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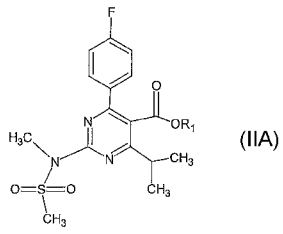
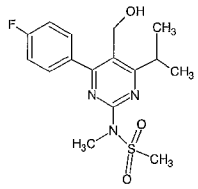
[Continued on next page]

(54) Title: PREPARATION OF ALKYL 4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONY)AMINO]-PYRIMIDINE-5-CARBOXYLATE AND ITS SUBSEQUENT CONVERSION TO N-[4-(4-FLUOROPHENYL)-5-FORMYL-6-ISOPROPYL PYRIMIDIN-2-YL]-N-METHYLMETHANESULFONAMIDE-A KEY INTERMEDIATE IN THE SYNTHESIS OF ROSUVASTATIN


(IIA)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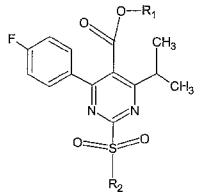
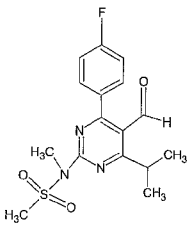

(D)


(II)

(57) Abstract: The present invention discloses a novel process to prepare a compound of formula (IIA). By reacting a compound of formula-[D], wherein R_1 is C_1 to C_6 alkyl, preferably R_1 is methyl or ethyl, more preferably R_1 is methyl ; and R_2 is C_1 to C_8 n-alkyl or branched alkyl, cycloalkyl, phenyl , benzyl or substituted phenyl group, preferably R_2 is methyl ; with N-methyl methanesulfonamide and a base, optionally with a salt of N-methyl methanesulfonamide, in suitable solvent(s) , to give a compound of formula (IIA), followed by converting compound of formula (IIA) to a compound for formula -[B], by a known process and finally converting a compound of formula (B) to a compound of formula (II), by a novel process using calcium hypochlorite / TEMPO as an oxidant.

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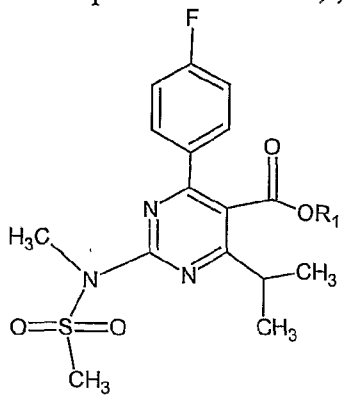
TITLE: Preparation of Alkyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsu]fonyl)amino]-pyrimidine-5-oarboxylate and its subsequent conversion to N-[4~(4-fluorophenyl)-5-formyl-6-isopropyl pyrimidm-2-ylJ-N-methylmethanesulfonamide-a Key intermediate in the synthesis of Rosuvastatin .

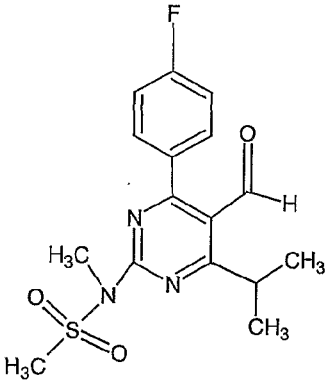
FIELD OF INVENTION :

The present invention discloses an improved process for the preparation of Alkyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidine-5-carboxylate [herein referred to as "Ester intermediate" – a compound of formula IIA] and its conversion to N-[4-(4-fluorophenyl)-5-formyl-6-isopropyl pyrimidin-2-yl]-N-methylmethanesulfonamide (herein referred to as aromatic aldehyde-a compound of formula- II) which is an intermediate in the preparation of Rosuvastatin(herein referred to as compound of formula-I) , the structures of which are as shown below.

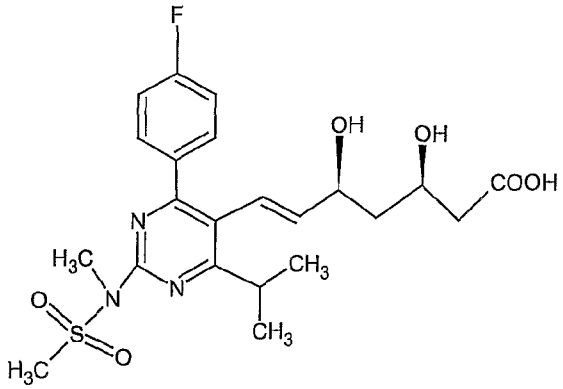


Formula - HA

wherein R_1 is Ci to C_6 alkyl, preferably R_1 is methyl or ethyl, more preferably Ri is methyl



Formula-II



Formula- 1

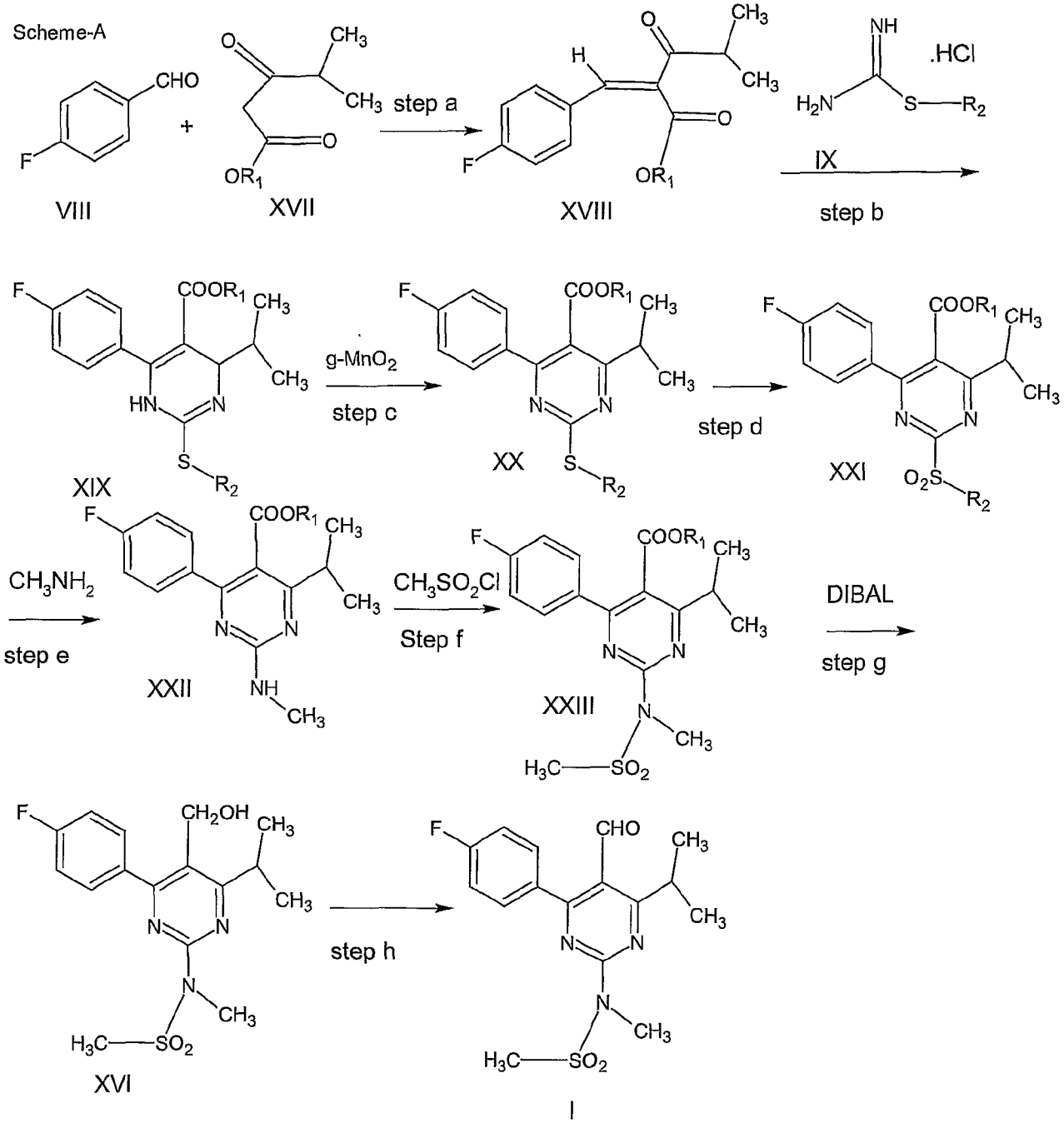
BACKGROUND OF INVENTION :

Watanabe M. et. Al in Japan Patent Application no. JP-3-188015 dated 1-7-1991, its corresponding US Patent no. 5260440 , EP0521471;and further in Bioorg. Med. Chem. 1997, vol. 5,No.2, 437-444 disclose a process for the preparation of ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-nethanesulfonyl-N-methylamino)pyrimidine-5-carboxylate wherein p-fluorobenzaldehyde is reacted with ethyl isobutyryl acetate to give an unsaturated ketoester, followed by cyclocondensation using s-methylisothiourea hydrogensulfate , followed by dehydrogenation with DDQ to give the corresponding pyrimidine which is then oxidized using m-chloroperbenzoic acid to give corresponding sulfonylpyrimidine, which is then reacted in the fifth stage with methyl amine in methanol and subsequent treatment with methane sulfonyl chloride to give ethyl 4-(4-fluorophenyl)-6-isopropyl -2-(N-methanesulphonyl-N-methylamino)pyrimidine -5-carboxylate.

This compound is reduced with DIBAL-H /toluene followed by TPAP (Tetrapropyl-ammonium, perruthenate) oxidation to give N-[4-(4-fluorophenyl)-5~formyl-6-isopropyl pyrimidin-2-yl]-N-methylmethanesulfonamide.

The use of column chromatography for purification in various steps such as aromatisation, reduction of ester to alcohol and oxidation of alcohol to aldehyde makes this process unattractive for industrial exploitation.

PCT Publication WO03/097614A2 describes the synthesis of aromatic aldehyde of formula-II as per Scheme-A:



R1 is Me ; R2 is benzyl

This process uses activated Y-MhO_2 for aromatization and a large excess of γ-$Mn0_2$ is used at the oxidation step of aryl alcohol to aldehyde conversion.

PCT Application WO 2004/103977 A2 describes the synthesis of ester intermediate of fomula-IIA (wherein Ri is methyl) in steps :

[1] p-Fluoro benzaldehyde is reacted with a mixture of methyl isobutyryl acetate, thiourea, lanthanum chloride heptahydrate and hydrochloric acid to give 4-(4-fluoro-phenyl)-6-isopropyl-2-thioxo-l,2,3,4-tetrahydro pyrimidine -5-carboxylic acid methyl ester
[2] The product of step-1 is reacted with potassium hydroxide and methyl iodide in methanol , worked up to give a tautomeric mixture of 6-(4-fluorophenyl)-4-isopropyl-2-methyl sulfanyl-l,6-dihydropyrimidme-5-carboxylic acid methyl ester.
[3] The product of step-2 is aromatized using DDQ in methylene chloride to give 4-(4-fluoro-phenyl)-6-isopropyl-2-methylsulfanyl-pyrimidme 5-carboxylic acid methyl ester
[4] The product of step-3 is reacted with mCPBA in dichloromethane to give 4-(4-fluoro-phenyl)-6-isopropyl-2-methanesulfonyl-pyrimidine 5-carboxylic acid methyl ester.
[5] The product of step-4 is reacted with methyl amine (8M in ethanol) to give 4-(4-fluoro-phenyl)-6-isopropyl-2-methylamino-pyrimidine 5-carboxylic acid methyl ester.
[6] The product of step-5 is reacted with sodium tert. pentoxide in dimethoxyethane followed by mesyl chloride to give 4-(4-fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)pyrimidine 5-carboxylic acid methyl ester.
This method of synthesis uses catalyst such as Lanthanum chloride heptahydrate in the first step DDQ in aromatization step, mCPBA in the conversion of methyl thio to methanesulfonyl compound.

US6841554 B2 , US2003/0045718 A1 describe the preparation of ester intermediate wherein a mixture of methyl 2-amino-4-(4-fhiorophenyl)-6-isopropyl-pyrirriidine -5-carboxylate, sodium tert. pentoxide are reacted in dimethoxyethane , with methane sulfonyl chloride and further treated with dimethyl sulfate to give methyl 4-(4-fluorophenyl)-6-isopropyl -2-[methyl(methylsulfonyl)amino]pyrimidine -5-carboxylate.

WO01/04100 , [Equivalent to US2003/0199695A1 , US20040181065,US6579984,] describe a process for preparing the 2-(N-methyl-N-methanesulfonylamino) pyrimidine compound in steps :
Reacting methyl isobutyryl acetate with 4-fluoro benzonitrile to produce methyl 2-[l-amino-l-(4-fluorophenyl)methylene-4-methyl-3-oxopentanoate;
Reacting the 2-[l-amino-l-(4-fluorophenyl)methylene]-4-methyl-3-oxopentanoate with N-cyano-N-methylmethanesulfonamide which is obtained by reaction between N-methyl methanesulfonamide and cyanogens chloride , to produce 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methanesulfonyl-N-methylamino)pyrimidine. It is described that the total yield (based on the amount of methyl isobutyrylacetate) is 45.5 %.

The process uses cyanogens chloride gas which is a toxic and hazardous reagent, difficult to handle on plant and results in impure products with low yields; requires long hour reaction time, and involve column chromatographic isolation procedure at different steps hence unsuitable for commercial manufacture.

US 20060004200 describes oxidation of [4-(4-fluorophenyl)-6-isopropyl-2-(N-Methyl-N-methylsulfonylamino)pyrimidin-5-yl]methanol using 2,2,6,6-tetramethylpiperidinyloxy free radical (TEMPO) in the presence of potassium bromide, sodium bicarbonate and sodium hypochlorite in a suitable solvent such as without limiting thereto, CH2C12, THF, Toluene, DMSO, DMF, N,N-dimethyl acetamide preferably CH_2Cl_2 at 0 to 5^0C, until the reaction is complete, such as for 1-2 hours. The product of this reaction i.e. 4-(4- fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylammo)-5-pyrimidine carbaldehyde is isolated by suitable workup.

It is therefore a longstanding need of the industry to provide a commercially feasible process which does not have disadvantages as mentioned in the prior art.

SUMMARY OF INVENTION :

The main object of the present invention is to provide a cost effective and commercially feasible process for preparation of N-[4-(4-fluorophenyl)-5-formyl-6-isopropyl pyrimidm-2-yl]-N-methylmethanesulfonamide.

Another object is to provide an improved process for preparing alkyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidine-5-carboxylate- [ester intermediate].

Yet another object of the invention is to provide a process for preparing ester intermediate which does not use strong bases like n-Butyl lithium, sodium hydride.

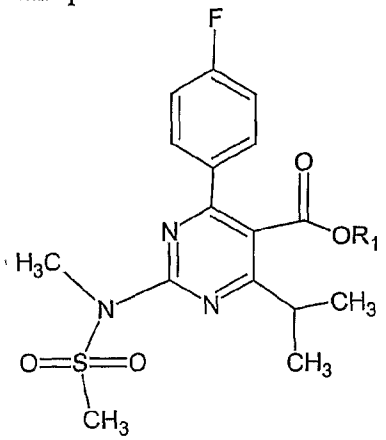
Yet another object of the invention is to provide a process for preparing ester intermediate without use of chromatographic separation at any stage of synthesis.

Yet another object of the invention is to provide a process for preparing ester intermediate without using toxic hazardous gas such as cyanogens chloride.

Yet another object of the invention is to provide a process for preparing ester intermediate without using heavy metal oxidizing agents like MnO_2 for aromatization step or in oxidation of alcohol to aldehyde step.

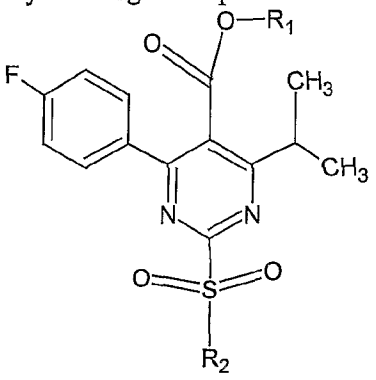
DETAILED DESCRIPTION OF THE INVENTION :

The present invention discloses a hovel process to prepare a compound of formula HA



Formula - IIA

By reacting a compound of formula-[D]

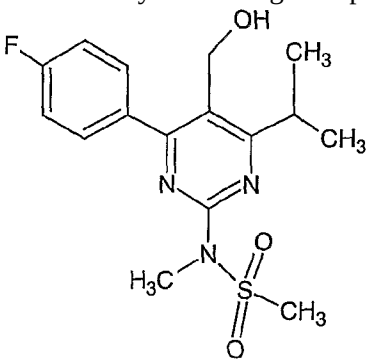


formula-[D]

wherein Ri is C_1 to C_6 alkyl, preferably Ri is methyl or ethyl, more preferably Ri is methyl ; and R_2 is Ci to C_8 n-alkyl or branched alkyl, cycloalkyl, phenyl , benzyl or substituted phenyl group, preferably R_2 is methyl ;

with N-methyl methanesulfonamide and a base, optionally with a salt of N-methyl methanesulfonamide, in suitable solvent(s) , to give a compound of formula—IIA,

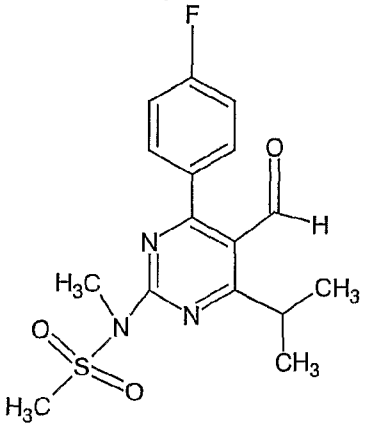
followed by converting compound of formula-IIA to a compound for formula - [B]



Formula-[B]

by a known process

and finally converting a compound of formula-[B] to a compound of formula-II

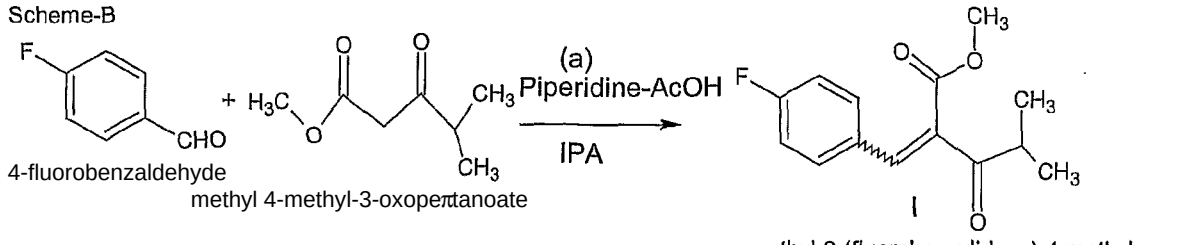


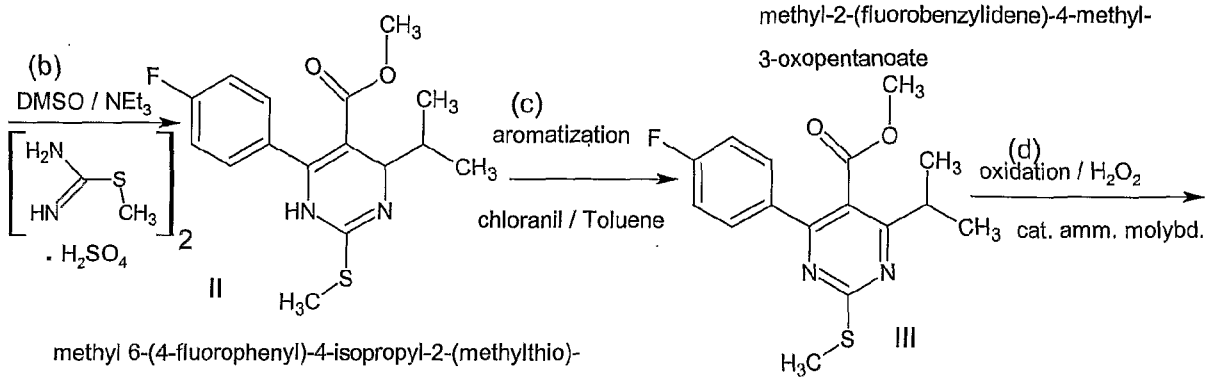
Formula-II

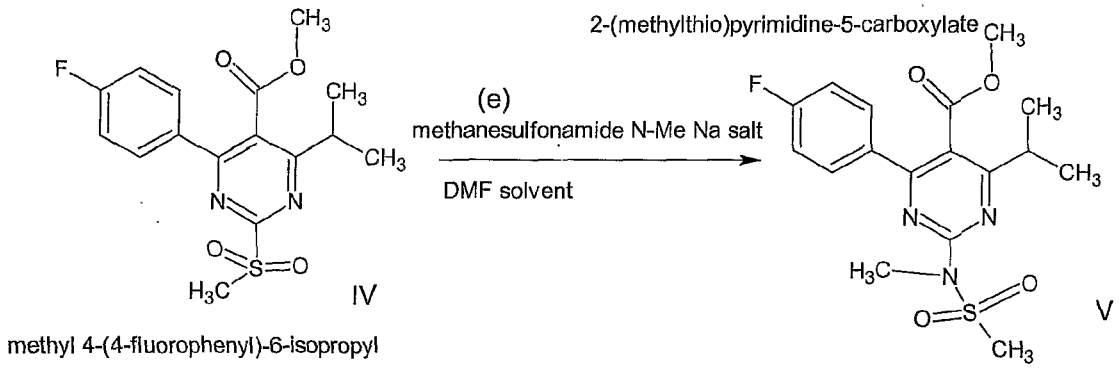
by a novel process using calcium hypochlorite / TEMPO as an oxidant.

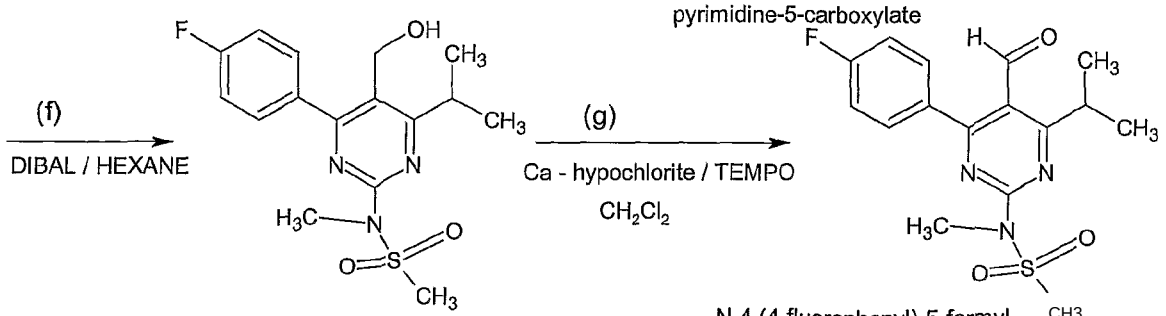
In a preferred embodiment of the invention , compound of formula-[D] ,wherein R_1, R_2 is methyl is converted to compound of formula-II , via compound of formula-[B], as described in scheme-B:

Scheme-B


4-fluorobenzaldehyde
methyl 4-methyl-3-oxopentanoate
(a)
Piperidine-AcOH
IPA
I
methyl-2-(fluorobenzylidene)-4-methyl-3-oxopentanoate


(b)
DMSO / NEt3
· H2SO4
II
methyl 6-(4-fluorophenyl)-4-isopropyl-2-(methylthio)-1,4-dihydropyrimidine-5-carboxylate
(c)
aromatization
chloranil / Toluene
III
methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio)pyrimidine-5-carboxylate
(d)
oxidation / H2O2
cat. amm. molybd.


IV
methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylsulfonyl)pyrimidine-5-carboxylate
(e)
methanesulfonamide N-Me Na salt
DMF solvent
V
methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidine-5-carboxylate


(f)
DIBAL / HEXANE
N-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-N-methylmethanesulfonamide
VI
(g)
Ca - hypochlorite / TEMPO
CH2Cl2
N-4-(4-fluorophenyl)-5-formyl 6-isopropy|pyrimidin-2-yl]-N-methylmethanesulfonamide
VII
AROMATIC ALDEHYDE INTERMEDIATE

Various steps and reaction conditions are elaborated below:
[a] Knoevenagel condensation can be carried out in solvents such as
C_{1-6} alcohols like isopropanol, ethanol, propanol, butanol; alkanes and cycloalkanes like hexane,heptane Cyclohexane , cyclopentane , cycloheptane or mixtures thereof; more preferably isopropanol,
Arenes like benzene,toluene, xylene etc. and mixtures thereof ; ethers such as THF,dioxane, n-butyl ether
The base catalyst used to effect the condensation is selected from weak acid salt of strong secondary nitrogeneous bases like piperidine acetate, pyrrolidine acetate,morpholine acetate, diethyl amine acetate, Diisopropylamine acetate; tertiary amines like triethyl amine, N-methyl morpholine, N-methylpyrrolidine,N-ethyl morpholine , N-ethyl pyrrolidine, diisopropyl ethylamine, DBU, DBN, TMEDA, Inorganic catalysts like bicarbonates, carbonates etc.The preferred catalyst is piperidine acetate.
Use can be made of molecular sieve to enhance reaction efficiency and Dean and stark method of separating water can be used for solvents which are lighter and immiscible with water.
The reaction is earned out at 25-150° C . As the ketoester to be used is to be converted to aromatic aldehyde, the alkyl part in the keto ester can be generic alkyl group which may be C_{1-6} alkyl group, preferably methyl.
By using methyl isobutyroylacetate and p-Fluorobenzaldehyde in IPA as solvent and using piperidine acetate as catalyst, 86 % yield of condensed ester is obtained with a GC purity of 98 %.

[b] The reaction of Knoevenagel product with S-alkyl [optionally benzyl] substituted thiourea gives cyclized dihydro pyrimidine with correspondingly substituted alkylthio [optionally benzyl thio] group.
The preferred compound is S-Methyl isothiouronium sulfate.
The solvents used for the cyclization is selected from polar aprotic solvents like dimethyl sulfoxide, N,N-dimethyl formamide, N,N-dimethyl acetamide of mixtures thereof ; nitriles like acetonitrile, propionitrile or mixtures thereof, often involving use of catalysts which favors the progress of reaction like molecular sieve or other optional water scavengers.
The preferred solvent is dimethyl sulfoxide.

[c] The aromatization of substituted dihydropyrimidine can be carried out using any known reagents like HNO_3, MnO_2, CrO_3, SeO_2 Pt, Pd, RaNi, S, Se, DDQ , Chloranil etc. The preferable is chloranil. Chloranil is recyclable thus not involving ant heavy metal contamination in the finished product.
The solvent selected for aromatization are such as dichloromethane, chloroform, benzene, toluene ,ethyl acetate or mixtures thereof preferably toluene.
The temperature of the reaction is between 25^0C to 150^0C , preferably 65^0C to 70°C.The progress of the reaction is monitored by TLC. After the reaction is over the reaction mass is cooled to room temperature and filtered .The organic phase is treated with water and tetrachloro hydroquinone is removed by washing the organic phase with aq. sodium hydroxide solution ,washed with water , dried over anhydrous sodium sulfate and solvent is removed under vacuum to isolate crude product. The crude material is crystallized in IPA to precipitate aromatized product i.e. methyl 4-(4-fluorophenyl)-6~isopropyl-2-(methylthio)-pyrimidine-5-carboxylate.

[d] Methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio)-pyrimidine-5-carboxylate is then converted to Methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methanesulfonyl)-pyrimidine-5-carboxylate by using various oxidizing agents such as organic peroxy compounds such as H_2O_2, perbenzoic acid, m-CPBA, aliphatic percarboxylic acids like peracetic acid, sodium and potassium periodates , sodium percarbonate, sodium perborate, magnesium monoperphthalate , urea-H_2O_2 optionally simultaneously using catalyst like sodium

tungstate, ammonium molybdate etc. The preferred reagent is hydrogen peroxide (50 % w/w) and using ammonium molybdate catalyst with it.
The solvent for the reaction is selected from protic solvents such as water, C_{1-4} alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol ; acids like acetic acid, propionic acid etc. or mixtures thereof .The preferred solvent is methanol. The reaction is exothermic and the temperature of the reaction being maintained at 50 to 52^{0}C and stirred at this temperature till all the starting material is consumed. The progress of the reaction is monitored by performing thin layer chromatography. After the reaction is over the reaction mass is cooled to 0 to 5^{0}C and the product is isolated by filtration. The wet cake is washed with solvent and the product is dried at 55 to 60^{0}C. The yield at this stage is about 88 %.

[e] Methyl 4-(4-fiuorophenyl)-6-isopropyl-2-(methanesulfonyl)-pyrimidine-5-carboxylate is then converted to Methyl 4-(4-fluoiOphenyl)-6-isopropyl-2-[methyl((methylsulfonyl)amino]-pyrimidine-5-carboxylate by using sodium salt of N-methyl methanesulfonamide acting as a nucleophile for displacing methylsulfonyl group at 2- position. This step offers a general methodology for replacement of pyrimidine 2- substituted alkylsulfonyl or arylsulfonyl group by N-methyl methanesulfonamide, where the alkylpart of alkylsulfonyl constitute Ci to C_8 aliphatic or branched chain alkyl or cycloaklyl group and aryl group may be phenyl or substituted phenyl group, preferably alkyl group is methyl or ethyl , more preferably methyl ; the preferred aromatic part of the arylsulfonyl group is phenyl or benzyl group.
The reagent required for this purpose can be procured from commercial sources or can be conveniently prepared as follows.
A 40 % solution of monomethyl amine is taken in the multi-necked flask and is cooled to 0 to2°C and to it is added dropwise methanesulfonyl chloride from dropping funnel. After stirring for about 1 hour, the reaction mass is raised to 25^{0}C and the reaction mass is stirred at 25-30^{0}C for 1 hour. The reaction mass is again cooled to O^{0}C and a concentrated solution of sodium hydroxide is added dropwise at 0 to 2^{0}C and stirred further for about one hour at 0 to 2^{0}C.Raise the temperature of the reaction mass to 25^{0}C and stirred at this temperature for one hour. The reaction mass is then cooled to 0 to 2^{0}C and stirred at 0 to 2^{0}C and filtered washed with chilled acetone and dried.
The use of sodium salt of N-methyl methanesulfonamide as a nucleophile has several special advantages due to its structural feature. The advantage lies in the acidity of N-H proton adjacent to -SO_2- group in the sulfonamide reagent and is far more acidic than N-H proton of aiyl methanamine . In the attachment of methanesulfonyl group, at the N-H proton of aryl methanamine, in the prior art process, a strong base like Butyl lithium is required , but in our case due to acidity of N-H proton in N-methyl methanesulfonamide even a base like NaOH is sufficient to knock off acidic proton. Alternatively N-methyl methanesulfonamide and other bases like DBU, diisopropylethyl amine, DBN, TMEDA etc which effect the abstraction a N-H proton in N-methyl methanesulfonamide ,can also be used. The solvent selected for nucleophilic substitution is selected from solvents like DMF, DMSO,NMP,N,N,N',N'-tetramethyl urea, l,3-Dimethyl-2-imidazolidinone, acetonitrile, sulfolane dimethylacetamide ,THF, dioxane , IPA, butanol, ,dichloromethane , chloroform, toluene etc. or mixtures thereof.
The temperature of the reaction is between 10 to 120^{0}C and is dependent on the choice of the solvent.
The preferred solvent is DMF and the the reaction is carried out preferably at 20 to 35 ^{0}C.
The progress of the reaction is monitored by performing thin layer chromatography. After the reaction is over, the reaction is quenched in chilled water and precipitated product Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl((methylsulfonyl)amino]-pyrimidine-5-carboxylate is isolated by filtration. The yield of this step is 92 to 95 % .

[fj Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl((methylsulfonyl)amino]-pyi imidine-5-carboxylate is converted to N-[4-(4-fluoiOphenyl)-5-(hydroxymethyl)-6-isopropyl ρyrimidin-2-yl]-N-methyl methanesulfonamide by caπying out reduction of an ester to alcohol. Reagents known in the literature for converting an ester to an alcohol can be used which comprises hydride base reagents like DIBAL, Vitride, $NaBH_4$ based reagents like tetrabutyl ammonium borohydride. DIBAL in hexane is a reagent of choice which cleanly converts an ester to an alcohol.

Solvent for the reaction is selected from hexane, toluene, cyclohexane, THF etc. The preferred solvent is hexane. The solvent selection is partly fixed by the reagent itself in that hydride based reducing agents are commercially offered in Hexane, toluene etc. so as far as possible use of single solvent is preferable although mixtures thereof can also be used depending on the solubility requirements of reactants and products formed.

The reduction is earned out at 10 to 80° C , preferably at 25 to 30^0C.

The progress of the reaction is monitored by thin layer chromatography. After the reaction is over , acetic acid is added dropwise followed by ethyl acetate. The reaction mass is quenched in water and the layers are separated. Aqueous phase is extracted with ethyl acetate and combined with main organic phase. The organic phase is washed with aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. After removal of solvents under vacuum , hexane is added and the product is stirred with hexane at room temperature and filtered to give N-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-N-methyl methanesulfonamide in 91 to 95 % yield with HPLC purity of 99.6 %

[gJN-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-N-methyl methanesulfonamide is converted to N~[4-(4-fluorophenyl)-5-formyl -6-isopropylpyrimidin-2-yl]-N-methyl methanesulfonamide- Aromatic aldehyde. There are many reagents in the literature to carry out this transformation., like MnO2, chromium based reagents , Ni-peroxide, hypochlorite based reagents like NaOCl —TEMPO. The preferred reagent according to present invention is Calcium hypochlorite and using catalytic quantity of TEMPO [2,2,6,6-Tetramethyl-l-piperidinyloxy, free radical].

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Solvent used for this reaction is from a class of halogenated solvents such as dichloromethane, chloroform. N-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-N-methyl methanesulfonamide is dissolved in dichloromethane and the solution is cooled to 0-to5°C. Catalytic quantity of TEMPO is added , followed by aq. KBr solution. A slurry of Ca hypochlorite in water is added at 0 to 5°C.After that a solution of sodium bicarbonate is added in a reaction mixture at 0 to 5^0C within 90 minutes. The reaction mass is maintained at 0 to 5^0C for 1 hour. The progress of the reaction is monitored by TLC. Repeat fresh addition of oxidant if required. Increase the temperature of the reaction mass. Added to it hyflo super eel, reaction mass is filtered and compound is isolated from dichloromethane phase. The residue left after removal of dichloromethane, is stirred with hexane and solid product N-[4-(4-fluorophenyl)-5-formyl -6-isopropylpyrimidin-2-yl]-N-methyl methanesulfonamide- Aromatic aldehyde is isolated from reaction mass by filtration and drying.

Yield= 85 to 90 %

Assay by HPLC=99.6%

The present invention is illustrated with non-limiting examples **as** follows:

Example-1

Preparation of 2-[(4-fluorophenyl) methylene-4 methyl-3-oxo pentanoic acid methyl ester

In a round bottom flask , equipped with stirrer, hot plate, water bath, condenser , thermometer and N_2 gas purging facility , charge 600 ml isopropyl alcohol, piperidine (30.08g, 0.3532 mol), acetic acid (21.2 g, 0.3530 mol), 4-methyl-3-oxopentanoic acid methyl ester (200g,1.3888 mol) and p-fluorobenzaldehyde (189.6g,1.528 mol) under nitrogen atmosphere at 25 ^{0}C to 35 ^{0}C . Stir reaction mass for 20 hrs and check the progress of the reaction on thin layer chromatography. Distill isopropyl alcohol under vacuum at 55 ^{0}C to 65 ^{0}C. Cool the reaction mass to 25 ^{0}C to 35 ^{0}C. Add 400 ml of dichloromethane at 25 ^{0}C to 30 ^{0}C into the flask and wash with 20% w/v aqueous sodium metabisulphite (2x 200 ml) ; 10% w/v sodium bicarbonate 400 ml , followed by 133 ml of water to get the neutral pH. Dry the organic layer over anhydrous sodium sulfate. Distill out dichloromethane under vacuum at the. temperature below 50 ^{0}C.
Weight of oily mass 298.5-303 gm
% yield = 86.11%
GC purity >97.7 %.

Example-2
Preparation of S-methyl isothiourea sulfate
In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer add at 25 ^{0}C to 30 ^{0}C , 77 ml of demineralized water, thiourea (10Og, 1.3137 mol) . Stir and add dimethyl sulfate (90.64g, 0.7186 mol) slowly over a period of 1.5 hours. Raise temperature to 80 ^{0}C and maintain for 30 minutes. Further raise temperature to reflux temperature and maintain for 5 hours. Cool the reaction mass to 25 to 35 ^{0}C and add 133 ml of isopropyl alcohol and stir for 60 minutes. Filter the mass and wash the cake twice with 73.5 ml of mixture (100 ml isopropyl alcohol : 47 ml deminaralized water). Dry the product at 70-75 ^{0}C.
Weight of dry product =148-152 gm.
% Yield = 80-82%;
Assay > 98.00 %

Example-3
Preparation of Methyl 6-(4-fluorophenyl)-4-isopropyl-2-(Methylthio)-l,4-dihydropyrimidine-5-carboxylate

In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer, charge 1800 ml of dimethyl sulfoxide at 25 to 35 ^{0}C. Add 2-[(4-fluorophenyl) methylene-4 methyl-3-oxo pentanoic acid methyl ester (60Og, 2.40 mol), S-Methyl isothiourea sulphate (373.2g, 1.3424 mol), and triethylamine (147.6g, 1.4588 mol). Stir the mass. Raise the temperature between 7O^{0}C to75 ^{0}C & maintain for 17 hrs. Check TLC for product formation. Cool the reaction mass to 10 to 15^{0}C. Add HCl solution (3036 ml of demineralised water & 480 ml of cone. HCl). Extract this aq. layer twice with 1020 ml toluene. Separate layers and discard toluene layer. To aqueous layer, add 780 ml of toluene into the flask at 25 to 35 ^{0}C. Add 882 ml of 20% aqueous ammonia slowly. Stir and settle for 30 minutes. Separate the aqueous layer and preserve toluene layer. Extract aqueous layer with 510 ml toluene separate layers and combine organic layer with main organic layer. Wash organic layer with 630 ml water. Dry this organic layer over sodium sulfate. Unload & weigh the organic layer. Volume of organic layer containing product = 1710 ml (1.5630 kg)
Yield: 49%; purity by HPLC- NLT 80%

Example-4
Preparation of Methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio) pyrimidine-5-carboxylate
In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer,

Charge toluene (249 ml) at 25 to 35 ^{0}C. Add p-Chloranil (42g, 0.1708 mol). Raise the temperature to 65 ^{0}C to 70 ^{0}C. Add Methyl 6-(4-fluorophenyl)-4-isopropyl-2- (methylthio)-l,4-dihydiOpyiimidine-5-carboxylate (205.25 g toluene solution) & 70 ml toluene at 65 to 70 ^{0}C over a period of 1 hour. Stir the mass at 65 to 70 ^{0}C for 4 hours. Check TLC for the completion of the reaction. Filter the contents at room temperature. Wash the wet cake with 42 ml of toluene. Add the filtrate (560 ml) into the flask at room temperature. Wash this organic layer twice with 2% aqueous NaOH solution (394 ml demineralized water + 7.88 gm NaOH) at 25 to 35^{0}C. Add organic layer into R.B. Flask. Wash this organic layer twice with (280 ml) of demineralized water at 25 to 35^{0}C. Diy organic layer using anhydrous sodium sulfate. Distill toluene under vacuum at 50-55 ^{0}C. Add (30 ml) of isopropyl alcohol into the flask. Raise the temperature & Stir the contents at 75 to 8O^{0}C for 15 minutes. Then cool to 25 to 35 ^{0}C. Again stir and cool to 0 to 2^{0}C & stir for 1 hour. Filter the contents. Wash the cake twice with (10 ml) chilled Isopropyl alcohol. Dry the material at 55 to 60 ^{0}C.
Yield = 25.88- 27.0 gm.;
%Yield= 52.12- 54.38 %
Purity by HPLC= 97.46 %
Assay= 97.44 %

Example-5
Preparation of Methyl 4-(4-fluorophenyl)-6-isopropyl-2- methyl sulfonylpyrimidine-5-carboxylate

In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer,
charge 1000 ml methanol, start stirring and add methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio)pyrimidine-5-carboxylate (100g,0.3125 mol) at 25°-30°C. Add ammonium molybdate tetra hydrate (4.95g, 0.004005 mol) & sulfuric acid (0.32g, 0.00326 mol) at 25°-30°C into the flask. Add 106.2 ml H_2O_2 (50%) drop wise in 30 minutes into the flask. Stir for 2 hrs at 40^{0}C - 45°C.Raise the temperature to 50^{0}C. Stir for 5 hr at 50^{0}C. Check TLC for completion of reaction. Cool the reaction mass to 0 ^{0}C. Stir 1 hr at 0 ^{0}C. Filter it & give 6 times (200 ml) water wash. Diy the material in dryer for 7-8 hr at 55^0-60°C.
Weight - 97.5-98.33 gm;
Yield = 0 .98w/w;
Yield = 88.63-89.39 %
Purity = 99 - 100 % by HPLC

Example-6
Preparation of Methyl sulphonamide-N-methyl sodium salt:
In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer,
charge 272 ml of monomethylamine .Stir and cool to O^{0}C. Add methanesulphonyl chloride (10Og, 0.8723 mol) drop wise into the flask at O^{0}C. Stir for 1 hr at O^{0}C. Raise the temperature of the contents of the flask to 25°-30°C. Stir for 1 hr at 25°-30°C. Cool the contents of the flask to O^{0}C. Add solution of sodium hydroxide (72gm NaOH in 72 ml water) drop wise at O^{0}C into the flask. Stir for 1 hr at O^{0}C. Raise the temperature of reaction mass to 25-30 ^{0}C and stir for 1 hr. Cool the contents of the flask to O^{0}C. Stir for 1 hr at 0^{0}C. Filter it; & give washing twice to the cake with (25 ml) chilled mixture of methanol: water 40:10 (at O^{0}C.) Wash the cake with 133 ml chilled acetone (at O^{0}C). Dry the wet cake at 55°-60°C for 5-6 hr.
Weight of dry product- 72.5-104 gm.
Actual Yield=1.476-1.55 w/w, 80-82%;
Assay = NLT- 73.71 % (as such basis) Assay =NLT - 92.33 % (on anhydrous basis);
Moisture = 22-25% W/W

Example-7
Preparation of Methyl 4-(4-Fluorophenyl)-6-isopropyl-2-(N-Methyl-N-Methyl Sulphonyl Amino) Pyrimidine-5- Carboxylate
In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer, charge 1000 ml DMF at 25-30^{0}C. Add Sodium salt of N-methyl methane sulphonamide (106g, 0.6310 mol), and Methyl 4-(4-fluorophenyl)-6-isopropyl-2-methyl sulfonylpyrimidine-5-carboxylate (10Og, 0.28406 mol) Stir for 1 hr at 30^{0}C. Check TLC for completion of reaction. Add 1000 ml of demineralized water of 2-5^{0}C. Stir 1 hr at 30°C.Filter it; give 5 X 200 ml water wash .Dry the material at 60°C-65°C for 8-10 hr.
Yield: - 100-102 gm.
% Yield - 92.42 - 95.19 %,
moisture NMT- 0.3 %w/w,
Purity by HPLC= 99.85 - 99.9 %

Example-8
Preparation of [4-(4-fiuorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl] methanol

In a round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer, charge 7.50 lit hexane and (1.00 kg, 2.625 mol) of Methyl 4-(4-Fluorophenyl)-6-isopropyl-2-(N-Methyl-N-Methyl Sulphonyl Amino) Pyrimidine-5- Carboxylate under stirring under N_2 atmosphere at 25- 30^{0}C . Add (6.81 lit, 6.708 mol) DIBAL-H (20 % in hexane) drop wise at 25-30^{0}C into the flask. Stir at 25-30^{0}C for 1 hr; check TLC for absence of starting material. Add 1.7 lit. acetic acid drop wise below 2O^{0}C. Add 10.0 lit of ethyl acetate. Stir well for 30.min. Add 7.0 lit water and 2.0 lit HCl into the flask & stir well for 15 min. Separate ethyl acetate layer. Extract the aqueous layer with 5.0-liter ethyl acetate. Add 5.0 liter 6% sodium bicarbonate solution into the flask & stir well for 15 min. (pH 8-9) Separate layer; Give 5.0 lit water wash (twice) to ethyl acetate layer. (pH neutral) Dry ethyl acetate layer over 0.5 kg anhydrous sodium sulphate. Distill ethyl acetate under vacuum at 45^{0}C. Remove traces of ethyl acetate with hexane stripping 5.0 lit (twice). Cool to 25-30^{0}C and add 5.0 lit hexane stir well for 30 min. and filter the solid. Give 1.0 lit hexane wash to the solid. Dry the material in oven at 55^{0}C.
Approx weight of solid = 0.8 kg,
Actual yield: - 0.85-0.88 kg;
Yield- 91.79-95.28%;
Purity by HPLC= 99.66 - 99.8 %

Example-9
Preparation of (4-fluorophenyl)-6-isopropyl-2(N-methyl-N-methylsulfonylamino)pyrimidine-5-carboxaldehyde

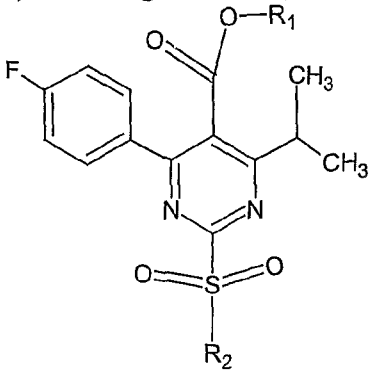
In 2-lit 3-neck flask round bottom flask equipped with stirrer, hot plate, water bath, condenser , thermometer, charge 750 ml of dichloromethane. Add (10Og, 0.283 mol) [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]methanol
and stir it to dissolve at RT. Cool the reaction mixture to O^{0}C Add TEMPO solution (450 mg TEMPO +50 ml dichloromethane) in reaction mixture at O^{0}C. Add KBr solution (3.4 gm KBr + 25 ml demineralized [DMjwater) in to reaction mixture between O^{0}C. Add the slurry of calcium hypochlorite (60.05 gm calcium hypochlorite + 200 ml demineralized water) portion wise into reaction mixture at O^{0}C within 15 min. Add

solution of sodium bicarbonate (sodium bicarbonate 46.8 gms + 468 ml DM water) drop wise in reaction mixture at 0^0C within 90 min. Maintain temperature of the reaction mass at 0^0C for 60 min. Check TLC for absence of starting material. Add calcium hypochlorite solution 2nd lot drop wise at 0^0C (2.9 gm Calcium Hypochlorite + 12 ml water) followed with sodium bicarbonate (2.25 gm Sodium bicarbonate + 22.5 ml water) solution at the same temperature. Stir reaction mixture at 0^0C for 15 min. Check TLC for absence of starting material. Raise the reaction mixture to RT. Separate dichloromethane [DCM] layer and aqueous layer. Extract aqueous layer with 2 X 100 ml DCM. Wash DCM layer with 2 X 100 ml DM water. Separate DCM layer. Dry DCM layer over 50 gm anhydrous sodium sulphates. Distill DCM layer under vacuum at 40°C.Remove traces of DCM with 100 ml hexane. Stir the reaction mixture with 320 ml hexane for 60 min at RT. Filter the slurry; give 2 X 100 ml hexane wash; suck dry for 15 min. Dry the solid at 50^0C in tray dryer.

Weight of solid -85 gm;
Yield - 85-90%
Purity by HPLC= 96.79 - 98.9 %;
Assay by HPLC= 99.05 - 99.63 %

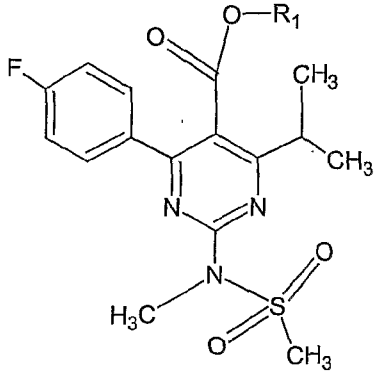
We claim :

1) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(1-methylethyl)-2-pyr midinyl]-N-methyl- methanesulfonamide comprising
   a) Reacting a of compound of formula -[D]



formula-[D]

with N-methyl methanesulfonamide and a base, optionally with a salt of N-methyl methanesulfonamide in suitable solvent(s) , to give a compound of formula -HA



Formula-IIA

wherein R_1 is Ci to *Ce* alkyl, preferably R_1 is methyl or- ethyl, more preferably Ri is methyl ; and R_2 is Ci to C_8 n-alkyl or branched alkyl, cycloalkyl, phenyl , benzyl or substituted phenyl group, preferably R_2 is methyl;

at temperature suitable to effect conversion of compound of formula [D] to a compound of formula-IIA ;

   b) converting compound of formula-IIA to corresponding primary alcohol by reduction of the ester group,
   c) oxidation of primary alcohol to an aryl aldehyde using calcium hypochlorite with TEMPO as catalyst in a solvent.

2) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2-pyrimidinyl]-N-methyl- methanesulfonamide as per claim(l), wherein Ri is methyl or ethyl, preferably methyl and R_2 is methyl.

3) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2-pyrimidinyl]-N-methyl- methanesulfonamide as per claim-1, wherein the preferred process for preparation of compound of formula-IIA (wherein R_1 is methyl) , in step-(a), involves the reaction of compound

of formula [D] wherein Ri and R_2 is each methyl, with sodium salt of N-methyl methanesulfonamide

4) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2- ρyiimidinyl]-N-methyl- methanesulfonamide , as pervclaim-1 wherein the solvent used for the process described in step-(a) is selected from DMF, $DMSO_5$NMP, N,N,N',N'-tetramethyl urea, l,3-Dimethyl-2-imidazolidinone acetonitrile, sulfolane dimethylacetamide ,THF, dioxane , IPA, butanol, ,dichloromethane , chloroform, toluene and their like or mixtures thereof ; preferably N,N-dimethyl formamide.
5) A process for preparing N-[4-(4-fluorophenyl)-5-fo πnyl-6-(l-methylethyl)-2-pyrimidinyl]-N-methyl- methanesulfonamide as per claim-1 , wherein the solvent in step-(c) is halogenated solvent such as dichloromethane, chloroform and their like, preferably dichloromethane.
6) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2-pyrimidinyl]-N-methyl- methanesulfonamide as per claim-1 , wherein step-(a) is carried out at 10-120^{u}C, preferably at 20-35 ^{0}C.
7) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2-pyrimidinyl]-N-methyl- methanesulfonamide as per claim-1 , wherein step-(c) is carried out at 0-lOOC, preferably 0 to 5 ^{0}C.
8) A process for preparing N-[4-(4-fluorophenyl)-5-formyl-6-(l-methylethyl)-2-pyiimidinyl]-N-methyl- methanesulfonamide as per claim-1 , wherein calcium hypochlorite with TEMPO as catalyst is used to convert primary alcohol to corresponding aldehyde in step(c).