitable for industrial production. Additionally, the process does not require the use of organometallic or highly toxic reagents, as in other prior art processes. Finally, the resulting compounds of formula (III) already include the leaving group required for subsequent reaction with the piperidinyll compound and so does not require additional reaction steps for its use in the preparation of Bilastine.