Microwave- or Microreactor-Assisted Conversion of Furfuryl Alcohols into 4-Hydroxy-2-cyclopentenones

Kathrin Ulbrich, Peter Kreitmeier, Oliver Reiser*

Institut für Organische Chemie der Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany
Fax +49(941)9434121; E-mail: oliver.reiser@chemie.uni-regensburg.de

Received 14 June 2010

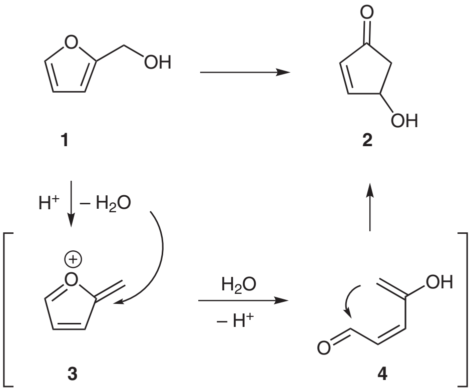
Abstract: The conversion of a variety of furfuryl alcohols, derived from renewable non edible resources such as bran, into 4-hydroxy-2-cyclopentenones was accomplished using microwave irradiation. In subcritical water (220 °C, 15.5 bar) without the need for any catalyst the reaction proceeds approximately two orders of magnitude faster with up to twice the yield compared to methods previously reported that apply conventional heating techniques. For the parent furfuryl alcohol the process could be transferred to a microreactor, allowing the synthesis of 4-hydroxy-2-cyclopentenone in a continuous flow system on multigram scale.

Key words: green chemistry, organic synthesis in water, microwave chemistry, carbohydrates, biomass, furfuryl alcohol

In recent years, increasing efforts are made to establish new technologies for the conversion of biomass into fuels or basic chemicals that can be further used for the production of fine chemicals, materials, or pharmaceuticals. The use of renewable resources is one of the key aspects of sustainable development considering upcoming changes on the oil market and thereby ensuring future supply of raw materials. The decline of fossil resources and therefore increasing oil prices will make products from biomass economically advantageous. Furthermore, the use of renewable resources is desirable since they are CO_2 neutral, nevertheless, also the technologies for converting them into viable products need to be energy-efficient and environmentally friendly.[1]

Many processes to convert biomass into fuel or fine chemicals start from starch (glucose), thus colliding with food production. Materials derived from nonedible renewable resources, ideally being produced as byproducts in the process of food production, are therefore especially valuable starting materials for chemistry. Therefore, we have a continuing interest to develop chemistry starting from furfural,[2] being produced from hemicellulose,[3] derived from agricultural waste products like bran or bagasse.[4]

Furfuryl alcohol (**1**) can be converted into 4-hydroxy-2-cyclopentenone (**2**), the latter being a valuable intermediate for the synthesis of natural products and analogues.[5] A number of protocols have been developed for this transformation, generally calling for heating **1** in aqueous media for 22–48 hours, giving rise to **2** in approximately 40–50% yield.[6] In this report we demonstrate that the synthesis of **2** can be achieved within minutes in water under subcritical conditions with considerably improved yields using microwave irradiation.[7,8] Moreover, we have been able to transfer those conditions to a microreactor in a continuous flow setup,[9] being especially attractive for large-scale synthesis.



Scheme 1 Conversion of furfuryl alcohol (**1**) into 4-hydroxy-2-cyclopentenone (**2**)

Following the leads previously reported and in agreement with the mechanism proposed calling for **3** as an intermediate protic conditions seem to be a requirement for the transformation of **1** to **2** (Scheme 1). Nevertheless, even under reflux conditions in water in the presence of various acids the reaction still proceeds sluggishly. Moreover, stability problems of **2** at higher temperatures are being encountered, making long reaction times not desirable. We therefore set out to investigate the rearrangement of furfuryl alcohols under more forcing conditions, that is, using microwave irradiation in closed vessels that readily allows to carrying out reactions well above the boiling point of water at elevated pressure.

Aqueous solutions of furfuryl alcohol (**1**, 0.25, 0.50 and 1 mol/L) were heated in water as solvent using a commercial mircowave (CEM Discover) in a closed vessel. At 300 W a maximum temperature of the reaction mixture of 200–210 °C and 15.5–17.6 bar was reached. Notably, with increasing concentrations of **1** faster upheating and higher end temperatures were observed, suggesting that **1** is especially effective in absorbing microwave irradiation.[10] In all cases **1** was completely consumed within 3–4 minutes, giving rise to the desired cyclopentenone **2** but being accompanied by polymeric byproducts. The forma-

SYNLETT 2010, No. 13, pp 2037–2040
Advanced online publication: 28.07.2010
DOI: 10.1055/s-0030-1258534; Art ID: Y01810ST

tion of the latter could be supressed at lower concentrations of **1** in water, giving rise to **2** in up to 80% yield (GC, Figure 1 and Figure 2).

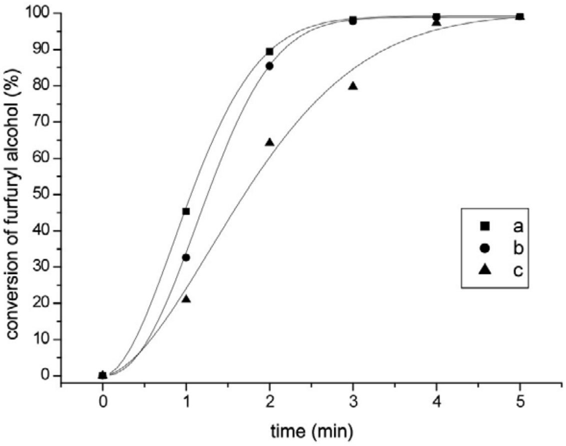


Figure 1 Conversion of furfuryl alcohol (**1**) in H_2O under microwave irradiation (300 W): a: 1.0 mol/L; b: 0.5 mol/L; c: 0.25 mol/L; conversion determined by GC with an internal standard method.

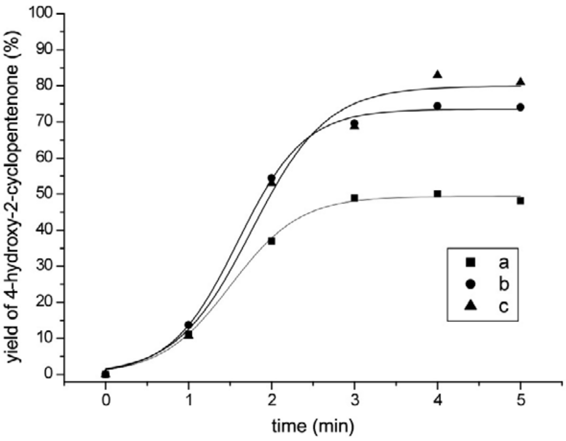
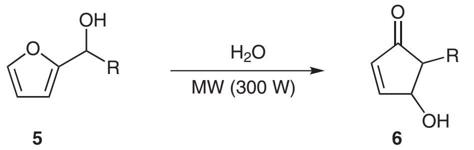


Figure 2 Yield (GC; decane as internal standard) of 4-hydroxy-2-cyclopentenone **2**: MW 300 W; H_2O as solvent; a: 1.0 mol/L; b: 0.5 mol/L; c: 0.25 mol/L.

Likewise, substituted furfurylalcohols **5a**–**d** could be rearranged successfully in water to the corresponding cyclopentenones **6a**–**d** in good yields under microwave irradiation within minutes (Table 1), again greatly shortening the reaction times compared to previous reports.[11] Only **5e** bearing an unpolar side chain did not undergo the desired reaction under the reaction conditions, most likey due to its low miscibility with water.

Table 1 Rearrangement of Substituted Furfuryl Alcohols **5**[a]



Entry	Compound	R	Time (min)	*syn*/*anti*	Yield (%)[b]
1	**5a**	Ph	2	1:5	96
2	**5b**	$CH_2CH=CHMe$	5	1:12	73
3	**5c**	Et	15	1:7	54
4	**5d**	*n*-pentyl	15	1:7	65
5	**5e**	*n*-dodecyl	30	–	0

[a] Conditions: **5** (1.5 mmol) in H_2O (6 mL), microwave irradiation (300 W) under closed vessel conditions (200–210 °C, 15 bar).

[b] Isolated yield.

Having found suitable conditions that greatly accelerate the rearrangement of furfuryl alcohols in a batch reactor, we next wanted to develop reaction conditions being suitable for upscale. Using **1** being arguably the most useful[5] furfuryl alcohol for this process, we investigated its rearrangement to **2** in a microreactor (Figure 3). An aqueous solution of **1** was passed through a reaction chamber consisting of a four-meter length of steel tube with a total volume of 1.77 mL, coiled up, and immersed in a heating bath at 240 °C by a HPLC pump (inlet A) within approximately one minute, thus closely resembling the temperature conditions previously present in the microwave reactor. However, in order to achieve complete conversion of **1** it was found to be beneficial to adjust the pH to 4 with acetic acid. Since some polymers form during time, we introduced toluene through a second inlet (B), the latter effectively dissolving the byproducts thus preventing blockage of the steel tube. Conveniently, the product **2** completely remains in the aqueous phase, thus after collection of the reaction mixture at the end of the reactor, only a simple separation of the organic phase and extraction of the aqueous phase with methyl-*tert*-butyl ether was needed for purification. After evaporation of water, **2** was obtained on a multigram scale in 87% yield (GC purity 97%), which could be further purified by distillation if desired (74% yield, GC purity 99%).

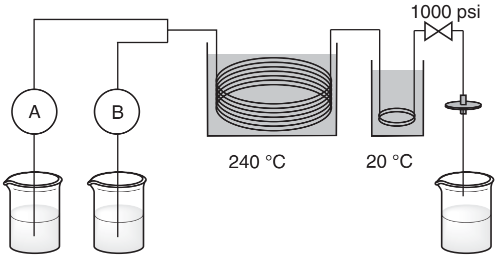


Figure 3 Microreactor setup: A: inlet for **3a** in water (0.25 mol/L) adjusted to pH 4 with AcOH at a flow rate of 1.8 mL/min, B: inlet for toluene at a flow rate of 0.2 mL/min; average residence time in the reactor 53 s.

In conclusion, the rearrangement of furfuryl alcohols can be greatly accelerated in water at high temperature and pressure (220–240 °C), conditions that can be readily achieved in a microwave or microreactor. The latter allowed the development of a continuous flow process for the rearrangement of furfuryl alcohol (**1**) to cyclopentenone **2** with considerable improvement of yield. The short residence time of **1** (<1 min) in the microreactor setup overcome problems of stability of the product **2** being encountered under conventional heating conditions that required reaction times of 22–48 hours.

Conversion of Furfuryl Alcohol (1) into 4-Hydroxy-2-cyclopentenone (2) in a Microreactor

Reactor Setup (Figure 3)
Two HPLC pumps (inlet A and B) were connected to a 5 m stainless steel tube (0.75 mm i.d.) via a T-connector; 4 m of this steel tube were coiled up and immersed in a heating bath, followed by a 0.3 m coiled cooling zone (approx. 20 °C). The outlet of the reactor was connected to a 68.9 bar back pressure regulator, followed by a 0.4 µm PTFE syringe filter (Ø 25 mm) to crack the resulting emulsion. The residence volume of the heated coil was 1.77 mL.

Procedure
A solution of 12.5 g (127 mmol) furfuryl alcohol (**1**) in H_2O was adjusted to pH 4.0 with diluted AcOH (total volume 500 mL). The heating bath was brought to 240 °C. The aq furfuryl alcohol solution was introduced to inlet A at a flow rate of 1.8 mL/min, toluene was introduced to inlet B at flow rate of 0.2 mL/min (total flow rate 2.0 mL/min, average residence time 53 s). Product collection started after 10 min to ensure steady state conditions. Then, 500 mL reaction mixture were collected over 250 min, corresponding to 450 mL of the aq furfuryl alcohol solution.

The aqueous phase was separated from the organic layer and washed with MeO*t*-Bu (3×30 mL). The H_2O was evaporated to give 9.79 g (87%) crude **2** as yellow-orange liquid, GC purity 97%. Short path distillation 10^{-2} mbar (oil bath temperature 80–85 °C) yielded 8.34 g (74%) **2** as a pale yellow liquid, GC purity 99%.

General Procedure for the Rearrangement of 5 under Microwave Reactions

A 10 mL closed microwave glass vessel was charged with the appropriate furfuryl alcohol **5** (1.5 mmol) in 6 mL of distilled H_2O. The reaction mixture was heated in the microwave at 300 W for the time indicated (Table 1). The aqueous phase was extracted with EtOAc, and the organic phase was evaporated. The crude product was purified by column chromatography.

4-Hydroxy-5-phenylcyclopenten-2-enone (5a)
Yield 96% (*trans*/*cis* = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (trans) = 7.60 (dd, 1 H, *J* = 2.2, 5.7 Hz), 7.35–7.26 (m, 3 H), 7.13–7.10 (m, 2 H), 6.31 (dd, 1 H, *J* = 1.3, 5.8 Hz), 4.95 (br s, 1 H), 3.42 (d, 1 H, *J* = 2.8 Hz), 2.69 (br s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 205.5, 161.9, 136.8, 134.0, 129.0, 128.6, 127.5, 79.0, 62.2. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*cis*) = 7.60 (dd, 1 H, *J* = 2.2, 5.7 Hz), 7.35–7.26 (m, 3 H), 7.13–7.10 (m, 2 H), 6.45 (dd, 1 H, *J* = 1.2, 5.8 Hz), 4.95 (br s, 1 H), 3.84 (d, 1 H, *J* = 6.3 Hz), 2.69 (br s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 205.5, 161.9, 136.8, 134.0, 129.0, 128.6, 127.5, 79.0, 62.2.

5-(But-2-enyl)-4-hydroxycyclopent-2-enone (5b)
Yield 73% (*trans*/*cis* = 12:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (dd, 1 H, *J* = 2.3, 5.8 Hz), 7.48–7.46 (dd, 1 H, *J* = 2.3, 5.8 Hz), 6.19–6.15 (m, 2 H), 5.98–5.87 (m, 1 H), 5.68–5.56 (m, 1 H), 5.15–4.98 (m, 4 H), 4.71 (br s, 2 H), 2.90–2.70 (m, 2 H), 2.38–2.37 (m, 1 H), 2.28–2.25 (m, 1 H), 1.22 (d, 3 H, *J* = 6.9 Hz), 0.94 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 207.6, 162.6, 162.4, 141.2, 139.2, 134.9, 134.6, 115.7, 114.6, 73.2, 72.6, 60.0, 59.3, 36.1, 35.8, 17.5, 14.6.

5-Ethyl-4-hydroxycyclopenten-2-enone (5c)
Yield 54% (*trans*/*cis* = 7:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (dd, 1 H, *J* = 5.8, 2.2 Hz), 6.20–6.17 (dd, 1 H, *J* = 5.8, 1.2 Hz), 4.7 (br s, 1 H), 2.22–2.16 (m, 1 H), 1.93–1.84 (m, 1 H), 1.58–1.48 (m, 1 H), 1.02 (t, 3 H, *J* = 7.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 208.2, 161.9, 134.4, 76.3, 56.6, 21.5, 11.6.

4-Hydroxy-5-pentylcyclopenten-2-enone (5d)
Yield 65% (*E*/*Z* = 1:1; *trans*/*cis* = 7:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.48 (dd, 1 H, *J* = 5.8, 2.2 Hz), 6.17–6.14 (dd, 1 H, *J* = 5.8, 1.2 Hz), 4.65 (m, 1 H), 2.14–2.18 (m, 1 H), 1.85–1.78 (m, 1 H), 1.42–1.29 (m, 6 H), 0.86 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 208.8, 162.2, 134.2, 70.1, 55.4, 31.9, 28.6, 27.0, 22.5, 14.1.

Acknowledgment

This work was supported by the Deutsche Bundesumweltstiftung (KONAROM, AZ 26920) and the Fonds der Chemischen Industrie.

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