Annexure 1

Written submission after the hearing held on June 05, 2017

Patent Application Number: IN 3712/CHE/2011
SEQUENT SCIENTIFIC LIMITED

Further to the hearing held on Monday, June 06, 2017, applicant respectfully submits the written submission. The following details are provided for differentiating instant invention with that of the cited prior art references in the hearing notice on inventive step.

Objections

Invention u/s 2(1)(j)

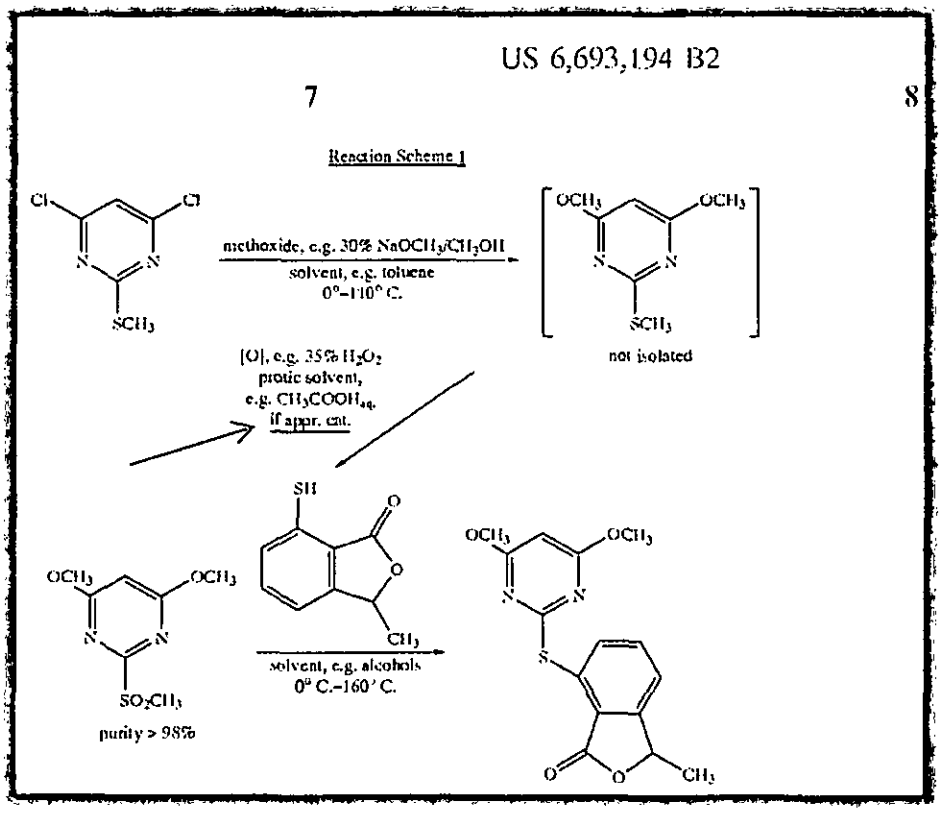
1. After consideration of reply to FER by the applicant, novelty of amended claims 1-6 can be recognized, but inventive step cannot be acknowledged for the following reason stated below: D1: US6600046B2, 29/06/2003; (cited as D1 in FER) D2: US6693194B2, 17/02/2004; Document D1 also discloses process for the preparation of 1-(6 methylpyridin-3-yl)-2-[(4-(methylsulphonyl) phenyl]ethanone (formula-I of instant application). The difference between D1 and instant application is D1 does not teach the oxidation in step (c) as in situ in the presence of H_2SO_4 & acetic acid and in absence of an alkali metal tungstate catalyst. Document D2 (see reaction scheme-I) teaches in situ oxidation of 4,6-dichloro-2-(methylthio)-1,3-pyrimidine to 4,6-dimethoxy-2-(methylsulfonyl)-1,3-pyrimidine using hydrogen peroxide and aprotic solvent like acetic acid and in the absence of alkali metal tungstate catalyst. Hence, a person with ordinary skilled in the art can oxidise formula-II of instant application from the teachings of D2 without using alkali metal tungstate catalyst to get formula-I without applying any inventive ingenuity. Therefore, the subject matter of amended claims 1-6 cannot be considered as involving an inventive step under section 2(1)(ja) of The Patents Act.

Applicant thanks the Controller for acknowledging novelty of claims 1 to 6 after considering the reply to FER.

D1, US6600046B2 and D2, US6693194B2 have been cited in the hearing notice for an objection under section 2(1)(j). It is clear that D1 does not teach hydrolysis and decarboxylation in presence of H_2SO_4 and in absence of mixture of acetic acid and HCl in step (b), the *in situ* oxidation in step (c) in the presence of H_2SO_4 & acetic acid and in absence of an alkali metal tungstate catalyst.

D2: US6693194B2 provides oxidation of 4,6-dichloro-2-(methylthio)-1,3-pyrimidine to 4,6-dimethoxy-2-(methylsulfonyl)-1,3-pyrimidine in presence of catalyst. The reaction scheme 1 indicates the use of appropriate catalyst. The appropriate catalyst used herein is sodium tungstate.

The reaction scheme 1 of D2 is shown below. The second step used an appropriate catalyst is indicated by an arrow.



Example H1 (Column 7 to column 8; Line 42) used 0.0015 mol of sodium tungstate catalyst along with 35% hydrogen peroxide solution (3.6 mol) in the oxidation step. As per the example of D2, a skilled artisan will be motivated to use a catalyst rather than avoiding the same. The

instant invention avoided the use of sodium tungstate catalyst, in turn producing tungsten free Ketosulfone.

Column 7 to Column 8 of Example H1 is reproduced below:

Line 43 in column 8 shows that the example indeed uses 0.0015 mol of sodium tungstate catalyst for oxidation.

methylnaphthalide in Reaction Scheme 1 is expediently carried out in an inert organic solvent, for example alcohols, ethers, ketones, nitrites or amides, for example isopropanol, tetrahydrofuran, butanone, acetonitrile or N,N-dimethylformamide, at temperatures of from 0° to 160° C. Such substitution reactions are described, for example, in EP-B-0 447 506.

The process according to the invention is illustrated in more detail by the example below.

EXAMPLE H1

Preparation of 4,6-dimethoxy-2-(methyl-sulfonyl)-1, 3-pyrimidine

At 20°–25° C., 525.6 g of 4,6-dichloro-2-(methylthio)-1, 3-pyrimidine (1.5 mol), as a solution in toluene (55.7%), are

tillate. 36 g of 100% acetic acid (0.6 mol) and 0–5 g of sodium tungstate (0.0015 mol) are then added to the toluene-free aqueous residue, and the entire mixture is heated to 78°–80° C. At this temperature, 350 g of a 35% hydrogen peroxide solution (3.6 mol) are added dropwise with vigorous stirring over a period of 4 hours. The oxidation is exothermic, and stirring is continued at 78°–80° C. for 1–2 hours until GC analysis shows complete conversion, i.e. no more 4,6-dimethoxy-2-(methyl-sulfoxide)-1,3-pyrimidine. To destroy excess oxidizing agent, 110 g of sodium hydrogen sulfite solution (40%, 0.412 mol) are added dropwise over a period of 30 minutes to the reaction mixture, until a test with KI-starch paper gives a negative result. 750 g of toluene are then added to the aqueous-acidic reaction mixture and, at 78°–80° C., 30% aqueous sodium hydroxide

Differences identified with the cited D2 with that of the instant invention is tabulated as shown below:

	D2: US6693194B2	IN3712/CHE/2011; Instant invention
1	Sodium tungstate catalyst was used for the oxidation of 4,6-dichloro-2-(methylthio)-1,3-pyrimidine to 4,6-dimethoxy-2-(methylsulfonyl)-1,3-pyrimidine	Oxidation in the absence of alkali metal tungstate catalyst of 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine to Ketosulfone
2	Hydrolysis and decarboxylation were not provided	Hydrolysing and decarboxylating 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine in presence of H_2SO_4 and in absence of mixture of acetic acid and HCl to obtain 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine (Claim 1; Step b)

Column 2; Lines 51 to 55 of D2 is reproduced below:

> The oxidation of the resulting and prepared 4,6-dimethoxy-2-(methylthio)-1,3-pyrimidine in the second step (Reaction Scheme 1) is expediently carried out in a protic solvent or a protic solvent mixture and, depending on the oxidizing agent used, if appropriate in the presence of a catalyst. Thus, expediently, a concentrated acid such as a carboxylic acid, for example 100% acetic acid, is added to the prepared aqueous reaction mixture from the first step, until a 1–80%, preferably 2–10%, aqueous solution of the corresponding carboxylic acid is obtained. To this end, depending on the oxidizing agent used, 0.1–0.2 mol % of a catalyst, based on 4,6-dimethoxy-2-(methylthio)-1,3-pyrimidine, such as a tungstate, for example sodium tungstate, is added, and this mixture is heated to from 70° to 90° C., preferably from 75° to 80° C. From 2 to 4 mol, preferably from 2.1 to 3 mol, of an oxidizing agent, such as a peroxide, for example 20–35% hydrogen peroxide solution, based on 4,6-dimethoxy-2-(methylthio)-1,3-pyrimidine, are then added dropwise. The exothermic oxi-

D2 clearly provided the use of a catalyst as mandatory for the oxidation. The specific example also used sodium tungstate catalyst. Therefore, any skilled person will not be motivated to avoid using catalyst for oxidation in view of D2.

The instant invention as claimed in claim 1 is for:

1. Hydrolysis and decarboxylation in presence of H_2SO_4 and in absence of mixture of acetic acid and HCl in step (b),
2. The *in situ* oxidation in step (c), and
3. Oxidation in step (c) in the presence of H_2SO_4 & acetic acid and in absence of an alkali metal tungstate catalyst.

The claimed invention as shown above in points 1 to 3, involve inventive step under section 2(1)(j).

Advantages provided in the specification of the present invention over the prior art references are reproduced below for convenience:

1. Reduction of a number of step by eliminating isolation of ketosulfide of formula II
2. Reduction in generation of toxic effluent
3. Elimination of use of methane sulfonic acid which would cause genotoxic impurities
4. Elimination of use of alkali metal tungstate as catalyst for the oxidation
5. It provides tungsten free Ketosulfone which is very desired for the industry.

In view of the foregoing, it is respectfully requested to allow the application for grant.