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Authors: Bartosz Wozniak, Anke Spannenberg, Yuehui Li, Sandra Hinze, and Johannes Gerardus de Vries

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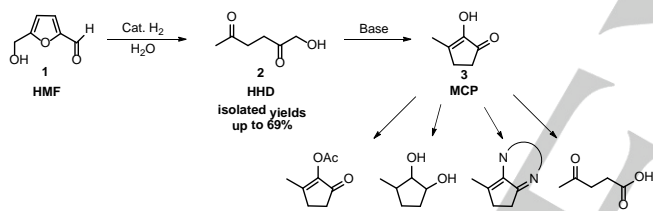


Cyclopentanone derivatives from 5-hydroxymethylfurfural via 1-hydroxyhexane-2,5-dione as intermediate

Bartosz Wozniak,^[a] Anke Spannenberg,^[a] Yuehui Li,^[b] Sandra Hinze,^[a] Johannes G. de Vries^{[a]*}

Abstract: An efficient strategy for the conversion of biomass derived 5-hydroxymethyl-furfural (HMF) to 2-hydroxy-3-methylcyclopent-2-enone (MCP) via intramolecular aldol condensation of 1-hydroxyhexane-2,5-dione (HHD) has been developed. Further transformations of MCP towards the diol, enol acetate, levulinic acid and N-heterocyclic compounds are also reported.

In view of the dwindling supply of fossil resources new scenarios need to be developed for the manufacture of the chemicals our lives depend upon, such as pharmaceuticals or plastics, which are currently derived from crude oil. We are interested in the catalytic conversion of platform chemicals derived from renewable resources to existing or new chemicals.^[1] 5-Hydroxymethylfurfural (HMF, Scheme 1, **1**) is obtained from the dehydration of fructose, and has become a well-known platform chemical for the production of numerous valuable chemicals, such as 2,5-furan-dicarboxylic acid.^[2] Recently, we became interested in the further development of 1-hydroxyhexane-2,5-dione (HHD, **2**), a product of the hydrogenation/hydrolytic ring opening of HMF (Scheme 1).



Scheme 1. Conversion of HMF (**1**) to MCP (**3**) via HHD (**2**) and further possible reactions.

Several catalytic systems have been reported to produce HHD. Hydrogenation of 5-HMF to HHD in acidic media catalysed by Pt/C was published by Mentech *et al.*^[3] Various heterogeneous catalysts were then reported for the hydrogenative ring opening of 5-HMF, including Rh-Re/SiO₂,^[4] Pd/C^[5,6] and Au nanoparticles on metal oxide supports.^[7,8] However, these require high H₂ pressures, with selectivities varying from 57% to 81%. Higher HHD selectivities are obtained in processes catalyzed by homogeneous catalysts.^[9-12] In particular, Cp*Ir(III)

half-sandwich complexes^[10-12] appeared to be most promising. Fu and co-workers^[12] increased the selectivity to 99%, by using such a complex with electron-donating ligands, and adjusting the pH during the reaction. However, they only obtained high conversions and selectivities using formic acid as the hydrogen source. None of the above papers reported an isolation procedure. The catalytic hydrogenation of 5-HMF to HHD still needs to be improved and development of an effective HHD isolation method remains a major challenge.^[10-12] Furthermore, to the best of our knowledge, no further conversions of HHD as a starting material have been reported.

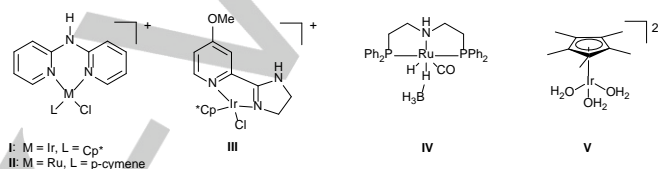


Figure 1. Iridium and ruthenium complexes used.

Herein, we present an improved protocol for the synthesis of HHD. We report the first isolation procedure as well as the full characterization of HHD. To establish HHD as a platform chemical we show its potential as a building block, namely its transformation to 2-hydroxy-3-methylcyclopent-2-enone (MCP, **3**) and potentially useful follow-up products.

Concerning the development of new homogeneous catalysts for the conversion of 5-HMF to HHD, limitations arise from the requirements of water solubility and stability under acidic conditions. Thus, activated base metal catalysts, used for hydrogenation and transfer hydrogenation reactions, did not show any selectivity towards HHD. We evaluated a series of air and moisture stable iridium and ruthenium complexes (Fig. 1) that

Table 1. Screening of catalysts I-V for HHD formation in aqueous media. ^[a]				
Entry	Catalyst	Time	Conv. (%) ^[b]	Yield (%) ^[b]
1	I	2 h	>99	76 (69) ^[c]
2	II	4 h	97	42
3	III	1 h	>99	60
4	IV	2 h	93	5
5	V	2 h	34	25
6 ^[d]	I	4 h	>99	67
7 ^[d]	III	4 h	>99	71

[a] Reaction conditions: 5-HMF (4 mmol), water (20 mL), I-V (0.5 mol%), 120 °C, 10 bar H₂. [b] Determined by ¹H NMR using (CH₃)₄NBF₄ as an internal standard. [c] Isolated yield. [d] 5-HMF (40 mmol), PBS (200 mL, 0.1 M, pH=2.5), cat (0.075 mol%), 140 °C, 20 bar H₂.

[a] B. Wozniak, Dr. A. Spannenberg, Dr. S. Hinze, Prof. Dr. J. G. de Vries

Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Str. 29a, 18059 Rostock
E-mail: johannes.devries@catalysis.de

[b] Prof. Y. Li

State Key Laboratory for Oxo Synthesis and Selective Oxidation
Institute of LICP, Lanzhou Institute of Chemical Physics (LICP),
Chinese Academy of Sciences
Lanzhou 730000 P.R. China

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have not been previously used for the hydrogenation of HMF to HHD. The best results were obtained with the half-sandwich [Cp*Ir(dpa)Cl]Cl (dpa= dipyridylamine) catalyst **I** (Table 1, entry 1), which is a known catalyst for water oxidation^[13] and the transfer hydrogenation of levulinic acid.^[14] Poor selectivities were observed with ruthenium complexes **II**, **IV** and **V**. After further optimization, the best results were obtained with **I** (0.5 mol%) with 10 bar H₂ at 120 °C in water and HHD was isolated in 69% yield. The major byproduct was found to be an insoluble polymeric solid, presumably humins, which is consistent with the observations of other groups.^[6,12] In addition, the utilization of phosphoric acid/sodium phosphate buffer solution allowed processing with lower catalyst loading (0,05 mol%), however no improvement in yield was observed.

Single crystals were grown from a DCM/pentane mixture at -30°C, and the crystal structure was determined for the first time by X-ray diffraction analysis (Figure 2). With reasonable amounts of clean compound in hand, we started to investigate further reactions using HHD as a starting material.

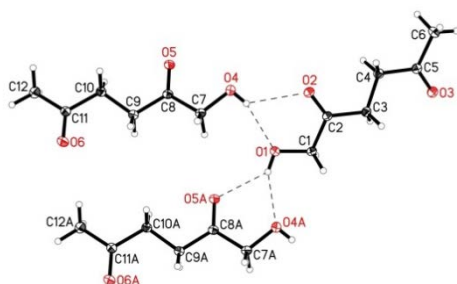
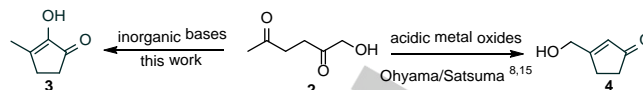


Figure 2. ORTEP representation of HHD (**2**) showing intermolecular O-H...O hydrogen bonds (for more details see Supporting Information). Displacement ellipsoids correspond to 30% probability.

Interestingly, base-promoted aldol condensation led to 2-hydroxy-3-methylcyclopent-2-enone (MCP, **3**) instead of the expected 3-hydroxymethyl-cyclopent-2-en-1-one (HCPEN, **4**) as shown in Scheme 2.^[8,15] MCP is a known flavor ingredient in roasted coffee and maple syrup, and is widely used in the food industry. It also finds use as a precursor for the biosynthesis of antibiotics,^[16] as fragrance in perfumery^[17] and as ligand in metal complexes.^[18] Several routes towards MCP are discussed in the literature, starting from isoprene,^[19] 2-keto-glutaric acid,^[20] dimethyl adipate^[21] or 1-acetoxy-3-buten-2-one.^[22] We report the efficient synthesis of MCP starting from biomass-derived 5-HMF in a two-step-process, involving HHD as an intermediate. We optimized the reaction by investigating the role of base in the aldol condensation reaction of HHD at 60°C (Table 2). Without base or in the presence of small amounts of KOH, no conversion was observed even after 8h (Table 2, entries 1-3). Increasing the KOH/HHD ratio to 1.5, full conversion was achieved in 15 minutes, yielding 72% of MCP (Table 2, entry 7). Similar results were obtained at room temperature after 1.5 h (Table 2, entry 8). Based on these results, we carried out further optimizations



Scheme 2. Aldol condensation products starting from **2**.

Table 2. Influence of the amount of base on the synthesis of MCP (**3**) from HHD (**2**)^[a]

Entry	KOH (eq.)	Time	Conv. (%) ^[b]	Yield (%) ^[b]
1	-	8 h	-	-
2	0.1	8 h	-	-
3	0.4	8 h	-	-
4	0.7	16 h	>99	47
5	1.0	1 h	>99	65
6	1.2	30 min	>99	68
7	1.5	15 min	>99	72
8	1.5	1.5 h	>99	70

[a] Reaction conditions: HHD (0.4 mmol), KOH, water (2 mL), 60°C. [b] Determined by TLC. [c] Reaction carried out at room temperature.

using 1.5 eq. of base at 60°C. The results of solvent and base screenings are shown in Table 3. Simple inorganic bases such as alkaline hydroxides promote the aldol condensation when water and alcohols were used as solvents (Table 3, entries 1-2, 5-6). However, the utilization of potassium *tert*-butoxide in THF led to full conversion in 5 minutes in higher isolated yield (Table 3, entry 9). It is worth to mention that no formation of **4** was observed. The only byproduct present was an insoluble polymeric substance, which was also reported by Ohyama, Satsuma and co-workers.^[15]

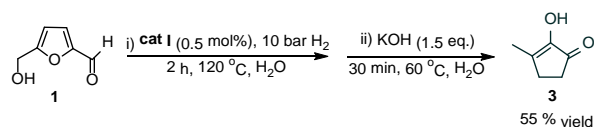
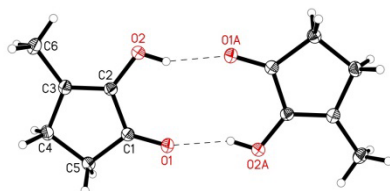
We also established a one-pot synthesis of MCP directly from 5-HMF. Under optimized conditions, the hydrogenation/hydrolytic ring opening of 5-HMF followed by intramolecular aldol condensation led to 55% isolated yield of MCP (Scheme 3). Crystals of MCP suitable for X-ray diffraction analysis were obtained (Figure 3).

We then turned our attention to the conversion of MCP into valuable biomass-based chemicals (Scheme 4). Hydrogenation of MCP catalysed by Ru-MACHO-BH^[23] (Figure 1, cat **IV**) (Scheme 4, i) gave full conversion of MCP (**3**) after 16 h. 3-Methyl-1,2-cyclopentanediol (**5**) was isolated in near-quantitative yield as a mixture of 3 diastereomers (3.3 : 1.6 : 5.0). Access to **5** is limited and its synthesis usually requires harsh conditions.^[24] Recently, **5** was used by Chavan and Bhanage in oxidative carbonylation reactions to form cyclic carbonates, which play an important role in pharmaceuticals, polymers and agrochemicals.^[25] The addition of sodium periodate to aqueous MCP solutions led to the formation of levulinic acid (**6**) (Scheme 4, ii), a well-known precursor for a variety of compounds with a broad range of applications.^[26]

Table 3. Solvent and base screening in the intramolecular aldol condensation of HHD.^[a]

Entry	Base	Solvent	Time	Conv. (%) ^[b]	Yield (%) ^[b]
1	NaOH	H ₂ O	15 min	>99	70
2	KOH	H ₂ O	15 min	>99	72
3	CsCO ₃	H ₂ O	20 h	>99	62
4	K ₃ PO ₄	H ₂ O	2 h	>99	71
5	KOH	EtOH	15 min	>99	61
6	KOH	MeOH	15 min	>99	57
7	KOH	ACN	24 h	-	-
8	KOH	THF	22 h	>99	60
9	KOtBu	THF	5 min	>99	80

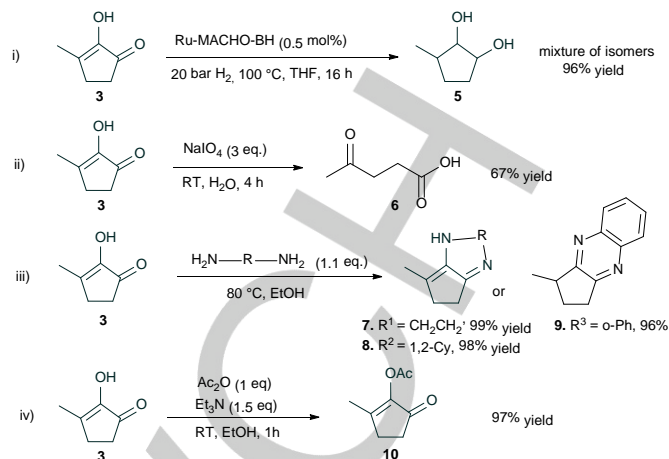
[a] Reaction conditions: HHD (0.4 mmol), base (0.6 mmol), solvent (2 mL), 60°C. [b] Determined by TLC.

**Scheme 3.** One-pot synthesis of MCP (**3**). Reaction conditions: i) 5-HMF (7.9 mmol), water (40 mL), cat (0.5 mol%), 120°C, 10 bar H₂, 2h, ii) KOH (11.9 mmol), 60°C, 30 min.**Figure 3.** ORTEP representation of MCP (**3**) showing intermolecular O-H...O hydrogen bonds (for more details see Supporting Information). Displacement ellipsoids correspond to 30% probability.

So, naturally occurring MCP is a potential alternative to 5-HMF for the production of **6**.

Furthermore, α,β -unsaturated imines **7** and **8** and quinoxaline derivative **9** were obtained in excellent yields by addition of diamines to MCP in EtOH at 80 °C (Scheme 4, iii). Unsaturated imines were used in numerous studies related to C-C and C-N bond formations,^[27] and quinoxalines are important pharmaceutical intermediates, based on their antiviral, anticancer and antifungal properties.^[28]

In another example, MCP was acetylated to the corresponding enol acetate **10** in excellent yield (Scheme 4, iv). This compound is of use in the synthesis of fragrances (e.g. dihydrojasnone).^[17]

**Scheme 4.** Conversion of MCP into valuable biomass-based chemicals. : i) MCP (2.2 mmol), RU-MACHO-BH (0.5 mol%), THF (10 mL), 10 bar H₂, 100°C, 16h; ii) MCP (2.2 mmol), NaIO₄ (6.6 mmol), H₂O (10 ml), RT, 6h; iii) MCP (2.2 mmol), diamine (2.4 mmol), EtOH (5 mL), 80°C; iv) MCP (4.45 mmol), Ac₂O (4.45 mmol), Et₃N (6.79 mmol), EtOH (5 mL), RT

In conclusion, we have described a novel pathway for the conversion of biomass-based 5-HMF into MCP *via* HHD. Aldol condensation of HHD using inorganic bases led to MCP as sole product. Both HHD and MCP were isolated and fully characterized. We obtained MCP directly from 5-HMF in 55% isolated yield. Finally, we demonstrated that MCP can be further transformed into useful building blocks in excellent yields.

Acknowledgements

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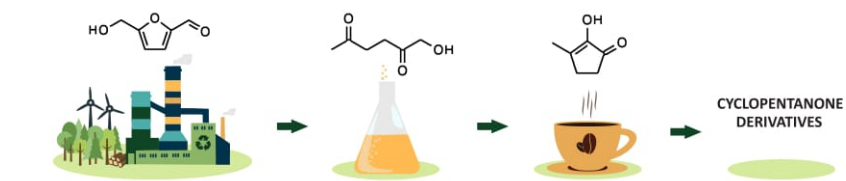
Keywords: biomass • homogeneous catalysis • platform chemical • renewable resources • cyclopentanone derivatives

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