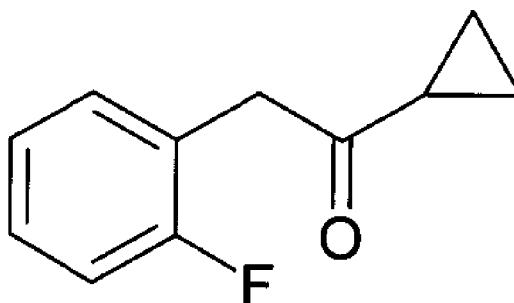




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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF PRASUGREL AND INTERMEDIATE THEREOF



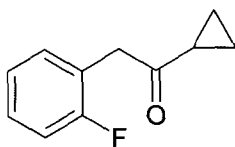
(1)

(57) Abstract: The invention relates to an industrial scale process for the preparation of 1-cyclopropyl-2-(2-fluorophenyl)-ethanone of the Formula (1) and the use of this compound for the preparation of prasugrel.



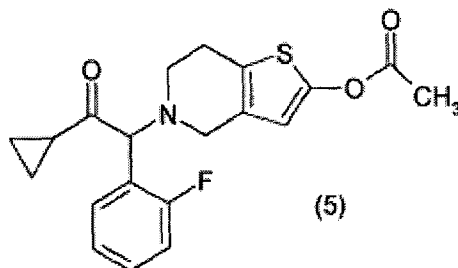
Improved process for the preparation of prasugrel and intermediate thereof

This invention relates to a process for the preparation of 1-cyclopropyl-2-(2-fluorophenyl)-ethanone of the Formula



(1)

and the use thereof for the preparation of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-yl-acetate of the Formula



(5)

having the international non-proprietary name /INN/ prasugrel. Said process is readily applicable on industrial scale manufacture.

Cyclopropyl-benzyl-ketones are important intermediates in the preparation of tetrahydro-thienopyridine derivatives used in pharmacy. One of the most important representatives of the tetrahydro-thienopyridine compound group is the 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-yl-acetate of the Formula (5) (INN prasugrel) which is suitable for the treatment of thrombosis and embolia.

Thrombosis inhibiting prasugrel and derivatives thereof and the process for the preparation of the same was first described in HU 211 785 and HU 211 876. The process of the present invention enables the industrial scale environment-friendly safe manufacture of high purity cyclopropyl-benzyl-ketone derivatives which are important structural elements of said compounds.

According to HU 218 785 and 211 786 the key intermediate of prasugrel, the 1-cyclopropyl-1-(2-fluorophenyl)-ethanone of the Formula (1) is prepared by reacting 2-fluoro-benzyl-magnesium bromide and cyclopropane-carbonitrile. The reaction is carried out at the boiling

point of diethyl ether, whereupon the complex formed is decomposed with an aqueous ammonium chloride solution, the product is extracted and subjected to purification by column chromatography. The yield of the process is 69 %.

5 In US 2003/134872, WO 2009/122440, WO 2009/966326 and WO 2009/62044 similar procedures are described. Cyclopropane carbonitrile is reacted with the Grignard compound formed from the corresponding benzyl bromide derivative. As solvent in each case diethyl ether is used.

10 According to the process described in HU 211.876 the 2-fluoro-benzyl-magnesium halide is not reacted with cyclopropane carbonitrile but rather with an acid chloride e.g. cyclobutane-carboxylic acid chloride. The reaction is performed at a very low temperature, namely at -70°C . The crude product is recovered by extraction and purified by column chromatography. The yield of the process is very low, and amounts only to 39 %.

15 In course of the above Grignard reactions used for the preparation of the compounds of the Formula (1) there is the possibility that one mole of the esters, nitriles and acid chlorides react with two moles of the Grignard reactant instead of one mole. This decreases the yield to a significant extent and additionally by-products containing a hydroxyl group are formed in the
20 reaction.

According to the process described in HU 211 785 and HU 211 876 the Grignard reactant is always formed from a bromo derivative. In the manufacturing process of the cyclopropyl benzyl ketone of the Formula (1) according to the present invention 2-fluoro-benzyl-bromide is replaced
25 by the corresponding cheaper 2-fluoro-benzyl-chloride.

The process disclosed in HU 211 876 is not suitable for industrial scale and economical manufacture. This is due to the fact that purification by column chromatography is unsuitable for the industrial scale manufacture of a large amount of material, an extremely large amount of
30 solvent is required which makes the process expensive and is disadvantageous because of environmental protection.

A further drawback of the reactions known from prior art is that according to HU 211 876 acid chlorides and acid anhydrides react with the corresponding benzyl magnesium bromide at a

temperature between -70°C and -50°C . Thus the above procedures have the following drawbacks in addition to the extremely low temperature: difficult industrial scale feasibility, high energy costs, expensive process and very low yield.

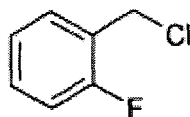
- 5 According to the process described in US 5.874.581 the compound of the Formula (1) is prepared by reacting 2 molar equivalents of 2-propyl-magnesium chloride with 2-fluoro-phenyl-acetic acid in tetrahydrofurane (THF) at the boiling point of the solvent. The complex thus obtained is reacted with cyclopropane carboxylic acid ethyl ester or cyclopropane carboxylic acid methyl ester at 5°C . The reaction mixture is stirred for 3 hours then decomposed by stirring
10 with hydrochloric acid. After neutralization the mixture is extracted, evaporated and fractionated in vacuo. The disadvantage of said process is that expensive starting materials (2-fluoro-phenyl-acetic acid) and more than two equivalents of the Grignard reactant are used in the synthesis yield 56 %. The purity of the product is not disclosed.
- 15 The process is accompanied by the disadvantage that in the preparation of 2-fluoro-phenyl-acetic acid the use of sodium cyanide is required. Additionally this process consists of more reaction steps than the process of the present invention. According to the examples the crude product is purified by distillation in high vacuo.
- 20 In HU 07/00756 (WO 2009/68923) a process is described according to drawing 1 in which the type of the alkyl halide used, the molar ratio applied and the temperature values are set forth. This process has several advantages, namely it is readily feasible on industrial scale, the batch size can be easily largened and no special equipment is needed. The reaction can be performed on industrial scale and no extreme reaction conditions are used. No highly toxic or corrosive
25 substances are required and the use of large amounts of solvents /e.g. column chromatography/ and extremely low temperatures $/-78^{\circ}\text{C}/$ are avoided. According to this prior art the reaction is to be carried out in ether type solvents.

However according to P0700756 the compound of the Formula (1) is prepared with a yield of
30 only 22.5-79.8 % , depending on the reaction conditions used, the solvents and the substituent of the amide nitrogen. Yields higher than 70 % could only be achieved if the Grignard reaction was prepared by using diethyl ether. According to Example (5) of P07/00756 the reaction is carried out without diethyl ether by using tertiary butyl methyl ether and the yield is only 60 %.

The use of diethyl is risky for environment protection and safety. The industrial scale use thereof is to be avoided. Thus the main drawback of the preparation of the compound of the Formula (1) is the use of diethyl ether. Diethyl ether is an extremely inflammable, easily evaporating compound, has a low boiling point (bp.: 34.6°C) and when contacted with air can form explosive peroxides. For this reason the use of diethyl ether requires severe safety measures and this solvent is to be stored under cool conditions, is to be protected from light and air and far from explosive equipment. When using diethyl ether explosion-proof apparatus is to be used. Due to the volatile character of diethyl ether during distillation in vacuo a large part of this solvent gets first into the vacuo system and then into the air, the recovery thereof is circumstantial and expensive, therefore problems of environmental protection arise. Additionally the possibility can not be excluded that in the future the industrial scale use of diethyl ether will be prohibited for reasons of safety and environmental protection. The analytical requirements of the process are also higher because the peroxide-free character of the solvent is to be controlled.

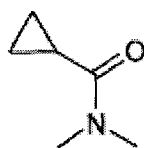
There was a strong need for the elaboration of a process which preserves the advantages of HU 07007556 but increases the yield and avoids the use of diethyl ether.

The above object has been solved by reacting 2-fluoro-benzyl chloride of the Formula



(2)

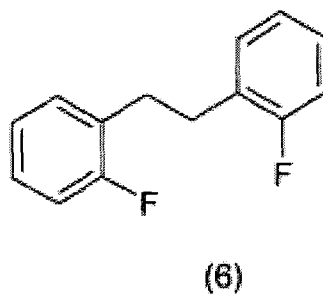
, magnesium and cyclopropane-carboxylic acid-dimethylamide of the Formula



(3) in a mixture of toluene and tetrahydrofuran or in methyl-tetrahydrofuran.

Methyl-tetrahydrofurane has two isomers, namely 2- and 3-methyl-tetrahydrofurane. According to the process of the present invention both isomers can be used, however 2-methyl-tetrahydrofurane proved to be more advantageous.

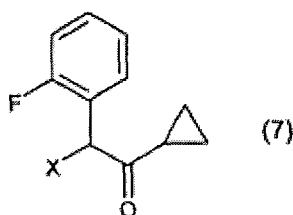
- 5 It has been found that when using ether-type solvents other than diethyl ether (tetrahydrofurane, tertiary butyl methyl ether, diisopropyl ether, dimethoxy ethane, formaldehyde acetals) for industrial scale Grignard reaction, the dibenzyl type by-product of the Formula



- 10 is responsible for the low yield.

Thus e.g. when using tetrahydrofurane, dimethoxy ethane or acetals in the reaction 7-96 % GC area % of the compound of the Formula (6) is formed.

- 15 It is the object of the present invention to recover the intermediate of the Formula (1) with good yield and high selectivity, and to avoid the use of diethyl ether. A further object is to prepare the next intermediate of the synthesis of presugrel – namely the halogeno ketone compound of the Formula



20

- if possible without introducing a further purification step.

We have surprisingly found that the formation of certain by-products can be suppressed by using as solvent in place of diethyl ether a mixture of tetrahydrofuran and toluene of a determined ratio, or methyl tetrahydrofuran.

- 5 According to our experiments a mixture of tetrahydrofuran and toluene provides the desired advantages only if the amount of tetrahydrofuran in the mixture is 3-20 vol. %.

It is surprising that tetrahydrofuran can be a component of the reaction mixture because if the reaction is carried out in tetrahydrofuran as sole solvent the crude product contains more than
10 80 of GC area % of the by-product of the Formula (6). On the other hand if we use a mixture of tetrahydrofuran and toluene containing 3-20 vol.% of tetrahydrofuran the formation of the Grignard reactant and the reaction easily takes place with a yield above 85 % and the amount of the dibenzyl contamination of the Formula (6) is also acceptable, namely below 10 %. Thus further purification of the product is not necessary. We have also found in a surprising manner
15 that selectivity can be significantly increased by adding the two starting materials (compounds of the Formula (2) and (3)) not subsequently but parallelly to the suspension of magnesium in a mixture of toluene and tetrahydrofuran. (In the examples we have shown that the amount of the compound of the Formula (6) can be reduced from 7.6 GC area % to 3.9 GC area %).

- 20 When using 2- or 3-methyl-tetrahydrofuran also a conversion above 85 % can be achieved whereby the amount of the dibenzyl derivative of the Formula (6) is below 3 GC /gas chromatography/ area %. This is so much the more surprising because when carrying out the reaction in tetrahydrofuran – which has similar physical and chemical properties – the crude product (yield 94.6 %) contains 80.6 GC area % of the dibenzyl derivative of the Formula (6).
25 When carrying out the reaction in 2-methyl-tetrahydrofuran the desired compound of the Formula (1) is obtained with a yield of 91 % and the crude product contains only 1.6 GC area % of the dibenzyl derivative of the Formula (6).

According to a preferred embodiment of the process of the present invention the intermediate of
30 the Formula (1) can be prepared by using in the reaction a mixture of toluene and tetrahydrofuran, in which the amount of tetrahydrofuran is 3-20 vol. %, preferably 5-20 vol. %, most advantageously 8-18 %. It is preferred to add the acid amide component in form of a solution – preferably in tetrahydrofuran – to the reaction mixture containing the Grignard compound. One may proceed preferably by adding the starting materials of the Formula (2) and

(3) not subsequently but parallelly to the suspension of magnesium formed with a mixture of toluene and tetrahydrofuran.

In the Grignard compound forming reaction 1.0-2.0 equivalents, preferably 1.3-1.8 equivalents, most preferably 1.5 equivalents of magnesium are added – related to the amount of the benzyl chloride derivative of the Formula (3) – and the magnesium is activated with iodine. The reaction is carried out at a temperature between 0°C and 100°C, preferably between 20°C and 50°C, most preferably between 20°C and 30°C. One may also proceed by first preparing the Grignard reactant, which reaction is most preferably performed between 20°C and 30°C, and the solution of the acid amide is added at 40-50°C.

According to the process of the present invention in the Grignard reaction a 5-10-fold, preferably 6-9-fold volume of a mixture of tetrahydrofuran and toluene is used, related to the amount of the starting material of the Formula (3).

One may proceed preferably by adding to a mixture of tetrahydrofuran and toluene, containing 10 vol. % of tetrahydrofuran, at room temperature the compound of the Formula (2), thereafter adding drop wise to the Grignard compound the tetrahydrofuran solution of the compound of the Formula (3) and keeping the reaction mixture at 40-50°C.

One may also proceed by adding to a mixture of with iodine activated magnesium in a 10 vol. % tetrahydrofuran containing tetrahydrofuran-toluene mixture at room temperature the compound of the Formula (2) and parallelly a tetrahydrofuran solution of the compound of the Formula (3).

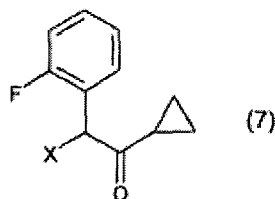
The reaction mixture obtained is worked up by methods known from prior art. The product is isolated and if desired purified.

According to the most preferable embodiment of the present invention magnesium is reacted with the benzyl chloride derivative of the Formula (2) in a 10-20-fold volume, preferably 15-20-fold volume of a tetrahydrofuran-toluene mixture – solvent ratio 1:12, preferably 1:9, whereupon parallelly with the formation of the Grignard compound 0.7-1.1 moles, preferably 0.85-0.95 moles – related to the benzyl chloride - of cyclopropane carboxylic acid dimethyl amide of the Formula (3) or a tetrahydrofuran solution thereof is added, said addition having

been completed the reaction mixture is stirred at 40-60°C, preferably 40-45°C for a period of 0.5-3 hours, preferably 1-2 hours. The reaction mixture is cooled, diluted hydrochloric acid is added, the organic phase is separated, washed, dried and evaporated, if necessary.

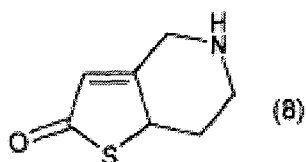
- 5 One may also proceed by reacting magnesium in a 5-15-fold vol. preferably 5-10-fold vol. amount of 2-methyl-tetrahydrofuran - related to the amide of the Formula (3) –with the benzyl chloride derivative of the Formula (2) at room temperature. The Grignard compound thus formed is reacted with a 0.7-1.1 molar amount, preferably 0.85-0.95 molar amount of cyclopropane-carboxylic acid-dimethylamide of the Formula (3) or a solution therefore formed with 2-methyl-
10 tetrahydrofuran or tetrahydrofuran. The reaction mixture is stirred at 40-60°C, preferably 40-45°C for a period of 0.5-3 hours, preferably 1-2 hours, cooled, whereupon diluted hydrochloric acid is added. The organic phase is separated, washed, dried, evaporated and if necessary evaporated.
- 15 The amount of the solvents used in the reaction is preferably selected so that the volume of the solvent should be a 5-20-fold, preferably 10-15 fold , most preferably 5-12 fold amount of that of the desired end product. A more diluted solution of the tetrahydrofuran-toluene mixture proved to be preferable; this solvent mixture can be used in a 10-20 fold, preferably 10-15 fold amount, related to the amount of the end product. The volume of methyl tetrahydrofuran is a 5-15 fold ,
20 preferably 8-12 fold amount, related to the amount of the end product. As methyl tetrahydrofuran preferably 2-methyl tetrahydrofuran can be used.

The intermediate of the Formula (1) is particularly suitable for the preparation of prasugrel. This process can be particularly preferably carried out by halogenating, preferably brominating or
25 chlorinating the intermediate of the Formula (1) prepared according to the present invention and subjecting the halogenated intermediate of the Formula

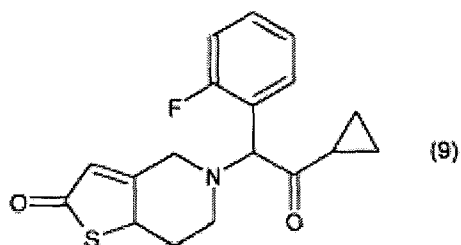


30 /wherein X is chlorine or bromine/ to the following reactions:

a/ reacting with a compound of the Formula

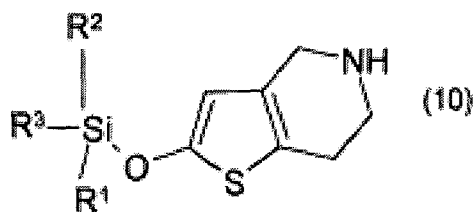


5 or an acid addition salt thereof, preferably with a salt formed with p-toluene-sulfonic acid, and thereafter acylating the compound of the Formula



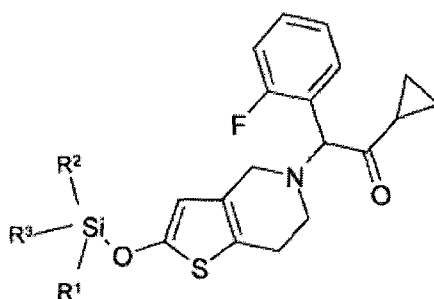
10 thus obtained; or

b/ reacting with the silyloxy derivative of the general Formula



15

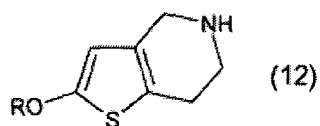
/wherein R^1 , R^2 and R^3 are identical or different and stand for C1-4 alkyl, whereby said substituent is preferably dimethyl-tert. butyl-silyloxy/, removing the silyl protecting group from the compound of the Formula



(11) thus obtained to yield the compound of the Formula (9) and subjecting said compound to acylation; or

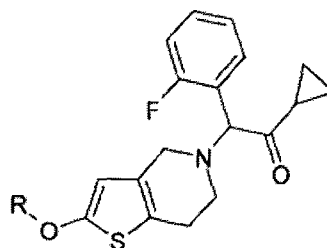
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c/ reacting with a compound of the general Formula



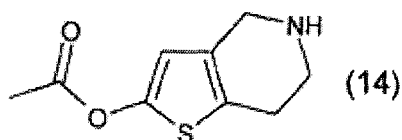
/wherein R is alkyl/ and converting the O-Alkyl group of the compound of the general Formula

10



(13) into an O-Acyl group; or

d/ reacting with the compound of the Formula



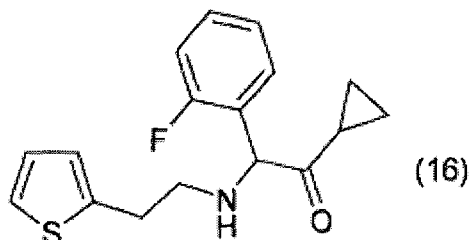
15

or

e/ reacting with the compound of the Formula

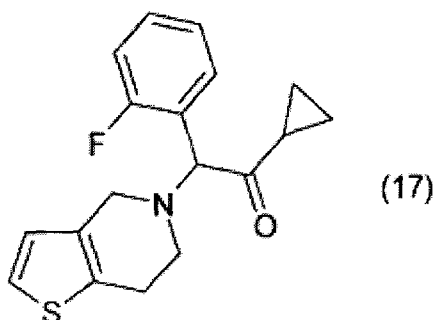


, subjecting the compound of the Formula



5

thus obtained to ring closure, oxidizing and acylating the compound of the Formula



thus obtained into the compound of the Formula (9), and

10 if necessary converting the compound of the Formula (5) thus obtained into a salt.

The above processes are known from prior art and belong to the general knowledge of the skilled art worker, with the exception of the preparation of the intermediate of the Formula (1) according to the present invention.

15

The intermediate of the Formula (7) can be prepared from the intermediate of the Formula (1) by adding to a mixture of the intermediate of the Formula (1) formed with p-toluene-sulfonic acid and acetonitrile N-bromo- or N-chloro-succinimide and working up the reaction mixture after the reaction is completed. The reaction can be carried out in any inert solvent (e.g. halogenated

solvents, acetonitrile). The reaction of a radical mechanism can be stimulated with the aid of radical forming compounds, peroxides or by irradiation with visible or UV light.

5 The p-toluene sulfonic acid salt of the compound of the Formula (8) can be prepared with good yields according to Example (7) of HU P1000565. Prasugrel can be preferably prepared according to a one-pot process by reacting the tetrahydro-thieno derivative of the Formula (8) in a dipolar aprotic solvent (preferably dimethyl formamide or acetonitrile) in the presence of a base (preferably an organic base e.g. N,N-diisopropyl-ethyl-amine (DIPEA)) with the bromo ketone derivative of the Formula (7) prepared according to the present invention, acylating the
10 compound of the Formula (9) formed in the reaction mixture with an acylating agent, preferably acetic anhydride, thereafter isolating prasugrel of the Formula (5) and if desired converting prasugrel into a salt.

According to an other embodiment of the process of the present invention the intermediate of the
15 Formula (1) is used for the preparation of prasugrel by brominating the compound of the Formula (1), reacting the halogeno ketone derivative of the Formula (7) thus obtained with the intermediate of the Formula (10) /wherein R^1 , R^2 and R^3 are identical or different and stand for C1-4 alkyl, wherein said substituent is preferably tert.butyl-dimethyl-silyloxy/ prepared according to US 5.874.581, removing the silyl group in tetrahydrofuran in the presence of
20 triethyl amine and 4-dimethylamino-pyridine and acylating the product with acetic anhydride without isolating the intermediate, as described in US 5.874.581.

According to the present invention the intermediate of the Formula (1) can also be used by reacting the compound of the Formula (12) prepared according to CN 101250192 with a
25 halogeno ketone of the general Formula (7) prepared from the intermediate compound of the Formula (1) obtained according to the present invention and thereafter removing the alkyl group, preferably methyl group, in acidic medium. The advantage of the process is that the use of a low temperature and inflammable and combustible materials can be avoided.

30 The intermediate of the Formula (1) of the present invention can also be used for the preparation of prasugrel by converting the compound of the Formula (1) into the intermediate of the general Formula (7) and reacting said compound in an inert solvent /a polar aprotic or apolar aprotic solvent, such as an ether e.g. diethyl ether, tetrahydrofuran, or a chlorinated solvent such as dichloro methane, dichloro ethane or carbon tetrachloride/ at room temperature in the presence

of a base, preferably an organic base with 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-yl-acetate of the Formula (14) and thereafter isolating the product.

One may also proceed by transforming the ketone of the Formula (1) prepared according to the present invention into a halogeno ketone of the Formula (7), reacting the compound of the Formula (7) with the 2-thiophen-ethylamine of the Formula (15) in the presence of a base and reacting the intermediate of the Formula (16) thus obtained with formaldehyde to yield the intermediate of the Formula (17). The 5-(2-fluoro- α -cyclopropyl-carbonyl-benzyl)-4,5,6,7-tetrahydro-4H-thieno[3,2-c]pyridine of the Formula (17) thus obtained is oxidized with hydrogen peroxide in the presence of copper sulphate with a yield of 75 % into the intermediate of the Formula (9) – this process is disclosed in CN 101531667 – whereupon the compound of the Formula (9) is converted into prasugrel by acylation.

Prasugrel obtained by any of the above procedures can be converted into any pharmaceutically acceptable salt. It is preferred to prepare e.g. the salts formed with hydrochloric acid or with organic acids e.g. maleic acid.

Our unexpected recognition - namely that the amount of the dibenzyl derivative of the Formula 6 can also be responsible for the low yield – has enabled an improvement of the use of the compound of the Formula (1) and the analytical classification thereof. By making use of said recognition we have used the dibenzyl derivative of the Formula (6) as analytical standard. For this reason we have elaborated a process for the preparation of the compound of the Formula (6).

Accordingly an object of the present invention is the preparation of the dibenzyl compound of the Formula (6) and the use thereof as analytical standard.

The compound of the Formula (6) can be prepared by preparing the Grignard compound of the Formula (4) from the compound of the Formula (2) with magnesium, adding to said compound of the Formula (4) a further 1 mole of the compound of the Formula (2), working up the reaction mixture as described in prior art, isolating and crystallizing the product. The product can be used as analytical standard in the process of the present invention for measuring the amount of said impurity. The compound of the Formula (6) can also be used as analytical standard by reactions in which the formation of the compound of the Formula (6) as contamination can be expected.

The advantage of the present invention is that the intermediate of the Formula (1) can be obtained in high yields under eliminating the use of diethyl ether. A further advantage is the significant increase of the yield. Contrary to the only example (example 5) of HU P07000756/ in which the reaction is carried out in methyl-tertiary-butyl-ether, i.e. without ether with a yield of 60 %, according to the present invention the intermediate of the Formula (1) can be prepared with a yield above 85 %. Thus according to the present invention the increase of the yield over that of prior art is more than 40 %. This makes the preparation of prasugrel significantly cheaper and the specific environment damaging character of the process has also considerable decreased.

The above advantages have been achieved with the aid of the process of the present invention by suppressing the formation the dibenzyl contamination of the Formula (6).

Further details of the present invention are to be found in the following examples without limiting the scope of protection to said examples.

Example 1

Preparation of the intermediate of the Formula (1) (tetrahydrofurane-toluene)

Into a round-bottomed flask 3.2 g (0.132 mole, 1.50 equivalent) of magnesium and 0.04 g of iodine are weighed in under slow argon flow. A mixture of 20 ml of tetrahydrofurane and 180 ml of toluene is added. To the mixture 14.2 g (0,098 mole, 1,11 equiv.) of 2-fluoro-benzyl chloride (Formula 2) are added and the mixture is stirred at room temperature. To the Grignard reactant thus obtained a solution of 10 g (0.088 mole, 1.0 equiv.) of cyclopropane-carboxylic acid dimethylamide (Formula (3)) and 20 ml of tetrahydrofurane is added; at the end of the addition the temperature reaches 40-45°C. The reaction mixture is allowed to stand at this temperature for an hour and a half. The mixture is then cooled with ice-cold water and a mixture of 23 ml of concentrated hydrochloric acid and 23 ml of water is added under cooling. The two phases are separated, the organic layer is washed with a sodium hydrogen carbonate solution and water, whereupon it is evaporated. The product is analysed by gas chromatography.

The weight of the crude product is 14.8 g (94.3 %).

The ratio of the dibenzyl contamination (Formula (6)) is 7.6 GC area %.

Example 2**Preparation of the intermediate of the Formula (1) (tetrahydrofurane-toluene)**

- 5 Into a round-bottomed flask 3.2 g (0.132 mole, 1.5 equiv.) of magnesium and 0.04 g of iodine are weighed in. A mixture of 20 ml of tetrahydrofurane and 180 ml of toluene is added. To the mixture parallelly 14.2 g (0.098 mole, 1.11 equiv.) of 2-fluoro-benzyl-chloride (Formula (2)) and a solution of 10 g (0.088 mole, 1.0 equiv.) of cyclopropane-carboxylic acid-dimethylamide (Formula (3)) in 20 ml of tetrahydrofurane is added. The addition having been completed the
- 10 reaction mixture is stirred at 40-45°C for a further hour and a half. Thereafter a mixture of 23 ml of concentrated hydrochloric acid and 23 ml of water is added under cooling. The two phases are separated, the organic layer is washed subsequently with a sodium hydrogen carbonate solution and water and thereafter dried. The product is analysed with gas chromatography.
- The weight of the crude product is 14.3 g (90.8 %)
- 15 The ratio of the dibenzyl contamination (Formula (6)) is 3.9 GC area %.

Example 3**Preparation of the intermediate (Formula (1)) (2-methyl-tetrahydrofurane)**

- 20 Into a round-bottomed flask 3.2 g (0.132 mole, 1.50 equiv.) of magnesium and 0.04 g of iodine are added in a slow argon current. To the mixture 60 ml of 2-methyl-tetrahydrofurane and thereafter 14.2 g (0.098 mole, 1.11 equiv.) of 2-fluoro-benzyl-chloride (Formula (2)) are added drop wise. To the Grignard reactant thus obtained a solution of 10 g (0.088 mole, 1.0 equiv.) of
- 25 cyclopropane-carboxylic acid-dimethylamide (Formula (3)) in 50 ml of tetrahydrofurane is added. The reaction mixture is allowed to stand at 40-45°C for an hour and a half whereupon a mixture of 23 ml of concentrated hydrochloric acid and 23 ml of water is added. The two phases are separated; the organic layer is washed with sodium hydrogen carbonate solution and water, washed with water and evaporated. The crude product is analysed with GC.
- 30 The weight of the crude product is 14.4 g (91.5 %)
- The ratio of the dibenzyl contamination (Formula (6)) is 1.6 GC area %.

Example 4

Preparation of 1,2-bis-(2-fluorophenyl)-ethane (Formula (6))

Into a 100 ml round-bottomed flask 1.50 g (0.062 mole, 0.6 equiv.) of magnesium and 45 ml of tetrahydrofuran are added. To the mixture 0.02 g of iodine is added and the mixture is heated to 65°C. To the mixture 15.0 g (12.3 ml, 0.104 mole, 1.0 equiv.) of 2-fluoro-benzyl-chloride (Formula (2)) are added and the reaction mixture is heated to boiling under stirring. The reaction mixture is cooled to 20°C and 20 ml of water are added. The solid material goes into solution whereupon the two phases are separated and the organic layer is evaporated at 45°C. The weight of the crude product is 21.70 g (95.8 %). The crude product is recrystallized from ethanol.

Yield 17.79 g (78.6 %). White crystals.

Mp.: 43-44°C.

¹H NMR (400 MHz, CDCl₃): 7,14 (m, 1H), 7,10 (m, 1H), 6,99 (m, 1H), 6,98 (m, 1H), 2,93 (s, 4H)

IR (KBr): 3044, 2938, 2869, 1948, 1915, 1797, 1705, 1615, 1584, 1490, 1458, 1229, 1183, 1086, 1031, 943, 843, 759 cm⁻¹

Elementary analysis: calc.: C: 77.05%, H: 5,54%; found: 77.12%, H: 5.63%

Example 5**Preparation of 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)-ethanone (Formula (7))**

Into a 100 ml round-bottomed flask 4.0 g of 98 % (according to GC analysis) of 1-cyclopropyl-2-(2-fluorophenyl)-ethanone, and thereafter 0.4 g of p-toluenesulfonic acid monohydrate and 12 ml of acetonitrile are added. The mixture is warmed to 40°C and at this temperature a solution of 4.0 g N-bromo-succinimide and 32 ml of acetonitrile is added. The reaction mixture is stirred at 40°C for 24 hours, then cooled to 20-25°C, whereupon 18 g of a 5 vol.% sodium hydroxide solution and 30 ml of tert. butyl-methyl-ether are added. The reaction mixture is stirred for 10 minutes and the phases are separated. The organic layer is washed twice with 20 ml of water each. The organic layer is evaporated. Thus 5,5 g of the desired product are obtained /main component 5.0 g (87 %). Pale yellow liquid.

GC content 91.0 %.

Example 6

Preparation of 2-acetoxy-5-(2-fluoro- α -cyclopropyl-carbonyl-benzyl)-4,5,6,7-tetrahydro4H-thieno[3.2-c]pyridine (prasugrel, Formula (5)) by reacting the thieno-pyridine derivative of the Formula (8) with the halogenated ketone of the Formula (7) via the intermediate of the Formula (9)

5

A mixture is prepared from 65.5 g (0.2 mole) of 5,6,7,7a-tetrahydro-4H-thieno-[3,2-c]pyridine-2-one (compound of the Formula (8)) p-toluenesulfonate and 160 ml of dimethyl formamide. 75.3 ml (56.9 g, 0.44 mole) of N,N-diisopropyl-ethylamine /DIPEA/ are added, whereupon 53.8 g of 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)-ethanone (GC content 95.5 %), compound of the Formula (7, X = Br) dissolved in 94 ml (88.7 g) of dimethyl formamide are added under cooling with ice-cold water within about 30 minutes. The reaction mixture is stirred at room temperature for an hour, whereupon 37.65 ml (28.43 g, 0.22 mole) of DIPEA are added and thereafter 28.4 ml (30.6 g, 0.30 mole) of acetic anhydride are added drop wise at 15-20°C under intensive stirring. The reaction mixture is stirred at room temperature for a further hour, whereupon the reaction mixture is poured on a mixture of ice-cold water and ethyl acetate. The phases are separated and the aqueous layer is extracted with ethyl acetate. The united organic layers are dried over magnesium sulphate. The solvent is removed in vacuo. To the evaporation residue ethanol is added, the mixture is cooled to 0-5°C, the crystals obtained are filtered and washed with ethanol. The crude prasugrel is recrystallized from ethanol.

Thus 41.1 g /55.0 %/ of a colourless crystalline product are obtained. HPLC purity larger than 99.80 %. Mp: 120-121°C.

Example 7

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Preparation of 5-(2-fluoro- α -cyclopropyl-carbonyl-benzyl)-4,5,6,7-tetrahydro4H-thieno[3.2c]-pyridine-2-one

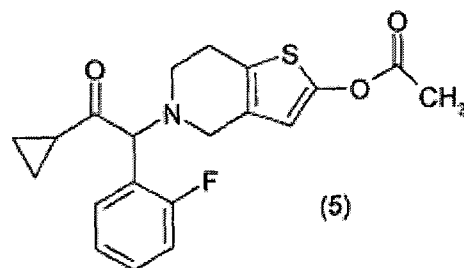
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To a mixture of 65.5 g (0.2 mole) of 5,6,7,7a-tetrahydro-4H-thieno[3.2-c]pyridine-2-one (compound of the Formula (8), PTSA salt) and 150 ml of dimethyl formamide 75.3 ml (56.9 g, 0.44 mole) of N,N-diisopropyl-ethyl amine /DIPEA/ are added, whereupon a solution of 55.4 g 2-bromo-1-cyclopropyl-2-(2-fluoro-phenyl)-ethanone (compound of the Formula (7)), GC content 92.8 %/ in dimethyl formamide is added drop wise during about 30 minutes. The reaction mixture is stirred at room temperature for an hour, and then poured onto a mixture of ice-cold water and ethyl acetate. The phases are separated; the aqueous layer is extracted with

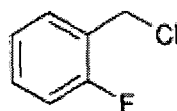
ethyl acetate. The united organic layers are dried over magnesium sulphate and the solvent is removed in vacuo. The product thus obtained can be directly used for the preparation of prasugrel.

Claims

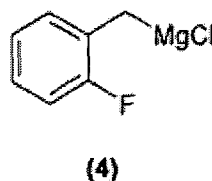
1. Process for the preparation of 2-acetoxy-5-(2-fluoro- α -cyclopropyl-carbonyl-benzyl)-4,5,6,7-tetrahydro-4H-thieno[3.2-c]-pyridine /prasugrel/ of the Formula



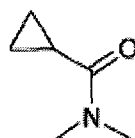
which comprises reacting 2-fluoro-benzyl chloride of the Formula



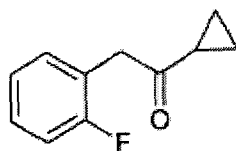
(2) with magnesium, adding to the Grignard reactant of the Formula



thus formed cyclopropane-carboxylic acid-dimethyl amide of the Formula



- (3), whereby the reaction is carried out in a mixture of toluene and tetrahydrofuran, in which mixture the amount of tetrahydrofuran is 3-20 vol. %, or in methyl-tetrahydrofuran as solvent, whereupon the ketone of the Formula

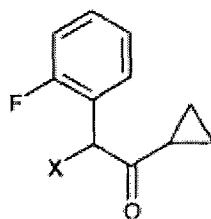


(1) thus obtained is converted into prasugrel in a manner known per se,

5

2. Process according to claim 1 wherein the intermediate of the Formula (1) prepared according to claim 1 is halogenated, preferably brominated or chlorinated and the halogenated intermediate of the Formula

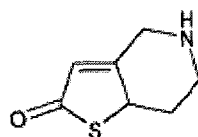
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(7) thus obtained /wherein X is chlorine or bromine/ is subjected to the following reactions:

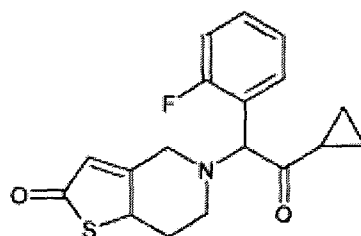
a/ reacting with the compound of the Formula

15



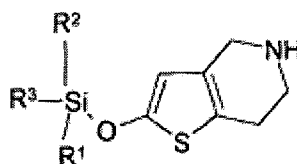
(8) or an acid addition salt, preferably with a salt formed with p-toluene-sulfonic acid, and thereafter acylating the compound of the Formula

20

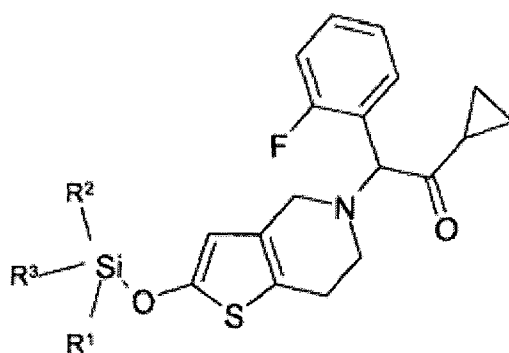


(9) thus obtained; or

5 b/ reacting with a silyloxy derivative of the general Formula



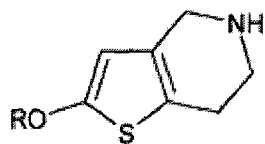
(10) /wherein R^1 , R^2 and R^3 are identical or different and stand for C1-4 alkyl, whereby said substituent is preferably dimethyl-tert. butyl-silyloxy/, removing the silyl protecting group from
10 the compound of the Formula



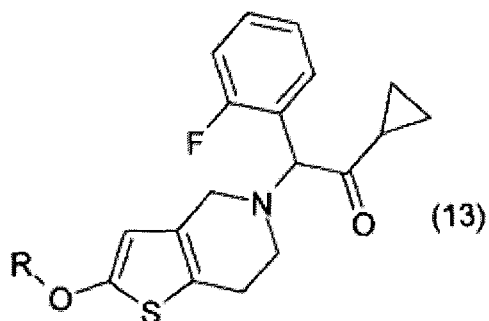
(11) thus obtained to yield the compound of the Formula 9 and subjecting said compound to acylation; or

15

c/ reacting with a compound of the general Formula



(12) /wherein R is alkyl/ and converting the O-Alkyl group of the compound of the general Formula

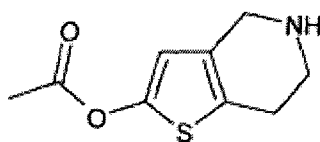


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(13) thus obtained into an O-Acyl group; or

d/ reacting with the compound of the Formula

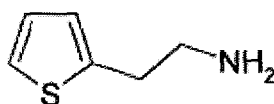
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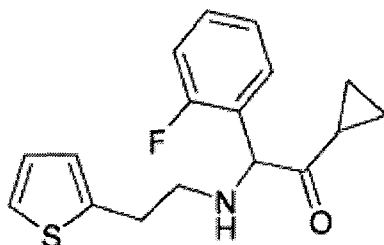
(14), or

e/ reacting with the compound of the Formula

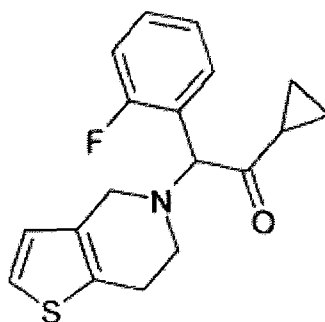
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(15), subjecting the compound of the Formula



(16) thus obtained to ring closure, oxidizing and acylating the compound of the Formula



5 (17) thus obtained into the compound of the Formula (9),
and if necessary converting the compound of the Formula (5) thus obtained into a salt.

3. Process for the preparation of a halogenated ketone derivative of the Formula (7) which
comprises reacting 2-fluoro-benzyl chloride of the Formula (2) with magnesium, adding to the
10 Grignard reactant of the Formula (4) thus obtained cyclopropane-carboxylic acid-dimethylamide
of the Formula (3), whereby the reaction is carried out in a mixture of toluene and
tetrahydrofurane, said mixture containing 3-20 vol. % of tetrahydrofurane, or in methyl-
tetrahydrofurane as solvent and thereafter halogenating the ketone of the Formula (1) thus
obtained.

15 4. Process for the preparation of 1-cyclopropyl-2-(2-fluorophenyl)-ethanone of the Formula (1)
by using 2-fluoro-benzyl-chloride of the Formula (2), magnesium and cyclopropane-carboxylic
acid-dimethyl amide of the Formula (3) as reactant which comprises carrying out the reaction in
a mixture of toluene and tetrahydrofurane, whereby said mixture contains 3-20 vol. % of
20 tetrahydrofurane, or in methyl-tetrahydrofurane as solvent.

5. Process according to any of claims 1-4 which comprises carrying out the preparation of the intermediate of the Formula (1) in a mixture of tetrahydrofuran and toluene, whereby said mixture contains preferably 5-20 % vol. %, most preferably 8-18 vol.% of tetrahydrofuran.

5 6. Process according to any of claims 1-5 which comprises preparing the intermediate of the Formula (1) by adding 2-fluoro-benzyl-chloride at a temperature of 0-100°C, preferably at 20-50°C, most preferably at 20-30°C to a suspension of magnesium formed with a solvent.

10 7. Process according to any of claims 1-6 which comprises preparing the intermediate of the Formula (1) by adding the starting materials of the Formula (2) and (3) parallelly to the suspension of magnesium formed with a mixture of toluene and tetrahydrofuran.

15 8. Process according to any of claims 1-7 which comprises preparing the intermediate of the Formula (1) by using in the Grignard reaction a mixture of tetrahydrofuran and toluene in a 10-20 fold volume, preferably in a 15-20 fold volume amount, or methyl-tetrahydrofuran in a 5-15 fold volume, preferably 5-10 fold volume amount, related to the amount of the starting material of the formula (3).

20 9. Process according to any of claims 1-8 which comprises preparing the intermediate of the Formula (1) by adding a solution of the compound of the Formula (3) formed with tetrahydrofuran to the reaction mixture.

25 10. Process according to any of claims 1-9 which comprises preparing the intermediate of the Formula (1) by using tetrahydrofuran in a 1-10 fold volume, preferably 4-6 fold volume amount, related to the amount of the cyclopropane-carboxylic acid dimethylamide of the Formula 3.

11. Process according to any of claims 1-10 which comprises using as methyl-tetrahydrofuran 2-methyl-tetrahydrofuran.

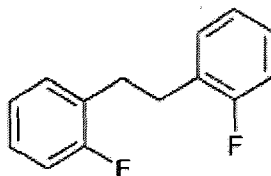
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12. Process according to any of claims 1-9 which comprises preparing the intermediate of the Formula (1) by reacting magnesium in a 10-20-fold volume, preferably 15-20-fold volume amount, related to the amount of the starting material of the Formula (3), of a tetrahydrofuran-toluene mixture of a volume ratio of 2:12, preferably 1:9 with the benzyl chloride derivative of

the Formula (2) at room-temperature, adding to the reaction mixture parallelly with the formation of the Grignard compound cyclopropane-carboxylic acid-dimethyl amide of the Formula (3) in a molar amount of 0.7-1.1 mole, preferably 0.85-0.95 mole, related to the benzyl chloride, the addition having been completed stirring the reaction mixture at 40-60°C, preferably at 40-45°C for a further period of 0.5-3 hours, preferably 1-2 hours, thereafter cooling the reaction mixture, adding diluted hydrochloric acid, separating the organic phase, washing said organic phase, drying, evaporating and if necessary evaporating.

13. Process according to any of claims 1-10 which comprises preparing the intermediate of the Formula (1) by reacting magnesium at room temperature in a 5-15 fold volume, preferably in a 5-10 fold volume amount of 2-methyl-tetrahydrofuran, related to the amount of the starting material of the Formula (3), with the benzyl chloride derivative of the Formula (2), the formation of the Grignard compound having been completed adding cyclopropane-carboxylic acid-dimethyl amide of the Formula (3) in a 0.7-1.1, preferably 0.85-0.95 molar amount, related to the benzyl chloride, to the reaction mixture, thereafter stirring the reaction mixture at 40-60°C, preferably 40-45°C for 0.5-3 hours, preferably 1-2 hours, then cooling the reaction mixture, adding diluted hydrochloric acid, separating the organic phase, washing said organic phase, drying, evaporating and if necessary evaporating.

14. Intermediate of the Formula (1) prepared by the process according to claims 4-10 wherein the 1,2-bis-(2-fluorophenyl)-ethane of Formula



(6) content of the product is smaller than 10 %, preferably smaller than 5 %, most preferably smaller than 2 %.

15. Process for the preparation of 1,2-bis-(2-fluorophenyl)-ethane of the Formula (6) which comprises reacting 2-fluoro-benzyl-chloride of the Formula (2) with magnesium in tetrahydrofuran, reacting the Grignard compound thus obtained with a further 0.9-1.1, preferably 1 molar amount of 2-fluoro-benzyl-chloride of the Formula 2 at 20-70°C, preferably

at 60-70°C, working up the reaction mixture, if necessary recrystallizing the product, preferably from methanol or ethanol.

16. Use of 1,3-bis-(2-fluoro-phenyl)-ethane of the Formula (6) as analytical standard.

