Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Electronic Supplementary Information (ESI)

Efficient synthesis of 5-(chloromethyl)furfural (CMF) from high fructose corn syrup (HFCS) using continuous flow processing

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Contents

1. Experimental

Materials and analysis

All reagents and solvents were used without further purification. Fructose was obtained from Sigma-Aldrich, sucrose from CSR and glucose, 32 % HCl and 37 % HCl from VWR Chemicals. The solvent dichloromethane (DCM) was obtained from Merck. Reaction conversions were calculated from ^{1}H NMR spectra, which were recorded on an AC-400 spectrometer (Bruker) in chloroform (from Cambridge Isotope Laboratories Inc.). The residual solvent peak at $\delta = 7.26$ ppm was used as an internal reference. Product compositions were confirmed by GC-FID and GC-MS. GC-mass spectra were obtained with a Clarus 600 GC mass spectrometer (Perkin Elmer) using electron impact ionization in the positive ion mode with an ionization energy of 70 eV. The gas chromatography was performed with a Perkin Elmer Elite-5MS GC column (30 m × 0.25 mm ID, 0.25 µm film thickness), with a temperature program of 40 °C for 2 min, then heating at 10 °C/min to 280 °C where the temperature was held for 4 min with a split ratio of 70, an injector temperature of 250 °C and the transfer line set to 250 °C. Ultra high purity helium was used as the carrier gas with a flow rate of 0.7 ml/min. GC-FID analysis was performed on a 6850 Series II gas chromatograph (Agilent) with a split/splitless inlet and a detector temperature of 250 °C. Separation was done on a BPX5 capillary column (Grace, 25 m × 0.32 mm ID, 0.50 µm film thickness), with a temperature program of 40 °C for 2 min, then heating at 10 °C/min to 280 °C where the temperature was held for 4 min with a split ratio of 50 and an injector temperature of 200 °C. High purity helium was used as the carrier gas with a flow rate of 2.4 ml/min.

Experimental configuration of the Vapourtec Flow Reactor

The Vapourtec R2/R4 system (Vapourtec Ltd) was fitted with a 10 ml, PFA, reactor module.[1] These modules may be operated in temperatures ranging from ambient to 150 °C. Separate unpowered PFA coils were used for pre-mixing and cooling (inside an ice bath) as required. The pumping unit was fitted with two, standard, Vapourtec HPLC pumps capable of delivering flow rates from 0.010 to 9.99 ml/min at reaction pressures of up to 42 bar. The Back Pressure Regulator (BPR) used was an adjustable, spring loaded pressure relief valve, specially designed by Cambridge Reactor Design (CRD) for our application. Using a Swagelok® pressure relief valve spring, the BPR could be operated at pressures between 3.4 and 24.1 bar.[2] All other plumbing of reactor lines was carried out using PFA tubing (1/16" OD, 0.040" ID) obtained from VICI and the appropriate PFA fittings from Upchurch Scientific.

Continuous flow synthesis of 5-(chloromethyl)furfural (CMF) from fructose

A solution of fructose in 37 % HCl was pumped at a defined flow rate into a T-piece where it was mixed with dichloroethane (DCE), pumped at another defined flow rate in a second channel. The combined flow stream was directed through a 10 ml flow coil and heated to 100 °C. Then, the flow stream was directed to a cooling coil, at rt before entering the 10 bar acid resistant BPR. The product mixture was collected at the reactor outlet, where it was filtered through a short plug of sand and celite 545®. The layers were separated and the aqueous layer was extracted with DCE (5 times). The combined organic layers were dried with $MgSO_4$ and neutralised with K_2CO_3. The mixture was then filtered and evaporated to afford the final crude product. The product purity was analysed by NMR and GC.

^{1}H NMR ($CDCl_3$, 400 MHz): 4.59 (s, 2H, CH_2), 6.57 (d, J = 3.6 Hz, 1H, Ar-H), 7.18 (d, J = 3.6 Hz, 1H, Ar-H), 9.62 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): 36.5 (CH_2), 111.9, 121.5 (Ar-H), 152.9, 156.0 (Ar-H), 177.7 (CHO) ppm. Spectroscopic data are in agreement with the literature.[3]

Continuous flow synthesis of 5-(chloromethyl)furfural (CMF) from sucrose

A solution of sucrose (commercial sugar, CSR Sugar) in 37% HCl was pumped at a defined flow rate into a T-piece where it was mixed with DCM. The combined flow stream was directed through a 10 mL flow coil and heated to 100 °C. The product mixture was then directed into a cooling coil, at rt before entering the 10 bar acid resistant BPR. The product mixture was collected at the reactor outlet, where it was filtered through a short plug of sand and celite 545®. The layers were separated and the aqueous layer was extracted with DCM (5 times). The combined organic layers were dried over $MgSO_4$ and neutralised with K_2CO_3. The mixture was then filtered and evaporated to afford the final crude product. The product purity was analysed by NMR and GC.

The product spectra were consistent with those obtained from the synthesis using fructose.

Continuous flow synthesis of 5-(chloromethyl)furfural (CMF) from high fructose corn syrup (HFCS)

High Fructose Corn Syrups were prepared according to the data sheets provided by Archer Daniels Midland Company (ADM).[4] The commercial syrups are composed of water, fructose, glucose and higher saccharides. They were modelled with water, fructose, glucose and sucrose (to substitute for the higher saccharides).

100 g of HFCS-90 was prepared by mixing 23 g of water, 69.3 g of fructose, 6.545 g of glucose and 1.155 g of sucrose. 100 g of HFCS-55 was prepared by mixing 23 g of water, 42.35 g of fructose, 31.57 g of glucose and 3.08 g of sucrose. The mixture was stirred and sonicated until a completely homogeneous sugar solution was obtained.

A solution of High Fructose Corn Syrup (HFCS-90 or 55) was pumped at a defined flow rate into a T-piece where it was mixed with 32 % HCl. This combined aqueous solution was then directed through a 10 ml pre-mixing flow coil at RT. It was then directed into a second T-piece where it was mixed with DCM, pumped at a defined flow rate in a third channel. The combined regent mixture was then directed through a 10 ml coil and heated to 100 °C. Following this the product mixture was directed to a cooling coil, immersed in an ice bath, before entering the 10 bar acid resistant BPR. The product mixture was collected at the reactor outlet, where it was filtered through a short plug of sand and celite 545®. The layers were separated and the aqueous layer was extracted with DCM (5 times). The combined organic layers were dried over $MgSO_4$ and neutralised with K_2CO_3. The mixture was then filtered and evaporated to afford the final crude product. The product purity was analysed by NMR and GC.

The product spectra were consistent with those obtained from the synthesis using fructose.

2. Additional figures and data

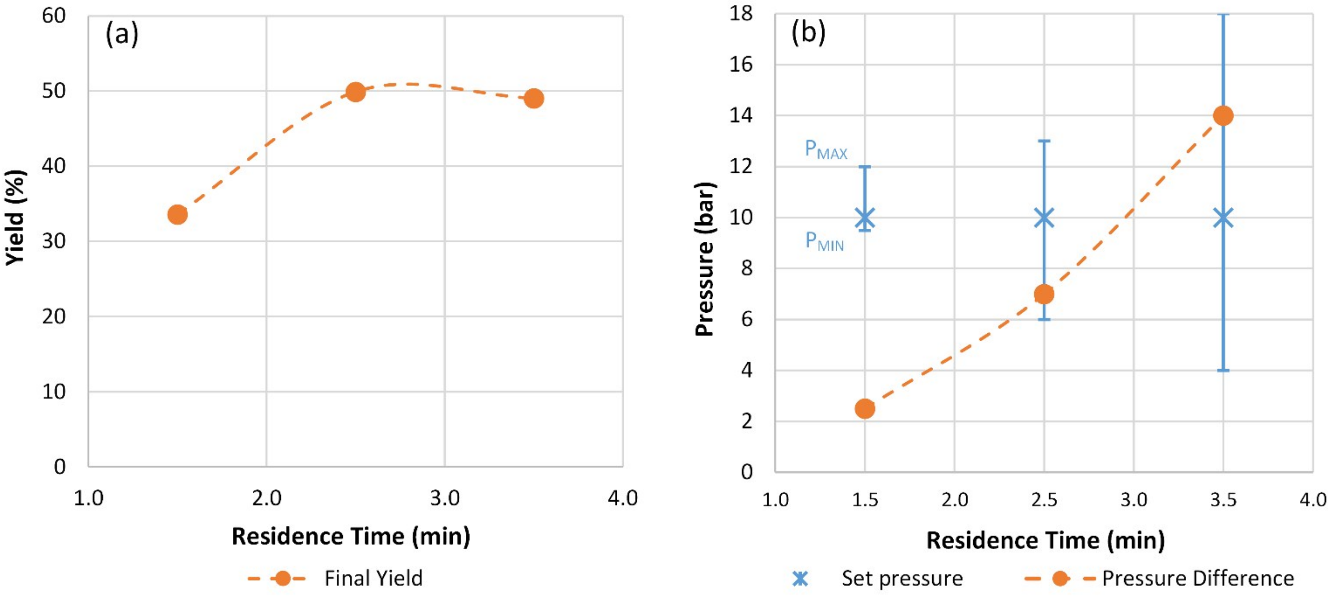


Figure S1 – **CMF from sucrose**. Influence of **residence time (τ)** on both (a) the final yield and (b) the system stability, measured as pressure difference between minimum and maximum observed system pressure, (1 g sucrose/10 ml, 100°C, 1:1 aq/org inlet flow rate ratio).

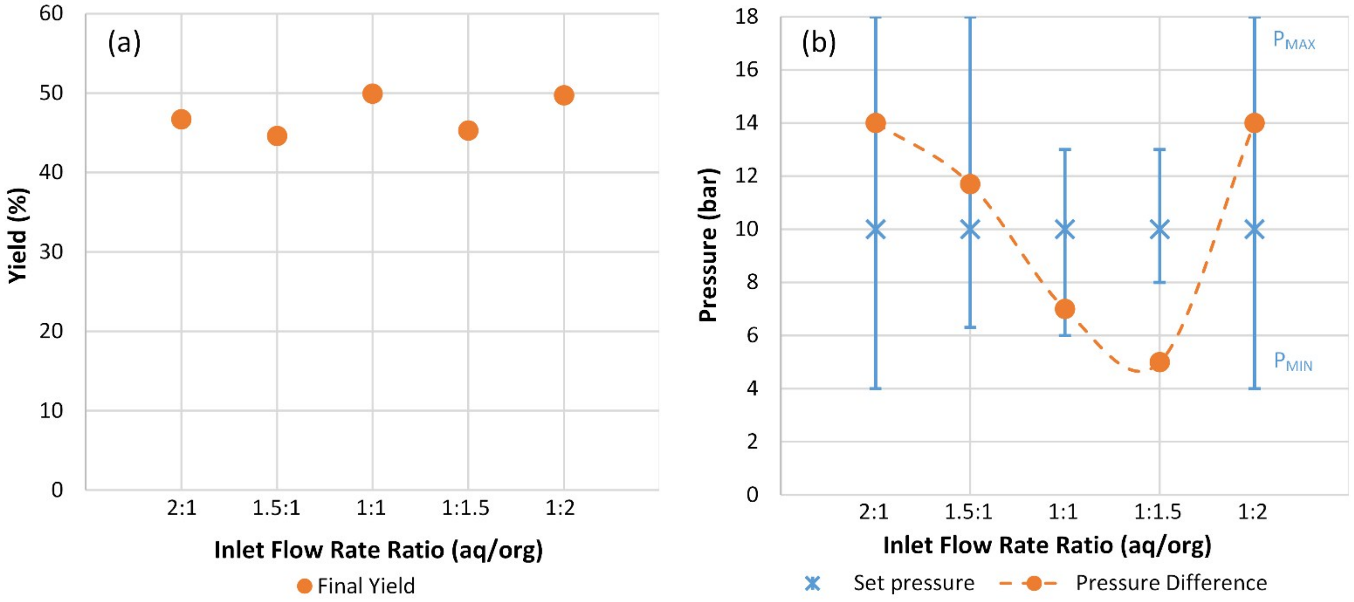


Figure S2 – CMF from sucrose. Influence of **inlet flow rate ratios** (aq/org) on both (a) the final yield and (b) the system stability, measured as pressure difference between minimum and maximum observed system pressure, (τ = 2.5 min, 1 g sucrose/10 ml, 100°C).

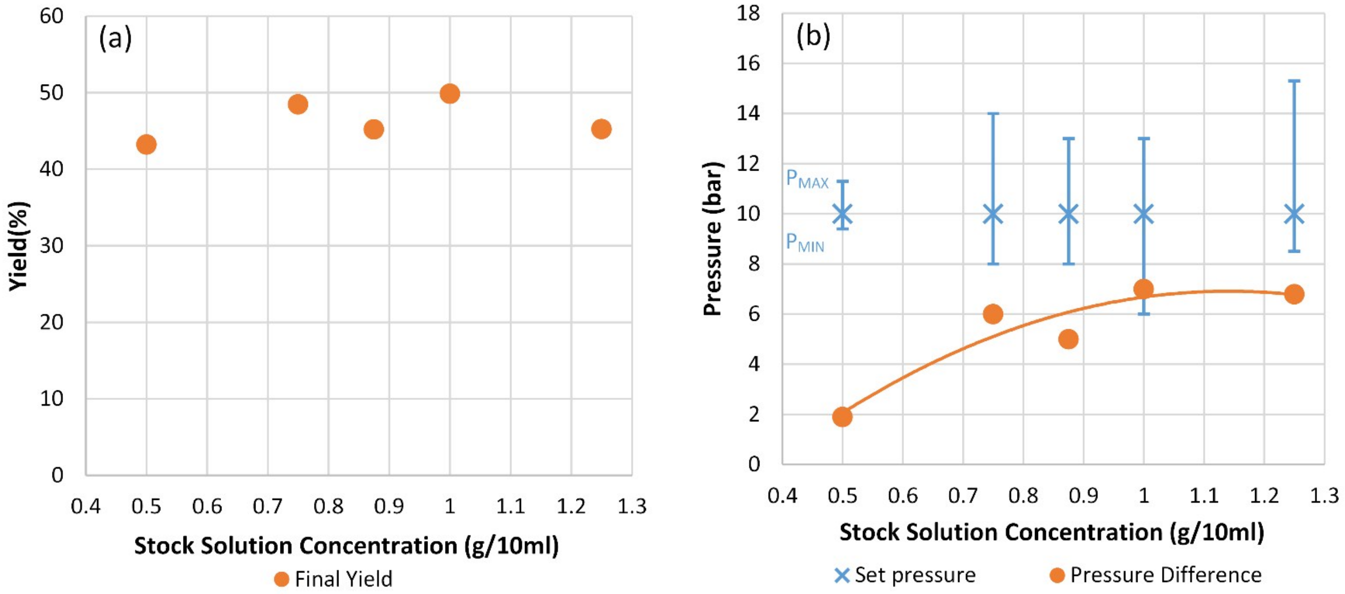


Figure S3 – CMF from sucrose. Influence of **stock solution concentration** on both (a) the final yield and (b) the system stability, measured as pressure difference between minimum and maximum observed system pressure, (τ = 2.5 min, 100°C, 1:1 aq/org inlet flow rate ratio).

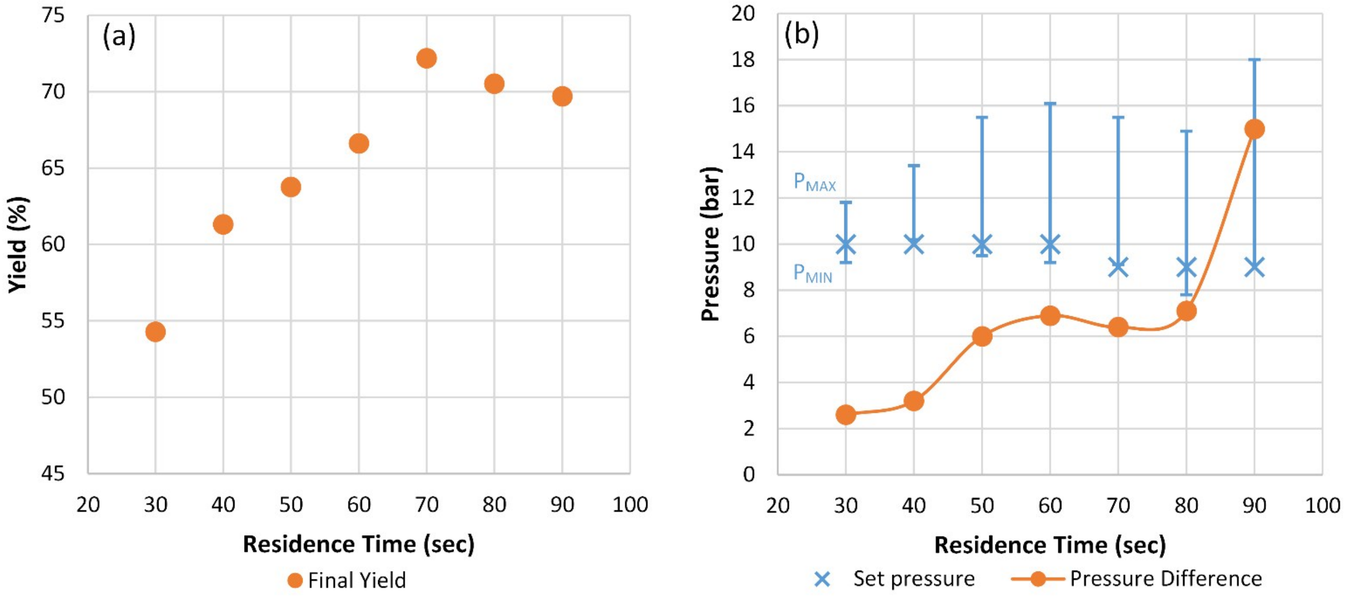


Figure S4 – CMF from HFCS-90. Influence of **residence time** on both (a) the final yield and (b) the system stability, measured as pressure difference between the minimum and maximum observed system pressure, (1 g/10 ml, 100°C, 1:1 aq/org inlet flow rate ratio).

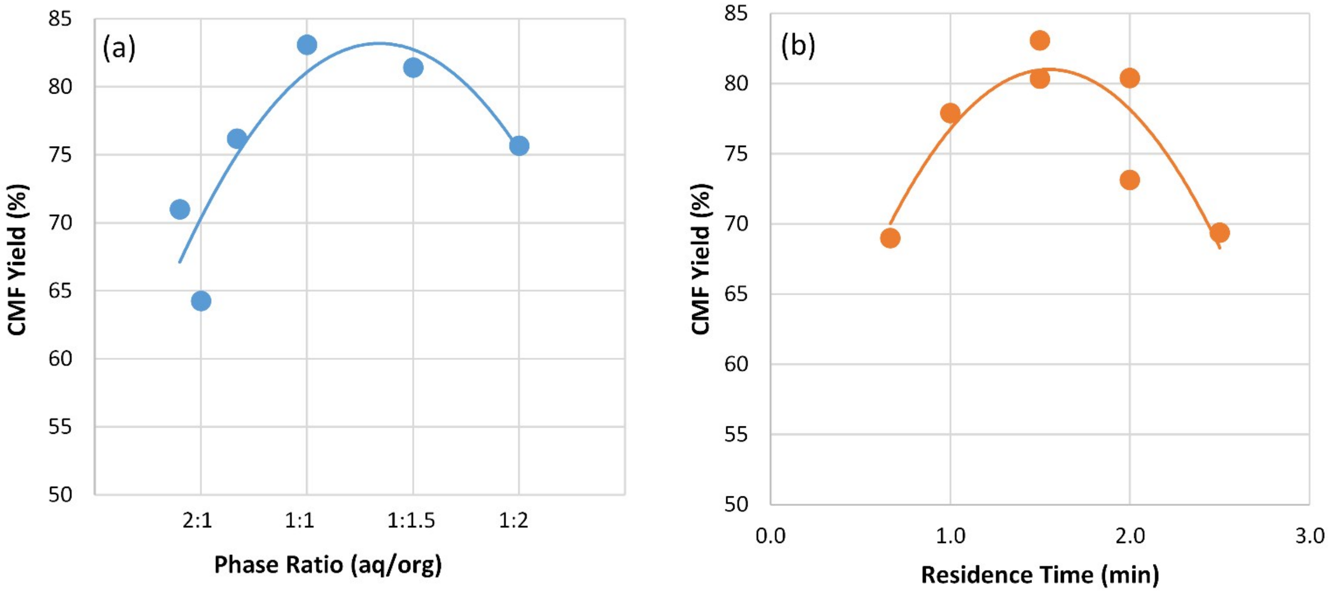


Figure S5 – CMF from HFCS-90. (a) Change in the yield of CMF with **ratio of aqueous to organic phase** delivered in the continuous reactor system at 100 °C and a residence time of 1.5 min. (b) Plot of CMF yield against **residence time** showing the clear maximum reached at a residence time of 1.5 min. Reactions performed at 100 °C and a 1:1 aqueous to organic phase ratio.

3. Comparison between HFCS-90 and HFCS-55 and investigation of pre-digestion

As detailed before, several types of syrup can be industrially provided. HFCS-55 and HFCS-42, respectively containing 55% and 42% of fructose, could be potential candidates for CMF production from cellulosic resources. However, since fructose is the most reactive species of the syrup, a lower yield is expected when using those syrups instead of HFCS-90. HFCS-55 was used in order to compare the CMF yield when reacting it in the same conditions as HFCS-90. A 70 sec residence time was used and as it was expected a dramatic drop of the yield occurred (from 72% to 48%, Figure S6a). As observed in Figure S6b, the HFCS-55 showed a better stability, which can be interpreted as a result of a lower amount of humics formed due to the lower conversion of fructose.

Final tests were carried out in order to gauge whether it was relevant or not to have the HFCS digested prior to reaction in the acidic medium. Pre-digestion basically is a result of a reaction occurring between sugar derivatives and acid when they have been in contact for a long-enough time. During pre-digestion the solution turned a yellow-orange colour, indicating that the dehydration had begun. Given the set-up of the reaction, the pre-mixing coil volume was fixed as well as the flow rate ratios. As a consequence the only way to vary the degree of pre-digestion of the mixture was to provide heating in the pre-mixing coil. Tests were undertaken to get an idea of the most appropriate temperature that could ensure pre-digestion without making the reaction progress too far, which was determined from the colouration occurring inside the pre-digestion reactor coil. The map shown on Figure S7 suggested that running the reaction at 50 °C for 70 s or less produces only little colouration and those could therefore be suitable conditions. However, as it can be observed in Figure S6a, the yield does not seem to be affected by the pre-digestion procedure, as very comparable results were obtained. However, it seemed to have an impact on the pressure stability (Figure S6b). The pressure difference was almost doubled for HFCS-90 when using pre-digestion conditions at 50 °C (the BPR got blocked) and it increased by 2 bar for HFCS-55. A basic explanation would be that pre-digesting the mixture could enhance the humin production, leading to of accumulation of solid matter inside the BPR, causing blockage.

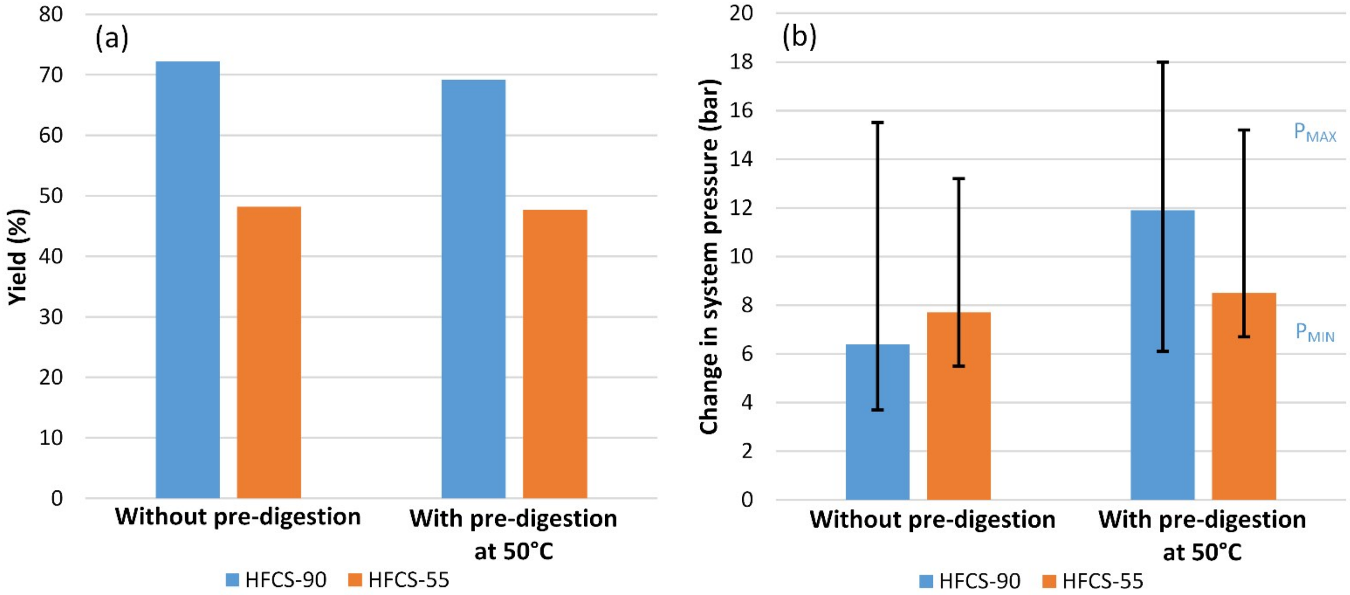


Figure S6 – Comparison between the reactivity of HFCS-90 and HFCS-55 (1g/10ml, 100°C, 1:1 aq/org inlet flow rate ratio, τ = 70 sec).

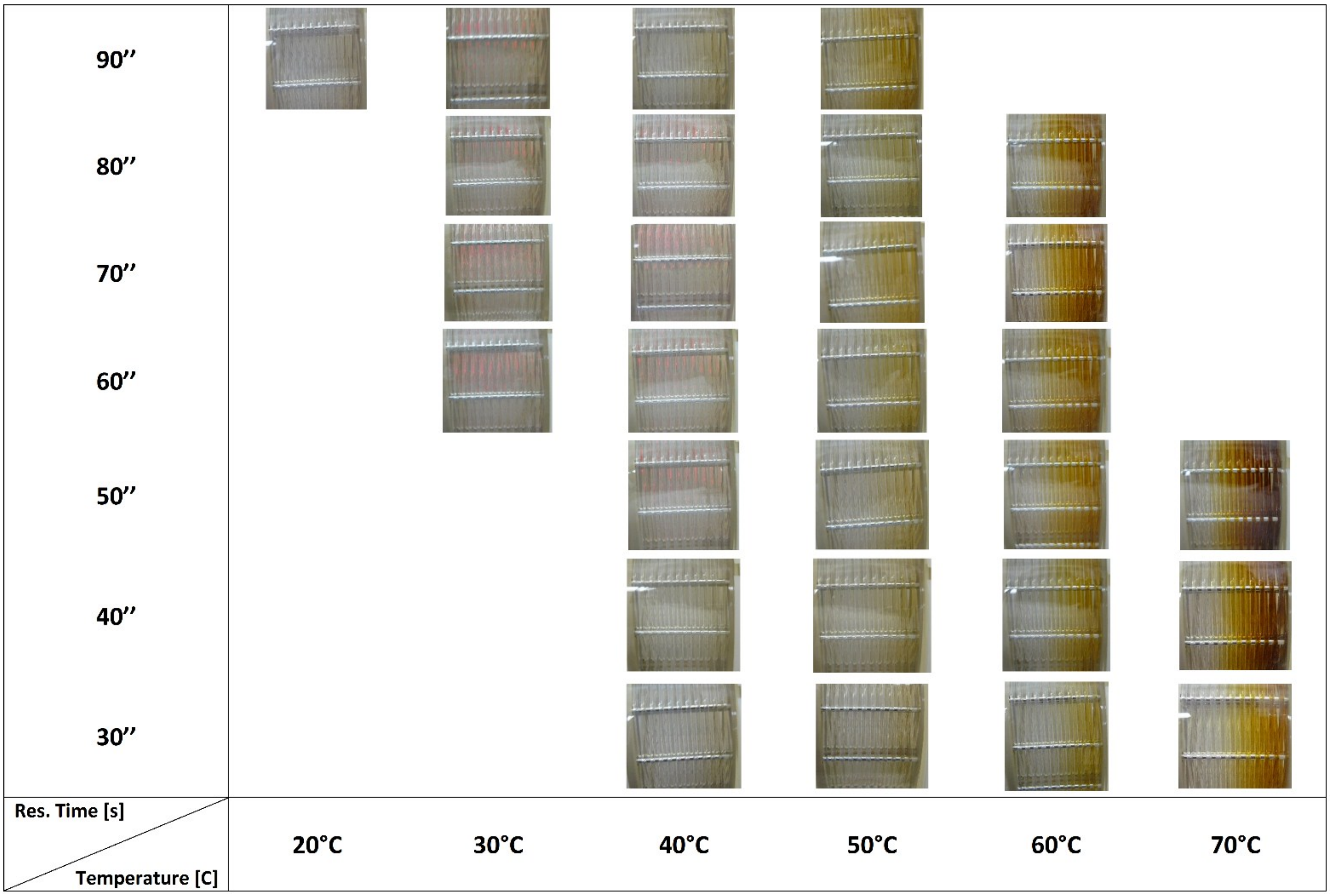


Figure S7 – Pre-digestion reactivity map.

Based on these results, it would be recommended to run the HFCS conversion with HFCS-90 as starting material without any pre-digestion, as no pre-digestion maximises the yield as well as the pressure stability of the overall system.

4. Spectral Data

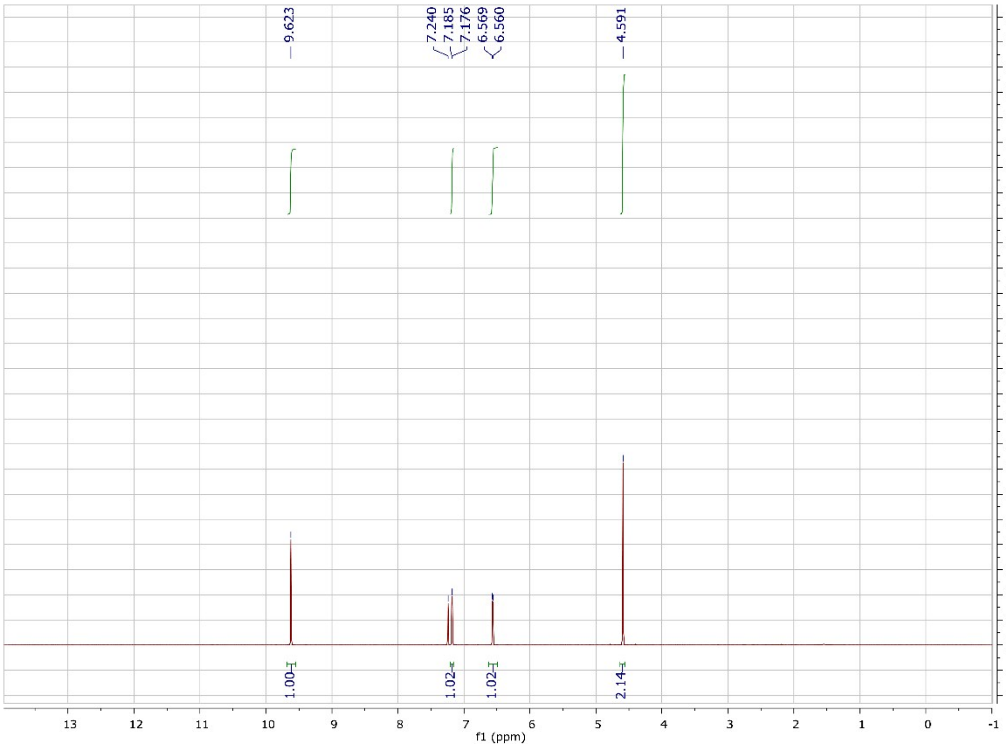


Figure S8 – 1H NMR spectrum of the CMF product.

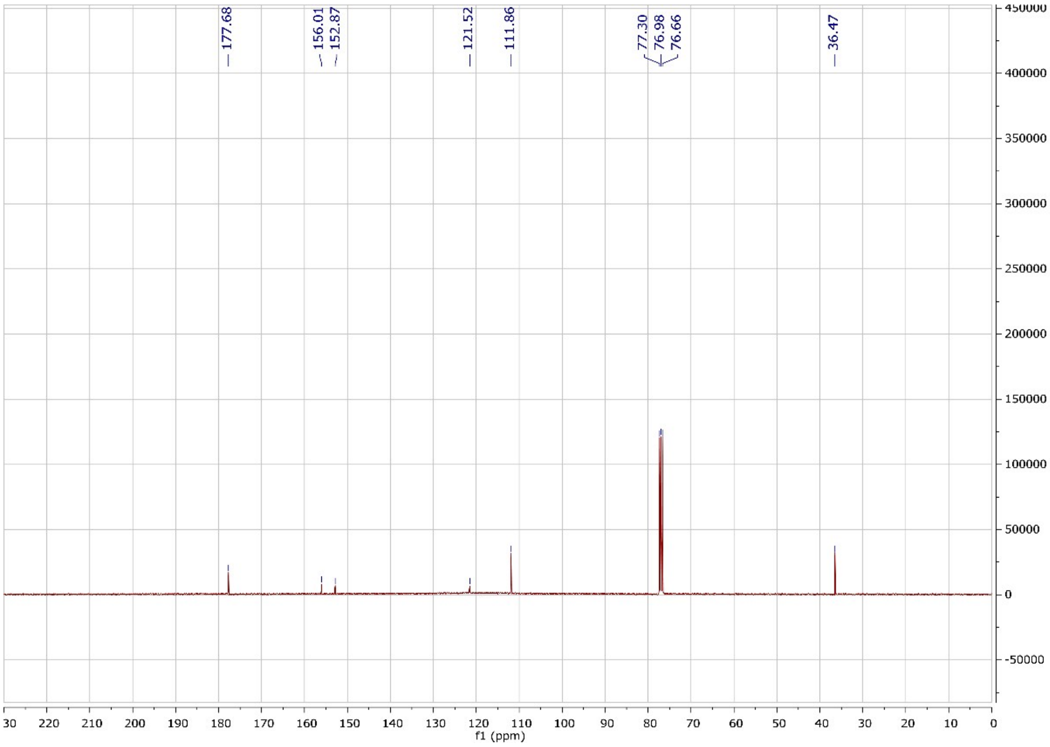


Figure S9 – ^{13}C NMR spectrum of the CMF product.

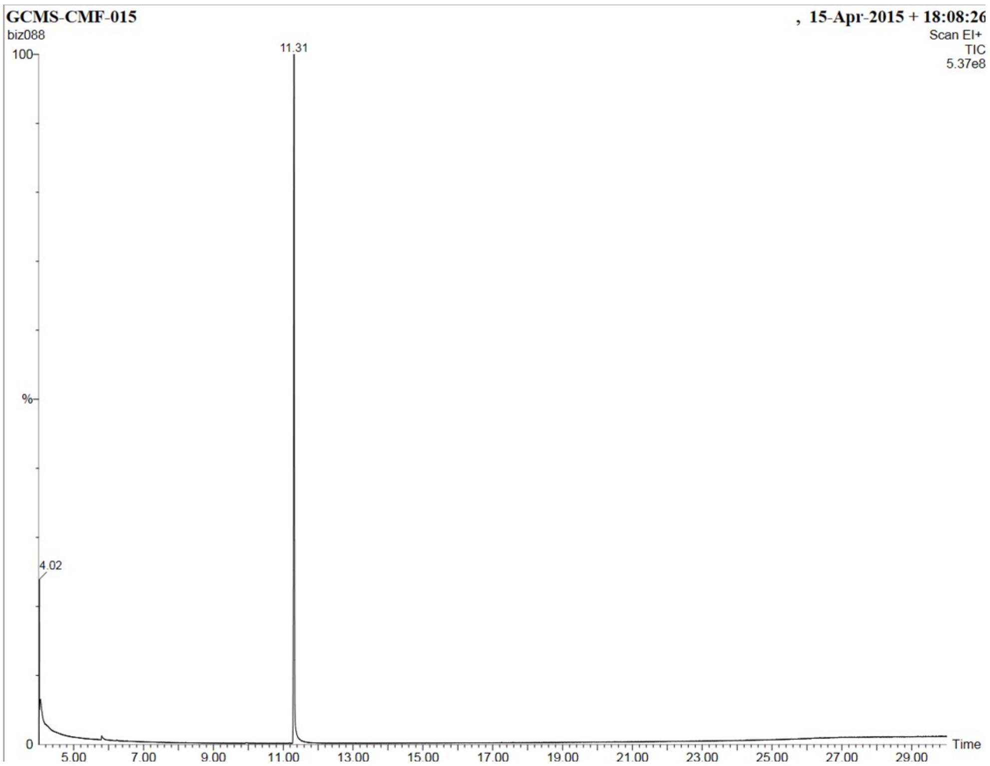


Figure S10 – GC chromatogram of the CMF product.

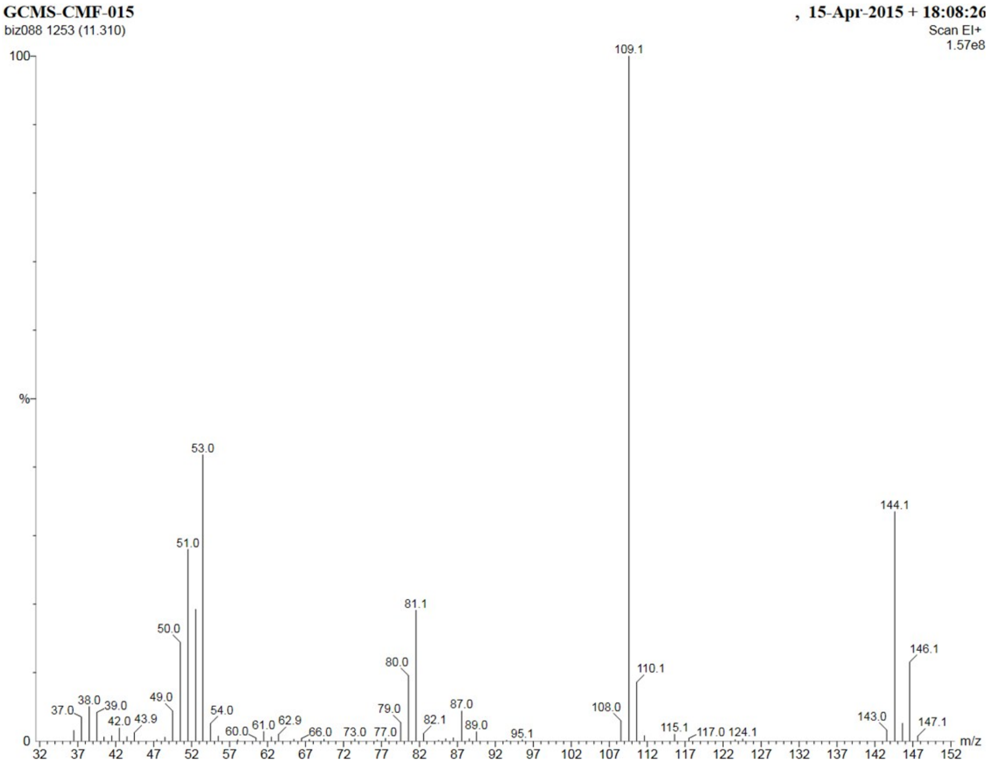
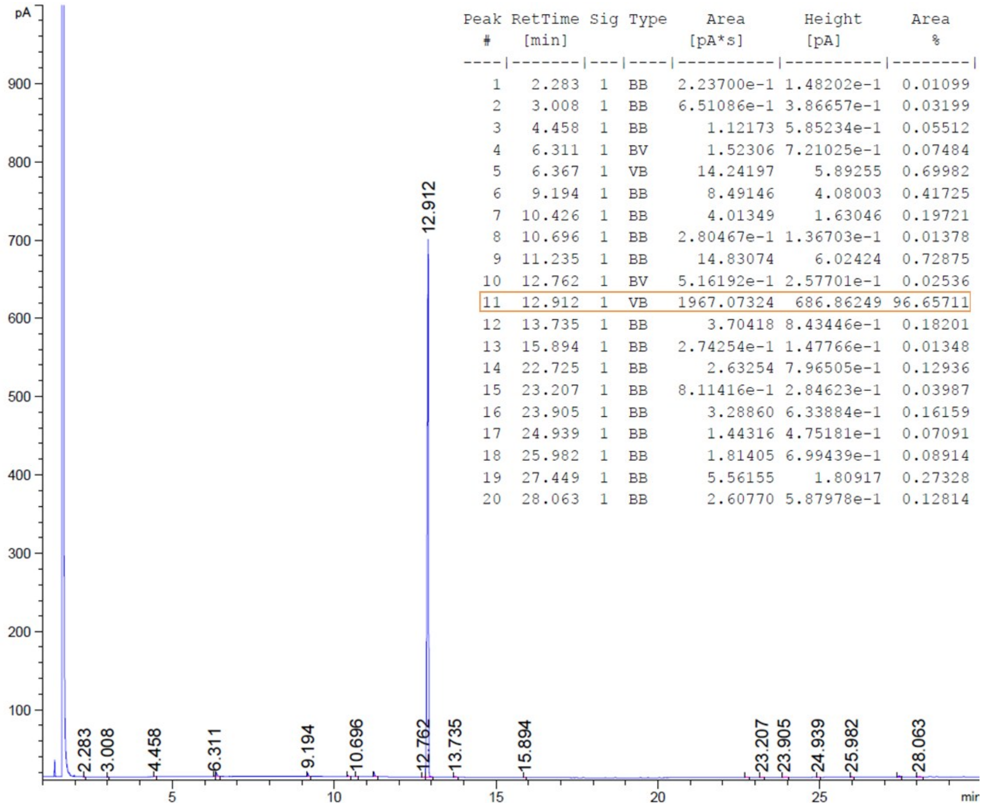


Figure S11 – Mass spectrum of CMF (peak at 11.31 min retention time).



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Peak RetTime Sig Type    Area      Height      Area
  #   [min]               [pA*s]     [pA]        %
----|-------|---|----|----------|----------|--------|
  1    2.283  1  BB   2.23700e-1 1.48202e-1  0.01099
  2    3.008  1  BB   6.51086e-1 3.86657e-1  0.03199
  3    4.458  1  BB      1.12173 5.85234e-1  0.05512
  4    6.311  1  BV      1.52306 7.21025e-1  0.07484
  5    6.367  1  VB     14.24197    5.89255  0.69982
  6    9.194  1  BB      8.49146    4.08003  0.41725
  7   10.426  1  BB      4.01349    1.63046  0.19721
  8   10.696  1  BB   2.80467e-1 1.36703e-1  0.01378
  9   11.235  1  BB     14.83074    6.02424  0.72875
 10   12.762  1  BV   5.16192e-1 2.57701e-1  0.02536
 11   12.912  1  VB   1967.07324  686.86249 96.65711
 12   13.735  1  BB      3.70418 8.43446e-1  0.18201
 13   15.894  1  BB   2.74254e-1 1.47766e-1  0.01348
 14   22.725  1  BB      2.63254 7.96505e-1  0.12936
 15   23.207  1  BB   8.11416e-1 2.84623e-1  0.03987
 16   23.905  1  BB      3.28860 6.33884e-1  0.16159
 17   24.939  1  BB      1.44316 4.75181e-1  0.07091
 18   25.982  1  BB      1.81405 6.99439e-1  0.08914
 19   27.449  1  BB      5.56155    1.80917  0.27328
 20   28.063  1  BB      2.60770 5.87978e-1  0.12814
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Figure S12: A typical GC-FID result obtained for CMF.

5. References

1 International Flow Chemistry Equipment|Vapourtec Ltd, https://www.vapourtec.com/, (accessed December 2016)

2 Swagelok.com the source for tube fittings, valves, and other fluid system components | Swagelok, https://www.swagelok.com/en, (accessed December 2016).

3 M. Brasholz, K. von Känel, C. H. Hornung, S. Saubern and J. Tsanaktsidis, *Green Chem.*, 2011, **13**, 1114.

4 ADM: Home, http://www.adm.com/en-US/Pages/default.aspx, (accessed January 2017).