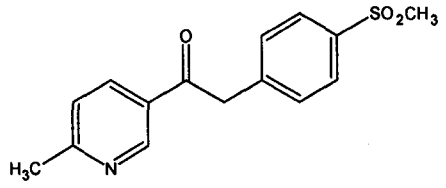
Field of Invention

The present invention relates to a novel process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula I.

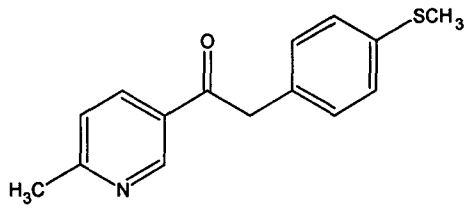


I

1-(6-methylpyridn-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone is an important intermediate for preparing COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action as described in R. S. Friesen et al., *Bioorganic & Medicinal Chemistry Letters* 8 (1998)2777-2782 and WO 98/0348.

Background of the Invention

There are many process described in the art for the preparation of 1-(6-methylpyridn-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone. WO 99/15503 of Merck & Co., Inc. describes its preparation by the reaction of a Grignard compound (4-thiomethylbenzylmagnessium chloride) and an amide (Weinreb amide) to give a ketosulfidecompound of formula II



II

and its subsequent oxidation.

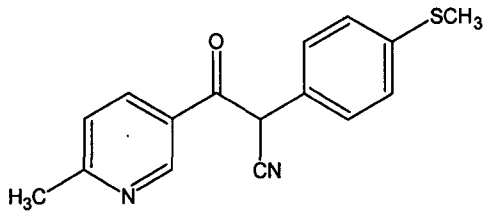
The oxidation reaction is carried out by using various oxidation systems like hydrogen peroxide, Oxone® ($2KHSO_5$-$KHSO_4$-K_2SO_4) or hydrogen

peroxide/acetic acid, preferably by using Oxone® or hydrogen peroxide in the presence of a catalyst, preferably Na2W04, under acid conditions. The presence of a second function which can be oxidized (the pyridine nitrogen atom) in the molecule to be oxidized causes the formation of compound II N-oxide as reaction by- product. The use of weak oxidation condition does not provide a good solution to the problem because, even if the formation of the N-oxide by-product is avoided, the oxidation of the sulphur atom is not complete resulting to the formation of sulphoxide derivatives, which are difficult to separate.

The other two patent applications WO 01/29004 and WO 01/07410 which describes the similar process also needs the presence of a catalyst, in particular of a wolfram derivative (Na2WO4) for carrying out the oxidation reaction of the last step.

WO 03/051843 describes the above oxidation without the presence of a catalyst by using an oxidant, in the presence of an acid, where the oxidant is a mixture of peracetic acid and hydrogen peroxide and the acid is methanesulphonic acid. The use of methanesulphonic acid is not preferred at industrial scale due to its role in formation of possible alkylating agents as impurities which may be of genotoxic nature.

US 6600046 describes a process for preparation of compound of formula I in three steps starting from 4-(methylthio)phenylacetonitrile. In this process 4-(methylthio)phenylacetonitrileis condensed with a 6-methylnicotinic ester in presence of an alkali metal alkoxide and an alkoholic solvent to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridineof formula III



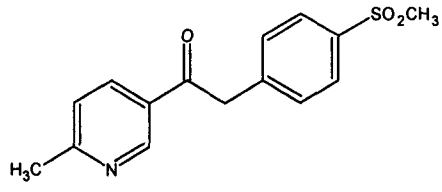
III

The product of compound of formula III after isolation, is subjected to hydrolysis and decarboxylationusing mixture of acetic acid & HCl, EDTA and sodium hydroxide to obtain 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine (i.e. ketosulfide) of formula II. The ketosulfide of formula II is isolated and in third step it is oxidised to obtain the end product ketosulfone of formula I using hydrogen peroxide, in presence of alkali metal tungstate(eg. $Na_4WO0.2H_4O$) and in an alcoholic solvent.

Thus most of the prior art uses mixture of acetic acid and hydrochloric acid for the hydrolysis and decarboxylation, and methanesulfonic acid as a second acid for oxidation. In the prior art process, the ketosulfide of formula II is isolated which needs additional workup and hence leads to loss of yield. Moreover, most of the prior art process uses alkali metal tungstate for oxidation of ketosulfide of formula II which leads to the presence of tungsten in the final compound as an impurity. It is very difficult to remove tungsten at this stage and in active pharmaceutical ingredient more than 10 ppm of tungsten is not allowed. The present inventors have developed a novel process, which overcomes most of the above stated drawbacks and is more convenint at industrial scale and have advantage from the economic and environmental viewpoints.

Summary of the Invention

The principal aspect of the invention is to provide a novel process for the preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula I.



I

comprising :

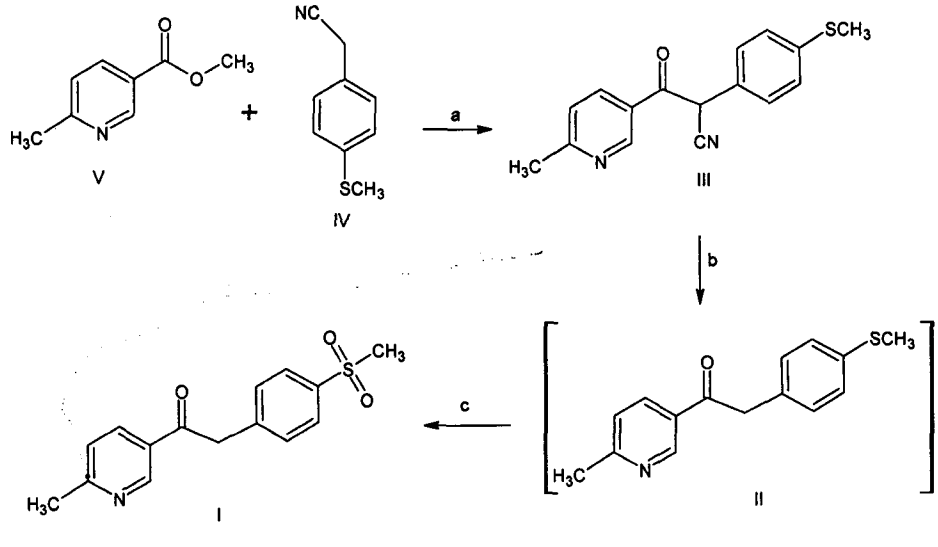
a) condensing 4-(methylthio)phenylacetonitrile with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine of formula III;

b) hydrolysing and decarboxylating3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine of formula III in presence of H_2SO_4 and in absence of mixture of acetic acid and HClto obtain 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II;

c) insitu oxidation of 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II in presence of hydrogen peroxide, H_2SO_4, & acetic acidand in absence of an alkali metal tungstate catalyst to give Ketosulfone of formula I; and

d) optionally the ketosulfone of formula I is purified by methanol to obtain tungsten free Ketosulfone.

The above process can be illustrated by below scheme:



In another aspect, the present invention avoids isolation of ketosulfide compound of formula II leading to a reduction of one step, which reduces the cost, effluent as well as the time cycle of the process significantly.

Detail Description of the Invention

Accordingly in an embodiment of the invention, the condensation in step (a) is carried out in presence of an alkali metal alkoxide, at temperature 70 to 110 °C, preferably 100 to 110°C.The alkali metal alkoxide is selected from sodium methoxide or potassium tertbutoxide. The reaction is preferably carried out in presence of lower alcohol such as methanol, ethanol and/or an aromatic hydrocarbon solvent such as toluene.

In another embodiment, the hydrolysis and decarboxylation in step (b) is carried out in acidic condition preferably in presence of H_2SO_4andin absence of acetic acid at a temperature 50 ^{0}C to 115 ^{0}C, preferably 90 to 110°C.

In yet another embodiment, the oxidation of 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II in step (c) is carried out using H_2SO_4, acetic acid and hydrogen peroxide. The pH is adjusted using aqueous ammonia.

In yet another embodiment, ketosulfone of formula I is purified by methanol hot pulping. If needed a methanol slurry wash is applied. After purification the obtained Ketosulfone is free from tungsten and the individual impurity is less than 0.1%.

A person skilled in the art will acknowledge that the present invention overcomes most of the common drawbacks and has following advantages:

- Reduction of a number of step by eliminating isolation of ketosulfide of formula II
- Reduction in generation of toxic effluent

- Elimination of use of methane sulfonic acid which would cause genotoxic impurities
- Elimination of use of alkali metal tungstate as catalyst for the oxidation
- It provides tungsten free Ketosulfone which is very desired for the industry.

The present invention is illustrated by the following examples, which are not to limit the scope of the invention.

Example:

Preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanon

(a) Preparation of 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine

The mixture of 4-methyl thiophenyl acetonitrile (1.0 kg), methyl-6-methyl nicotinate (1.104Kg) and toluene (5.0 L) were heated to 90-95°C under stirring. To the above reaction mass sodium methoxide solution (0.496 kg in 1.656 L of methanol) was added slowly. Toluene (5.0L) was added and maintained at 105-110°C for 6 hours. After completion of the reaction, the reaction mass was cooled to 25-30°C. and DM water (2.0L) and acetic acid (0.54kg) were added into it. The reaction mass was stirred, filtered, dried and slurry was washed first with toluene (2.0L) and then with DM water. Dry under vacuum at 60-70°C till moisture content less than 0.5%.

Yield = (1.6 kg) 1.6 w/w

(b) In-situ preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone

DM water (1.78 L) and concentrated sulfuric acid (3.4 kg) were stirred and heated in RBF at 25-30 °C. The solution was heated to 60-65°C.and3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine (1.25kg) was added into it

in lots. The reaction mass was further heated to 95-100°C and maintain till the completion of reaction. After completion of the reaction the mass was cooled to 20-25°C. Acetic acid (1.96 kg) was added and cooled to 6-10°C. 48% hydrogen peroxide (0.258kg) was added drop wise and stirred at 10-12°C till the completion of reaction. After completion of the reaction, DM water (3.75 L) was added at 5-10°C. and the excess hydrogen peroxide was neutralized using sodium thiosulpahte solution (0.12kg of sodium thiosulphate in 0.36 L of DM water) at 5-10°C.Filter the reaction mass at 10-15° C. The filtration bed was washed with DM water (0.62 L) and the clear filtrate was taken in another RBF at 5-10°C., pH was adjusted to 7.5-8.0 using ammonia solution (8.5 kg) at below 15°C and stirred. The reaction mass was filtered, dried under vacuum. The wet ketosulfone (≈ 2.04 kg) in 6.2 L water was heated to 50-55°C and stirred. The reaction mass was cooled to 25-30°C, filtered under vacuum, washed with DM water (0.62L) and dried under vacuum at 25-30°C. The product was washed under vacuum at 65-70°C till moisture content comes less than 5%.

(c) Purification of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanon

Ketosulfone crude (1.125kg) was stirred in methanol (3.375 L) for 10 minutes at 25-30°C. The reaction mass was heated to 75-80 °C for three hours. The reaction mass was cooled slowly to 25-30°C, stirred for 1 hour and filter under vacuum 25-30°C.The product was washed with methanol (0.56 L), dried for 1hour at 25-30°C.

Dry wt≈ 1.12 kg

Individual impurity: < 0.1%