



Purification of 5-hydroxymethylfurfural (hmf) by crystallization

Riisager, Anders; Jensen, Jacob S.; Ståhlberg, Tim Johannes Bjarki; Woodley, John

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Riisager, A., Jensen, J. S., Ståhlberg, T. J. B., & Woodley, J. (2013). Purification of 5-hydroxymethylfurfural (hmf) by crystallization. (Patent No. *WO2013024162*).

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



WIPO | PCT



(10) International Publication Number
WO 2013/024162 A1

(43) International Publication Date
21 February 2013 (21.02.2013)

- (51) **International Patent Classification:**
C07D 307/46 (2006.01)
- (21) **International Application Number:**
PCT/EP2012/066125
- (22) **International Filing Date:**
17 August 2012 (17.08.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
PA 2011 00627 18 August 2011 (18.08.2011) DK
61/524,963 18 August 2011 (18.08.2011) US
- (71) **Applicant (for all designated States except US):** DAN-
MARKS TEKNISKE UNIVERSITET [DK/DK]; Anker
Engelunds Vej 1, DK-2800 Kgs. Lyngby (DK).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** STÅHLBERG, Tim
[SE/DK]; Møntmestervej 46, 3.tv, DK-2400 København
NV (DK). JENSEN, Jacob Skibsted [DK/DK]; Pileg-
aardsvej 41, st. th., DK-2730 Herlev (DK). RIISAGER,
Anders [DK/DK]; Rønnevangshusene 138, DK-2630
Taastrup (DK). WOODLEY, John M. [GB/DK]; Sorte-
dam Dossering 79, 3, th., DK-2100 København Ø (DK).
- (74) **Agent:** ZACCO DENMARK A/S; Hans Bekkevolds Allé
7, DK-2900 Hellerup (DK).
- (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, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,
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, 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,
ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))



WO 2013/024162 A1

(54) **Title:** PURIFICATION OF 5-HYDROXYMETHYLFURFURAL (HMF) BY CRYSTALLIZATION

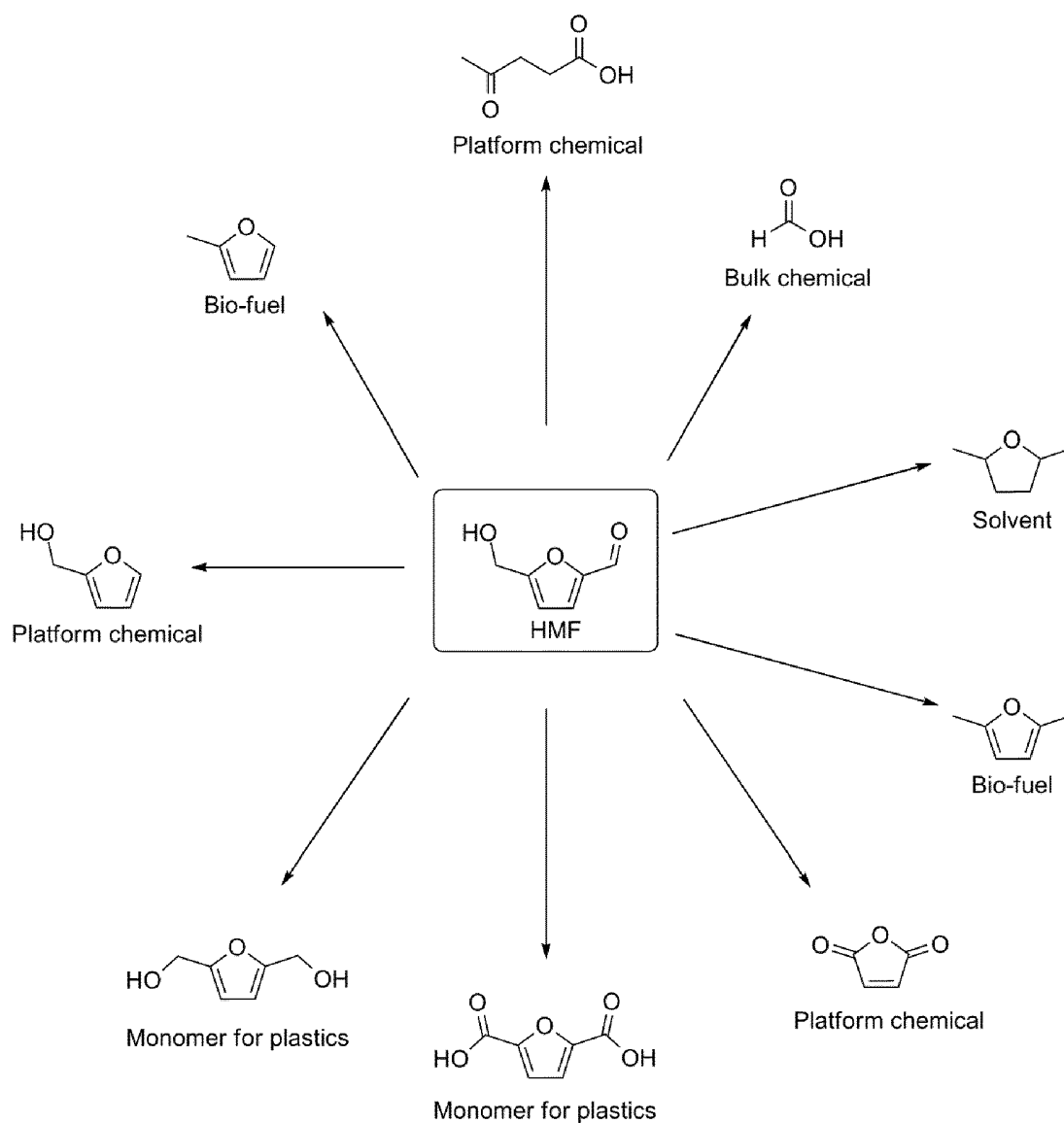
(57) **Abstract:** This invention relates to an efficient procedure for purifying HMF by crystallization at low temperature from an organic solvent.

Purification of 5-hydroxymethylfurfural (HMF) by crystallization

Background:

- 5 Many chemical compounds needed for various industries have for many years been derived from the petrochemical industry. However, due to increases in the price of crude oil and a general awareness of replacing petrochemicals with renewable resources there has been and still is a wish to base the production of chemical compounds on renewable resources.
- 10 5-Hydroxymethylfurfural (HMF) is an example of such a compound because it is derived from dehydration of sugars making it derivable from renewable biomass resources. HMF can for example be converted to 2,5-dimethylfuran which is a liquid biofuel or to 2,5-furandicarboxylic acid by oxidation. The latter compound, 2,5-furandicarboxylic acid (FDA), can be used as a replacement of terephthalic acid in the production of polyesters such as polyethylene-
- 15 terephthalate (PET) and polybutyleneterephthalate (PBT).

Examples of interesting derivatives produced from HMF in addition to FDA are shown below:



In certain applications the purity of HMF is crucial. For such purposes an efficient purification method that affords HMF with high purity and minimal loss on purification is essential.

- 5 However, the low melting point of HMF and its high solubility in most common solvents renders its purification by crystallization particularly difficult.

Only a few papers and patents discuss the industrial scale production of HMF, and even fewer discuss the actual isolation of HMF. Furthermore, there is surprisingly little information on the purification of HMF, another vital aspect of large scale production. Even though the exact future application of HMF at this stage is unknown, a robust purification protocol would
5 be of the essence. A few examples can be found in the literature such as purification by distillation, chromatography and crystallization. However, these methods either involve the use of environmentally questionable solvents such as CH_2Cl_2 or excessive solvent use. Moreover, many of the methods have insufficient data on purity. The limited amount of published purification procedures for HMF could be due to its low melting point making
10 crystallization, the preferred purification method for large scale production, more difficult.

There is thus a need for developing an efficient procedure for purifying crude HMF.

Figures:

15 Graph 1: DSC spectrum of HMF recorded on Perkin Elmer PYRIS Diamond DSC comprising an event with a peak at about $30\text{ }^\circ\text{C}$ ($\pm 2\text{ }^\circ\text{C}$).

Graph 2: FTIR spectrum of HMF recorded on Perkin-Elmer "spectrum one", 16 scans, 4 cm^{-1} using Perkin-Elmer "Universal ATR sampling accessory".

20 Summary of the invention:

In their search for a purification procedure the inventors screened a number of conventional organic solvents in order to attempt a crystallization of crude HMF from a reaction mixture. From this survey it turned out that pure HMF can be precipitated in solid form at temperatures below zero from a solution of crude HMF in an organic solvent or solvent mixture having a
25 freezing point of $-50\text{ }^\circ\text{C}$ or lower, such as dialkyl ethers $\text{R}_1\text{-O-R}_2$, wherein R_1 and R_2 are individually selected from linear $\text{C}_1\text{-C}_6$ alkyl groups, branched $\text{C}_3\text{-C}_6$ alkyl groups and cyclic $\text{C}_3\text{-C}_6$ alkyl groups, which solution may further contain from 0-10% by volume of a different organic solvent selected from esters $\text{R}_3\text{-COOR}_4$ and aromatic hydrocarbons ArR_5R_6 , wherein
30 R_3 and R_4 are individually selected from linear $\text{C}_1\text{-C}_6$ alkyl groups, branched $\text{C}_3\text{-C}_6$ alkyl groups and cyclic $\text{C}_3\text{-C}_6$ alkyl groups, and wherein ArR_5R_6 denotes a phenyl ring substituted

with two substituents R_5 and R_6 individually selected from hydrogen, halogen, linear C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups, and isolated eg. by filtration without melting.

Methyl tert-butyl ether (MTBE) is an example of such a solvent. When decreasing the temperature to $-30\text{ }^\circ\text{C}$, a white precipitate of HMF was formed from a solution of crude HMF in MTBE. The precipitate could be filtered off and washed with MTBE and subsequently 1-pentane. The low boiling point of pentane enabled efficient drying of HMF without melting the product. The purity was found to be $>99\%$ according to HPLC and the yield app 90% .

10 **In a first aspect** the invention thus relates to a process for isolating pure 5-hydroxymethyl-furfural (HMF) in solid form, comprising the steps of:

- a) Providing a solution of crude HMF in an organic solvent or solvent mixture having a freezing point of $-50\text{ }^\circ\text{C}$ or lower,
- b) Optionally filtering said solution to remove insoluble particles,
- 15 c) Cooling the obtained solution to reach a final temperature of between 0 and $-40\text{ }^\circ\text{C}$,
- d) Optionally adding crystallization seed crystals,
- e) Stirring the resulting suspension at the final temperature until the precipitation is deemed complete,
- f) Isolating the precipitated solid HMF by filtering the suspension at the final
20 temperature,
- g) Optionally washing the isolated solid HMF with a low-boiling hydrocarbon like 1-pentane,
- h) Drying the isolated solid HMF, optionally *in vacuo*.

25 In a preferred embodiment of the invention the organic solvent or solvent mixture in step a) of the process of the first aspect is selected from one or more dialkylethers R_1 -O- R_2 wherein R_1 and R_2 are individually selected from linear C_1 - C_6 alkyl groups, branched C_3 - C_6 alkyl groups and cyclic C_3 - C_6 alkyl groups, which solution further contains from 0 - 10% by volume of a different organic solvent selected from esters R_3 -COOR₄ and aromatic hydrocarbons ArR_5R_6 ,
30 wherein R_3 and R_4 are individually selected from linear C_1 - C_6 alkyl groups, branched C_3 - C_6

alkyl groups and cyclic C₃-C₆ alkyl groups, and wherein ArR₅R₆ denotes a phenyl ring substituted with two substituents R₅ and R₆ individually selected from hydrogen, halogen, linear C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups.

5 In another embodiment the cooling of the solution in step c) is carried out at a rate of between 0.5-2 °C per minute.

In another embodiment the precipitation and isolation of the precipitated solid HMF is conducted at final temperature of between -25 and -35 °C, preferably around -30 °C.

10 In another embodiment the solution of crude HMF in an organic solvent or solvent mixture is provided by dissolving crude HMF in 3-5 volumes (L per kg crude HMF) of said organic solvent or solvent mixture, optionally by heating.

15 In another embodiment the solution of crude HMF in an organic solvent or solvent mixture is provided directly during extractive work-up of the chemical process leading to crude HMF by using said organic solvent or solvent mixture for the extraction, optionally followed by partial removal of said organic solvent or solvent mixture by evaporation until a solution containing 3-5 volumes organic solvent or solvent mixture (L per kg crude HMF) is achieved.

20 In a preferred embodiment R₁ is methyl and R₂ is selected from *tert*-butyl and cyclopentyl.

In another preferred embodiment the dialkylether is methyl *tert*-butyl ether (MTBE).

25 In another preferred embodiment HMF is isolated in >90% crystalline form having a chemical purity of at least 95% by weight, preferably at least 99% by weight.

In another embodiment the HMF obtainable by a process according to any one of the embodiments of the invention is crystalline and further characterized by having a differential

scanning calorimetry curve substantially identical to Graph 1 comprising an event with a peak at about 30 °C (± 2 °C).

In another embodiment the HMF obtainable by a process according to any one of the
5 embodiments of the invention is crystalline and further characterized by an ATR-FTIR spectrum substantially identical to Graph 2.

Experimental:

10 Crude HMF produced from a literature procedure (R. M. Musau *et al.*, Biomass 1987, 13, 67–74) was dissolved in 4 volumes (L solvent/kg product) of MTBE at room temperature. The temperature was decreased to -30 °C and after 30 minutes crystal formation was observed. The mixture was left to crystallize for 12 hours after which the crystals were filtered off at -30 °C. The crystals were washed with of 1-pentane (1 volume) and sucked dry (90 % yield,
15 >99 % pure by HPLC).

The crystals were analyzed by Differential Scanning Calorimetry (Graph 1) and attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy (Graph 2).

20 The described procedure is superior compared to previously described crystallization methods because of the high yield (>90%) and high purity (>99%) of the isolated product which may be achieved, and because industrially acceptable solvents like MTBE may be employed. Furthermore, the described procedure is superior to chromatographic methods because of the modest consumption of solvent. Finally, the overall procedure may be further
25 optimized using appropriate anti-solvents, by applying seeding and/or by adjusting temperature ramps during the precipitation step.

Claims:

1. A process for isolating pure 5-hydroxymethylfurfural (HMF) in solid form, comprising the steps of:
 - a) Providing a solution of crude HMF in an organic solvent or solvent mixture having a freezing point of -50 °C or lower,
 - b) Optionally filtering said solution to remove insoluble particles,
 - c) Cooling the obtained solution to reach a final temperature of between 0 and -40 °C,
 - d) Optionally adding crystallization seed crystals,
 - e) Stirring the resulting suspension at the final temperature until the precipitation is deemed complete,
 - f) Isolating the precipitated solid HMF by filtering the suspension at the final temperature,
 - g) Optionally washing the isolated solid HMF with a low-boiling hydrocarbon like 1-pentane,
 - h) Drying the isolated solid HMF, optionally *in vacuo*.

2. The process of claim 1 wherein the organic solvent or solvent mixture in step a) is selected from one or more dialkylethers R_1-O-R_2 wherein R_1 and R_2 are individually selected from linear C_1-C_6 alkyl groups, branched C_3-C_6 alkyl groups and cyclic C_3-C_6 alkyl groups, which solution further contains from 0-10% by volume of a different organic solvent selected from esters R_3-COOR_4 and aromatic hydrocarbons ArR_5R_6 , wherein R_3 and R_4 are individually selected from linear C_1-C_6 alkyl groups, branched C_3-C_6 alkyl groups and cyclic C_3-C_6 alkyl groups, and wherein ArR_5R_6 denotes a phenyl ring substituted with two substituents R_5 and R_6 individually selected from hydrogen, halogen, linear C_1-C_6 alkyl groups and C_1-C_6 alkoxy groups.

3. The process of claim 1 or 2 wherein the cooling of the solution in step c) is carried out at a rate of between 0.5-2 °C per minute.

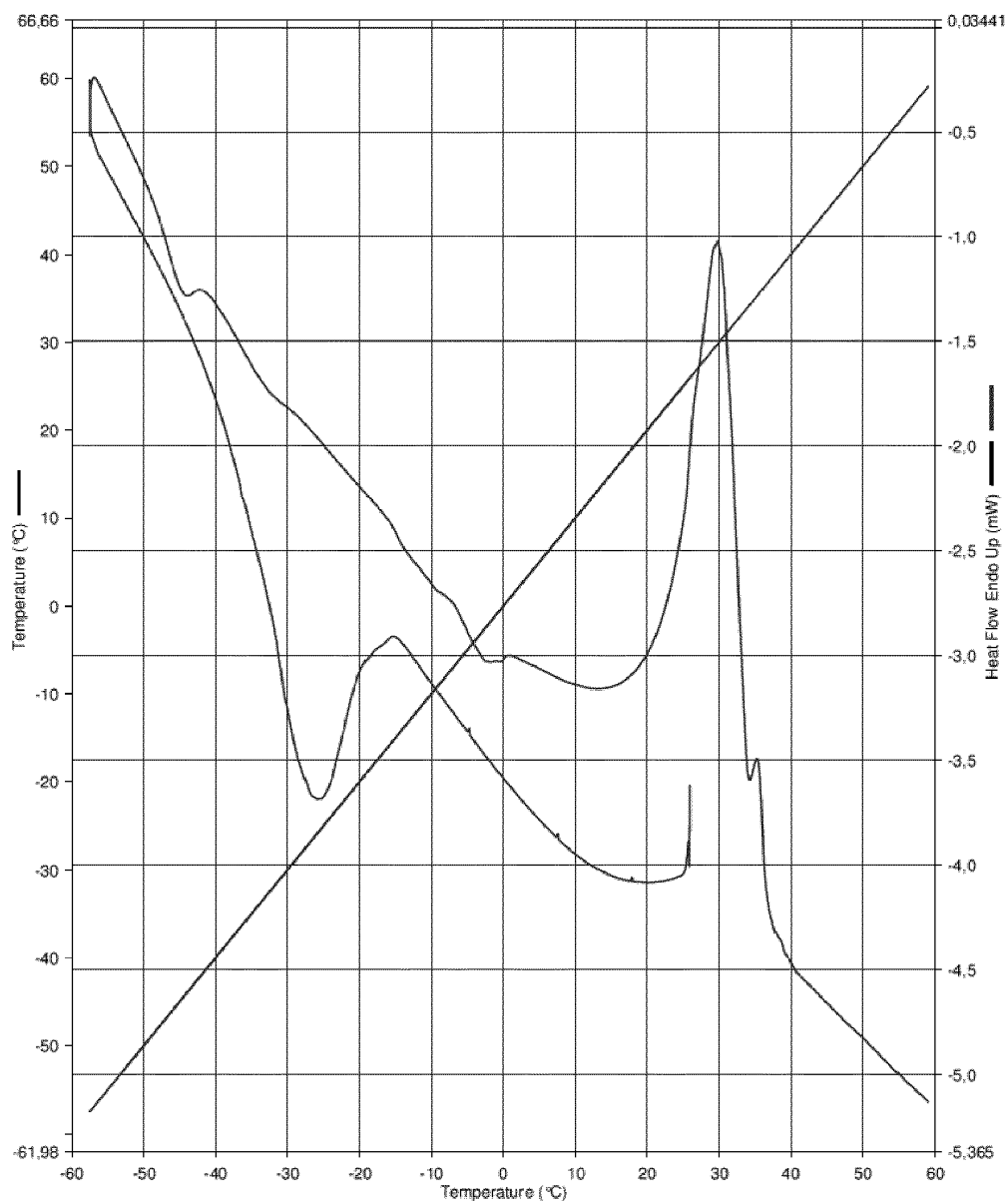
4. The process of any one of the preceding claims wherein the precipitation and isolation of the precipitated solid HMF is conducted at final temperature of between -25 and -35 °C, preferably around -30 °C.

5. The process of any one of the preceding claims wherein the solution of crude HMF in an organic solvent or solvent mixture is provided by dissolving crude HMF in 3-5 volumes (L per kg crude HMF) of said organic solvent or solvent mixture, optionally by heating.

- 5 6. The process of claim 1-4 wherein the solution of crude HMF in an organic solvent or solvent mixture is provided directly during extractive work-up of the chemical process leading to crude HMF by using said organic solvent or solvent mixture for the extraction, optionally followed by partial removal of said organic solvent or solvent mixture by evaporation until a solution containing 3-5 volumes organic solvent or solvent mixture (L per kg crude HMF) is achieved.
- 10 7. The process of any one of the preceding claims wherein R₁ is methyl and R₂ is selected from tert-butyl and cyclopentyl.
- 15 8. The process of any one of the preceding claims wherein the dialkylether is methyl *tert*-butyl ether (MTBE).
- 20 9. The process of any one of the preceding claims wherein HMF is isolated in >90% crystalline form having a chemical purity of at least 95% by weight, preferably at least 99% by weight.
10. Crystalline HMF obtainable by a process according to any one of claims 1-9 further characterized by having a differential scanning calorimetry curve substantially identical to Graph 1 comprising an event with a peak at about 30 °C (± 2 °C).
- 25 11. Crystalline HMF obtainable by a process according to any one of claims 1-9 further characterized by an ATR-FTIR spectrum substantially identical to Graph 2.

GRAPH 1

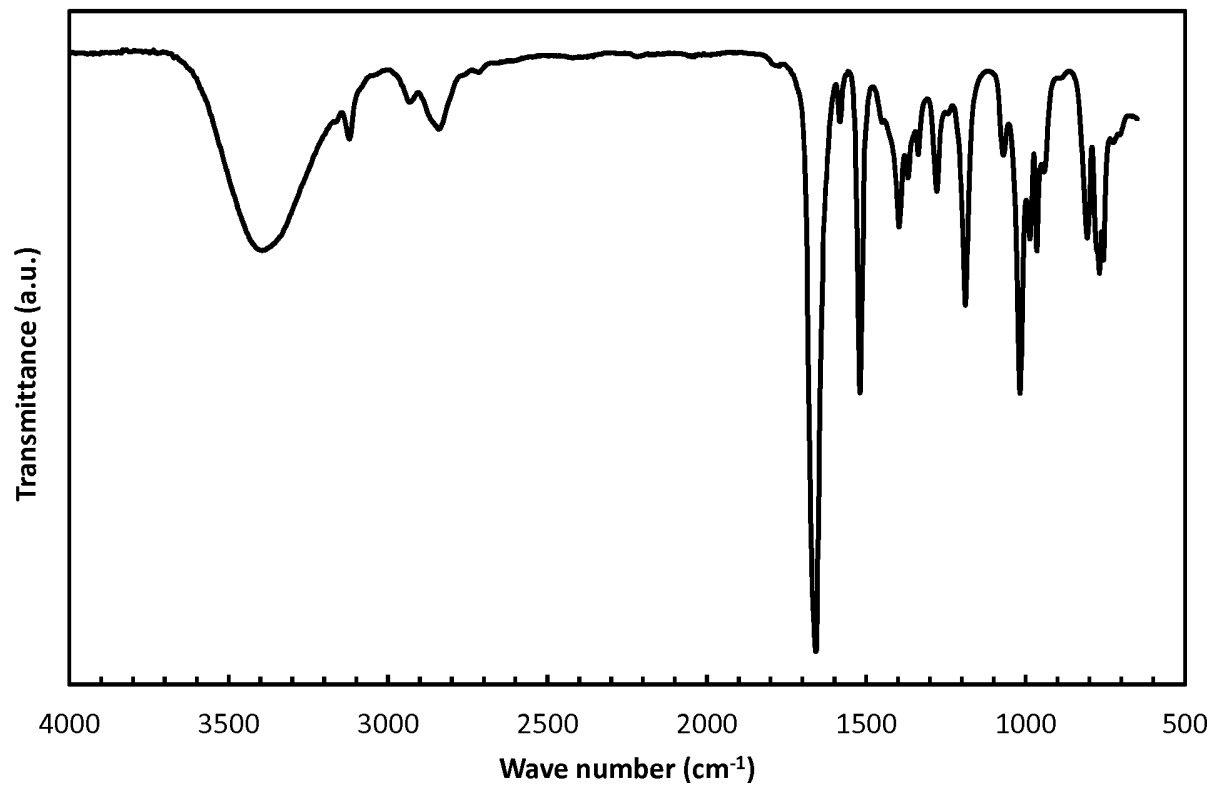
Filename: C:\Program Files\Pyris\Da...tim-hmf-2.pdtd
Operator ID: BH
Sample ID: TIM-HNF
Sample Weight: 8.800 mg
Comment:



18-08-2011 13:56:45

1) Cool from 25.00°C to -60.00°C at 2.00°C/min 2) Heat from -60.00°C to 60.00°C at 2.00°C/min

GRAPH 2



INTERNATIONAL SEARCH REPORT

International application No PCT/EP2012/066125

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D307/46 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) C07D		
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, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR 2 669 635 A1 (FURCHIM [FR]) 29 May 1992 (1992-05-29) claim 14 -----	1-11
Y	DATABASE WPI Thomson Scientific, London, GB; AN 2009-L64526 XP002661148, & CN 101 475 543 A (SHANXI COAL CHEM INST [CN]) 8 July 2009 (2009-07-08) abstract -----	1-11
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance	"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	
"E" earlier application or patent but published on or after the international filing date	"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	
"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)	"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	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"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	Date of mailing of the international search report	
16 October 2012	24/10/2012	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lauro, Paola	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/066125

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2669635	A1	NONE	

CN 101475543	A	08-07-2009	NONE
