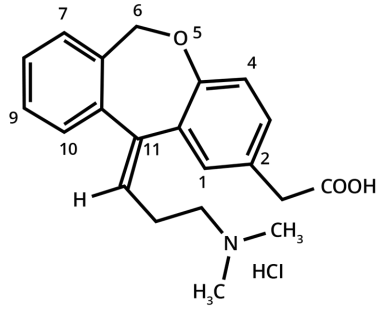
Curia's Patented Process For Intermediates Useful For Manufacturing The API Olopatadine HCl

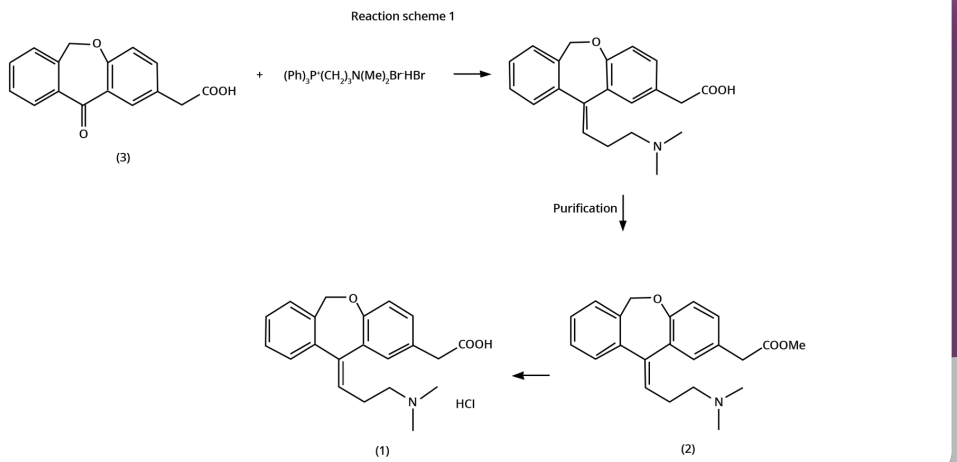
Olopatadine hydrochloride [(Z)-11-(3 dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride], has the following formula:



Synthetic methods for preparing Olopatadine and pharmaceutically acceptable salts thereof were described in different patents such as: EP214779, U.S. 4,871,865, EP235796, and U.S. 5,116,863.

Patent EP214779 described two general processes to produce Olopatadine, one of them involving a Wittig reaction and the other a Grignard reaction followed by a dehydration step.

U.S. 5,116,863 described the production of Olopatadine hydrochloride by several different processes, two of which include a Grignard reaction for introducing the side chain at position 11 and a third process in which said side chain is introduced at position 11 by means of a Wittig reaction. It is described in Example 9 how the Wittig reaction was performed on the 6,11-dihydro-1′-oxodibenz[b,e]oxepin-2-acetic acid substrate (3), also known as Isoxepac, which was reacted with (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in the presence of n-butyl lithium, giving rise to a Z/E mixture of Olopatadine, together with salts of phosphorus which, after purification by means of transforming it into the methyl ester of Olopatadine (2) and subsequent hydrolysis, give Olopatadine hydrochloride (1), as shown in the following Reaction Scheme 1.



In the process shown in Reaction Scheme 1, there are some drawbacks, such as:

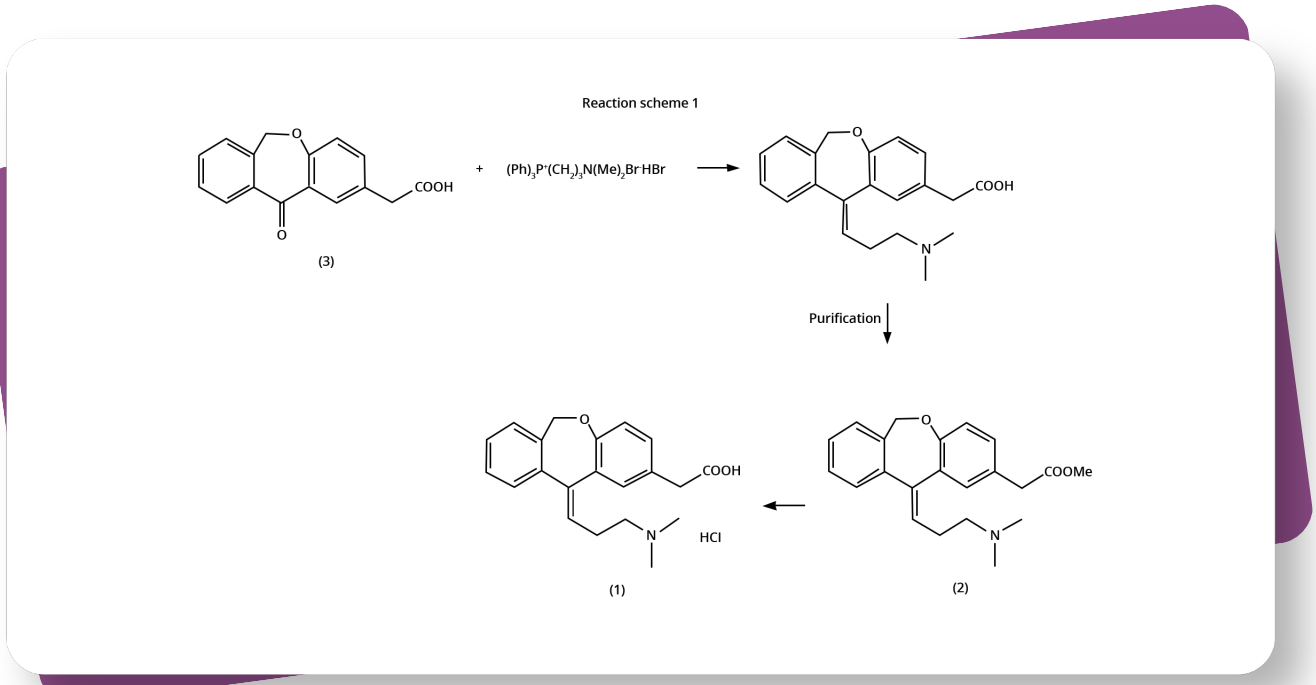
- Using an excess of up to 5 equivalents per equivalent of the Wittig reagent [(Ph)3 P+ (CH2)3 N(Me)2 Br− HBr] related to Isoxepac (3)
- A dangerous reagent is used à (n-butyl lithium)
- The process includes several extractions and changes of pH, in addition to esterification and subsequent saponification
- The Z/E isomer ratio obtained in said process was not described

Thus due to the numerous steps, the process affords low yields and is expensive.

Ohshima E. et al., in J. Med. Chem., 1992, 35:2074-2084, described several methods for synthesizing Olopatadine hydrochloride and other compounds of similar structure by means of Grignard reactions in some cases, and by means of Wittig reactions in other cases, for introducing the side chain 3-dimethylaminopropylidene. Following the synthetic scheme shown in Reaction Scheme 1, they started from type (3) compounds with free carboxylic acid and used (i) as base, n-butyl lithium, in a ratio relative to the type (3) compound of 7.5 equivalents of base/equivalent of type (3) compound and (ii) as Wittig reagent, (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide, in a ratio relative to the type (3) compound of 4.9 equivalents of the Wittig reagent/equivalent of type (3) compound.

Once the Wittig reaction was carried out, to better isolate the products, the acid was subsequently esterified and purified by column chromatography; the obtained Z/E isomer ratio was described as 2:1. In said article, the authors (page 2077) acknowledge that when they try to perform this same Wittig reaction starting from a type (3) compound having an ester group instead of a carboxylic acid, the reaction does not occur and the starting material is recovered without reacting. This described process has several drawbacks since it needs large amounts of both the Wittig reagent and the base, n-butyl lithium. In addition, it needs esterification, column purification, saponification and purification again, whereby the global process seems inefficient for industrial purposes.

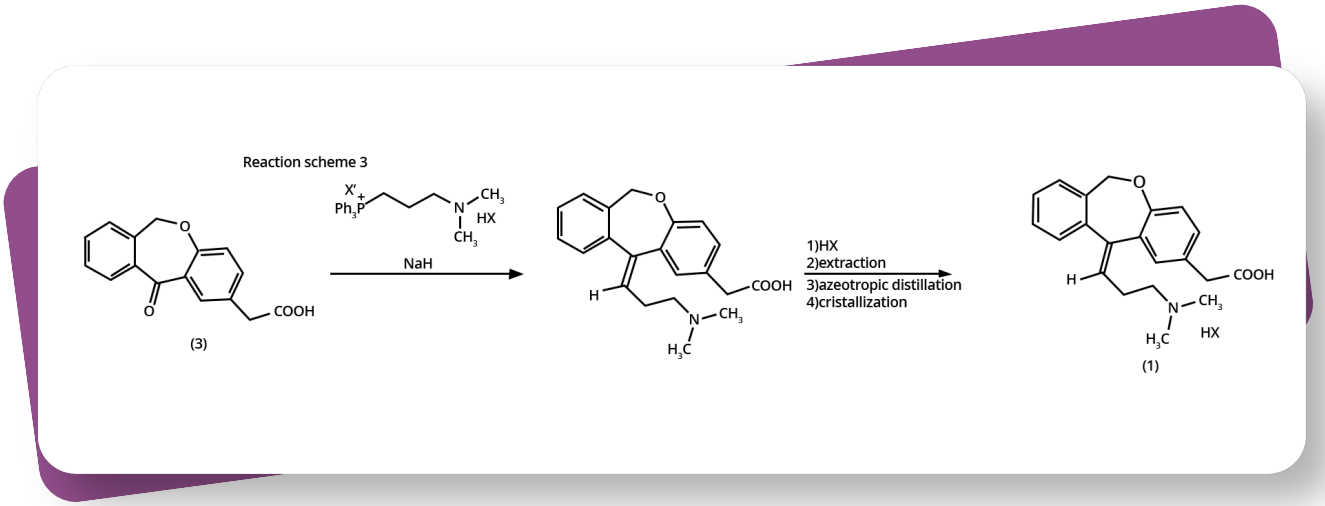
WO2006/010459 described the synthesis of Olopatadine hydrochloride by means of a process in which a Wittig reaction was also performed but, this time, on an open substrate with final cyclization to form an oxepin intermediate by means of Pd catalyst, as shown in Reaction Scheme 2.



The process shown in Reaction Scheme 2 has several drawbacks:

- A high number of synthetic steps
- The use of palladium catalysts , which increase the cost of the process
- The obtained Z/E isomer ratio, which was described as only 2.5:1 in favor of the Z isomer
- The need to use ion exchange resins and chromatography columns, together with the use of dangerous reagents such as lithium aluminium hydride, n-butyl lithium , or Jones reagent, make the process unfeasible on an industrial scale.

Application US2007/0232814 described obtaining Olopatadine hydrochloride by means of a process which includes a Wittig reaction between Isoxepac (3) and the corresponding Wittig reagent (3-dimethylaminopropyl)-triphenylphosphonium halides or salts thereof, using sodium hydride (NaH) as a base, whereby Olopatadine base is obtained, which, after subsequent formation of an additional salt (essential for the production and isolation of the product of interest) and purification, yields Olopatadine hydrochloride (1), as shown in Reaction Scheme 3.

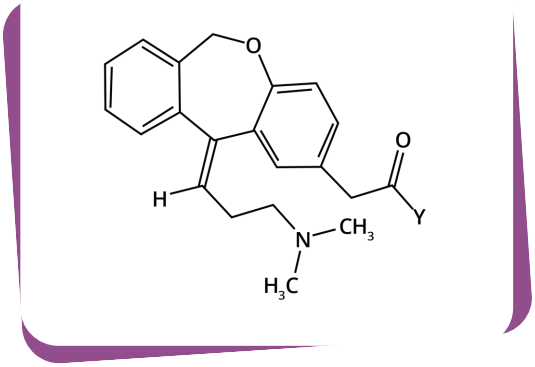


In the process shown in Reaction Scheme 3, the amounts of Wittig reagent and of base used are very high since, when the Wittig reagent is used in the form of salt, 2.7 equivalents and 8.1 equivalents of base (NaH) are used, whereas, if the free Wittig reagent is used, 2.7 equivalents and 4.0 equivalents of base (NaH) are used.

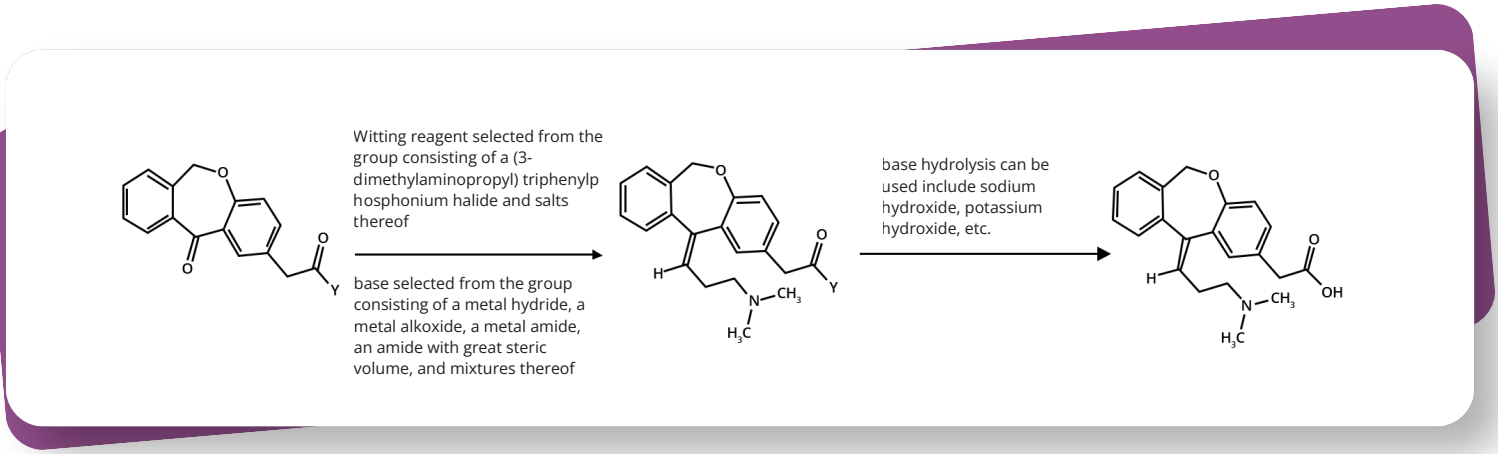
In these conditions, the reaction can last more than one day, and the obtained Z/E isomer ratio is only 2.3:1, which results in a relatively low final yield and makes subsequent purification necessary. Thus, the mentioned drawback of the described process makes it not attractive from the industrial point of view.

Curia's Patented Process

Curia's scientists found that a compound of formula 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid esters or amides, or a salt or solvate thereof, is a key intermediate in the manufacture of Olopatadine HCl.



Despite being discarded by prior art documents, the solution provided by Curia's scientists was based on the fact that they observed that it was surprisingly possible to efficiently obtain (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Olopatadine) and salts thereof by means of a process comprising performing a Wittig reaction between a Wittig reagent selected from a (3-dimethylaminopropyl)-triphenylphosphonium halide and salts thereof, with an ester or with a 6,11-dihydro-1′-oxodibenz[b,e]oxepin-2-acetic acid amide, in the presence of a base, an organic solvent and, optionally, an organic polar aprotic cosolvent ; subsequently, subjecting the obtained compound (Olopatadine ester or amide) to a hydrolysis reaction of the protected carboxylic acid to obtain the corresponding free acid (Olopatadine), and, if desired, converting said compound into a salt.



A process such as the one provided by Curia's scientists has several advantages since the use of very dangerous reagents such as n-butyl lithium is not required, and lower relative amounts of reagents than those previously described in prior art documents for this type of reactions are used, allowing better isolation and higher purity of the product without having to use costly purification techniques (e.g., chromatography), thus making this process more advantageous from the industrial point of view.

Surprisingly, high Z/E isomer ratios, up to 4:1, are obtained, increasing the global yield of the reaction compared to the previously described processes, further enabling simpler isolation of the product.

For further details, please check Curia Spain patent US 9,000,195 B2.

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