One-Pot, Two-Step, Practical Catalytic Synthesis of 2,5-Diformylfuran from Fructose[†]
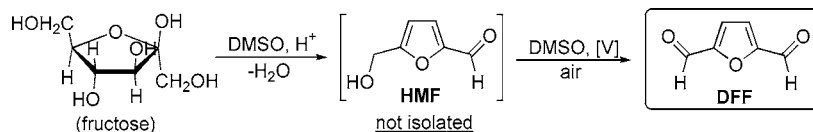
Gary A. Halliday, Robert J. Young, Jr., and Vladimir V. Grushin*

Central Research and Development, E. I. DuPont de Nemours & Co., Inc., Experimental Station, Wilmington, Delaware 19880-0328

vlad.grushin-1@usa.dupont.com

ABSTRACT

A practical, one-pot, two-step catalytic method is described for the synthesis of 2,5-diformylfuran (DFF) from fructose via dehydration to 5-(hydroxymethyl)furfural (HMF), followed by in situ catalytic air-oxidation.

Abundant and inexpensive, naturally occurring carbohydrates are currently viewed as most promising "renewable resources", a feedstock for the Green Chemistry of the future.[1,2] However, efficient and selective transformations of readily available carbohydrates to useful, polyfunctional molecules are still very rare. In this paper, we report the first simple and practical catalytic method for the preparation of 2,5-diformylfuran (DFF) directly from fructose.

There have been numerous reports describing various useful applications[1a] of 2,5-diformylfuran as a monomer;[3] as the starting material for the synthesis of drugs,[4] antifungal agents,[5] nematocides,[6] and ligands;[7] in photography;[8] as a cross-linking agent for poly(vinyl alcohol) for battery separators;[9] as a component for foundry sand binders;[10] for metal electroplating;[11] in analytical chemistry;[12] as a precursor for organic metals;[13] and in electrooptical devices,[14] organic

[†] Contribution No. 8291.

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phosphors, and luminophores.[15] Furthermore, 5-substituted 2-furaldehydes may be of considerable interest as intermediates for the synthesis of pharmaceuticals.[16] Despite its proven usefulness, DFF is commercially available only in milligram quantities and is expensive (ca. $30−65 per 100 mg).

The only practical route to DFF is selective oxidation of 5-(hydroxymethyl)furfural (HMF), which can be prepared via dehydration of fructose (Scheme 1).[1a,17] Being only
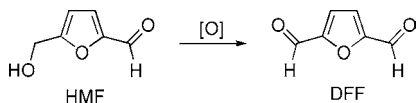
Scheme 1. Dehydration of Fructose to HMF
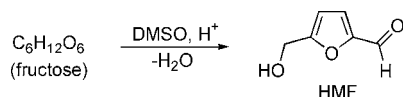
moderately stable, HMF can be produced in good yield if reaction 1 is run in DMSO, the only solvent known to *both* efficiently *promote* the dehydration and *stabilize* the desired product. However, due to the high solubility of HMF in DMSO, water, and other polar media, isolation of HMF from DMSO reaction solutions represents a challenging problem. The latter leads to the current limited availability and high cost of HMF (ca. $15−44 per 1 g, from different suppliers).

While a number of methods have been reported[18] for HMF to DFF oxidation (Scheme 2), all of them but one[18e] require

Scheme 2. Oxidation of HMF to DFF

costly *isolated and purified* HMF. The (AcO)$_2$O-induced Pfitzner−Moffatt-type oxidation of HMF[18b] has been performed[18e] on DMSO solutions of HMF generated via

thermal dehydration of fructose. These reaction solutions of HMF in DMSO/H$_2$O must be dried via a series of solvent extractions, in a multireactor setup, prior to the oxidation step.[18e]

Herein, we report a simple one-pot, two-step DFF synthesis that obviates the costly HMF isolation step and employs air, the most economical oxidant. In the first step of the process (Scheme 1), HMF is generated in 70−80% yield at ca. 100% conversion (GC−MS) by heating fructose in DMSO at 80−135 °C in the presence of H-form of a cation exchanger resin. The resin is then filtered off, a vanadium catalyst (oxide, phosphate, etc.; see below) added to the reaction mixture, and the second (Scheme 2), air-oxidation step is performed at 150 °C, 1 atm to produce DFF. The latter is then effortlessly isolated and purified to give DFF of >99% purity. Careful optimization of both reaction steps (see below) resulted in up to 45% overall yield of DFF calculated on fructose.[19]

Step 1: Fructose to HMF. Although fructose to HMF dehydration reaction (Scheme 1) is well-known,[1a,17] optimization appeared necessary. The noncatalytic thermal dehydration of fructose in DMSO at 150−160 °C has been claimed[18e,20] to produce HMF in 85−92% yield. We studied this reaction by quantitative GC−MS analysis (external standard; accuracy ±5% determined with freshly prepared known samples) which indicated yields of only 55−70% under the specified[18e,20] conditions. The recently published[21] synthesis of HMF from fructose in DMSO in the presence of lanthanide salts afforded, in our hands, HMF in 45−55% yield, in contrast with up to >90% yield reported.[21] Performing the dehydration in the presence of homogeneous Bronsted acid catalysts (0.1−5% H$_2$SO$_4$ or H$_3$PO$_4$) in a broad range of temperatures (80−135 °C) furnished HMF in only 10−50% yield. The best yields of HMF (70−80%, up to 85%) were achieved by running the dehydration in the presence

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(19) **Representative Procedures for DFF Synthesis.** (a) BioRad AG 50W-X8, 100−200 mesh cation-exchange resin (5 g; H-form, freshly activated by washing with acetonitrile and drying) was stirred with a solution of fructose (11.25 g; 62.4 mmol) in DMSO (50 mL) at 110 °C for 5 h to produce HMF in 85% yield (GC−MS). After cooling to room temperature and filtering off the resin, the dark solid-free solution (43 mL) was treated with VOHPO$_4$·0.5H$_2$O (0.39 g; 5 mol %). After air was bubbled through this mixture (vigorous stirring) at 150 °C for 13.5 h, GC−MS analysis indicated full conversion of HMF and 52% yield of DFF (based on fructose). Because small quantities of Me$_2$SO$_2$ and Me$_2$S (**ATTENTION!** unpleasant odor) were produced during the oxidation step, the outgoing gas was bubbled through bleach (NaOCl) to oxidize the Me$_2$S and fully destroy the odor. The reaction mixture was diluted with dichloromethane (300 mL), filtered, washed with water, passed through silica gel, and evaporated. The yield of crude DFF as a yellow crystalline solid was 3.2 g (41% based on fructose). Purification by vacuum sublimation followed by Soxhlet extraction (cyclohexane)/filtration through silica gel produced white or pale-yellow DFF of >99% purity, mp 108−110 °C (lit. mp 108−109 °C, see: Carpenter, A. J. *Tetrahedron* **1985**, *41*, 3803). ^{1}H NMR (CDCl$_3$, 20 °C) δ: 7.4 (s, 2H, furan H), 9.8 (s, 2H, CHO). ^{13}C NMR (CD$_2$Cl$_2$, 20 °C) δ: 120.4 (s, CH), 154.8 (s, qC), 179.7 (s, CHO), as previously reported.[18o] MS: *m/z* = 124. (b) A solution of fructose (16.87 g; 93.7 mmol) in DMSO (75 mL) was stirred at 80 °C with 3.75 g of BioRad AG 50W-X8, 100−200 mesh cation-exchange resin (H-form; pre-washed with water, MeOH, and dried) for 25.5 h to produce HMF in 77% yield (GC). After filtration, the solution (73 mL) was oxidized with air in the presence of V$_2$O$_5$ (0.66 g; 5 mol %) at 150 °C, as described above. After 17 h full conversion of HMF was observed (GC−MS) and the standard workup gave 4.83 g of DFF (42% based on fructose).

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of a Dowex-type ion-exchange resin,[22] BioRad AG 50W-X8, 100−200 mesh at 80−110 °C.[19]

Step 2: HMF to DFF Oxidation. The Peterson−Larock O_2/Pd(OAc)$_2$/DMSO system[23] exhibited low activity in HMF to DFF oxidation (conversions <10%). We then found that *pure* HMF can be O_2-oxidized to DFF in DMSO in the presence of bimetallic PdX$_2$−CuX (X = Cl, Br) catalysts.[24] Although both the initial efficiency and selectivity of the Pd−Cu catalysis were excellent, the catalyst quickly lost activity as the reaction occurred, probably because water was formed during the oxidation. In accord with that, no oxidation took place when the Pd−Cu system was applied to DMSO solutions of HMF obtained via dehydration of fructose (Scheme 1) and hence containing water by definition. Attempts to oxidize HMF to DFF with the recently reported Sheldon catalyst[25] were unsuccessful.

Having attempted oxidation of HMF in the presence of late-transition-metal complexes, we explored a series of vanadium catalysts to perform step 2 (Scheme 2). We were pleased to find that various inorganic vanadium compounds, such as V_2O_5 and VOHPO$_4$·0.5H$_2$O efficiently catalyzed air-oxidation of HMF to DFF in DMSO at 150 °C and 1 atm.[19,26] Most importantly, the vanadium compounds exhibited catalytic activity for air-oxidation of not only pure HMF in pure DMSO but also HMF produced via dehydration of fructose, as described above. The oxidation was more facile for control samples prepared with commercial crystalline HMF and pure DMSO, indicating that water and/or side products of step 1 (Scheme 1) decreased the catalyst efficiency. Catalytic activity of a series of vanadium compounds was determined by running the oxidation on a DMSO solution of HMF generated from fructose in 74% GC yield (Table 1). This

Table 1. Air-Oxidation of HMF Generated from Fructose in DMSO (See Text) in the Presence of Vanadium Catalysts (150 °C, 1 atm)

run	vanadium catalyst (5%)	time, h	% yield of DFF calcd on HMF	% yield of DFF calcd on fructose
1	V_2O_5	13	58	43
2	(VO)$_2$P$_2$O$_7$ on silica (1:1)	16.5	60	44
3	γ-VOPO$_4$	19	56	41
4	δ-VOPO$_4$	13	60	44
5	VOHPO$_4$·0.5H$_2$O	13	61	45
6	VO(PO$_3$)$_2$	19	49	36
7	[(VO)$_4$P$_2$O$_7$(OMe)$_4$]$^{-4}$ (2,4,6-collidinium$^+$)$_4$	13	54	40
8	[(VO)$_{12}$(PhPO$_3$)$_8$(OH)$_{12}$]$^{-4}$ (2,4,6-collidinium$^+$)$_4$	16.5	31	23
9	(VO)$_4$(Ph$_2$PO$_2$)$_2$(OMe)$_6$(MeOH)$_2$	16.5	47	35

stock solution was then divided into equal portions to which different vanadium compounds (5 mol %) were added to catalyze the oxidation reaction.

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(23) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.

(24) For instance, stirring a solution of HMF (305 mg), PdBr$_2$ (4 mg), and CuBr (20 mg) in DMSO (2 mL) under O_2 (1 atm) at 160 °C for 2, 4, and 6 h resulted in 70, 75, and 78% conversion, respectively, at ca. 100% selectivity.

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As seen from Table 1, all vanadium compounds were catalytically active, exhibiting comparable efficiencies and selectivities. Most of the simple inorganic vanadium catalysts (entries 1−5) exhibited similar activity which was noticeably higher than that of the polynuclear complexes containing organic ligands (entries 7−9). The least expensive and most readily available catalyst, V_2O_5, exhibited one of the higher efficiencies for the process. Therefore, it is V_2O_5 that we used for most preparative DFF syntheses.

Unlike HMF, DFF is a low-polar, hydrophobic compound which can be easily isolated[19] from the reaction solutions due to its insolubility in water and good solubility in many organic solvents. The crude product contaminated with small amounts of Me$_2$SO$_2$ and Me$_2$S[19] was purified by vacuum sublimation, followed by Soxhlet extraction with cyclohexane and simultaneous filtration through silica gel in a double-thimble setup (Figure 1). The once vacuum sublimed crude
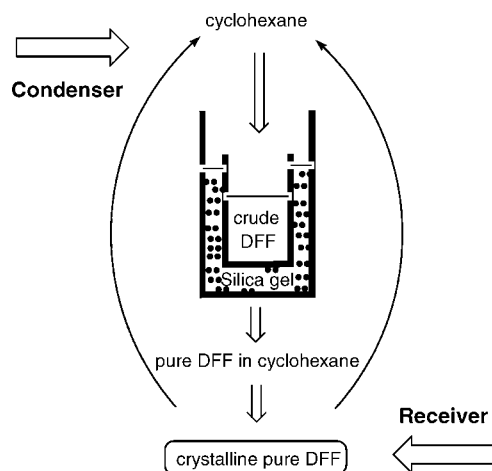

Figure 1. Double-thimble design for one-step purification of DFF via extraction−filtration through silica gel−crystallization in a single Soxhlet setup.

DFF was placed in the inner thimble, which was centered inside the outer, larger thimble, as shown in Figure 1. The space between the two thimbles was filled with silica gel to trap Me$_2$SO$_2$ and other impurities during the extraction. Once the Soxhlet extraction was complete, long needles of DFF (>99% purity) crystallized from the cyclohexane solution in the receiver upon cooling to room temperature. Due to its remarkable stability toward oxygen, DFF can be isolated, purified, and stored in air, without any sign of oxidation.

In conclusion, the first practical, catalytic method has been developed for the synthesis of 2,5-diformylfuran directly from fructose, a readily available and inexpensive renewable resource.

(26) For stoichiometric and semi-catalytic oxidations of *purified* HMF on supported V catalysts in toluene, see ref 18j,k,m.