DESCRIPTION

TITLE OF INVENTION: [A METHOD FOR PRODUCING LENALIDOMIDE]

TECHNICAL FIELD

[0001] The present disclosure relates generally to the technical field of medicinal chemical synthesis technology, specifically to the method for producing lenalidomide.

BACKGROUND

[0002] The following discussion of the background to the invention is intended to facilitate an understanding of the present invention only. It should be appreciated that the discussion is not an acknowledgement or admission that any of the material referred to was published, known or part of the common general knowledge of the person skilled in the art in any jurisdiction as at the priority date of the invention.

[0003] Lenalidomide, commercially known as Revlimid and chemically referred to as 3-(4-amino-1-oxo-1,3-dihydroisoindol-2-yl)piperidine-2,6-dione (refer to FIG. 7a for Lenalidomide's structural formula), is a pioneering development by Celgene Corporation. It is extensively utilized in managing fatal hematologic disorders and various cancers. Lenalidomide exhibits broad immunomodulatory properties, including the upregulation of cytokine IL-2 which promotes T cell production, suppression of tumor necrosis factor TNF-α production, and amplification of natural killer cell toxicity. Initially receiving FDA approval in early 2006 for Myelodysplastic Syndromes (MDS) treatment, lenalidomide emerged as the first and sole efficacious medication for MDS, with clinical data showing that 64% of MDS patients could avoid transfusions post-treatment. By 2008, its approval extended to treating Multiple Myeloma (MM), marking it as the leading therapeutic for MM, alongside its efficacy in Mantle Cell Lymphoma (MCL). In June 2013, lenalidomide received FDA endorsement for treating relapsed or refractory MCL, targeting patients who experienced relapse or progression after undergoing two chemotherapy rounds, including bortezomib.

[0004] There are various conventional methods for producing lenalidomide. Notably, the process described in US Patent Application US5635517A involves a lenalidomide synthesis through a five-step reaction, as depicted in FIG. 7b. This process is marked by its intricate procedural demands, resulting in products of relatively low purity, elaborate and labor-intensive separation and purification requirements, increased production

expenses, and its general impracticality for large-scale application. Similarly, the synthesis method introduced in Chinese Patent Application CN101580501A, shown in FIG. 7c, at the initial reaction phase, face challenges such as low yield and a high level of impurities, thereby complicating subsequent purification steps. Additionally, the employment of sodium amide in the second step of this method introduces significant safety concerns due to the compound's hazardous nature in terms of handling and storage, consequently amplifying the risks associated with the large-scale production process.

[0005] Consequently, despite numerous existing lenalidomide synthesis methodologies, they share common shortcomings, including intricate process requirements, diminished synthesis efficacy, heightened production expenses, compromised safety protocols, environmental concerns, and challenges in scaling for industrial output.

[0006] There exists a need to improve the method for producing lenalidomide and alleviate at least one of the aforementioned problems.

SUMMARY

[0007] Specifically, to address the above-mentioned technical problems, the present invention specifically uses the following technical solutions:

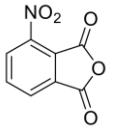
[0008] Accordingly, in accordance with one aspect of the present invention, there is provided a method for producing a chemical compound, comprising the following steps of:

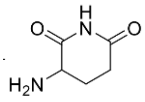
[0009] S101 reacting a first compound with a second compound in an amide formation reaction to obtain a third compound;

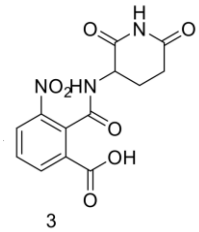
[0010] S102 undergoing a condensation reaction with the third compound to obtain a fourth compound;

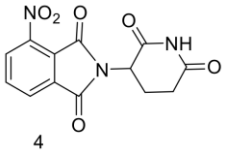
[0011] S103 undergoing a reduction reaction with the fourth compound to obtain a fifth compound;

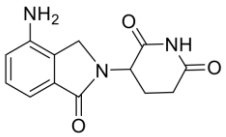
[0012] wherein: the first compound has a structure of Formula 1

[0013]  ; the second compound has a structure of Formula 2

[0014]  ; the third compound has a structure of Formula 3

[0015]  ; the fourth compound has a structure of Formula 4

[0016]  ; and the fifth compound has a structure of Formula 5

[0017]  .

[0018] In some embodiments, the first compound is dissolved in a solvent, then the second compound is added, stirred, heated, and reacted at a temperature of 25 to 50 °C for 2 – 4 hours.

[0019] In some embodiments, the solvent is selected from one or more of toluene, ethylbenzene, and chloroform.

[0020] In some embodiments, the molar ratio of the first compound to the second compound is 1: (1 to 1.1), and the mass ratio of the first compound to the solvent is 1: (2 to 5).

[0021] In some embodiments, a first acid is added to a first reaction mixture obtained after the step of S101, stirred, heated, and the third compound is reacted at a temperature of 45 to 60°C for 2-5 hours.

[0022] In some embodiments, the first acid is polyphosphoric acid.

[0023] In some embodiments, the weight ratio of the first acid to the first compound is 1: (10 to 20).

[0024] In some embodiments, a second reaction mixture obtained after the step of S102 is cooled down to a temperature of 0-10°C.

[0025] In some embodiments, the second reaction mixture is filtered to obtain a first filter cake, which is further dried to yield the fourth compound.

[0026] In some embodiments, the fourth compound is placed in a reactor with a catalyst and a second acid, the air in the reactor is replaced with an inert gas, then with a reducing gas, and heated to maintain the reactor at a temperature of 25 to 50°C for 2-8 hours.

[0027] In some embodiments, the catalyst is a palladium-on-carbon catalyst.

[0028] In some embodiments, the palladium-on-carbon catalyst contains 5 to 10% by weight of palladium.

[0029] In some embodiments, the mass ratio of the fourth compound to the catalyst is 1: (0.2 to 0.4).

[0030] In some embodiments, the second acid is acetic acid.

[0031] In some embodiments, the mass ratio of the fourth compound to the second acid is 1: (8 to 10).

[0032] In some embodiments, the inert gas is nitrogen.

[0033] In some embodiments, the reducing gas is hydrogen.

[0034] In some embodiments, the pressure of the reducing gas is 0.2-1MPa.

[0035] In some embodiments, the reactor is a high-pressure reactor.

[0036] In some embodiments, a third reaction mixture obtained after the step of S103 is first stirred with water, and then filtered to obtain a second filter cake, which is further dried to yield the fifth compound.

[0037] Other aspects and features of the present invention will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] In the figures, which illustrate, by way of non-limiting embodiments only, embodiments of the present invention,

[0039] **[FIG. 1]:** shows the Mass Spectrometry (MS) spectrum of the solid product prepared in Embodiment 1 of the present invention;

[0040] **[FIG. 2]:** shows the Proton Nuclear Magnetic Resonance (^1H NMR) spectrum of the solid product prepared in Embodiment 1 of the present invention;

[0041] **[FIG. 3]:** shows the Carbon-13 Nuclear Magnetic Resonance (^13C NMR) spectrum of the solid product prepared in Embodiment 1 of the present invention;

[0042] **[FIG. 4]:** shows the Mass Spectrometry (MS) spectrum of the solid product prepared in Embodiment 4 of the present invention;

[0043] **[FIG. 5]:** shows the Proton Nuclear Magnetic Resonance (^1H NMR) spectrum of the solid product prepared in Embodiment 4 of the present invention;

[0044] **[FIG. 6]:** shows the Carbon-13 Nuclear Magnetic Resonance (^13C NMR) spectrum of the solid product prepared in Embodiment 4 of the present invention;

[0045] **[FIG. 7a]:** shows the formula of Lenalidomide;

[0046] **[FIG. 7b]:** shows a conventional method for producing lenalidomide, as disclosed in the US patent application document US5635517A; and,

[0047] **[FIG. 7c]:** shows a conventional method for producing lenalidomide, as disclosed in the Chinese patent application document CN101580501A.

DETAILED DESCRIPTION

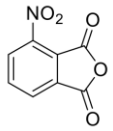
[0048] Throughout this document, unless otherwise indicated to the contrary, the terms “comprising”, “consisting of”, “having” and the like, are to be construed as non-exhaustive, or in other words, as meaning “including, but not limited to”.

[0049] Furthermore, throughout the document, unless the context requires otherwise, the word “include” or variations such as “includes” or “including” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

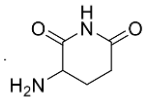
[0050] Unless defined otherwise, all other technical and scientific terms used herein have the same meaning as is commonly understood by a skilled person to which the subject matter herein belongs.

[0051] According to various embodiments there is provided a method for producing a chemical compound, comprising the following steps of: S101 reacting a first compound with a second compound in an amide formation reaction to obtain a third compound; S102 undergoing a condensation reaction with the third compound to obtain a fourth compound; S103 undergoing a reduction reaction with the fourth compound to obtain a fifth compound; wherein:

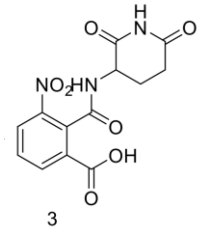
[0052] the first compound has a structure of Formula 1



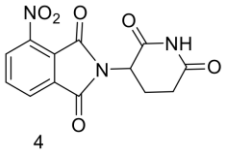
1 ; the second compound has a structure of Formula 2



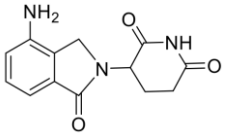
2 ; the third compound has a structure of Formula 3



3 ; the fourth compound has a structure of Formula 4

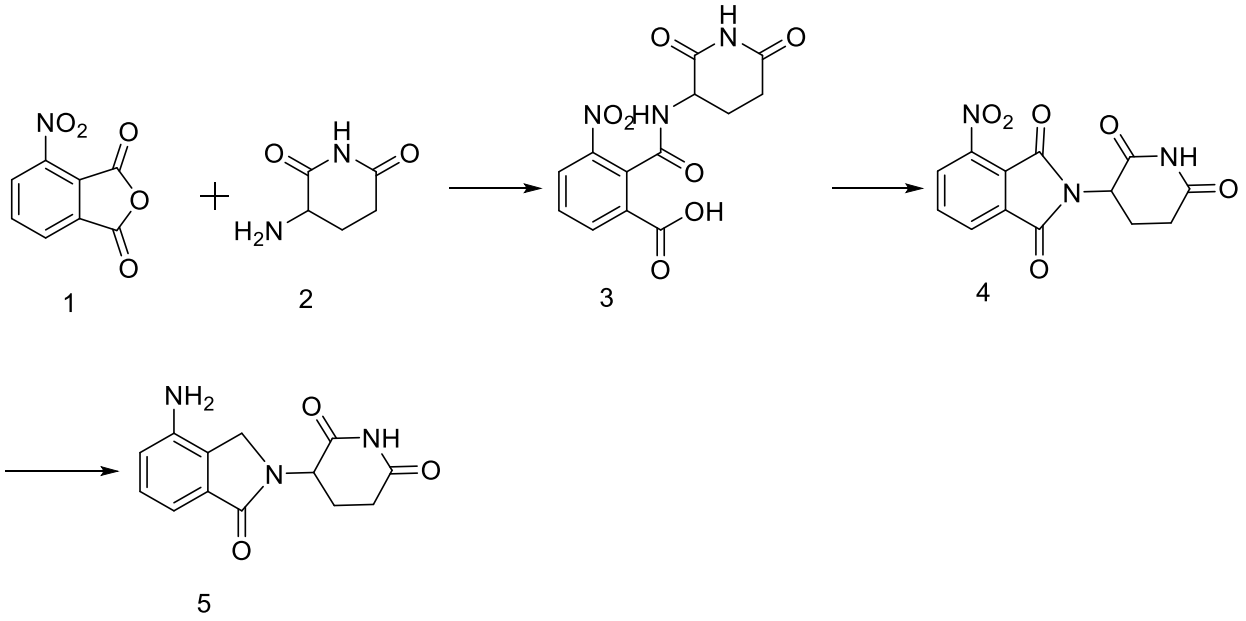


4 ; and the fifth compound has a structure of Formula 5



5 .

[0053] The synthesis route of the above method is summarized below in Reaction Scheme (I):



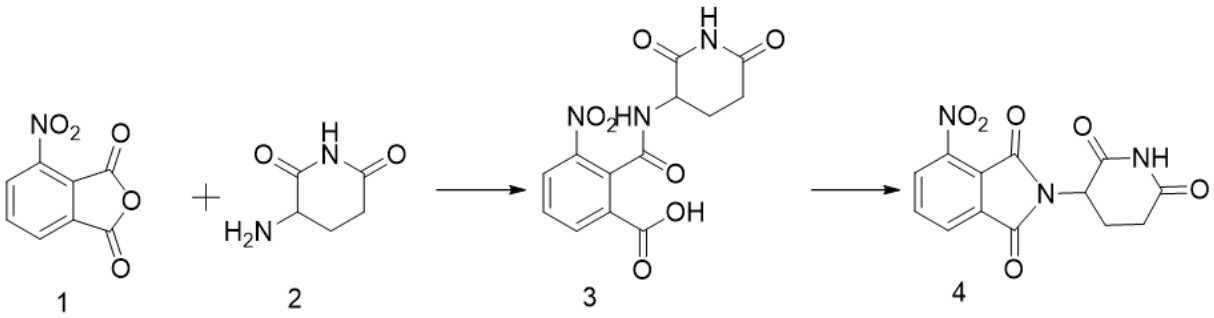
Reaction Scheme (I)

[0054] Clear to a skilled artisan in the technical field, the raw materials, reagents, or apparatuses employed in the embodiments described herein, unless otherwise specified, are readily available through standard commercial channels or can be procured using established methodologies known in the field.

[0055] Various aspects of the present invention are described in details below, according to various embodiments.

[0056] 1. Preparation of Intermediate 6,3-Dioxo-2-(2,6-Dioxopiperidin-3-yl)-5-Nitroisoindoline

[0057] Utilizing the synthesis pathway outlined in reaction scheme (II) presented below, we synthesize the intermediate compound, 6,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline (fourth compound, having a structure of Formula 4). This process involves starting with 3-nitrophthalic anhydride (first compound, having a structure of Formula 1) and 3-amino-2,6-piperidinedione (second compound, having a structure of Formula 2) to obtain a third compound having a structure of Formula 3. Clear to skilled artisan in the field, both the first compound and the second compound are readily accessible via standard commercial sources.



Reaction Scheme (II)

[0058] The present invention discloses three methods for preparing the intermediate compound (Formula 4), as described in Embodiments 1 – 3 below.

[0059] **Embodiment 1:**

[0060] In the procedure of Embodiment 1, 100 grams of the compound described by Formula 1, followed by 200 grams of toluene, and then 66.35 grams of the compound outlined in Formula 2, were added in sequence to a three-necked flask. This concoction was subjected to stirring under a protective blanket of nitrogen gas, ensuring the internal temperature of the mixture was carefully controlled to remain within the range of 25-30°C, a condition that was maintained steadfastly for a duration of four (4) hours. Subsequent to this initial reaction phase, an additional component, specifically 5 grams of polyphosphoric acid, was introduced into the mixture. This addition necessitated an elevation in the reaction's ambient temperature, which was then meticulously adjusted to fall between 45-50°C and was maintained at this heightened level for a further five (5) hours. Upon the completion of this stage, the mixture was allowed to cool down to a chilly 0-10°C, after which it underwent a filtration process. The resultant filter cake was not immediately processed; instead, it was subjected to a drying period under an air current

at 60°C, extending over 12 hours. This procedure yields a significant quantity of solid product, such as 150.95 grams, which achieves a yield of 95.91% alongside an HPLC purity of 96.4824%. To corroborate the identity and purity of this product, it was analyzed using both mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy, with the findings affirming an alignment with the anticipated characteristics for the intermediate compound specified as Formula 4. The analysis results are shown in FIG. 1 – FIG3, and the experimental data are summarized below:

MSm/z:{[M-H]-}302.29.

^{1}H NMR (400 MHz, DMSO) δ=11.18(s, 1H), 8.52-8.03(m, 3H), 5.22(dd,J=12.9,5.4,1H), 3.05-2.53(m, 3H), 2.09(dtd, J=12.8,5.2,2.2, 1H).

^{13}C NMR (101 MHz, DMSO) δ=173.17, 169.96, 165.64, 162.99, 144.90, 137.26, 133.48, 129.33, 127.76, 123.03, 49.91, 31.34, 22.20.

[0061] Embodiment 2:

[0062] Following a similar but distinct protocol to that described in Embodiment 1, Embodiment 2 illustrates another protocol to synthesizing the intermediate compound, 6,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline (Formula 4). In this procedure, 100 grams of the compound as defined in Formula 1 and 200 grams of toluene were introduced into a three-necked flask. This initial addition was followed by the introduction of 66.35 grams of the compound described in Formula 2. Under the protection of a nitrogen atmosphere to prevent any unwanted reactions, the contents were stirred to ensure a homogeneous mixture. The temperature was then carefully elevated to a range of 35-40°C, slightly higher than that in Embodiment 1, and maintained for a period of 3 hours, which is an hour less than the time allowed in the previous embodiment.

[0063] Upon completion of the reaction under these adjusted conditions, the mixture was allowed to cool down to ambient room temperature. This step was followed by the addition of 5 grams of polyphosphoric acid, a catalyst aimed at facilitating the subsequent reaction stage. The temperature of the mixture was then raised again, this time to a range of 55-60°C, slightly higher than in the previous step, and the reaction was allowed to proceed for 3 hours, thus ensuring the complete transformation of reactants into the desired intermediate product.

[0064] After the reaction, the mixture was cooled to a temperature range of 0-10°C to

solidify the products and facilitate their separation from the reaction medium. The mixture was then filtered, and the solid residue, or filter cake, was collected. This filter cake was subjected to drying under a flow of air at 60°C for 12 hours, a step to remove any residual solvents and maintain the stability of the product. This protocol resulted in the acquisition of 147.46 grams of a solid product (Formula 4), which corresponds to a yield of 93.91% and demonstrates an HPLC purity of 94.2843%.

[0065] The synthesized solid product was analysed to verify its composition and purity. The analytical techniques employed, including mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy, confirmed that the results were in concordance with the theoretical expectations for the intermediate compound (Formula 4).

[0066] **Embodiment 3:**

[0067] Embodiment 3 discloses another variant of the synthesis process for the intermediate compound, 6,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline (fourth compound, having a structure of Formula 4). Embodiment 4 further diversifies the experimental conditions used in the synthesis pathway and offers a comparison to Embodiments 1 and 2 to underline both the continuity and variations in methodology for preparing the fourth compound.

[0068] Initially, 100 grams of the first compound (3-nitrophthalic anhydride), along with 200 grams of toluene, are placed into a three-necked flask, consistent with the setup in Embodiments 1 and 2. To this setup, 66.35 grams of the second compound (3-amino-2,6-piperidinedione) are added. As in the previous embodiments, the mixture is stirred under a nitrogen atmosphere to maintain an inert environment, preventing other undesirable side reactions.

[0069] Diverging from Embodiment 1's temperature protocol but aligning more closely with Embodiment 2, the reaction temperature is elevated to the 45-50°C range immediately. However, unlike Embodiment 2, where the reaction duration at elevated temperature was set for 3 hours, in Embodiment 3, this duration is reduced to 2 hours.

[0070] After this period, a significant modification in the methodology is introduced: 10 grams of polyphosphoric acid, double the amount used in Embodiments 1 and 2, are added to the reaction mixture. This increase in catalyst concentration suggests an approach to enhancing the reaction's progress. The mixture is then maintained at 45-

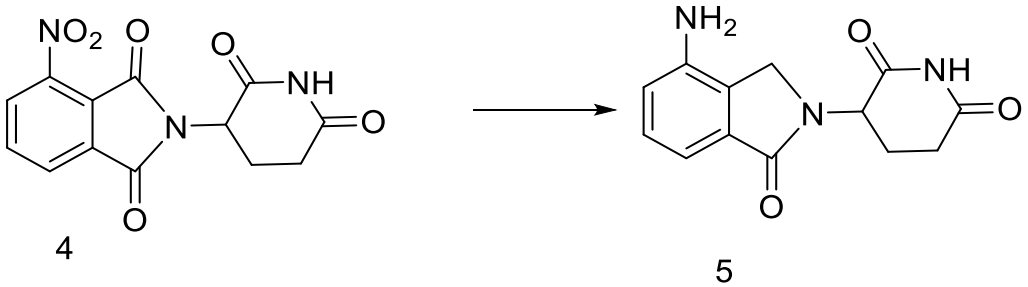
50°C, identical to the initial reaction condition, for another 2 hours.

[0071] Upon completion of the reaction, the process of cooling the mixture to 0-10°C, filtering, and drying the filter cake at 60°C for 12 hours follows the established protocol in Embodiments 1 and 2. This procedural consistency ensures that the drying process effectively removes all residual solvents, securing the stability and purity of the product. The outcome of Embodiment 3 is the acquisition of 147.76 grams of the solid product, demonstrating a yield of 94.10% and an HPLC purity of 97.4762%.

[0072] Among the methods described in the three embodiments, all achieve significant yield and purity, and accordingly can be implemented to prepare the fourth compound. Nevertheless, among the three, Embodiment 3 appears to achieve better results in terms of the purity of the final product, reaching 97.4762% HPLC purity, which is the highest among the three. This suggests that the adjustments made to the reaction conditions, specifically the increased amount of polyphosphoric acid and the optimized temperature and duration, could help enhance the reaction's selectivity and efficiency. In terms of yield, Embodiment 1 and Embodiment 3 are comparable, with Embodiment 1 having the highest yield at 95.91%. However, the slight difference in yield between Embodiment 1 and Embodiment 3 could offset by the notable improvement in purity in Embodiment 3.

[0073] **2. Preparation of Lenalidomide**

[0074] Utilizing the synthetic pathway delineated by reaction scheme (III) presented below, we advance to the preparation of lenalidomide (fifth compound, having a structure of Formula 5). This process employs the intermediate compound, identified as Formula 4, which was synthesized in any of the preceding Embodiments 1 – 3.



Reaction Scheme (III)

[0075] **Embodiment 4:**

[0076] Embodiment 4 discloses the synthesis of lenalidomide, employing the fourth compound as the starting intermediate.

[0077] In this procedure, 50 grams of the intermediate compound (Formula 4) is introduced into a 1L stainless steel high-pressure reactor. This is followed by the addition of 400 grams of acetic acid, serving as the solvent, and 20 grams of a 5% palladium on carbon catalyst. The high-pressure reactor is initially purged with nitrogen gas to displace any air, ensuring an inert atmosphere. This step is helpful for preventing unwanted oxidative reactions that could compromise the purity of the final product. Subsequently, hydrogen gas is introduced to replace the nitrogen, establishing a reductive environment necessary for the hydrogenation reaction to proceed.

[0078] The reaction mixture is stirred and the temperature is maintained at 25°C. Under these conditions, the reaction is allowed to proceed for 8 hours. It is required in this step to ensure complete hydrogenation without compromising the integrity of the sensitive functional groups present in the intermediate.

[0079] Upon completion of the reaction, the mixture is cooled to room temperature, marking the end of the hydrogenation process. The reactor's contents are then filtered to separate the solid product from the liquid phase. To further purify the product, 100 grams of water is added to the filtrate, stirred for 1 hour to precipitate any remaining impurities. The mixture is filtered again, and the collected solid, now significantly purified, is subjected to vacuum drying at 80°C for 12 hours. This drying step is implemented to remove any residual solvents, ensuring the stability and purity of lenalidomide.

[0080] The outcome of this procedure is the acquisition of 40.12 grams of lenalidomide, representing a yield of 93.87%. The product's purity, assessed via HPLC, is determined to be 98.2413%. This high level of purity underscores the efficacy of the synthesis and purification steps outlined in this embodiment.

[0081] Mass spectrometry and Nuclear Magnetic Resonance (NMR) spectroscopy are employed to confirm the structure of the synthesized lenalidomide (see FIG. 4 – FIG. 6), and the experimental data are summarized below:

MSm/z:{[M-H]-}258.39.

^{1}H NMR (400 MHz, DMSO)δ=11.01(s,1H), 7.25-6.77(m, 3H), 5.43(s,2H),

5.12(dd,J=13.3, 5.1, 1H), 4.18(dd,J=39.1,17.0,2H), 3.05-2.55(m,2H), 2.45-1.91(m, 2H).

^{13}C NMR (101 MHz, DMSO) δ=173.41, 171.73, 169.42, 144.08, 132.73, 129.34, 126.09, 116.94, 110.96, 52.01, 46.03, 31.72, 23.24.

[0082] These analytical techniques provide definitive evidence of the product's identity, matching the expected structure of lenalidomide and validating the success of the synthesis process.

[0083] **Embodiment 5:**

[0084] Embodiment 5 presents an alternative approach within the framework of synthesizing lenalidomide, employing subtle yet strategic modifications to the catalyst concentration and adjustment of reaction parameters. This variation emphasizes the robustness and flexibility of the synthetic process that utilizes the intermediate compound from Embodiments 1-3, illustrating the method's capability to maintain high standards of yield and purity under varied conditions.

[0085] In this procedure, 50 grams of the intermediate compound (the fourth compound) is introduced into a 1L stainless steel high-pressure reactor. This is accompanied by the addition of 400 grams of acetic acid, which serves as the reaction medium. A notable modification in this embodiment is the utilization of a 10% palladium on carbon catalyst at a quantity of 10 grams, an adjustment aimed at exploring the effect of a higher catalyst concentration on the hydrogenation process.

[0086] The reactor atmosphere is replaced with nitrogen gas to create an inert environment for preventing any unwanted side reactions. Following this, hydrogen gas is introduced to replace the nitrogen, setting the stage for the hydrogenation reaction to occur under reductive conditions.

[0087] Adjusting the reaction parameters, the temperature is set at 40°C, offering a slight increase from Embodiment 4, with the anticipation that this would contribute to the efficiency of the reaction. The mixture is then stirred at this temperature for 3 hours, a reduction in reaction time compared to Embodiment 4, predicated on the enhanced catalytic activity offered by the increased palladium concentration.

[0088] After the reaction is concluded, the mixture is cooled to room temperature and

then filtered to isolate the solid product from the reaction medium. To further purify this product, 100 grams of water is added to the filtrate, stirred for an hour to facilitate the precipitation of any remaining impurities. Following filtration, the solid product is dried under vacuum at 80°C for 12 hours to remove any residual moisture or solvent.

[0089] This adaptation yields 39.82 grams of lenalidomide, marking a yield of 93.17%. The product's purity, as evaluated through High-Performance Liquid Chromatography (HPLC), registers at 97.3243%. Such results affirm the effectiveness of this synthesis route, with mass spectrometry and Nuclear Magnetic Resonance (NMR) spectroscopy confirming the product's identity aligns with the anticipated structure of lenalidomide (compound 5).

[0090] **Embodiment 6:**

[0091] Embodiment 6 further illustrates the adaptability and robustness of the methodology for synthesizing lenalidomide, marking another variation in the sequence of experiments designed to explore the effect of minor adjustments on the overall synthesis outcome. This embodiment leverages the intermediate compound, Formula 4, synthesized from any of the previously detailed Embodiments 1-3, to produce lenalidomide, emphasizing the process's consistency in yielding a high-quality pharmaceutical compound.

[0092] In this procedure, a consistent quantity of 50 grams of the intermediate compound (the fourth compound) is utilized, introduced into a 1L stainless steel high-pressure reactor, similar to the setups in Embodiments 4 and 5. The solvent remains unchanged, with 400 grams of acetic acid used to dissolve the intermediate, preparing it for the step of hydrogenation. The catalyst used in this embodiment is also 10% palladium on carbon, maintaining the 10-gram quantity seen in Embodiment 5. This consistency in catalyst selection and quantity aims to explore the effects of temperature variations on the reaction's efficiency and the final product's purity and yield.

[0093] The preparation for the reaction follows the established protocol: purging the reactor with nitrogen gas to create an inert atmosphere, thereby preventing any unwanted oxidative reactions, followed by introducing hydrogen gas to establish the reductive conditions necessary for hydrogenation.

[0094] The adjustment in Embodiment 6 lies in the reaction temperature, set at 50°C,

and the reaction duration, reduced to 2 hours. These modifications are intended to test the hypothesis that higher temperatures and shorter reaction times might further optimize the reaction efficiency without compromising the final product's quality.

[0095] Following the completion of the hydrogenation reaction, the reactor is cooled to room temperature. The contents are then filtered to separate the solid product from the liquid phase. To enhance the purity of the lenalidomide produced, 100 grams of water is added to the filtrate, stirred for an hour to facilitate the precipitation of impurities. This solution is filtered, and the resultant solid is dried under vacuum at 80°C for 12 hours, a step to ensure the removal of all residual solvents.

[0096] This optimized set of conditions yields 39.76 grams of lenalidomide, resulting in a yield of 93.03%. The purity, as assessed by High-Performance Liquid Chromatography (HPLC), reaches 97.1624%, demonstrating the effectiveness of this synthesis approach. The structural integrity and purity of the lenalidomide produced are confirmed through analytical techniques such as mass spectrometry and Nuclear Magnetic Resonance (NMR) spectroscopy, affirming the compound's identity aligns with the anticipated structure of compound 5.

[0097] Embodiment 6 not only underscores the flexibility of the synthesis process in accommodating various reaction conditions but also reaffirms the methodology's capability to consistently produce lenalidomide with high purity and substantial yield. Embodiment 6, together with Embodiments 4 and 5, collectively demonstrates that even with adjustments in catalyst concentration, temperature, and duration, the synthesis method remains effective and reliable, offering multiple avenues to achieve the desired outcome of high-quality lenalidomide.

[0098] Moreover, as demonstrated in Embodiments 4 to 6, the methodology of this invention could incorporate palladium on carbon hydrogenation in conjunction with acetic acid as the solvent. This approach efficiently meets the requirements for nitro group reduction while the acidic milieu from acetic acid aids in the selective reduction of amide carbonyl groups at optimal temperatures and hydrogen pressures, leading to the targeted product. Consequently, this method is advantageous for scaling up to large, industrial-scale production, ensuring the synthesis of lenalidomide remains both efficient and effective.

[0099] Technical Advantages of the Present Invention

[0100] Distinct from conventional approaches, this invention leverages cost-effective and widely accessible starting materials, specifically 3-nitrophthalic anhydride (the first compound) and 3-amino-2,6-piperidinedione (the second compound), to synthesize lenalidomide (the fifth compound) via an efficient three-step reaction process. This innovative method is characterized by a streamlined number of steps, employing relatively gentle reaction conditions, straightforward operations, and eliminating the need for specialized equipment. Initially, the method focuses on synthesizing an intermediate, 6,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline (the fourth compound), utilizing a one-pot approach, subsequently followed by a reduction step using palladium on carbon to derive lenalidomide. The process yields the intermediate compound (the fourth compound) with a yield exceeding 93% and a purity surpassing 94%, while the final lenalidomide product (the fifth compound) reaches yields above 93% and a purity above 97%, thereby achieving superior yield and purity metrics throughout the invention's stages.

[0101] When juxtaposed with conventional methods, the lenalidomide synthesis protocol proposed by this invention demonstrates several significant advantages:

[0102] Uniqueness of Synthesis Route: The invention introduces a synthesis pathway previously unreported in scientific literature, achieving impressive yields above 93% and purities exceeding 97%, marking a significant advancement in the field.

Mild Reaction Conditions: The method operates under gentle conditions, eliminating the need for complex machinery or the use of dangerous, highly toxic chemicals and specific reagents, thereby promoting operational safety and eco-friendliness. For instance, as detailed previously, synthesizing the intermediate compound (the fourth compound) in this invention uses a two-step one-pot approach within milder reaction environments. Specifically, the first compound combines with the second to yield the third compound, with the process occurring at a modest temperature range of 25 to 50°C and requiring only 2 to 4 hours. Subsequently, the third compound is cyclized with polyphosphoric acid as a catalyst to form the intermediate compound (the fourth compound), maintaining temperatures between 45 to 60°C over a period of 2 to 5 hours. Clear to skilled artisan in the field, such conditions are notably mild and straightforward to control. Consequently, this synthesis pathway of the present invention is more conducive to seamless execution,

achieving high product yields effectively. Therefore, this method aligns well with industrial production norms, promising broader and more efficient adoption.

[0103] Simplified Purification: Unlike conventional methods that often involve challenging separations, the intermediates in this process are effortlessly isolated through simple filtration and drying techniques, obviating the need for laborious purification methods like column chromatography.

[0104] Accessibility of Materials: The starting materials and reagents required for this synthesis are readily available commercially, contributing to a reduction in production costs and facilitating the scalability of the method.

[0105] Operational Simplicity and Safety: With its ease of operation, abbreviated production cycle, and elevated safety profile, this method is eminently suitable for scaling up to meet industrial demands for lenalidomide production.

[0106] These technical advantages underscore the present invention's capacity to provide a more efficient, safer, and cost-effective alternative for the production of lenalidomide, thereby holding significant promise for large-scale industrial application and contributing to broader accessibility of this important therapeutic agent.

[0107] It should be further appreciated by the person skilled in the art that variations and combinations of features described above, not being alternatives or substitutes, may be combined to form yet further embodiments falling within the intended scope of the invention.

As would be understood by a person skilled in the art, each embodiment, may be used in combination with other embodiment or several embodiments.

Claims

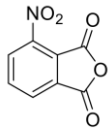
Claim 1. A method for producing a chemical compound, comprising the following steps of:

S101 reacting a first compound with a second compound in an amide formation reaction to obtain a third compound;

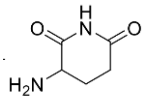
S102 undergoing a condensation reaction with the third compound to obtain a fourth compound;

S103 undergoing a reduction reaction with the fourth compound to obtain a fifth compound;

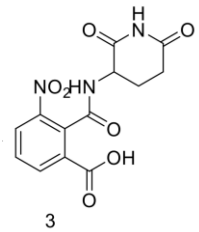
wherein: the first compound has a structure of Formula 1



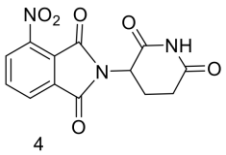
1 ; the second compound has a structure of Formula 2



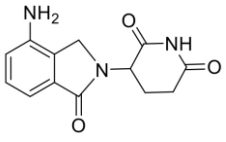
2 ; the third compound has a structure of Formula 3



3 ; the fourth compound has a structure of Formula 4



4 ; and the fifth compound has a structure of Formula 5



5 .

Claim 2. The method according to the Claim 1, wherein the first compound is dissolved in a solvent, then the second compound is added, stirred, heated, and reacted at a temperature of 25 to 50 °C for 2 – 4 hours.

Claim 3. The method according to Claim 2, wherein the solvent is selected from one or more of toluene, ethylbenzene, and chloroform.

Claim 4. The method according to Claim 2 or Claim 3, wherein the molar ratio of the first compound to the second compound is 1: (1 to 1.1), and the mass ratio of the first compound to the solvent is 1: (2 to 5).

Claim 5. The method according to Claim 1, wherein a first acid is added to a first reaction mixture obtained after the step of S101, stirred, heated, and the third compound is reacted at a temperature of 45 to 60°C for 2-5 hours.

Claim 6. The method according to Claim 5, wherein the first acid is polyphosphoric acid.

Claim 7. The method according to Claim 5 or Claim 6, wherein the weight ratio of the first acid to the first compound is 1: (10 to 20).

Claim 8. The method according to anyone of the preceding claims, wherein a second reaction mixture obtained after the step of S102 is cooled down to a temperature of 0-10°C.

Claim 9. The method according to Claim 8, wherein the second reaction mixture is filtered to obtain a first filter cake, which is further dried to yield the fourth compound.

Claim 10. The method according to anyone of the preceding claims, wherein the fourth compound is placed in a reactor with a catalyst and a second acid, the air in the reactor is replaced with an inert gas, then with a reducing gas, and heated to maintain the reactor at a temperature of 25 to 50°C for 2-8 hours.

Claim 11. The method according to Claim 10, wherein the catalyst is a palladium-on-carbon catalyst.

Claim 12. The method according to Claim 11, wherein the palladium-on-carbon catalyst contains 5 to 10% by weight of palladium.

Claim 13. The method according to Claim 11, wherein the mass ratio of the fourth compound to the catalyst is 1: (0.2 to 0.4).

Claim 14. The method according to Claim 10, wherein the second acid is acetic acid.

Claim 15. The method according to Claim 14, wherein the mass ratio of the fourth compound to the second acid is 1: (8 to 10).

Claim 16. The method according to Claim 10, wherein the inert gas is nitrogen.

Claim 17. The method according to Claim 10, wherein the reducing gas is hydrogen.

Claim 18. The method according to Claim 17, wherein the pressure of the reducing gas is 0.2-1MPa.

Claim 19. The method according to Claim 10, wherein the reactor is a high-pressure reactor.

Claim 20. The method according to anyone of Claims 10 – 19, wherein a third reaction mixture obtained after the step of S103 is first stirred with water, and then filtered to obtain a second filter cake, which is further dried to yield the fifth compound.