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(21) International Application Number: PCT/GB00/01793 (22) International Filing Date: 11 May 2000 (11.05.00) (30) Priority Data: 99303812.4 17 May 1999 (17.05.99) EP (71) Applicant (for all designated States except US): QUEST INTERNATIONAL B.V. [NL/NL]; Huizerstraatweg 28, NL-1411 GP Naarden (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): DAVEY, Paul, Nicholas [GB/GB]; "Bleak House", Ulley Road, Kennington, Ashford, Kent TN24 9HU (GB). TSE, Chi-Lam [-/GB]; 5 The Mews, Bath Road, South Willesborough, Ashford, Kent TN24 0JB (GB). (74) Agent: KEITH W NASH & CO.; 90-92 Regent Street, Cambridge CB2 1DP (GB).	(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: REACTIONS USING LEWIS ACIDS		
(57) Abstract <p>In a method of performing a chemical reaction using a Lewis acid, after the reaction is complete, the Lewis acid is extracted from the reaction product in the form of an aqueous solution, followed by drying of the aqueous solution of the Lewis acid. The dried Lewis acid can be reused in a further similar reaction. The method can be repeated several times, using the same batch of Lewis acid, without the activity and specificity of the Lewis acid being significantly affected. The invention has been used to good effect in the ene reaction of isopulegol from citronellal, the Diels-Alder reaction of myrcene and 3-methyl-3-penten-2-one and the rearrangement reaction of α-pinene oxide to campholenic aldehyde using zinc bromide as a Lewis acid catalyst. The invention can thus provide an environmentally acceptable and efficient method for using Lewis acids in industrial processes.</p>		

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Title: Reactions using Lewis acids

Field of the Invention

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This invention relates to reactions using Lewis acids and concerns a method of performing a chemical reaction involving a Lewis acid, and products resulting from such reaction.

Background to the Invention

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Lewis acids in the form of metal salts, eg zinc bromide, aluminium chloride etc, are widely used in organic reactions, often on a manufacturing scale, with the Lewis acid commonly functioning as a catalyst, eg in ene-reactions, Diels-Alder reactions, rearrangement reactions and Friedel-Crafts reactions.

15

However, there are several disadvantages associated with their use.

Practical difficulties may arise when using Lewis acids in that the Lewis acids may be difficult to recover and reuse.

20

Some Lewis acids may also present serious environmental issues on disposal. For example, the Lewis acid, zinc bromide, has been reported to be a serious water pollutant as it is capable of destroying sewage treatment bacteria, thus, harming the biochemical phase of sewage treatment (Holderich, W.F. & Heinz, D. in *Catalysis*, edited by Spivey, J.J., The Royal Society of Chemistry, London, 1999, pp148-182).

25

The present invention is based on a novel approach to reactions using a Lewis acid that can overcome such practical difficulties.

Summary of the Invention

In its broadest aspect the present invention provides a method of performing a chemical
5 reaction involving a Lewis acid, comprising carrying out the reaction involving the Lewis
acid; extracting from the reaction products the Lewis acid in the form of an aqueous
solution; and drying the aqueous solution of the Lewis acid.

The dried Lewis acid can be reused as a catalyst in a further reaction. It is found that the
10 method of the invention can be repeated several times, using the same batch of Lewis acid,
without the activity and selectivity of the Lewis acid being significantly affected. The
invention can therefore overcome the problems noted above, enabling quantitative recovery
of a Lewis acid and hence enabling repeated reuse of the Lewis acid with consequent
reduction in cost of raw materials and avoidance of the cost of disposal of used Lewis acid.

15 The Lewis acid may be, for example, zinc bromide, zinc chloride, zinc iodide, other metal
salts, or mixtures thereof. Preferably, the Lewis acid is zinc bromide.

The invention is applicable to a range of chemical reactions using Lewis acids, including
20 ene-reactions, Diels-Alder reactions, rearrangement reactions and Friedel-Crafts reactions.

The desired chemical reaction may be carried out in a suitable organic solvent, such as
cyclohexane, benzene, xylene, toluene or mixtures thereof. The currently preferred solvent
is toluene as it gives good reaction rates and selectivity. Toluene is also a cheap, safe
25 solvent and so is well suited to industrial use.

The Lewis acid is conveniently extracted from the reaction products by adding water,
preferably deionised water, and separating the aqueous fraction typically from an organic
solvent fraction containing the reaction products.

30 Drying of the aqueous solution of the Lewis acid may be performed using techniques
including vacuum dehydration; chemical drying eg with dried molecular sieve material,

anhydrous magnesium sulphate or sodium sulphate; physical drying techniques, for instance pervaporisation with selective membrane technology; azeotropic distillation; or a mixture of such techniques. Preferably, the drying of the aqueous solution of the Lewis acid is performed by azeotropic distillation.

5

Azeotropic distillation may be performed using any suitable solvent that gives an azeotrope with water, is inert to the Lewis acid, has a low solubility in water and preferably is suitable for the reaction. Suitable solvents include, but are not limited to, cyclohexane, benzene, xylene and toluene. Preferred for use herein is toluene.

10

After azeotropic drying, the dried Lewis acid in the solvent is ready for reuse in a reaction and it is simply necessary to add further reagents. The Lewis acid can be recycled and reused in this way several times.

15

The method of the invention may be preceded by an initial step of drying the Lewis acid so that it is in a stable state to take part in the reaction. The initial drying step may be carried out independently of the reaction, or alternatively, the Lewis acid may be dried *in situ* in a reaction mixture. Whether it is appropriate to dry the Lewis acid *in situ* will depend upon whether the reactants and products of a particular reaction are thermally stable under the drying conditions employed and whether the optimum temperature for carrying out the reaction is compatible with the temperature at which the Lewis acid is dried. Typically, either means of drying the Lewis acid reactivates it to act as a catalyst in the reaction. Drying may be performed by the techniques described above, and is preferably performed by azeotropic distillation eg with toluene of an aqueous solution of the Lewis acid.

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25

Lewis acid by this method has the beneficial consequence that it is not necessary to use the Lewis acid reagent in anhydrous form. Some Lewis acids, eg zinc bromide, are expensive in their anhydrous form and difficult to maintain in anhydrous condition, being hygroscopic. It is thus beneficial not to have to use the reagent in anhydrous form but instead to be able to use an aqueous solution of Lewis acid, which is a cheaper starting material that does not require special storage and handling.

30

In a preferred aspect, the invention provides a method of performing a chemical reaction involving a Lewis acid, comprising the steps of:

- 1) drying an aqueous solution of Lewis acid;
 - 5 2) using the dried Lewis acid in the chemical reaction;
 - 3) adding water to the reaction products of step 2) and separating an aqueous solution of the Lewis acid; and
 - 4) repeating steps 1) to 3).
- 10 Steps 1) to 3) can be repeated several times, thus reusing the same Lewis acid in several reactions, without significantly affecting the activity and specificity of the Lewis acid in the reaction.

In one embodiment the invention provides a method for performing an ene reaction
15 involving a Lewis acid.

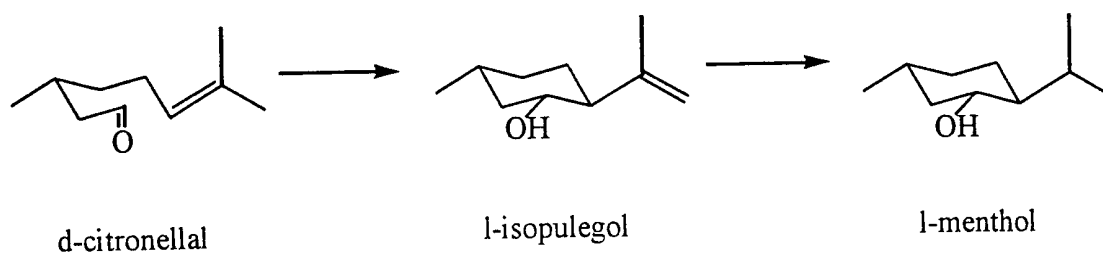
For example, the invention has been used to good effect in the preparation of 2-isopropenyl-5-methylcyclohexanol, known as isopulegol, from 3,7-dimethyl-6-octenal, known as citronellal, by a catalytic ene reaction. Isopulegol and citronellal both exist in two
20 enantiomeric forms, which are respectively (1R,2S,5R)-2-isopropenyl-5-methylcyclohexanol and (1S,2R,5S)-2-isopropenyl-5-methylcyclohexanol; and (7S)-3,7-dimethyl-6-octenal and (7R)-3,7-dimethyl-6-octenal. Mixtures of enantiomers of each of these materials are nevertheless referred to in this specification in the singular, eg as isopulegol, so that references to isopulegol may refer to one or other enantiomeric form or a mixture of
25 enantiomers. Similar considerations apply to citronellal.

Isopulegol is a known fragrance material, with its most important use being as a precursor for (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol, known as l-menthol, prepared by a known hydrogenation reaction. l-menthol (or (-)-menthol) is particularly favoured and is
30 widely used, eg in dental flavours. It is known to make isopulegol by cyclisation of citronellal using a Lewis acid catalyst. Powdered anhydrous zinc bromide has been found to be one of the most selective catalysts in the cyclisation reaction, as described in Nakatani et

al, Synthesis 1978, 147. In this known process zinc bromide is required in stoichiometric amounts and is effectively consumed in the process, and moreover can present waste disposal problems, being not only a marine toxin, but also a water pollutant as described above. Zinc bromide is also hygroscopic and wet zinc bromide is much less reactive than the anhydrous form. Hence precautions are required in the storage and usage of zinc bromide to avoid moisture.

Thus, in one of the preferred aspects of the invention, there is provided a method of preparing isopulegol from citronellal, comprising reacting citronellal in the presence of a Lewis acid catalyst to cause cyclisation of citronellal to produce isopulegol; extracting from the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

As noted above isopulegol exists in two enantiomeric forms. For use as a precursor for the production of menthol, it is desirable to have (1R,2S,5R)-2-isopropenyl-5-methylcyclohexanol (l-isopulegol or (-)-isopulegol) as this produces (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexanol, l-menthol, on hydrogenation. l-menthol is generally the most preferred form of menthol, as noted above. When using (7R)-3,7-dimethyl-6-octenal, (d-citronellal or (+)-citronellal) as the starting material, the invention shows good selectivity for l-isopulegol in preference to other isomers, so the reaction takes place without loss of optical purity. The reaction of d-citronellal to produce l-isopulegol and subsequent conversion into l-menthol can be represented as follows:



Similarly, by starting with a racemic mixture of citronellal, ie a mixture of the d- and l- forms, a racemic mixture of isopulegol and then menthol can be produced. Thus, the optical purity of the materials is maintained through the process. As well as maintaining optical purity, the invention can produce isopulegol in good yields.

The dried Lewis acid can be reused in the cyclisation of a further batch of citronellal to isopulegol, without loss of reactivity and selectivity. The invention can therefore overcome the problems noted above associated with the prior art, enabling quantitative recovery of Lewis acid and hence enabling repeated reuse of Lewis acid with consequent reduction in cost of raw materials and avoidance of the cost of disposal of used zinc bromide.

The Lewis acid may be, for example, zinc bromide, zinc chloride, zinc iodide, other metal salts or mixtures thereof. Zinc bromide generally gives the best yield and selectivity and so is favoured in the conversion of citronellal to isopulegol.

10

The cyclisation reaction is carried out in a suitable organic solvent, such as cyclohexane, benzene, xylene, toluene or mixtures thereof. The currently preferred solvent is toluene as it gives good reaction rates and selectivity. Toluene is also a cheap, safe solvent and so is well suited to industrial use.

15

The cyclisation reaction is conveniently carried out at a temperature in the range -15°C to 30°C , with a temperature of about 0°C giving good compromise results in terms of yield and selectivity.

The Lewis acid is conveniently extracted from the reaction products by adding water, preferably deionised water, and separating the aqueous fraction from the organic solvent fraction containing isopulegol.

Drying of the aqueous solution of the Lewis acid may be performed using techniques including vacuum dehydration; chemical drying eg with dried molecular sieve material, anhydrous magnesium sulphate or sodium sulphate; physical drying techniques, for instance pervaporisation with selective membrane technology; azeotropic distillation; or a mixture of such techniques. Of the techniques tested, azeotropic distillation is currently favoured as the resulting dried Lewis acid is found to give best product yields and selectivity. It may be convenient to precede azeotropic distillation by optional vacuum dehydration.

30

Azeotropic distillation may be performed using any suitable solvent that gives an azeotrope with water, is inert to the Lewis acid, has low solubility in water and preferably is suitable for the cyclisation reaction. Suitable solvents include those mentioned above, ie cyclohexane, benzene, xylene and toluene, with toluene currently being favoured.

5

After azeotropic drying, the dried Lewis acid in the solvent is ready for reuse in the cyclisation reaction and it is simply necessary to add a further batch of citronellal. The Lewis acid can be recycled and reused in this way several times without loss of catalytic activity and selectivity.

10

The preferred method of the invention will generally be preceded by an initial step of drying the Lewis acid so that it is in a suitable state to act as a catalyst in the cyclisation reaction. Drying may be performed by the techniques described above, and is preferably performed by azeotropic distillation with toluene of an aqueous solution of the Lewis acid. Such initial

15 drying has the beneficial consequence that it is not necessary to use as a reagent anhydrous Lewis acid, eg zinc bromide. Anhydrous zinc bromide is expensive and difficult to maintain in anhydrous condition as it is a hygroscopic material; instead an aqueous solution of Lewis acid can be used as a reagent, which is a cheaper starting material that does not require special storage and handling.

20

In a further preferred aspect the invention thus provides a method of preparing isopulegol from citronellal, comprising the steps of:

- 1) drying an aqueous solution of zinc bromide by azeotropic distillation using toluene;
- 2) using the dried zinc bromide as a catalyst for cyclisation of citronellal to produce
- 25 isopulegol;
- 3) adding water to the reaction products of step 2) and separating an aqueous solution of zinc bromide from the toluene solution of isopulegol; and
- 4) repeating steps 1) to 3).

30

Steps 1) to 3) can be repeated several times, thus reusing the same zinc bromide on several batches of citronellal, without significantly affecting the activity and specificity of the zinc

bromide in the cyclisation reaction. The method can give good yields of isopulegol of desired optical form even after repeated re-use of the zinc bromide.

5 The invention can thus provide an environmentally acceptable and efficient process for the production of isopulegol from citronellal, in both racemic and enantiomerically pure forms.

The invention includes within its scope isopulegol prepared by the method of the invention.

The isopulegol can be converted into menthol, eg by hydrogenation.

10

The invention also covers use of the isopulegol so prepared for the preparation of menthol, and the resulting menthol.

15 As noted above, the invention enables conversion of d-citronellal to l-isopulegol and then l-menthol, while a racemic starting material produces racemic products.

In another embodiment the invention provides a method for performing a Diels-Alder reaction involving a Lewis acid.

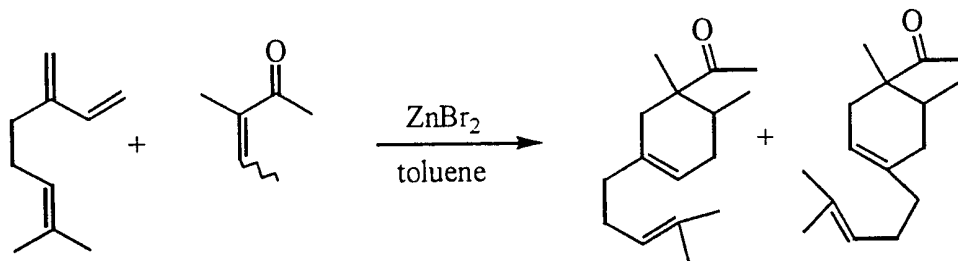
20 The structure of the diene and dienophile employed in the Diels-Alder reaction, will often determine the rate of reaction. Depending on the nature of the reactants, a faster rate of reaction may be brought about, for example, by conducting the reaction at high temperatures or by employing a catalyst. Catalytic Diels-Alder reactions tend to be more selective in the product formed than the corresponding thermally induced reactions. However, as has been
25 discussed above, there are a number of disadvantages associated with the use of Lewis acids as catalysts in chemical reactions.

The invention however has been used to good effect in catalytic Diels-Alder reactions, specifically, in the preparation of intermediates of perfumery ingredients.

30

For example, the invention may be employed to good effect in the Diels-Alder reaction of 7-methyl-3-methylene-1,6-octadiene, known as myrcene, with 3-methyl-3-penten-2-one to

give a mixture of 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone as follows:



The products of the Diels-Alder reaction afford a mixture of bicyclic compounds which are useful intermediates in the preparation of perfumery ingredients having a floral, woody and ambergris odour.

Thus, in a further preferred aspect of the invention, there is provided a method of preparing a mixture of 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone from 7-methyl-3-methylene-1,6-octadiene and 3-methyl-3-penten-2-one, comprising reacting 7-methyl-3-methylene-1,6-octadiene and 3-methyl-3-penten-2-one in the presence of a Lewis acid to cause a Diels-Alder reaction to produce a mixture of 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone; extracting from the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

The Diels-Alder reaction is conveniently carried out at a temperature in the range 100°C to 140°C, preferably 100°C to 130°C. Additionally, the Diels-Alder reaction is carried out in a suitable solvent, such as for example, toluene.

The preferred Lewis acid in the Diels-Alder reaction is zinc bromide, wherein zinc bromide is preferably employed as an aqueous solution. Conveniently, in one embodiment of the present invention, the aqueous solution of the Lewis acid may be dried *in situ* during the course of the Diels-Alder reaction by azeotropic distillation using toluene when both the reactants and Diels-Alder adducts are stable under these drying conditions and the temperature for carrying out the Diels-Alder reaction is typically, the same as the

temperature for drying the Lewis acid. The Lewis acid is then extracted from the reaction products by adding water, and separating the aqueous fraction from the organic solvent fraction containing the Diels-Alder adducts.

- 5 The recovered aqueous solution of the Lewis acid may then be subject to further drying *in situ* in a further Diels-Alder reaction of myrcene with 3-methyl-3-penten-2-one, thus, being reused as a catalyst in this reaction.

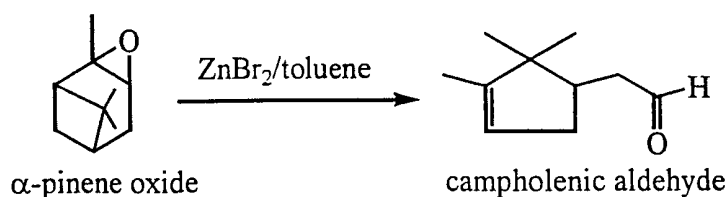
Employing a fresh aqueous solution of zinc bromide may result in a yield as high as 71.96%
10 of the desired adducts. Recovery and reuse of the zinc bromide may afford a 73.27% yield of the desired adducts.

The invention includes within its scope 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone prepared by the method of the invention.
15

In a further embodiment the invention provides a method for performing a rearrangement reaction involving a Lewis acid.

- 20 Lewis acids are capable of activating functional groups such as for example aldehydes, ketones, epoxides, acetals and olefins to induce a rearrangement of the molecule.

For example, the invention has been used successfully in rearrangement reactions, specifically in the rearrangement of 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane, known as α -pinene oxide, to (2,2,3-trimethyl-3-cyclopenten-1-yl)acetaldehyde, known as campholenic aldehyde, as is shown below:
25



The aldehyde is a useful intermediate in the synthesis of a variety of woody, musky and sandalwood fragrance ingredients.

Thus in an even further preferred aspect of the invention, there is provided a method of preparing (2,2,3-trimethyl-3-cyclopenten-1-yl)acetaldehyde from 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane comprising reacting 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane in the presence of a Lewis acid catalyst to cause rearrangement of 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}] octane to produce (2,2,3-trimethyl-3-cyclopenten-1-yl) acetaldehyde; extracting from the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

The rearrangement reaction is conveniently carried out at a temperature in the range 100°C to 140°C.

The preferred Lewis acid in this rearrangement reaction is zinc bromide and the reaction is typically carried out in toluene. The reaction may be preceded by an initial step of drying the Lewis acid. Once the reaction is complete, the Lewis acid is extracted from the reaction products by adding water, and separating the aqueous fraction from the organic solvent fraction containing campholenic aldehyde. The recovered aqueous solution of zinc bromide is then conveniently dried by azeotropic distillation using toluene. After azeotropic drying, the dried zinc bromide in toluene is ready for use in a further rearrangement reaction of α -pinene oxide. Good yields of campholenic aldehyde are obtained. The dried Lewis acid can be recycled and reused in the conversion of two further batches of α -pinene oxide to campholenic aldehyde, without loss of activity or selectivity.

25

The invention thus includes within its scope (2,2,3-trimethyl-3-cyclopenten-1-yl)acetaldehyde prepared by the method of the invention.

The invention will be further described, by way of illustration, in the following non-limiting examples.

30

Example 1 – Drying of zinc bromide and preparation of isopulegol

To a 250ml 3-neck flask, equipped with a Dean & Stark (D&S) trap, were added 80ml
5 toluene and 50.21 gram 80%(w/w) aqueous zinc bromide solution. The mixture was heated
up to boiling and water was trapped and separated into the lower layer as the distillation
proceeded. About 8.8ml of water was trapped and there was no increase in the amount of
water after refluxing for 8 hours. A white, slightly pink, suspension resulted. The
suspension was then cooled to 4°C.

10

Racemic citronellal (68.80g, 0.45 mol) was added to the suspension over 3 hours by pump at
0.4g/min. at 2-5°C and stirred vigorously. The citronellal had purity 91.81% rpa with 4.35%
isopulegol and 2.22% pulegol, ORD=+2.0. The resulting mixture was stirred for another 1.5
hours. According to GC, the reaction was completed by this stage. The reaction mixture
15 was then quenched with deionised (DI) water (3x100ml). The organic layer was then
washed with brine (1x50ml). The yield of isopulegol was found to be 87.14% by GC
analysis.

The zinc content of the aqueous solution was determined by atomic absorption analysis and
20 it was found that zinc was totally recovered in the aqueous extraction.

The recovered zinc bromide was dried and used in a further cyclisation reaction under the
same conditions. Thus, 200ml toluene was added to the zinc bromide solution, and the
mixture was refluxed with a D&S trap for 8 hours. Citronellal was pumped in to the
25 suspension at 0.4g/min. for 2 hours 15 min at 2-5°C. 53.95g citronellal was added and the
solution was stirred for a further 3 hours. According to GC, the reaction was complete by
this stage. The reaction mixture was then washed with deionised water (2x50ml). The yield
of isopulegol was found to be 85.85% by GC analysis. Moreover, the diastereoselectivity of
the two cycles were similar.

Example 2 – Repeated recycling of zinc bromide and its application in the cyclisation of citronellal

5 Experiments similar to those of Example 1 using azeotropic drying of toluene were carried out on a larger scale using reagents from the same source. The experiments were carried out using a 10 litre jacketed reactor with a Dean & Stark trap, condenser, mechanical stirrer and thermocouple.

10 GC Method: GC: HP6890 series
Column: Model No. HP 19091J-412
HP-5 5% PhenylMethylsilxane Capillary
30.0mX320µmX0.25µm nominal
Temp Program: 70°C, hold 1 minute, ramp 3°C/min., 280°C

15 a) First Cycle, Dehydration of Zinc Bromide Solution.

In a 10l jacketed reactor, equipped with a D & S trap and thermocouple, 2.5l toluene was added and the reactor was heated up to 126°C, at which point toluene was refluxed at a reasonable rate. To the refluxing toluene, with an addition funnel, the zinc bromide solution
20 (350.40g zinc bromide in 600ml water) was added slowly over 2 hours with vigorous stirring (~80rpm). The reflux continued for another 8 hours. 600ml water was removed and no more water was trapped. A pinkish white suspension resulted.

b) First Cycle, Cyclisation of Citronellal

25

To the suspension resulting from step (a) cooled to 0°C and stirred vigorously (~80rpm), racemic citronellal was pumped in at 4.76g/min. 600.24g citronellal was added after 2 hours and 6 min. The solution (most of the zinc bromide was dissolved at this point) was further stirred at +1-0°C for 1.5 hours. According to GC and TLC, the reaction was completed by
30 this stage. To the reaction mixture, 600ml DI water was added with stirring. The aqueous phase was separated and removed. The organic phase was washed with another 600ml DI water and separated. The yield of isopulegol was found to be 88.29% by GC analysis.

The pH of the zinc bromide solution = 5.47

c) Second Cycle, Dehydration of Zinc Bromide Solution

5

In a 10l jacketed reactor, equipped with a D&S trap and thermocouple, 2.5l toluene was added and the reactor was heated up to 126°C, at which point toluene was refluxed at a reasonable rate. To the refluxing toluene, with an addition funnel, the zinc bromide solution and the combined aqueous phase from step (b) was added slowly over 3 hours with vigorous stirring (~80rpm). The reflux continued for 7.5 hours. A suspension of zinc bromide in toluene resulted.

d) Second Cycle, Cyclisation of Citronellal.

15 To the suspension resulting from step (c) cooled to 0°C and stirred vigorously (~80rpm), racemic citronellal was pumped in at 4.76g/min. 600.16g citronellal was added after 2 hours and 6 min. The solution (most of the zinc bromide was dissolved at this point) was further stirred at +1-0°C for 1.5 hours. According to GC and TLC, the reaction was completed by this stage. To the reaction mixture, 600ml DI water was added with stirring. The aqueous
20 phase was separated and removed. The organic phase was washed with another 600ml DI water and separated. The yield of isopulegol was found to be 87.90% by GC analysis with similar diastereoselectivity when compared with the first cycle.

The pH of the zinc bromide solution = 5.56

25

e) Third Cycle, Dehydration of Zinc Bromide Solution.

To the 1.2 litre zinc bromide solution from step (d), procedure (c) was applied. A pinkish suspension of zinc bromide in toluene resulted.

30

f) Third Cycle, Cyclisation of Citronellal.

To the suspension resulting from step (e) cooled to 0°C and stirred vigorously (~80rpm), citronellal was pumped in at 4.76g/min. 694.61g citronellal was added after 2 hours and 40 min. The solution (most of the zinc bromide was dissolved at this point) was further stirred at +2-0°C for 1.5 hours. According to GC and TLC, the reaction was completed by this stage. To the reaction mixture, 600ml DI water was added with stirring. The aqueous phase was separated and removed. The organic phase was washed with another 600ml DI water and separated. The yield of isopulegol was found to be 82.26% by GC analysis with similar disastereoselectivity compare with the first cycle.

10 The pH of the zinc bromide solution = 5.36

g) Fourth Cycle, Dehydration of Zinc Bromide Solution

To the 1.2l zinc bromide solution from step (f), procedure (c) was applied. A suspension of zinc bromide in toluene resulted.

h) Fourth Cycle, Cyclisation of Citronellal.

To the suspension resulting from step (g) cooled to 0°C and stirred vigorously (~80rpm), racemic citronellal was pumped in at 4.76g/min. 600.10g citronellal was added after 2 hours and 14 min. The solution (most of the zinc bromide was dissolved at this point) was further stirred at +2-0°C for 1.5 hours. According to GC and TLC, the reaction was completed by this stage. To the reaction mixture, 600ml DI water was added with stirring. The aqueous phase was separated and removed. The organic phase was washed with another 600ml DI water and separated. The yield of isopulegol was found to be 86.22% by GC analysis with similar disastereoselectivity compared with the first cycle.

The pH of the zinc bromide solution = 5.08

30 The pH of the aqueous zinc bromide after each cycle was measured to see if substantial hydrolysis occurred. There was a very slight drop in pH after 4 cycles.

This Example shows that the selectivity and reactivity of the zinc bromide was maintained at similar levels, as the zinc bromide was recycled three times. From the pH study, no significant hydrolysis took place when zinc bromide was repeatedly recycled.

5 Similar results have been obtained with manufacturing scale reactions.

Example 3 – Cyclisation of d-citronellal to l-isopulegol

10 Experiments were carried out using commercially available d enriched citronellal, having a d/l enantiomeric ratio of about 90/10. Isopulegol having a l/d enantiomeric ratio of about 90/10 was produced, showing that optical purity is maintained when using as a catalyst in the cyclisation reaction zinc bromide dried by azeotropic distillation of an aqueous solution.

15 Materials: Citronellal: 90% min.
refractive Index: 1.448
optical rotation, $[\alpha]_D$: + 11.2 ($[\alpha]_D$ of d-citronellal = + 10.6, reported in Dictionary of Organic Compounds, 4th Ed. Vol. 2 pp. 716)
d/l enantiomeric ratio = 90.60/9.40 measured by chiral
20 GC (conditions specified below)
Zinc Bromide: 98% min.

Chiral GC conditions:

25 CITRONELLAL

Machine: Carlo Erba HRGC5300 with split injector and FID

Column: Diacetyl tert-butyldimethylsilyl beta cyclodextrin

Dimensions: 25m*0.25mm*0.15 μ m

30 Linear velocity: 16.69cm/sec

Temperature Prog: 80° 1°/min 150°(10min); Flow rate: 0.473ml/min

Split Flow: Ratio 200:1

Concentration: 0.3%

Retention time: t=23.544 min
t=24.085 min

Resolution achieved: separation $R_s=1.29$

5

ISOPULEGOL

Machine: HP 5890 GC with split injector and FID

Column: CP-Cyclodextrin-B-236-M-19

10 Dimensions: 48m*0.25mm*0.25 μ m

Linear velocity: 23.8cm/sec

Temperature Prog: 70° 3°/min 200°; Flow rate: 1.14ml/min

Split Flow: 130:1

Concentration: 0.1%

15 Name of the sample (-)isopulegol + racemic isopulegol

Retention time: t=21.62 (5%) (+)isopulegol; t=21.78 (81%) (-)isopulegol

NOTE:- (-)isopulegol co-elutes with one enantiomer of iso-isopulegol

Procedure

20

To 200ml toluene in a 1litre 3-neck flask, equipped with water-cooled condenser, Dean & Stark trap, mechanical stirrer, thermometer and addition funnel, heating under gentle reflux, a solution of zinc bromide (made by dissolving 29.14g zinc bromide in 30ml deionised water) was added over 30 minutes. The heating was continued for 3 hours; no more water

25 was collected in the trap. A pale pink suspension of zinc bromide in toluene resulted. The suspension was cooled in an ice bath to +3°C. 44.68g of citronellal was added dropwise to the suspension over 2 hours and the temperature was kept at 0-3°C. The mixture was then further stirred for another 2 hours. 60ml deionised water was then added to the reaction

30 layer was washed with another 60ml portion of deionised water. A toluene solution of isopulegol was obtained. The ratio of the enantiomers of isopulegol was then measured by

chiral GC analysis under the conditions as detailed above. The ratio of isopulegol 1:d was found to be 90.90:9.10.

Example 4 – Hydrogenation of isopulegol to menthol

5

Crude isopulegol produced as described in Example 1, using zinc bromide dried by azeotropic distillation (containing 73.31% isopulegol) was hydrogenated after removal of all the toluene.

10 To the isopulegol (257.89g, 1.227mol) in a 1 litre Buchi flask, 5% Pd/C (4.84g, 2.28 mmol metal) was added. The suspension was purged with nitrogen and pressurised with hydrogen to 5 bars. The suspension was then stirred at 1200 rpm at room temperature and the hydrogen pressure was maintained at 2-5 bars. The reaction was followed by GC and was shown to be complete in 2 hours. The catalyst was then filtered off using a plug of Celite
15 (Celite is a Trade Mark) and the filtered catalyst was washed with hexane (3x30ml). (Celite is a diatomaceous earth, about 95% SiO₂). After the removal of solvent, 260.8g crude product was obtained. Isopulegol was found to be quantitatively hydrogenated.

Example 5 - Diels-Alder reaction of myrcene and 3-methyl-3-penten-2-one

20

To a 1 litre 3-neck flask, equipped with a thermometer, mechanical stirrer, Dean & Stark trap and condenser, which was flushed with nitrogen and maintained under a nitrogen atmosphere, were added myrcene (179.25g, 1.32 mole), toluene (122.69g, 1.33 mole), 3-methyl-3-penten-2-one (122.69g, 1.26 mole) and an aqueous zinc bromide solution, 70%
25 (16.65g, 29.4 mmole). The mixture was agitated and heated to reflux (about 100°C initially). Water was collected in the Dean & Stark trap, and toluene was returned to the flask. The heating was continued for 12 hours, after which time, the reaction was found to be complete by GC analysis. The reaction mixture was cooled to 50°C under nitrogen. 25ml deionised water was then added to the reaction mixture, stirred for 15 minutes and the
30 aqueous and organic layers were allowed to separate. The aqueous layer containing the zinc bromide solution was removed and the organic layer washed with another 25ml portion of deionised water. The crude reaction mixture comprising the Diels-Alder adducts contained

in the toluene organic layer was analysed by internal standard GC and the conversion was found to be 95% (based on the amount of myrcene used) and the selectivity was 76%. Hence the combined % yield of the Diels-Alder adducts based on myrcene was 71.96%.

- 5 GC Conditions for determining reaction completion and performing an analysis of the crude reaction mixture:

GC: HP 6890 Series Plus
Column: HP19091A-102, Ultra 1 Methyl Siloxane
10 25.0m x 200.00 μ m x 0.33 μ m nominal
Carrier gas: Nitrogen.
Temp Program: 140°C, hold 5 minutes, ramp 40°C/min to 220°C, hold 8 min.; total run time 15 min.

- 15 Example 6 - Diels-Alder reaction of myrcene and 3-methyl-3-penten-2-one with recycled zinc bromide.

To a 1 litre 3-neck flask, equipped with a thermometer, mechanical stirrer, Dean & Stark trap and condenser, which was flushed with nitrogen and maintained under a nitrogen
20 atmosphere, were added myrcene (179.25g, 1.32 mole), toluene (93.09g, 1.01 mole), 3-methyl-3-penten-2-one (122.69g, 1.26 mole) and the aqueous recycled zinc bromide solution of Example 5, 70% (16.65g, 29.4 mmole). The mixture was agitated and heated to reflux (about 100°C initially). Water was collected in the Dean & Stark trap, and toluene was returned to the flask. The heating was continued for 12 hours, after which time, the reaction
25 was found to be complete by GC analysis. The reaction mixture was cooled to 50°C under nitrogen. 25ml deionised water was then added to the reaction mixture and stirred for 15 minutes, and the aqueous and organic layers were allowed to separate. The aqueous layer containing the zinc bromide solution was removed and the organic layer was washed with another 25ml portion of deionised water. The crude reaction mixture comprising the Diels-
30 Alder adducts contained in the toluene organic layer was then analysed by internal standard GC and the conversion was found to be 97% (based on the amount of myrcene used) and the

selectivity was 75%. Hence the combined % yield of the Diels-Alder adducts based on myrcene was 73.27%.

The GC conditions are outlined in Example 5 above.

5

Example 7 - Zinc Bromide catalysed rearrangement of α -pinene oxide

Materials:

10 α -pinene oxide: ex Aldrich, purity 97%, Cat. No.: 21,830-8

Zinc bromide: ex Aldrich, purity 98%, Cat. No.: 21,632-1

Toluene: ex Fisher Scientific, Laboratory Analysed Reagent

15

Procedure:

(a) Fresh Zinc bromide

20 To a 500ml 3-neck flask, equipped with an addition funnel, thermometer, Dean & Stark trap, condenser and mechanical stirrer, was added an aqueous solution of zinc bromide (20g, 0.8%, 0.71mmol) and 100ml toluene. The mixture was heated to reflux with vigorous stirring and water was retained in the trap. No further water was collected after refluxing for 30 minutes. A suspension of anhydrous zinc bromide in toluene resulted.

25

α -Pinene oxide (11.22g, 73.8mmol) in 50ml toluene was added to the zinc bromide suspension dropwise from an addition funnel over 2 hours. The temperature of the reaction mixture during the addition was kept at 113-117°C (toluene was gently refluxed). After the addition was complete, the reaction mixture was vigorously stirred for 90 minutes at 113-
30 117°C, after which time the reaction was found to be complete by GC analysis. The reaction mixture was then cooled to room temperature and 25ml deionised water was added. The aqueous layer was removed and the organic layer was washed with another 25ml of

deionised water and separated. The organic layer was found to contain 138.57g of crude product. The crude product was analysed by internal standard GC and found to contain 6.22% campholenic aldehyde. Hence the yield of the reaction was 79.19%.

5 (b) First Recycle of Zinc Bromide

To a 500ml 3-neck flask, equipped with an addition funnel, thermometer, Dean & Stark trap, condenser and mechanical stirrer, was added 100ml toluene. The 50ml zinc bromide solution recovered from step (a) was then added to toluene. The mixture was heated to
10 reflux with vigorous stirring and water was retained in the trap. No further water was collected after refluxing for 90 minutes. A suspension of anhydrous zinc bromide in toluene resulted.

α -Pinene oxide (10.61g, 69.8mmol) in 50ml toluene was added to the zinc bromide
15 suspension dropwise from an addition funnel over 2 hours. The temperature of the reaction mixture during the addition was kept at 113-117°C (toluene was gently refluxed) and the reaction vigorously stirred. After the addition was complete, the temperature of the reaction was maintained at 113-117°C and the mixture was further stirred for 90 minutes. The
20 reaction was found to be complete after this time by GC analysis. The reaction mixture was then cooled to room temperature and 25ml deionised water was added to the reaction mixture. The aqueous layer was removed and the organic layer was washed with another 25ml of deionised water and separated. The organic layer was found to contain 128.35g of crude product. The crude product was analysed by internal standard GC and found to contain 6.17% campholenic aldehyde. Hence the yield of the reaction was 76.95%.

25

(c) Second Recycle of Zinc Bromide

To a 500ml 3-neck flask, equipped with an addition funnel, thermometer, Dean & Stark trap, condenser and mechanical stirrer, was added 100ml toluene. The 50ml zinc bromide
30 solution recovered from step (b) was then added to the toluene. The mixture was heated to reflux with vigorous stirring and water was retained in the trap. No further water was

collected after refluxing for 90 minutes. A suspension of anhydrous zinc bromide in toluene resulted.

5 α -Pinene oxide (11.40g, 75mmol) in 50ml toluene was then added to the zinc bromide suspension dropwise from the addition funnel over 2 hours. The temperature of the reaction mixture during the addition was kept at 113-117°C (toluene was gently refluxed). After the addition was complete, the reaction mixture was vigorously stirred for 90 minutes, at 113-117°C, after which time the reaction was found to be complete by GC analysis. The reaction mixture was then cooled to room temperature and 25ml deionised water was added. The
10 aqueous layer was removed and the organic layer washed with another 25ml of deionised water and separated. The reaction yielded 142.76g of crude product. The crude product was analysed by internal standard GC and found to contain 5.89% campholenic aldehyde. Hence the yield of the reaction was 76.04%.

15 Internal Standard GC conditions for the analysis of campholenic aldehyde:

GC Method: GC: HP6890 series
Column: Model No. HP 19091J-102
HP-5 5% PhenylMethylsiloxane Capillary
20 25mx200 μ m x0.33 μ m nominal
Carrier gas: Hydrogen
Temp Program: 50°C, hold 1.5 minutes, ramp 31.57°C/min to 250°C, hold 4.75 min.
Internal standard used: tetradecane
Response factor: 1.1481

25

Claims

1. A method of performing a chemical reaction involving a Lewis acid, comprising carrying
5 out the reaction involving the Lewis acid; extracting from the reaction products the Lewis
acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.
2. A method according to claim 1, wherein the Lewis acid is extracted from the reaction
10 products by adding water, and separating the aqueous fraction from an organic solvent
fraction containing the reaction products.
3. A method according to claim 1 or 2, wherein drying of the aqueous solution of the Lewis
acid is performed by azeotropic distillation.
- 15 4. A method according to claim 3, wherein the azeotropic distillation is performed using
toluene.
5. A method according to any one of claims 1 to 4, wherein the dried Lewis acid is reused as
a catalyst in a further reaction.
20
6. A method according to any one of the preceding claims, preceded by an initial step of
drying the Lewis acid.
7. A method according to any one of the preceding claims, wherein the Lewis acid is zinc
25 bromide.
8. A method according to any one of claims 1 to 7, wherein the chemical reaction is carried
out in toluene.
- 30 9. A method, according to any one of the preceding claims, of performing a chemical
reaction involving a Lewis acid, and comprising the steps of:
 - 1) drying an aqueous solution of Lewis acid;

- 2) using the dried Lewis acid in the chemical reaction;
- 3) adding water to the reaction products of step 2) and separating an aqueous solution of the Lewis acid; and
- 4) repeating steps 1) to 3).

5

10. A method according to any one of claims 1 to 9, of preparing isopulegol from citronellal, comprising reacting citronellal in the presence of a Lewis acid catalyst to cause cyclisation of citronellal to produce isopulegol; extracting from the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

10

11. A method according to claim 10, wherein the cyclisation reaction is carried out at a temperature in the range -15°C to 30°C , preferably about 0°C .

15

12. A method according to claims 10 or 11, wherein l-isopulegol is prepared from d-citronellal, without change in optical purity.

13. A method according to any one of claims 10 to 12, further comprising converting the resulting isopulegol to menthol.

20

14. Isopulegol prepared by the method of any of claims 1 to 13.

15. Menthol prepared by the method of claim 14.

25

16. A method according to any one of claims 1 to 9, of preparing a mixture of 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone from 7-methyl-3-methylene-1,6-octadiene and 3-methyl-3-penten-2-one, comprising reacting 7-methyl-3-methylene-1,6-octadiene and 3-methyl-3-penten-2-one in the presence of a Lewis acid to cause a Diels-Alder reaction to produce a mixture of 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone and 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]ethanone; extracting from

30

the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

17. A method according to claim 16, wherein the Diels-Alder reaction is carried out at a temperature in the range 100°C to 140°C, preferably 100°C to 130°C.

18. A method according to claim 16 or 17, wherein the drying of the aqueous solution of the Lewis acid is performed *in situ* during the course of the reaction.

19. A method according to any one of claims 1 to 9, of preparing (2,2,3-trimethyl-3-cyclopenten-1-yl)acetaldehyde from 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane comprising reacting 2,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane in the presence of a Lewis acid catalyst to cause rearrangement of 2,7,7-trimethyl-3-oxatricyclo [4.1.1.0^{2,4}] octane to produce (2,2,3-trimethyl-3-cyclopenten-1-yl) acetaldehyde; extracting from the reaction products the Lewis acid in the form of an aqueous solution; and drying the aqueous solution of the Lewis acid.

20. A method according to claim 19, wherein the rearrangement reaction is carried out at a temperature in the range 100°C to 140°C.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01793

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C01G9/04 C07B61/00 C07C29/56 C07C29/17 C07C35/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C01G C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *P* document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

15 August 2000

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INTERNATIONAL SEARCH REPORT

International Application No

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