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Declarations under Rule 4.17:

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(54) Title: PROCESS FOR THE PRODUCTION OF 5-HYDROXYMETHYLFURFURAL

(57) Abstract: The present invention concerns a process for the production of 5-hydroxymethylfurfural (HMF) from a hexose via a catalytic dehydration reaction in the presence of bis(perfluoroalkylsulfonimide) acid or salts thereof catalysts, and derivatives.



PROCESS FOR THE PRODUCTION OF 5-HYDROXYMETHYLFURFURAL

The present invention concerns a process for the production of 5-hydroxymethylfurfural (HMF) from a hexose via a catalytic dehydration reaction in the presence of bis(perfluoroalkylsulfonimide) acid or salts thereof catalysts, and derivatives.

PRIOR ART

5-Hydroxymethylfurfural (HMF) is a biomass-derived compound that can be applied to the synthesis of precursors of pharmaceuticals, furanose-based polymers, monomers of polymers such as polyamide, and other organic intermediates that can lead to numerous chemical products. As example, oxidation routes of HMF to 2,5-furandicarboxylic acid (FDCA) are well known.

The synthesis of HMF through acid-catalyzed dehydration of monosaccharides has been known for many years. In this respect, many researchers have widely studied the synthesis of HMF from hexose in the past decades. Various types of acid catalysts have been employed in the dehydration reaction, such as mineral acids, for example, sulfuric, hydrochloric, phosphoric acid, and organic acids, for example, citric acid, maleic acid, acetic acid, etc. In spite of simple process, easy operation, low investment, and improving the yield of HMF to a certain extent by using mineral acids as catalysts, they suffer from some limitations in consideration of equipment corrosion, recycling, and difficulties in separation. Solid acid catalysts, for example, ion exchange resin, H-zeolite, metal sulfated, zirconium phosphate, niobic acid, and niobium phosphate overcome some restrictions of mineral acids mentioned above. Nevertheless, solid acid

catalysts also possess some drawbacks because of relatively lower fructose conversions and longer reaction times.

The catalytic dehydration of fructose to 5-hydroxymethylfurfural (HMF) was investigated by using various rare earth metal trifluoromethanesulfonates, that is, $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, $\text{Ho}(\text{OTf})_3$, $\text{Sm}(\text{OTf})_3$, $\text{Nd}(\text{OTf})_3$ as catalysts in DMSO in Carbohydrate Research 346 (2011) 982–985. However, even the best of this catalyst such as $\text{Sc}(\text{OTf})_3$ provides an insufficient HMF yield and a generation of formic acid resulting from the reaction of HMF with water.

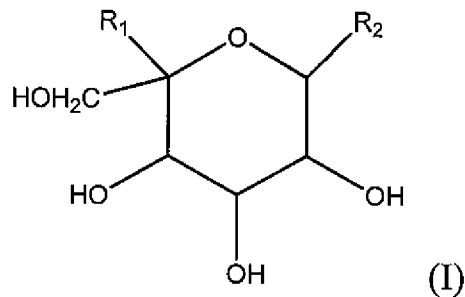
It exists then a need to provide a new generation of environmentally-friendly catalysts to produce HMF permitting then to shift from conventional petrochemical feedstocks towards biomass-based feedstocks, with a better yield and a good reaction selectivity while avoiding the generation of formic acid in the medium.

INVENTION

It appears now that the use of particular bis(perfluoroalkylsulfonimide) acid or salts thereof on hexoses permits to produce 5-hydroxymethylfurfural (HMF) with a high yield and a very low generation of formic acid. Moreover, the reaction is efficient with a catalyst loading that remains relatively low.

The present invention concerns then a process for the production of 5-hydroxymethylfurfural (HMF) from a compound of formula (I) or its corresponding cyclic five-membered structure, via a catalytic dehydration reaction in the presence of catalyst of formula (II)

- Formula (I):



5 wherein :

R^1 is H or OH

R^2 is H or OH

- Formula (II):



wherein:

- RF and R'F, which are identical or different, each represent a perhalogen radical; and

- M is H or a metal element chosen from alkali metal, alkali earth metal,
15 transition metal and lanthanide metal

- n is an integer equal to the valence of M.

The present invention also concerns a HMF susceptible to be obtained according to the process of the invention.

20

Dehydration reaction of the present invention is defined as a chemical reaction that involves the loss of water from the reacting molecule. Dehydration reactions are a subset of elimination reactions involving one or several hydroxyl group(s) (-OH).

25

Formula (I)

Compounds of formula (I) according to the present invention is preferably chosen in the group consisting of: D-glucose and D-fructopyranose.

- 5 D-fructopyranose is the cyclic six-membered structure of the D-fructose. In solution, D-fructopyranose exists as a mixture generally comprising 70% D-fructopyranose and about 22% D-fructofuranose. The open isomer D-glucose gives rise to two distinct cyclic forms: D-glucopyranose, and D-glucofuranose.

10

It has to be noticed that it's perfectly possible to use several compounds of formula (I) during the reaction of the present invention.

- Concentration of compound of formula (I) may be comprised between 0.001
15 and 10 mol.L⁻¹, when a solvent is used in the reaction medium.

Catalyst of formula (II)

- Concerning the catalyst of formula (II), RF and R'F, which are identical or different, represent a perhalogen radical, which is preferably having from 1 to
20 12 carbon atoms. Halogen atoms in the perhalogen radicals may be for example F or Cl. Preferably RF and R'F, which are identical or different, represent CF₃.

- Metal elements of the periodic table may be chosen in the group consisting
25 of:

- alkali metals, such as K or Cs,
- alkaline earth metals, such as Ca,
- lanthanides, such as La or Ce, and
- transition metals, such as Ti, Y, Zn, Cu or Fe.

Metal elements M of period 4 are particularly preferred, such as Ca and Cu.

5 Catalysts of the present invention are preferably chosen in the group consisting of: $\text{H}(\text{NTf}_2)$, $\text{K}(\text{NTf}_2)$, $\text{Y}(\text{NTf}_2)_3$, $\text{La}(\text{NTf}_2)_3$, $\text{Zn}(\text{NTf}_2)_2$, $\text{Cs}(\text{NTf}_2)$, $\text{Ca}(\text{NTf}_2)_2$, $\text{Fe}(\text{NTf}_2)_3$, $\text{Cu}(\text{NTf}_2)_2$, $\text{Ti}(\text{NTf}_2)_4$ and $\text{Ce}(\text{NTf}_2)_3$.

10 A combination of two or more catalysts of the present invention may be used during the reaction of the present invention, notably in blend. As example, a combination of $\text{H}(\text{NTf}_2)$ and $\text{Cu}(\text{NTf}_2)_2$ is particularly preferred.

Catalyst loading during the reaction may be comprised between 0.01 and 100 mol%, preferably between 1 and 30, in relation with the molar amount of the compound of formula (I).

15 Catalyst of the invention may be used in a homogeneous or heterogeneous way.

20 Catalyst may be supported on a carrier, such as for example one of the oxides, carbons or organic or inorganic resins. Notably, the carrier may be selected from the group consisting of silica, alumina, zirconia, titania, ceria, magnesia, lanthania, niobia, yttria, zeolite, perovskite, silica clay, and iron oxide and mixtures thereof. The catalyst may be supported on a carrier in any convenient fashion, particularly by adsorption, ion-exchange, grafting, 25 trapping, impregnation, or sublimation.

Reaction of the present invention may be carried out by using a catalyst-ligand complex in which catalyst is the compound of formula (II). Although there are no particular restrictions on the ligand in the present invention

provided it is a Lewis base having the ability to coordinate to a catalyst of formula (II), ligand is preferably chosen in the family of carbene ligand, π -type ligand phosphorous ligand, oxygen ligand and nitrogen ligand. Suitable ligands to be used according to the present invention are phosphorus ligands
5 such as halophosphites such as fluorophosphites, phosphites, phosphinites, phosphonites, and phosphine. Monodentate phosphine ligands and bidentate diphosphine ligand such as xantphos are particularly preferred.

It has to be noticed that the catalyst-ligand complex may be prepared before
10 the start of the reaction of the present invention or in situ at the start or during the reaction.

Solvent

The process of the present invention may be carried out without solvent. It is
15 also possible to use a solvent or a combination of solvents for the reaction, preferably solvents able to dissolve the compound of formula (I) and also solvent able to dissolve the compound of formula (I) and the compound of formula (II).

20 Preferred solvents used in the reaction medium of the present invention are polar aprotic solvent, more preferably selected among:

- linear ethers, such as diethylether, dimethoxyethane or cyclic ethers, such as tetrahydrofuran, dioxane or dimethyltetrahydrofuran,
- esters, such as methyl or ethyl formate, propylene or ethylene carbonate,
25 or butyrolactones,
- nitriles, acetonitriles, benzonitriles,
- nitrate derivatives, such as nitromethane or nitrobenzene,
- amides, such as dimethylformamide, diethylformamide and N-methylpyrrolidone,

- sulfones, such as dimethyl sulfone, tetramethylene sulfone and other sulfolanes.
- sulfoxides, such as DMSO.

5 Notably, when the medium of the reaction comprises a polar aprotic solvent, said medium comprises less than 10 wt % of water, notably at the start of the reaction.

Parameters

- 10 The temperature at which reaction is performed may vary in a large range, but in general it is preferred that the reaction is carried out at a temperature from 0 and 300°C, more preferably between 50 and 150°C. Temperatures may be reached either thermically or by microwave irradiation.
- 15 Pressure range of the reaction may be comprised between 1 and 100 bar. Reaction of the present invention may be carried out for a range time comprised between 10 min to 24 hours.

This reaction may be conducted in any conventional equipment suitable to
20 effect production of HMF. This reaction may be carried out in a continuous or a discontinuous fashion. For example, suitable equipments include a stirred tank or loop reactor.

End of reaction may be carried out by stop of the temperature and cooling of
25 the reaction medium, notably air cooling.

The efficiency of the process of the present invention can be monitored by any conventional analytical means, such as Infrared spectroscopy, NMR, Raman spectroscopy, GC and HPLC.

At the end of the reaction, catalysts may be eventually neutralized and/or removed by distillation, extraction or washings. Said catalysts may notably be recycled to the reactor.

5

HMF of interest can be purified by well known methods of the technical field, such as distillation, crystallization, liquid extraction or extraction with a polymer to adsorb HMF.

- 10 The examples provided here further describe and demonstrate embodiments of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitation of the present invention

EXPERIMENTAL PART

15 **Example 1: D-fructose**

5 mol% of different catalysts are blended with 0.2 mol.L⁻¹ of D-fructose in DMSO. Reaction occurs under microwave irradiation at a temperature of 120°C for 1 hour.

- 20 Results determined by ¹H NMR analysis (with biphenyl as internal reference) are mentioned in Table 1 :

Table 1

N°	Catalyst	HMF yield (%)	Formic acid yield (%)
C1	No	38	3
C2	Sc(OTf) ₃	67	7
C3	Bi(NTf ₂) ₃	8	25
C4	Al(NTf ₂) ₃	60	6
1	Zn(NTf ₂) ₂	68	3
2	Cs(NTf ₂)	70	2
3	Ca(NTf ₂) ₂	75	< 1
4	Fe(NTf ₂) ₃	86	3
5	Ce(NTf ₂) ₃	86	2
6	Cu(NTf ₂) ₂	87	0
7	Ti(NTf ₂) ₄	85	< 1
8	H(NTf ₂)	75	< 1
9	50/50 mol % of H(NTf ₂) + Cu(NTf ₂) ₂	92	< 1

It appears then that the use of the following catalysts H(NTf₂), Zn(NTf₂)₂, Cs(NTf₂), Ca(NTf₂)₂, Fe(NTf₂)₃, Ce(NTf₂)₃ and Cu(NTf₂)₂ permits to provide
5 a better yield (68-87%), in comparison with the best described triflate Sc(OTf)₃ (67%).

Example 2: Ligands

5 mol% of different catalysts are blended with 0.2 mol.L⁻¹ of D-fructose in
10 DMSO and 5 mol % of xantphos ligand [4,5-Bis(diphenylphosphino)-9,9-

dimethylxanthene]. Reaction occurs under microwave irradiation at a temperature of 120°C for 1 hour.

Results determined by ^1H NMR analysis (with biphenyl as internal reference)

5 are mentioned in Table 2 :

Table 2

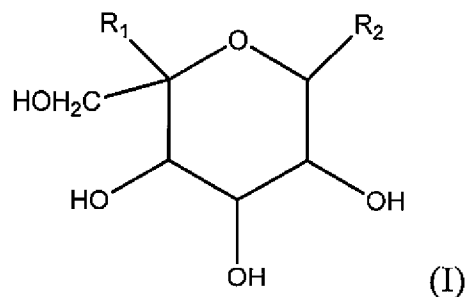
N°	Catalyst	HMF yield (%)	Formic acid yield (%)
10	$\text{Cu}(\text{NTf}_2)_2$	97	< 1
11	$\text{Ti}(\text{NTf}_2)_4$	97	< 1

10 It appears then that a diphosphine ligand such as Xantphos is efficiently activating $\text{Ti}(\text{NTf}_2)_4$ and $\text{Cu}(\text{NTf}_2)_2$ that permits to provide a higher yield to the reaction while avoiding generation of formic acid.

WHAT IS CLAIMED IS:

1. Process for the production of 5-hydroxymethylfurfural from a compound of formula (I) or its corresponding cyclic five-membered structure, via a catalytic dehydration reaction in the presence of catalyst of formula (II)

- Formula (I):



wherein :

R^1 is H or OH

R^2 is H or OH

- Formula (II):



wherein:

- RF and R'F, which are identical or different, each represent a perhalogen radical; and

- M is H or a metal element chosen from alkali metal, alkali earth metal, transition metal and lanthanide metal

- n is an integer equal to the valence of M.

2. A process according to claim 1, wherein the compound of formula (I) is chosen in the group consisting of: D-glucose and D-fructopyranose.

3. A process according to claim 1 or 2, wherein concentration of compound of formula (I) is comprised between 0.001 and 10 mol.L⁻¹, when a solvent is used in the reaction medium.

5

4. A process according to anyone of claims 1 to 3, wherein metal elements of the periodic table are in the group consisting of:

- alkali metals, such as K or Cs,
- alkaline earth metals, such as Ca,
- 10 - lanthanides, such as La or Ce, and
- transition metals, such as Ti, Y, Zn, Cu or Fe.

5. A process according to anyone of claims 1 to 4, wherein catalyst is chosen in the group consisting of: H(NTf₂), K(NTf₂), Y(NTf₂)₃, La(NTf₂)₃,
15 Zn(NTf₂)₂, Cs(NTf₂), Ca(NTf₂)₂, Fe(NTf₂)₃, Cu(NTf₂)₂, Ti(NTf₂)₄ and Ce(NTf₂)₃.

6. A process according to anyone of claims 1 to 3, wherein catalyst is a combination of H(NTf₂) and Cu(NTf₂)₂.

20

7. A process according to anyone of claims 1 to 6, wherein the catalyst loading during the reaction is comprised between 0.01 and 100 mol%, in relation with the molar amount of the compound of formula (I).

25 8. A process according to anyone of claims 1 to 7, wherein the catalyst is a catalyst-ligand complex.

9. A process according to anyone of claims 1 to 8, wherein a solvent is used in the reaction medium.

10. A process according to claim 9, wherein the solvent is a polar aprotic solvent, selected among:

- linear ethers or cyclic ethers,
- 5 - esters,
- nitriles, acetonitriles, benzonitriles,
- nitrate derivatives,
- amides,
- sulfones, and
- 10 - sulfoxides.

11. Process according to anyone of claims 1 to 10, wherein the temperature of the reaction is comprised between 0 and 300°C.

- 15 12. 5-hydroxymethylfurfural susceptible to be obtained according to the process of claims 1 to 11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2012/084870

A. CLASSIFICATION OF SUBJECT MATTER

C07D 307/46 (2006.01) i

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: C07D 307

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)

SIPOABS, DWPI, CNABS, CPRSABS, CNKI, REGISTRY, CAPLUS(STN), hydroxymethylfurfural, hydroxy w methylfurfural, hydroxy w methyl w furfural, hydroxymethyl w furfural, HMF, hexose?, fructose?, glucose?, carbohydrate?, +saccharide?, pentose?, +imide+, search according to the structures of the starting compounds and the target compound in claim 1, CAS RN: 67-47-0

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Wang, Fenfen et al., Dehydration of fructose to 5-hydroxymethylfurfural by rare earth metal trifluoromethanesulfonates in organic solvents, Carbohydrate Research, 10 March 2011 (10.03.2011), vol. 346, pages 982-985, see the whole document, especially page 985	1-11
X	the same as above	12
A	Zhang, Zehui et al., Catalytic conversion of carbohydrates into 5-hydroxymethylfurfural by germanium(IV) chloride in ionic liquids, ChemSusChem, 2011, vol. 4, pages 131-138, see the whole document, especially page 137	1-11
X	the same as above	12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“E” earlier application or patent but published on or after the international filing date	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&” document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
03 July 2013 (03.07.2013)

Date of mailing of the international search report
29 Aug. 2013 (29.08.2013)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2012/084870

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Zhang, Yanmei et al., Molecular aspects of glucose dehydration by chromium chlorides in ionic liquids, Chem. Eur. J., 2011, vol. 17, pages 5281-5288, see the whole document, especially page 5287	1-11
X	the same as above	12
A	CN 102399203 A (UNIV ZHEJIANG) 04 April 2012 (04.04.2012) see the whole document, especially the examples	1-11
X	the same as above	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2012/084870

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

I: Claims 1-11 relate to processes for the production of 5-hydroxymethylfurfural;

II: Claim 12 relates to 5-hydroxymethylfurfural susceptible to be obtained according to the process of claims 1 to 11.

The same or corresponding technical feature between the two groups of claims is as follows: 5-hydroxymethylfurfural. However, this compound has been disclosed in D1(Wang, Fenfen et al., Dehydration of fructose to 5-hydroxymethylfurfural by rare earth metal trifluoromethanesulfonates in organic solvents, Carbohydrate Research, 10 March 2011 (10.03.2011), vol. 346, pages 982-985, see the whole document, especially page 985). It means that the same or corresponding technical feature of the above claims does not make a contribution over the prior art and can not be considered as a special technical feature within the meaning of PCT Rule 13.2. Therefore, the application does not meet the requirement of unity of invention as defined in PCT Rule 13.1.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2012/084870

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 102399203 A	04.04.2012	None	