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Process for the preparation of 3-cyano-4-isobutoxybenzothiamide

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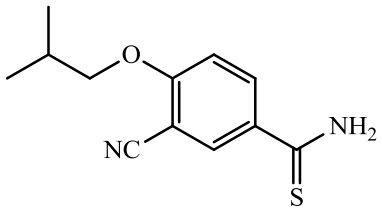
Process for the preparation of 3-cyano-4-isobutoxybenzothiamide

Field of the invention:

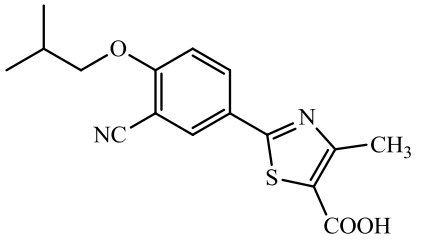
The present invention provides an improved process for the preparation of 3-cyano-4-isobutoxybenzothiamide which is used as the key starting material of Febuxostat and the compound is represented by the following structural formula-1.



Formula-1.

Background of the invention:

Febuxostat was approved by the European Medicines and the U.S. Food and Drug Administration and it is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Febuxostat is marketed by Takeda Pharmaceuticals with the brand names Adenuric (EU) and Uloric (US). Febuxostat is chemically known as 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid and represented by the following structural formula-A.



Formula-A

Brief description of the invention:

The first embodiment of the present invention is to provide an improved process for the preparation of 3-cyano-4-isobutoxybenzothiamide compound of formula-1.

The second embodiment of the present invention is to provide an improved process for the preparation of methyl 3-cyano-4-isobutoxybenzoate compound of formula-6.

Detailed description of the invention:

As used herein the term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; "ether solvents" such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

The "suitable base" used in the present invention can be selected from but not limited to "inorganic bases" selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal amides" such as sodium amide, potassium

amide, lithium amide and the like; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; ammonia; "organic bases" like dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine (DIPEA), diisobutylamine, triethylamine, triisopropyl amine, tributylamine, tert.butyl amine, pyridine, piperidine, 4-dimethylaminopyridine (DMAP), quinoline, imidazole, N-methylimidazole, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), dimethylaniline, N-methylmorpholine (NMM), 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,6-lutidine and the like; "organolithium bases" such as methyl lithium, n-butyl lithium, lithium diisopropylamide (LDA) and the like; "organosilicon bases" such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and the like or their mixtures.

The "suitable acid" used in the present invention can be selected from but not limited to "inorganic acids" such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; and "organic acids" such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, oxalic acid, malonic acid, maleic acid, fumaric acid, malic acid, succinic acid, citric acid, aspartic acid, tartaric acid, mandelic acid, benzoic acid, salicylic acid, substituted/unsubstituted alkyl/aryl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and the like.

The first embodiment of the present invention provides an improved process for the preparation of 3-cyano-4-isobutoxybenzo thiamide compound of formula-1, comprising:

a) Reacting compound of formula-6 with amidating agent in presence of a suitable base in a suitable solvent to provide the compound of formula-7,
b) reacting the compound of formula-7 with a suitable sulfurizing agent and optionally in presence of a suitable base in a suitable solvent to provide the compound of formula-1,
c) optionally purifying the compound of formula-1.

Wherein, amidating agents in step-a) is a suitable ammonia source selected from ammonia,

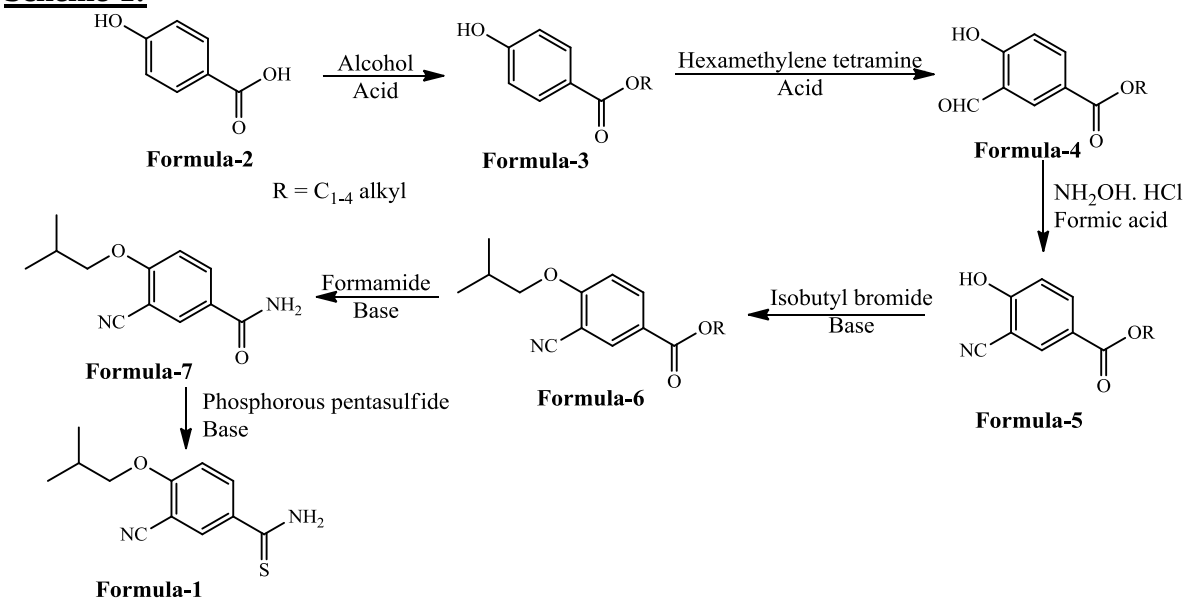
formamide; sulfurizing agent in step-b) is selected from phosphorus pentasulfide and 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide is also known as a Lawesson's reagent; the suitable base in steps-a) to b) is selected form organic or inorganic base; suitable solvents in step-a) to step-b) can be selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid, hydrochloric acid, sulfuric acid and the like or mixtures thereof.

The second embodiment of the present invention provides an improved process for the preparation of methyl 3-cyano-4-isobutoxybenzoate compound of formula-6, comprising of reacting compound of formula-5 with isobutyl bromide in presence of a suitable base optionally in presence of a suitable catalyst in a suitable solvent to provide the compound of formula-6.

Suitable solvent can be selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid, hydrochloric acid, sulfuric acid and the like or mixtures thereof.

The present invention represented in the scheme-1.

Scheme-1:



The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provides as illustration only and hence should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 4-Hydroxybenzonitrile

A mixture of 4-Hydroxybenzaldehyde (100 g), toluene (200 ml), hydroxylamine hydrochloride (68.28 g) and sodium formate (111.38 g) heated to azeotropic reflux temperature and collected the water. Cooled the reaction mixture to 55-60°C and distilled off the solvent. Co-distilled with water and cooled to 25-30°C. Water (200 ml) added to the obtained compound at 25-30°C and stirred at the same temperature. Filtered the solid and washed with water. The obtained solid was added to water (150 ml), heated to 40-45°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filter the solid, washed with water and dried to get the title compound.

Example-2: Preparation of methyl 4-hydroxybenzoate

Sulfuric acid (35.5 g) was slowly added to the solution of 4-hydroxy benzoic acid (100 g) in methanol (250 ml) at 25-30°C. Heated the reaction mixture to 65-70°C and stirred the reaction mixture at the same temperature. Distilled off the solvent completely form the reaction mixture under reduced pressure and cooled to 25-30°C. Water was added to the reaction mixture and stirred at the same temperature. Basified the reaction mixture using aqueous sodium carbonate solution at 25-30°C and ethyl acetate was added to it. Both the organic and aqueous layers were separated. Distilled off the solvent from the organic layer and co-distilled with cyclohexane. Cyclohexane (100 ml) was added to the obtained compound at 25-30°C and stirred at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound.

Example-3: Preparation of methyl 3-cyano-4-isobutyl benzoate

Methyl 4-hydroxy benzoate (180 g) and followed by hexamethylene tetramine (199.02 g) was added to pre-cooled methane sulfonic acid (540 ml) at 15-20°C, heated the reaction mixture to 90-95°C and stirred at the same temperature. The reaction mixture was cooled to 25-30°C and dichloromethane was added to the reaction mixture. Aqueous hydrochloric acid

was added to the reaction mixture at 25-30°C and stirred at the same temperature. Separated the both the organic and aqueous layers and the aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with water. Distilled off the solvent completely from the organic layer. Formic acid (405 ml), hydroxylamine hydrochloride (74.98 g) and sodium formate (61.15 g) were slowly added to the above obtained compound at 25-30°C. The reaction mixture was heated to 105-110°C and stirred at the same temperature. The reaction mixture was cooled to 25-30°C; quenched the reaction mixture with aqueous sodium carbonate solution and stirred at the same temperature. Filtered the solid and washed with water. Dimethyl formamide (324 ml) was added to the obtained compound at 25-30°C. Potassium carbonate (126.38 g) and isobutyl bromide (100.23 g) were added to the above mixture at 25-30°C, heated to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, quenched the reaction with water and stirred at the same temperature. Filtered the solid and washed with water. The obtained compound was added to the mixture of water and methanol. Heated the mixture to 60-65°C and stirred. Cooled the mixture to 25-30°C and stirred. Filtered the solid, washed the solid with the mixture of methanol and water and dried to get the pure title compound.

Example-4: Preparation of methyl 3-Cyano-4-isobutoxybenzothioamide

Sodium methoxide solution (166.74 ml) was slowly added to pre-cooled mixture of methyl 3-cyano-4-isobutyl benzoate (90 g), formamide (43.44 g) and dimethyl formamide (270 ml) at 0-5°C and stirred at the same temperature. The reaction mixture was quenched with water at 0-10°C and stirred the obtained mixture. Filtered the solid, washed with water and dried. Tetrahydrofuran (355 ml) added to the above obtained compound at 25-30°C and cooled to 0-5°C. Phosphorus pentasulfide (37.80 g) was added to the reaction mixture at 0-5°C, raised the temperature of the reaction mixture to 25-29°C and stirred at the same temperature. Cooled the reaction mixture to 0-5°C, water added to it. Aqueous sodium carbonate solution was added to the reaction mixture. Distilled off the solvent completely from reaction mixture. Water added to it at 25-30°C and stirred at the same temperature. Filtered the solid and washed with water. Obtained compound was recrystallized from methanol to get the title compound.

Example-5: Preparation of Ethyl 2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate

Phosphorous pentasulfide (139.93 g) was slowly added in lot-wise to the pre-cooled mixture of acetonitrile (34.46 g) and isopropyl alcohol (150 ml) at 0-5°C and stirred at the same temperature. 4-Hydroxy benzonitrile (100 g) followed by hydrochloric acid (400 ml) was added to the above mixture at 0-5°C. Heated the reaction mixture to 42-48°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with water and dried the obtained solid. Isopropanol (500 ml) was added to the obtained compound at 25-30°C. Ethyl-2-chloroacetoacetate (138.17 g) was added to the above mixture, heated to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound.

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