

DOI: 10.1002/cctc.201400023

NaBr/DMSO-Induced Synthesis of 2,5-Diformylfuran from Fructose or 5-(Hydroxymethyl)furfural

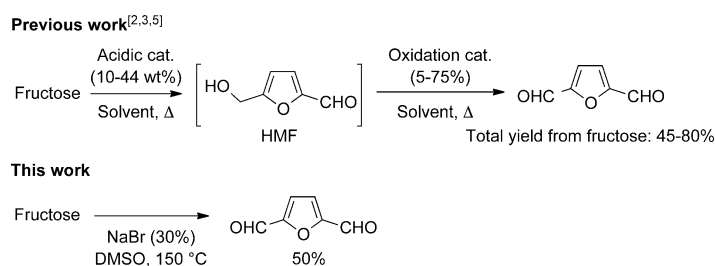
Caroline Laugel,^[a, b] Boris Estrine,^{*[a]} Jean Le Bras,^{*[b]} Norbert Hoffmann,^[b] Sinisa Marinkovic,^[a] and Jacques Muzart^[b]

2,5-Diformylfuran (DFF) was obtained by heating a solution of 5-(hydroxymethyl)furfural in DMSO. The addition of acids or salts improved the selectivity, especially if bromides were employed. Good yields of DFF were obtained with HBr or NaBr as the catalyst. One-pot procedures were developed from fructose, which led to DFF in medium yields. This transformation occurs through the formation of 5-(bromomethyl)furan-2-carbaldehyde followed by a Kornblum-type reaction. In the presence of bromide salts, the in situ formation of the catalyst involves the thermolysis of DMSO and the association of the resulting strong acids with the bromides.

2,5-Diformylfuran (DFF) is an important platform molecule that can be synthesized from renewable resources.^[1] Such a compound is produced by oxidation of 5-(hydroxymethyl)furfural (HMF), which is prepared by dehydration of carbohydrates such as fructose. The routes reported for the synthesis of DFF are mostly based on the oxidation of pure HMF, but its high price limits the production of DFF. This drawback and the low stability of HMF in organic solvents have led to the development of one-pot procedures from fructose to avoid the isolation of HMF. DMSO is known to promote dehydration efficiently and to stabilize HMF, and one-pot methods have therefore been developed in such a solvent. Grushin reported the first practical method for the synthesis of DFF directly from fructose by using a two-step procedure involving the dehydration of fructose by an acidic resin followed by filtration of the resin and air oxidation of the resulting HMF by vanadium catalyst at 150 °C. Thus, DFF was isolated in 45% overall yield.^[2] The one-pot synthesis of DFF from fructose was achieved in 80% yield through the stepwise addition of the catalyst, that is, a magnetic solid acid, Fe₃O₄-SBA-SO₃H, and a porous manganese oxide, K-OMS-2. However, the oxidation step required

0.75 equivalents of the catalyst.^[3] A one-pot/two-step synthesis of DFF was achieved by catalytic conversion of glucose over CrCl₃·6H₂O/NaBr followed by NaVO₃·2H₂O-catalyzed oxidation, and DFF was obtained in 55% yield based on glucose; the one-pot process led to the formation of DFF in 18% yield.^[4] DFF was synthesized from glucose in 25% yield in *N,N*-dimethylformamide through isomerization, dehydration, and oxidation through the stepwise addition of hydroxalcite, Amberlyst-15, and Ru/hydroxalcite catalysts.^[5] The two latter catalysts also allowed the preparation of DFF from fructose in 49% yield.^[5] Notably, these one-pot syntheses of DFF usually require the stepwise addition of the catalyst; the coexistence of both dehydration and oxidation catalysts from the initial stage of the reactions produces low yields of DFF owing to undesired side reactions that convert carbohydrates into humins.

Herein, we report that simple salts, in one-pot transformations, can replace transition-metal catalysts for the conversion of fructose or HMF into DFF in DMSO as the solvent (Scheme 1). Preliminary mechanistic studies are also discussed.



Scheme 1. Synthesis of DFF from fructose.

The dehydration of fructose is known to occur in DMSO at high temperature.^[1a,6] This transformation is generally performed in a few hours at 150 °C. Upon studying the stability of HMF in DMSO at this temperature, we observed that DFF was produced after 18 h in 30% yield (Table 1, entry 1).^[7] We suspected that the decomposition products of DMSO at high temperature could act as catalysts for the oxidation of HMF. Swern observed that thermolysis of DMSO in air led to the formation of strong acids such as sulfuric and methanesulfonic acids.^[8] We indeed observed acidification of the reaction mixture.^[9] Various Brønsted acids were then evaluated as catalysts for the oxidation of HMF in DMSO. Full conversion of HMF was achieved by using H₂SO₄ (30 mol%), and thermal conditions gave better selectivity than microwave irradiation (Table 1, entries 2 and 3). HCl, HI, and PTSA·H₂O (PTSA = *p*-toluenesulfonic acid)

[a] Dr. C. Laugel, Dr. B. Estrine, Dr. S. Marinkovic
Green Chemistry Department
Agro-industrie Recherches et Développements
Route de Bazancourt, Pomaclé 51110 (France)
E-mail: b.estrine@a-r-d.fr

[b] Dr. C. Laugel, Dr. J. Le Bras, Dr. N. Hoffmann, Dr. J. Muzart
Institut de Chimie Moléculaire de Reims, UMR 7312
CNRS-Université de Reims Champagne-Ardenne
UFR des Sciences Exactes et Naturelles, Reims 51100 (France)
E-mail: jean.lebras@univ-reims.fr

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/cctc.201400023>.

Entry	Catalyst, loading [mol%]	DFF, yield [%] ^[b]
1	–	30
2	H ₂ SO ₄ , 30	54
3 ^[c]	H ₂ SO ₄ , 30	29
4	HCl, 30	28
5	HI, 30	53 ^[d]
6	PTSA·H ₂ O, 30	29
7	HBr, 30	85 (75)
8	LiBr, 30	66
9	NH ₄ Br, 30	61
10	NaI, 30	7
11	NaCl, 30	10
12	NaBr, 30	85 (75)

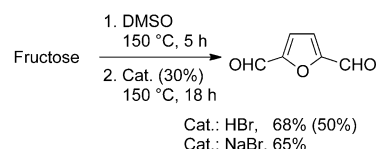
[a] Conditions: HMF (1.0 mmol), catalyst, DMSO (2 mL), 150 °C, 18 h, conversion 100%. [b] Yields were determined by GC analysis; yields of the isolated products are given in parentheses. [c] Performed under microwave irradiation (115 W, 20 min, T_{max} = 127 °C). [d] The formation of FFCA was observed.

were less efficient, whereas HBr greatly improved the selectivity and provided the product in good yield (Table 1, entries 4–7).^[10] Given that strong acids can be obtained from the thermolysis of DMSO, simple halide compounds were also tested as additives. Bromides were more efficient than chlorides and iodides, and NaBr led to a good yield of DFF (Table 1, entries 8–12).

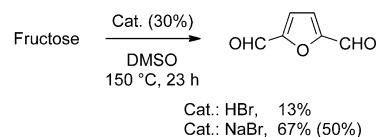
Other solvents such as DMF, sulfoxides, and sulfolane were tested in the presence of NaBr, but they all led to inferior results (Table S1, Supporting Information). The influence of the amount of NaBr, the concentration of HMF, and the temperature was then studied in DMSO (Table S2). Increasing the concentration of HMF from 5.7 to 11.4 wt% had no impact on the yield (Table S2, entries 1 and 2), whereas a concentration of 22.8 wt% HMF led to 57% yield (Table S2, entry 3). When the amount of catalyst was reduced to 10 mol% by using a 11.4 wt% HMF solution, the yield was 71% (Table S2, entry 4). A higher temperature (170 °C) with a 5.7 wt% HMF solution and 30 mol% catalyst was detrimental to the yield (Table S2, entry 5), whereas a high yield of DFF (84%) was reached with 10 mol% catalyst at 170 °C (Table S2, entry 6). At this temperature, an increase in the concentration of HMF had a negative impact on the efficiency of the process (Table S2, entry 7). The best conditions for the oxidation of HMF into DFF are the use of 30 mol% NaBr, 150 °C, and concentrations of HMF between 5.7 and 11.4 wt%.

The one-pot synthesis of DFF from fructose was then studied. In the absence of a catalyst, a low yield (12%) was observed. A two-step procedure was first evaluated on the basis of the DMSO-induced dehydration of fructose followed by an oxidation step performed in the presence of HBr or NaBr. DFF was obtained in 65–68% yield according to GC analysis (Scheme 2a). The influence of the nature of the catalyst was much more pronounced if the procedure was performed in one step. The presence of HBr in the initial stage of the transformation had a strong negative impact on the yield of DFF, whereas a good yield (67%, according to GC analysis) was ob-

a. Two-step procedure



b. One-step procedure



GC yields, isolated yields in parenthesis

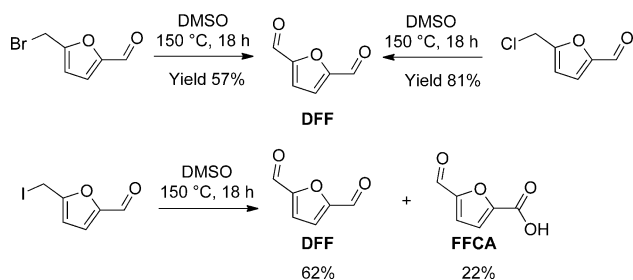
Scheme 2. One-pot preparation of DFF from fructose.

tained with NaBr (Scheme 2b). The concentration of HBr was probably too high during the dehydration step of fructose, which led to secondary reactions. The yield of the isolated product was 50% for the one-pot procedure from fructose by using NaBr and for the two-step procedure with the use of HBr as the catalyst.

A mechanism was proposed for the dehydration of fructose to HMF in which DMSO acted as the catalyst.^[11] We rather suspect that the strong acids produced during the thermolysis of DMSO are the true catalytic species.^[12] Concerning the oxidation step, we envisaged three possible pathways (Figure S1). We first envisioned that protonation of the alcohol group of HMF leads to the formation of a cationic intermediate, which would undergo nucleophilic addition of DMSO. Intramolecular deprotonation of a hydrogen atom to lead to DFF and Me₂S could follow two paths: through the formation of an ylide or through direct deprotonation of the hydrogen atom at C1 (Figure S1a). A similar approach would involve (halogenomethyl)furan-2-carbaldehyde as neutral intermediate (Figure S1 b). The last pathway would involve the protonation of DMSO. The resulting sulfonium would react with the alcohol functionality of HMF. Intramolecular rearrangement would lead to DFF, Me₂S, and H₂O (Figure S1 c). This last step does not depend on the structure of HX, and the results showed that the nature of the counteranion of the acid had a strong impact on the efficiency of the reaction. The first two approaches are more credible, and the main differentiation between these two paths is the nature of the intermediate, which would be ionic or neutral. We therefore prepared (halogenomethyl)furan-2-carbaldehydes and studied their reactivities in DMSO.

Upon heating 5-(bromomethyl)furan-2-carbaldehyde and 5-(chloromethyl)furan-2-carbaldehyde in DMSO at 150 °C for 18 h, DFF was obtained in 57 and 81% yield, respectively (Scheme 3). Under similar conditions, 5-(iodomethyl)furan-2-carbaldehyde led to DFF in 62% yield and to 5-formylfuran-2-carboxylic acid (FFCA) in 22% yield (Scheme 3). The formation of FFCA was also observed for the HI-catalyzed oxidation of HMF (Table 1, entry 5).

The kinetics of oxidation of 5-(bromomethyl)furan-2-carbaldehyde and the catalyzed oxidation of HMF in the presence of HBr in DMSO were monitored (Figure 1). Both kinetics followed



Scheme 3. Reactions of (halogenomethyl)furan-2-carbaldehydes in DMSO.

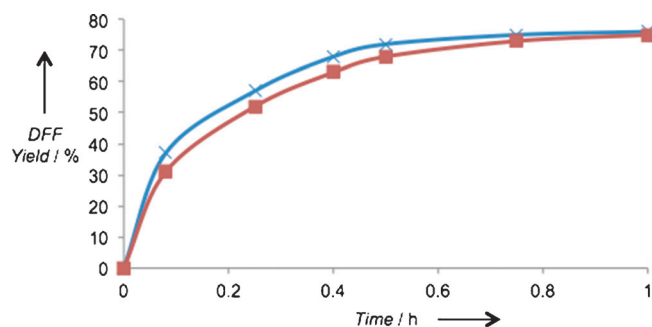


Figure 1. Kinetics of the oxidation of 5-(bromomethyl)furan-2-carbaldehyde and HMF. Conditions: HMF (1 mmol), HBr (0.3 mmol), DMSO (2 mL), and 150 °C (■); 5-(bromomethyl)furan-2-carbaldehyde (1 mmol), DMSO (2 mL), 150 °C (×).

a similar trend, which suggested that the slow step of the HBr-catalyzed oxidation of HMF is the oxidation of 5-(bromomethyl)furan-2-carbaldehyde by DMSO. The catalyzed oxidation would occur through a Kornblum-type reaction, in which the counteranion of the acid would act as a base (Scheme S1 b).

The kinetics of oxidation of HMF in the presence of NaBr and HBr as catalysts were compared (Figure 2). An induction period was observed in the presence of NaBr, whereas this

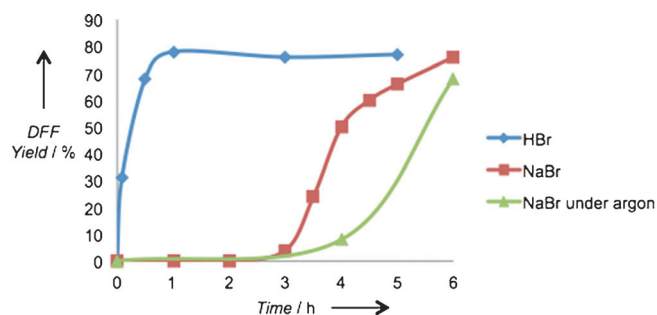


Figure 2. Kinetics of the oxidation of HMF in the presence of HBr or NaBr. HMF (1.0 mmol), HBr or NaBr (0.3 mmol), DMSO (2 mL), 150 °C, air or argon.

phenomenon was nonexistent with HBr. The induction period is probably related to the formation of strong acids by thermolysis of DMSO in air. Indeed, under an atmosphere of argon, the induction period was more pronounced (Figure 2).

The kinetics of the oxidation of HMF in the presence of strong acids were then monitored (Figure 3). No induction period was observed in the presence of such species. However,

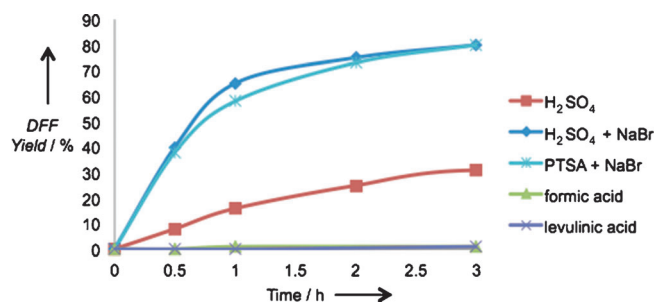


Figure 3. Kinetics of the oxidation of HMF in the presence of acids and NaBr. HMF (1.0 mmol), acid (0.3 mmol), NaBr (0 or 0.3 mmol), DMSO (2 mL), 150 °C.

a low selectivity was observed with H₂SO₄ owing to the formation of 5-[(methylthio)methyl]furan-2-carbaldehyde as a by-product. Upon using NaBr in conjunction with H₂SO₄, the yield of DFF improved. A similar result was achieved by using a mixture of PTSA-H₂O and NaBr. The association of a strong acid with NaBr led to the in situ formation of HBr and to the formation of the neutral 5-(bromomethyl)furan-2-carbaldehyde intermediate, which induced a selective transformation. In the absence of NaBr, the strong acid led to the formation of the more reactive cationic intermediate (Scheme S1 a), which afforded an unselective reaction.

Finally, given that levulinic and formic acids can be produced from HMF,^[12] we monitored the oxidation of HMF in their presence (Figure 3). These weak acids were strong enough to catalyze the dehydration of fructose,^[12] but they did not show any activity for the oxidation of HMF in DMSO (Figure 3).^[12]

In conclusion, the preparation of DFF from fructose or HMF in DMSO generally requires transition-metal catalysts, and we showed that simple halides (acids or salts) could induce this transformation. Bromides led to the best results, and DFF was prepared from fructose through a one-pot reaction under simple conditions. The in situ formation of strong acids from the thermolysis of DMSO seemed to be involved as catalysts, and the presence of bromides increased the selectivity. Such catalyzed procedures can be involved if DMSO is used as the solvent and should be taken into account especially if halides are present in the reaction mixture.

Acknowledgements

The authors gratefully acknowledge financial support by the Champagne-Ardenne Region and FEDER for this project (Furasynth program).

Keywords: 2,5-diformylfuran · carbohydrates · fructose · oxidation · oxygen heterocycles

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Received: January 10, 2014

Revised: February 3, 2014

Published online on March 12, 2014