

# Synthesis, chemistry and applications of 5-hydroxymethylfurfural and its derivatives

Jarosław Lewkowski

*Department of Organic Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, POLAND*

*E-mail: [JLEWKOW@kryisia.uni.lodz.pl](mailto:JLEWKOW@kryisia.uni.lodz.pl)*

(received 26 Jun 05; accepted 31 Jul 01; published on the web 08 Aug 01)

## Contents

### Introduction

#### **PART A. 5-HYDROXYMETHYLFURFURAL (HMF)**

##### **1. A historical outline of studies on 5-hydroxymethylfurfural (HMF)**

##### **2. Aspects of the synthesis of HMF**

2.1. The mechanism of the fructose dehydration

2.2. The kinetics of the HMF synthesis

##### **3. Chemical conversions of HMF**

3.1. Reactions of the Hydroxymethyl Group

3.1.1. The formation of esters

3.1.2. The formation of ethers

3.1.3. The formation of halides

3.1.4. The oxidation

3.2. Reactions of the Formyl Group

3.2.1. The reduction

3.2.2. Condensation reactions

3.2.3. Oxidation reactions

3.3. Reactions of the furan ring

3.4. The polymerisation of HMF

3.5. Electrochemical conversions of HMF

#### **PART B. 2,5-FURANDICARBALDEHYDE (FDC)**

##### **4. The Synthesis of 2,5-Furandicarbaldehyde (FDC)**

##### **5. The Chemistry and Applications of 2,5-Furandicarbaldehyde (FDC)**

#### **PART C. 2,5-FURANDICARBOXYLIC ACID (FDCA)**

##### **6. Methods for Synthesis of 2,5-Furandicarboxylic Acid (FDCA)**

##### **7. The Chemistry and Applications of 2,5-Furandicarboxylic Acid (FDCA)**

### Conclusions

### References

## Introduction

The prospect of exciting research activity in the chemistry of furfural derived compounds such as 5-hydroxymethylfurfural (HMF), 2,5-furandicarbaldehyde and 2,5-furan-dicarboxylic acid prompted the writing of this article. As the field of application of these compounds is really enormous, it is no wonder that research in this area, starting at the end of 19<sup>th</sup> century, is still being developed. Numerous important scientific groups are carrying out studies on the synthesis, and applications of HMF and its derivatives. Notable among these are, Gaset (Toulouse), Descotes (Lyon), Lichtenthaler (Darmstadt), and Gelas (Clermont-Ferrand). Not only academic scientists are interested in this subject, the chemical industry, is represented by sugar companies such as Beghin-Say, and Süddeutsche Zucker. Despite this interest, there are not many comprehensive monographs or reviews covering the chemistry of HMF. Two classic reviews, by Newth<sup>1</sup> and by Feather and Harris,<sup>2</sup> appeared in 1951 and 1973 respectively. Reviews by Gaset *et al.*,<sup>3</sup> Faury *et al.*<sup>4</sup> and by Kuster<sup>5</sup> are more recent, but they are not detailed. An important review review by Cottier and Descotes<sup>6</sup> appeared in 1991.

This review is written to update those above, to summarize the contributions of the last 100 years; and to emphasize recent developments especially in electrochemistry, and on dialdehyde and diacid chemistry.

## PART A. 5-HYDROXYMETHYLFURFURAL (HMF)

### 1. A historical outline of studies on 5-hydroxymethylfurfural (HMF)

5-Hydroxymethylfurfural (HMF) 1 has been of interest since the last decade of the 19<sup>th</sup> century. In 1895 Düll<sup>7</sup> and Kiermeyer<sup>8</sup> working independently, published a method of synthesis and chemical reactions of the compound, which they called “oxymethylfurfurol”.

Later on, British chemists started their conquest; Fenton,<sup>9</sup> Gostling<sup>10</sup> and Robinson<sup>11</sup> published the results of their studies on HMF. In 1919, Middendorp<sup>12</sup> presented the full and the detailed study concerning the synthesis, the physical characterisation and the chemical behaviour of HMF.

Several years later other authors published their results, as for example Reichstein<sup>13,14</sup> and Haworth and Jones<sup>15</sup> – especially the latter brought immense progress in the chemistry of HMF. They worked out the modern method of its synthesis and studied the mechanism of its formation. From among a great number of papers concerning the chemistry of HMF, Karashima's article is worth mentioning.<sup>16</sup> He worked out the method of synthesis of 5-acetoxymethylfurfural directly from HMF and fully characterised this compound. He reported also the formation of 5-hydroxymethylfurfurylideneacetic acid by the Perkin condensation of HMF with acetic anhydride.

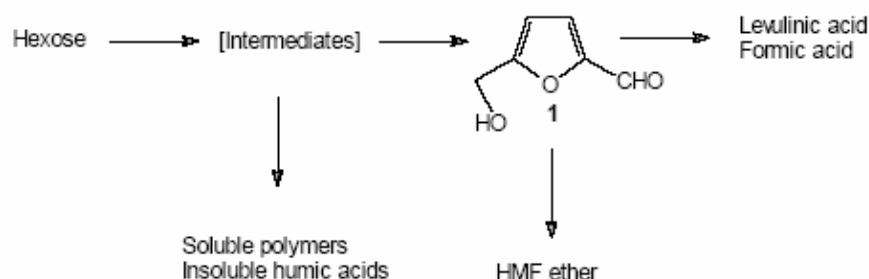
Till now, over 1000 papers have been published, which is a proof for the great importance of this kind of compounds. It is not possible in this work to quote all of these articles, but some reviews are worth mentioning. In the “Advances in Carbohydrate Chemistry” series, two articles were published, first by Newth<sup>1</sup> in 1951, the second appeared 20 years later by Feather.<sup>2</sup> Moye<sup>17</sup> has written a review describing methods of the preparation and industrial applications of HMF.

Later, in the 80's, two papers were published; Gaset *et al*<sup>3</sup> reviewed industrial methods of the preparation of HMF, Faury<sup>4</sup> dealt with newest chemical conversions of this compound.

Recently, Kuster<sup>5</sup> as well as Cottier and Descotes<sup>6</sup> have summarised the last 30 years of HMF chemistry. As for the application of 5-hydroxymethylfurfural in the polymer chemistry, Moore and Kelly<sup>18</sup> and ten years later Gandini<sup>19</sup> reviewed this problem.

## 2. Aspects of the synthesis of HMF

The synthesis of HMF is based on the triple dehydration of hexoses. Various substrates can be used: hexoses themselves, oligo- and polysaccharides as well as converted industrial wastes<sup>20</sup>. The acid catalysed dehydration leads, apart from HMF to various side-products (Scheme 1).



**Scheme 1**

Looking at the Scheme 1, one could have an impression that the synthesis of HMF is very simple. But studies performed by a number of independent scientists demonstrated that the chemistry of the formation of HMF is very complex; it includes a series of side-reactions, which influence strongly on the efficiency of the process. The decomposition to levulinic acid and the polymerisation to humic acids are the most important factors decreasing the yield of HMF.

The Scheme 1 is a general one and shows only the most representative products. Antal *et al.*<sup>21</sup> analysed very profoundly the reaction of sugar decomposition in an aqueous solution and they found four groups of products formed in the course: the isomerisation, the dehydration, the fragmentation and the condensation. Van Dam<sup>22</sup> and Cottier<sup>23</sup> showed that the aqueous and non-aqueous processes led to about 37 products. They demonstrated that the reactions carried out in an aqueous medium provoked the degradation of HMF and that the polymerisation occurred in both aqueous and non-aqueous media.

### 2.1. The mechanism of the fructose dehydration

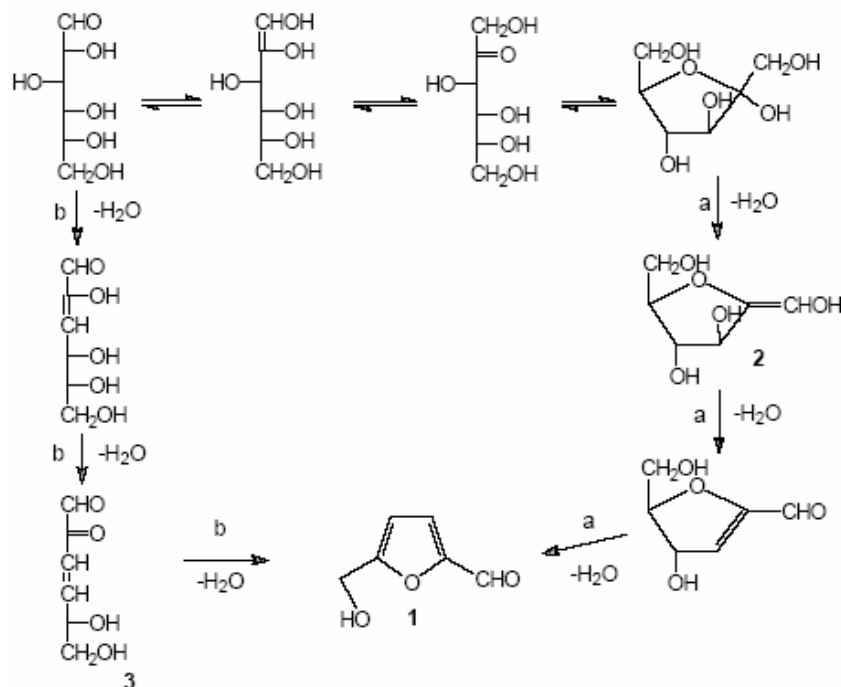
As it has been already mentioned, Haworth and Jones<sup>15</sup> were the first to suggest the mechanism of the dehydration of fructose leading to HMF. Modern studies performed by Van Dam<sup>22</sup>, Kuster<sup>5</sup> and Antal<sup>21</sup> showed that the dehydration of hexoses (especially fructose and glucose) went through one of two possible pathways (Scheme 2). Path 'a' included the transformation of ring systems, while the path 'b' is based on acyclic compounds.

Antal<sup>21</sup> proved experimentally that the mechanism of the HMF formation went through cyclic intermediates. The most significant evidence is:

- Easy formation of HMF from fructose or a fructose part of sucrose
- 2,5-Anhydro-D-mannose converts easily into HMF<sup>1</sup>. This compound is a parent aldehyde

to the enol **2**.

• When the reaction was carried out in D<sub>2</sub>O starting from fructose, deuterium was absent in HMF. If 3-deoxyglycosulose **3** formed in the course of the reaction, one should expect a carbon-deuterium bond due to the keto-enol tautomerism<sup>2</sup>.



**Scheme 2**

## 2.2. The kinetics of the HMF synthesis

All described methods of the synthesis of HMF require the utilisation of the thermal dehydration of hexoses in acidic medium. These conditions cause some difficulties in isolation of HMF, especially as HMF is a very active and unstable compound. Kuster<sup>5</sup> established factors determining the rate of the formation of HMF:

- The sort of the substrate and the hydrolysis degree
- The kind and the concentration of a catalyst
- The time and the temperature of the reaction
- The concentration of a polymer and the rate of the polymerisation
- The type of solvent and the stability of HMF in given conditions

The synthesis is more efficient and more selective when started from keto-hexoses than from aldohexoses. For example, the hydrolysis of sucrose in an aqueous medium is much faster than the dehydration and a glucose part is always present in a post-reaction mixture. It is to state that due to a greater stability of the structure of glucose, it enolyses in a very low degree and the enolisation is a determining factor of the HMF formation from glucose (Scheme 2). Moreover, glucose can condense to form oligosaccharides bearing reducing groups, which may react with intermediates or with HMF itself. This would result in a cross-polymerisation. Despite, glucose is still utilised in industry for the preparation of HMF because of its price lower than fructose<sup>6</sup>.

The dehydration of hexoses is catalysed by protonic acids as well as by Lewis acids. First syntheses of HMF were catalysed by oxalic acid<sup>7,8,12,15</sup> and till now nearly one hundred inorganic and organic compounds were positively qualified as catalysts for the HMF synthesis. Cottier<sup>6</sup> divided catalysts into five groups; they are collected in Table 1.

Iodine catalysis allowed performing the dehydration even from aldohexoses. Bonner et al.<sup>24,25</sup> using this method, converted sucrose into HMF in 20% yield. Morikawa<sup>26</sup> utilised iodine as a catalyst to obtain HMF in 64% yield.

**Table 1. Group of Catalysts**

Organic acids	Inorganic acids	Salts	Lewis acids	Others
Oxalic acid	Phosphoric acid	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> /SO <sub>3</sub>	ZnCl <sub>2</sub>	Ion-exchange resins
Levulinic acid	Sulphuric acid	Pyrid/PO <sub>4</sub> . <sub>3</sub>	AlCl <sub>3</sub>	Zeolites
Maleic acid	Hydrochloric acid	Pyrid/HCl	BF <sub>3</sub>	
p-TsOH	Iodine or Hydroiodic acid generated <i>in situ</i>	Aluminium salts Th and Zr ions Zirconium phosphate Ions: Cr, Al., Ti, Ca, In ZrOCl <sub>2</sub> Vo(SO <sub>4</sub> ) <sub>2</sub> , TiO <sub>2</sub> V-porphyrine Zr, Cr, Ti-porphyrine		

The use of organic and inorganic salts in the synthesis of HMF was the subject of numerous works. Mednic<sup>27,28</sup> proposed to utilise ammonium phosphates (the yield 23%), triethylamine phosphate (36%) or pyridinium phosphate. The latter allowed obtaining HMF in 44% yield. Nakamura<sup>29</sup> invented the catalysis with zirconium phosphate and zirconyl chloride, a further development of this method<sup>30</sup> allowed improving the yield up to 90%.

Fayet and Gelas<sup>31</sup> utilised various pyridinium salts: poly-4-vinylpyridinium hydrochloride as well as pyridinium trifluoroacetate, hydrochloride, hydrobromide, perbromate and p-toluenesulfonate. Starting from fructose, they obtained HMF in 70% average yield.

Smith<sup>32</sup> as well as Garber and Jones<sup>33</sup> proposed utilising ammonium sulphate; Hales *et al.*<sup>34</sup> as well as scientists from Atlas Powder Lab.<sup>35</sup> applied chromium trichloride or zinc chloride. Works concerning the application of ion-exchange resins for the synthesis of HMF are the most numerous. Nakamura<sup>36</sup> investigated the influence of a strongly acidic ion exchange resin and obtained HMF in 80% yield. Gaset et al.<sup>37,38</sup> utilised Levatit® SPC-108, to form HMF in 70-80% yield. Researchers from Noguchi Institute<sup>39</sup> patented the use of ion-exchange resins such as Amberlite® IR-116 or Diaion® PK-228 cross-linked with divinylbenzene. Some authors<sup>40,41</sup> claimed Diaion® PK-216 to be the most efficient. In both cases HMF was obtained in 90% yield.

Apart from the methods described above, it is worth to mention works by Mercadier,<sup>42</sup>

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.