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IMPROVED PROCESS FOR THE PREPARATION OF 4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

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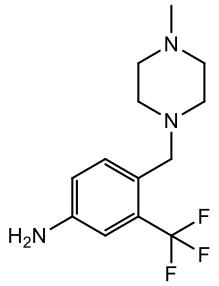
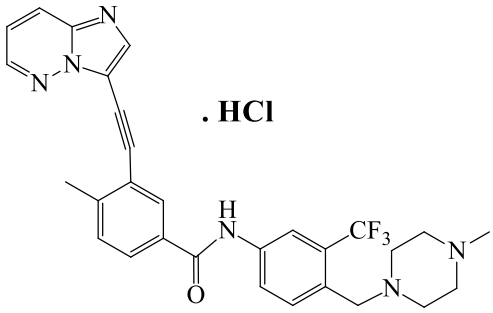
IMPROVED PROCESS FOR THE PREPARATION OF 4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

The present invention relates to an improved process for the preparation of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline formula (1).



Formula (1)

4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline is used in the preparation of Ponatinib hydrochloride.



Ponatinib Hydrochloride

Detailed description of the invention

The term "Solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diisopropyl ether, diethyl ether, methyl tert-butyl ether, 1,2-dimethoxy ethane, tetrahydrofuran, Trifluoroacetic anhydride, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like;

"nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” such as methanol, ethanol, n- propanol, isopropanol, n-butanol, isobutanol, t-butanol, n-pentanol, isopentanol, 2-nitroethanol, ethylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, benzyl alcohol, phenol, or glycerol and the like; “polar-aprotic solvents" such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "polar solvents" such as water or mixtures thereof.

As used herein the present invention, the term “base” is selected from inorganic bases like “alkali metal hydroxides” such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, “alkali metal carbonates” such as caesium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, rubidium carbonate and the like; “alkali metal hydrides” such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia; and organic bases such as triethyl amine, methyl amine, ethyl amine, diisopropylethylamine; “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium ethoxide, potassium tert-butoxide thereof.

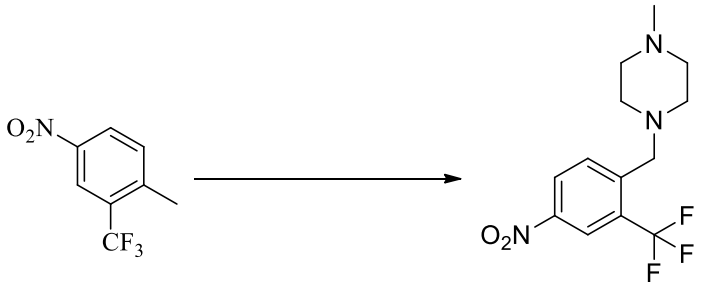
Abbreviations:

AIBN - Azobisisobutyronitrile

DBDMH - 1,3-Dibromo-5,5-dimethylhydantion

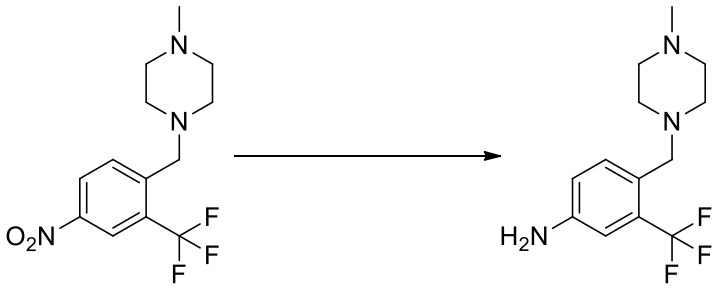
In first embodiment, the present invention relates to an improved process for the preparation of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline formula (1), comprising:

a) brominating the compound of 1-methyl-4-nitro-2-(trifluoromethyl)benzene formula (3) in presence of AIBN, DBDMH, followed by coupling with 1-methylpepirazine and treating the obtained compound with ethyl acetate hydrochloride to provide 1-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine dihydrochloride dihydrate formula (2),



Formula (3) Formula (2)

b) reducing 1-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine dihydrochloride dihydrate formula (2) with Iron-ammonium chloride in the presence of methanol and water to provide 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline formula (1),



Formula (2) Formula (1)

wherein solvent and base used in step-a) and step-b) defined as above.

Further, 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline formula (1) can be converted to Ponatinib hydrochloride according to any of the processes known in the art.

The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention:

Examples

Example 1: Preparation of 1-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine dihydrochloride dihydrate formula (2).

Acetonitrile (1000 ml) and was added to 1,3-dibromo-5,5-dimethylhydantoin (167.25 g) at 25-30°C and stirred for 10 minutes. Azobisisobutyronitrile (24 g) was added to the above mixture at 25-30°C and stirred for 10 minutes. Heated the reaction mixture to 45-55°C and stirred for 20 minutes. 1-methyl-4-nitro-2-(trifluoromethyl)benzene (50.0 g) formula (3) and acetonitrile (200 ml) were added to the above mixture at 45-55°C. Heated the mixture to 70-80°C and stirred for 18 hours. Cooled the mixture to 25-30°C Sodium thiosulfate was added to mixture and stirred for 20 minutes. Aqueous sodium carbonate solution was added to the mixture at 25-30°C and stirred for 20 minutes. Methyl tert-butyl ether was added to the mixture at 25-30°C and stirred for 30 minutes. Layers were separated and aqueous sodium chloride solution was added to the organic layer and stirred for 15 minutes.

Triethylamine (82.21 ml) was added to the organic layer and cooled the reaction mixture to 10-15°C. 1-Methylpiperazine (21.66 ml) and methyl tert-butyl ether (25 ml) was slowly added to the mixture at 10-15°C and stirred for 10 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 25 minutes. Aqueous sodium thiosulfate solution was added to the mixture and stirred for 25 minutes. Layers were separated. Cooled the organic layer to 10-15°C and stirred for 10 minutes. Ethyl acetate hydrochloride solution was added to the mixture at 10-15°C and stirred for 5 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 40 minutes. Water was added to the mixture. Filtered the mixture through hyflow bed and washed the bed with water. Layer were separated. Methyl tert-butyl ether was added to aqueous layer at 25-30°C and stirred for 20 minutes. Layer were separated. Aqueous sodium carbonate solution was added to the aqueous layer and stirred for 20 minutes. Methyl tert-butyl ether (250 ml) was added to aqueous layer at 25-30°C and stirred for 20 minutes. Layer were separated. Cooled organic layer to 10-15°C and stirred for 10 minutes. Ethyl acetate hydrochloride was added to the organic layer and stirred for 2 hours. Filtered the solid and washed with methyl tert-butyl ether. Tetrahydrofuran (250 ml) was added to the obtained compound. Heated the mixture to 45-55°C and stirred for 1 hour. Cooled the mixture to 25-30°C and stirred for 1 hour. Filtered the solid and washed with tetrahydrofuran and dried to get the title compound. Yield: 48 gms; 214.1°C-215.5°C.

Example 2: Preparation of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl) aniline formula (1).

Water (500 ml) was added to 1-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl) piperazine dihydrochloride dihydrate (100 g) formula (2) at 25-30°8C and stirred for 10 minutes. Methanol (200 ml) and ammonium chloride (101.59) was added to the mixture at 25-30°C and stirred for 20-30 minutes. Cooled the temperature of the mixture to 10-15°C and stirred for 30 minutes. Iron powder (36.5 g) was added to mixture at 10-15°C and stirred for 20 minutes. Raised the temperature of the mixture to 25-30°C and stirred for 6 hours. Neutral carbon (5 g) was added to the mixture and stirred for 30 minutes. Filtered the mixture through hyflow bed and washed with water. Ethyl acetate (500 ml) was added to the mixture at to 25-30°C and stirred for 10 minutes. Ammonia (300 ml) was added to the mixture and stirred for 20 minutes. Filtered the mixture through hyflow bed and washed with ethyl acetate. Layers were separated. Aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with water. Carbon was added to the organic layer and filtered the mixture through hyflow bed and washed with ethyl acetate. Distilled the organic layer and then co-distilled with a mixture of cyclohexane. Filtered the solid and washed with water. Cyclohexane (500 ml) was added to the obtained solid. Heated the mixture to 50-55°C and stirred for 2 hours. Cooled the mixture to 15-20°C and stirred for 4 hours. Filtered the precipitated solid, washed with cyclohexane and dried to get the titled compound.

Yield: 53 gms; M.R: 110°C-120.8°C.

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