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Mechanochemically Initiated Achmatowicz Rearrangement

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MECHANOCHEMICALLY INITIATED ACHMATOWICZ REARRANGEMENT

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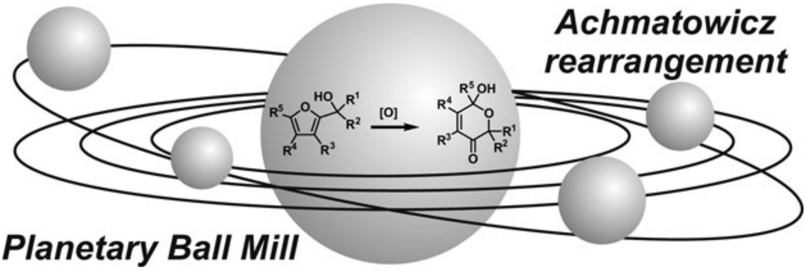
GRAPHICAL ABSTRACT



Abstract *The Achmatowicz rearrangement converts furfuryl alcohols, obtainable from renewable carbohydrates, into 6-hydroxy-2H-pyrane-3(6H)-ones, which are versatile intermediates for organic synthesis. We describe here the first examples of a solvent-free mechanochemical Achmatowicz rearrangement. Furfuryl alcohols were prepared from furfurals using mechanochemically initiated reductions and Reformatsky reactions. Mechanochemical reaction conditions for the Achmatowicz rearrangement of the obtained furfuryl alcohols were optimized and applied to a series of derivatives, yielding the corresponding rearrangement products in yields of 39 to 95%.*

Keywords Achmatowicz rearrangement; ball mill; furfural; mechanochemistry; solvent-free

INTRODUCTION

Compounds derived from carbohydrates are a sustainable alternative to oil-based chemicals and their use in chemical synthesis becomes more important with depleting fossil carbon resources. In particular, the synthesis of furans from carbohydrates is well established and a long-known route. Furfural (**1a**) is readily obtained

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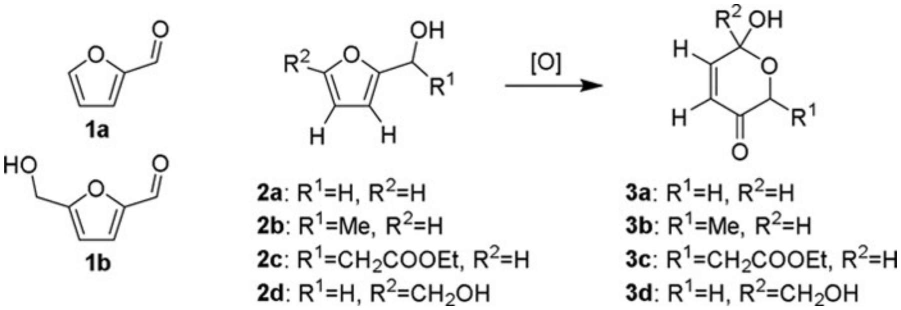


Figure 1. Carbohydrate-based chemicals furfural (**1a**) and HMF (**1b**) and the Achmatowicz rearrangement.

from hemicellulose by acid catalysis[1] and the dehydration of fructose over solid acid catalysts[2] gives 5-hydroxymethylfurfural (HMF, **1b**). However, a broader synthetic applicability of the heteroarenes as starting materials is limited by their stability. An elegant way to introduce functionality and increase their chemical reactivity is the Achmatowicz rearrangement, leading to 6-hydroxy-2*H*-pyrane-3(6*H*)-ones (Fig. 1).[3] These pyranones are valuable synthetic intermediates, which have been used in the synthesis of antimicrobials,[4] monosaccharides and their analogs,[5] natural products, and several drugs.[6]

Several methods have been developed for the Achmatowicz rearrangement, allowing a one-step procedure from a furfural alcohol derivative to the corresponding 6-hydroxy-2*H*-pyrane-3(6*H*)-one. The Achmatowicz rearrangement requires a stoichiometric oxidant like *N*-bromosuccinimide (NBS)[6a] or *m*-chloroperoxybenzoic acid (*m*CPBA),[4] which are the most commonly used oxidizing reagents, but also catalysts such as vanadyl acetylacetonate ($VO(acac)_2$) or titanium tetra (isopropoxide) ($Ti(Oi\text{-}Pr)_4$) in combination with *tert*-butylhydroperoxide are suitable oxidizing agents.[7] Enzymatic[8] or singlet oxygen[9]-mediated oxidations have also been reported. The Achmatowicz reaction in solution is well established. Alternative solvent-free reaction conditions could be mechanochemically performed in a ball mill. Mechanochemistry is so far only rarely applied in organic synthesis, but offers particular advantages if reactants are insoluble, their solubility is incompatible, or solvents should be entirely avoided.[10]

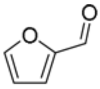
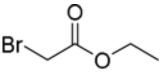
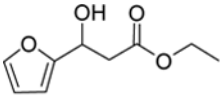
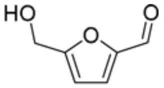
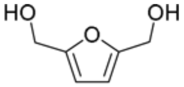
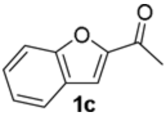
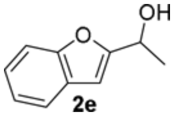
Herein, we describe the first mechanochemical Achmatowicz reaction of furfuryl alcohols to 6-hydroxy-2*H*-pyrane-3(6*H*)-ones. The furfuryl starting materials are derived from carbohydrate precursors and were also obtained from ball milling under solvent-free reaction conditions.

RESULTS AND DISCUSSION

Mechanochemical Synthesis of Starting Materials

Furfural (**1a**) and its derivatives were used to obtain starting materials for the Achmatowicz rearrangement under solvent-free mechanochemical reaction conditions. Naimi-Jamal et al. already demonstrated the reduction of **1a** to furfuryl alcohol (**2a**) through ball milling with sodium borohydride.[11] Common reduction strategies such as Grignard,[12] Reformatsky,[12,13] or Luche reactions[12,13] were

Table 1 Synthesis of furfuryl alcohol derivatives through ball milling

Entry	Reactant A	Reactant B	A/B	Product	Yield (%)[a]
1[b]	 **1a**	 **4**	1:3	 **2c**	38
2	 **1b**	$NaBH_4$	1:10	 **2d**	Traces
3	 **1c**	$NaBH_4$	1:10	 **2e**	72[c]/64

[a] Yields were not optimized.
[b] w%: Zn:NH_4Cl:**1a** = 10:4:1.
[c] The reaction was performed with additional choline chloride.

previously also investigated under solvent-free conditions. Following these methods we performed the reduction on selected furfuryl derivatives through ball milling, yielding substituted furfuryl alcohol derivatives, which served as precursors for the Achmatowicz rearrangement (Table 1). All reactions were performed in a planetary ball mill containing 10 agate milling balls (8–10 mm) with a drive of 425 rpm and a reaction time of 60 min.

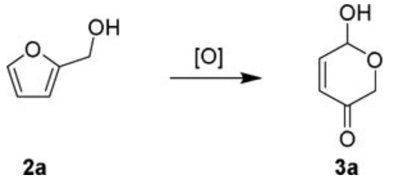
The Reformatsky reaction (Table 1, entry 1) in the ball mill uses zinc as the reduction agent.[14] The sodium borohydride reduction of 5-hydroxymethylfurfural (HMF) (**1b**) (Table 1, entry 2) and ketone **1c** (Table 1, entry 3) through ball milling afforded the corresponding alcohol **2e** in good yield, but compound **2d** was only obtained in traces and synthesized according to literature.[15] The addition of choline chloride as an additive was investigated in the conversion of ketone **1c** (Table 1, entry 3) and gave a slightly improved yield of 72%. Furfuryl alcohol (**2a**) and DL-1-(2-furyl) ethanol (**2b**) are commercially available as starting materials for the Achmatowicz rearrangement.

Mechanochemical Achmatowicz Rearrangement

The reaction conditions (Table 2) such as oxidant, solid support, and ball mill parameters for the Achmatowicz rearrangement were optimized using furfuryl alcohol (**2a**). All reactions were performed in a planetary ball mill containing 10 agate milling balls (8–10 mm) with 425 rpm.

Although NBS is one of the most common oxidizing agents for the Achmatowicz reaction, **3a** was not obtained (Table 2, entries 1–4). The same result was observed for the use of manganese oxide (MnO_2) (Table 2, entry 5) or potassium permanganate ($KMnO_4$) (Table 2, entry 6). Variation of the starting material to **2b**, the addition of water, or the change of the solid support did not yield the expected

Table 2 Mechanochemical Achmatowicz reaction of **2a** with different oxidants[a]



Entry	[O]	Time (min)	Solid support	2a/[O]	Yield (%)
1	NBS	30	Al_2O_3	1:1	—
2	NBS	30	Al_2O_3	1:2	—
3	NBS	30	Quartz sand	1:1	—
4	NBS	60	Quartz sand	1:1	—
5	MnO_2	60	Quartz sand	1:1	—
6	$KMnO_4$	60	Quartz sand	1:2	—
7	*m*CPBA	30	Al_2O_3	1:1	45
8	*m*CPBA	30	Quartz sand	1:1	47

[a] **2a** / solid support = 1:10.

Achmatowicz product. However, the use of *m*CPBA resulted in the desired product **3a** (Table 2, entries 7 and 8). The reaction was performed in the presence of acidic α -aluminium oxide (α-Al_2O_3) or quartz sand. The solid supports showed no significant difference in yield (45% and 47%) under similar reaction conditions. Quartz sand proved to be advantageous in the workup, as it is removed by filtration. The

Table 3 Variation of reaction time and ratio of **2a** and *m*CPBA

Entry	**2a**/*m*CPBA	Time (min)	Yield (%)
1	1:1	7	39
2	1:1	15	53
3	1:1	30	47
4	1:1	60	45
5	1:2	7	64
6	1:2	15	92
7	1:2	30	95

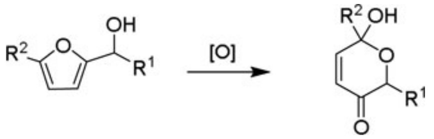
Table 4 Comparison of different reported Achmatowicz rearrangement methods with ball milling conditions

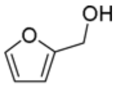
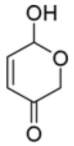
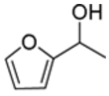
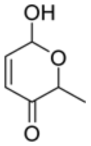
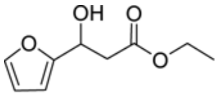
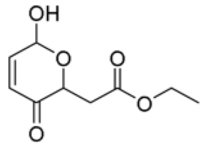
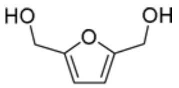
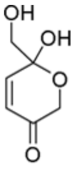
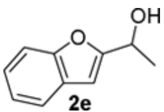
Entry	Method	Reagent	Yield (%)
1	*m*CPBA (ball mill)	**2a**	95
2	*m*CPBA (solvent free, no ball mill)	**2a**	80
3	*m*CPBA (first publication) [4]	**2a**	48
4	*m*CPBA (solvent: CH_2Cl_2) [16]	**2a**	88
5	Br_2/MeOH [3]	**2a**	73
6	NBS/MeOH [6a]	**2b**	63

variation of the reaction time and the ratio between **2a** and the oxidant *m*CPBA (Table 3) increased the product yield further to 95% in 30 min.

A yield of 92% is already obtained after 15 min (Table 3, entry 6). Long ball milling times (Table 3, entry 4) may decrease the product yield due to thermal decomposition of the product.

Table 5. Mechanochemically initiated Achmatowicz rearrangement with furfuryl alcohol derivatives[a]



Entry	Reagent	Time (min)	Product	Yield (%)
1	 **2a**	30	 **3a**	95
2	 **2b**	15	 **3b**	71 [dr 2:1]
3	 **2c**	30	 **3c**	84 [dr 3:1]
4	 **2d**	30	 **3d**	63,[b,c] 55,[d] 45[e]
5	 **2e**	105	—	—

[a] Ratio of reagent / *m*CPBA = 1:2.

[b] 5:1 mixture of **3d** and the corresponding hemiacetal **5**.

[c] w%: **2d** / choline chloride = 1:1.

[d] w%: **2d** / choline chloride / quartz sand = 1:1:8.

[e] w%: **2d** / quartz sand = 1:10.

Table 4 compares literature-reported methods for the Achmatowicz reaction [3,4,16] with our optimized mechanochemical conversion (Table 4, entry 1) of furfuryl alcohol **2a** to 6-hydroxy-2*H*-pyrane-3(6*H*)-one (**3a**). The ball mill gives good yields without using solvents or external cooling of the reaction mixture (Table 4, entries 3–6). To illustrate the effect of continuous ball milling on the reaction progress, the identical reaction mixture was ground and mixed, yielding 80% of product (Table 4, entry 2).

The reaction protocol for the Achmatowicz rearrangement in a ball mill was then applied to several furfuryl alcohol derivatives (Table 5).

To investigate if the size of R^1 (Table 5) influences the Achmatowicz rearrangement, the furfuryl derivatives **2b** and **2c** were used under the optimized reaction conditions. Both reactions afforded the expected product in good yields. Neither the methyl group of **2b** nor the more bulky ethyl ester group of **2c** affect the formation of the Achmatowicz reaction (Table 5, entries 2 and 3). For **2b** a reaction time of 15 min was sufficient (Table 5, entry 2). Furan-2,5-diyldimethanol (**2d**) was tested as a solid starting material in the Achmatowicz reaction. This reaction gave the expected product **3d** in moderate yield in a 5:1 mixture with the corresponding hemiacetal **5**. The conditions for the solid starting material **2d** were modified using only choline chloride without quartz sand, which increased the yield from 45% (only quartz sand), 55% (choline chloride and quartz sand), to 63%. The Achmatowicz rearrangement for furfuryl alcohol **2e** did not proceed in the ball mill. The conversion of **2e** by the Achmatowicz rearrangement has not been described by other methods. A reason for this could be the complete loss of the aromaticity of the benzofuran moiety of **2e**.

CONCLUSION

In summary, we have described the first mechanochemically initiated Achmatowicz rearrangement in a planetary ball mill using *m*CPBA as oxidant, quartz sand as solid support, and choline chloride as additive. Using optimized reaction conditions, furfuryl alcohol derivatives were converted to the corresponding 6-hydroxy-2*H*-pyrane-3(6*H*)-ones with yields up to 95% and reaction times of only 15 to 30 min. The starting materials for the Achmatowicz reaction were likewise obtained through ball milling: Mechanochemically initiated reductions or Reformatsky reactions of furfural (**1a**) and derivatives gave access to different substituted furfuryl alcohol derivatives.

The mechanochemically initiated Achmatowicz rearrangement is an efficient alternative procedure to reported methods in solution to obtain valuable intermediates for organic synthesis from renewable bulk chemicals.

EXPERIMENTAL

6-Hydroxy-2*H*-pyran-3(6*H*)-one (3a)[17]

The agate beaker was equipped with 10 agate milling balls, quartz sand (1.50 g), **2a** (87 μL, 1.0 mmol), and *m*CPBA (345 mg, 2.0 mmol) and milling was performed for 30 min. The reaction mixture was diluted with water (15 mL) and filtered. The water was removed by lyophilisation, and **3a** (108 mg, 95%) was thus obtained as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (dd, 1H, $J = 3.1$, 10.4 Hz, 5-H), 6.17 (d, 1H, $J = 10.4$ Hz, 4-H), 5.64 (d, 1H, $J = 3.1$ Hz, 6-H), 4.58 (d, 1H, $J = 16.9$ Hz, 2-H), 4.14 (d, 1H, $J = 16.9$ Hz, 2-H).

FUNDING

Financial support by the Fonds der chemischen Industrie is gratefully acknowledged.

SUPPORTING INFORMATION

Full experimental data and ^{1}H NMR data for compounds **2c,e** and **3b,c,d** can be accessed on the publisher's website.

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