AN IMPROVED PROCESS FOR THE PREPARATION OF CELECOXIB

The present invention relates to an improved process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula (I), by condensing 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV), Formula (IV) with 4-hydrazinophenylsulfonamide (V) or its acid addition salt Formula (V) in a solvent selected from water and in presence of acid. The present invention also relates to the process for the purification of Celecoxib in a solvent mixture.
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AN IMPROVED PROCESS FOR THE PREPARATION OF CELECOXIB

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of 4-[(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide of Formula (I).

![Formula I]

BACKGROUND OF THE INVENTION

Selective inhibitors of cyclooxygenase-2 (COX-2) have demonstrated effective anti-inflammatory activity with reduced gastrointestinal side effects, as compared to other antiinflammatory agents, e.g., NSAIDs, which inhibit both the constitutive form of cyclooxygenase (COX-1), and the inducible form of the enzyme (COX-2). Particularly effective structural classes of selective COX-2 inhibitors are the 1,5-diarylpyrazoles. 4-[(5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (Celecoxib) is a 1,5-diarylpyrazole compound, which has been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis and osteoarthritis. Celecoxib is the active ingredient used in the Celebrex, which is marketed by Pharmacia Corporation.
G.D. Searle & Co., has disclosed Celecoxib and its pharmaceutically acceptable salts in US 5,466,823.

US 5,466,823, also discloses a process for the preparation of Celecoxib, which comprises reacting 4-methylacetophenone (II) with 1-ethyltrifluoroacetate (III) in the presence of methyl t-butyl ether and sodium methoxide, followed by recrystallisation from isoctane to produce 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV), which is further condensed with 4-hydrazinophenylsulfonamide hydrochloride (V) in the presence of ethanol to produce crude Celecoxib, which is recrystallised from ethyl acetate and isoctane to give Celecoxib (I).

The process is as shown in Scheme -I below:

```
  H3C
O

  O
H3C

  CF3
C=O
C2H5

  HI

  O
H3C

  CF3
C=O
H3C

  H2N\n\n\nO\nS\nO\nN\n\n\n\nCF3
H3C

  H2N\n\n\nO\nS\nO\nN\n\n\n\nCF3
H3C

  ETOAc /iso-octane

  Scheme-I
```
The above process involves isolation of the intermediate 1-(4-methylphenyl)-4,4,4-
trifluorobutane-1,3-dione (IV) by crystallization, before condensing with 4-
sulphonamido-phenylhydrazine, which adds to the cost and complexity of the
synthesis.

Further, the above process proceeds with less selectivity to Celecoxib, which is having
about 4 wt. % of regioisomer (VI) by-product under commercial conditions.

US 6,150,534 discloses a process for the preparation of Celecoxib, which comprises,
condensing 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) with 4-
sulphonamido-phenylhydrazine in presence of an amide solvent at controlled
temperature to produce amide solvate of Celecoxib, which is further desolvated by
recrystallization from isopropanol and water.

The above process also involves isolation of the intermediate 1-(4-methylphenyl)-
4,4,4-trifluorobutane-1,3-dione (IV) by crystallization, before condensing with 4-
sulphonamido-phenylhydrazine.

US 5,892,053 discloses a process for the preparation of Celecoxib by condensing 4-
methylacetophenone (II) with 1-ethyltrifluoro acetate (III) to produce 1-(4-
methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV), which is further reacted with 4-
hydrazinophenylsulfonamide (V) in presence of aqueous mixture of alcohol and acid
to produce Celecoxib.

US 6,579,988 discloses a preparation of Celecoxib via novel intermediate compound
of formula VII.
US 2007/0004924 A1 discloses a process for the preparation of Celecoxib by condensing 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) with 4-hydrazinophenylsulfonamide (V) in presence of a solvent system containing an organic solvent, the salt of the 4-sulphonamidophenylhydrazine having a solubility in the organic solvent at least 0.05 M.

US 2008/0234491 A1 discloses the condensation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) with 4-hydrazinophenylsulfonamide (V) or its acid addition salts in the presence of a solvent medium comprising an alkyl ester, water or mixtures thereof to produce Celecoxib. Further, crystallization of crude Celecoxib is carried out in toluene alone.

It is generally difficult to separate the regioisomer through crystallization from Celecoxib, which typically require two to three crystallizations to achieve desired Celecoxib purity. The second and third crystallization adds time to the manufacturing process and thus negatively impacts product throughput. Additionally, a second and third crystallization reduces yield as some Celecoxib remains uncrystallized and is not recovered from the liquid phase.

Hence, there is a need to develop a process, which provides 4-[[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) with high selectivity with respect to its regioisomer (VI).
Further, there is a need to develop a purification process, which reduces the unwanted regio-isomer to a pharmaceutically acceptable limit, which in turn provides Celecoxib of high purity and improved yield.

In view of the above, the instant invention describes a process, which produces Celecoxib with regioisomer (VI) to less than 2.5% by HPLC analysis. The instant invention also describes a purification process using specific solvent mixture, which results in pure crystalline Celecoxib Form III, having regioisomer (VI) less than 0.1 % by HPLC analysis.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide a simple and effective process for the preparation of Celecoxib with high purity and good yields on a commercial scale.

SUMMARY OF THE INVENTION

The present application provides an improved process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) of Formula I,

![Formula I](image)

which comprises:

condensing 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV),
with 4-hydrazinophenylsulfonamide (V) or its acid addition salt,

\[
\begin{align*}
\text{Formula IV} & \\
\begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{C} \text{F}_3
\end{array}
\end{align*}
\]

in a solvent selected from water and in presence of acid to produce 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula I.

According to an embodiment, the present invention also provides a process for the purification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) of Formula I, comprises:

(i) preparing a solution of crude Celecoxib in a solvent mixture;
(ii) optionally, filtering the solution of step (i);
(iii) precipitating Celecoxib Form III by cooling the solution;
(iv) isolating pure Celecoxib in crystalline Form III.

DETAILED DESCRIPTION OF THE INVENTION

1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) is condensed with 4-hydrazinophenylsulfonamide (V) or its acid addition salt in a solvent selected from water, inert organic solvent to produce 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) of Formula I. The acid addition salts of compound of the formula IV includes, but are not limited to, hydrochloride, hydrobromide, sulfate, nitrate, oxalate, mesylate, methane sulfonate, and tartrate,
preferably, hydrochloride salt. The suitable inert organic solvents for the above reaction include but are not limited to ketone solvents, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, n-butanone, and tertiary-butyl ketone; nitrile solvents, such as acetonitrile and propionitrile; halogenated solvents, such as dichloromethane, ethylene dichloride, and chloroform; esters, such as ethyl acetate, n-propylacetate, isopropyl acetate, and tertiary-butyl acetate; aprotic polar solvents, such as N,N-dimethylformamide, dimethylsulfoxide, and N,N-dimethylacetamide; ethers, such as diisopropyl ether, tetrahydrofuran and 1,4-dioxane; hydrocarbon solvents, such as cyclohexane, toluene and xylene; and mixtures thereof. The preferred solvent is water. The reaction may be performed at a temperature ranging from about 25°C to about reflux temperature of the solvent or mixture of solvents used for the reaction.

The above reaction is conducted in presence of an acid selected from aqueous hydrochloric acid, aqueous sulfuric acid, p-toluene sulfonic acid, trifluoroacetic acid, and acetic acid to maintain the pH of the reaction mixture is below 7. More preferably, aqueous HCl is added. Crude Celecoxib (I) produced may be isolated by precipitation of compound from the reaction mixture, which may be performed by cooling the reaction mixture, followed by addition of an organic solvent selected from alcohols such as methanol, ethanol, isopropanol or aromatic hydrocarbons such as toluene, xylene, ethyl benzene and mixtures thereof solvents. The preferred solvent is mixture of methanol and toluene.

It has been observed that preparation of Celecoxib (I) using above reaction conditions results in regioisomer of compound (VI) to less than 2.5% by HPLC analysis.

In another embodiment, the present invention further provides a process for the purification Celecoxib (I).

The process comprises dissolving crude Celecoxib in a solvent mixture, precipitating Celecoxib Form III by cooling the solution to about 0-5°C, and isolating crystalline
Celecoxib Form III. Optionally, the crude Celecoxib is dissolved in a solution at a temperature from about 40°C to about the boiling temperature of the solvent. Optionally, the Celecoxib Form III is isolated by filtration. Optionally, the solution is treated with carbon, followed by filtration to remove insoluble material. The step of cooling the reaction is performed by cooling the solution to a temperature from about -10°C to 25°C temperature. The solvent mixture is selected from the group consisting of alcohol: toluene such as methanol: toluene, ethanol: toluene, isopropanol: toluene, n-butanol: toluene, t-butanol: toluene. The ratio of alcohol to toluene may range from about 2.5:97.5 (v/v) to about 8:92 (v/v), preferably 5:95 (v/v).

It has been observed that purification of crude Celecoxib using above solvent mixture results in pure crystalline Celecoxib Form III, having regioisomer less than 0.1% by HPLC analysis.

The following examples are provided to illustrate the invention and are merely for illustrative purpose only and should not be construed to limit the scope of the invention.

**EXAMPLES:**

**EXAMPLE 1**

**Stage-1:**

**Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV)**

4-Methylnactophenone (50 g, 0.373 mol) was dissolved in toluene (250 ml) and 30% methanolic sodium methoxide solution (80.6 g, 0.447 mol), followed by 1-ethyltrifluoroacetate (63.58 g, 0.447 mol) were added at 25-30°C. Temperature of the reaction mass was raised to 55-60°C and stirred ~ 4 hr to complete the reaction. The reaction mass was cooled to 20-25°C and washed with 10% aqueous hydrochloric acid (200 ml). The layers were separated and concentrated the organic layer at 50-55°C
under reduced pressure to produce 80 g of L-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) as an oily mass.

Stage-2:
Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) (I)

1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV) (80 g, 0.348 mol), 4-hydrazinophenylsulfonamide (V) (77.74 g, 0.348 mol) and concentrated hydrochloric acid (18.6 g) were added to DM water (500 ml) and heated to 98-100 °C. The mass was stirred for 4 hr to complete the reaction. The reaction mass was cooled to 70-75 °C and a mixture of toluene (600 ml) and methanol (10 ml) was added to the reaction mass. After 1 hr stirring at 70-75 °C, the reaction mass was cooled to 20-25 °C, the product was filtered and washed with toluene (100 ml) followed by DM water (200 ml). The product obtained was dried at 55-60 °C under reduced pressure to produce 115 g of Celecoxib crude.

Chromatographic purity: 99% (by PTPLC, by area normalization)

Preparation of Celecoxib Form-III

Celecoxib crude (50 g) was dissolved in a mixture of toluene (300 ml) and methanol (20 ml) at 55-60 °C. Carbon (2 g) was added and stirred for 15 min, the resulting solution was filtered through hyflo and washed with toluene (50 ml). The combined filtrate was stirred at 50-55 °C for 1 hr, further the reaction mass was cooled and stirred another 1 hr at 0-5 °C. The product was filtered and washed with chilled toluene (50 ml). The product was dried at 55-60 °C under reduced pressure to obtain 40 g of Form III Celecoxib.

Chromatographic purity: 99.8% (by HPLC, by area normalization)
Example 2:

**Preparation of Celecoxib Form-III**

Celecoxib crude (50 g) was dissolved in a mixture of toluene (250 ml) and ethanol (25 ml) at 60-65°C. Carbon (2 g) was added and stirred for 15 min, the resulting solution was filtered through hyflo and washed with toluene (50 ml). The combined filtrate was stirred at 50-55°C for 1 hr, further the reaction mass was cooled and stirred another 1 hr at 0-5°C. The product was filtered and washed with chilled toluene (50 ml). The product was dried at 55-60°C under reduced pressure to obtain 41 g of Form III Celecoxib.

Chromatographic purity: 99.8% (by HPLC, by area normalization).

Example 3

**Preparation of Celecoxib Form-III**

Celecoxib crude (50 g) was dissolved in a mixture of toluene (250 ml) and isopropanol (25 ml) at 60-65°C. Carbon (2 g) was added and stirred for 15 min, the resulting solution was filtered through hyflo and washed with toluene (50 ml). The combined filtrate was stirred at 50-55°C for 1 hr, further the reaction mass was cooled and stirred another 1 hr at 0-5°C. The product was filtered and washed with chilled toluene (50 ml). The product was dried at 55-60°C under reduced pressure to obtain 41 g of Form III Celecoxib.

Chromatographic purity: 99.8% (by HPLC, by area normalization)
WE CLAIM

1. A process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) of Formula I,

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \begin{array}{c} \text{N} \ \\
\text{CF}_3 \\
\end{array} \\
\text{H}_2\text{C} \\
\end{array}
\]

Formula I

which comprises:

condensing 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (IV),

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CF}_3 \\
\text{H}_2\text{C} \\
\end{array}
\]

Formula IV

with 4-hydrazinophenylsulfonamide (V) or its acid addition salt,

\[
\begin{array}{c}
\text{H} \\
\text{NNH}_2 \\
\text{SO}_3\text{NH}_2 \\
\end{array}
\]

Formula V

in a solvent selected from water and in presence of acid to produce 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula I.

2. The process according to claim 1, wherein the acid is selected from aqueous hydrochloric acid, aqueous sulfuric acid, p-toluene sulfonic acid, trifluoroacetic acid, and acetic acid.
3. The process according to claim 2, wherein the acid is aqueous hydrochloric acid.

4. A process for the purification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib) of Formula I, which comprises:
   (i) preparing a solution of crude Celecoxib in a solvent mixture;
   (ii) optionally, filtering the solution of step (i);
   (iii) precipitating Celecoxib Form III by cooling the solution;
   (iv) isolating pure Celecoxib in crystalline Form III.

5. The process according to claim 4, wherein solvent mixture is selected from the group consisting of alcohol: toluene.

6. The process according to claim 5, wherein solvent alcohol is selected from methanol, ethanol, isopropanol, n-butanol t-butanol.

7. The process according to claim 4, wherein the ratio of alcohol to toluene may range from about 2.5:97.5 (v/v) to about 8:92 (v/v), preferably 5:95 (v/v).

8. The process according to claim 6, wherein the step of cooling the reaction is performed by cooling the solution to a temperature from about -10 °C to 25°C temperature.