August 2021

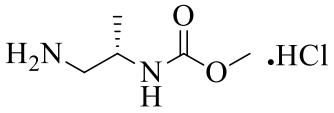
Process for the preparation of (S)-methyl (1-aminopropan-2-yl)carbamate hydrochloride

MSN Laboratories Private Limited, R&D Center; Srinivasan Thirumalai Rajan; Sajja Eswaraiah; Vijayavitthal T. Mathad; Nagunuri Ganapathi Chary

Process for the preparation of (S)-methyl (1-aminopropan-2-yl)carbamate hydrochloride

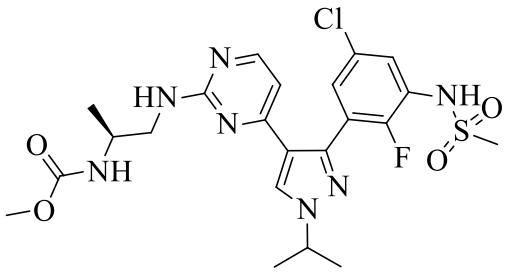
Abstract:

Process for the preparation of (S)-methyl (1-aminopropan-2-yl)carbamate hydrochloride of formula-1, which is represented by the following structural formula:



Formula-1

which is key intermediate for the preparation of Encorafenib, which is chemically known as methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate.



Encorafenib

Introduction:

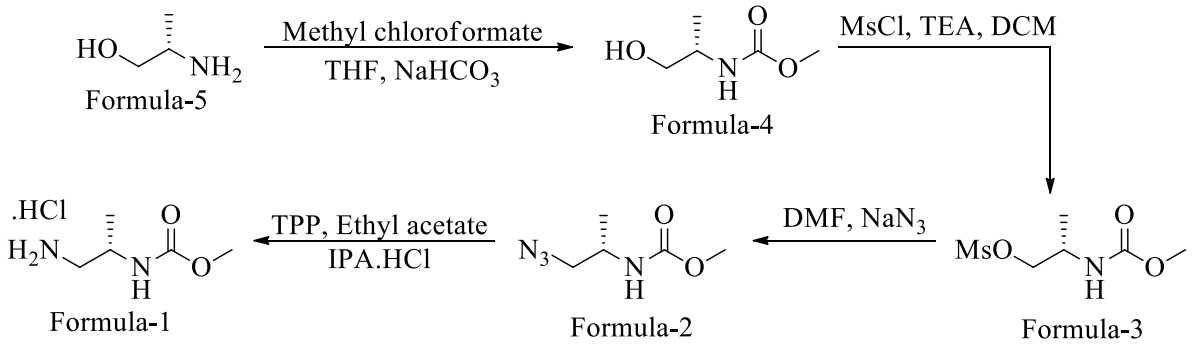
Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC50) of Encorafenib against BRAFV600E, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The Encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, Encorafenib inhibits in vitro and in vivo BRAFV600E, D and K mutant melanoma cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Encorafenib is approved by USFDA and Europe in combination with Binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate is disclosed in US8501758 B2.

US8501758 B2 discloses process for the preparation of methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl) amino] propan-2-yl}carbamate.

Disclosed herein the process for the preparation of (S)-methyl (1-aminopropan-2-yl)carbamate hydrochloride of formula-1, schematically as mentioned below:



The compound of Formula-5 used in the present invention is prepared by method reported in Journal of Organic Chemistry, 62(11), 3586-3591, 1997 or any other methods known in the art.

Experimental Section:

Preparation of (S)-methyl (1-hydroxypropan-2-yl)carbamate of Formula-4.

S-Alaninol of formula-5 (150.0 gm) was dissolved in tetrahydrofuran (750.0 ml) at 25-30ºC and stirred for 10 minutes. Sodium bicarbonate (251.6 gm) was added to the mixture at 25-30ºC and stirred for 10 minutes. Cooled the mixture to 0-5ºC. Methyl chloroformate (171.2 ml) was slowly added to the mixture at 0-5ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 3 hours. Filtered the mixture and washed with tetrahydrofuran. Distilled off the solvent completely from the filtrate under vacuum at below 45ºC and co-distilled with dichloromethane to obtained title compound.

Preparation of (S)-2-((methoxycarbonyl)amino)propyl methanesulfonate of Formula-3.

The compound of formula-4 was dissolved in dichloromethane (750.0 ml) at 25-30ºC and stirred for 15 minutes. Cooled the mixture to 0-5ºC. Triethylamine (606.25 gm) and

methanesulfonyl chloride (343.15 gm) were added to the mixture at 0-5ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 3 hours. Water was added to the mixture at 25-30ºC and stirred for 15 minutes. Layers were separated. Dichloromethane was added to the aqueous layer. Layers were separated. Combined the total organic layers. Sodium bicarbonate solution was added to the organic layer at 25-30ºC and stirred for 10 minutes. Layers were separated. Water was added to the organic layer at 25-30ºC and stirred for 10 minutes. Layers were separated. Distilled off the organic layer at below 45ºC under vacuum to obtained title compound.

Preparation of (S)-methyl (1-aminopropan-2-yl)carbamate hydrochloride of Formula-1.

The compound of formula-3 was dissolved in dimethylformamide (900.0 ml) at 25-30ºC. Sodium azide (129.8 gm) was added to the mixture at 25-30ºC. Raised the temperature of the mixture to 70-75ºC and stirred for 3 hours. Cooled the mixture to 25-30ºC. Ammonium chloride solution was added to the mixture at 25-30ºC and stirred for 10 minutes. Ethyl acetate was added to the mixture at 25-30ºC and stirred for 15 minutes. Layers were separated. Ethyl acetate was added to the aqueous layer and stirred for 15 minutes. Layers were separated. Combined the total organic layers. Sodium chloride solution was added to the organic layer at 25-30ºC and stirred for 10 minutes. Layers were separated. Sodium chloride solution was added to the organic layer at 25-30ºC and stirred for 10 minutes. Layers were separated.

Triphenylphosphine (419.04 gm) was added lot wise for five lots to the above obtained organic layer at 20-25ºC and stirred for 80 minutes. Raised the temperature of the mixture to 25-30ºC and stirred for 2 hours. Cooled the mixture to 10-15ºC and stirred for 60 minutes. Filtered the unwanted solid and washed with ethyl acetate at 10-15ºC. Distilled off the solvent completely from the filtrate under vacuum at below 60ºC. Ethyl acetate (450.0 ml) was added to the obtained compound at 25-30ºC. Cooled the mixture to 10-15ºC. IPA.HCl (383.6 ml) solution was slowly added to the mixture at 10-15ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 2 hours. Filtered the solid, washed with ethyl acetate and dried to obtained title compound. Yield: 150.0 gm; M.R: 168-174ºC.

****