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(54) Title: A PROCESS FOR THE SYNTHESIS OF (E) -2-[1 - (4 - METHYL PHENYL) -3-(1-PYRRONYL)-1 - PROPENYL] PYRIDINE (TRIPROLIDINE)

(57) Abstract: A Process for the synthesis of (E) - 2 - [1 - (4 - methyl phenyl) -3- (1- pyrrolidinyl)-l- propenyl] pyridine (TRIPROLIDINE) by reacting 2-(l-pyrrolidino)ethyl triphenyl phosphonium bromide with 2-(p-toluoyl) pyridine in presence of aprotic solvent and a base, isomeising in presence of acid catalyst.

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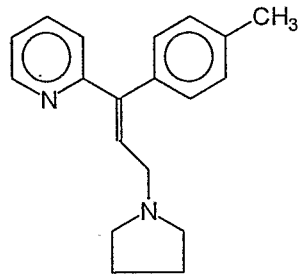
A PROCESS FOR THE SYNTHESIS OF (E) – 2 - [1 - (4 - METHYL PHENYL) – 3 - (1 - PYRROLIDINYL) – 1 - PROPENYL] PYRIDINE (TRIPROLIDINE)

FIELD OF INVENTION

The present invention provides a process for the synthesis of (E)-2-[1-(4 - methylphenyl) – 3 - (1 - pyrrolidinyl) – 1 - propenyl] pyridine (Triprolidine) of Formula I and salts thereof.



I

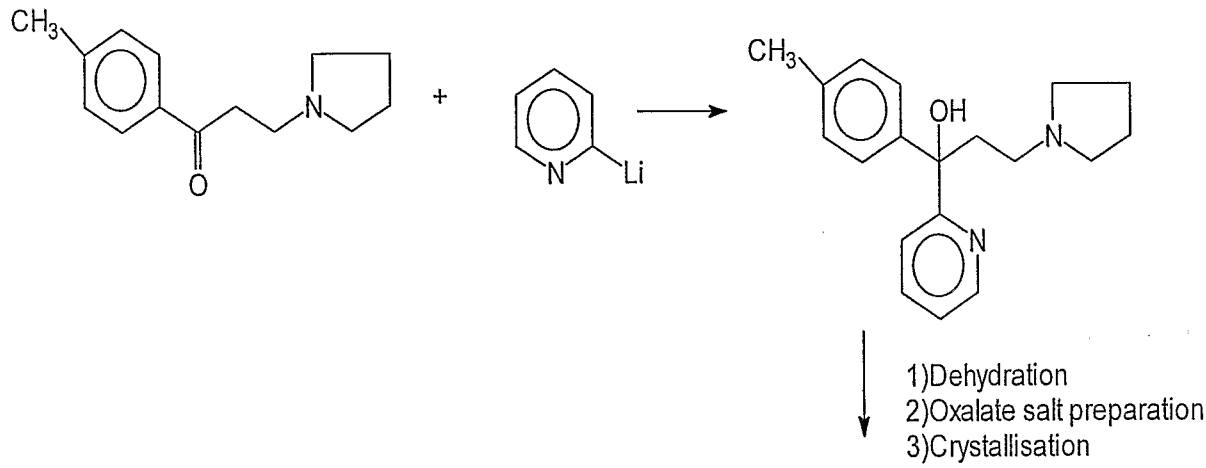
Triprolidine of the Formula I is first generation antihistamine. Its hydrochloride salt is an over-the-counter antihistamine and is used to combat the symptoms associated with allergies and is some times combined with other cold medications designed to provide general relief for flu-like symptoms. The most common side effect is drowsiness. It is sold in the market under trade names Actidil and Myidil.

PRIOR ART

The conventional process for the synthesis of oxalate salt of active isomer of 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidino prop-1-ene (Triprolidine) is described in US patent no. 2712020 (1955) which comprises dehydration of 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidino-propane-1-ol with aqueous sulphuric acid followed by

conversion into oxalate salt and recrystallisation from methanol. The tertiary amino carbinol viz., 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidino-propane-1-ol was prepared by reacting 1-(4-methylphenyl)-3-pyrrolidino-propanone with 2-pyridyl lithium. 2-Pyridyl lithium was made from n-butyl lithium and 2-bromopyridine at very low temperatures in an atmosphere of dry nitrogen as shown in scheme-1

Scheme-1

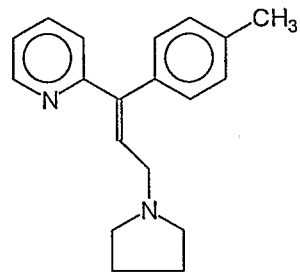


Triprolidine oxalate

In the above known method, a reaction using hazardous n-butyl lithium is involved in preparation of 2-pyridyl lithium. Further the reaction involving p-methyl-beta pyrrolidino propiophenone and 2-pyridyl lithium has been carried out at a very low temperature. Thus usage of n-butyl lithium and low temperature reactions pose industrial difficulties with this known procedure.

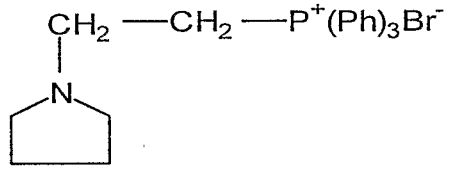
STATEMENT OF THE INVENTION

The object of the invention is to obviate the disadvantages of the prior art by eliminating the hazardous chemical n-butyllithium and low temperature reactions by providing a process for the synthesis of (E) – 2 - [1 - (4 - methylphenyl) – 3 - .(1-pyrrolidinyl)-1-propenyl] pyridine (Triprolidine) of the Formula I and salts thereof comprising

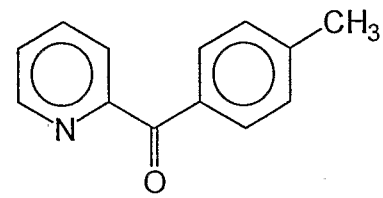


I

a) reacting 2-(1-pyrrolidino)ethyl triphenyl phosphonium bromide of the Formula II with 2-(p-toluoyl) pyridine of the Formula III in presence of aprotic solvent and a base to obtain 2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl] pyridine



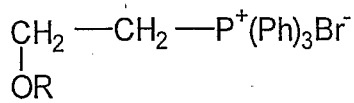
II



III

b) Isomerising 2 -[1-(4-methylphenyl) - 3-(1-pyrrolidinyl)-1-propenyl] pyridine in presence of acid catalysts to obtain compound of the Formula I.

The compound of the Formula II is obtained; by reacting 2-alkoxy/aryloxy ethyl bromide with triphenyl phosphine in presence of aprotic solvents to obtain 2-alkoxy/aryloxy ethyl triphenyl phosphonium bromide of the Formula IV;



R= alkyl or aryl

IV

and reacting compound of the Formula IV with pyrrolidine to obtain compound of Formula II

The compound of the Formula III is obtained; by reacting 2-halopyridine with magnesium in presence of aprotic solvent to obtain 2-pyridyl magnesium halide which on reacting with N,N-disubstituted 4-methyl benzamide gives the compound of the Formula III.

The aprotic solvents are hexane, toluene, tetrahydrofuran, diethyl ether, methylene dichloride or ethylene dichloride. The base is alkali metal hydrides or alkoxides such as sodium ethoxide or sodium t-butoxide or potassium t-butoxide. The acid catalyst used is sulphuric acid, methane sulphonic acid or mixture thereof.

DETAILS OF INVENTION

The chemicals used in the preparation of (E)-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl] pyridine are 2-(1-pyrrolidino)ethyl triphenyl phosphonium bromide of Formula II and 2-(p-toluoyl)pyridine of Formuala III which were condensed by Wittig method. This method yielded a mixture of E and Z isomers of compound of formula I. The ratio of cis (Z) and trans (E) isomers depends on the reagents and solvents used and also on reaction conditions. The ratio of E to Z varied from 10:90 to 33:67 depending upon experimental conditions. The solvent used in Wittig reaction is an aprotic solvent such as hexane, toluene, tetrahydrofuran, diethyl ether, methylene dichloride or ethylene dichloride. The base used is alkali metal hydrides or alkoxides like sodium ethoxide or sodium t-butoxide or potassium t-butoxide in temperature range 0 to 110 °C.

Different ratios of E:Z isomeric mixture obtained was isomerised and purified to get E isomer of the compound of Formula I in the presence of acid catalyst such as methane sulphonic acid, sulphuric acid or mixture thereof followed by oxalate salt preparation and crystallization from organic solvents. The isomerization can be done using 85% sulphuric acid, methane sulphonic acid or a mixture of different ratios of methane sulphonic acid and sulphuric acid. The temperature for isomerization

reaction ranged from 120 to 190 °C. Sulphuric acid reagent is harsh with some material loss compared to methane sulphonic acid which is relatively mild and offers better yield of the required product. The isomeric ratio of E:Z could be pushed to a maximum ratio of 90:10. Further enrichment of E isomer to more than 99% was effected by preparation of various acid salts using acids like hydrochloric acid, sulphuric acid, oxalic acid, tartaric acid, malic acid, succinic acid and crystallization using organic solvents like toluene, ethyl acetate, acetone, ethyl methyl ketone, isopropyl alcohol.

The compound 2-(1-pyrrolidino) ethyl triphenyl phosphonium bromide is obtained ; by addition of triphenyl phosphine to 2-alkoxy/aryloxy ethyl bromide to obtain 2-alkoxy/aryloxy ethyl triphenyl phosphonium bromide. This addition reaction has been carried out in solvents like toluene, xylene, dimethylformamide, butyl acetate and butanol at a temperature range 100 to 150 °C. This is further reacted with pyrrolidine in solvents like aliphatic alcohols such as methanol, isopropyl alcohol, n-butanol at a temperature 30-60° C.

The compound 2-(p-toluoyl) pyridine is obtained by reacting substituted pyridine with substituted toluene. One of these two is substituted by Cl or Br and the other is substituted by CN or $CONR_2$.

The Grignard compound from Cl or Br compound by reacting with magnesium in solvents such as tetrahydrofuran, diethyl ether, diisipropyl ether, methyl t-butyl ether, dioxan, toluene preferably a mixture of toluene and THF at a temperature range from 25 to 60 ° C. Reacting this with other compund substituted by CN or $CONR_2$.

EXAMPLES

a) 2-(1-pyrrolidino)-ethyl triphenyl phosphonium bromide is obtained by refluxing Triphenyl phosphine (300 gm, 1.14 mole) and 2-methoxy ethyl bromide (200gm, 1.43 mole) in toluene (1 lt) for 24 hours. Reaction mass was then cooled to 30°C and filtered to obtain 2-Methoxy ethyl triphenyl phosphonium bromide (450gm, 78%) which is further reacted

with pyrrolidine (96gm, 1.37 mole) in methanol (500ml) at 60 °C for 2 hours. Distilled off methanol and the solid obtained was suspended in toluene (1lt), then cooled to 30 °C and filtered to obtain 2-(1-pyrrolidino)-ethyl triphenyl phosphonium bromide (450gm, 91%).
NMR (D_2O) δ : 1.67 (m,4H), 2.46 (m,4H), 2.78 (m,2H), 3.41 (m,2H), 7.68 (m, 15H)

b) To a stirred solution of magnesium (25gm, 1.04 mole) in tetrahydrofuran (400ml), 2-chloropyridine (100gm, 088 mole) was added over a period of 1 hour at around 40 °C after intiating the reaction. Stirred the reaction mass for further 1 hour at that temperature. 4-Methyl-N,N-dimethyl benzamide (75 gm, 0.46mole) was added slowly over a period of 1 hour at that temperature. Continued stirring for 4 more hours at 40 °C. Reaction mass was then quenched in ammonium chloride solution (200gm in 1lt water) at 10 °C. The product was then extracted into toluene (3x200ml). Toluene layer was then evaporated under reduced pressure to get the crude product (105gm). This on distillation yielded 65gm of pure 2-(4-toluoyl) pyridine (72%).

NMR ($CDCl_3$) δ : 2.41 (s,3H), 7.27 (d,2H), 7.49 (dt, 1H), 7.86(dt,1H), 7.97(d,2H), 7.99(d, 1H), 8.70 (d, 1H)
MS: m/z 197 (M^+)

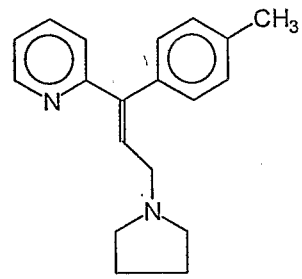
c) To a stirred solution of 2-(p-toluoyl)pyridine (40.0 gm, 0.2 mole) and 2(1-pyrrolidino)ethyl triphenylphosphonium bromide (104.0 gm, 0.23 mole) in methylene chloride (400ml) at 10 °C was added potassium t-butoxide (52.0gm, 0.46 mole) slowly over a period of 1 hour. Continued stirring for further two hours. Washed the reaction mixture with water to remove inorganics and then extracted the product into aqueous oxalic acid solution (25gm in 250 ml water). Then basified the aqueous layer and the product is reextracted into toluene (3x 200ml). Evaporation of toluene layer gave reddish brown oil (40.0gm, 76% yield) consisting of about 2 parts of Z and 1 part of E isomer of triprolidine.

Isomerisation of Z &E isomeric mixture of Triprolidine (40gm) to E isomer was achieved by heating with 1:1 mixture of methane sulphonic acid and con. sulphuric acid (80ml) at 140 °C for 6 hours. The product obtained was converted into oxalate salt and crystallized from ethylmethyl ketone. The oxalate salt was then neutralized with ammonia

and extracted into toluene. Toluene layer was then evaporated to get E-isomer of Triprolidine base. The Triprolidine base (22gm) was disloved in ethylmethyl ketone(150ml) and then added con.HCl (8.75ml). Cooled the reaction mass to 0 °C and filtered the mass and dried to get Triprolidine HCl of required purity (20gm).

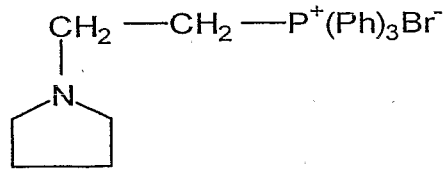
We claim

1. A process for the synthesis of (E) – 2 - [1 - (4 - methylphenyl) – 3 - (1-pyrrolidinyl)-1-propenyl] pyridine (Triprolidine) of the Formula I and salts thereof comprising



I

a) reacting 2-(1-pyrrolidino)ethyl triphenyl phosphonium bromide of the Formula II with 2-(p-toluoyl) pyridine of the Formula III in presence of aprotic solvent and a base to obtain 2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl] pyridine



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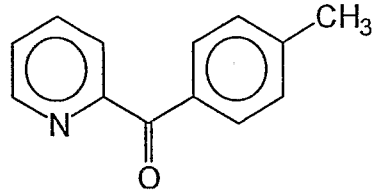
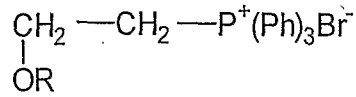


III

b) Isomerising 2 -[1-(4-methylphenyl) - 3-(1-pyrrolidinyl)-1-propenyl] pyridine in presence of acid catalysts to obtain compound of the Formula I.

2. A process as claimed in claim 1. wherein compound of the Formula II is obtained ; by reacting 2-alkoxy/aryloxy ethyl bromide with triphenyl phosphine in presence of aprotic solvents to obtain 2-alkoxy/aryloxy ethyl triphenyl phosphonium bromide of the Formula IV;



R= alkyl or aryl

IV

and reacting compound of the Formula IV with pyrrolidine to obtain compound of Formula II

3. A process as claimed in claim 1, wherein compound of the Formula III is obtained ; by reacting 2-halopyridine with magnesium in presence of aprotic solvent to obtain 2-pyridyl magnesium halide which on reacting with N,N-disubstituted 4-methyl benzamide gives the compound of the Formula III.

4. A process as claimed in claims 1 to 3, wherein aprotic solvents are hexane, toluene, tetrahydrofuran, diethyl ether, methylene dichloride or ethylene dichloride.

5. A process as claimed in claims 1 to 3, wherein bases are alkali metal hydrides or alkoxides such as sodium ethoxide or sodium t-butoxide or potassium t-butoxide.
6. A process as claimed in claim 1, wherein acid catalyst used is sulphuric acid, methane sulphonic acid or mixture thereof.

7. A compound (E)-2 - [1-(4-methylphenyl) – 3 - (1-pyrrolidinyl)-1-propenyl] pyridine (Triprolidine) of the Formula I and salts thereof; whenever prepared by the process as claimed in any of the above claims.

8. A process for the synthesis of (E)–2-[1-(4 – methyl lphenyl –3 - (1-pyrrolidinyl)-1-propenyl] pyridine (Triprolidine) and salts thereof substantially such as herein described and exemplified.