



(43) International Publication Date
30 December 2015 (30.12.2015)

(10) International Publication Number
WO 2015/197586 A1

- (51) **International Patent Classification:**
C07C 37/16 (2006.01) *C07C 39/07* (2006.01)
- (21) **International Application Number:**
PCT/EP2015/064050
- (22) **International Filing Date:**
23 June 2015 (23.06.2015)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
14173672.8 24 June 2014 (24.06.2014) EP
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** MANUFACTURE OF 2,4,6-TRIMETHYLPHENOL

(57) **Abstract:** The present invention is directed to a process for the manufacture of 2,4,6-trimethylphenol by reacting phenol or ortho-cresol or 2,6-xylenol with methanol in the gas phase and in the presence of a catalyst, whereby the catalyst comprises Ga₂O₃ or additionally MgO. Catalysts consisting of Ga₂O₃ or catalysts consisting of Ga₂O₃ and MgO may also be used successfully.

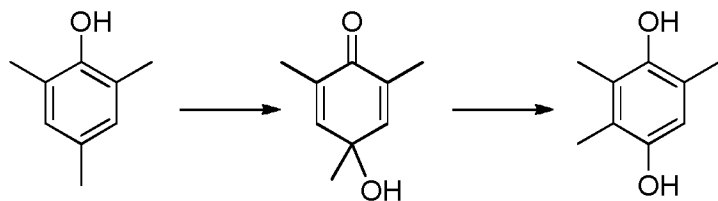


WO 2015/197586 A1

Manufacture of 2,4,6-trimethylphenol

The present invention is directed to a process for the manufacture of 2,4,6-trimethylphenol by reacting phenol or ortho-cresol (o-cresol) or 2,6-xylenol with methanol in the gas phase and in the presence of a catalyst, whereby the catalyst comprises gallium oxide, which preferably further contains magnesium oxide. In a preferred embodiment of the present invention, the catalyst consists of gallium oxide and magnesium oxide. The term “consisting of” in the context of the present invention means that the total amount of gallium oxide and magnesium oxide ideally sums up to 100 weight-%. It is, however, not excluded that small amounts of impurities (such as e.g. any other metal) or non-reactive additives may be present in amounts of less than 5 weight-%, preferably less than 1 weight-%, more preferably less than 0.5 weight-%, based on the total weight of the methylation catalyst. The term “gallium oxide and magnesium oxide” also encompasses mixed oxides of gallium and magnesium, as well as any mixture of Ga_2O_3 and MgO , and mixtures of any modifications thereof. Preferably the catalyst comprising Ga_2O_3 and MgO has a weight ratio of Mg to Ga from 1:1 to 15:1.

2,4,6-Trimethylphenol is an important intermediate for TMHQ (2,3,5-trimethylhydroquinone) being itself one of the building blocks of Vitamin E. The reaction sequence starting with 2,4,6-trimethylphenol and leading to TMHQ is e.g. described in US 4,612,401 (Rhone Poulenc), DE 2 314 600 (Teijin) and EP-A 084 158 (Mitsubishi) and shown in the following scheme 1.



Scheme 1

The process of the present invention is now further described in more detail below.

Catalyst

In an embodiment of the present invention the catalyst comprises gallium oxide.

In a preferred embodiment of this embodiment the catalyst further comprises
5 magnesium oxide. Thus, a catalyst comprising gallium oxide and magnesium oxide
may also be used. The term “gallium oxide and magnesium oxide” also
encompasses mixed oxides of gallium and magnesium, as well as any mixture of
 Ga_2O_3 and MgO , and mixtures of any modifications thereof. These (mixed) oxides of
gallium and magnesium do not have a spinel structure.

10 In a further embodiment of the present invention the catalyst consists of gallium
oxide. The term “consisting of” in the context of the present invention means that
the total amount of gallium oxide ideally is 100 weight-%. It is, however, not
excluded that small amounts of impurities (such as e.g. any other metal) or non-
15 reactive additives may be present in amounts of less than 5 weight-%, preferably
less than 1 weight-%, more preferably less than 0.5 weight-%, based on the total
weight of the catalyst.

20 In another embodiment of the present invention the catalyst consists of gallium
oxide and magnesium oxide. Hereby also mixed oxides of gallium and magnesium
are encompassed, as well as any mixture of Ga_2O_3 and MgO , and mixtures of any
modifications thereof. The term “consisting of” in the context of the present
invention means that the total amount of gallium oxide and magnesium oxide
ideally sums up to 100 weight-%. It is, however, not excluded that small amounts of
25 impurities (such as e.g. any other metal) or non-reactive additives may be present
in amounts of less than 5 weight-%, preferably less than 1 weight-%, more
preferably less than 0.5 weight-%, based on the total weight of the catalyst.

30 In preferred embodiments of the present invention the catalysts either comprising
gallium oxide/s and magnesium oxide/s or consisting of gallium oxide/s and
magnesium oxide/s have a weight-ratio of magnesium to gallium in the range of
from 1:1 to 15:1. Especially preferred are those catalysts where the weight-ratio
of magnesium to gallium is either 2 : 1 or 6 : 1 or 10 : 1. The best results obtained
with phenol are catalysts with a weight ratio of Mg to Ga of 10:1. The best results

obtained with o-cresol are catalysts with a weight ratio of Mg to Ga of 2:1. The best results obtained with 2,6-xylenol are catalysts with a weight ratio of Mg to Ga of 10:1.

- 5 In a preferred embodiment of the present invention the catalyst with all preferences and limitations as given above does not contain iron oxide in contrast to the catalysts disclosed in EP-A 019 476.

- 10 In a further preferred embodiment of the present invention the catalyst consisting of gallium oxide with all preferences and limitations as given above does neither contain titanium oxide nor indium oxide in contrast to US 5,245,089 and US 3,418,379, respectively.

15 Process for the manufacture of the catalysts

Usually the catalysts are prepared as follows:

- a) dissolving gallium nitrate and optionally magnesium nitrate in the desired ratio in water;
- b) providing a sodium carbonate solution with a concentration in the range of 0.3 to 2 M (preferably with a concentration in the range of 0.8 to 1.5 M) and a pH value in the range of 7.5 to 10 (preferably a pH value in the range of 8 to 9), whereby the molar ratio of sodium carbonate to the sum of gallium nitrate and optionally magnesium nitrate is 5 : 1;
- c) dropping the solution obtained in step a) into the solution obtained in step b) under stirring, while adjusting the pH to a value in the range of 6 to 8 (preferably to a value in the range of 6.5 to 7.5) and keeping the temperature in the range of 50 to 60°C;
- d) filtering the solution obtained in step c) to obtain the solid catalyst;
- e) washing the solid catalyst obtained in step d) with water;
- 25 f) drying the solid catalyst obtained in step e);
- 30 g) calcinating the dried solid catalyst obtained in step f) in air.

The steps are now described in more detail below.

Step a)

This step is usually performed at room temperature, but may be also performed at temperatures above room temperature. It is only important that the salts, i.e. gallium nitrate and optionally magnesium nitrate, become dissolved. The pressure at which this step is performed is not critical. It is also possible to use other magnesium or gallium salts such as magnesium halogenides or gallium halogenides as long as the salts are removed by the calcination step g).

Step b)

If needed the pH value is adjusted by means of concentrated HNO_3 . Other acids may also be suitable, if other salts of Ga and Mg are used. Thus, it is e.g. possible to use concentrated hydrogen chloride if Ga chloride and Mg chloride are used.

Step c)

The pH is preferably adjusted with concentrated sodium hydroxide. Other bases such as other alkaline bases and earth alkaline bases may also be suitable as long as the formed salts are better soluble than MgO and Ga_2O_3 . Stirring is continued for about 30 to 45 minutes.

Step d)

For filtering any suitable filter such as a Büchner filter may be used.

Step e)

The washing with water is preferably continued until the elution water shows a pH value of 7.

Step f)

The drying may be carried out at a temperature in the range of from 100 to 150°C for 4 to 48 hours. In one embodiment of the process of the present invention the drying is carried out at 120°C for 4 hours, in another embodiment of the process of the present invention the drying is carried out at 110°C for 12 hours.

Step g)

The calcination is preferably carried out at a temperature in the range of from 400 to 600°C, for a time in the range of 4 to 15 hours. More preferably the calcination is carried out at 450°C for 8 hours.

5

The methylation reactions according to the present invention are now described in more detail below. The GHSV (gas hourly space velocity) is thereby in the range of from 3200 h⁻¹ to 4000 h⁻¹, more preferably the GHSV is around 3600 h⁻¹.

10

Processes of the present inventiona) Methylation of phenol to 2,4,6-trimethylphenol (see also examples 1-3)

Preferably the reaction, i.e. the methylation of phenol to 2,4,6-trimethylphenol, is carried out at a temperature in the range of from 250 to 600°C, preferably at a temperature in the range of from 400 to 500°C.

Preferably the molar ratio of phenol to methanol is in the range of from 1:3 to 1:30, more preferably it is in the range of from 1:3 to 1:15, most preferably it is in the range of from 1:3 to 1:8.

Preferably the pressure is in the range of from 1 to 10 bara (bar absolute), more preferably it is 1 bara.

During the reaction water may also be present. Hereby the molar amount of water is at most 20 times the molar amount of phenol.

b) Methylation of o-cresol to 2,4,6-trimethylphenol (see also examples 5-7)

Preferably the reaction, i.e. the methylation of o-cresol to 2,4,6-trimethylphenol, is carried out at a temperature in the range of from 250 to 600°C, preferably at a temperature in the range of from 400 to 500°C.

30

Preferably the molar ratio of o-cresol to methanol is in the range of from 1:2 to 1:30, more preferably it is in the range of from 1:2 to 1:15, most preferably it is in the range of from 1:3 to 1:8.

- 5 Preferably the pressure is in the range of from 1 to 10 bara (bar absolute), more preferably it is 1 bara.

During the reaction water may also be present. Hereby the molar amount of water is at most 20 times the molar amount of o-cresol.

10

c) Methylation of 2,6-xyleneol to 2,4,6-trimethylphenol (see also examples 8-14)

Preferably the reaction, i.e. the methylation of 2,6-xyleneol to 2,4,6-trimethylphenol, is carried out at a temperature in the range of from 250 to 600°C, preferably at a temperature in the range of from 400 to 500°C.

15

Preferably the molar ratio of 2,6-xyleneol to methanol is in the range of from 1:1 to 1:20, more preferably it is in the range of from 1:2 to 1:15, most preferably it is in the range of from 1:2 to 1:6.

- 20 Preferably the pressure is in the range of from 1 to 10 bara (bar absolute), more preferably it is 1 bara.

During the reaction water may also be present which is very advantageous in this reaction because it strongly limits the deactivation of the catalyst. Hereby the
25 molar amount of water is at most 20 times the molar amount of 2,6-xyleneol.

The invention is now further illustrated in the following non-limiting examples.

Examples

30

All examples have been carried out according to the general procedure.

General procedure

In a typical experiment, 1 cm³ of catalyst is loaded in the reactor, with particles having a size in the range of from 30 to 60 mesh, prepared by compressing the powder into particles, then crushed and sieved. The liquid mixture is then prepared, with the desired methanol/phenolic compound molar ratio, loaded in the syringe and installed on the pump. The gas flow rate is then set up and regulated (typically N₂), with a flow rate that is typically equal to 20 mL/min (when the reaction temperature is 400°C). The temperature of the reactor is then raised, and when the needed temperature is reached, the reaction time is started. Typical conditions are: 1 second of contact time (GHSV 3600 h⁻¹), calculated on the basis of the overall gas/vapour flow. The overall content of organics in the inlet flow (phenol + methanol) is between 15 and 18 volume%; it may change within this interval because the N₂ flow is changed in function of the reaction temperature used. Moreover, if also water is fed, by means of a second syringe and pump, the N₂ flow is decreased proportionally, so to keep the overall flow of inert (after vaporisation of water) constant. The amount of organic fed (and vaporised) is typically 0.46 mL/h.

During the experiment, the outlet flow is made bubbling in a isopropanol solution, and the compounds which cannot be condensed are then sent to the vent. After 50 minutes of reaction time, the syringe is stopped, and the N₂ is let flow for some minutes more. The isopropanol solution is transferred in a vessel, brought to 25 mL volume with isopropanol, then 20 microL of standard are added (n-decane), and then the mixture is analysed by GC (Thermo Instrumento, capillary column HP5, FID detector).

Examples 1-4: Methylation of phenol to 2,4,6-trimethylphenol

Example 1: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to 1

Selectivity: 79%

Conversion: 100%

Feed: MeOH/Phenol = 5 : 1 (molar ratio)

Temperature: 450°C

Example 2: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to 1

Selectivity: 62%

Conversion: 100%

Feed: MeOH/water/Phenol = 10 : 5 : 1 (molar ratio)

Temperature: 410°C

5

Example 3: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to 1

Selectivity: 66%

Conversion: 100%

Feed: MeOH/Phenol = 10 : 1 (molar ratio)

10 Temperature: 450°C

Example 4: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 2 to 1

Selectivity: 45%

Conversion: 100%

15 Feed: MeOH/water/Phenol = 10 : 5 : 1 (molar ratio)

Temperature: 400°C

Examples 5-7: Methylation of o-cresol to 2,4,6-trimethylphenol

20 Example 5: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 2 to 1

Selectivity: 58%

Conversion: 76%

Feed: o-cresol/water/MeOH = 1 : 5 : 5 (molar ratio)

Temperature: 350°C

25

Example 6: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 2 to 1

Selectivity: 54%

Conversion: 76%

Feed: o-cresol/MeOH = 1 : 5 (molar ratio)

30 Temperature: 350°C

Example 7: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 6 to 1

Selectivity: 46%

Conversion: 53%

Feed: o-cresol/water/MeOH = 1 : 5 : 5 (molar ratio)

Temperature: 350°C

5 Examples 8-14: Methylation of 2,6-xyleneol to 2,4,6-trimethylphenol

Example 8: Use of Ga₂O₃ as catalyst

Selectivity: 66%

Conversion: 8%

Feed: 2,6-xyleneol/water/MeOH = 1 : 5 : 5 (molar ratio)

10 Temperature: 400°C

Example 9: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 2 to 1

Selectivity: 78%

Conversion: 51%

15 Feed: 2,6-xyleneol/water/MeOH = 1 : 5 : 5 (molar ratio)

Temperature: 400°C

Example 10: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 6 to 1

Selectivity: 69%

20 Conversion: 42%

Feed: 2,6-xyleneol/water/MeOH = 1 : 5 : 5 (molar ratio)

Temperature: 400°C

Example 11: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to

25 1

Selectivity: 96%

Conversion: 74%

Feed: 2,6-xyleneol/water/MeOH = 1 : 5 : 5 (molar ratio)

Temperature: 400°C

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Example 12: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to

1

Selectivity: 84%

Conversion: 38%

Feed: 2,6-xylenol/MeOH = 1 : 5 (molar ratio)

Temperature: 400°C

Example 13: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to

5 1

Selectivity: 93%

Conversion: 28%

Feed: 2,6-xylenol/MeOH = 1 : 2.5 (molar ratio)

Temperature: 400°C

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Example 14: Use of a Mg-Ga-oxide-catalyst with a weight ratio of Mg to Ga of 10 to

1

Selectivity: 94%

Conversion: 52%

15 Feed: 2,6-xylenol/water/MeOH = 1 : 2.5 : 2.5 (molar ratio)

Temperature: 400°C

Claims

1. Process for the manufacture of 2,4,6-trimethylphenol by reacting phenol or o-cresol or 2,6-xilenol with methanol in the gas phase and in the presence of a catalyst, whereby the catalyst comprises Ga_2O_3 .
5
2. The process according to claim 1, whereby the catalyst further comprises MgO .
3. The catalyst according to claim 2, whereby the catalyst has a Mg/Ga ratio from 1:1 to 15:1.
4. The process according to claim 1, whereby the catalyst consists of Ga_2O_3 and does preferably neither contain titanium oxide nor indium oxide.
10
5. The process according to claim 1 or 2, whereby the catalyst consists of Ga_2O_3 and MgO , preferably with a Mg/Ga ratio from 1:1 to 15:1.
6. The process according to any one or more of the preceding claims, whereby the catalyst does not contain iron oxide(s).
7. The process according to any one or more of the preceding claims, whereby the reaction is carried out at a temperature in the range of from 250 to 600°C, preferably at a temperature in the range of from 400 to 500°C.
15
8. The process according to any one or more of the preceding claims, whereby in case phenol is reacted with methanol, the molar ratio of phenol to methanol is in the range of from 1:3 to 1:30.
20
9. The process according to any one or more of the preceding claims, whereby in case o-cresol is reacted with methanol, the molar ratio of o-cresol to methanol is in the range of from 1:2 to 1:30.
10. The process according to any of the preceding claims, whereby in case 2,6-xilenol is reacted with methanol, the molar ratio of 2,6-xilenol to methanol is in the range of from 1:1 to 1:20.
25
11. The process according to any of the preceding claims, whereby water is present during the reaction.

12. The process according to claim 11, whereby the molar amount of water is at most 20 times the molar amount of phenol, o-cresol and 2,6-xyleneol, respectively.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/064050

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07C37/16 C07C39/07
 ADD.

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)
 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 practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 371 306 A (WOO SEONG-IHL [KR] ET AL) 6 December 1994 (1994-12-06)	1-3,6-8
Y	claims; examples; table 5 -----	4,5,9-12
X	EP 0 019 476 A2 (MITSUI PETROCHEMICAL IND [JP]) 26 November 1980 (1980-11-26) cited in the application claims; examples 2,8,14,27,38,31-34 -----	1,2,6,7
Y	GB 1 451 091 A (TEIJIN LTD) 29 September 1976 (1976-09-29) page 1, line 34 - line 4; claims; examples -----	5,9-12
Y	US 3 418 379 A (PARSEY EDWARD S ET AL) 24 December 1968 (1968-12-24) cited in the application claims; examples ----- -/-	4



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

26 August 2015

Date of mailing of the international search report

03/09/2015

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/064050

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JYH-HARNG KE ET AL: "Ortho-Alkylation of Phenol with Methanol Using Pb-Cr Promoted Magnesium Oxide Catalysts", JOURNAL OF THE CHINESE CHEMICAL SOCIETY, vol. 51, no. 6, 1 December 2004 (2004-12-01), pages 1407-1410, XP55209472, ISSN: 0009-4536, DOI: 10.1002/jccs.200400206 the whole document -----	1-12
A	WON CHOON CHOI ET AL: "Balancing acidity and basicity for highly selective and stable modified MgO catalysts in the alkylation of phenol with methanol", CATALYSIS TODAY, vol. 63, no. 2-4, 1 December 2000 (2000-12-01), pages 229-236, XP55209419, ISSN: 0920-5861, DOI: 10.1016/S0920-5861(00)00464-8 tables 1,2 -----	1-12
A	US 5 245 089 A (IRICK JR GETHER [US] ET AL) 14 September 1993 (1993-09-14) example 7 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/064050

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