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Synthesise the novel pyrimidine derivative which is use as intermediate of the HIV drug

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Abstract
An efficient protocol is developed for the synthesis of Pyrimdine HIV intermediate 2-(4-cyanophenylamino) pyrimidin-4-yl-4-methylbenzenesulfonate via a simple two-step approach. Initially 4-[(4-Hydroxypyrimidin-2-yl) amino] benzonitrile was prepared by reacting 2-Methylthio-4-pyrimidinone with 4-Amino benzonitrile in Propionic acid. Then 4-[(4-Hydroxypyrimidin-2-yl) amino] benzonitrile was reacted with 4-Toluenesulfonyl chloride in presence of triethyl amine to generate the novel pyrimidine derivative 2-(4-Cyanophenylamino) pyrimidin-4-yl-methylbenzenesulfonate. This pyrimidine derivative afforded the target compound of HIV drug. The significant advantages of the method include cost-effectiveness, excellent yield and scope for large-scale production.

Keywords: Methylbenzene sulfonate, toluene sulfonyl, pyrimidine HIV intermediate

Introduction
Pyrimidine are known to possess a wide range of pharmacological applications. Hence, pyrimidine analogues have attracted significant attention in the design and development of pharmacologically potent molecules and in innovative organic synthesis. Pyrimidine derivatives such as thymine and uracil are indispensable building blocks in nucleic acids, RNA and DNA. In the past few years several pyrimidine derivatives with good antiviral activities and clinical applications have been reported. The reverse transcriptase (RT) is an important substantial enzyme in the HIV-1 (human immunodeficiency virus type-1) life cycle and it is a key target for antiretroviral chemotherapy. Based on their structural features, the RT-inhibitors can be divided into two main classes, *viz*. nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The NNRTIs have received extensive attention in viral therapy because of their low cytotoxicity and high specificity. They have played an important role in antiretroviral therapy for the treatment of HIV infection. Recently, the Food & Drug Administration, USA (FDA) has approved Etravirine (TMC125) and Rilpivirine (TMC278), the new generation diarylpyrimidine analogues of NNRTIs-family for use in HIV therapy. These conjugates represent a new class of highly potent NNRTIs, so far. They specifically interact with the allosteric hydrophobic site of the enzyme in a noncompetitive manner, which is located nearly 10 Å away from the active site. The cytochrome P450 enzyme CYP3A4 also plays a major role in the metabolism of Rilpivirine (RPV).RPV is one of the most successful scaffolds suited for structural modifications. Numerous efforts have been made for the synthesis of Rilpivirine derivatives and have been found promising anti-viral activity against both wild-type and mutant viruses. However, numerous steps involved in the synthesis and poor yields, limit the viability of the existing literature reported schemes. In this communication, a cost-effective and efficient protocol for large-scale synthesis of Novel pyrimidine intermediate for Rilpivirine, 2-(4-Cyanophenylamino)pyrimidin-4-yl-methylbenzenesulfonate, through a facile two-step reaction and also with this intermediate is giving the good yield and quality for the preparation of Rilpivirine by continuous process.

Experimental Section
Material Methodology
Preparation of 4-[(4-Hydroxypyrimidin-2-yl) amino] benzonitrile (5)
2-Methylthio-4-pyrimidinone (100gm,1.0 eq.) and 4-aminobenzonitrile (124.64,1.5 eq.) were taken into propionic acid (5.0 V) into dried round bottom flask and heated the mass up to 120 ^{o}C and stir for 25 hrs and monitor the reaction completion through TLC.

Cool the reaction mass at room temperature and filter further wash with propionic acid(1.0 V) followed by water (3.0).taken the wet solid and slurry into Acetone (5.0) then dry into air Oven and found the off white solid-114 gm, Yield-76.7% w/w. MS (ESI): m/ z=212.90 $(M+H)^+$

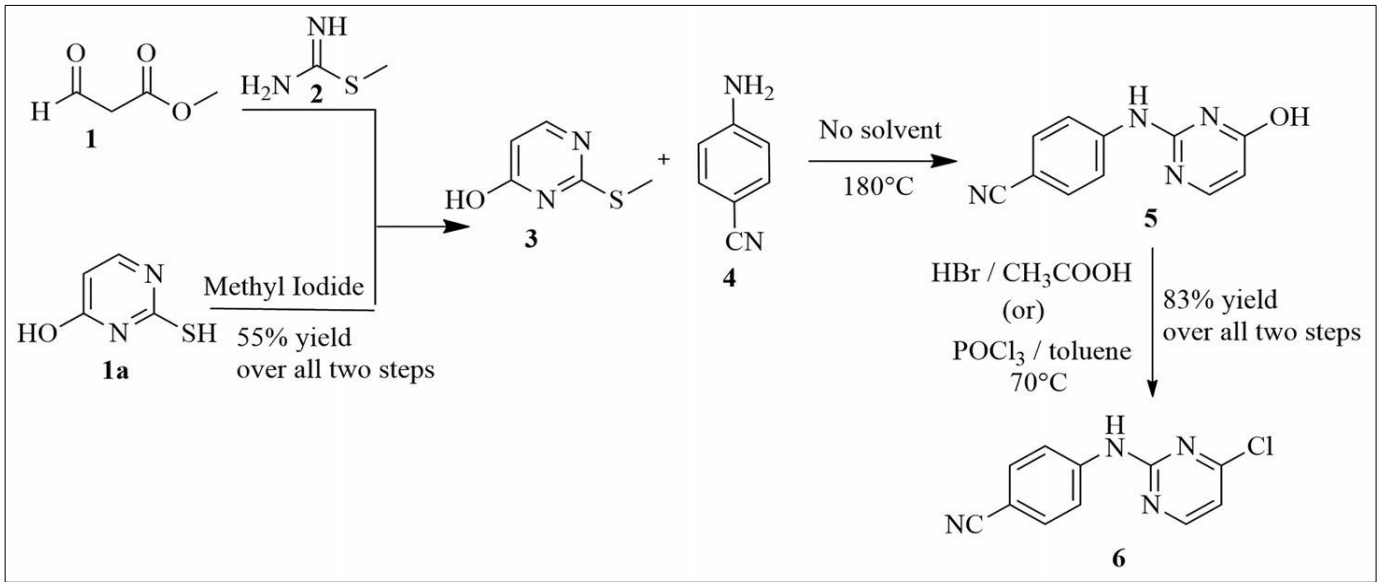
Preparation of 2-(4-Cyanophenylamino) pyrimidin-4-yl-methylbenzenesulfonate (8)

Taken 4-[(4-Hydroxypyrimidin-2-yl) amino] benzonitrile (5) (100.5 gm, 1. 0 eq.) into Acetonitrile (3.0 V) at room temperature and add the triethylamine (101.19 gm, 0.99 eq.), Cool the mass up to 5 to 10 ^oC. Slowly add a solution of 4-toluenesulfonyl chloride (prepared by dissolving 4-toluenesulfonyl chloride, [113.19 g, 1.2 eq.] in acetonitrile [189 mL (1.8v)]) to the reaction mass at 5 to 10 ^oC. Stir the mass for 2 h and check the reaction completion by TLC. After reaction completion slowly add water (5.0V).Stir 1.0 h at 5 to 10 ^oC, filter the mass and wash with water (2.0 V).unload the wet solid and dry into air oven, Dry weight-164.2 gm, Yield - 1.56 w/w.

1 H NMR (400 MHz, DMSO): δ =2.50 (s,3H,-CH3), 6.75 (d, J=5.2 Hz,1H), 7.49 (d, J=8.4Hz,2H) 7.67(dd, J=8.8Hz, 4H),7.94 (d, J=8.4Hz,2H) 8.62 (1H, J=5.2Hz,d) 10.45 (1H,S) MS (ESI): m/ z=367.10 $(M+H)^+$

Result and Discussion

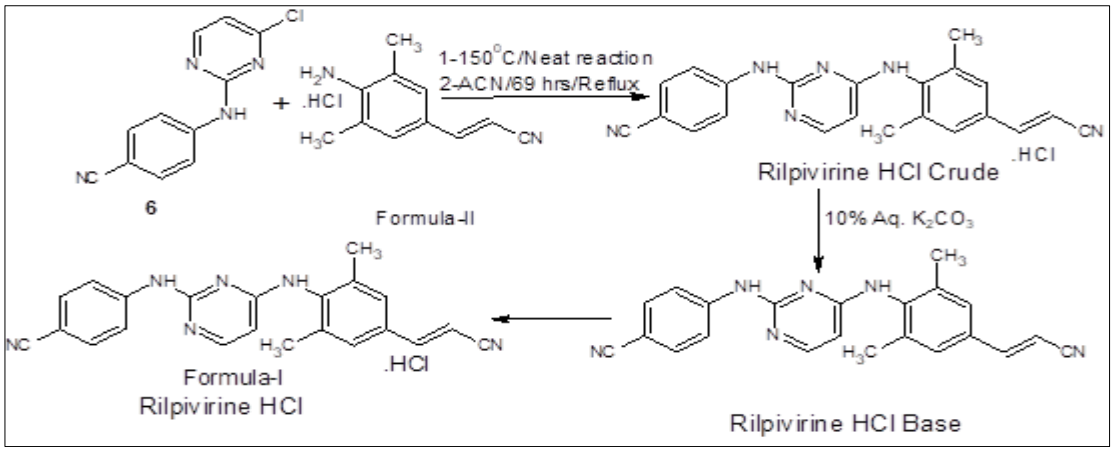
Literature survey reveals the sequence of the reaction step for the production of the proposed target molecule (Scheme 1). Compound 3 is obtainable from two different methods, one by reacting substrates 1 and 2 and the other from reaction of 2-(methylthio) pyrimidin-4-ol, 1a with methyl iodide. Then, by the reaction of 4-aminobenzonitrile, 4 with 2-(methylthio) pyrimidin-4-ol, 3 at 180 ^0C under solvent-free conditions, 4-((4-hydroxypyrimidin-2-yl) amino) benzonitrile, 5 was generated. The compound 5 was halogenated with either hydrobromic acid or phosphorous oxychloride at 70 ^0C in toluene to produce the target molecule, 4-((4-chloropyrimidin-2-yl) amino) benzonitrile, which the key intermediate for Rilpivirine synthesis. The use of iodomethane, during the reaction process, causes side reactions and generates impurities. Large-scale usage of highly toxic and expensive methyl iodide is challenging and undesirable. When the two reactants are heated to 180^0C to obtain a rigid solid, high temperature generates more impurities and results in poor yields. Handling rigid solid is also not convenient for further steps and to upscale for industrial production. Furthermore, the use of phosphorus oxychloride, a highly toxic reagent, is risky to the workforce, and impurities cannot be completely removed during the subsequent purification step. Hence, such a step needs to be eliminated for safety reasons as well as upscaling the production.



Scheme 1-Reported method for synthesis of 4-((4-chloropyrimidin-2-yl)amino)benzonitrile, 6.

U.S. Patent No. 7,125,879 ("the '879 patent") discloses HIV inhibiting pyrimidine derivatives such as rilpivirine and its hydrochloride salt form. The '879 patent further discloses various processes for the preparation of Rilpivirine, which includes condensation of 3-(4-amino-3,5-dimethyl phenyl)-acrylonitrile of Formula II either in free base or hydrochloride salt with 4-(4-chloropyrimidin-2-ylamino) benzonitrile of Formula III at temperature of 150°C for 1 hour followed by treatment with mixture of 10% potassium carbonate, methylene chloride and methanol and then the product rilpivirine was isolated by column chromatography. The '879 patent discloses another process for the preparation of Rilpivirine by condensation of Formula II as its hydrochloride salt with Formula III in acetonitrile at reflux temperature for 69 hours followed by resultant Rilpivirine hydrochloride product was isolated by filtration under hot condition at 55°C. Basification of the obtained solid with 10% aqueous solution of potassium carbonate followed by obtained Rilpivirine free base refluxed in 65 volumes of isopropanol to obtain Rilpivirine.

The process disclosed in the '879 patent is schematically represented as follows



Scheme 2: Reported method for synthesis of Rilpivirine from by reported method

The synthesis of rilpivirine as discussed in the '879 patent has certain drawbacks as it involves.

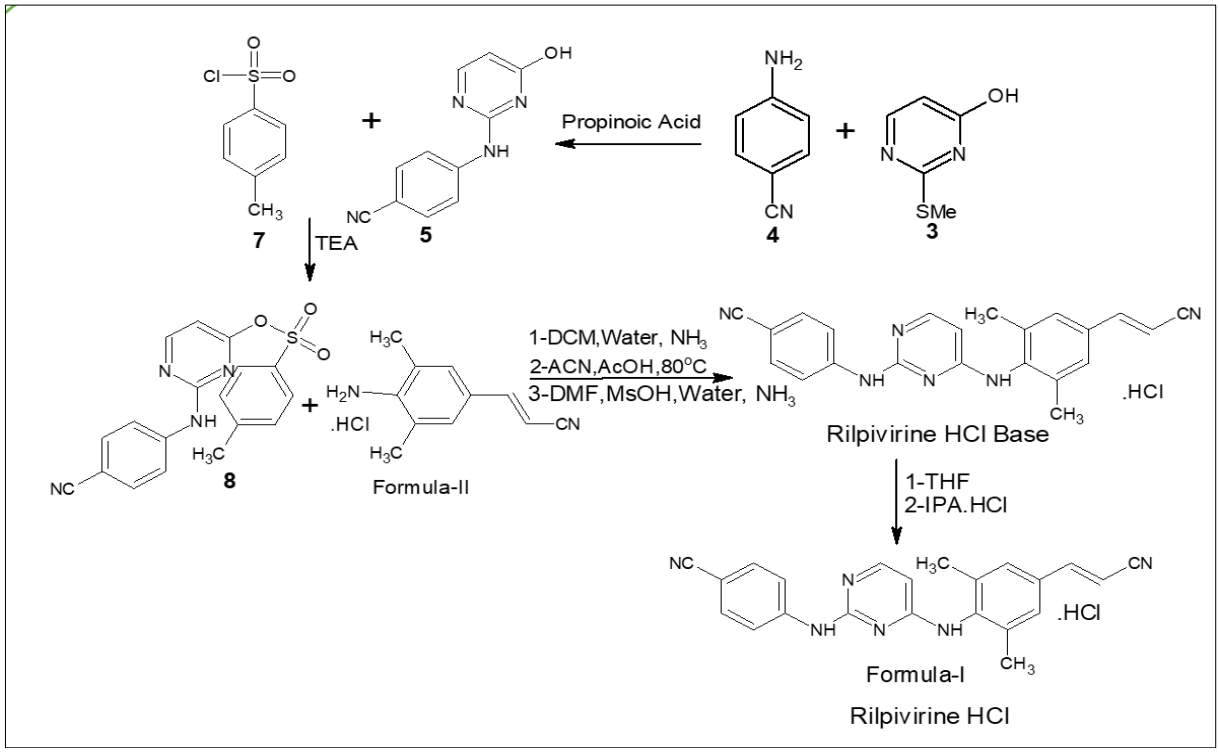
i) As per this patent Z-isomer formation about 10-12% during reaction which is removed by multiple stage purification.

ii) Use of neat reaction conditions extremely at high temperature of about 150°C and involves tedious chromatographic purifications makes the process not viable for large scale manufacturing.

iii) Reaction in presence of acetonitrile at reflux for a period about 69 hours. The prolonged period of reaction maintenance leads to an increase in the manufacturing cycle time and decrease in the product yield and quality.

iv) Isolation of crude rilpivirine hydrochloride at hot conditions such as filtration of crude at temperature 55°C. Solid filtration at high temperature is not viable, particularly on commercial scale operations for producing API's and thus requires utmost care to use.

v) Use of large volumes of solvent for purification of Rilpivirine free base, requires high capacity apparatus and thus involves more operational occupancy, which in turn result to an increase in the manufacturing cost, particularly on large scale production of Rilpivirine.



Scheme: 3-Synthetic route for the preparation of Novel Derivative-8 and furmula-1

In the present work, the modified synthetic route to the target compounds 8 and Formaula-1 is described in Scheme 3. This simple synthetic approach utilized easily available substrates,4-amino benzonitrile , 4 with 2-(methylthio) pyrimidin-4-ol, 3 at 120 ºC in propionic acid to generate 4-((4-hydroxypyrimidin-2-yl) amino) benzonitrile, 5. The compound 5 was reacted with p-toluene sulfonyl chloride, 7 with presence of triethylamine to from novel Pyrimidine derivative -(4-cyanophenylamino) pyrimidin-4-yl-4-methylbenzenesulfonate, 8. The compound 8 further reacted with formula-II in acetonitrile with presence of acetic acid to form the HIV drug Rilpivirine.

Conclusion

In summary, we have described an efficient new approach for the synthesis of 2-(4-Cyanophenylamino) pyrimidin-4-yl-methylbenzenesulfonate starting from 4-((4-hydroxypyrimidin-2-yl) amino) benzonitrile with scope for bulk production.

The main features of this Novel pyrimidine derivative is preparation eco-friendly process include cost-effectiveness and excellent yields of Rilpivirine, which makes this protocol an attractive and valuable alternative to the current methodologies.

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