R. K. DEWAN & CO.
ADVOCATES, TRADE MARK
& PATENT ATTORNEYS
INDIA

REPLY TO THE EXAMINATION REPORT

Date: August 18th, 2022

To,

The Controller of Patents,

Original Jurisdiction: Patent Office, Mumbai

Application No: 201821012075

Applicant: Ami Organics Pvt. Ltd.

Controller: Dr. Subramaniyan S P, Controller of Patents, Patent office, Chennai

Date of Mailing of FER: 12/04/2022

Normal period of filing FER reply: 12/10/2022

Respected Sir,

INTRODUCTORY COMMENTS

In response to the First Examination Report (FER) the following amendments and submissions are respectfully submitted in connection with objections raised in the "Examination Report" with the assumption that the proposed amendments and submission made herein are up to the satisfaction of the Controller as per the provision of Section 15, and we request the Controller to consider the application in order for a grant.

The Applicant submits that in case some objections still remain, the application be disposed as per the provisions of Section 15 to be read along with Section 80 and Rule 28(5).

SUMMARY OF SUBMISSION:

Claims 1-16 were on record at the time of receiving the First Examination Report (FER). The limitations of claim 3 have been incorporated in claim 1 in order to meet the requirements. The term "can be" is replaced by "is" in original claim 9(amended claim 8) in order to meet the raised requirements. Further, the term "greater than" is replaced by the term "in the range of" in original claims 1, 10, 15 and 16 (amended claims 1, 9, 14 and 15). The support for the

same is found on lines 22-24 on page 3, lines 3-4 on page 4 and line 13 on page 14 of the as filed specification. Still further, the term "below" has been deleted from original claims 14 and 15(amended claims 13 and 14) and the ranges of temperature have been defined. The support for the same is found on lines 19-21 on page 10 and lines 6-8 on page 11 of the as filed specification. The applicant submits that through such amendments, no new matter has been added, and all the amendments to the claims are based on the original specification as filed and within the scope of the invention. This version of total 1-15 claims supersedes all the previous versions of the claims and is pending for a grant.

Table 1: List of amended, original and cancelled claims

Serial No	**Claim Number**		**Status**
	Old	**New**	
1.	1	1	Amended
2.	2	2	Original
3.	3	-	Cancelled
4.	4	3	Original
5.	5	4	Original
6.	6	5	Original
7.	7	6	Original
8.	8	7	Original
9.	9	8	Amended
10.	10	9	Amended
11.	11	10	Original
12.	12	11	Original
13.	13	12	Original
14.	14	13	Amended
15.	15	14	Amended
16.	16	15	Amended

PART-II: DETAILED TECHNICAL REPORT

(1). NOVELTY:

The Ld. Controller is of the opinion that claim(s) (1-16) lack(s) novelty, being anticipated in view of disclosure in the document cited under reference D1 for the following reasons:

D1: Fuqiang Zhu et al.,"Development of a Robust Process for the Preparation of High-Quality 4-Methylenepiperidine Hydrochloride" Org. Process Res. Dev. 2018, 22, 1, 91-96. DOI: 10.1021/acs.oprd.7b00350

Therefore, in view of the disclosure of D1, claims 1-16 lack novelty and, hence, do not constitute an invention u/s 2(1) (j) of the Patents Act, 1970 (as amended).

The Applicant respectfully disagrees with the Ld. Controller in view of the following explanation:

The differences between amended claim 1 of the present application and D1 have been shown in table 1 below:

Table 1: Differences between the features of amended claim 1 of the present application and D1:

	Present application	D1
A process for preparing 4-methylene piperidine hydrochloride	a. alkylating 1-benzylpiperidine-4-one to obtain 1-benzyl-4-methylidenepiperidine	✓
	b. debenzylating 1-benzyl-4-methylidenepiperidine to obtain N-carbethoxy-4-methylene piperidine	✓
	c. deprotecting N-carbethoxy-4-methylene piperidine to obtain 4-methylidenepiperidine	✓
	d. forming a salt of 4-methylidenepiperidine to obtain	✓

	4-methylene piperidine hydrochloride having purity greater than 95%	
	step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation	× 20°C to 30°C

From the table 1 above, it can be seen that the step (a) of alkylation in the process of preparation of 4-methylene hydrochloride of the present application is carried out at a temperature of 60 °C to 80 °C whereas in D1 the alkylation step is carried out at a temperature of 20°C to 30°C.

Therefore, amended claim 1 is novel over the cited document D1. Original claims 2-16 (amended claims 2-15) are novel by virtue of dependency on amended claim 1.

In view of the above explanation, the Ld. Controller is requested to waive the objection.

(2). INVENTIVE STEP:

The Ld. Controller is of the opinion that claim(s) (1-16) lack(s) inventive step, being obvious in view of teachings of cited document under reference D1:

D1: Fuqiang Zhu et al.,"Development of a Robust Process for the Preparation of High-Quality 4-Methylenepiperidine Hydrochloride" Org. Process Res. Dev. 2018, 22, 1, 91-96. DOI: 10.1021/acs.oprd.7b00350

Since the subject matter of claims is not novel, therefore their inventive steps cannot be acknowledged u/s 2(1) (ja) of the Patents Act, 1970 (as amended). To prove an inventive step, the applicant should relate the distinguishing features of the present application over the cited prior art document to a surprising technical effect or make it plausible that this distinguishing feature is not obvious in light of the cited documents.

The Applicant respectfully disagrees with the Ld. Controller in view of the following explanation:

Amended claim 1 of the present application discloses a process for preparing 4-methylene piperidine hydrochloride comprising the following steps:

a. alkylating 1-benzylpiperidine-4-one to obtain 1-benzyl-4-methylidenepiperidine;

b. debenzylating 1-benzyl-4-methylidenepiperidine to obtain N-carbethoxy-4-methylene piperidine;

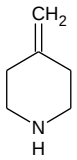
c. deprotecting N-carbethoxy-4-methylene piperidine to obtain 4-methylidenepiperidine; and

d. forming a salt of 4-methylidenepiperidine to obtain 4-methylene piperidine hydrochloride having purity in the range of 95% to 99%;

wherein the step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation.

The Applicant submits that 4-methylenepiperidine is used as an active intermediate for the preparation of Effinaconazole, which is an effective anti-fungal drug. 4-methylenepiperidine moiety is used as a reactant in the final step of the preparation of Effinaconazole, therefore quality of 4-methylenepiperidine will significantly impact quality of final API product.

4-Methylenepiperidine [CAS no. 144230-50-2] is represented as



Several methods are reported for the synthesis of 4-methylenepiperidine. However, these methods are associated with drawbacks such as obtaining product with low yield and/ or low purity. Further, these methods involve tedious purification, thereby resulting in an expensive process.

There is, therefore, felt a need to provide a simple and economical process for the preparation of 4-methylenepiperidine.

D1 discloses preparation of 4-methylenepiperidine hydrochloride. In the present application, the step of alkylation of 1-benzylpiperidine-4-one is carried out at a temperature of 60 °C to 80 °C whereas in **D1** the step of alkylation of N-benzylpiperidinone is carried out at a temperature of 20-30°C (*Kindly refer lines 36-37 on page 6 and lines 39-40 in the experimental section on page 13 of D1*).

Conventionally, the Wittig reaction is carried out at lower temperature, preferably in the range of 0 °C to 30 °C. However, in accordance with the present invention, the reaction is carried out at higher temperature in the range of 50 °C to 90 °C. At lower temperatures the rate of reaction is very slow; moreover at lower temperatures, the reaction does not lead to completion.

In order to support the above point, the Ld. Controller's attention is directed towards the experiments on pages 12-14 of the as filed specification. It can be seen that from N-benzyl piperidone (II) (70 gm), 55 gm of pure 4-methylidenepiperidine hydrochloride (I) is obtained by carrying out the process steps and reaction conditions as claimed in amended claim 1 of the present application. The yield of pure 4-methylidenepiperidine hydrochloride of the present application is **89.85%.** Whereas, as can be seen from experimental section on pages 13-15 of D1 the yield of 4-methylenepiperidine hydrochloride is **83.5%.** Therefore, the yield of 4-methylene piperidine hydrochloride obtained by carrying out the process steps and reaction conditions as claimed in amended claim 1 of the present application is much higher than obtained by the process disclosed in D1.

A person skilled in the art after referring to D1 would not at all be motivated to carry out the alkylation step at 60 °C to 80 °C instead of 20-30°C.

In the process of the present application the first organic layer comprising 1-benzyl-4-methylidenepiperidine is directly used without any purification. Further, the intermediate N-carbethoxy-4-methylene piperidine (4-methylidenepiperidine-1-carboxylate (IV) is obtained with high purity and therefore is used directly in the next step without further purification. High purity of N-carbethoxy-4-methylene piperidine (4-methylidenepiperidine-1-carboxylate (IV) helps in obtaining high purity of 4-methylidenepiperidine hydrochloride. The process of the present application is simple and employs inexpensive and easily available reagents. Thus, the process of the present application is economical.

Therefore, 4-methylene piperidine hydrochloride prepared by the process of the present application is obtained with high purity along with high yield due to the use of higher temperatures in the alkylation step. Further, the process of the present application does not involve tedious purification steps, thereby resulting in an economical process. The process of the present application is simple and employs inexpensive and easily available reagents.

In view of the above explanation, claim 1 is inventive over the cited document D1. Original claims 2-16 (amended claims 2-15) are inventive by virtue of dependency on claim 1.

In view of the above explanation, the Ld. Controller is requested to waive the objection.

(3). NON PATENTABILITY:

The Ld. Controller is of the opinion that claim(s) (1-16) are statutorily non-patentable under the provision of clause 3(d) of Section 3 for the following reasons:

The subject matter of claims 1-16 falls within the scope of section 3(d) of the Patents Act 1970 as the said claims are related to a process for preparing 4-methylene piperidine

hydrochloride which does not result in a new product or employs at least one new reactant. Therefore, the said claims are not allowable.

The Applicant respectfully disagrees with the Ld. Controller in view of the following explanation:

Conventionally several methods are reported for the synthesis of 4-methylenepiperidine. However, these methods are associated with drawbacks such as obtaining product with low yield and/or low purity. Further, these methods involve tedious purification, thereby resulting in an expensive process.

As stated above in the reply to inventive step in the process of preparation of 4-methylene piperidine hydrochloride of the present application the first organic layer comprising 1-benzyl-4-methylidenepiperidine (III) is directly used without any purification. Further, the intermediate N-carbethoxy-4-methylene piperidine (4-methylidenepiperidine-1-carboxylate (IV) is obtained with high purity and therefore is used directly in the next step without further purification. High purity of N-carbethoxy-4-methylene piperidine (4-methylidenepiperidine-1-carboxylate (IV)) helps in obtaining high purity of 4-methylidene piperidine hydrochloride. The process of the present application avoids tedious purification steps.

In the present application, the alkylation of 1-benzylpiperidine-4-one is carried out at a higher temperature in the range of 60 to 80°C to obtain 1- benzyl-4-methylidenepiperidine. Conventionally, the Wittig reaction is carried out at lower temperature, preferably in the range of 0 °C to 30 °C. Further, the closest prior art document D1 also discloses the alkylation reaction to be carried out at lower temperatures i.e. 20 to 30°C(*Kindly refer lines 36-37 on page 6 and lines 39-40 in the experimental section on page 13 of D1*). However, the applicant submits that at lower temperatures the rate of reaction is very slow; moreover at lower temperatures, the reaction does not lead to completion. This is supported by the yield of the product 4-methylene piperidine hydrochloride obtained by the present application and that obtained in D1. In the present application the yield of the product 4-methylene piperidine hydrochloride obtained is 89.85% whereas in D1 the yield of product 4-methylene piperidine hydrochloride obtained is 83.5%.

Therefore, the process of the present application is simple and employs inexpensive and easily available reagents. Thus, the process of the present application is economical.

Therefore, the process claimed in original claims 1-16 (amended claims 1-15) of the present application is a new one and does not attract Section 3(d) of the Patent Act.

(4). SUFFICIENCY OF DISCLOSURE:

The Ld. Controller is of the opinion that the complete specification does not fully and particularly describe the invention and its operation and the method by which it is to be performed in respect of:

The applicant fails to comply with section 10(4) (c) of the patents act 1970 because the invention in principle claim 1 is not sufficiently disclosed. Various necessary parameters of the reaction such as temperature, time, amount and type of catalyst and solvent, etc. should be clearly defined as well as brought out in the main claim for a better understanding of the scope of the present application.

Amended claim 1 of the present application discloses a process for the preparation of 4-methylidenepiperidine hydrochloride. 4-methylene piperidine hydrochloride prepared by the process of the present application is obtained with high purity along with high yield due to the use of higher temperatures in the range of 60°C to 80°C in the alkylation step. Further, the necessary parameters like reaction temperature have been included in amended claim 1. Therefore, all the essential and inventive features for the preparation of 4-methylene piperidine hydrochloride are included in amended claim 1 of the present application. The best method of performing the invention is explained by way of examples on pages 12-14 of the as filed specification wherein the process steps as claimed in claim 1 and the alkylation temperature has been clearly defined. Therefore, the Ld. Controller is requested to take the same on record and waive the objection.

(5). CLARITY AND CONCISENESS:

Claim(s) 1-16 are not clearly worded in respect of:

Claims 1-16 are not clear with respect to term "greater than" "can be" "below" etc. The said terms fail to clearly set forth the meets and bounds of the invention. Therefore, the said claims should be modified to meet the demand of section 10(4) of the patents act, 1970 as amended.

The claims of the present application have been amended suitably. The term "below" in original claims 14 and 15 (amended claims 13 and 14) has been replaced with a proper temperature range. The temperature ranges in original claim 14(amended claim 13) are well supported by lines 19-21 on page 10. Further, the temperature ranges in original claim 15(amended claim 14) are well supported by lines 6-8 on page 11 of the as filed specification. Further, the purity of 4-methylene piperidine is well supported by experimental details, step

IV on pages 13-14 of the as filed specification. Therefore, the Ld. Controller is requested to take the same on record and waive the objection.

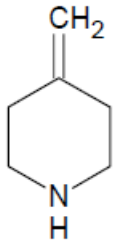
(6). OTHERS REQUIREMENTS:

(I) Relevant prior art cited in FER should be included in "Background of The Information" and distinguished technical features should be clearly described to ascertain the scope of the invention.

The Applicant submits that the drawbacks of the conventional process known to the applicant at the time of filing of the application have been clearly disclosed in the background of the as filed specification.

In the background art it has been disclosed that 4-methylenepiperidine is used as an active intermediate for the preparation of Effinaconazole, which is an effective anti-fungal drug. 4-methylenepiperidine moiety is used as a reactant in the final step of the preparation of Effinaconazole, therefore quality of 4-methylenepiperidine will significantly impact quality of final API product.

4-Methylenepiperidine [CAS no. 144230-50-2] is represented as



Several methods are reported for synthesis of 4-methylenepiperidine. However, these methods are associated with drawbacks such as obtaining product with low yield and/ or low purity. Further, these methods involve tedious purification, thereby resulting in an expensive process.

There is, therefore, felt a need to provide a simple and economical process for the preparation of 4-methylenepiperidine.

Hence, the background of the present application is suitably drafted to disclose the drawbacks of conventional processes of preparation of 4-methylene piperidine hydrochloride and the technical advancements brought by the process of the present application. Thus, the background prior art known to the applicant at the time of filing the application has been

disclosed in the specification alogwith its drawbacks and explaining improvement of the process of the present application over the known art.

Therefore, the Ld. Controller is requested to waive the objection.

PART-III: FORMAL REQUIREMENTS

Statement & Under Taking (Form 3 Details)

1.Details regarding applications for Patents that may be filed outside India from time to time for the same or substantially the same invention should be furnished within six months from the date of filing of the said application under clause (b) of subsection (1) of section 8 and rule 12(2) of the Patents Act 1970, as amended.

The applicant respectfully submits that no foreign filing has been made in respect of the present patent application. Therefore, requirements of Section 8 remain moot.

2. Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, in respect of the same or substantially the same invention filed in all the major Patent office's such as USPTO, EPO, JPO, etc., along with appropriate English translation where applicable, should be submitted within a period of six months from the date of receipt of this communication as provided under section 8(2) of the Patents Act 1970, as amended.

The applicant respectfully submits that no foreign filing has been made in respect of the present patent application. Therefore, requirements of Section 8 remain moot.

PRAYER

It is therefore submitted that:

(a) in view of the detailed observations submitted herein, the office objections may be dropped, withdrawn or waived, as the case is being;

(b) in view of all office requirement(s) having been met by the Applicant the application may be favorably considered for early grant without hearing;

(c) a hearing opportunity to be given to the Applicant under Section 14, in the interest of natural justice in case of any outstanding issue/objections;

(d) In case, the applicant unable to attend hearing either non receipt of hearing notice or mail failure of hearing notice due to technical snag at the Patent Office server or due to any other reason's, the applicant authorized attorney may be called over phone on the scheduled hearing date to ascertain the status/intention of the applicant in context of application.

Even the applicant not appeared for hearing, the Controller proceed with the application as per provision of Rule 28(5) to be read along with Section 15 and 80 and thereafter only pass reasoned order.

Rule 28(5): *After hearing the applicant, or without a hearing if the applicant has not attended or has notified that he does not desire to be heard, the Controller may specify or permit such amendment of the specification as he thinks fit to be made and may refuse to grant the patent unless the amendment so specified or permitted is made within such period as may be fixed.*

(e) if any further requirement, clarification is required by the Controller, the Applicant is ready to consider the amendments proposed by the Controller to his satisfaction under the provisions of **Section 15, Rule 28(5)** prior to the Controller passing an order in this matter.

(f) in case, the Controller prima facie after going through the written submission is of the adverse opinion to the applicant's interest, a hearing opportunity be given under Section 80.

Dated this 17th of August 2022

MOHAN RAJKUMAR DEWAN, IN/PA-25
of R.K.DEWAN & COMPANY
AGENT FOR THE APPLICANT

TO,
THE CONTROLLER OF PATENTS,
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Enclosures
1) Amended claims (Marked copy)
2) Amended claims (Clean copy)