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## Solvent-free mechanochemical oxidation and reduction of biomass-derived 5-hydroxymethyl furfural†

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The simultaneous synthesis of 5-hydroxymethyl-2-furoic acid and 2,5-hydroxymethylfuran from biomass-derived 5-hydroxymethyl furan was developed using a solvent-free mechanochemical approach. The results obtained for the Cannizzaro disproportionation reaction show quantitative conversions of the starting materials with reaction times of only 5 min. Employing solvent-free conditions allows for a more sustainable synthetic approach that is reflected in an  $E_{\text{factor}}$  7 times smaller than that in previous reports. Additionally, initial results of the use of a sacrificial reagent, with the same solvent-free mechanochemical approach, for the selective reduction and oxidation of HMF are presented.

### Introduction

In the last decades, an uncontrolled overexploitation of fossil resources has led to increasing levels of emissions produced during the extraction and utilization of petrochemical-based raw materials, thereby contributing to global warming.<sup>1</sup> Sustainable chemical resources, coupled with greener methodologies, have therefore become an attractive target for academic research and potential industrial application.<sup>2</sup> The need to find new sustainable resources for energy production has been accompanied by a search for new sources of small molecules for the synthetic organic industry.<sup>3</sup> In this context, much attention has been paid to biomass as a potential source for a wide variety of small molecules.<sup>4–7</sup> Every year, 170 billion tons of biomass are produced by photosynthesis. Seventy five percent of this material can be classified as carbohydrates, but only less than 4% is used as food and non-food consumables, which leads to a vast accumulation of an untapped raw material.<sup>8,9</sup>

The dehydration of common hexoses has been reported to efficiently produce 5-hydroxymethylfurfural (HMF) as one of

the major products. HMF is a versatile small molecule that can serve as a substrate for the production of a multitude of furan derivatives (Fig. 1).<sup>10,11</sup> These biomass-derived platform chemicals have potential application in multiple fields of synthetic chemistry.<sup>12</sup>

Previous reports have demonstrated the oxidation of HMF into 2,5-furandicarboxylic acid (FDCA) using various supported transition metal heterogeneous catalysts including PtBi/C,<sup>13</sup> Pd/PVP,<sup>14</sup> Au/HT,<sup>15</sup> and Ru/C,<sup>16</sup> among others,<sup>17–20</sup> but the partial oxidation into 5-hydroxymethylfuroic acid (HMFA) or even 2,5-diformylfuran (DFF) has been scarcely reported due to the challenge in preventing complete oxidation (FDCA). Domínguez de María<sup>21</sup> and Li<sup>22</sup> reported enzyme-mediated methodologies in which HMFA and DFF were obtained employing lipases and alcohol oxidases with good yields, but with long reaction times.

The conversion of HMF into HMFA and 2,5-dihydroxymethylfuran (DHMF) is an important transformation that has been scarcely reported when compared to the synthesis of the higher oxidation state derivatives like FDCA.<sup>16,23–25</sup> Nonetheless, these molecules have been highlighted as important potential bio-monomers for the synthesis of polymers, such as polyurethane foams<sup>26,27</sup> and polyesters.<sup>28</sup>

In 2013, Afonso and co-workers reported the use of a Cannizzaro disproportionation reaction to synthesize both HMFA and DHMF simultaneously from HMF, under basic conditions.<sup>29</sup> The Cannizzaro reaction was originally reported

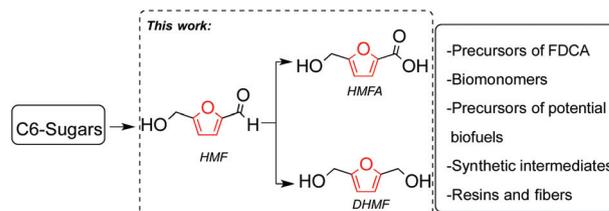


Fig. 1 Biomass derived furans with potential use as eco-friendly starting materials.

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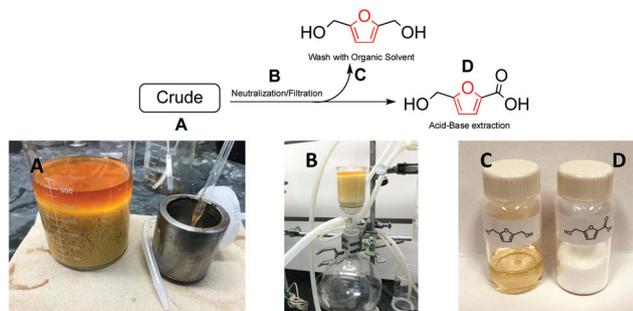
in the 1850s as a facile mode to synthesize benzoic acids.<sup>30–32</sup> One of the most prescient limitations of this reaction is that it allows for a maximum transformation of only 50% of the starting material into a specific target (either the reduced or oxidized product), which limits the efficiency of the overall reaction. For the modification of HMF, however, employing the Cannizzaro disproportionation takes advantage of this reactivity, since the simultaneous production of both HMFA and DHMF is beneficial due to their potential applications as biomass-derived platform chemicals.<sup>32–34</sup> Our goal is to develop conditions that allow for the synthesis of these biomass-based materials with an even smaller impact on the environment through a solvent-free methodology.

Solvents represent an estimated 80 to 90% by mass of the waste produced in a typical pharmaceutical batch chemical operation.<sup>35</sup> A valuable strategy to circumvent this issue is the use of mechanochemistry, which refers to solvent-free chemical transformations induced by mechanical energy, such as compression, shear, or friction.<sup>36</sup> The environmental benefits in the use of these greener reactions are extended to the work-up (Fig. 2) and purification processes, often overlooked sources of chemical waste.<sup>37</sup>

## Results and discussion

With the aim of developing new efficient and innovative methodologies for the production of the potential biomass-derived platform chemicals HMFA and DHMF, Cannizzaro solvent-free conditions were explored. The reaction was performed mechanically assisted with manual grinding, automatic grinding, lysis milling and planetary ball milling (Table 1).<sup>38</sup>

Initial results derived from the conditions of previous work have satisfactory reproducibility when water was employed as the solvent for the Cannizzaro reaction of HMF (entry 1), but when the reaction was carried out for 36 hours at room temperature, decomposition appears to have occurred, as no product was observed by GC-MS and <sup>1</sup>H NMR analysis. Even though the reaction proceeds with an acceptable yield, it was a valuable step towards greener conditions and hence the use of a solvent-free mechanochemical approach was evaluated.



**Fig. 2** Schematic representation and photographs regarding the large scale work-up and isolation of the compounds (see experimental section for details).

**Table 1** Optimization for the solvent-free mechanochemical Cannizzaro disproportionation of HMF

Entry	Base (equiv.)	Conditions	Time	%HMFA	%DHMF
1	NaOH (1.1)	24 °C [0.2 M] in H <sub>2</sub> O	24 h	67	67
2	NaOH (1.1)	24 °C [0.2 M] in H <sub>2</sub> O	36 h	<5	23
3	NaOH (1.1)	Manual grinding <sup>a</sup>	5 min	64	64
4	KOH (1.1)	Lysis milling <sup>b</sup>	5 min	12	12
5	KOH (1.1)	Auto. grinding <sup>c</sup>	5 min	76	76
6	KOH (2.0)	Manual grinding <sup>a</sup>	5 min	88	88
7	KOH (1.1)	Ball milling <sup>d</sup>	5 min	66	66
8	KOH (2.0)	Ball milling <sup>d</sup>	5 min	>99	>99
9	KOH (3.0)	Manual grinding <sup>a</sup>	5 min	87	87

<sup>a</sup> Reaction done under manual grinding with a mortar and pestle.

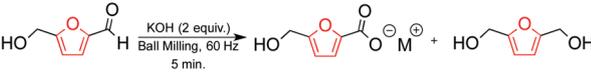
<sup>b</sup> FastPrep24, MP Biomedicals, used with ceramic beads at max. speed.

<sup>c</sup> Automatic mortar and pestle. <sup>d</sup> Planetary ball mill at 60 Hz.

Employing a slight excess of NaOH under manual grinding for 5 minutes gave a 64% disproportionation of the starting material that was essentially equivalent in yield to the solution reaction while using no solvent, and reducing the reaction time from 24 hours to 5 minutes (entry 3).

New mechanochemical techniques have been developed over the years to automatize solvent-free approaches to physical and chemical transformations. Lysis mill machines have been employed as mechanochemical tools in synthetic chemistry,<sup>39</sup> and we investigated the use of ceramic beads to perform the disproportionation reaction under solvent-free conditions (entry 4), but only a 12% yield was obtained. When the same reaction conditions were attempted with an automatic grinding apparatus, the yield increased to 76% (entry 5). An increase to 2 equivalents of base achieved an 88% yield, but no further increase was observed with 3 equivalents of base (entries 6 and 9). Recent publications highlight the efficiency of employing ball milling systems in organic synthesis, especially under solvent-free conditions.<sup>40,41</sup> When assessing the efficiency of the reaction using a ball milling system, a quantitative conversion was achieved with two equivalents of base (entry 8) in five minutes without the use of solvents. Identical results were obtained with different alkaline hydroxides.

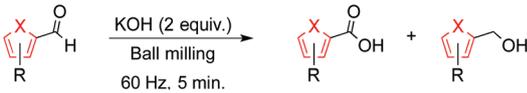
Given the potential quantities of DHMF and HMFA that will be needed for industrial applications, we decided to explore the efficiency of our optimized solvent-free methodology in larger reaction scales. Scaling up of the solvent free conditions from 200 mg up to 12.80 g provided the products in excellent yields in all cases (Table 2). When the 12.8 g reaction was spun for 7 min instead of 5 min, a quantitative yield was obtained (Table S2†). These series of experiments suggest the continued efficiency of using a solvent-free approach for the synthesis of these small molecules at an industrial scale, with new machineries that can take tons of material for grinding purposes, highlighting the potential for sizable reductions in industrial chemical waste production.

**Table 2** Scale-up for the disproportionation reaction using the planetary ball mill apparatus


Entry	HMF scale	%HMFA	%DHMF
1	0.200 g	>99	>99
2	0.400 g	>99	>99
3	0.800 g	>99	>99
4	3.200 g	96	96
5	12.80 g	92	92

It is remarkable to say that the optimized reaction is both efficient in time and in its green chemistry indicators,<sup>42</sup> with an  $E_{\text{factor}}$  of 0.55. Previous reports<sup>29</sup> describe a methodology with an  $E_{\text{factor}}$  of approximately 3.6, considering a 90% of reuse of the solvent, and 34 when no-solvent is recycled. This new solvent-free approach pushes the limits of this chemical transformation in both simplicity and green efficiency.

Initially this method was developed towards biomass-derived 5-hydroxymethylfurfural, however efforts were undertaken to evaluate the optimized conditions with other substrates for Cannizzaro disproportionation reactions (Table 3).

**Table 3** Scope of different aldehydes with the optimized disproportionation reaction conditions


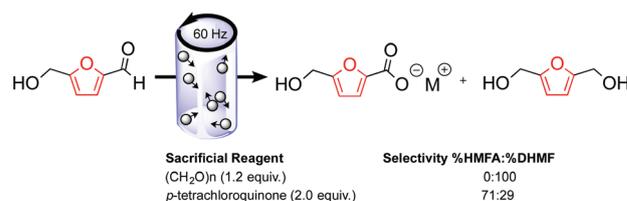
Entry	Substrate	% Acid	% Alcohol
1		>99	>99
2		>99	>99
3		>99	>99
4		98	98
5		>99	>99
6		90	91
7		98	98
8		95	94
9		95	95
10		92	92

Disproportionation was found to occur in excellent yields for several aromatic aldehydes (Table 3). Nonetheless, as the reaction is carried out in highly basic media, the scope is limited to substrates that do not bear any base-sensitive functionalities. A variety of other biomass derived furanocarboxaldehydes and their derivatives (entries 1–3) gave quantitative yields for this disproportionation. We also evaluated the possibility of employing benzaldehydes as substrates with the optimized conditions, and found that these also exhibited excellent results, with quantitative yields for arenes bearing different functionalities. This reaction represents a great advantage when compared to the classical Cannizzaro approach in both time and reagents. For in-solution Cannizzaro disproportionation, reported reaction times vary from a few hours to days, but with the solvent-free mechanochemical conditions reported herein, this time is reduced to only 5 minutes or less.

Cannizzaro disproportionation leads to a theoretical maximum of only 50% of the starting material transformed into a primary alcohol and 50% to a carboxylic acid, which limits the quantity of the desired material produced. To mitigate this outcome, some groups have studied the use of sacrificial agents in a cross-Cannizzaro reaction.<sup>43,44</sup> For this, a stoichiometric amount of a sacrificial molecule is employed within the reaction that can be fully reduced or oxidized, with the objective of transforming the starting material to the corresponding fully oxidized or reduced moiety, respectively.

Towards this end, we evaluated several sacrificial agents in order to control the production of one of the two possible Cannizzaro products for this reaction.

Several sacrificial reagents were employed for the cross-Cannizzaro reaction of HMF, including several readily available aldehydes (Table S1†). Benzaldehyde, acetaldehyde and D-glucose did not enhance the selectivity of the desired products. Anisaldehyde gave a small selectivity (1.2 : 1) favouring the synthesis of DHMF, but when paraformaldehyde was employed in slight excess, the reaction was specific towards the synthesis of DHMF, affording 90% yield. The oxidation of HMF to HMFA definitely represents a bigger challenge synthetically, since the presence of the primary alcohol creates a wider range of possible oxidation products. Based on the reported mechanism for the cross-Cannizzaro reaction, it is necessary to have first a nucleophilic addition of the hydroxide anion into the aldehyde moiety of HMF, to produce a tetrahedral intermediate that collapses through a hydride transfer

**Fig. 3** Preliminary results of the selective solvent-free mechanochemical cross Cannizzaro reaction of HMF employing sacrificial reagents.

to the sacrificial agent, producing a carboxylic acid group. For this reason, we decided to employ *p*-quinones as our sacrificial reagents as these are known to be readily available, excellent hydride acceptors.<sup>45</sup> After evaluating several *p*-quinones, a 7 : 3 selectivity towards the oxidation of HMF was obtained, albeit in relatively low yields (Fig. 3). These preliminary results indicate that the solvent-free complete conversion of HMF selectively to HMFA is possible and further studies toward this aim are currently underway.

## Conclusions

A new solvent-free, facile protocol was developed for the simultaneous synthesis of 5-hydroxymethylfuroic acid and 2,5-dihydroxymethylfuran through the Cannizzaro disproportionation under mechanochemical assistance with a planetary ball milling apparatus of biomass-derived 5-hydroxymethylfurfural, with an  $E_{\text{factor}}$  of 0.55, (7 times smaller than that in previous reports), and a reaction time of 5 min. The optimized conditions proved adaptable to several aromatic aldehydes, including other biomass derivatives of HMF, affording excellent yields. Also, initial results towards the selective oxidation or reduction of HMF *via* a cross-Cannizzaro reaction under solvent-free conditions are presented, with promising preliminary results that will be expanded in future work.

It is of tremendous importance to develop reactions that allow for the efficient transformation of biomass-derived materials to useful synthetic intermediates. This work highlights the importance of not only the employment of renewable sources, but also synthetic targets that use greener reaction conditions that minimize waste and use of solvents, especially when these reactions are expected to occur at industrial scales in the future.

## Experimental section

### General procedure for the disproportionation reaction

To the reaction vessel was added an aldehyde (0.8 mmol, 1 equiv.), finely ground and oven-dried KOH (1.6 mmol, 2 equiv.), and 7 stainless steel balls (8 mm diameter) and then the vessel was closed with a stainless lid wreathed with a rubber seal. The apparatus was set to run for 5 min at a 60 Hz frequency. The reaction mixture is dissolved in water and extracted with EtOAc three times. Organic extracts are combined and dried over  $\text{Na}_2\text{SO}_4$ . After filtration the solvent is evaporated under vacuum to obtain the corresponding primary alcohol. The aqueous portion of the extraction is acidified to pH 2 with conc. HCl to precipitate the desired carboxylic acid, which is collected through vacuum filtration.

### For HMF

Once the reaction is complete (general procedure) the crude is diluted with EtOH and transferred into a beaker, and then the pH was brought to 7 with concentrated HCl. The suspension

was then filtered through a short Celite pad. Once the solvent is evaporated under vacuum, the solid/oil mixture is washed three times with EtOAc. After evaporating the solvent of the combined EtOAc washes, a pale yellow oil is obtained (DHMF). For the solid that did not solubilize with the EtOAc washes, recrystallization in EtOH:EtOAc (2 : 98) was performed. Additionally this salt can be converted to free acid after an acid–base extraction. For a detailed description of the procedure please refer to the ESI†.

## Conflicts of interest

The authors declare no conflicts of interest.

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## Notes and references

- 1 F. Cherubini, *Energy Convers. Manage.*, 2010, **51**, 1412–1421.
- 2 A. Corma Canos, S. Iborra and A. Velty, *Chem. Rev.*, 2007, **107**, 2411–2502.
- 3 P. Gallezot, *Chem. Soc. Rev.*, 2011, **41**, 1538–1558.
- 4 J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539–554.
- 5 T. Werpy and G. Petersen, *Top Value Added Chemicals from Biomass Volume I — Results of Screening for Potential Candidates from Sugars and Synthesis Gas Top Value Added Chemicals From Biomass Volume I : Results of Screening for Potential Candidates*, Springfield, VA., 2004, vol. 1.
- 6 L. Deng, J. Li, D. M. Lai, Y. Fu and Q. X. Guo, *Angew. Chem., Int. Ed.*, 2009, **48**, 6529–6532.
- 7 C. Li, G. Xu, X. Liu, Y. Zhang and Y. Fu, *Ind. Eng. Chem. Res.*, 2017, **56**, 8843–8849.
- 8 H. Röper, *Starch/Staerke*, 2002, **54**, 89.
- 9 C. O. Tuck, E. Perez, I. T. Horvath, R. a. Sheldon and M. Poliakoff, *Science*, 2012, **337**, 695–699.
- 10 R.-J. Van Putten, J. C. Van Der Waal, E. De Jong, C. B. Rasrendra, H. J. Heeres and J. G. De Vries, *Chem. Rev.*, 2013, **113**, 1499–1597.
- 11 L. T. Mika, E. Cséfalvay and Á. Németh, *Chem. Rev.*, 2018, **118**, 505–613.
- 12 A. A. Rosatella, S. P. Simeonov, R. F. M. Frade and C. A. M. Afonso, *Green Chem.*, 2011, **13**, 754–793.

- 13 M. Kroger, U. Prufse and K.-D. Vorlop, *Top. Catal.*, 2000, **13**, 237–242.
- 14 B. Siyo, M. Schneider, M. M. Pohl, P. Langer and N. Steinfeld, *Catal. Lett.*, 2014, **144**, 498–506.
- 15 N. K. Gupta, S. Nishimura, A. Takagaki, K. Ebitani, K. Jitsukawa and K. Kaneda, *Green Chem.*, 2011, **13**, 824.
- 16 G. Yi, S. P. Teong and Y. Zhang, *Green Chem.*, 2016, **18**, 979–983.
- 17 R. Fang, R. Luque and Y. Li, *Green Chem.*, 2016, **18**, 3152–3157.
- 18 R. Fang, R. Luque and Y. Li, *Green Chem.*, 2017, **19**, 647–655.
- 19 P. Tan, G. Li, R. Fang, L. Chen, R. Luque and Y. Li, *ACS Catal.*, 2017, **7**, 2948–2955.
- 20 R. Fang, P. Tian, X. Yang, R. Luque and Y. Li, *Chem. Sci.*, 2018, **9**, 1854–1859.
- 21 M. Krystof, M. Pérez-Sánchez and P. Domínguez de María, *ChemSusChem*, 2013, **6**, 826–830.
- 22 Y.-Z. Qin, Y.-M. Li, M.-H. Zong, H. Wu and N. Li, *Green Chem.*, 2015, **17**, 3718–3722.
- 23 United States Patents Office, *United States Pat.*, US9617234B1, 2017, 1–16.
- 24 Z. Zhang and K. Deng, *ACS Catal.*, 2015, **5**, 6529–6544.
- 25 S. Xu, P. Zhou, Z. Zhang, C. Yang, B. Zhang, K. Deng, S. Bottle and H. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 14775–14782.
- 26 A. Gandini and M. Belgacem, *Prog. Polym. Sci.*, 1997, **22**, 1203–1379.
- 27 S. Boufi, A. Gandini and M. N. Belgacem, *Polymer*, 1995, **36**, 1689–1696.
- 28 E. De Jong, M. A. Dam, L. Sipos and G.-J. M. Gruter, in *ACS Symposium Series*, 2012, vol. 1105, pp. 1–13.
- 29 S. Subbiah, S. Simenon, J. Esperanca, L. P. Rebelo and C. Afonso, *Green Chem.*, 2013, **15**, 2849–2853.
- 30 S. Cannizzaro, *Ann. Chem. Pharm.*, 1853, **88**, 129–130.
- 31 T. A. Geissman, in *Organic Reactions*, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011, pp. 94–113.
- 32 E. S. Kang, D. W. Chae, B. Kim and Y. G. Kim, *J. Ind. Eng. Chem.*, 2012, **18**, 174–177.
- 33 J. Ohyama, A. Esaki, Y. Yamamoto, S. Arai and A. Satsuma, *RSC Adv.*, 2013, **3**, 1033–1036.
- 34 J. N. Chheda, G. W. Huber and J. A. Dumesic, *Angew. Chem., Int. Ed.*, 2007, **46**, 7164–7183.
- 35 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.
- 36 R. B. Nasir Baig and R. S. Varma, *Chem. Soc. Rev.*, 2012, **41**, 1559–1584.
- 37 R. S. Varma, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5866–5878.
- 38 D. Margetić and V. Štrukil, in *Mechanochemical Organic Synthesis*, Elsevier, 2016, pp. 1–54.
- 39 Y. Fang, N. Salamé, S. Woo, D. S. Bohle, T. Friščić and L. A. Cuccia, *CrystEngComm*, 2014, **16**, 7180–7185.
- 40 A. Stolle, B. Ondruschka, A. Krebs and C. Bolm, in *Innovative Catalysis in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2012, pp. 327–349.
- 41 A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.*, 2011, **40**, 2317–2329.
- 42 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273.
- 43 S. E. Hazlet and D. A. Stauffer, *J. Org. Chem.*, 1962, **27**, 2021–2024.
- 44 R. D. Tiwari and N. P. Srivastava, *Recl. Trav. Chim. des Pays-Bas*, 2010, **75**, 254–256.
- 45 J. P. Cheng, K. L. Handoo, J. Xue and V. D. Parker, *J. Org. Chem.*, 1993, **58**, 5050–5054.