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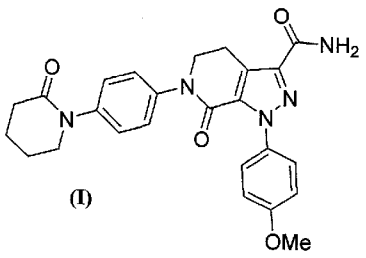
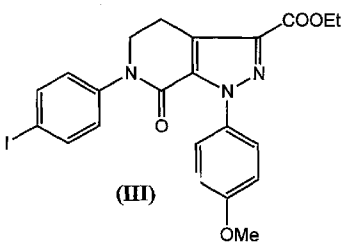
(54) Title: A METHOD OF PREPARING APIXABAN



(I)



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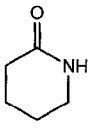

(IV)

(57) Abstract: The object of the present solution provides a method preparing apixaban of formula (I) in which ethyl 6-(4-iodophenyl)- 1 -(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo [3,4- *c*]pyridine-3-carboxylate of formula (III) is reacted with piperidin-2-one of formula (IV) in the presence of a base and a ligand and under catalysis by copper or by copper (II) ions, wherein a phosphoric acid salt is used as the base and an amine from the group of 1,2-diamines is used as the ligand in an aprotic solvent, and ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1- piperidin-1-yl)phenyl] -4, 5,6,7-tetrahydro-1*H*-pyrazol-[3,4-c]pyridine-3-carbvoxylate is prepared, which is converted, by reaction with ammonia in a suitable solvent, to apixaban of formula (I), which is isolated and optionally crystallized.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

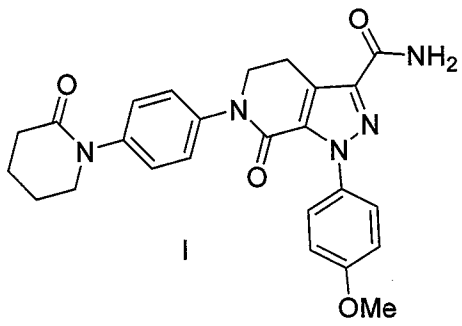
Published:

— *with international search report (Art. 21(3))*

A method of preparing APIXABAN

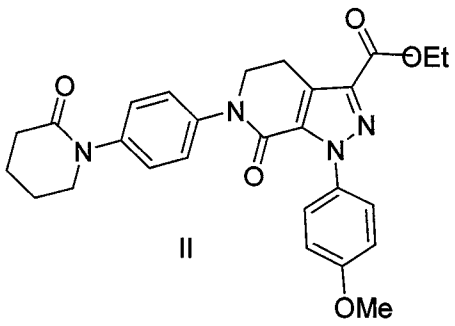
Technical Field

The invention relates to a new procedure for preparing apixaban of formula I, chemically 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, especially to an intermediate of its preparation (II), chemically ethyl ester of 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid, by a modified Ullmann reaction.



I

(I)

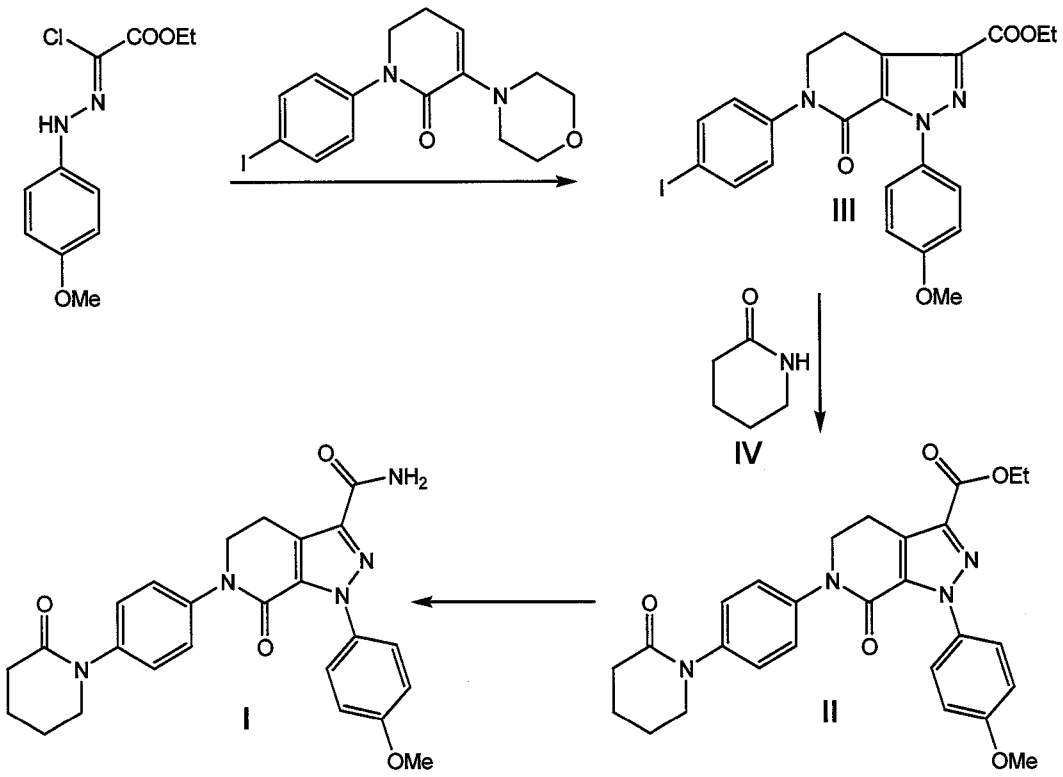


II

(II)

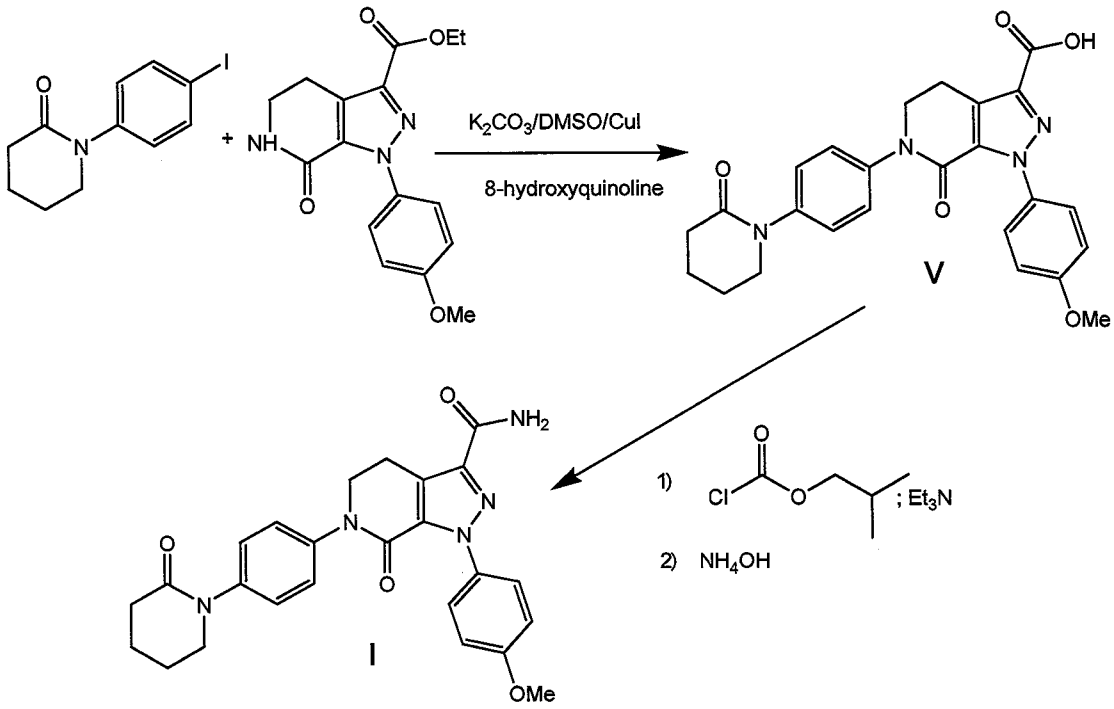
Background Art

Apixaban, a compound acting as an anticoagulant, which is used for the treatment of both venous and arterial thromboembolism, was first described in the document EP 1 427 415, which describes the basic synthetic approaches to the preparation of apixaban and similar molecules and briefly also describes pharmaceutical formulations. It this patent the sequence of reactions illustrated in Scheme 1 is used for its preparation.



Scheme 1

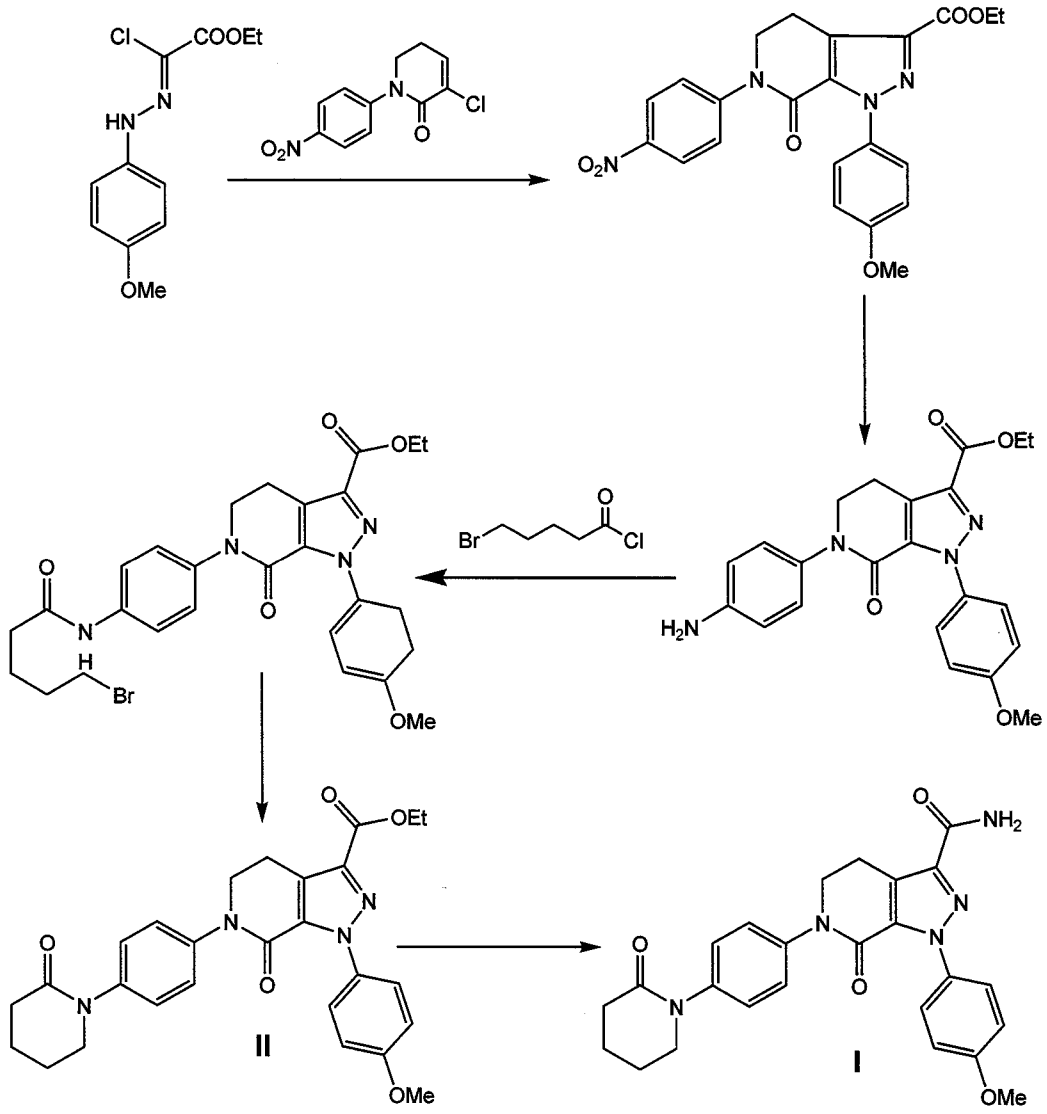
Synthesis of apixaban is also described in the later WO03049681, according to which, inter alia, apixaban of formula I is prepared as indicated in Scheme 2.



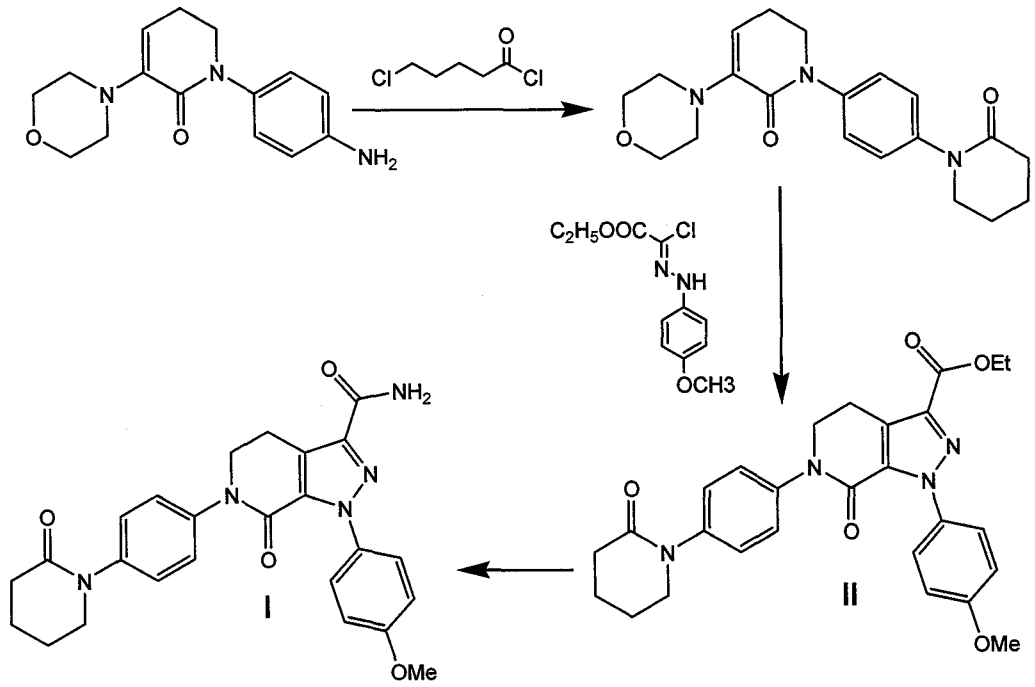
Scheme 2

Both these methods use the Ullmann reaction, i.e. arylation of an amide catalyzed by copper or copper (II) ions in the presence of a base. This reaction requires relatively harsh conditions - 125°C/10 hours, wherein at the same time saponification of the ester function occurs and according to an example in WO03049681 the acid of formula **V** was prepared in 68% yield. This acid was then converted to a mixed anhydride, which provided, after treating with ammonium hydroxide, apixaban of formula I in the yield of 70% over both said steps.

More recent patent applications US 20060069258 (Scheme 3) and CN 2011101967145 (Scheme 4) prepare apixaban using a different sequence of synthetic steps and do not use the Ullmann reaction for preparation of the intermediate of formula II.

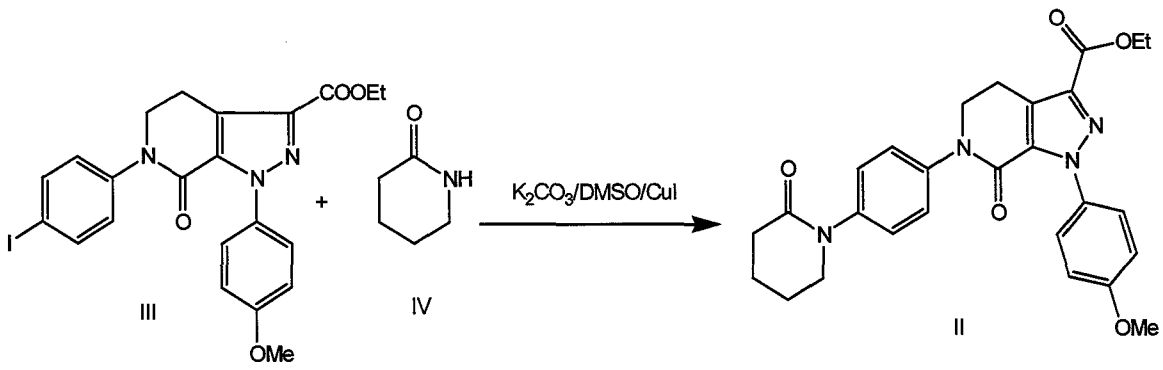


Scheme 3



Scheme 4

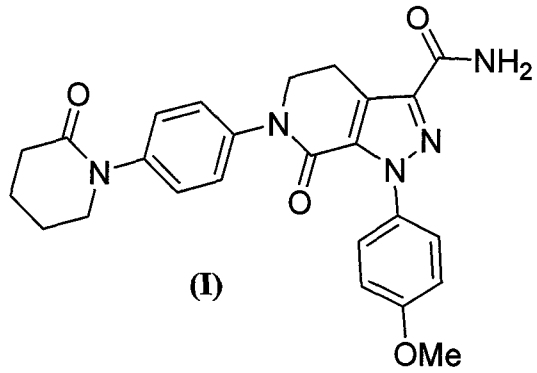
The method described in the patent literature and in a review article published by workers of the Bristol-Myers Squibb Company (*J. Med. Chem.* **2007,** *50,* 5339-5356), see Scheme 5, carries the reaction out in dimethyl sulfoxide with potassium carbonate as the base and cuprous iodide as the catalyst at 130°C for 24 hours. After purifying by column chromatography the product is described as brown foam and the yield reported is 21%.



Scheme 5

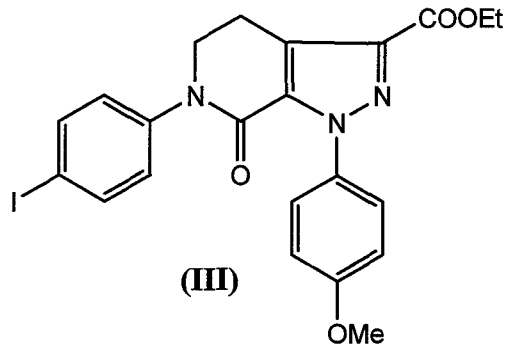
Disclosure of Invention

The object of this invention provides a method for the preparation of apixaban of formula **I**



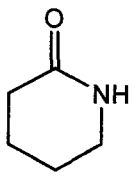
(I)

in which ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate of formula **III**



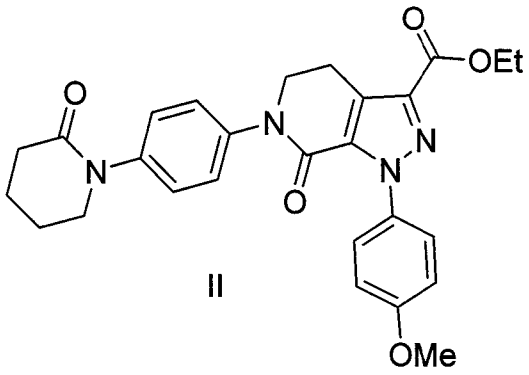
(III)

is reacted with piperidin-2-one of formula **IV**



(IV)

in the presence of a base and a ligand and under catalysis of copper or copper(II) ions, wherein a salt of phosphoric acid is used as the base and an amine selected from the group of 1,2-diamines in an aprotic solvent is used as the ligand and ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridin-3-carboxylate of formula **II**



II

(II)

is prepared, which is converted, by reaction with ammonia in a suitable solvent, to apixaban of formula **I,** which is isolated and optionally crystallized.

1,2-Diamines as ligands are added in amounts in the range of 20-60 molar %, more specifically in amounts in the range of 30-40 molar %.

In the most convenient embodiment potassium phosphate K_3PO_4 is used as the phosphoric acid salt and *N,N'*-dimethylethylenediamine is used as the ligand.

Suitable solvents for this reaction are, e.g., solvents from the group of ethers, expressed by the general formula R^1-O-R^2, wherein R^1 and R^2 are identical or different and are selected from the group including a C_1 to C_5 alkyl or cycloalkyl, cyclopentyl methyl ether being especially suitable.

The above mentioned Ullmann reaction is carried out at elevated temperatures, especially at the boiling temperature of the solvent used for the reaction.

The resulting compound of formula **II** is transformed to apixaban of formula **I** using well-know procedures, e.g. by reaction of the compound **II** with ammonia in a suitable solvent. The reaction of the compound **II** to apixaban is carried out in ethylene glycol, preferably with heating, e.g. to 120 °C, and at an elevated pressure. The resulting apixaban is conveniently isolated by adding the ethylene glycol solution after the reaction and cooling to a C_1 to C_4 alcohol and isolating the resulting precipitated solid apixaban. In particular, the ethylene glycol solution after the reaction and cooling, is added, i.e. slowly added dropwise or poured, into ethanol. This procedure of isolation of apixaban provides a simple method that is suitable for application in the industrial scale and avoids further chromatographic purification, as described, e.g., in *J. Med. Chem.* **2007**, 50, page 5354.

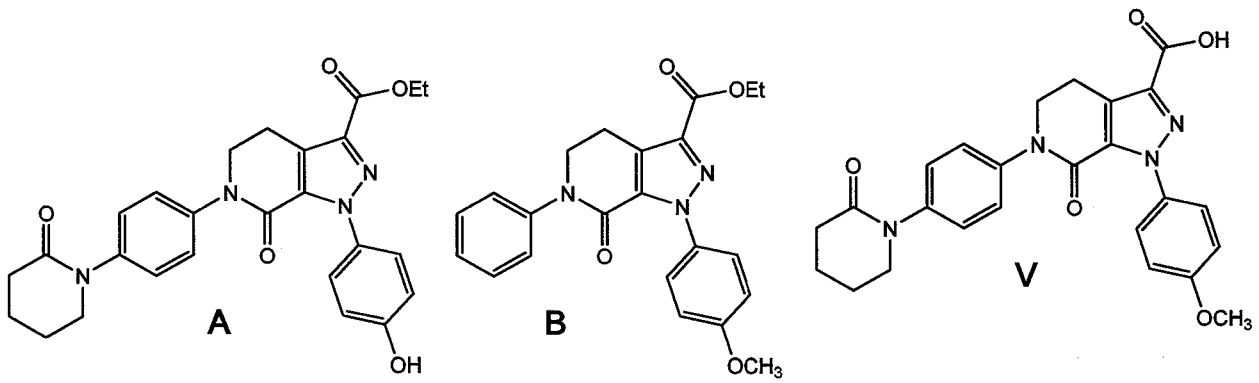
Apixaban prepared this way can be further crystallized by methods known from the state of the art, e.g., from an ethylene glycol/ethanol mixture.

The preparation method in accordance with this invention provides a process that allows preparing apixaban in two reaction steps in a high yield.

The key step in this preparation method consisted in finding a modified process of preparation of the intermediate **II**. In general, this is a reaction of an aryl iodide with a cyclic amide, which is sometimes referred to as the Goldberg reaction – *N*-arylation of amides catalyzed by copper. It is an alternative of the technologically and economically more demanding palladium-catalyzed Buchwald-Hartwig amination.

Within the development of a procedure suitable for industrial-scale application emphasis must be placed on the technological aspects of the process. Therefore, a series of experiments have been carried out to optimize individual parameters of the reaction.

Reproducing the procedure described in the Experimental Part of the article *J. Med. Chem.* **2007,** *50,* on page 5354, preparation of the compound **39**, we have found out that under the particular conditions the conversion was really very low, reaching only ca. 30%, leaving ca. 30% of the starting iodo derivative III in the reaction mixture and generating several impurities, out of which we have identified the compounds of formulae **A, B** and **V** (Scheme 6) as the main ones. The isolate obtained this way must be purified with column chromatography. The isolation procedure makes it possible to separate the ester **II** from the acid **V**, but it must be converted to apixaban via a mixed anhydride, see Scheme 2.



Scheme 6

In optimizing the above-mentioned process we have focused on optimization of individual constituents that influence the Ullmann reaction - base, solvent, catalyst and ligand.

Base

The reaction is carried out with inorganic bases of the type of alkali metal hydroxides, alkali metal carbonates, preferably Cs_2CO_3, alkali metal phosphates. The best results have been achieved with potassium phosphate as the base in a two- to five-fold molar amount; ground or micronized potassium phosphate can be conveniently used.

Solvent

Another important parameter of the reaction is the solvent used. With regard to the expected mechanism of the reaction an aprotic polar environment has to be selected. In addition, a relatively high reaction temperature needs to be achieved, which makes the selection of solvents rather limited. No satisfactory results have been achieved with dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) or toluene. The modern high-boiling solvent cyclopentyl methyl ether (CPME) with the boiling point of 106°C and density of 0.86 g/cm^3 has proved to be suitable. The solvent is characterized by strongly hydrophobic properties, solubility of water in CPME is only 0.3% and it can be dried both with a molecular sieve and by azeotropic distillation. Its advantage from the work safety point of view also includes its very low proneness to form peroxides. Other advantages of this solvent are a low heat value necessary for its distillation (290KJ/lkg at the boiling point), which reduces the energy costs of the process, and last but not least, its stability towards bases even at a high temperature.

Catalyst

Copper powder, copper(I) or copper(II) salts can be used as the source of copper(II) ions. The use of the price convenient and air stable cuprous iodide in an amount of 5-10 mole % has been evaluated as optimum.

Ligand

The Ullmann reaction in accordance with the patent EP 1 427 415 was carried out without the addition of a ligand. We have tested the reaction in the same arrangement with the addition of 1,10-phenanthroline without any principal improvement of the conversion or limitation of the occurrence of impurities. As a suitable type of ligands, the group of 1,2-diamines has been

selected in amounts of 20-60 mole %, more specifically in amounts of 30-40 mole %. Results of the same quality have been achieved both with *N,N'*-dimethylethylenediamine and with *trans-N,N'*-dimethylcyclohexane-1,2-diamine. A reaction carried out using *n*-hexylamine did not have such a positive result.

Preparation of the API

The isolation of apixaban from the reaction mixture described in the basic patent requires purification of the product on a silica gel column. This approach is not suitable for technological applications. We have unexpectedly found out that if the reaction mixture is slowly dosed to ethanol, apixaban will precipitate out from the solution in the form of well filterable crystals in a sufficient yield.

Experimental Part

Analytic method used for monitoring of the conversion:

High-Performance Liquid Chromatography

Instrumentation: Hitachi Elite LaChrom HPLC, DAD detector

Column: Purospher RP8e, 250 x 4.0 mm, 5um (Merck)

Mobile phase: A: phosphate buffer 0.02 M KH_2PO_4, pH 2.7 ± 0.05 adjusted with H_3PO_4

B: acetonitrile

Elution: gradient

Time (min.)	Flow rate (ml/min.)	% A	% B
0	1.0	90	10
2	1.0	90	10
25	1.0	20	80
30	1.0	20	80
35	1.0	10	90

Sample solvent: methanol

Detection: spectrophotometric, 283 nm

Injection volume: 20 µl

Analysis time: 35 min

Tested solution: 1 mg / 1 ml

Reference Example 1 (WO2003049681)

Preparation of ethyl 6-(4-iodophenyl)-1-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate **III**

The preparation was carried out in an inert atmosphere (argon). 2-Chloro-2-[2-(4-methoxyphenyl)hydrazono] acetic acid ethyl ester (14.1 g; 0.055 mol) was dissolved in 140 ml of ethyl acetate. The solution was cooled to 0-5°C in an iced water bath. The solution being stirred, 1-(4-iodophenyl)-3-morpholin-4-yl-5,6-dihydro-1*H*-pyridin-2-one (21.1 g; 0.055 mol) was added in portions. After stirring up, triethylamine (11.1 g; 0.110 mol) was added dropwise to the reaction mixture at 0-5 °C. The cooling of the reaction mixture was interrupted and the temperature was left to rise to the room level. Then, heating was started up to reflux. The reflux temperature of the reaction mixture was maintained for ca. 120 min. Completion of the reaction was monitored by means of HPLC. The reaction mixture was cooled to 0-5°C again and concentrated hydrochloric acid (27.5 ml; 0.275 mol) diluted with distilled water in the 1:1 ratio was slowly added dropwise. Being cooled, the reaction mixture was stirred for ca. 1 h. Then, another 55 ml of water was added and the resulting suspension was stirred for another 2 h while being cooled. The separated product was isolated by filtration and dried in vacuo at 50°C for 24 h. The product **III** was obtained in the yield of 21.3 g; i.e. 75 % and HPLC quality of 95 %.

Reference Example 2 (*J. Med. Chem.* **2007**, *50*, 5339-5356)

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6- [4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate III (2,6 g, 5 mmol), piperidin-2-one (0.69 g, 7 mmol), K_2CO_3 (0.82 g, 5.9 mmol) and DMSO (10 ml) were mixed in a reaction vessel. Nitrogen was bubbled through the mixture for 30 min. Then CuI (0.19 g, 1 mmol) was added. The mixture was heated to 130°C for 24 h, cooled and an HPLC analysis of the reaction mixture was carried out. It was found that the conversion was only 30%, the reaction mixture contained 30% of the starting compound III and the rest consisted of impurities.

Example 1

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (536 mg; 1.04 mmol) was dissolved in 5 ml of cyclopentyl methyl ether in a 10 ml sealable pressure container. Piperidin-2-one (128 mg; 1.30 mmol), CuI (10 mg; 0.052 mmol), K_3PO_4 (440 mg; 2,1 mmol) and *N,N'*-dimethylethylenediamine (37 mg; 0.42 mmol) were added. A stirrer was inserted in the container and it was closed under an inert atmosphere. Being stirred by a magnetic stirrer the mixture was heated up in an oil bath to 110°C for 6 h. After cooling the reaction mixture was diluted with a solvent, the solid salts were isolated by filtration and thoroughly washed on the filter. The filtrate was concentrated and the crude product was obtained in the yield of 84%.

Example 2

Preparation of ethyl 1-(4-methoxyfenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (0.52 g; 1.01 mmol) was dissolved in 1 ml of toluene in sealable pressure vessel fitted with a magnetic stirrer; piperidin-2-one (0.123 g; 1.24 mmol), CuI (9.6 mg; 0.05 mmol), K_2CO_3 (0,28 g; 2.03 mmol) and *N,N'*-dimethylethylenediamine (11 µl; 0.1 mmol) were added. Being intensively stirred the mixture was heated in an oil bath to 115°C for 6 hours. The conversion was monitored with HPLC. After the above mentioned period the reaction mixture only contained 5.6 % of the product. The main constituent of the reaction mixture was the starting compound.

Example 3

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (0.538 g; 1.04 mmol) was dissolved in 1 ml of DMF in a sealable pressure container fitted with a magnetic stirrer; piperidin-2-one (0.15 g; 1.5 mmol), CuI (18.4 mg; 0.096 mmol), K_3PO_4 (0.457 g; 2.15 mmol) and *N,N'*-dimethylethylenediamine (15 µl; 0.136 mmol) were added. Being intensively stirred, the mixture was heated in an oil bath to 90°C for 20 hours. The conversion was monitored with HPLC. After the above mentioned period the reaction mixture contained 36% of the product 30.3% of the acid **V** and 2.5% of the starting compound. After cooling the reaction mixture was diluted with water and the product was extracted with ethyl acetate. After concentration the product was obtained in the yield of 0.237 g, i.e. 48.6%, with the HPLC content of the desired substance of 68%.

Example 4

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (0.522 g; 1.0 mmol) was dissolved in 5 ml of *n*-hexylamine in a sealable pressure vessel fitted with a magnetic stirrer; piperidin-2-one (0.146 g; 1.47 mmol), CuI (12.2 mg; 0.064 mmol) and K_3PO_4 (0.547 g; 2.58 mmol) were added. Being intensively stirred the mixture was heated up in an oil bath to the temperature of 90°C for ca. 20 h. The conversion was monitored with HPLC. After the above mentioned period the reaction mixture contained 15.8% of the product, 20.3% of the starting substance, 2.2% of the acid **V** and the rest consisted of impurities.

Example 5

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (10.4 g; 0.02 mol) was dissolved in 100 ml cyclopentyl methyl ether in a flask fitted with a reflux condenser and anchor stirrer; piperidin-2-one (2.6 g; 0.026 mol), CuI (0.33 g; 1.7 mmol), K_3PO_4 (10.6 g; 0.05 mol) and *N,N'*-dimethylethylenediamine (0.82 g; 9.3 mmol) were added. Being intensively stirred the mixture was heated in an oil bath to the reflux temperature for ca. 6 h. The conversion was monitored with HPLC. After cooling the reaction mixture was diluted with the solvent, the solid salts were isolated by filtration and thoroughly washed on the filter. The filtrate was concentrated and the crude product was obtained in the yield of 83%.

Example 6

Preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate

The preparation was carried out in an inert atmosphere (argon). Ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (7.8 g; 0.015 mol) was dissolved in 90 ml of cyclopentyl methyl ether in a flask fitted with a reflux condenser and an anchor stirrer; piperidin-2-one (1.9 g; 0.0195 mol), CuI (0.25 g; 1.3 mmol), K_3PO_4 (9.6 g; 0.045 mol) and *trans N,N'*-dimethylcyclohexane-1,2-diamine (0.9 g; 6.3 mmol) were added. Being intensively stirred the mixture was heated in an oil bath to the reflux temperature for ca. 8 h. The conversion was monitored with HPLC. After cooling the reaction mixture was diluted with 100 ml of water, the product was extracted with ethyl acetate, 3x 50 ml. The combined extracts were washed with brine and concentrated at a reduced pressure. The crude product was obtained in the yield of 89%.

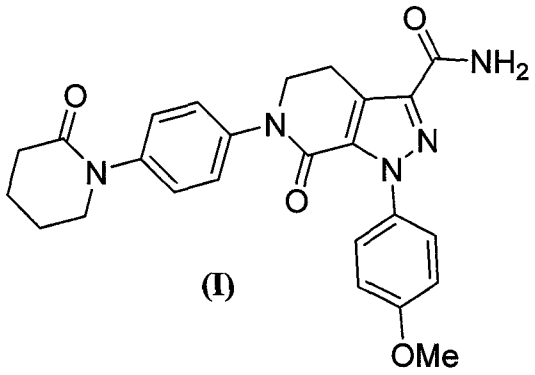
Example 7

Preparation of apixaban

Ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate (4.5 g; 9.2 mmol) was sealed in an ampoule with 40 ml of ethylene glycol containing 15% by weight of ammonia. The ampoule was placed in an oil bath and heated up to 120°C for 1 h. After cooling the reaction mixture was poured to 50 ml of ethanol. The crystalline product was separated in the yield of 90%.

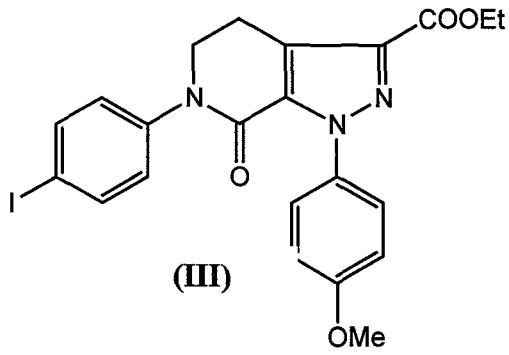
Claims

1. A method of preparing apixaban (**I**)



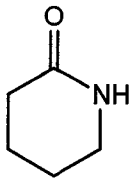
(I)

in which ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate of formula **III**



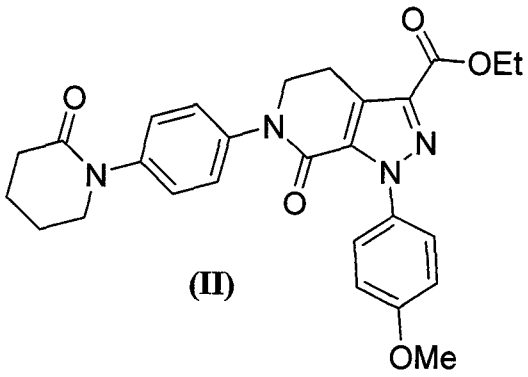
(III)

is reacted with piperidin-2-one of formula **IV**



(IV)

in the presence of a base and a ligand and under catalysis by copper or by copper(II) ions, characterized in that, using a salt of phosphoric acid as the base and a ligand selected from the group of 1,2-diamines in an aprotic solvent, ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazol-[3,4-*c*]pyridine-3-carboxylate of formula **II**



(II)

is prepared, which is converted, by reaction with ammonia in a suitable solvent, to apixaban of formula **I**, which is isolated and optionally crystallized.

2. The method according to claim 1, characterized in that the salt of phosphoric acid is potassium phosphate.

3. The method according to claim 2, characterized in that potassium phosphate is used in an amount in the range of 2 to 5 equivalents.

4. The method according to claims 1-3, characterized in that the suitable ligand from the group of 1,2-diamines is used in an amount in the range of 20 to 60 molar %.

5. The method according to claim 4, characterized in that the suitable ligand from the group of 1,2-diamines is *N,N'*-dimethylethylenediamine.

6. The method according to claims 1-5, characterized in that the aprotic solvent is selected from the group of ethers of general formula R^1-O-R^2, wherein R^1 and R^2 are identical or different and are selected from the group including C_1 to C_5 alkyls or cycloalkyls.

7. The method according to claim 6, characterized in that the aprotic solvent is cyclopentyl methyl ether.

8. The method according to claims 1-7, characterized in that the reaction is carried out at the boiling temperature of the aprotic solvent.

9. The method according to claim 1, characterized in that the solvent for the reaction of the compound II with ammonia is ethylene glycol.

10. The method according to claims 1-9, characterized in that isolation of apixaban is carried out by adding an ethylene glycol solution of the compound II with ammonia to a C_1 to C_4 alcohol and isolating the precipitated solid apixaban.

11. The method according to claim 10, characterized in that the alcohol is ethanol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000149

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2014	19/02/2014

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PINTO D ET AL: "Discovery of 1-[4-(Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban, BMS-562247), a Highly Potent, Selective, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 50, 1 January 2007 (2007-01-01), pages 5339-5356, XP007915445, ISSN: 0022-2623, DOI: 10.1021/JM070245N [retrieved on 2007-03-10] cited in the application Scheme 6., Compound 40; page 5343, left-hand column Present Reference Example 2	1-11
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