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(54) Title: ANHYDROUS BIORENEWABLE SOLVENTS

(57) Abstract: Anhydrous BioRenewable solvents y-valerolactone (GVL) and dimethyl isosorbide (DMI) and methods of preparing. The methods of preparing stable anhydrous GVL or DMI include the steps of (a) providing: an inert atmosphere, GVL or DMI having water content greater than 50 ppm, and dried molecular sieves; (b) contacting the GVL or DMI with the dried molecular sieves in the inert atmosphere for a time sufficient to reduce the water content of the GVL or DMI to less than 50 ppm, (c) transferring the dried GVL or DMI to a sealable container and (d) sealing the container, wherein the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least one year. The anhydrous GVL and DMI solvents are useful in chemical synthesis, such as peptide synthesis and organometallic reactions, in which other BioRenewable solvents cannot be satisfactorily used due to water content.

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ANHYDROUS BIORENEWABLE SOLVENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Appl. No. 63/612,625, filed December 20, 2023, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] The current landscape of chemical solvents, as dictated by the European Union Chemicals Strategy for Sustainability and the criteria developed by the European Chemicals Agency (ECHA), is signaling a shift away from toxic solvents such as N-methylpyrrolidone (NMP) and dimethylformamide (DMF). Despite their high toxicity, the physical and chemical properties of NMP and DMF make them highly versatile solvents that are used in a wide variety of applications in such diverse fields as pharmaceutical manufacture, pesticide production, manufacture of adhesives and synthetic fibers, and battery manufacturing.

[0003] Although different, less toxic solvents, and particularly BioRenewable solvents are being evaluated to meet this shift, many of the currently proposed solutions are inadequate for many applications. For example, many chemical reactions, including peptide synthesis and organometallic reactions, both important in pharmaceutical synthesis, require anhydrous solvents. Commercially available BioRenewable solvents, such as γ-valerolactone (GVL) and dimethyl isosorbide (DMI), often have water contents of 2000 ppm or higher, rendering them unsuitable for such applications.

[0004] One solution to the need for anhydrous solvents is to dry the solvent just prior to use. However, drying solvents requires specialized equipment, such as a glove box with nitrogen purge, which many labs do not have available. A drying step also reduces lab efficiency due to

the time necessary to prepare the anhydrous solvent and potentially the need to re-dry the solvent before the next use.

[0005] A need exists for more sustainable solvents that are useful in diverse chemical reactions without the environmental and health drawbacks of conventional solvents. More particularly, a need exists for commercially available, anhydrous, sustainable solvents, such as anhydrous GVL and anhydrous DMI.

SUMMARY

[0006] Provided are methods for preparing stable anhydrous γ-valerolactone (GVL) or dimethyl isosorbide (DMI) including the steps of (a) providing an inert atmosphere, GVL or DMI with a water content greater than 50 ppm, and dried molecular sieves; (b) contacting the GVL or DMI with the dried molecular sieves in the inert atmosphere for a time sufficient to reduce the water content of the GVL or DMI to less than 50 ppm, (c) transferring the dried GVL or DMI to a sealable container and (d) sealing the container, wherein the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least one year.

[0007] In some embodiments, the GVL or DMI of step (a) has a water content of greater than 1000 ppm before drying; in other embodiments, the GVL or DMI of step (a) has a water content of greater than 1500 ppm before drying; and in still other embodiments, the GVL or DMI of (a) has a water content of greater than 2000 ppm before drying.

[0008] The dried molecular sieves may be selected from zeolites, active carbons and combinations thereof. In some embodiments, the dried molecular sieves are selected from molecular sieves with pores in the range from 3 Å to 5 Å.

[0009] In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 2 hours to about 6 hours. In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours to about 5 hours. In some embodiments,

the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours.

[0010] The dried GVL or DMI is transferred to a sealable container, in some embodiments the sealed container is a drum, in other embodiments, it is a bottle; in still other embodiments, the sealable container is a septum bottles.

[0011] In some embodiments, the water content of the dried GVL or DMI in the sealable container remains under 50 ppm for at least one year. In other embodiments, the water content of the dried GVL or DMI in the sealable container remains under 50 ppm for at least two years.

[0012] Further provided are solvents comprising γ-valerolactone or dimethyl isosorbide having a water content of less than 50 ppm.

DETAILED DESCRIPTION

[0013] Provided herein are methods for preparing stable anhydrous versions of GVL (γ-Valerolactone) and DMI (Dimethyl Isosorbide), serving as sustainable alternatives to traditional toxic solvents like NMP and DMF. The anhydrous solvents provided herein, distinctly characterized by a water content of less than 50 ppm, may be derived from sustainable and renewable sources. Especially well-suited for peptide synthesis, organometallic reactions, and a wide spectrum of chemical operations, the solvents' introduction aligns seamlessly with the directives of the EU Chemicals Strategy for Sustainability. Beyond their eco-friendly attributes, GVL and DMI promise enhanced safety in handling and operations, marking a transformative shift in solvent technology.

[0014] The anhydrous GVL and DMI prepared by the methods described herein have many advantages over both conventional solvents, such as NMP and DMF, and conventional non-anhydrous versions of GVL and DMI. Such advantages include their anhydrous nature, provided using

the methods described herein, and greener properties than conventional, petroleum-based solvents.

[0015] Both GVL and DMI are of BioRenewable origin, being derived from renewable resources, significantly reducing carbon footprint and reliance on petroleum-based solvents. GVL and DMI are safer alternatives to NMP and DMF, reducing the risks associated with handling, storage and disposal. Anhydrous GVL and DMI are well-suited to many applications across multiple chemical reactions, and in particular, peptide synthesis, organometallic reactions, and both organic and inorganic chemistry.

[0016] Additionally, anhydrous GVL and DMI provide alignment with Regulatory Directions. Use of these solvents complies with the direction set by the EU Chemicals Strategy for Sustainability, offering an immediate solution for industries looking for sustainable alternatives.

[0017] Commercially available sources of GVL and DMI have water content levels around 2000 parts per million (ppm) making them unsuitable for applications that are water sensitive and require anhydrous solvents, such as peptide synthesis, organometallic reactions, and so forth, without a time-consuming drying step requiring specialized equipment.

[0018] The present methods utilize a dry atmosphere, also referred to as an inert atmosphere, such as a glove box with a flow of dry, non-reactive gas, such as nitrogen, to prepare the anhydrous BioRenewable solvents. Dried molecular sieves are placed in a pre-dried vessel in the glove box and the GVL or DMI is introduced to the molecular sieves and remain in contact with the molecular sieves, with flow of the dry, non-reactive gas, until the water contact of the solvent is less than 50 ppm. The dried solvent is then placed in a sealable container, such as a drum, bottle, or septum bottle, and sealed, under the dry, non-reactive gas until use. The dried solvent remains dry in the sealed container for at least one year, and preferably, for at least two years.

[0019] As used herein, the term “anhydrous” with respect to the solvent, means having a water content of 50 ppm or less. Water content can be measured using known methods such as Karl Fischer titration or gas chromatography using a Watercol™ column (available from MilliporeSigma).

[0020] The term “BioRenewable solvent” refers to solvents sourced from renewable, sustainable biobased materials, significantly lowering their environmental impact. γ-valerolactone (GVL) and dimethyl isosorbide (DMI) are exemplary BioRenewable solvents that can be dried to anhydrous using the methods described herein.

[0021] The term “dry, non-reactive gas,” otherwise referred to as “inert gas,” as used herein, refers to a gas that does not readily react with its surroundings, and in particular, with the solvents used herein. Exemplary dry, non-reactive gases, i.e., inert gases, include, e.g., N_2, He, Ar and so forth. In a preferred embodiment, the dry, non-reactive gas is N_2. Flow of the dry, non-reactive gas through a glove box provides an inert atmosphere in which methods provided herein can be employed.

[0022] “Molecular sieves” refers to materials with pores of uniform size. Microporous molecular sieves, i.e., having pore sizes of less than 20 Å, preferably in the range from 3 Å to 5 Å are preferred for the methods described herein. Exemplary microporous molecular sieves include, e.g., zeolites, i.e., aluminosilicate minerals and active carbons. “Dried molecular sieves,” used in the methods provided herein may be purchased pre-dried, or may be dried using conventional methods.

[0023] “Sealable containers” useful to store the anhydrous solvents once dried include, but are not limited to drums, bottles, and septum bottles. Larger containers may be used to store anhydrous solvents for later repackaging into smaller containers, preferably under the flow of a dry, non-reactive gas, such as N_2.

[0024] When the anhydrous solvent is stored in septum bottles, the solvent typically stays anhydrous for at least 5 to 6 weeks once

punctured. The increased water content in such punctured septum bottle depends on factors such as the number of punctures, gauge of needle used, and so forth.

[0025] The term “stable” when used with respect to the anhydrous solvents provided herein means that the anhydrous solvent maintains a water content of less than 50 ppm for up to one year, and preferably, two years in the sealed container.

[0026] The methods for preparing stable anhydrous γ-valerolactone (GVL) or dimethyl isosorbide (DMI) including the steps of (a) providing: (i) an inert atmosphere, preferably by flushing a dry, non-reactive gas such as N_2 through a glove box, (ii) GVL or DMI with a water content greater than 50 ppm, and (iii) dried molecular sieves; (b) contacting the GVL or DMI with the dried molecular sieves in the inert atmosphere for a time sufficient to reduce the water content of the GVL or DMI to less than 50 ppm, (c) transferring the dried GVL or DMI to a sealable container and (d) sealing the container, wherein the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least one year, and preferably remains under 50 ppm for at least 2 years.

[0027] Commercially available GVL and DMI have significant water content, typically significantly higher than 1000 ppm, and typically around 2000 ppm. The methods described herein are useful for GVL or DMI having a water content over 50 ppm, though the methods is useful for much higher water concentrations as well. In some embodiments, of step (a) has a water content of greater than 1000 ppm before drying; in other embodiments, the GVL or DMI of step (a) has a water content of greater than 1500 ppm before drying; and in still other embodiments, the GVL or DMI of (a) has a water content of greater than 2000 ppm before drying, and in still other embodiments, the GVL or DMI of (a) has a water content of greater than 3000 ppm before drying.

[0028] The dried molecular sieves may be selected from zeolites, i.e., crystalline aluminosilicate minerals, active carbons and combinations

thereof. In some embodiments, the dried molecular sieves are selected from molecular sieves with pores in the range from 2 Å to 10 Å. It should be understood that molecular sieves have uniform pore sizes, rather than ranges of pore size, so molecular sieves within the above range would have a pore size of 2 Å, 3 Å, 4 Å, 5 Å, 6 Å, 7 Å, 8 Å, 9 Å or 10 Å. In some preferred embodiments, the molecular sieves have a pore size of 3 Å, 4 Å or 5 Å. Combinations of molecular sieves with different pore sizes may also be used, e.g., a combination of 4 Å and 5 Å may be used in the methods described herein. Other combinations may also be used.

[0029] In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 2 hours to about 24 hours. In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours to about 6 hours. In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours to about 5 hours. In some embodiments, the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours. The specific contact time for a particular batch of solvent may be determined by removing small samples of solvent during the drying process and testing the water content, e.g., by Karl Fischer titration. The drying process may be stopped once the water content is less than 50 ppm.

[0030] The dried GVL or DMI is transferred to a sealable container, in some embodiments the sealed container is a drum, in other embodiments, it is a bottle; in still other embodiments, the sealable container is a septum bottles. The anhydrous solvent may be stored in the sealable container for an extended period. In other embodiments, the anhydrous solvent may be stored in a first sealable container, then later transferred to a different sealable container at a later time. The container-to-container transfer is preferably done in a dry atmosphere to maintain the low water content of the solvent.

[0031] In some embodiments, the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least one year. In

some embodiments, the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least two years.

[0032] Further provided are γ-valerolactone and dimethyl isosorbide having a water content of less than 50 ppm.

[0033] An exemplary use for the anhydrous solvents described herein is peptide synthesis, which is a critical chemical process that heavily relies on solvents. Traditionally, peptide synthesis employs the use of solvents like NMP and DMF, both of which have environmental and health concerns. With the introduction of the anhydrous versions of GVL and DMI, a chemist can opt for GVL or DMI as the solvent of choice, ensuring the reactions are performed under anhydrous conditions. Given the ultra-low water content, these solvents minimize the risk of unwanted side reactions, especially in sensitive peptide couplings. Furthermore, since GVL and DMI are safer to handle, there's a reduced risk during handling, transfer, and post-reaction cleanup. After the synthesis, GVL or DMI can be removed through standard procedures, but with a more environmentally conscious disposal method due to their greener nature.

[0034] EXAMPLES

[0035] Example 1. Dimethyl Isosorbide. This experiment employed both 3 Å and 4 Å molecular sieves. The molecular sieves were carefully placed into a pre-dried glass vessel. Next, 100mL of either DMI was introduced to the sieves. Inside a glove bag continuously flushed with N_2, the solvent remained in contact with the molecular sieves for approximately 4 hours. Post this duration, roughly 10 mL of each solvent was decanted into an amber QC vial equipped with a septum. Karl-Fischer analysis confirmed a water content of less than 50 ppm.

[0036] Example 2. γ-Valerolactone. The same procedure was carried out substituting GVL for DMI. Karl-Fischer analysis confirmed a water content of less than 50 ppm.

[0037] Example 3. Bulk γ-Valerolactone. Bulk GVL was transferred from carboys into a 30 gallon stainless steel drum through a column of 5 Å molecular sieves using a pump and stainless steel filter. The GVL was recirculated for 5 hours, with samples removed and analyzed by Karl Fischer (KF) and gas chromatography (GC) at regular intervals during the drying process. The results are summarized in the table below.

γ-Valerolactone		
Time (hours)	KF (ppm)	GC (%)
0 (starting material)	1802.3	99.8714
0 (after transfer)	852.6	99.8766
1	297.1	99.8313
2	137.5	99.8325
3	85.8	99.8797
4	58	99.8782
5	46	99.8846

The process progressed well with no observed issues. By the fifth hour, the water content of the GVL was less than 50 ppm. GC values were not affected by the molecular sieve treatment.

[0038] The examples provided herein are illustrative in nature and are not meant to limit the scope of the invention as defined by the claims.

The invention claimed is:

1. A method for preparing stable anhydrous γ-valerolactone (GVL) or dimethyl isosorbide (DMI) comprising the steps

(a) providing

an inert atmosphere,

GVL or DMI with a water content greater than 50 ppm, and

dried molecular sieves,

(b) contacting the GVL or DMI with the dried molecular sieves in the inert atmosphere for a time sufficient to reduce the water content of the GVL or DMI to less than 50 ppm,

(c) transferring the dried GVL or DMI to a sealable container and

(d) sealing the container,

wherein the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least one year.

2. The method of claim 1 wherein the GVL or DMI of step (a) has a water content of greater than 1000 ppm before drying.

3. The method of claim 2 wherein the GVL or DMI of step (a) has a water content of greater than 1500 ppm before drying.

4. The method of claim 3 wherein the GVL or DMI of (a) has a water content of greater than 2000 ppm before drying.

5. The method of any of claims 1 to 4 wherein the dried molecular sieves are selected from zeolites, active carbons and combinations thereof.

6. The method of any of claims 1 to 5 wherein the dried molecular sieves are selected from molecular sieves with a pore size in the range from 3 Å to 5 Å.

7. The method of claim 1 wherein the GVL of (a) is contacted with molecular sieve 5 Å in (b).

8. The method of claim 1 wherein the DMI of (a) is contacted with molecular sieve 3 Å in (b).

9. The method of any of claims 1 to 8 wherein the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 2 to about 6 hours.

10. The method of claim 9 wherein the GVL or DMI of (a) is contacted with the molecular sieve in (b) for about 4 hours to about 5 hours.

11. The method of any of claims 1 to 10 wherein the sealable container is selected from the group consisting of drums, bottles, and septum bottles.

12. The method of any of claims 1 to 11 wherein the water content of the dried GVL or DMI in the sealed container remains under 50 ppm for at least two years.

13. An anhydrous solvent comprising γ-valerolactone, wherein the anhydrous solvent has a water content of less than 50 ppm.

14. The anhydrous solvent of claim 13, wherein the anhydrous solvent is capable of maintaining a water content of less than 50 ppm for at least one year when stored in a sealable container.

15. The anhydrous solvent of claim 14, wherein the sealable container is selected from the group consisting of a drum, a bottle and a septum bottle.

16. The anhydrous solvent of claim 15, wherein the anhydrous solvent is capable of maintaining a water content of less than 50 ppm for at least two years.

17. An anhydrous solvent comprising dimethyl isosorbide, wherein the anhydrous solvent has a water content of less than 50 ppm.

18. The anhydrous solvent of claim 17, wherein the anhydrous solvent is capable of maintaining a water content of less than 50 ppm for at least one year when stored in a sealable container.

19. The anhydrous solvent of claim 18, wherein the sealable container is selected from the group consisting of a drum, a bottle and a septum bottle.

20. The anhydrous solvent of claim 19, wherein the anhydrous solvent is capable of maintaining a water content of less than 50 ppm for at least two years.